Determining the effectiveness of harm reduction interventions in the prevention of hepatitis C virus transmission among people who inject drugs in Scotland

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Summary

The hepatitis C virus (HCV) is highly prevalent among people who inject drugs (PWID) in Scotland and the large majority of new HCV infections occurring in Scotland are within this population group. Harm reduction interventions, mainly sterile injecting equipment provision (IEP) and opioid substitution treatment (OST), to prevent the transmission of blood-borne viruses among PWID, were implemented in Scotland in the late 1980s/early 1990s. More recently, government policy initiatives, particularly the Hepatitis C Action Plan for Scotland, have stipulated the scale-up of these interventions. The overarching aim of this thesis was to investigate the impact of harm reduction interventions on the transmission of HCV among PWID in Scotland. Five secondary objectives were addressed in order to fulfil the main aim: (i) to review the international literature on the effectiveness of IEP and OST in preventing HCV transmission; (ii) to determine the association between self-reported sharing of needles/syringes and incident/prevalent HCV infection; (iii) to determine the association between sharing non-needle/syringe injecting paraphernalia and incident HCV infection; (iv) to determine the incidence of HCV among PWID in Scotland; and (v) to determine the association between self-reported uptake of IEP/OST and incident HCV infection.

To address the first thesis objective, a systematic review of the literature was undertaken to identify existing international research evidence (published up to March 2007) for the effectiveness of harm reduction interventions. While HCV was the main outcome of interest, HIV and injecting risk behaviour (IRB) were also considered. A review of reviews approach identified: insufficient evidence that sterile needle and syringe provision (NSP) was effective in preventing HCV transmission; tentative evidence that NSP was effective in preventing HIV transmission; sufficient evidence to support the effectiveness of NSP in reducing self-reported IRB; and little to no evidence on needle/syringe vending machines, outreach NSP or the provision of other injecting paraphernalia (spoons, filters, water) in relation to any of the outcomes. With regard to OST, the findings were: insufficient evidence to show that OST has an impact on HCV transmission; sufficient evidence to support the effectiveness of continuous OST in reducing HIV transmission; and sufficient evidence to support the effectiveness of OST in reducing IRB by reducing the frequency of injection, the sharing of injecting equipment and injecting risk scores. An update to the review of reviews was undertaken to include literature published through March 2011, and found that little changed as a result of additional published reviews: in the main, the evidence statement for the effectiveness of OST with regard to HCV was upgraded from

insufficient to tentative. The finding of weaker evidence with regard to biological outcomes (e.g. HCV, HIV), as compared with behavioural outcomes, indicated that low levels of IRB may be insufficient to reduce high levels of transmission, particularly for HCV.

The subsequent chapter aimed to address the second thesis objective, by summarising, and exploring factors that explained the variation in, the measure of association between self-reported sharing of needles/syringes and HCV prevalence/incidence among PWID. A systematic review and meta-analysis were undertaken to identify and combine the results of European studies of HCV prevalence (or incidence) among those who reported ever/never (or recent/non-recent) sharing of needles/syringes. Among the 16 cross-sectional studies and four longitudinal studies identified, the pooled prevalence of HCV was 59% among PWID who reported never sharing needles/syringes and the pooled incidence of HCV was 11% among PWID who reported not recently sharing needles/syringes. Random effects meta-analysis generated a pooled odds ratio (OR) of 3.3 (95% confidence interval [CI] 2.4-4.6), comparing HCV infection among those who ever (or recently) shared needles/syringes relative to those who reported never (or not recently) sharing. Differences in pooled ORs were found when studies were stratified by recruitment setting (prison vs. drug treatment sites), recruitment method (outreach vs. non-outreach), sample HCV prevalence and sample mean/median time since onset of injecting. High incidence/prevalence rates among those who did not report sharing needles/syringes during the risk period may be a result of a combination of unmeasured risk factors (such as sharing non-needle/syringe injecting paraphernalia) and reporting bias. Study design and population were found to be modifiers of the size and strength of association between HCV and needle/syringe-sharing.

To address the third thesis objective, the risk of HCV associated with sharing injecting paraphernalia (spoons, filters and water) was investigated using data from the 2008-09 and 2010 sweeps in a series of national cross-sectional surveys of PWID in Scotland, collectively called the Needle Exchange Surveillance Initiative (NESI). Logistic regression was used to examine the association between recent HCV infection (anti-HCV negative and HCV-RNA positive individuals) and self-reported measures of injecting equipment sharing in the six months preceding interview. Twelve percent of the sample reported sharing needles/syringes and 40% reported sharing paraphernalia in the previous six months. The adjusted odds ratios (AORs) for sharing needles/syringes (with or without paraphernalia) and sharing only paraphernalia in the last six months were 6.7 (95% CI 2.6-

17.1) and 3.0 (95% CI 1.2-7.5), respectively. Among those who reported not sharing needles/syringes, sharing spoons and sharing filters were significantly associated with recent HCV infection (AOR 3.1, 95% CI 1.3-7.8 and 3.1, 95% CI 1.3-7.5, respectively); sharing water was not. This cross-sectional approach to the analysis of the association between sharing paraphernalia and incident HCV infection demonstrated consistent results with previous longitudinal studies. The prevalence of paraphernalia-sharing in the study population was high, potentially representing a significant source of HCV transmission.

Addressing the fourth and fifth thesis objectives, a method to determine the incidence of HCV among PWID using a cross-sectional design was applied, and the associations between self-reported uptake of harm reduction interventions (OST and IEP) and recent HCV infection were examined. This was undertaken on data from the first sweep (2008-09) of NESI. Twenty-four recent HCV infections (as defined above) were detected, yielding incidence rate estimates ranging from 10.8-21.9 per 100 person-years. After adjustment for confounders, those with high needle/syringe coverage had reduced odds of recent infection (AOR 0.32, 95% CI 0.10-1.00, p=0.050). In the Greater Glasgow and Clyde region only, there were reduced odds of recent infection among those currently receiving OST, relative to those on OST in the last six months but not currently (AOR 0.04, 95% CI 0.001-1.07, p=0.055). The effect of combined uptake of OST and high needle/syringe coverage was only significant in unadjusted analyses (OR 0.34, 95% CI 0.12-0.97, p=0.043; AOR 0.48, 95% CI 0.16-1.48, p=0.203).

The final analysis chapter built on the previous chapter investigating the association between uptake of harm reduction interventions and recent HCV infection, by using data from three sweeps of the NESI survey, undertaken in 2008-09, 2010 and 2011-12. A framework to triangulate different types of evidence – 'group-level/ecological' and 'individual-level' – was applied. Data on service provision (injecting equipment provision and methadone dispensation) were also collated and analysed. Ecological analyses examined changes in intervention provision, self-reported intervention uptake, self-reported risk behaviour and HCV incidence; individual-level analyses investigated relationships within the pooled survey data. The approach to deriving estimates for incidence, and associated uncertainty ranges, was modified from that applied to the first sweep of NESI. A decline in HCV incidence, per 100 person-years, from 13.6 (95% CI 8.1-20.1) in 2008-09 to 7.3 (95% CI 3.0-12.9) in 2011-12 was observed, a period during which increases in the coverage of OST and IEP, and decreases in the frequency of injecting and sharing of injecting equipment, were also seen. Individual-level evidence

demonstrated that combined OST and high coverage of needles/syringes were associated with reduced risk of recent HCV in analyses that were unweighted (AOR 0.29, 95% CI 0.11-0.74) and weighted for frequency of injecting (AOR_w 0.05, 95% CI 0.01-0.18). There was no additional effect found for high paraphernalia coverage. The combination of harm reduction interventions may have averted an estimated 1,400 new HCV infections and 1,000 new chronic infections between 2008 and 2012.

The body of work in this thesis represents a novel contribution to the evidence base: it was the first large-scale, national application of a method designed to determine incidence of HCV using a cross-sectional design, and the first study to apply a framework to triangulate the evidence from different designs in order to investigate the association between harm reduction interventions and HCV transmission. This thesis does not propose to be able to establish a definitive causal link between IEP/OST and the prevention of HCV transmission. It does, however, provide sufficiently plausible evidence that the scale-up of a combination of harm reduction interventions in Scotland between 2008 and 2012 contributed to the reduction in HCV incidence observed. Components of the thesis have already influenced existing policy and practice in Scotland and internationally. Regarding future policy in this area, the evidence generated and presented here supports, at least, the maintenance of the HCV prevention investment in Scotland, and certainly the consideration of further scale-up.

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Author's declaration

The work in this thesis was undertaken part-time at Health Protection Scotland between October 2008 and March 2014 under the joint supervision of Professor Sharon Hutchinson (Health Protection Scotland, Glasgow Caledonian University), Professor Olivia Wu (University of Glasgow) and Professor David Goldberg (Health Protection Scotland, Glasgow Caledonian University).

This thesis comprises original work carried out by Norah Palmateer, with the exception of the contributions detailed below.

Chapter 2: The following were undertaken jointly by Norah Palmateer and Jo Kimber: creation of search terms, literature searches, screening of abstracts and full texts, extraction of data, derivation of critical appraisal criteria and critical appraisal of full texts. The synthesis and writing for the part relating to IEP was undertaken mainly by Norah Palmateer. The synthesis and writing for the part relating to OST was undertaken mainly by Jo Kimber; this section is included in the appendices (Appendix A) and has been further revised and edited by Norah Palmateer. A summary of the latter (written by Norah Palmateer) is included in the main body of the thesis.

Chapter 3: Screening of abstracts and full texts was undertaken jointly by Norah Palmateer, Hamish Innes and Christian Schnier.

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This thesis has not been submitted in part or in whole to any other university for any other degree.

Definitions/Abbreviations

AOR	Adjusted odds ratio
AOR_w	Weighted adjusted odds ratio
anti-HCV	HCV antibodies
BBV	Blood-borne virus
CI	Confidence interval
DBS	Dried blood spot
EIA	Enzyme-linked immunoassay
GG&C	Greater Glasgow and Clyde
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV-RNA	Hepatitis C viral ribonucleic acid
HIV	Human immunodeficiency virus
IDU	Injecting drug user
IEP	Injecting equipment provision
IRB	Injecting risk behaviour
IRR	Incidence rate ratio
MMT	Methadone maintenance treatment
MSM	Men who have sex with men
NESI	Needle Exchange Surveillance Initiative
NHS	National Health Service
NSP	Needle and syringe provision
OR	Odds ratio
OST	Opioid substitution treatment
PCR	Polymerase chain reaction
PWID	People who inject drugs
RCT	Randomised controlled trial
RDS	Respondent-driven sampling
RNA	Ribonucleic acid
RR	Risk ratio
SVR	Sustained viral response
UAT	Unlinked anonymous testing

1 Introduction and Background

1.1 Background to the hepatitis C virus (HCV)

In the 1970s, it was recognised, among blood transfusion recipients, that a distinct infectious agent was causing hepatitis above and beyond what was attributable to the known hepatitis viruses at the time (A and B); it was initially called 'non-A, non-B hepatitis' (Seeff, 2009). In 1989, the cause of this non-A, non-B hepatitis was identified, cloned and named the hepatitis C virus (HCV) (Choo et al., 1989; Kuo et al., 1989).

1.1.1 The virus

HCV is a member of the family *Flaviridae*, comprising viruses whose genomes (genetic material) consist of ribonucleic acid (RNA) (Ohno and Lau, 1996; Simmonds, Mutimer, and Follett, 1998). During the process of viral replication (i.e. generating copies of the viral genome and packaging these into new viruses), RNA viruses typically incorporate many errors (Holland, 1998); this high mutation rate of the HCV genome results in the extensive genetic variability observed in HCV quasispecies (populations of viruses that have variability in their genomes but are genetically related) (Argentini et al., 2009; Farci, 2011; Ferrari et al., 1999). The genetic variation in HCV has resulted in the virus being classified into different genotypes, 1 through 6, although the latter are further divided into numerous subtypes (Simmonds et al., 2005; Simmonds, Mutimer, and Follett, 1998).

1.1.2 Modes of transmission

HCV is most commonly transmitted through percutaneous exposure to infected blood (Lavanchy, 2011). Exposures may include injection drug use (i.e. sharing needles/syringes), receiving blood or blood products, accidental needle-stick injury and the use of unsterile instruments for activities that break the skin (e.g. medical/dental procedures, tattooing) (Anonymous, 1999a).

Studies have, however, identified cases that do not report any of the above risk factors (Ackerman, Ackerman, and Paltiel, 2000). Household or sexual transmission have been proposed as potential routes of infection, although their respective contributions have been debated, and they are likely to be relatively rare with respect to the transmission routes above. Household transmission is thought to occur through the sharing of personal items

such as razors or toothbrushes, which may become contaminated with small amounts of blood. The plausibility of this route has been demonstrated – for example, hepatitis C viral RNA (HCV-RNA) contamination of the toothbrushes of infected individuals has been shown – and epidemiological studies have indicated an increased risk among non-sexual household contacts of HCV-infected persons (Lock et al., 2006). Similarly, the plausibility of sexual transmission of HCV has been confirmed by the detection of HCV-RNA in the semen of HCV-infected men; although this has not been consistently verified (Debono et al., 2000; Leruez-Ville et al., 2000). Epidemiological studies of sexual transmission have generally demonstrated no increased risk among discordant heterosexual couples, but an increased risk of transmission among human immunodeficiency virus (HIV) co-infected individuals, particularly men who have sex with men (MSM) (Tohme and Holmberg, 2010).

Finally, vertical (mother-to-child) transmission is possible, but also rare; although, similarly, the risk of transmission increases when the mother is HCV-HIV co-infected (Conte et al., 2001).

1.1.3 Disease progression

1.1.3.1 Acute infection

The early stages of HCV infection are generally asymptomatic: acute infection with HCV only produces symptoms in approximately 5% of cases, which may include jaundice, fatigue, anorexia and nausea. Acute infection can, very rarely, result in fulminant liver failure (Simmonds, Mutimer, and Follett, 1998).

A proportion of newly-infected individuals will spontaneously clear HCV: a review of longitudinal studies of acute HCV estimated a mean clearance rate of 26% (Micallef, Kaldor, and Dore, 2006). Studies have, however, reported a wide range of clearance rates; the variation in rates of resolution has been shown to be associated with the study population and methodology (Amin et al., 2007; Seeff, 2009). For example, higher rates of spontaneous resolution have been reported among children and women (Amin et al., 2007; Seeff, 2009). The period of viraemia (the presence of virus in the bloodstream) among those who spontaneously resolve infection has been shown to be short-lived; nevertheless, there is some indication of increased liver-related morbidity in this group relative to the general population (Innes et al., 2011). The median time to spontaneous viral clearance has been reported to be approximately four months (Grebely et al., 2014).

1.1.3.2 Chronic infection

The individuals with viral persistence are considered to have chronic HCV infection and are at risk of progressive liver disease including cirrhosis, decompensated cirrhosis and hepatocellular carcinoma (Alter and Seeff, 2000; Seeff, 2009). Studies of the natural history of HCV infection have documented diverse rates of the development of these long-term outcomes, primarily due to different patient populations, study designs and durations of follow-up (Seeff, 2009). One of the largest reviews/meta-analyses of chronic HCV infection involved 111 studies and estimated that 16% (95% confidence interval [CI] 14%-19%) of individuals develop cirrhosis within 20 years of infection, although this figure was 7% (95% CI 4%-12%) for studies undertaken in non-clinical settings (Thein et al., 2008). Among persons with HCV infection and cirrhosis, the development of hepatocellular carcinoma has been estimated at 1-8% per year (Fassio, 2010). Host, viral and environmental factors can contribute to the variation in disease progression: factors include age at the time of infection, gender, race, co-infection with HIV or hepatitis B virus (HBV), HCV genotype and alcohol consumption (El-Serag, 2012; Seeff, 2009).

Studies of deaths among HCV mono-infected persons have found that they have two to five times the risk of liver-related mortality as compared with non-infected persons, after adjustment for the confounding effects of alcohol and drug-related deaths (Grebely and Dore, 2011).

1.1.4 Immunology and diagnostics

One of the major serologic markers for HCV infection is the presence of HCV antibodies (anti-HCV). The presence of anti-HCV indicates that an individual has mounted an immune response to the HCV virus (i.e. has been exposed to HCV), but it does not confirm whether an infection is current or resolved (Table 1-1). The first test to detect anti-HCV became available in 1991 (Choo et al., 1989; Kuo et al., 1989). The current, most widely-used tests are third-generation enzyme-linked immunoassays (EIAs) (Pawlotsky, 1999). Immunoblot asssays were previously used for confirmatory testing, but are now not considered useful given the high sensitivity and specificity of the EIAs (Seme et al., 2005).

Nucleic acid amplification testing can be used to detect the presence of HCV-RNA (Busch et al., 2000). Polymerase chain reaction (PCR) assays are most commonly used for this purpose (Pawlotsky, 1999). The detection of HCV-RNA indicates that an individual has a current infection; thus, in combination with anti-HCV, an individual's HCV-RNA status

can help to determine whether he/she is not infected, has a resolved infection, has a current infection, or has recently been infected (Table 1-1).

HCV-RNA is usually detectable within a few weeks of first exposure to the virus. By contrast, seroconversion (the formation of antibodies) generally does not occur until several weeks, or even months, after infection (Busch et al., 2000). The resulting interval, when the virus is present but antibodies have not yet been formed, has been called the 'pre-seroconversion window period' (Page-Shafer et al., 2008). Several studies have measured the duration of this window period (Table 1-2) with estimates in human subjects ranging from 28 to 84 days (approximately one to three months); however, the largest studies ($n > 50$) have estimated a mean duration of 51 to 56 days (Glynn et al., 2005; Page-Shafer et al., 2008).

HCV antigen testing detects the circulating core HCV viral protein (antigen) and is sometimes used as a lower-cost alternative for nucleic acid amplification testing, although it has a lower sensitivity (Seme et al., 2005).

1.1.5 Treatment

The standard treatment for HCV infection over the last decade has been pegylated interferon and ribavirin, which achieves sustained viral response (SVR) rates (i.e. viral clearance rates) of up to 80% in patients with genotypes 2 and 3, and up to approximately 50% in patients with genotype 1 (Pawlotsky, 2013). Further research on the HCV life cycle has fostered the development of a class of drugs called direct-acting antivirals (Pawlotsky, 2013). Two of these, boceprevir and telaprevir, have been approved for use in treating HCV genotype 1 patients and have been shown in clinical trials to improve the SVR rates in this group (Pawlotsky, 2013; Welsch et al., 2012).

Historically, many people who inject drugs (PWID) have not been considered for treatment owing to perceptions that they will not adhere to treatment regimens and the risk of re-infection following treatment for those who continue to inject (Cox and Thomas, 2013). A systematic review and meta-analysis examined studies of treatment among people who use drugs, more than half of whom were injectors, and found good adherence rates, as well as a low rate of re-infection (Aspinall et al., 2013). Current guidelines recommend that efforts should be made to treat PWID (Anonymous, 2002) and recommendations for the management of PWID with HCV have recently been published (Robaeys et al., 2013)

1.1.6 Vaccine

Although there are vaccines under development, there is currently no vaccine available to protect against infection with HCV (Roohvand and Kossari, 2012). Chimpanzee models have been used to study immunity to HCV, and have demonstrated that immunity can follow from both infection and vaccination (Cox and Thomas, 2013). Some follow-up studies of PWID have shown higher rates of re-infection among those who were previously infected as compared to never infected PWID, but comparatively higher rates of viral clearance (Corson et al., 2011) – as well as a lower magnitude and shorter duration of viraemia – among the former compared with the latter (Cox and Thomas, 2013). These findings suggest that, while immunity might not be sterilising, it may protect against chronic infection (Cox and Thomas, 2013). The first clinical trial of an HCV vaccine among PWID began in 2012 with the aims of assessing safety and effectiveness – the latter in terms of reduced incidence of chronic HCV infection among uninfected PWID, as compared to placebo (Cox and Thomas, 2013).

1.2 Global epidemiology of HCV infection

1.2.1 Prevalence of HCV

Previous published estimates of the number of individuals infected with HCV globally have ranged from 130 million to 170 million, corresponding to approximately 2% to 3% of the global population (Anonymous, 2004; World Health Organization, 1997; World Health Organization, 2011). More recently, a systematic review and meta-analysis estimated that, in 2005, the world-wide prevalence of anti-HCV was 2.8% (95% uncertainty interval 2.6-3.1%), corresponding to 185 million people (Mohd et al., 2013). Prevalence rates vary regionally, ranging from less than 1.5% in, for example, North America to greater than 3.5% in North Africa and the Middle East. Western Europe, as a region, is estimated to fall within the moderate prevalence range (1.5 to 3.5%), with an anti-HCV prevalence of 2.4% (uncertainty interval 2.2-2.7%), corresponding to 10 million people estimated to have antibodies to HCV (Mohd et al., 2013).

There is also substantial regional variation in HCV prevalence across the countries within Western Europe: <1% in countries such as France, Germany, Norway, Sweden and the United Kingdom; 1 to 2% in Portugal, Switzerland and Poland; 2 to 3% in Spain; and >3% in Italy and Romania (Cornberg et al., 2011). The regional variation is likely caused by historical variation in the relative contribution of risk factors for HCV (Cornberg et al.,

2011). For example, in Germany, Norway, Sweden and the United Kingdom, injecting drug use accounts for the majority of prevalent infections (Jarvis et al., 2005); by contrast, Italy has a large burden of HCV infection associated with the multi-use syringes that were used to deliver therapeutic injections (e.g. vitamins) in the 1960s and 1970s (Cornberg et al., 2011).

In most industrialised countries, a large proportion of transmission was historically attributable to contaminated blood and blood products; however, with the advent of the screening test for anti-HCV, this route of transmission has virtually been eliminated (Lavanchy, 2011). Injecting drug use increased in the 1970s and 1980s (Geraghty, 2011; Kaya et al., 2004; Robertson and Richardson, 2007), and is now the main risk factor for HCV infection in these countries.

A recent systematic review identified and synthesised international studies of HCV prevalence among PWID and found a central prevalence estimate of 67%, corresponding to an estimated 10 million anti-HCV positive PWID globally (range 6 million to 15.2 million). While there was a large range of reported rates across countries, prevalence rates among PWID of over 50%, over 60% and over 80% were reported in 49, 37 and 12 countries, respectively (out of 77 countries with eligible reports) (Nelson et al., 2011). At the time of the latter review, there were an estimated 16 million PWID at risk of HCV infection worldwide (Mathers et al., 2008); however, more recent estimates put this figure at 14 million PWID worldwide (range 11.2 to 22.0 million) (United Nations Office on Drugs and Crime, 2013).

1.2.2 Incidence of HCV

HCV incidence has been less widely reported than HCV prevalence because it is more difficult to measure: given that acute HCV infection is usually asymptomatic, new infections are generally not notified and counted. The direct measurement of incidence has generally focused on risk groups such as PWID and MSM, and has involved follow-up to ascertain seroconversion (Lavanchy, 2011). In contrast to HCV prevalence, no pooled global estimate of incidence among non-incarcerated PWID has been reported; however, a number of studies have reported incidence rates among selected local PWID populations. A review (comprising studies published to December 2006) (Hagan et al., 2008) identified 10 studies that reported a median cumulative incidence of 20.7% (interquartile range: 11.57-29.81) among PWID in the community. A more recent review and meta-analysis of

HCV in prisons found a summary incidence rate of 16.4 per 100 person-years (95% CI 0.8-32.1) among prisoners with a history of injecting (Larney et al., 2013).

1.3 Epidemiology of HCV infection in Scotland

1.3.1 Diagnosed cases

By the end of 2012, more than 33,000 cases of anti-HCV positivity had been diagnosed in Scotland (14% of whom are known to have died as of 31 December 2011), representing approximately 0.8% of the Scottish population aged 15 to 59. Ninety percent of the HCV-diagnosed individuals, for whom a risk factor is recorded, reported having injected drugs (Health Protection Scotland, 2012). Because of the generally long asymptomatic period after acquisition of HCV infection, there is often a long delay between the date of infection and date of diagnosis; consequently, many individuals in Scotland remain undiagnosed. There are an estimated 50,000 living individuals thought to be chronically infected with HCV in Scotland (Hutchinson et al., 2006).

1.3.2 Prevalence of HCV

Seroprevalence surveys have been undertaken in various population groups in Scotland. The prevalence of anti-HCV among groups surveyed in the 1990s and early 2000s (and the year surveyed and geographical region) are as follows: women giving birth 0.3-0.4% (2000, Scotland), blood donors 0.008% (2003, Scotland), healthcare workers 0.28% (1996, Glasgow) and MSM attending genitourinary medicine clinics 0.6% (1996-1997, Scotland). Slightly higher prevalence rates have been detected among renal dialysis patients (3.9%), non-injector inmates (3.5-4.0%) and children surveyed at a dental school (3%) (Hutchinson et al., 2006); but the highest rates have been, and continue to be, observed among PWID.

HCV prevalence among PWID in Scotland has been derived from a programme of unlinked anonymous testing (UAT) for HCV of residual sera from PWID who had undergone named HIV testing (Hutchinson et al., 2002). This programme was undertaken in the four largest National Health Service (NHS) Board areas in Scotland – Greater Glasgow and Clyde (formerly Greater Glasgow)[1], Lothian, Tayside and Grampian. These four areas contain the major cities in Scotland of Glasgow, Edinburgh, Dundee and

[1]The former Argyll and Clyde NHS Board was dissolved in 2006 and the Clyde portion was allocated to the Greater Glasgow NHS Board. Thus, figures up to, and including, 2006 pertain to the Greater Glasgow NHS Board and figures from 2007 onward pertain to the Greater Glasgow and Clyde NHS Board.

Aberdeen, respectively. Figures 1-1 and 1-2 illustrate the changes in HCV prevalence over time among all PWID tested and among those aged <25 years, respectively; the data are also presented in Table 1-3. While the UAT system did not permit the elucidation of current or former injecting status, those in the younger age group were more likely to be current injectors, and any infections in this group were more likely to be relatively new infections. In 1990, anti-HCV prevalence rates of 91% and 69% were detected among PWID aged <25 in Glasgow and Lothian, respectively, and in Tayside in 1993, 57% prevalence was detected among <25s. Prevalence of HCV was estimated to have declined substantially by 1997 in Glasgow (43%) and Lothian (13%), likely indicative of a decline in HCV incidence (Goldberg et al., 2001). Between 1997 and 2000, there were no significant changes in HCV prevalence in any of the four NHS Boards among <25s (Hutchinson et al., 2002). There was a significant reduction among <25s in Tayside between 1999 and 2009, but non-significant reductions in the other three NHS Boards over this period (Health Protection Agency, 2011a). Latterly (1999 to 2009 approximately), significant reductions in HCV prevalence among all PWID were seen in Lothian and Tayside, but not in Greater Glasgow and Clyde or Grampian (Health Protection Agency, 2011a).

Further to the above prevalence estimates, cross-sectional community-wide surveys of PWID have been conducted in Glasgow since the early nineties (Taylor et al., 2000). Participants provided voluntary saliva samples, which were tested for the presence of anti-HCV. Prevalence rates detected in these surveys have generally been lower than those reported from the UAT system, although the surveys have involved more selected PWID populations. These demonstrated a decline in HCV prevalence from 79% in 1990 to 66% in 1996 (Hutchinson et al., 2006).

1.3.3 Incidence of HCV

The prevalence of anti-HCV is useful to determine the extent of the problem; however, since a prevalent infection could have been acquired at any time in the past, prevalence does not provide information about the current levels of transmission. Although numerous studies have been undertaken to establish the prevalence of HCV infection in Scotland, the incidence of infection is less well described. Given the very low prevalence rates of HCV in non-PWID population groups, incidence studies have focused on infections likely to have been acquired by means of injecting drug use. Published measures of HCV incidence in the United Kingdom are presented in Table 1-4. Incidence rates from community studies

in Greater Glasgow ranged from 21.1 to 29.0 per 100 person-years, at various time points between 1990 and 2000. Studies undertaken in prison settings in Scotland revealed incidence rates ranging from 11.9 to 21.0 per 100 person-years. Very high HCV incidence rates have been detected in other parts of the United Kingdom: 41.8 per 100 person-years in London in 2001-2002 and 38 to 47 per 100 person-years in Bristol in 2006. In contrast, much lower rates were reported in Wales, Leeds and Birmingham (5.9, 7.6 and 5.2 per 100 person-years, respectively) more recently. The most up-to-date estimates of the incidence of HCV among PWID in Scotland will be presented later in this thesis.

1.3.4 Size of the injecting population

Log-linear modelling of capture-recapture data was first applied in Greater Glasgow to estimate the number of PWID in Glasgow (who were currently injecting) in 1990 (Frischer et al., 1993). The capture-recapture approach involves the extraction of records (including identifier information) on PWID from available data sources, the matching of these records, and the analysis of the overlap between the data sources using log-linear modelling. This approach was later applied to generate estimates for all of Scotland for 2000, 2003, 2006 and 2009 (Table 1-5). Although the CIs for most of the estimates overlap and therefore one cannot be certain, the trend in the central estimate suggests a decline between 2000 and 2003, an increase between 2003 and 2006 and a decline again by 2009. The most recent figures put the size of the injecting population at approximately 15,000 to 16,000 individuals (Overstall et al., 2014).

1.4 Preventing HCV among people who inject drugs

Harm reduction is generally defined as the policies, programmes, services and actions that work to reduce the health (and other) harms that are associated with the use of drugs (Newcombe, 1992). The main harm reduction interventions are generally considered to be sterile injecting equipment provision (IEP) and opioid substitution treatment (OST). While the focus of this thesis is primarily HCV, it is recognised that harm reduction interventions have a role in preventing not only other blood-borne viruses (BBVs) – for example, HIV and HBV – but also bacterial infections.

1.4.1 Injecting equipment provision services

IEP services are a critical component of harm reduction interventions to reduce the transmission of BBVs among PWID. Traditionally, these services involved the distribution

of sterile needles/syringes in exchange for used ones, hence the term 'needle exchange'. The terminology has evolved over time, reflecting the changing nature of the service. An alternative name – needle and syringe provision (NSP) – was introduced, more recently, to indicate that the return of used needles/syringes is not necessarily a pre-requisite for the provision of new sterile needles/syringes. In turn, NSP has been replaced by IEP, reflecting that these services often provide injecting equipment other than needles/syringes, which may include such items as spoons (also called cookers or containers), filters, water ampoules and citric acid (collectively referred to as injecting paraphernalia). IEP will be used throughout this thesis to refer to these services. The settings for these services can vary – from fixed-site specialist services, to pharmacies, to vending machines. Other approaches may involve outreach provision of sterile injecting equipment through, for example, mobile vans.

Injecting paraphernalia may consist of such items as spoons (on which to heat and/or prepare drugs), filters (to remove particles when drawing drugs up into a syringe), water (to rinse syringes or mix with drugs) and citric acid (to dissolve drugs). Most IEP services provide advice on safer injecting practices and an assessment of client needs; some will also offer access to a range of other resources including (either on-site or through referral) BBV testing, wound care and access to other health and social care services.

IEP services may also distribute non-injection drug use equipment (for smoking or snorting drugs); this type of equipment is out of the scope of this thesis, because of the undefined risk of transmission of HCV from sharing this type of equipment[2].

1.4.2 Opioid substitution treatment

OST refers to the treatment of opioid addiction through the administration of pharmacological agents (usually legal opioids), which eliminate or reduce withdrawal symptoms but cause minimal intoxication. Although opioid substitutes may be used to assist in detoxification, OST generally corresponds to 'maintenance', whereby an individual is stabilised on a dosage for a given length of time. Methadone is the most commonly used drug for maintenance, followed by buprenorphine (White, 2011). OST is usually administered orally under medical supervision.

[2]Although HCV transmission through sharing equipment for smoking/snorting is biologically plausible (Aaron et al., 2008; Fischer et al., 2008), and the sharing of smoking/snorting implements have been associated with increased risk of HCV in epidemiological studies (Macias et al., 2008; Tortu et al., 2004), it is likely to be a much less important source of HCV transmission as compared with injecting equipment.

Although the primary goal of OST is to reduce, or ideally eliminate, illegal opioid use among those treated, it is recognised that OST plays a role in the prevention of BBVs by reducing the frequency of injecting (whether complete cessation is achieved or not), and thus reducing the opportunity for sharing needles/syringes or other equipment.

1.4.3 Other prevention interventions

Other interventions that have the potential to reduce the transmission of HCV among PWID include: information, education and counselling; HCV testing/screening (knowledge of HCV status); drug consumption rooms; antiviral treatment for HCV infection; promoting non-injecting routes of drug administration; preventing transitions into injecting drug use; and bleach disinfection of needles/syringes. These interventions are not considered within this thesis.

1.4.4 History of harm reduction interventions in Scotland

The recreational injecting of the 1970s and 1980s gave HCV an efficient means of transmission: the virus had unknowingly been circulating among PWID populations during this time (Gore et al., 1998; Hutchinson et al., 2006). As stated above, when the test to detect antibodies to HCV became available in 1991, prevalence rates of HCV of greater than 90% were detected among regional PWID populations in Scotland (Goldberg et al., 2001).

IEP was initially introduced in Scotland as a response to the HIV epidemic among PWID in the late 1980s/early 1990s, when prevalence rates of HIV reached as high as 50% in PWID populations in the east of Scotland (Robertson et al., 1986; Ronald, Robertson, and Roberts, 1992). By the mid-1990s, HIV transmission was largely under control in this population group (McIntyre et al., 2001); in contrast, high prevalence rates of HCV persisted (Goldberg et al., 2001; Goldberg, Cameron, and McMenamin, 1998). Thus, although the early motivation for establishing harm reduction interventions in Scotland was HIV, the evolution of these interventions has, in more recent times, been driven by the desire to curb HCV transmission.

The first pilot needle exchange in Scotland was established in Glasgow in 1987 (Gruer, Cameron, and Elliott, 1993). Historical figures for the number of sterile needles/syringes distributed are available only for Glasgow, because of their being reported in a peer-reviewed publication (Gruer, Cameron, and Elliott, 1993) and in Greater Glasgow NHS

Board AIDS Control Act reports (Greater Glasgow Health Board, 1997). These illustrate an increase from 2,600 to over one million needles/syringes distributed between 1988 and 2007 (Figure 1-3). Needle/syringe distribution figures have been routinely reported at a national level from 2007/08 onwards, and will be presented later in this thesis. Reporting on the numbers of other items of injecting paraphernalia distributed began in 2008/09.

Oral methadone has been, and continues to be, the most commonly prescribed opioid substitute in Scotland. The timing of the establishment of schemes to provide methadone to PWID varied across NHS Boards, but generally began in the late 1980s/early 1990s (Greenwood, 1990). A scheme in Glasgow – involving general practitioners, pharmacists and a specialised drug problem service – was established in 1994, although individual practitioners were dispensing methadone earlier than that (Gruer et al., 1997). The number of methadone mixture prescriptions dispensed in Scotland has been reported since 1995, and has increased from approximately 130,000 to nearly 500,000 prescriptions dispensed annually (Figure 1-4). Although the number of individuals receiving methadone in Scotland has not been routinely reported, we can infer that this number has increased over time, assuming that prescription practices have not changed drastically. One prescription corresponds to multiple dispensations (i.e. occasions on which methadone is dispensed to the prescription-holder) and the number of dispensations per prescription has remained consistent (at approximately 12) between 1998 and 2010. In contrast, the average dose per dispensation has increased from 68mg to 97mg over the same period, indicating that on average higher doses are being prescribed to stabilise patients (Information Services Division, 2012a).

1.5 Policy context

The Scottish Government became aware of the public health problem posed by HCV as a result of a number of factors leading up to, and culminating in, the Hepatitis C Action Plan for Scotland: prevalence surveys and laboratory reports of diagnoses that established the extent of infection (Goldberg, Cameron, and McMenamin, 1998; Hutchinson et al., 2002; McLeod et al., 2006); a needs assessment undertaken in 1999 (Howie et al., 2000) that made recommendations for improvements in HCV services; and awareness-raising by non-statutory organisations such as the UK Hepatitis C Trust. The Action Plan, however, was the first major policy initiative to include funding attached to the recommendations.

1.5.1 The Hepatitis C Action Plan for Scotland (2006-2011)

In 2006, the Scottish Executive released Phase I of the Hepatitis C Action Plan for Scotland (Goldberg et al., 2008; Scottish Executive Health Department, 2006). The aims of the plan were: to prevent the spread of HCV, particularly among PWID; to diagnose HCV-infected persons, particularly those who would most benefit from treatment; and to ensure that those infected receive optimal treatment, care and support. The first phase was undertaken during September 2006 to March 2008, and involved establishing a governance structure to oversee this phase and gathering evidence to inform proposals and actions for the development of HCV services during Phase II. Three working groups were formed, corresponding to the areas of (i) prevention, (ii) testing, treatment, care and support and (iii) education, training and awareness-raising. Using evidence gathered by means of systematic reviews of the literature and reviews of existing Scottish services, among other methods, the working groups developed 'issues' and corresponding 'actions'.

In relation to IEP, the Prevention Working Group derived the following issues: (i) that there are widespread variations in the provision and uptake of injection equipment by PWID across Scotland, (ii) that, apart from guidelines on the number of sets of needles/syringes that can be given to PWID, comprehensive National Guidelines for the provision of injecting equipment do not exist and (iii) that the re-use/sharing of injection equipment among PWID is still highly prevalent and HCV transmission among PWID throughout Scotland is very common. The resulting actions to address these issues were published in Phase II of the Action Plan, to be undertaken during the period May 2008 – March 2011 (Scottish Government, 2008a). The actions on prevention mainly relate to the prevention of HCV through IEP, reflecting the fact that PWID constitute the large majority of infected individuals, and that the main purpose of IEP is to prevent BBV transmission (unlike, for example, OST). The Phase II actions relevant to IEP are:

Action 14: "National Guidelines for services providing injection equipment to IDUs [injecting drug users] will be developed"; and

Action 15: "Services providing injection equipment (needles/syringes and other injection paraphernalia) will be improved in accordance with the Guidelines referred to in action 14 above. Improvements will be made in terms of the i) quantity (increasing access to and uptake of equipment through innovative, including outreach, approaches) ii) quality (e.g.

the colour coding of equipment to avoid sharing) and, iii) nature (e.g. the provision of equipment other than needles/syringes), of provision".

A total of £36.7 million was allocated to the 14 NHS Boards in Scotland as part of the Action Plan, £8 million of which was for the development of prevention services (Scottish Government, 2008a).

1.5.2 Guidelines for services providing injecting equipment in Scotland

The National Needle Exchange Guidelines (Action 14 of the Hepatitis C Action Plan for Scotland) were first released as interim guidelines in 2009 before official publication in 2010 (Scottish Government, 2010). The guidelines consist of 17 recommendations and are organised into three sections: developing an IEP programme; increasing distribution of injecting equipment; and improving the effectiveness and consistency of IEP services. The recommendations are summarised in Table 1-6.

1.5.3 The Sexual Health and Blood Borne Virus Framework (2011-2015)

Building on the HCV Action Plan and other relevant policies, the Scottish Government's Sexual Health and Blood Borne Virus Framework merges HCV with three other policy areas – sexual health, HIV and HBV (Scottish Government, 2011). Although broader in scope and focused on outcomes, rather than processes, the Framework nevertheless aims to continue the work of the Action Plan in relation to prevention of HCV among PWID. The Framework outcome that is relevant to HCV prevention is:

Outcome 1: "Fewer newly acquired blood borne virus and sexually transmitted infections".

1.5.4 Legal framework for injecting equipment provision in Scotland

In Scotland (and indeed in the United Kingdom (Stimson, 1988)), there has generally been an acceptance of the public health benefits of IEP by policymakers and a greater tolerance for these services among the general public, as compared with some countries – for example, the United States of America – where many services have had to operate illegally and no central funding for IEP was provided (Anonymous, 1999b; Paone et al., 1999).

Nevertheless, in Scotland, there were initially restrictions on IEP services. Prior to 2002, there were strict limits on the number of needles/syringes that could be distributed from IEP services: an individual was allowed to receive five sets on the first visit, up to 15 sets at visits thereafter (subject to the return of the same number of sets) and up to 30 sets if collecting equipment for someone else or in the case of public holidays (Taylor et al., 2005). The Lord Advocate reviewed these guidelines and, in December 2002, these limits were increased to 20 sets on the first visit, 60 sets on visits thereafter (as previously, subject to returns) and 120 sets for holiday periods.

Another relevant legal decision with implications for IEP services was the decision to allow the provision of sterile paraphernalia. Prior to 2003, providing non-needle/syringe injecting equipment to PWID was prohibited by the UK Misuse of Drugs Act. In recognition of the potential risk of HCV transmission from sharing these items, their provision became legal in August 2003.

1.5.5 The Road to Recovery (2008–)

The Road to Recovery: A New Approach to Tackling Scotland's Drug Problem – the Scottish Government's drug and alcohol strategy – was launched in 2008. While the focus of the Action Plan was limited to IEP, the latter policy had the potential to impact on the delivery of OST in Scotland (Scottish Government, 2008b). The Road To Recovery sets out a programme of reform to tackle Scotland's drug problem, placing recovery from drug use as the central theme. The strategy encompasses a wide range of policy areas including law enforcement and protection of children and families, but the most relevant to this thesis is the chapter 'Promoting Recovery', which sets out aspirations for service providers, and the chapter 'Making it Work', which outlines more specific action for implementation.

The former chapter is informed by two reports published by the Scottish Advisory Committee on Drug Misuse (Scottish Advisory Commitee on Drug Misuse Essential Care Working Group, 2008; Scottish Advisory Commitee on Drug Misuse Methadone Project Group, 2007) and advocates the need to extend and integrate existing services to support recovery, the key roles of general practice and pharmacy, the need for person-centred care and the importance of carers and families. The latter chapter outlines action (that had already commenced) to set up the Delivery Reform Group, whose remit includes: developing an outcomes-based framework for assessing and managing local performance;

developing a statement of the strategic functions that need to be carried out at a local level in order to deliver the strategy; and developing accountability arrangements between central and local government.

The Government's approach to 'Preventing Drug Use' (Chapter 2 in the strategy) may also indirectly impact on the provision of OST services in Scotland by preventing/reducing drug use, thereby reducing demand for treatment. While the approach to addressing the underlying causes of drug use (for example, their economic strategy and their early years intervention policy) may prevent drug use in the longer term, other initiatives to address the proximate factors associated with drug use (for example, substance misuse education within the school curriculum) may have a more immediate impact on rates of drug use and, potentially, injecting drug use.

1.6 Aims and objectives of this thesis

The Scottish Government policies – the HCV Action Plan, the Sexual Health and Blood Borne Virus Framework and the Road to Recovery – imply the possibility of significant changes in harm reduction services. Reflecting the opportunity to examine the impact of harm reduction interventions contemporaneous with this period of potential change, the primary aim of this thesis is therefore to investigate the impact of IEP and OST on the transmission of HCV among PWID in Scotland.

The objectives of this thesis are:

i. To review the international literature on the effectiveness of IEP and OST in preventing HCV transmission among PWID;

ii. To determine the association between self-reported sharing of needles/syringes and incident/prevalent HCV infection among PWID;

iii. To determine the association between sharing non-needle/syringe injecting paraphernalia and incident HCV infection among PWID in Scotland;

iv. To determine the incidence of HCV among PWID in Scotland; and

v. To determine the association between self-reported uptake of harm reduction interventions (IEP and OST) and incident HCV infection among PWID in Scotland.

1.7 Structure of this thesis

This thesis will consist of five main chapters. Each chapter is essentially a 'stand-alone' piece of work; however, a common narrative links them, as they all contribute to the overall thesis aim of examining the impact of IEP and OST on the transmission of HCV among PWID in Scotland. Chapter 2, addressing the first objective, sets the scene by reviewing the international literature to establish the state of existing evidence for the effectiveness of these interventions in preventing HCV among PWID. Chapter 3 addresses the second objective, and consists of a systematic review and meta-analysis to quantify the association between self-reported sharing of needles/syringes and incident and prevalent HCV infection. Chapter 4, addressing the third objective, investigates the association between sharing injecting paraphernalia (i.e. spoons, filters and water) and recent (incident) HCV infection using data from national cross-sectional surveys of PWID undertaken in Scotland. To answer the fourth and fifth objectives, Chapter 5 also uses the cross-sectional survey data to determine the incidence of HCV, and to examine the association between self-reported uptake of harm reduction interventions and recent HCV infection. Chapter 6 builds on and refines the analysis conducted in Chapter 5, using additional data from subsequent surveys in the same series. Finally, Chapter 7 summarises the thesis findings, derives conclusions on the body of evidence and makes recommendations for policy and research.

1.8 Epidemiological study designs for examining the impact of harm reduction interventions

Epidemiological studies can be classified by whether they are attempting to answer questions of aetiology or effectiveness (Reeves et al., 2011). Chapters 3 and 4 will address aetiological questions (i.e. are needles/syringes and paraphernalia associated with HCV transmission) whereas Chapters 2, 5 and 6 will address questions of effectiveness (i.e. are harm reduction interventions effective in preventing HCV transmission).

Regardless of the above, the central aim of epidemiological studies is usually to establish a causal relationship between the exposure (in the case of aetiology) or intervention (in the case of effectiveness) and the outcome of interest. The hierarchy of epidemiological study designs for determining causation is well accepted, with the randomised controlled trial (RCT) representing the 'gold standard' (Academy of Medical Sciences, 2007). There has been much discourse in the literature about the applicability of this design hierarchy to the

public health context, given that these types of studies were initially developed to investigate biomedical interventions: for example, clinical trials of new medicines (Barreto, 2005). Although RCTs have been advocated for evaluating public health interventions (Macintyre, 2011), they may not be appropriate, or possible, for a number of reasons including: (i) that the intervention is already well established; (ii) that the intervention has been shown to be efficacious but its effectiveness has not been demonstrated; and/or (iii) that there are ethical issues with conducting an experimental study where the intervention is withheld from a control group.

The interventions under study here share many of these characteristics. For example, NSP has been widely implemented in Scotland for some time (see section 1.4.4). The efficacy of NSP essentially does not need to be demonstrated, since it is known that using a sterile needle/syringe for a given injection will not transmit a BBV (it is likely because of this perceived efficacy that NSP was implemented before there was evidence to demonstrate its effectiveness)[3]. Thus, since it is already widespread and efficacious, it is generally accepted that it would be unethical to introduce experimental conditions where a control group was denied access to sterile needles/syringes (Lurie, 1997).

In contrast, pre-Action Plan, the provision of sterile injecting paraphernalia was not assumed to be efficacious (primarily because the evidence for sharing paraphernalia as a risk factor for HCV was weak at the time), nor was its distribution widespread in Scotland (although some NHS Boards were already distributing it). One randomised study design that has been increasingly applied to public health interventions is the cluster-randomised trial, whereby clusters of individuals (e.g. schools, hospitals, communities) are randomised to receive/not receive the intervention (Donner and Klar, 2004). This type of design would theoretically have been an option to investigate the impact of providing sterile paraphernalia by randomising NHS Boards to distribute (or not) paraphernalia via their IEP services (and also would have reduced the likelihood that the distinction between exposed and unexposed groups would be diluted by individuals obtaining paraphernalia from others, as might occur in an individually randomised study). However, this was not seen to be feasible in relation to evaluating the impact of the Action Plan, since the distribution of paraphernalia was explicitly recommended in the National Needle Exchange Guidelines

[3]Using the analogy of assessing a vaccine, the efficacy measures whether the vaccine has the intended effect on individuals under 'ideal conditions', whereas the effectiveness measures the 'real-world' situation with regard to whether it produces the intended effect when an immunisation programme is delivered to a population (Barreto, 2005).

and since NHS Boards, not researchers, had control over the implementation of these guidelines.

Thus, in cases where experimental studies are not practicable, observational study designs must be relied upon to investigate these associations. Much discussion has focused on this issue, i.e. if randomised studies cannot be undertaken, but observational studies are seen as less valid, then how is an evidence base generated for many public health interventions (Black, 1996; Kirkwood, 2004; Lurie, 1997; Medical Research Council, 2009; Victora, Habicht, and Bryce, 2004)?

A common theme that has emerged, as this area of evaluation develops, is the value of an approach that combines evidence from diverse study designs to support causal inferences. For example, the Medical Research Council states that, if non-experimental methods are used, "wherever possible, evidence should be combined from different sources that do not contain the same weaknesses" (Medical Research Council, 2009). Others have similarly recommended a strategy involving several evaluative elements with different designs (Academy of Medical Sciences, 2007; Kirkwood et al., 1997; Lurie, 1997; Medical Research Council, 2011). Such evaluations have successfully been undertaken to investigate the impact of other public health interventions, for example the Scottish smoking ban (Pell et al., 2008).

An additional theme that has emerged is the importance of understanding the processes that lead from the intervention(s) to the outcome(s): this has sometimes been referred to as a 'theory of change'. Traditional epidemiological studies have usually focused solely on outcomes, but these types of designs can be limited in producing explanations if failure to implement the intervention properly results in the intervention not producing the expected change(s) in the outcome(s). The Medical Research Council recommends undertaking a process evaluation since it "…can be used to assess fidelity and quality of implementation, clarify causal mechanisms, and identify contextual factors associated with variation in outcomes" (Craig et al., 2008). Examples of studies that have elucidated (or plan to elucidate) the processes between interventions and outcomes include RCTs with embedded process evaluations (Medical Research Council, 2009) and the planned evaluation of Scotland's Alcohol Strategy (Beeston et al., 2011), the latter of which adopts a theory of change approach.

These topics are being explored here because the overall aim of this thesis is to investigate the impact of IEP and OST on the transmission of HCV among PWID in Scotland. The approach applied in Chapter 6 of this thesis (and utilising/building on data and analyses undertaken in prior chapters), borrows from the above themes and is described further in the chapter.

1.9 Publications arising from this thesis

Publications arising from the thesis chapters are as follows:

Chapter 2: Palmateer, N., Kimber, J., Hickman, M., Hutchinson, S., Rhodes, T. and Goldberg, D., 2010. 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*, 105(59), pp.844-859.

Chapter 3: Palmateer, N. E., Hutchinson, S. J., Innes, H., Schnier, C., Wu, O., Goldberg, D. J. and Hickman, M., 2013. Review and meta-analysis of the association between self-reported sharing of needles/syringes and hepatitis C virus prevalence and incidence among people who inject drugs in Europe. *Int J Drug Policy*, 24(2), pp.85-100.

Chapter 4: Palmateer, N., Hutchinson, S., McAllister, G., Munro, A., Cameron, S., Goldberg, D., and Taylor, A., 2014. Risk of transmission associated with sharing drug injecting paraphernalia: analysis of recent hepatitis C virus (HCV) infection using cross-sectional survey data. *J Viral Hepat*, 21(1), pp.25-32.

Chapter 5: Allen, E. J., Palmateer, N. E., Hutchinson, S. J., Cameron, S., Goldberg, D. J. and Taylor, A., 2012. Association between harm reduction intervention uptake and recent hepatitis C infection among people who inject drugs attending sites that provide sterile injecting equipment in Scotland. *Int J Drug Policy*, 23(5), pp.346-52.

Chapter 6: Palmateer, N.E., Taylor, A., Goldberg, D.J., Munro, A., Aitken, C., Shepherd, S.J., McAllister, G. and Hutchinson, S.J. Rapid decline in HCV incidence among people who inject drugs associated with national scale-up in coverage of sterile injecting equipment and opiate substitution therapy. *PLOS ONE*, under review.

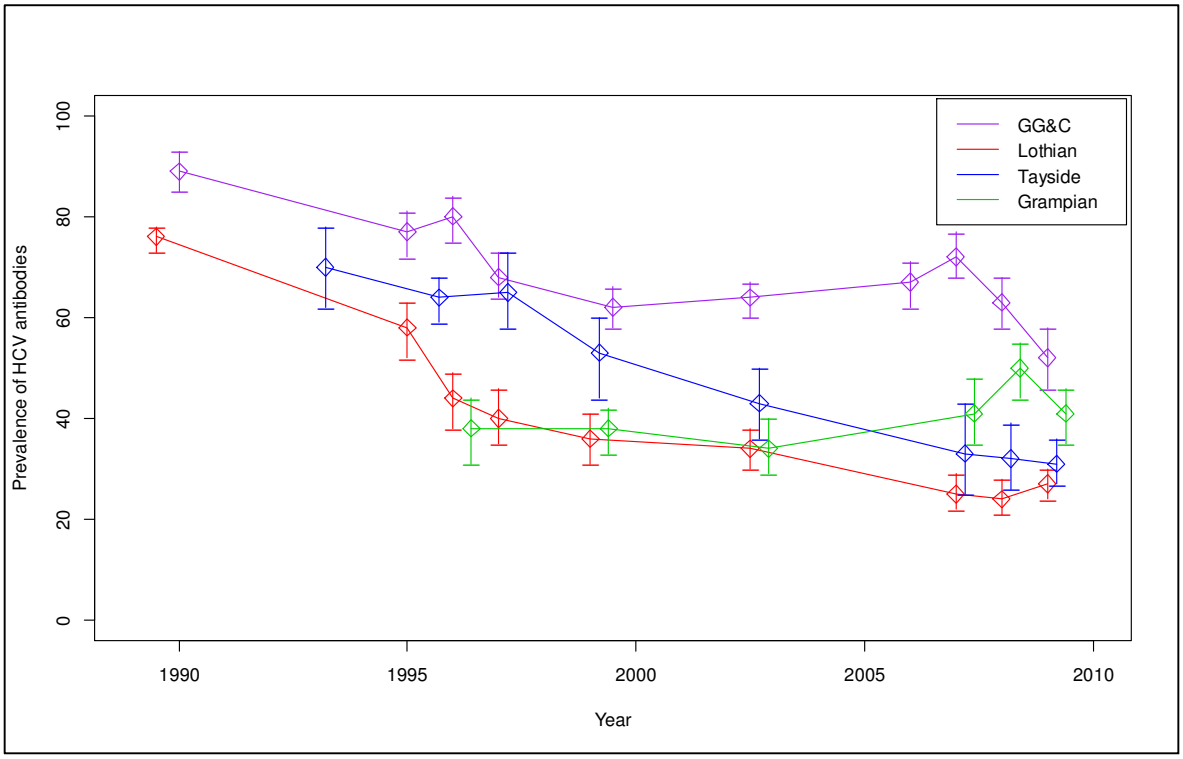


Figure 1-1. Prevalence of anti-HCV among PWID who had a named HIV test by NHS Board area, 1989-2009
GG&C: Greater Glasgow and Clyde
Diamonds represent the central prevalence estimates and the vertical bars represent the 95% CIs. Estimates have been staggered slightly along the x-axis for ease of viewing.

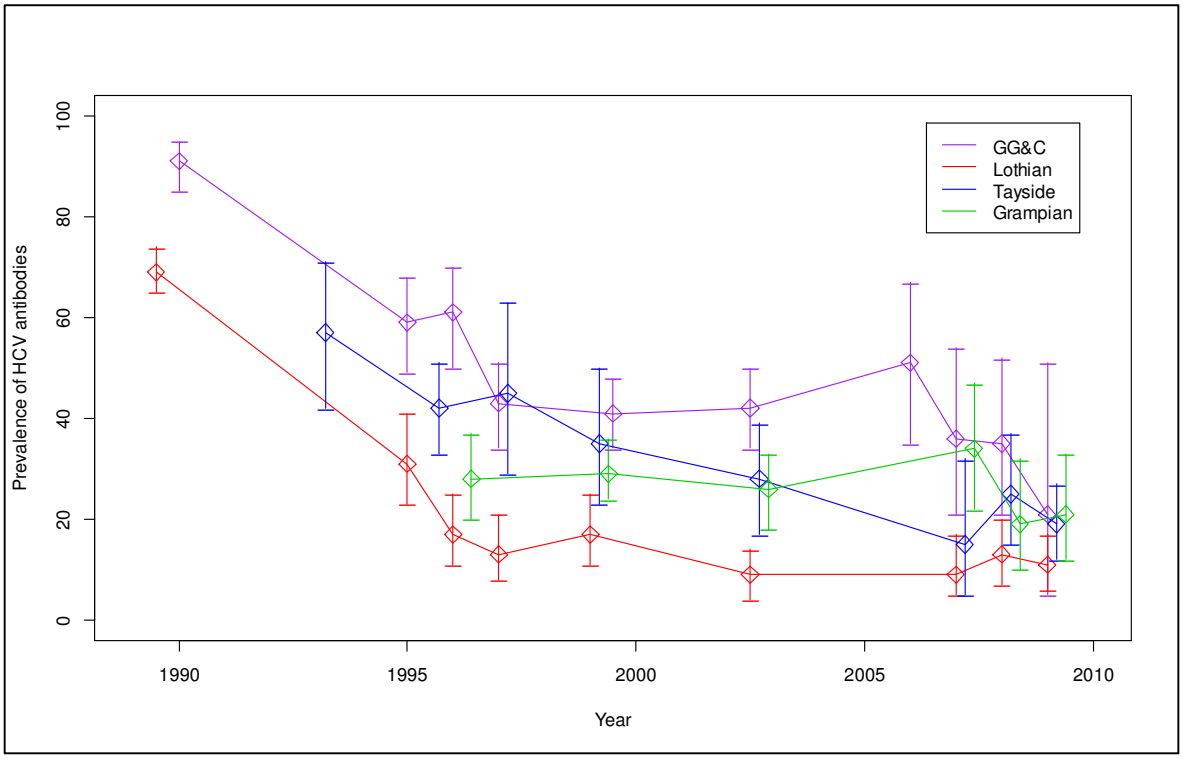


Figure 1-2. Prevalence of anti-HCV among PWID aged <25 years who had a named HIV test by NHS Board area, 1989-2009
GG&C: Greater Glasgow and Clyde
Diamonds represent the central prevalence estimates and the vertical bars represent the 95% CIs. Latter years have been grouped to reduce the size of the CIs (Glasgow 2006 & 2007 and 2008 & 2009; and 2007-2009 for Grampian and Tayside). Estimates have been staggered slightly away from the calendar year for ease of viewing.

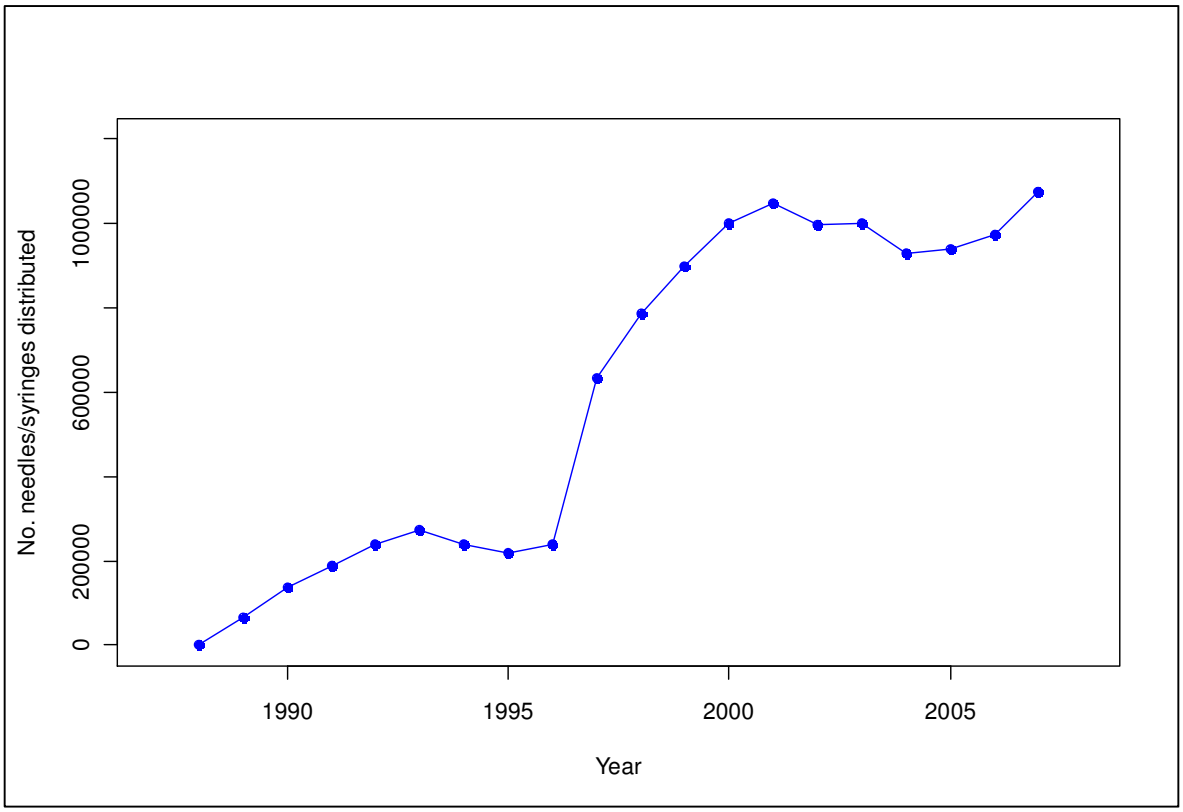


Figure 1-3. Number of sterile needles/syringes distributed per year, Greater Glasgow, 1988 to 2007 Figures to 2006 are for Greater Glasgow NHS Board; figures from 2007 onward also include the Clyde area of the former Argyll and Clyde NHS Board, following its dissolution. Data are from Gruer et al. (1993), AIDS Control Act Reports (Greater Glasgow Health Board, 1997) and ISD (Information Services Division, 2009). For 1993 onward, years refer to financial years, e.g. 1993 represents the 1993/94 financial year.

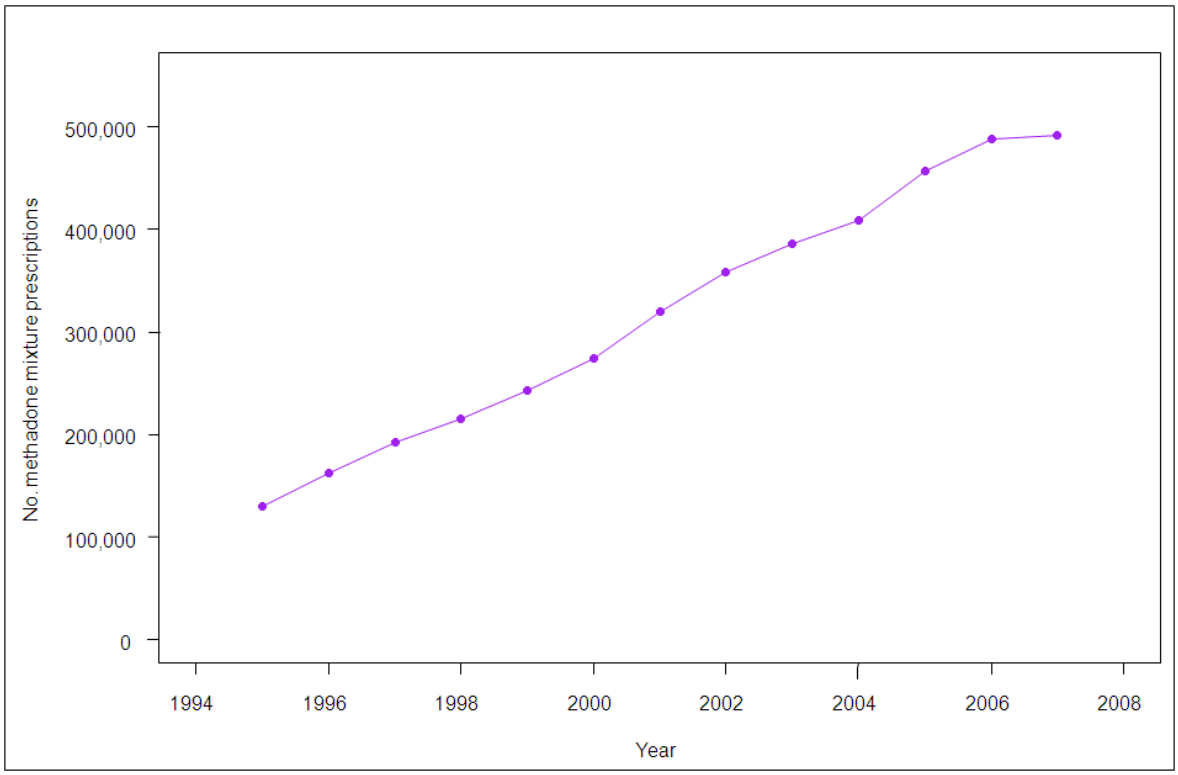


Figure 1-4. Number of methadone mixture prescriptions dispensed in Scotland, 1995-2007
Data from Drug Misuse Statistics Scotland (Information Services Division, 2012a). Years refer to financial years, e.g. 1994 represents the 1994/95 financial year.

Table 1-1. Interpretation of HCV serologic test results

		Anti-HCV[a]	
		Negative	**Positive**
HCV-RNA[a]	**Negative**	Not infected (susceptible)	Resolved/past infection
	Positive	'Window period' (recent) infection	Current infection

[a]Assumes no false positive or negative test results and no fluctuations in viraemia

Table 1-2. Duration of HCV pre-seroconversion window period in published studies

Reference	**Mean**	**95% CI**	**Range**	**Population studied**	**Sample size**
Farci et al., 1991	78 days (11.2 wks)	-	77-84 days	Blood transfusion recipients	5
Farci et al., 1992	88.2 days (12.6 wks)	-	40-189 days	Chimpanzees	6
Glynn et al., 2005	56.3 days	44.8-67.8	75% within 30-65	Plasma donors	77
Netski et al., 2005	42 days	-	28-63 days	People who inject drugs	8
Page-Shafer et al., 2008	50.9 days	46.1-55.8	-	Plasma donors	58

Table 1-3. Prevalence of anti-HCV among PWID who had a named HIV test by NHS Board area, 1989-2009

		Greater Glasgow		Grampian		Lothian		Tayside	
		Aged <25	**All**	**Aged <25**	**All**	**Aged <25**	**All**	**Aged <25**	**All**
1990	**% (95% CI)**	91 (85-95)	89 (85-93)	-	-	69 (65-74)[a]	76 (73-78)[a]	-	-
1993	**% (95% CI)**	-	-	-	-	-	-	57 (42-71)	70 (62-78)
1995	**% (95% CI)**	59 (49-68)	77 (72-81)	-	-	31 (23-41)	58 (52-63)	-	-
1996	**% (95% CI)**	61 (50-70)	80 (75-84)	28 (20-37)	38 (31-44)	17 (11-25)	44 (38-49)	42 (33-51)[a]	64 (59-68)[a]
1997	**% (95% CI)**	43 (34-51)	68 (64-73)	-	-	13 (8-21)	40 (35-46)	45 (29-63)	65 (58-73)
1999	**% (95% CI)**	41 (34-48)[a]	62 (58-66)[a]	29 (24-36)	38 (33-42)	17 (11-25)	36 (31-41)	35 (23-50)	53 (44-60)
2002/2003[a]	**% (95% CI)**	42 (34-50)	64 (60-67)	26 (18-33)	34 (29-40)	9 (4-14)	34 (30-38)	28 (17-39)	43 (36-50)
2006	**% (95% CI)**	51 (35-67)	67 (62-71)	-	-	-	-	-	-
2007	**% (95% CI)**	36 (21-54)	72 (68-77)	34 (22-47)	41 (35-48)	9 (5-17)	25 (22-29)	15 (5-32)	33 (25-43)
2008	**% (95% CI)**	35 (21-52)	63 (58-68)	19 (10-32)	50 (44-55)	13 (7-20)	24 (21-28)	25 (15-37)	32 (26-39)
2009	**% (95% CI)**	21 (5-51)	52 (46-58)	21 (12-33)	41 (35-46)	11 (6-17)	27 (24-30)	19 (12-27)	31 (27-36)

This table has been modified and updated from Hutchinson et al. (2002).

[a]For Greater Glasgow, 1999 samples were taken in 1999/2000; for Lothian, 1990 samples were taken 1989/1990; and for Tayside, 1996 samples were taken in 1995/1996. In these instances, and for all areas in 2002/2003, it was not possible to separate the anti-HCV results of the specimens into the appropriate calendar years.

Table 1-4. Published estimates of HCV incidence in the United Kingdom, in approximate chronological order

Region	Method	Setting/ recruitment	Sample type	Inclusion criteria	Year(s)	No. of PWID	No. of SCs	Exposure/ follow-up time	Incidence per 100 PY (95%CI)
Greater Glasgow	Using HCV prevalence and date of commencement of injecting[a]	Community surveys	Saliva	Injected in last two months	1990-1993	550	356	1264.8	28.1 (25.3-31.2)
Greater Glasgow	Unlinked anonymous testing among PWID with two or more specimens	Stored serum specimens originally collected for HIV testing	Serum	People who had ever injected	1993-1998	31	11	38.8	28.4 (15.7-51.2)
Greater Glasgow	Using HCV prevalence and date of commencement of injecting[a]	Community surveys	Saliva	Injected in last two months	1994, 1996	173	79	373.8	21.1 (16.9-26.3)
Greater Glasgow, Grampian, Lanarkshire, Forth Valley	Documentation of SC (date of SC defined as endpoint of follow-up)	Prison	Saliva	Inmates who began injecting in 1992-1996	1994-1996	114	42	203.5	21.0 (14-28)
Greater Glasgow	Using HCV prevalence and date of commencement of injecting[a]	Community surveys	Saliva	Injected in last six months	1999	283	130	523.2	24.8 (20.9-29.5)
Lanarkshire	Documentation of SC	Prison	Saliva	Prisoners who ever injected	1999-2000	69	4	33.5	11.9 (4.5-31.8)
Greater Glasgow	Using HCV prevalence and date of commencement of injecting[a]	Community surveys	Saliva	Injected in last six months	2001-2002	385	228	785.9	29.0 (25.5-33.0)
London (Judd et al., 2005a)	Documentation of SC	Community prospective cohort study	Saliva	Injected in last four weeks and <30 years old or <six years injecting	2001-2002	151	53	Not stated	41.8 (31.9-54.7)
Wales (Craine et al., 2009)	Documentation of SC	Community prospective cohort study	DBS	Injected in last four weeks	2004-2006	286	17	287.33	5.9 (3.4-9.5)
Bristol (Hope et al., 2011)	Extrapolation of incidence from those in pre-SC window period	Community survey (RDS)	DBS	Injected in last four weeks	2006	115	14[b]	N/A	38-47[c]
Leeds (Turner et al., 2011)	Extrapolation of incidence from those in pre-SC window period	Community survey (RDS)	DBS	Injected in last four weeks	2008	120	2[b]	N/A	7.6
Birmingham (Turner et al., 2011)	Extrapolation of incidence from those in pre-SC window period	Community survey (RDS)	DBS	Injected in last four weeks	2009	310	2[b]	N/A	5.2

This table has been modified and updated from Roy et al. (2007b).
DBS: dried blood spot; PY: person-years; RDS: respondent-driven sampling; SC: seroconversion
[a]Assuming that HCV has been acquired since onset of injecting and taking the midpoint of the exposure period (i.e. the time elapsed since onset of injecting) as the date of acquisition of infection
[b]Number of recent infections (anti-HCV negative and HCV-RNA positive)
[c]95% CIs were not calculated: the range of incidence rates is generated from the range in the estimated duration of the window period

Table 1-5. Estimates of the size of the injecting population, Scotland, 2000-2009

Year	Central estimate	95% CI	Reference	Data sources and censoring	Sources
2000	22,805	15,835 - 43,030	Hay et al., 2001	4 data sources	GP reports to SDMD, agency reports to SDMD, social enquiry reports, HCV diagnoses
2003	18,737	17,731 - 20,289	Hay et al., 2005	4 data sources	SDMD, social enquiry reports, HCV diagnoses, hospital records
	16,700	14,300 - 20,900	Overstall et al., 2014	4 data sources, censoring	SDMD, social enquiry reports, HCV diagnoses, hospital records
	16,500	14,200 - 20,800	Overstall et al., 2014	3 data sources	SDMD, social enquiry reports, hospital records
2006	23,933	21,655 - 27,143	Hay et al., 2009	4 data sources	SDMD, social enquiry reports, HCV diagnoses, hospital records
	22,900	16,300 - 27,00	Overstall et al., 2014	4 data sources, censoring	SDMD, social enquiry reports, HCV diagnoses, hospital records
	24,000	19,500 - 29,700	Overstall et al., 2014	3 data sources	SDMD, social enquiry reports, hospital records
2009	15,200	11,500 - 18,600	Overstall et al., 2014	4 data sources, censoring	SDMD, social enquiry reports, HCV diagnoses, hospital records
	16,000	11,500 - 19,400	Overstall et al., 2014	3 data sources	SDMD, social enquiry reports, hospital records

Table 1-6. National Needle Exchange Guidelines recommendations

Recommendation	Summary of recommendation
1: Planning and developing IEP services	In planning and developing services that provide injecting equipment, NHS Boards, together with local partners, should undertake a number of tasks (needs assessment, stakeholder consultation, advertise and promote IEP services) to ensure that services are able to meet the needs of their clients effectively
2: Choosing appropriate models of delivery	NHS Boards and other service commissioners should ensure that a range of IEP services are provided using models of delivery appropriate to their injecting populations and the geography in their locality, based on an assessment of local needs
3: Meeting the needs of sub-populations of injectors	In deciding which models of service provision to use, service commissioners and service providers should give special consideration to the specific needs of sub-populations of injectors (new injectors, women, sex workers, homeless injectors, steroid users, minority ethnic groups, people enrolled in drug treatment programmes, people in custody)
4: Opening times	There should be out-of-hours and weekend access within each NHS Board area corresponding to the needs of local injecting populations
5: Provide one needle per injection	IEP services should provide, free of charge, as many needles as an individual client requires, within the limits of the Lord Advocate's Guidance
6: Provide other non-needle drug injecting equipment	IEP services should provide, free of charge: acidifiers, cookers, filters, water for injections and pre-injection swabs. These items should be supplied in sufficient quantities to enable the use of one item per each injection
7: Secondary distribution	If a client states he/she is supplying injecting equipment to others, it is acceptable to provide supplies for the purpose of secondary distribution
8: Provide methods for syringe identification	A method of equipment identification should be made available to clients who inject in the company of other injectors in order that they can identify their own equipment and avoid accidental sharing
9: Training of IEP service staff	All individuals involved in the distribution of injecting equipment should receive appropriate training prior to providing a service or during induction
10: Identifying and responding to the individual client's needs	All clients attending a service for the first time should be asked how often they inject, what they are injecting, how often they visit the IEP service and whether they are collecting supplies for anyone else
11: Service user education	When providing needles and injecting equipment, IEP services should educate clients about: washing their hands with soap and water before injecting, the correct use of each item of injecting equipment, the risks of sharing injecting equipment and the correct methods of disposing of used injecting equipment
12: Getting client feedback	All IEP service providers should put in place mechanisms for identifying and responding to client feedback at regular intervals - at least annually
13: Monitoring, evaluation and audit	IEP services should have systems for monitoring, evaluation and audit to enable on-going needs assessment at a local level
14: BBV testing and vaccination for IEP clients	IEP services should encourage clients to be tested annually for HCV. In addition, wherever possible, all IEP services should make available vaccination and testing on-site
15: Improving integration between IEP services and other services	All IEP services should be able to signpost or formally refer clients to treatment for drug misuse. In addition, IEP services should be able to signpost or formally refer clients to other broader health and social support services

Table 1-6 (continued).

16: Ensuring the safe disposal of used injecting equipment	As part of wider risk assessment procedures, NHS Boards should ensure that all services in their area have robust policies and procedures in place in relation to the safe disposal of used injecting equipment
17: Hepatitis B vaccination for staff	NHS Boards should work together with employers to facilitate vaccination for Hepatitis B, free of charge, for all staff who are responsible for delivering an IEP service

This table has been adapted from the Scottish National Injecting Equipment Provision Guidelines (Scottish Government, 2010).

2 Evidence for the effectiveness of sterile injecting equipment provision and opioid substitution treatment in preventing HCV transmission among people who inject drugs: a review of reviews

2.1 Background

This chapter aims to address the first objective of the thesis, which is to review the international literature on the effectiveness of IEP and OST in preventing HCV transmission among PWID. This chapter forms part of a larger piece of work that examined other harm reduction interventions, in addition to IEP and OST: information/education/counselling and outreach; knowledge of HCV status; HCV antiviral treatment; use of drug consumption rooms; promotion of non-injecting routes of drug administration; structural interventions; and provision of bleach for disinfection of needles/syringes (Palmateer et al., 2009). This larger review also considered evidence for the impact of interventions in specific settings (prisons), and in specific populations (young PWID), and considered the cost-effectiveness of interventions. The section set out below (2.2) relates solely to IEP interventions. As detailed in the Author's Declaration, because another individual contributed substantially to the section on OST, it is included as an appendix (Appendix A). The latter is summarised in section 2.3. The remaining interventions are outwith the scope of this thesis and are therefore not included.

2.2 Injecting equipment provision

2.2.1 Introduction

Since the inception of 'needle exchanges' in resource-rich countries, numerous studies of their impact on BBVs have been undertaken. As a result, there is an ample body of literature consisting not only of primary studies, but also of reviews. Therefore, rather than a review of the primary literature, this chapter presents a review of the secondary literature, i.e. a 'review of reviews'[4]. This approach – developed as a response to the increasing number of reviews of effectiveness of public health interventions in the literature (Kelly et

[4] It is recognised that this methodological area has been further developed since the work for this chapter was undertaken and this type of meta-review is now called an 'overview of reviews'. Recent developments in the methodology and updated results are discussed in section 2.4.

al., 2002) – provides a more efficient way of summarising the body of evidence for an intervention.

IEP services potentially comprise a range of separate interventions and were thus divided into the following categories based on the setting and items provided: fixed-site specialist NSP, alternative modes of NSP (pharmacies, vending machines and outreach) and the provision of (non-needle/syringe) injecting paraphernalia. Although the main outcome of interest was HCV, the scope was widened to include HIV and injecting risk behaviour (IRB). These additional outcomes were included because (i) it was hypothesised that there would be a potential paucity of studies looking at HCV specifically, (ii) there are notable parallels between HIV and HCV in that both are transmitted via blood-to-blood contact and both have had high prevalence rates recorded among populations of PWID and (iii) IRB is on the 'causal pathway' between the interventions and outcomes (i.e. a reduction in IRB needs to be achieved in order to affect BBV transmission). An additional objective of this chapter was to identify gaps and inconsistencies in the evidence base to inform further analysis.

2.2.2 Methods

2.2.2.1 Inclusion and exclusion criteria

Systematic reviews, syntheses, or meta-analyses looking at the effectiveness of injecting equipment interventions in relation to the prevention of HCV, HIV, or IRB among PWID were considered for inclusion. The relevant interventions were: (i) NSP, (ii) alternative modes of NSP via pharmacies, vending machines, or outreach and (iii) the provision of sterile injecting paraphernalia. The outcomes considered were HCV prevalence or incidence, HIV prevalence or incidence and self-reported IRB. IRB was considered to include the borrowing, lending, or reuse of needles/syringes or paraphernalia. Papers that only considered the sexual transmission of HCV or HIV were excluded, as were papers that did not report their literature review methods. The literature search was limited to English language reviews only.

2.2.2.2 Search strategy

The following electronic databases were searched: CINAHL, Cochrane Library, EMBASE, IBSS, MEDLINE and PsycINFO; the search terms used are presented in Appendix B. The publications of key international agencies were also searched: the European Monitoring

Centre on Drugs and Drug Addiction, the National Institute on Drug Abuse, the US Institute of Medicine, the United Nations Office on Drugs and Crime Prevention and the World Health Organization. All databases were searched from 1980 to March 2007, with the exception of CINAHL, which was searched from 1982 to March 2007.

At the screening stage it became apparent that the relevant reviews from the 1980s and 1990s had been superseded by more recent reviews; consequently, the period was restricted to 2000 onwards. The reviews that were published earlier than 2000 were checked to see whether their exclusion would influence the findings. There were eight review papers excluded because they were published earlier than 2000 (Brettle, 1991; Des Jarlais and Friedman, 1998; Friedman and Des Jarlais, 1991; Heimer, 1998; Paone et al., 1995; Vlahov and Junge, 1998; Watters, 1996; Wong, 1995), which were revisited and examined for references relating to the interventions and outcomes of interest. From these eight reviews, 23 relevant published primary papers were identified. Eighteen (Bruneau et al., 1997; Des Jarlais et al., 1994; Des Jarlais et al., 1995; Des Jarlais et al., 1996; Donoghoe et al., 1989; Groseclose et al., 1995; Hagan et al., 1991; Hagan et al., 1995; Hart et al., 1989; Hartgers et al., 1989; Heimer et al., 1993; Hurley, Jolley, and Kaldor, 1997; Kaplan, 1994; Kaplan and Heimer, 1994; Ljungberg et al., 1991; Strathdee et al., 1997; van Ameijden et al., 1992; Watters et al., 1994) out of the 23 papers were covered by the post-2000 reviews that were ultimately selected (including three that duplicated data from papers that were covered). Of the remaining five, four would not have been relevant for various reasons: one was related to methadone treatment (Metzger et al., 1993); one was a mathematical modelling study (Lurie and Drucker, 1997); one was a statistical methodology paper (Kaplan and Heimer, 1992b); and for one, the full text was unable to be retrieved (Wodak and Gold, 1986). The one missed article related to HIV as an outcome and would not have changed the conclusions (Des Jarlais et al., 1998).

2.2.2.3 Review selection

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

2.2.2.4 Critical appraisal

The selected reviews were critically appraised using a tool based on that developed by the Health Development Agency (Table 2-1), which considers the strength of the methods used to identify the relevant literature, the appraisal of the primary literature, the quality of methodological analysis (in the case of meta-analyses) and the appropriateness of the conclusions (Kelly et al., 2002). The papers were then categorised as one of the following: (i) to be included as data where the whole of the review is judged to be of high quality; (ii) to be included as data where only part of the review is judged to be of high quality; or (iii) to be included only as potential background or contextual material (Kelly et al., 2002). Papers categorised as (i) or (ii) were included as high-quality ('core') reviews and the remaining papers were retained as 'supplementary' reviews, not considered to be of sufficient quality to rely on the authors' conclusions but viewed as potentially providing complementary information on the effectiveness of the interventions. Meta-analyses were not necessarily assigned a higher score than other types of reviews; reviews had to satisfy the majority of the critical appraisal criteria in order to be classed as a core review.

2.2.2.5 Data extraction and synthesis

From each review, information was extracted on the reviewers' assessment of the evidence and the number, design and findings of relevant primary studies. Information on primary studies was extracted from the reviews; in the case where reviews reported discrepant study findings, the primary studies were consulted.

The level of evidence in support of (or discounting) the effect of an intervention was classified as: 'sufficient'; 'tentative'; 'insufficient'; or 'no' evidence from reviews. These were derived using a framework (Table 2-2) based on the quality of the reviews, the reviewers' conclusions and the designs/findings of the primary studies included in the reviews (Ellis et al., 2003). With regard to study design, a summary of the typical epidemiological study designs and the 'weight of evidence' that was attributed to them, for the purposes of this review of reviews, is presented in Table 2-3. While RCTs were considered to be the most robust study design, longitudinal cohort and case-control designs were considered to be less robust, whereas ecological, serial cross-sectional and cross-sectional designs were considered to the weakest. While it is recognised that the potential to make inferences about cause-effect relationships in case-control studies is the same as in cross-sectional analysis if the outcome is prevalent cases of disease, the case-control

studies included in the evidence base were verified and all found to examine incident cases of disease (thus the outcome can be assumed to have followed the exposure in time).

2.2.3 Results

The literature search generated 1083 references after exclusion of duplicates (Figure 2-1). Abstracts were reviewed and 976 were excluded, leaving 43 papers related to injecting equipment interventions to be screened. Full screening eliminated a further 25, leaving 18 for critical appraisal. Of the 18 papers, three were judged to be core reviews and the remainder were retained as supplementary reviews. Five (three core and two supplementary) were drawn upon for evidence (Table 2-4). A critical appraisal summary for the supplementary reviews not included in the evidence base is given in Appendix C.

The findings of the reviews (and primary studies) are presented below (and in Table 2-5) for each intervention and outcome. With regard to the results of primary studies, a 'positive' finding refers to an observed reduction in the stated outcome (e.g. HCV prevalence) associated with the intervention, a 'negative' finding refers to an increase in the outcome associated with the intervention and 'no association' refers to no statistically significant association between the outcome and intervention. Where a review reported a study finding as positive or negative, it was assumed that the result was statistically significant at the 5% level even if this was not explicitly stated; where a review reported 'no association', it was assumed that this indicated a non-statistically significant result.

2.2.3.1 Needle and syringe provision

2.2.3.1.1 Effects on HCV Incidence/Prevalence

Three core reviews (Gibson, Flynn, and Perales, 2001; Tilson et al., 2007; Wodak and Cooney, 2004) and one supplementary review (Wright and Tompkins, 2006) considered the impact of NSP on HCV incidence or prevalence. The core reviews primarily focused on HIV outcomes and, therefore, may not have identified all of the relevant HCV-related literature: Wodak and Cooney referred to only one HCV study (Hagan et al., 1995), Tilson et al. identified six (Des Jarlais et al., 2005b; Hagan et al., 1995; Hagan and Thiede, 2000; Mansson et al., 2000; Sarkar et al., 2003; Taylor et al., 2000) and Gibson et al. included three (Hagan et al., 1995; Hagan et al., 1999; Lamden et al., 1998). None of these reviews examined HCV in any depth, and only Tilson et al. drew conclusions, stating there was

moderate evidence that “HIV prevention programs that include NSP” have less of an impact on HCV transmission than on HIV transmission.

The three core reviews covered seven primary studies between them and the supplementary review, which focused exclusively on HCV outcomes, included an additional nine relevant papers (Goldberg et al., 2001; Goldberg, Cameron, and McMenamin, 1998; Hernandez-Aguado et al., 2001; Hutchinson et al., 2002; MacDonald et al., 2000; Patrick et al., 2001; Smyth, Keenan, and O'Connor, 1999; Somaini et al., 2000; van Ameijden et al., 1993), although three of them present duplicate data (Goldberg et al., 2001; Goldberg, Cameron, and McMenamin, 1998; Hutchinson et al., 2002) (Table 2-6). There were seven primary studies with positive findings, but these mainly involved weaker designs. The stronger study designs (cohorts) mainly showed either no association or negative findings between NSP and HCV seroconversion. Given an absence of clear statements from the core reviews, and inconsistent evidence from the primary studies identified by the reviews, it was concluded that the level of evidence is insufficient (Table 2-5).

2.2.3.1.2 Effects on HIV Incidence/Prevalence

Three core reviews examined HIV prevalence/incidence, covering 16 primary studies between them. The findings of these studies are summarised in Table 2-7. Tilson et al. identified four prospective cohort studies (Bruneau et al., 1997; Mansson et al., 2000; Schechter et al., 1999; Strathdee et al., 1997), two case-control studies (Patrick et al., 1997; van Ameijden et al., 1992), three ecological studies (Des Jarlais et al., 2005b; Hurley, Jolley, and Kaldor, 1997; MacDonald et al., 2003) and two serial cross-sectional studies (Des Jarlais et al., 2005a; Hammett et al., 2006); others (Coutinho, 2005; Des Jarlais et al., 1995) that did not form part of their evidence base, were also included in their discussion. They highlighted the findings of two prospective cohort studies conducted in Montreal and Vancouver (Bruneau et al., 1997; Strathdee et al., 1997) that reported higher incidence of HIV seroconversion among needle exchange attenders, but acknowledged that a number of factors could have contributed to, or accounted for, these results, including: that high-risk individuals are more likely to use needle exchange (selection bias) and the availability of clean injecting equipment through sources other than needle exchange (dilution bias). They also made reference to four ecological studies demonstrating declining HIV prevalence/incidence in the context of needle/syringe programme provision or expansion (Des Jarlais et al., 1995; Des Jarlais et al., 2005b; Hurley, Jolley, and Kaldor, 1997;

MacDonald et al., 2003). Tilson et al. concluded that "the evidence of the effectiveness of NSE [needle and syringe exchange] in reducing HIV prevalence is considered modest, based on the weakness of these study designs."

Wodak and Cooney stated "there is compelling evidence that increasing the availability and utilization of sterile injecting equipment by IDU [injecting drug users] reduces HIV infection substantially." This review, however, did not consider separately the effects of NSP on HIV transmission vs. IRB: possibly, the evidence of effectiveness of NSP in reducing IRB had a bearing on conclusions drawn with respect to HIV. Of the 38 studies they reviewed, 10 were relevant to HIV (Bruneau et al., 1997; Des Jarlais et al., 1996; Heimer et al., 1993; Hurley, Jolley, and Kaldor, 1997; Ljungberg et al., 1991; MacDonald et al., 2003; Monterroso et al., 2000; Patrick et al., 1997; Schechter et al., 1999; Strathdee et al., 1997); five had positive findings (Des Jarlais et al., 1996; Heimer et al., 1993; Hurley, Jolley, and Kaldor, 1997; Ljungberg et al., 1991; MacDonald et al., 2003), two had negative findings (Bruneau et al., 1997; Strathdee et al., 1997) and three did not find an association (Monterroso et al., 2000; Patrick et al., 1997; Schechter et al., 1999). Four of the five positive findings were generated by studies with weaker designs (Heimer et al., 1993; Hurley, Jolley, and Kaldor, 1997; Ljungberg et al., 1991; MacDonald et al., 2003).

Gibson et al. reviewed studies published up until 1999; all were covered in the later reviews discussed above. Particular consideration of potential bias was given for the studies with negative results, but not for those with protective findings. They concluded that there is "substantial evidence that syringe exchange programs are effective in preventing HIV risk behaviour and HIV seroconversion among IDU [injecting drug users]". However, as above, their conclusions were apparently inconsistent with the HIV studies reviewed: two studies showed an increased risk of HIV infection associated with NSP (Bruneau et al., 1997; Strathdee et al., 1997), one showed a protective effect of NSP (Des Jarlais et al., 1996) and three showed no association (Patrick et al., 1997; Schechter et al., 1999; van Ameijden et al., 1992).

Reflecting on the findings of the primary studies (Table 2-5; Table 2-7), the most rigorous (cohort and case-control) provided conflicting evidence. The conclusions of Tilson et al. are consistent with the equivocal results from cohort and case-control studies; furthermore, this review undertook the most rigorous evaluation of the primary studies and was the only review to consider HIV incidence/prevalence as a separate outcome. Thus, on the basis of a tentative statement from one core review, supported by consistent evidence from less

robust primary studies, it was concluded that there is tentative review-level evidence to support the effectiveness of NSP in reducing HIV transmission.

2.2.3.1.3 Effects on self-reported injecting risk behaviour

Self-reported IRB has been studied more frequently than biological outcomes (HCV and HIV), and this is reflected in the numbers of primary studies (43 in total) identified by the three core reviews (Table 2-8).

Tilson et al. identified 25 studies (Bluthenthal et al., 2000; Cox et al., 2000; Des Jarlais et al., 2000; Gibson et al., 2002; Hagan et al., 1993; Hagan and Thiede, 2000; Hammett et al., 2006; Hart et al., 1989; Hartgers et al., 1992; Huo et al., 2005; Keene et al., 1993; Klee et al., 1991; Longshore, Bluthenthal, and Stein, 2001; Monterroso et al., 2000; Ouellet, Huo, and Bailey, 2004; Schoenbaum, Hartel, and Gourevitch, 1996; van Ameijden and Coutinho, 1998; van Ameijden, van den Hoek, and Coutinho, 1994; van den Hoek, van Haastrecht, and Coutinho, 1989; Vazirian et al., 2005; Vertefeuille et al., 2000; Vlahov et al., 1997; Watters et al., 1994; Wood et al., 2002; Wood et al., 2003), 14 of which were longitudinal cohorts, and demonstrated reductions in self-reported needle-sharing (lending or borrowing needles/syringes) (Bluthenthal et al., 2000; Cox et al., 2000; Gibson et al., 2002; Hagan and Thiede, 2000; Hart et al., 1989; Huo et al., 2005; Monterroso et al., 2000; Ouellet, Huo, and Bailey, 2004; Schoenbaum, Hartel, and Gourevitch, 1996; van Ameijden and Coutinho, 1998; van den Hoek, van Haastrecht, and Coutinho, 1989; Vertefeuille et al., 2000; Vlahov et al., 1997; Wood et al., 2002). They concluded that there was moderate evidence to show that “multi-component HIV prevention programs that include needle and syringe exchange” are associated with a reduction in self-reported sharing of needles and syringes.

Wodak and Cooney identified 28 primary studies of IRB (needle/syringe borrowing, lending, or reuse); among these, there were 24 positive (Bluthenthal et al., 1998; Bluthenthal et al., 2000; Cox et al., 2000; Des Jarlais et al., 1994; Donoghoe et al., 1989; Frischer and Elliott, 1993; Gibson et al., 2002; Gleghorn, Wright-De Aguero, and Flynn, 1998; Guydish et al., 1995; Guydish et al., 1998; Hartgers et al., 1989; Heimer et al., 1998; Keene et al., 1993; Monterroso et al., 2000; Oliver et al., 1994; Paone et al., 1994; Peak et al., 1995; Power and Nozhkina, 2002; Schoenbaum, Hartel, and Gourevitch, 1996; Singer et al., 1997; van Ameijden and Coutinho, 1998; van Ameijden, van den Hoek, and Coutinho, 1994; Vlahov et al., 1997; Watters et al., 1994), one negative (Klee et al., 1991),

one indeterminate result (Klee and Morris, 1995) and two showing no association (Donoghoe, Dolan, and Stimson, 1992; Hartgers et al., 1992). The reviewers did not formulate any conclusions specifically regarding IRB.

The 23 studies identified by Gibson et al. were covered by the other two core reviews (Bluthenthal et al., 1998; Des Jarlais et al., 1994; Donoghoe et al., 1989; Donoghoe, Dolan, and Stimson, 1992; Frischer and Elliott, 1993; Guydish et al., 1995; Guydish et al., 1998; Hartgers et al., 1989; Hartgers et al., 1992; Keene et al., 1993; Klee et al., 1991; Klee and Morris, 1995; Oliver et al., 1994; Paone et al., 1994; Peak et al., 1995; Schoenbaum, Hartel, and Gourevitch, 1996; Singer et al., 1997; van Ameijden and Coutinho, 1998; van Ameijden, van den Hoek, and Coutinho, 1994; Vlahov et al., 1997; Watters et al., 1994), with the exception of two (Broadhead, van Hulst, and Heckathorn, 1999); (Hagan, Des Jarlais, and Friedman, 1994). Both studies were suggestive of a protective effect of NSP: Broadhead, van Hulst, and Heckathorn (1999) noted an increase in the reported reuse and sharing of syringes after the closure of a needle exchange, and Hagan, Des Jarlais, and Friedman (1994) observed a decline in the proportion borrowing used syringes among needle exchange attendees (pre vs. post-intervention comparison). The authors concluded that there is substantial evidence that NSP is effective in preventing HIV risk behaviour among PWID.

Table 2-5 lists the types of studies included within the three core reviews: out of 43 studies, 39 were positive and 20 of these were cohort studies. Thus, based on consistent evidence across multiple robust studies, as well as moderate to strong statements of evidence in support of an effect of NSP on IRB from two core reviews, it was concluded that there is sufficient review-level evidence to support the effectiveness of NSP in reducing self-reported IRB.

2.2.3.2 Pharmacy access to needles/syringes

2.2.3.2.1 Effects on HCV Incidence/Prevalence

No reviews were identified that examined the effects of pharmacy access to needles/syringes on HCV incidence or prevalence.

2.2.3.2.2 Effects on HIV Incidence/Prevalence

One core review examined the effectiveness of pharmacy access to needles/syringes in reducing HIV prevalence (Wodak and Cooney, 2004): two relevant studies were identified (Table 2-9). The first, a serial cross-sectional study conducted in the UK, observed declines in HIV prevalence coinciding with a period of increased access to needles/syringes through pharmacies and needle exchanges (Hunter et al., 1995). The second, a cross-sectional survey, found a lower HIV prevalence in diabetic PWID, who had ready access to sterile syringes through pharmacies, compared with non-diabetic PWID (Nelson et al., 1991). They also referred to two studies as evidence of "replication of findings": Des Jarlais et al. (1995) found that pharmacy exchange was a common characteristic of cities that had maintained HIV prevalence rates of less than 5% over the previous five years, and De Jong, Tsagarelli, and Schouten (1999) observed a low HIV infection rate in Georgia, where syringes were readily available in pharmacies.

Wodak and Cooney concluded that "there is reasonable evidence that pharmacy availability of sterile injecting equipment does provide specific benefits in addition to those derived from NSPs." Despite a tentative statement of effectiveness from a core review, the evidence is based on a small number of primary studies with weak designs, and was therefore considered to be insufficient.

2.2.3.2.3 Effects on self-reported injecting risk behaviour

Tilson et al. and Wodak and Cooney examined seven studies of the effects of pharmacy access to needles/syringes on IRB (Table 2-10). Tilson et al. identified two studies (both serial cross-sectional) that compared IRB before and after liberalisation of the laws permitting syringe sale from pharmacies in New York and Connecticut (Groseclose et al., 1995; Pouget et al., 2005): both found that reports of syringe-sharing among PWID declined. The authors concluded: "…A few studies have examined the impact on drug-related HIV risk, and found suggestive evidence of a reduction." Wodak and Cooney reported the results of a further five cross-sectional studies (Calsyn et al., 1991; Gleghorn et al., 1995; Ingold and Ingold, 1989; Nelson et al., 1991; Richard, Mosier, and Atkinson, 2002): all findings were positive. Given consistent evidence from less robust studies identified within two core reviews, it was concluded that the level of evidence is tentative.

2.2.3.3 Needle/syringe vending machines

2.2.3.3.1 Effects on HCV Incidence/Prevalence

No reviews were identified that examined the effects of vending machines on HCV transmission.

2.2.3.3.2 Effects on HIV Incidence/Prevalence

One core review (Wodak and Cooney, 2004) reported the results of a cross-sectional study of PWID (Obadia et al., 1999), which found that primary users of vending machines were less likely to be HIV positive, although this was not significant after adjustment. Although the authors stated that "access to sterile needles and syringes from community pharmacies and syringe vending machines was shown in all nine studies to be effective in reducing risk behaviour and HIV seroprevalence", this conclusion was based on one study of vending machines with a weak design and it was therefore concluded that there was insufficient evidence.

2.2.3.3.3 Effects on self-reported injecting risk behaviour

Tilson et al. and Wodak and Cooney both mentioned a cross-sectional pilot study of vending machines in a German prison (Heinemann and Gross, 2001), although their reporting of the study results differs. Wodak and Cooney reported that significant decreases in needle-sharing subsequent to the introduction of the programme were found, whereas Tilson et al. stated that this study showed that PWID will use vending machines as a source of sterile needles/syringes. Other studies discussed by these reviews looked at the characteristics of vending machine users and the acceptability of machines. Tilson et al. concluded that there was insufficient evidence of the effectiveness of vending machines in reducing HIV risk; the conclusions of Wodak and Cooney are as above, for HIV.

A supplementary review, published after the date the literature search was undertaken, was identified (Islam and Conigrave, 2007). This review cited a paper summarising experiences with vending machines in prison (Stover and Nelles, 2003): the reviewers stated that machines in Germany and Switzerland reduced syringe-sharing significantly, although the study designs were not reported.

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

2.2.3.4 Outreach needle/syringe provision

2.2.3.4.1 Effects on HCV Incidence/Prevalence, HIV Incidence/Prevalence and self-reported injecting risk behaviour

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

2.2.3.5 Provision of sterile drug injecting paraphernalia

2.2.3.5.1 Effects on HCV Incidence/Prevalence and HIV Incidence/prevalence

No reviews were identified that examined injecting paraphernalia provision in relation to HCV or HIV outcomes.

2.2.3.5.2 Effects on self-reported injecting risk behaviour

Tilson et al. identified four relevant studies (Table 2-11): a cohort study (Ouellet, Huo, and Bailey, 2004) and a cross-sectional study (Longshore, Bluthenthal, and Stein, 2001) both found that the provision of paraphernalia was associated with declines in paraphernalia-sharing, whereas two other cohort studies (Hagan and Thiede, 2000; Huo et al., 2005) found no association between use of needle exchange (which presumably provided paraphernalia, although this was not explicitly stated) and reductions in paraphernalia-sharing. Given the lack of a statement of evidence from a core review, and inconsistent evidence from a small number of studies, it was concluded that the level of evidence is insufficient.

2.2.4 Discussion

There was insufficient evidence from these reviews to conclude that NSP is effective in preventing HCV transmission among PWID. The body of evidence was slightly more robust in relation to HIV prevention (i.e. a larger number of studies and more with positive findings); however, discrepancies were noted between core reviews – in the studies they identified, their reports of study designs and findings and the conclusions they drew from their respective bodies of evidence – and it was possible only to conclude that the evidence

for the effectiveness of NSP in preventing HIV transmission is tentative. Another finding of this review of reviews is that ecological studies have suggested more consistently a positive impact of NSP on HCV and HIV than individual-level observational studies. In contrast to the findings pertaining to biological outcomes (HCV and HIV), there was sufficient evidence to demonstrate that NSP is effective in reducing self-reported IRB. There was also tentative evidence to suggest that pharmacy provision, in addition to dedicated NSP, is effective in reducing such behaviour. With regard to the remaining interventions (vending machines, outreach NSP, provision of injecting paraphernalia), there was no or insufficient review-level evidence either to support or to discount their effectiveness in relation to any of the outcomes.

The findings highlight an absence of reviews that have been undertaken for many of the interventions considered here; for some (vending machines, outreach, provision of injecting paraphernalia), this probably reflects a lack of primary studies. For NSP and HCV, no high quality (core) reviews have addressed this association specifically, although at least 14 studies had been published to December 2002. For NSP and HIV, at least 16 primary studies examined this association, but previous reviews (Gibson, Flynn, and Perales, 2001; Wodak and Cooney, 2004) seem to have overstated the evidence in their assessment of these studies (Amundsen, 2007). In general, reviews gave more consideration to issues of bias and limitations in studies with negative findings than in studies with positive (protective) findings, and thus may have ascribed less importance to negative findings when synthesising the evidence.

It is important, however, to emphasise that the conclusions of insufficient/tentative evidence do not equate to evidence for lack of effectiveness for these interventions: these findings may, in part, be attributable to limitations of the primary studies. One of the criticisms of studies investigating NSP effectiveness in preventing BBVs is that they do not measure accurately the coverage or intensity of the intervention delivered (i.e. the amount of injecting equipment distributed) (Lurie, 1997). Many of the NSP sites studied had strict limits on the numbers of needles/syringes that could be distributed at any one visit and, therefore, were likely not providing adequate amounts for clients' needs. Thus, residual sharing, even among PWID who access NSP sites regularly, is likely to occur. Modelling studies have predicted reductions in HIV and HCV as NSP coverage is increased or as IRB decreases (Kretzschmar and Wiessing, 1998; Vickerman, Hickman, and Judd, 2007); however, the optimal level of coverage required to reduce HIV and HCV

transmission is unknown and will depend on the local context, including the baseline prevalence of HCV/HIV, levels of IRB and injecting networks.

Further consideration of the limitations of the primary studies helps to explain the finding of a discrepancy between the results of ecological studies and individual-level studies (cohort and case-control). Individual-level, non-randomised studies of PWID are difficult to design and execute, and thus highly susceptible to bias. In cohort studies, for example, two groups, such as NSP site attenders and non-attenders, are usually compared with respect to the outcome. This measurement of the exposure to the intervention has generally been limited because: (i) these groups are 'self-selecting' and thus may be inherently different with respect to characteristics, including injecting risk, that can influence the outcome (Lurie, 1997) and (ii) the distinction between exposed and unexposed groups is often inadequate (for example, unexposed individuals may have access to clean needles/syringes from other sources or exposed individuals may still be engaging in injecting risk despite high uptake of NSP), potentially diluting the effect size (Gibson, Flynn, and Perales, 2001). Ecological studies, by contrast, are more likely to report a positive association: because one cannot isolate the effects of a single intervention nor control for confounding factors in an ecological study, such studies may in fact be measuring the impact of several interventions and/or other factors. This is consistent with a recent study that found no independent effect of either NSP or methadone maintenance treatment, but that those participating in both services had a reduced incidence of HIV and HCV (Van Den Berg et al., 2007).

All of the evidence for NSP effectiveness is based on observational study designs, i.e. exposure to NSP has not been randomised. Observational studies, as discussed above, are generally at risk of confounding and selection bias. However, it is logistically and ethically difficult to conduct a randomised trial for interventions such as NSP, which have face validity and have already been widely introduced (Lurie, 1997). It has been suggested that community randomised trials, comparing a basic package of services with an enhanced package, are a feasible alternative study design. These trials would randomise participants on a group basis, rather than an individual basis, thereby avoiding some of the biases associated with observational designs (Tilson et al., 2007).

Another methodological issue is that the primary studies might not have been adequately powered to detect an impact of NSP. Few of the reviews addressed this issue in their reporting of the studies and, therefore, it was usually unclear whether equivocal findings

were due to a lack of power or truly represented no association. Others (Bastos and Strathdee, 2000) have suggested reasons why evaluations of NSP have not been conclusive, contending that evaluations have not taken into account the numerous contextual factors, for example, NSP infrastructure and policies and local environmental conditions, that may influence their effectiveness.

The reliance on self-reported risk behaviour is a problem for epidemiological studies examining the effectiveness of harm reduction interventions. Although it has been suggested that self-reported behaviour by heroin users and PWID can be reliable (Darke, 1998; Goldstein et al., 1995), it is uncertain whether this reliability applies to all behaviours. Limitations of self-reported injecting risk may explain the finding of greater strength of evidence for behavioural measures than for biological measures. First, differential reporting of risk behaviour between exposed and unexposed groups could bias measures of the effectiveness of NSP; for example, if PWID exposed to NSP are more sensitised to the risks of sharing and more reluctant to report this behaviour than unexposed individuals. Secondly, some modelling studies (Vickerman et al., 2006) have suggested that the association between IRB and HIV/HCV transmission does not follow a dose-response relationship; rather, a reduction in injecting risk has to surpass a threshold level before changes in HIV/HCV transmission are observed. Consequently, a change in IRB may have no impact on HIV/HCV incidence, thereby limiting the usefulness of IRB as a proxy measure for the effectiveness of an intervention.

A limitation of the review of reviews methodology is that it is unknown whether gaps in the evidence might be filled by recent primary research. To verify this, a search of the primary English language literature was undertaken, which identified several recent cohort studies of NSP and HCV/HIV (Hagan, Thiede, and Des Jarlais, 2004; Roy et al., 2007a; Van Den Berg et al., 2007; Wood et al., 2007). Although these studies generally presented improvements upon previous research in terms of larger sample sizes, careful adjustment for potential confounders and improved measurements of NSP uptake, none found an independent effect of NSP on HCV or HIV seroconversion. The conclusions drawn here are supported by a more recent review undertaken for the National Institute for Health and Care Excellence (Jones et al., 2008).

Another limitation of the methodology is the reliance on the reviewers' accounts of the designs and findings of the primary studies. In considering the primary evidence, study design was used as a proxy for study quality; however, other factors – for example, sample

size and recruitment strategy – affect the integrity of a study's results. The likelihood of having missed primary studies is a possibility for HCV, which the core reviews did not set out specifically to examine. To compensate for this, the studies identified by a supplementary review that focused on HCV as an outcome were included. With regard to HIV and IRB, three core reviews examined these outcomes as their primary objective and, given the large number of studies identified for each outcome and the large overlap between the studies identified by each review, it is likely that the key primary studies for the years searched have been captured.

Countries face a challenge in reducing, or maintaining low, prevalence of BBVs among PWID and good quality research is fundamental to formulating policy on the development of public health interventions. The findings of this review do not justify closing or hindering the introduction of NSP, given that the evidence remains strong regarding self-reported IRB and given that there is no evidence of negative consequences from the reviews examined here. A step change in evaluations of harm reduction interventions is recommended so that future evaluations: (i) focus on biological outcomes rather than behavioural outcomes and are powered to detect changes in HCV incidence; (ii) consider complete packages of harm reduction interventions rather than single interventions; (iii) are randomised where possible (preferably at the community level); and (iv) compare additional interventions or increased coverage/intensity of interventions with current availability.

2.3 Opioid substitution treatment

2.3.1 Summary of findings with regard to HCV, HIV and IRB

The extended version of this section can be found in Appendix A. Three core reviews (Gowing et al., 2004; Sorensen and Copeland, 2000; Tilson et al., 2007) and one supplementary review (Wright and Tompkins, 2006) that examined OST and any of the outcomes were identified.

The relationship between OST and HCV was examined by only one supplementary review (Wright and Tompkins, 2006). Of the five studies identified by that review (four cohort, one nested case-control), all had neutral findings (i.e. none found any statistically significant difference in the risk of HCV among those who were receiving OST vs. those who were not, nor observed declines in HCV over time associated with OST) although the definition of OST varied between studies (Crofts et al., 1997; Rezza et al., 1996; Selvey,

Denton, and Plant, 1997; Thiede, Hagan, and Murrill, 2000; van Ameijden et al., 1993). Since the Wright and Tompkins review was published, however, an additional six relevant cohort studies were identified (Craine et al., 2009; Dolan et al., 2003; Dolan et al., 2005; Hallinan et al., 2004; Maher et al., 2006; Miller et al., 2004), three of which found a lower incidence of HCV among those on uninterrupted or longer-term OST (Craine et al., 2009; Dolan et al., 2005; Miller et al., 2004). Nevertheless, a conclusion of insufficient evidence was arrived at, given the absence of a statement from a core review and the predominantly equivocal findings from a large number of robust studies: three positive findings all generated from cohort studies, but eight studies of various designs (one RCT, six cohort and one case-control) showing no association.

The three core reviews (Gowing et al., 2004; Sorensen and Copeland, 2000; Tilson et al., 2007) covered eight primary studies of the association between OST and HIV, consisting of two RCTs, four cohort studies, one case-control study and one cross-sectional study (Dolan et al., 2003; Hartel and Schoenbaum, 1998; Metzger et al., 1993; Moss et al., 1994; Novick et al., 1990; Rhoades et al., 1998; Serpelloni et al., 1994; Williams et al., 1992). Four of these studies found a positive association, i.e. a reduced risk of HIV infection associated with a higher dosage of, or continuous, OST. One retrospective study did not observe any HIV seroconversions in a cohort of patients on OST. The remaining two studies, both RCTs, did not find any HIV seroconversions in either of the treatment or control arms, but this was potentially due to a short follow-up period and low baseline prevalence of HIV. Thus, based on consistent evidence from multiple robust studies, as well as moderate to strong statements of evidence in support of an effect of OST from three core reviews, there was considered to be sufficient review-level evidence to support the effectiveness of OST in preventing HIV transmission. Nevertheless, it is of note that two of the reviews gave the following caution about the ‘self-selected’ samples: since participants were not randomly allocated to exposed (OST) and unexposed (no OST, discontinuous OST, or short-term OST) groups (with the exception of the RCTs), systematic differences between the groups – other than the exposure – may account for the differences in HIV seroconversion.

With regard to studies of OST and IRB, the measurement of IRB in these studies could generally be classified into three categories: prevalence and frequency of injection, sharing of injecting equipment and scores of drug-related risk.

Twenty studies, of varying design, looked at self-reported prevalence and/or frequency of injecting and all found statistically significant decreases in these behaviours (Abbott et al., 1998; Baker et al., 1995; Ball et al., 1988; Batki et al., 1989; Brooner et al., 1998; Camacho et al., 1996; Chatham et al., 1999; Dolan et al., 2003; Gossop et al., 2000; Greenfield, Bigelow, and Brooner, 1995; Iguchi, 1998; King et al., 2000; Kwiatkowski and Booth, 2001; Magura et al., 1991; Meandzija et al., 1994; Saxon, Calsyn, and Jackson, 1994; Shore et al., 1996; Simpson et al., 1995; Stark et al., 1996b; Strang et al., 2000). The three reviews also presented 14 studies showing significant decreases in self-reported sharing of injecting equipment (Camacho et al., 1996; Caplehorn and Ross, 1995; Chatham et al., 1999; Dolan et al., 2003; Gossop et al., 2000; Greenfield, Bigelow, and Brooner, 1995; Grella et al., 1996; Klee et al., 1991; Longshore et al., 1993; Magura et al., 1991; Margolin et al., 2003; Rhoades et al., 1998; Saxon, Calsyn, and Jackson, 1994; Stark et al., 1996b) and three studies that found no difference (Baker et al., 1995; Calsyn et al., 1991; King et al., 2000). These study designs were a mix of pre- vs. post-OST comparisons, comparisons of treatment vs. non-treatment samples and longitudinal in-treatment samples comparing retention in OST vs. drop-out.

Finally, five studies (Abbott et al., 1998; Avants et al., 1998; Baker et al., 1995; Chatham et al., 1999; Sees et al., 2000) examined drug-related HIV risk behaviour scores using various validated tools: three found significant decreases in the scores before and after OST, one found a non-significant reduction in risk scores between a methadone maintenance and methadone detoxification group and one found reduced risk scores in a cohort of individuals currently receiving OST, as opposed to those who were previously or never on OST.

The conclusions of the reviews, based on evidence from one RCT and numerous observational studies, led to the statement that the evidence was sufficient to support the effectiveness of OST in reducing injecting frequency, the sharing of injecting equipment and injecting risk scores.

2.3.2 Discussion

The evidence from reviews was insufficient to conclude that OST has an impact in reducing HCV incidence; however, there was sufficient review-level evidence that OST is effective in reducing HIV incidence and self-reported IRB. The findings for OST thus echo those for IEP: limited evidence for an impact on HCV, more evidence for an impact on

HIV and the most evidence for an impact on IRB (with regard to the conclusions of the reviews and the number and robustness of studies).

As with IEP, a conclusion of insufficient or tentative evidence (in this case, in relation to HCV) does not necessarily equate to evidence for lack of effectiveness, as the strength of evidence is highly correlated with aspects of study quality. The early studies of the association between OST and HCV – which tended to have short follow-up times and 'crude' definitions of OST – did not provide evidence for an impact. By contrast, later studies, which included improved classification of exposure groups – based on dosage, continuity of treatment and length of treatment – mostly demonstrated reduced HCV incidence associated with OST uptake. Thus, the choice of outcome measure used can greatly affect the findings.

Although the studies of OST discussed here have also been mostly observational, five RCTs were undertaken: one examining HIV (Dolan et al., 2003), one examining HIV and IRB (Rhoades et al., 1998) and three examining IRB (Avants et al., 1998; Margolin et al., 2003; Strang et al., 2000). All of the studies that looked at IRB as the outcome had positive findings, whereas the studies of HIV found no association. It is notable, however, that the latter two RCTs potentially did not allow sufficient follow-up time, or have enough participants, to observe any HIV seroconversions.

As with IEP, there is greater strength of evidence for HIV, as compared with HCV. This is likely a result of two factors: (i) the smaller body of literature with respect to HCV and (ii) the different nature of the two viruses and their epidemics within injecting populations. Regarding the latter, the higher prevalence of HCV in many injecting populations, combined with its higher infectivity relative to HIV (Bell, 1997; Centers for Disease Control and Prevention, 1998), means that each sharing event carries a higher probability of HCV infection than HIV infection. Consequently, there is a need to achieve a greater reduction in IRB to reduce HCV transmission: the reduced levels of IRB detected in studies of IEP and OST may therefore translate into a reduction in HIV, but not HCV.

Several of the reviews included here emphasise that it is often difficult to study the effects of a single intervention in isolation from other interventions that may have been delivered concurrently. This is a limiting feature of many of the study designs that have been used to investigate the effectiveness of harm reduction interventions, particularly ecological study designs. On the other hand, Tilson et al. (2007) stressed that particular harm reduction

interventions may be effective as components of an overall harm reduction programme, rather than alone. A study of the combined effects of OST and NSP, which found reduced incidence of HCV among those who reported uptake of both OST and NSP (but no significant effects of either intervention alone), provides support for this assertion (Van Den Berg et al., 2007).

Given the parallels between the evidence bases for the effectiveness of IEP and OST, the same recommendations as stated in section 2.2.4 apply here: give preference to biological rather than behavioural outcomes, consider complete packages of harm reduction interventions rather than single interventions, randomise interventions where possible, and compare additional interventions or increased coverage/intensity of interventions with current availability.

2.4 Update on review of reviews since original work was undertaken

2.4.1 Updated findings

As part of a separate programme of work, the review of reviews was updated to include reviews published through March 2011 (European Centre for Disease Prevention and Control and European Monitoring Centre for Drugs and Drug Addiction, 2011a; European Centre for Disease Prevention and Control and European Monitoring Centre for Drugs and Drug Addiction, 2011b; Macarthur et al., 2014). The changes in evidence statements between the original and the updated review of reviews, as well as details of the additional reviews and studies contributing to the evidence base, are presented in Table 2-12. Despite updating the evidence base by four years, only four evidence statements were changed as a result of the additional literature identified. In some cases (e.g. NSP and HCV, pharmacy NSP and HIV/IRB), additional evidence was insufficient to alter the original evidence statement. By contrast, the evidence statement for the effectiveness of outreach NSP with respect to HIV was upgraded from none to insufficient, as was the evidence statement for injecting paraphernalia with respect to HCV. Additionally, the evidence statement for the effectiveness of injecting paraphernalia with regard to IRB was upgraded from insufficient to tentative; as was the evidence for OST with regard to HCV.

2.4.2 Comment on methodology

At the time of undertaking the original work for this chapter, there were relatively limited resources in development to guide a review of reviews process (Kelly et al., 2002) – particularly with respect to grading the reviews and synthesising the evidence to derive conclusions. Since then, the Cochrane Collaboration has developed guidance on this methodology, which is now referred to as an 'overview of reviews' (Becker and Oxman, 2011). However, this methodology is primarily designed to provide overviews of Cochrane Intervention Reviews and would not necessarily have been a suitable methodology to apply here. The Cochrane Overview method does not specifically recommend a critical appraisal tool for assessing review quality but suggests that some checklists are available; however, these instruments would not have been largely applicable since they are designed for systematic reviews of randomised studies. A tool for reviews of non-randomised studies is not currently available, but is under development (AMSTAR, 2012). The Cochrane Handbook also does not explicitly provide any particular guidance with regard to mediating between the evidence in the reviews and deriving conclusions. This lack of guidance is perhaps because they are unlikely to have encountered discrepancies between different reviews' conclusions, or been unsure of the reviews' quality assessments of the primary studies, given that Cochrane Overviews are intended to: (i) summarise reviews addressing the effects of two or more interventions for a single health problem (not multiple reviews addressing the same intervention, as here) and (ii) summarise Cochrane Intervention Reviews (and can therefore be assured of the rigour with which these were undertaken).

In summary, much of the development work in this 'meta-review' area has been focused on systematic reviews or meta-analyses of studies that are generally more robust than the studies that have been undertaken to investigate harm reduction interventions and, consequently, a Cochrane Overview of reviews would likely not have been recommended to address the objectives in Chapter 2. Despite the acknowledged limitations, the methodology applied in Chapter 2 was sufficiently rigorous, systematic and appropriate for the purposes of this thesis (Ellis et al., 2003; Kelly et al., 2002).

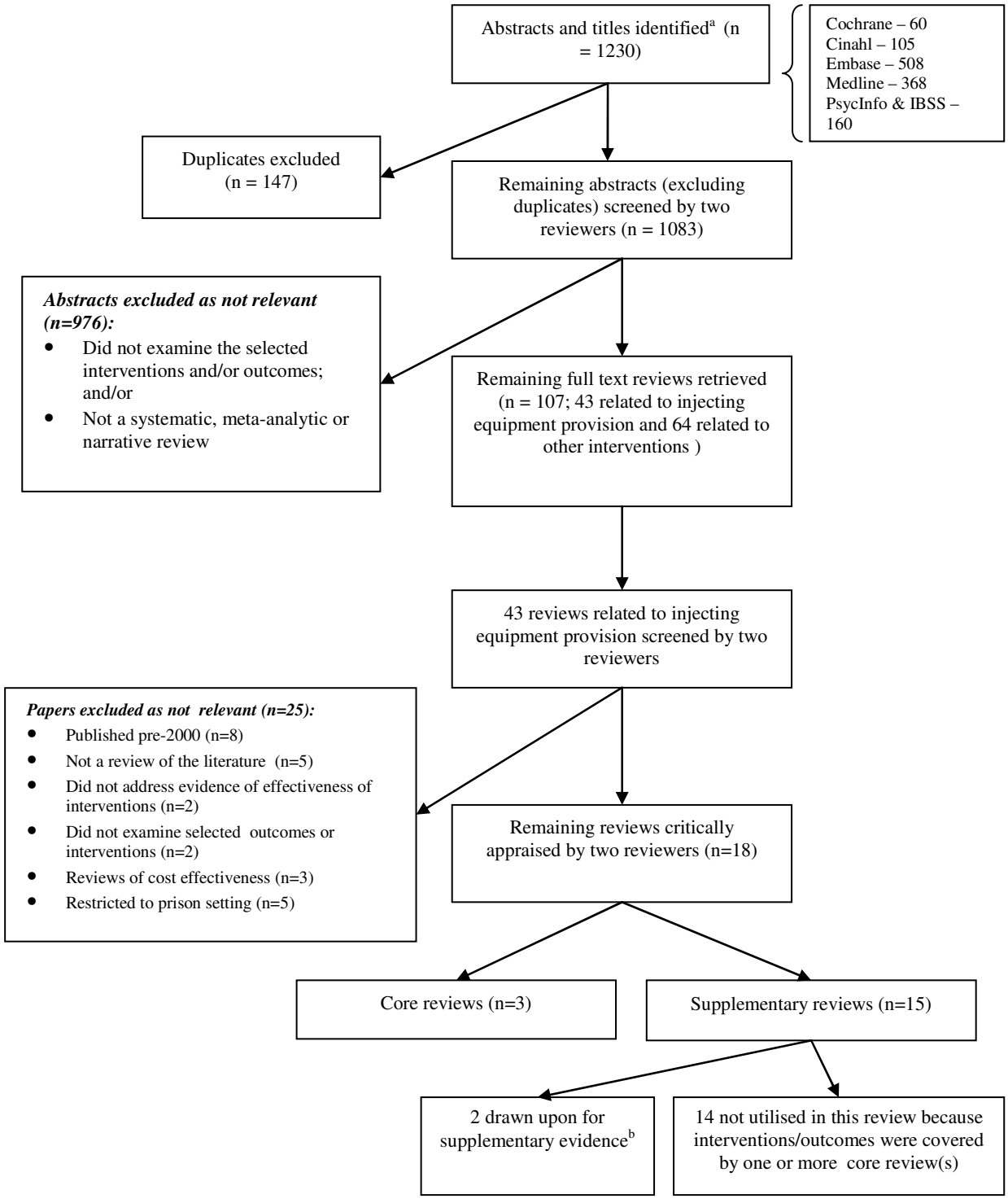


Figure 2-1. Papers identified in the review of reviews
[a]In addition to reviews of injecting equipment provision interventions, the initial search also included reviews of the following interventions: opioid substitution treatment; information, education, counselling and outreach; HCV testing and knowledge of HCV status; drug consumption rooms; treatment for HCV infection; promotion of non-injecting routes of administration; structural interventions; and bleach disinfection of needles/syringes.
[b]One review (Islam and Conigrave, 2007) was identified after the search was carried out

Table 2-1. Critical appraisal criteria for reviews

Does the paper have a clearly focused aim or research question?
Study identification
Are details given of: Databases and years searched Grey literature searched Search terms used Inclusion criteria used What materials were excluded
Critical appraisal
Do the authors address the quality (rigour) of the included studies?
Data presentation
Are sufficient data from individual studies included to mediate between data and interpretation/conclusions?
Synthesis and interpretation
Does the review make clear what steps have been taken to deal with potential bias? Do the authors consider whether the results could be due to chance (p-values and confidence intervals)? Do the authors acknowledge any other limitations to the research, including weakness in their own approach? Has more than one assessor been involved?
For meta-analyses:
Are the studies addressing similar research questions? Are the studies sufficiently similar in design? Are the results similar from study to study (test of heterogeneity)? Are the reasons for any variation in the results discussed?

Modified from Kelly et al. (2002)

Table 2-2. Framework for deriving evidence statements from reviews

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

Modified from Ellis et al. (2003)

Table 2-3. Summary of study designs used to assess effectiveness of harm reduction interventions

Study design	Type	Description	Weight of evidence	Example	Establishes temporal sequence[a]	Main limitations	Strength of causal interpretations
Randomised controlled trial	Experimental	Researchers control which individuals are exposed to the intervention by random assignment; individuals are then followed over time to see who develops the outcome	Very robust	Dolan et al. (2003) randomly assigned participants to receiving methadone or a waitlist control group; groups were followed up and HIV incidence was compared	Yes	Often not feasible to undertake an RCT to evaluate harm reduction interventions	Strongest – randomisation should theoretically eliminate selection bias
Cohort (with non-randomised control group)	Observational	Individuals with and without the exposure (i.e. exposed vs. not exposed to a harm reduction intervention) are followed over time and compared to see if they develop the outcome	Robust	Bruneau et al. (1997) followed users and non-users of NSP sites and compared HIV incidence between the two groups	Yes	High probability of selection bias; loss to follow-up	Potentially limited by systematic differences in the comparison groups
Cohort (pre vs. post-intervention comparison)	Observational	The outcome is compared, in a single group of individuals, before and after (and sometimes during) the implementation of an intervention	Robust	Vlahov et al. (1997) interviewed a sample of PWID who enrolled at an NSP site at baseline, two weeks and six months later and compared IRB between these times	Yes	Loss to follow-up; risk of confounding by changes over time in factors (other than the intervention) that may impact the outcome of interest	Limited by lack of a comparison group – other factors could be causing and/or contributing to the association

Table 2-3 (continued).

Study design	Type	Description	Weight of evidence	Example	Establishes temporal sequence[a]	Main limitations	Strength of causal interpretations
Case-control	Observational	Individuals who have the outcome (cases) are identified and their past exposure to the intervention is compared with that of patients who do not have the outcome (controls)	Robust	Hagan et al. (1995) compared prior use of syringe exchange between HCV-infected PWID (cases) and non-infected PWID (controls)	Yes	Information on the exposure is usually ascertained retrospectively, therefore there is a risk of inaccuracy and recall bias (if controls recall exposure differently from cases)	Potentially limited by sources of bias
Ecological	Observational	The exposure and outcome variables are measured at the population or community-level	Weaker	MacDonald et al. (2003) compared HIV prevalence over time in cities with and without NSP	Usually	High risk of confounding by changes over time in factors (other than the intervention) that may impact the outcome of interest	Highly limited – other factors could be causing and/or contributing to the association
Serial cross-sectional	Observational	The prevalence (or incidence) of the exposure and outcome are measured at multiple points in time in comparable samples drawn from the same population	Weaker	van Ameijden et al. (1992) compared IRB among different samples of PWID recruited (from the same sites) in successive years: 1986, 1987, 1988, 1989/90 and 1991/92	Yes	High risk of confounding by changes over time in factors (other than the intervention) that may impact the outcome of interest	Highly limited – other factors could be causing and/or contributing to the association
Cross-sectional	Observational	The prevalence of the exposure and outcome are measured (and the association between them is usually determined) at one particular point in time	Weaker	Longshore, Bluthenthal, and Stein (2001) tested the correlation between the frequency of attendance at NSP sites and injecting-risk behaviour among a sample of IDUs interviewed on a single occasion	No	High risk of confounding by other factors; cannot know whether exposure precedes outcome	Highly limited – due to lack of time dimension

[a]Between exposure and outcome

Table 2-4. Summary of reviews of injecting equipment interventions included in the review of reviews

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

[a]Number of primary studies in the review, listed by outcome

Table 2-5. Summary of evidence used in the derivation of evidence statements for each intervention (a) NSP, (b) pharmacy NSP, (c) vending machines, (d) outreach NSP and (e) provision of injecting paraphernalia and each outcome (HCV, HIV and self-reported IRB)

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

Table 2-5 (continued).

Outcome	Gibson et al. (2001)	Tilson et al. (2007)	Wodak and Cooney (2004)	Primary studies[a]	Evidence statement
Self-reported IRB		Tentative statement of evidence in support of pharmacy NSP, based on consistent evidence from a small number of weak studies	Tentative statement of evidence in support of pharmacy NSP providing benefits in addition to dedicated NSP, based on consistent evidence from multiple weaker studies	Consistent evidence from multiple weaker studies; 7 studies 7 positive (2 SCS and 5 CS) 0 negative 0 no association	Tentative evidence
(c) Needle/syringe vending machines					
HCV					No evidence
HIV		No statement of evidence	Statement of evidence in support of vending machines, but conflicting with the primary studies reviewed	Insufficient evidence; 1 study: 0 positive 0 negative 1 no association (1 CS)	Insufficient evidence
Self-reported IRB		Statement of insufficient evidence	Statement of evidence in support of vending machines, but conflicting with the primary studies reviewed	Insufficient evidence; 1 study: 1 positive (1 CS) 0 negative 0 no association	Insufficient evidence
(d) Outreach NSP					
HCV					No evidence
HIV					No evidence
Self-reported IRB					No evidence
(e) Provision of injecting paraphernalia					
HCV					No evidence
HIV					No evidence
Self-reported IRB		No statement of evidence		Inconsistent evidence from a small number of studies; 4 studies: 2 positive (1 COH, 1 CS) 0 negative 2 no association (2 COH)	Insufficient evidence

COH: cohort; CC: case-control; EC: ecological; SCS: serial cross-sectional; CS: cross-sectional

[a]Findings of primary studies were extracted from reviews. A positive finding refers to a reduction in the stated outcome associated with the intervention; a negative finding refers to an increase in the outcome associated with the intervention and 'No association' refers to no change in the outcome, or a change that did not reach statistical significance, associated with the intervention. Where a review reported a study finding as positive or negative, it was assumed that the result was statistically significant even if this was not explicitly stated.

Table 2-6. Summary of results of primary studies of the effectiveness of NSP with respect to HCV prevalence/incidence outcomes, by study design

Design	Author and year[a]	Finding[b]				Overall finding[c]
		Gibson et al. (2001)	Tilson et al. (2007)	Wodak and Cooney (2004)	Wright and Tompkins (2006)	
Case-control	Hagan et al., 1995	Positive	Positive	Positive	Positive	Positive
Cohort	Hagan and Thiede, 2000		N/A[d]			N/A
Cohort	Hagan et al., 1999	No association			No association	No association
Cohort	Mansson et al., 2000		Negative		Negative	Negative
Cohort	Patrick et al., 2001				Negative	Negative
Cohort	Van Ameijden, 1993				No association	No association
Cross-sectional	Lamden et al., 1998	No association				No association
Cross-sectional	Smyth, Keenan, and O'Connor, 1999				Positive	Positive
Cross-sectional	Somaini et al., 2000				Positive	Positive
Cross-sectional	Taylor et al., 2000		Positive		Positive	Positive
Ecological	Des Jarlais et al., 2005b		Positive (in appendices, not in text)			Positive
Serial cross-sectional	Goldberg et al. 2001; Goldberg, Cameron, and McMenamin, 1998; Hutchinson et al. 2002				Positive	Positive
Serial cross-sectional	Hernandez-Aguado et al., 2001				No association	No association
Serial cross-sectional	MacDonald et al., 2000				Positive	Positive
Serial cross-sectional	Sarkar et al., 2003		No association			No association

[a]Studies are those identified by Gibson et al. (2001), Tilson et al. (2007), Wodak and Cooney (2004) and Wright and Tompkins (2006)
[b]A positive finding refers to a reduction in the stated outcome associated with the intervention, a negative finding refers to an increase in the outcome associated with the intervention and 'no association' refers to no statistically significant association between the intervention and outcome
[c]Overall finding based on consensus between the reviews; primary studies were verified where discrepant findings were reported
[d]Study reports self-reported IRB outcomes only

Table 2-7. Summary of results of primary studies of the effectiveness of NSP with respect to HIV prevalence/incidence outcomes, by study design

Study design	Author and year[a]	Finding[b]			Overall finding[c]
		Gibson et al. (2001)	Tilson et al. (2007)	Wodak and Cooney (2004)	
Case-control	Patrick et al., 1997	No association	No association	No association	No association
Case-control	van Ameijden et al., 1992	No association	No association		No association
Cohort and nested case-control	Bruneau et al., 1997	Negative	Negative	Negative	Negative
Cohort (Meta-analysis to combine HIV incidence data from three prospective cohort studies)	Des Jarlais et al., 1996	Positive		Positive	Positive
Cohort	Mansson et al., 2000		Positive		Positive
Cohort	Monterroso et al., 2000			No association[d]	No association
Cohort	Schechter et al., 1999	No association	Negative	No association	No association
Cohort	Strathdee et al., 1997	Negative	Negative	Negative	Negative
Cross-sectional: random sample of syringes returned to an NSP	Heimer et al., 1993			Positive	Positive
Cross-sectional	Ljungberg et al., 1991			Positive	Positive
Ecological	Des Jarlais et al., 1995		Positive		Positive
Ecological	Des Jarlais et al., 2005b		Positive		Positive
Ecological	Hurley, Jolley, and Kaldor, 1997		Positive	Positive	Positive
Ecological	MacDonald et al., 2003[e]		Positive	Positive	Positive
Serial cross-sectional	Des Jarlais et al., 2005a		Positive		Positive
Serial cross-sectional	Hammett et al., 2006		Positive		Positive

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

[b]A positive finding refers to a reduction in the stated outcome associated with the intervention, a negative finding refers to an increase in the outcome associated with the intervention and 'no association' refers to no statistically significant association between the intervention and outcome

[c]Overall finding based on consensus between the reviews; primary studies were verified where reviews reported discrepant findings

[d]Although listed as a study with a positive finding in their review, Wodak and Cooney also state that the result was not statistically significant

[e]Also reported as Health Outcomes International

Table 2-8. Summary of results of primary studies of the effectiveness of NSP with respect to self-reported IRB outcomes, by study design

Study design	Author and year[a]	Finding[b]			Overall finding[c]
		Gibson et al. (2001)	Tilson et al. (2007)	Wodak and Cooney (2004)	
Cohort	Bluthenthal et al., 2000		Positive	Positive	Positive
Cohort	Cox et al., 2000		Positive	Positive	Positive
Cohort	Donoghoe et al., 1989	Positive		Positive	Positive
Cohort	Gibson et al., 2002		Positive	Positive	Positive
Cohort	Hagan and Thiede, 2000		Positive		Positive
Cohort	Hagan, Des Jarlais, and Friedman, 1994	Positive			Positive
Cohort	Hart et al., 1989		Positive		Positive
Cohort	Hartgers et al., 1992	No association	No association	No association	No association
Cohort	Huo et al., 2005		Positive		Positive
Cohort	Monterroso et al., 2000		Positive	Positive	Positive
Cohort	Oliver et al., 1994	Positive		Positive	Positive
Cohort	Ouellet, Huo, and Bailey, 2004		Positive		Positive
Cohort	Schoenbaum, Hartel, and Gourevitch, 1996	Positive	Positive	Positive	Positive
Cohort	van Ameijden and Coutinho, 1998	Positive	Positive	No association	Positive
Cohort	van den Hoek, van Haastrecht, and Coutinho, 1989		Positive		Positive
Cohort	Vertefeuille et al., 2000		Positive		Positive
Cohort	Vlahov et al., 1997	Positive	Positive	Positive	Positive
Cohort	Wood et al., 2002		Positive		Positive
Cohort	Wood et al., 2003		Positive		Positive
Cohort (retrospective)	Heimer et al., 1998			Positive	Positive
Cohort retrospective)	Paone et al., 1994	Positive		Positive	Positive
Cross-sectional	Bluthenthal et al., 1998	Positive		Positive	Positive
Cross-sectional	Donoghoe, Dolan and Stimson, 1992	No association		No association	No association
Cross-sectional	Frischer and Elliott, 1993	Positive		Positive	Positive
Cross-sectional	Gleghorn, Wright-De Aguero, and Flynn, 1998			Positive	Positive
Cross-sectional	Guydish et al., 1995	Positive		Positive	Positive
Cross-sectional	Guydish et al., 1998	Positive		Positive	Positive
Cross-sectional	Hagan et al., 1993		Positive		Positive

Table 2-8 (continued).

Study design	Author and year[a]	Finding[b]			Overall finding[c]
		Gibson et al.	Tilson et al.	Wodak and Cooney	
Cross-sectional	Hartgers et al., 1989	Positive		Positive	Positive
Cross-sectional	Keene et al., 1993	Positive	Positive	Positive	Positive
Cross-sectional	Klee and Morris, 1995	Indeterminate		Indeterminate	Indeterminate
Cross-sectional	Klee et al., 1991	Negative	Negative	Negative	Negative
Cross-sectional	Longshore, Bluthenthal, and Stein, 2001		Positive		Positive
Cross-sectional	Power and Nozhkina, 2002			Positive	Positive
Cross-sectional	Vazirian et al., 2005		Positive		Positive
Ecological	Des Jarlais et al., 2000		Positive		Positive
Serial cross-sectional	Broadhead, van Hulst, and Heckathorn, 1999	Positive			Positive
Serial cross-sectional	Des Jarlais et al., 1994	Positive		Positive	Positive
Serial cross-sectional	Hammett et al., 2006		Positive		Positive
Serial cross-sectional	Peak et al., 1995	Positive		Positive	Positive
Serial cross-sectional	Singer et al., 1997	Positive		Positive	Positive
Serial cross-sectional	van Ameijden, van den Hoek, and Coutinho, 1994	Positive	Positive	Negative	Positive
Serial cross-sectional	Watters et al., 1994	Positive	Positive	Positive	Positive

[a]Studies are those identified by Gibson et al. (2001), Tilson et al. (2007) and Wodak and Cooney (2004); van Haastrecht et al. (1996), Kaplan (1991), Kaplan et al. (1994) and Kaplan and Heimer (1995) are excluded from this table because they examined other outcomes (mortality, syringe return rates)

[b]A positive finding refers to a reduction in the stated outcome associated with the intervention, a negative finding refers to an increase in the outcome associated with the intervention and 'no association' refers to no statistically significant association between the intervention and outcome

[c]Overall finding based on consensus between the reviews; primary studies were verified where reviews reported discrepant findings

Table 2-9. Results of primary studies of the effectiveness of pharmacy access to needles/syringes with respect to HIV prevalence/incidence outcomes, by study design

Study design	Author and year[a]	Finding[b]
Cross-sectional	Nelson et al., 1991	Positive
Serial cross-sectional	Hunter et al., 1995	Positive

[a]Studies are those identified by Wodak and Cooney (2004)
[b]A positive finding refers to a reduction in the stated outcome associated with the intervention, a negative finding refers to an increase in the outcome associated with the intervention and 'no association' refers to no statistically significant association between the intervention and outcome

Table 2-10. Summary of results of primary studies of the effectiveness of pharmacy access to needles/syringes with respect to self-reported IRB outcomes, by study design

Study design	Author and year[a]	Finding[b]		Overall finding[c]
		Tilson et al. (2007)	Wodak and Cooney (2004)	
Cross-sectional	Calsyn et al., 1991		Positive	Positive
Cross-sectional	Gleghorn et al., 1995		Positive	Positive
Cross-sectional	Ingold and Ingold, 1989		Positive	Positive
Cross-sectional	Nelson et al., 1991		Positive	Positive
Cross-sectional	Richard, Mosier and Atkinson, 2002		Positive	Positive
Serial cross-sectional	Groseclose et al., 1995	Positive	Positive	Positive
Serial cross-sectional	Pouget et al., 2005	Positive		Positive

[a]Studies are those identified by Tilson et al. (2007) and Wodak and Cooney (2004)
[b]A positive finding refers to a reduction in the stated outcome associated with the intervention, a negative finding refers to an increase in the outcome associated with the intervention and 'no association' refers to no statistically significant association between the intervention and outcome
[c]Overall finding based on consensus between the reviews; primary studies were verified where reviews reported discrepant findings

Table 2-11. Summary of results of primary studies of the effectiveness of providing sterile drug injecting paraphernalia with respect to self-reported IRB outcomes, by study design

Study design	Author and year[a]	Finding[b]
Cohort	Hagan and Thiede, 2000	No association
Cohort	Huo et al., 2005	No association
Cohort	Ouellet, Huo, and Bailey, 2004	Positive
Cross-sectional	Longshore, Bluthenthal, and Stein, 2001	Positive

[a]Studies are those identified by Tilson et al. (2007)
[b]A positive finding refers to a reduction in the stated outcome associated with the intervention, a negative finding refers to an increase in the outcome associated with the intervention and 'no association' refers to no statistically significant association between the intervention and outcome

Table 2-12. Additional evidence identified and updated evidence statements for the review of reviews of the effectiveness of interventions in preventing IRB and HCV/HIV transmission among PWID

Intervention	Outcome	Original evidence statement	Additional evidence identified	Updated evidence statement[a]
NSP	HCV	Insufficient evidence	Two additional supplementary reviews (Hong and Li, 2009; Nacopoulos, Lewtas, and Ousterhout, 2010) covering three additional studies (Holtzman et al., 2009; Neaigus et al., 2008; Wu et al., 2007)	No change
	HIV	Tentative evidence	None	No change
	IRB	Sufficient evidence	None	No change
Pharmacy NSP	HCV	No evidence	None	No change
	HIV	Insufficient evidence	One additional core review (Jones et al., 2010) covering two additional studies (Miller et al., 2002a; Singer et al., 1997)	No change
	IRB	Tentative evidence	One additional core review (Jones et al., 2010) covering six additional studies (Bluthenthal et al., 2004; Fisher et al., 2003; Khoshnood et al., 2000; Obadia et al., 1999; Rhodes et al., 2004; Singer et al., 1997)	No change
Needle/ syringe vending machines	HCV	No evidence	None	No change
	HIV	Insufficient evidence	One additional core review (Jones et al., 2010) covering no additional studies	No change
	IRB	Insufficient evidence	One additional core review (Jones et al., 2010) covering one additional study (Obadia et al., 1999); one additional supplementary review (Islam, Wodak, and Conigrave, 2008) covering one additional study (Islam et al., 2008)	No change
Mobile vans (outreach NSP)	HCV	No evidence	None	No change
	HIV	No evidence	One additional core review (Jones et al., 2010) covering one additional study (Miller et al., 2002b)	Insufficient evidence
	IRB	No evidence	None	No change

Table 2-12 (continued).

Intervention	Outcome	Original evidence statement	Additional evidence identified	Updated evidence statement[a]
Sterile injecting paraphernalia	HCV	No evidence	One additional core review (Gillies et al., 2010) covering one additional study (Morissette et al., 2007)	Insufficient evidence
	HIV	No evidence	None	No change
	IRB	Insufficient evidence	One additional core review (Gillies et al., 2010) covering 11 additional studies (Bluthenthal et al., 1998; Colon et al., 2009; Guydish et al., 1998; Heimer et al., 2002; Huo and Ouellet, 2007; Kipke et al., 1997; Morissette et al., 2007; Sears et al., 2001; Sears, Weltzien, and Guydish, 2001; Stoltz et al., 2007; Vlahov et al., 1997)	Tentative evidence
OST	HCV	Insufficient evidence	One additional supplementary review (European Centre for Disease Prevention and Control and European Monitoring Centre for Drugs and Drug Addiction, 2011b) covering an additional study (Van Den Berg et al., 2007) and a meta-analysis/pooled analysis (Turner et al., 2011)	Tentative evidence
	HIV	Sufficient evidence	None	No change
	IRB	Sufficient evidence	None	No change

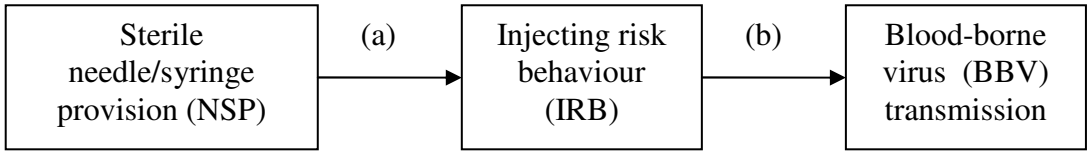
[a]Evidence statements as described in MacArthur et al. (2014)

3 Systematic review and meta-analysis of the association between self-reported sharing of needles/syringes and HCV prevalence and incidence among people who inject drugs in Europe

3.1 Introduction

The previous chapter reviewed the association between sterile NSP, among other interventions, and self-reported IRB, HIV and HCV; one of the findings was sufficient evidence of an impact of NSP on self-reported IRB. Given that IRB is on the 'causal pathway' between NSP and HIV/HCV (i.e. IRB must first be reduced in order to affect BBV transmission; Box 3-1), one might expect also to have seen evidence for an impact on HIV and HCV; however, this was not the case. While several potential reasons for the lack of evidence for biological outcomes were proposed in Chapter 2 (e.g. few primary studies, crude measures of NSP uptake, selection bias), this observed discrepancy between the evidence for behavioural outcomes (i.e. self-reported IRB) and the evidence for biological outcomes (i.e. HIV, HCV) may suggest that reductions in self-reported IRB do not necessarily translate into reductions in HCV/HIV transmission. Thus, as illustrated in Box 3-1, there is evidence for relationship (a), but there is still uncertainty regarding relationship (b). Insight may therefore be gained by examining further the relationship indicated by (b).

Box 3-1. Schematic diagram of impact of NSP



The specific relationship that will be addressed in this chapter is the association between sharing needles/syringes and HCV. Many studies have investigated the association between sharing needles/syringes and HCV, usually with the aim of examining risk factors for HCV incidence or prevalence. Despite the relatively large body of literature, only one study has reviewed/meta-analysed studies of this association (Pouget, Hagan, and Des Jarlais, 2012). The lack of reviews/meta-analyses may be because it seems obvious that needle/syringe-sharing should be associated with HCV. While this is true, studies of

incident and prevalent HCV have reported substantially different effect sizes for this association, as well as surprisingly high rates of infection among those who report not sharing needles/syringes (Denis et al., 2000; Judd et al., 2005b; Rezza et al., 1996). Additionally, the aim of the previous review/meta-analysis was to establish the *risk* of HCV associated with needle/syringe-sharing and so included only studies reporting HCV incidence (Pouget, Hagan, and Des Jarlais, 2012). In contrast, given the aforementioned range of effect sizes across studies, a pooled estimate of the magnitude of association (including both studies of incidence and prevalence) is of interest in itself. Furthermore, exploration of the potential reasons for the variation and/or inconsistencies – including the high rates of HCV among those who report not sharing at all – may yield important insights.

This chapter therefore aims to: (i) review the literature for studies that have reported a measure of the association between self-reported sharing of needles/syringes and HCV; (ii) summarise the size of this association; (iii) explore potential factors that account for the variation in the size of this association between studies; and (iv) consider potential explanations for apparent inconsistencies. Investigating this relationship may help to ascertain the relative contribution of needle/syringe-sharing to HCV transmission and to define issues with its measurement, thus informing prevention strategies and future research.

3.2 Methods

3.2.1 Study identification

This systematic review and meta-analysis builds on an earlier systematic review of the literature, undertaken to identify studies of HCV prevalence and incidence among PWID in the European Union (Roy et al., 2002). The Roy et al. review identified studies, published between January 1990 (shortly after HCV was first identified (Choo et al., 1989)) and December 2000, through a computerised search of MEDLINE and EMBASE and from the bibliographies of retrieved articles. To update this review, two additional literature searches (Box 3-2) were undertaken of the same electronic databases to identify studies reporting the association between self-reported sharing of needles/syringes and either (i) HCV prevalence or (ii) HCV incidence, published between January 2001 and September 2011. The reference lists of selected published reviews related to HCV were also searched

(Hagan et al., 2007; Hagan, Pouget, and Des Jarlais, 2011; Lelutiu-Weinberger et al., 2009; Palmateer et al., 2010).

Box 3-2. Terms used in the two literature searches

(i) Prevalence studies

1. exp Hepatitis C/ or (hepatitis c or HCV).mp.
2. (intravenous drug use$ or inject$ drug use$ or drug addict$ or drug abuse$ or drug misuse$).mp.
3. risk behavio?r.mp. or (shar$ and (needle$ or syringe$ or inject$ equipment or inject$ paraphernalia)).mp. or (shar$ and (needle$ or syringe$ or inject$ equipment or inject$ paraphernalia)).tw. or (risk factor$).ti,ab.
4. ($prevalen$ or $positiv$).mp.
5. 1 and 2 and 3 and 4

(ii) Incidence studies

1. exp Hepatitis C/ or (hepatitis c or HCV).mp.
2. (intravenous drug use$ or inject$ drug use$ or drug addict$ or drug abuse$ or drug misuse$).mp.
3. risk behavio?r.mp. or (shar$ and (needle$ or syringe$ or inject$ equipment or inject$ paraphernalia)).mp. or (shar$ and (needle$ or syringe$ or inject$ equipment or inject$ paraphernalia)).tw. or (risk factor$).ti,ab.
4. ($inciden$ or $conver$).mp.
5. 1 and 2 and 3 and 4

3.2.2 Inclusion/exclusion criteria

Eligible studies reported either (i) HCV prevalence (or incidence) among PWID who reported ever and never (or recent and non-recent) sharing of needles/syringes or (ii) an association between HCV prevalence (or incidence) and ever (or recently) having shared needles/syringes among PWID. HCV infection was defined as the detection of an HCV marker using a serological or saliva test. Ideally, sharing would have been defined as receptive needle/syringe-sharing (i.e. using a needle/syringe that had previously been used by someone else) rather than distributive sharing (i.e. passing on a used needle/syringe to someone else); however, most studies did not provide a definition of needle/syringe-sharing and therefore no restrictions were placed on studies in relation to this criterion. Studies were excluded if they: (i) did not present sufficient data to quantify the association between HCV prevalence or incidence and sharing needles/syringes; (ii) did not present the risk of HCV infection separately from other infections (e.g. HIV, HBV); (iii) did not distinguish needles/syringes from other injecting paraphernalia; (iv) involved antiviral

treatment for HCV infection; or (v) were based on self-reported HCV status. Studies were restricted to those conducted in countries of the European Union. Where two or more papers were generated from the same study, the paper that presented an analysis of the largest sample size was retained. Non-English language publications were considered for inclusion.

3.2.3 Study selection and data extraction

The abstracts retrieved in the literature searches described above were screened by two reviewers for potential relevance; full text papers for the selected abstracts were obtained and further screened by at least two reviewers. The following information was extracted, where available, from each paper: study dates; geographical area; recruitment site(s); sample size; mean and/or median age; proportion male; time since onset of injecting; method of ascertainment of needle/syringe-sharing (eg. interview, self-complete questionnaire, etc.); measurement of HCV infection (eg. saliva or serum test and test used); proportion reporting sharing injecting paraphernalia (filters, spoons and/or water); overall HCV prevalence (at baseline for cohort studies); number of HCV-positives (or seroconverters) and HCV-negatives (or non-seroconverters) who did and did not report sharing needles/syringes; unadjusted/adjusted odds ratios (ORs), risk ratios (RRs), or incident rate ratios (IRRs); and covariates that were adjusted for. Additionally, for cohort studies, information on numbers of participants followed up and lost to follow-up, mean length of follow-up, frequency of study visits and overall incidence was collected.

3.2.4 Quality assessment

The approach to assessing the quality of studies focussed on assessing the 'risk of bias and precision' of studies. Relevant items from a previously developed tool (Viswanathan and Berkman, 2012) were used to create two proformas (Appendix D) – one for cross-sectional and one for cohort studies. Items (common to both study designs) were grouped into the following categories: sample definition and selection (non-response rate, choice of comparison group, representativeness of sample), measurement of exposure and outcome (validity and reliability of tools, consistency of application), analysis (adjustment for confounding and effect modification, appropriateness of statistical methods) and sample size. An additional category – follow-up – was included for cohort studies, which considered the adequacy of follow-up time, the attrition rate and differences in attrition between comparison groups. For each item in the proforma, a study was categorised as either high, moderate or low, with 'high' indicating high risk of bias or poor precision. If a

study did not provide any information to address a particular item, the item was assigned a high risk of bias by default. Studies were then assigned an overall category of high/moderate/low, based on their respective proportions of these items.

3.2.5 Data synthesis and analysis

ORs and RRs of HCV infection associated with categories of exposure (needle/syringe-sharing), and their standard errors, were generated from the raw data in each paper. Where a paper presented the OR and 95% CIs, but not the underlying data, the following calculation was used to derive an estimate of the standard error of the log OR:

$$SE(logOR) = \left(\frac{\frac{(ln(UCL) - ln\,(LCL))}{2}}{1.96} \right)$$

where SE is the standard error, UCL is the upper 95% confidence limit and LCL is the lower 95% confidence limit.

Meta-analysis, based on the random effects model, was conducted to generate a pooled estimate of the association between needle/syringe-sharing and HCV prevalence/incidence. Statistical heterogeneity among the studies was assessed using the chi-square test for homogeneity and the extent of inconsistency between the study findings was examined using the I^2 statistic. The latter measures the proportion of the total variation in the study estimates that is attributable to heterogeneity, with values greater than 50% corresponding to substantial heterogeneity (Higgins and Thompson, 2002). Sensitivity analyses were undertaken to examine the influence on the summary effect measure of varying the outcome measurement scale (i.e. OR or RR), using the adjusted odds ratio (AOR) instead of unadjusted and excluding studies at high risk of bias. To examine the role of selected study-level characteristics (for example, recruitment setting) on heterogeneity, meta-regression and stratified analyses were explored. There were insufficient studies to generate meaningful results from multivariable meta-regression and therefore only univariable analyses were carried out. Publication bias was assessed by constructing a funnel plot and examining it for asymmetry (Sterne et al., 2011). Statistical analyses were performed in Stata version 9.2.

3.3 Results

A total of 1,047 abstracts and 128 full text papers were reviewed, yielding 16 cross-sectional studies (Cook et al., 2001; Denis et al., 2000; Galeazzi et al., 1995; Girardi et al., 1990; Hedouin and Gosset, 1998; Holbach et al., 1998; Huntington et al., 2010; Judd et al., 2005b; Malliori et al., 1998; Mathei et al., 2005; Sanchez, 1998; Serfaty et al., 1997; Sherriff and Mayon-White, 2003; Stark et al., 1995; Stark et al., 1996a; Taylor et al., 2008) and four longitudinal cohort studies (Craine et al., 2009; Foley and Abou-Saleh, 2009; Rezza et al., 1996; Van Den Berg et al., 2007) for the prevalence and incidence components of the review, respectively (Figure 3-1). One of the studies classified as cross-sectional was, in fact, a cohort study; however, the paper presented the relevant HCV prevalence data for the baseline visit of the study cohort and is therefore considered to have a cross-sectional design for the purposes of this meta-analysis (Galeazzi et al., 1995). Eight studies were carried out between 1989 and 1995 (Denis et al., 2000; Galeazzi et al., 1995; Girardi et al., 1990; Malliori et al., 1998; Rezza et al., 1996; Sanchez, 1998; Stark et al., 1995; Stark et al., 1996a), five in the latter half of the 1990s (Cook et al., 2001; Hedouin and Gosset, 1998; Holbach et al., 1998; Mathei et al., 2005; Taylor et al., 2008) and four during the early 2000s (Craine et al., 2009; Huntington et al., 2010; Judd et al., 2005b; Sherriff and Mayon-White, 2003). One study spanned two decades (Van Den Berg et al., 2007) and two did not report the study dates (Foley and Abou-Saleh, 2009; Serfaty et al., 1997).

3.3.1 Characteristics of the cross-sectional studies

The 16 studies included in the prevalence component of the review were carried out in seven western European countries and ranged in size from 56 to 720 participants (Table 3-1). The majority recruited participants at drug treatment sites (n=9). Twelve studies used an interviewer-administered questionnaire to ascertain information about IRB, two studies used a self-completed questionnaire and two studies did not specify how this information was obtained. All studies defined prevalent HCV as the presence of HCV antibodies; four studies used a saliva test and the remaining used a serum test.

Overall HCV prevalence ranged from 45% to 90% (Table 3-2) and the proportion of the sample who reported ever sharing needles/syringes ranged from 41% to 93%. Among PWID who reported ever and never sharing needles/syringes, prevalence of HCV ranged from 48% to 94% and 33% to 82%, respectively. The pooled prevalence of HCV was 59%

among PWID who reported never sharing needles/syringes. Fifteen studies reported unadjusted ORs (Huntington et al. reported only an AOR) of the association between ever sharing needles/syringes and prevalent HCV infection, ranging from 1.2 to 13.5; twelve of these associations were significant at the 5% level. Seven studies reported AORs, which ranged from 1.0 to 5.9, five of which were significant at the 5% level.

3.3.2 Characteristics of the longitudinal cohort studies

The studies retrieved in the incidence component of the review were conducted in the UK, Italy and the Netherlands (Table 3-1) and had effective sample sizes of 286, 62, 106 and 168 (Table 3-3). Three of these studies detected incidence rates of HCV ranging from 5.9 to 28.6 per 100 person-years. The fourth study (Van Den Berg et al., 2007) did not report an overall incidence rate, since follow-up occurred over a period of 20 years; rather, it reported a decline in incidence from 27.5 per 100 person-years in the late 1980s to around 2 per 100 person-years more recently. One study (Craine et al., 2009) that assessed risk behaviour during the year preceding the follow-up interview reported a needle/syringe-sharing rate of 20%. Two studies examined risk behaviour in the preceding six months and reported needle/syringe-sharing rates of 2% (Rezza et al., 1996) and 27% (Foley and Abou-Saleh, 2009). The pooled incidence of HCV was 11% among PWID who reported not sharing needles/syringes during the risk period. Unadjusted ORs of the association between recent needle/syringe-sharing and incident HCV infection ranged from 2.3 to 4.3, only one of which was significant at the 5% level. Only one cohort study reported an AOR of 3.7 (not statistically significant).

3.3.3 Meta-analysis

Meta-analysis of unadjusted ORs generated a random effects pooled OR of 3.34 (95% CI 2.42-4.62), comparing HCV infection among those who ever (or recently) shared needles/syringes relative to those who reported never (or non-recent) sharing. There was substantial heterogeneity and inconsistency between the study effect sizes (χ^2=66.1, p<0.001 and I^2=72.8%). A forest plot of the individual unadjusted ORs and the pooled OR is presented in Figure 3-2.

3.3.4 Sensitivity analysis

Table 3-4 presents the results of a sensitivity analysis comparing the effects of analysis scale (further stratified by study design), adjustment for confounding and risk of bias on

the pooled effect size. The pooled OR was very similar across study designs (cross-sectional and longitudinal), indicating that the pooled OR was robust to variation in this study characteristic. The pooled RR for longitudinal studies (2.70, 95% CI 1.78-4.10) was similar to the pooled OR for these studies (3.43, 95% CI 1.95-6.05). The sensitivity analysis also revealed that the effect size was relatively robust to adjustment for confounding (OR 3.34, 95% CI 2.42-4.62 vs. AOR 3.46, 95% CI 1.77-6.76) and to exclusion of studies at high risk of bias (OR 3.34, 95% CI 2.42-4.62 vs. OR 3.46, 95% CI 2.34-5.14).

3.3.5 Stratified analysis and meta-regression

Because a large proportion of the variability was likely a result of between-study heterogeneity, stratified analysis and meta-regression were carried out to investigate the effects of selected study characteristics. A number of study characteristics were significant ($p<0.05$) in univariable meta-regression (Table 3-5). Studies that recruited participants in prison had a pooled OR of 5.92 (95% CI 2.83-12.40) vs. 2.72 (95% 1.97-3.76) among studies that recruited from drug treatment settings (p=0.038). Studies that employed outreach methods had a lower pooled OR than those that did not (1.53, 95% CI 1.20-1.95 vs. 3.93, 95% CI 2.94-5.27, p=0.004). The linearity of continuous variables (time since onset of injecting and HCV prevalence) were verified by plotting these study-level variables against the respective study log ORs (Figures 3-3 and 3-4). Studies with a higher sample mean/median time since onset of injecting generally had lower ORs (ratio of ORs 0.86, 95% CI 0.78-0.95, p=0.003, for each one year increase in the mean/median). Higher sample HCV prevalence was associated with increased odds of HCV infection, giving a ratio of ORs of 1.02 (95% CI 1.00-1.03, p=0.037) per percentage point increase in prevalence. Adjusted meta-regression analysis was attempted, but results were not meaningful because there were insufficient studies, and are therefore not shown.

3.3.6 Funnel plot

A funnel plot, plotting the unadjusted log OR vs. its standard error for each study, is presented in Figure 3-5. This figure demonstrates an asymmetrical shape, with most studies having relatively low standard errors (i.e. a narrow spread on the vertical axis), with a few exceptions, and relatively wide range (on the horizontal axis) of effect sizes among those with low standard errors. No statistical tests for funnel plot asymmetry were performed because of the small number of studies and the substantial between-study heterogeneity (Sterne et al., 2011).

3.4 Discussion

This meta-analysis generated a pooled OR of greater than three, comparing the odds of HCV infection among PWID who report sharing needles/syringes with PWID who report not sharing needles/syringes. This study is the first pooled association between prevalent/incident HCV infection and needle/syringe-sharing. A previous study has used meta-analysis to investigate the association between needle/syringe-sharing and incident HCV (Pouget, Hagan, and Des Jarlais, 2012). That study reported a pooled RR of 1.97 (95% CI 1.57-2.49) associated with needle/syringe-sharing, which is lower than the estimated RR of 2.7 for incidence studies derived here (although it should be noted that this estimate is based on only four studies). Differences between the pooled risk estimates could be due to several factors relating to local injecting populations, such as population HCV prevalence and/or injecting networks (Aitken et al., 2004; Burt, Thiede, and Hagan, 2009).

The results also highlight the high rates of HCV infection among individuals who do not report needle/syringe-sharing, with incidence rates of up to 19% and prevalence rates of up to 82% among those who reported having not recently or never shared needles/syringes, respectively. It is possible that other risk factors, not measured in the studies included in this review, could account for some of the HCV infection among those reporting not sharing, such as sexual contact with HCV-infected individuals, needle-stick injury and tattooing. Sexual contact and needle-stick injuries are plausible but unlikely to account for much of the HCV burden in the PWID population (Judd et al., 2005b; Tohme and Holmberg, 2010). Some infections may be attributable to tattooing with unsterile equipment, which has been documented among PWID, occurring particularly in prisons (Hellard, Aitken, and Hocking, 2007; Tohme and Holmberg, 2012; Vescio et al., 2008). Other behaviours that are more likely to explain some of the HCV infection among those who reported not sharing needles/syringes include sharing injecting paraphernalia (e.g. spoons, filters, water), backloading/frontloading (i.e. using a pre-used syringe to prepare and distribute drugs) and accidental sharing. The latter has been observed in situations where PWID cohabit or inject together (Taylor et al., 2004), and there is evidence to suggest that backloading/frontloading may be a common practice (Thiede et al., 2007). The potential for HCV transmission due to sharing injecting paraphernalia is significant, given that these are highly prevalent behaviours among PWID (ranging from 47% to 83% in the studies included here); however, only three of the included studies adjusted for this (Denis

et al., 2000; Holbach et al., 1998; Rezza et al., 1996) and only eight studies reported the proportion of their sample that engaged in these behaviours.

It is unlikely, however, that the unmeasured behaviours discussed above would entirely account for the substantial levels of infection among those reporting not sharing needles/syringes. A larger, perhaps more intractable, problem is that of misclassification of risk. Studies of IRB inevitably rely on self-reported measures. Numerous studies have examined the reliability of self-report of risk behaviours among PWID (De Irala et al., 1996; Goldstein et al., 1995; Petry, 2001), but few have assessed their validity (Darke et al., 1991). An individual's responses may be subject to social desirability bias (i.e. underreporting of stigmatised behaviours), which could result in a dilution of the effect sizes if an individual who has engaged in risk behaviour (and is HCV-positive) does not disclose this information. The extent of underreporting is unknown but will be related to a respondent's willingness to disclose sensitive information, and will thus depend on the setting, the interviewer and the questionnaire used. Differential bias could also exist: for example, if individuals are more likely to report sharing injecting paraphernalia (as this type of sharing is less stigmatised than needle/syringe-sharing), the result could be an overestimate of the risk associated with this type of behaviour. Qualitative studies have found a discrepancy in self-reported sharing, with repeated and longer interviews finding a much greater level of sharing than reported in the first instance or to short quantitative surveys (Craine et al., 2004). A comprehensive qualitative review may provide greater insight into misclassification of sharing behaviour.

There was strong evidence of between-study heterogeneity, for which an explanation was sought by examining differences in study-level variables. Although the analysis lacked statistical power to undertake a multivariable meta-regression, univariable analysis suggested that study-level characteristics – recruitment setting, recruitment method, baseline HCV prevalence of the study sample and mean/median time since onset of injecting of the study sample – were potential modifiers of the pooled association between needle/syringe-sharing and HCV prevalence/incidence. Studies that recruited participants in prison generally showed larger effect sizes compared with studies that recruited participants in drug treatment settings, which may reflect that individuals who have been incarcerated tend to engage in riskier behaviour, both inside and outside prison (Carvell and Hart, 1990; Jurgens, Ball, and Verster, 2009).

By contrast, studies that recruited at drug treatment sites generally had lower ORs of the association between needle/syringe-sharing and HCV. It could be hypothesised that undertaking studies in settings that are linked to treatment for drug misuse (and particularly where the individual undertaking the interview is involved in the respondent's treatment) may be subject to social desirability bias. Studies that recruited respondents using outreach methods (defined as any method to recruit outwith fixed-site services, e.g. street recruitment) had a lower pooled OR than studies that did not. A possible explanation for this observation could be that these methods generally target young and high risk PWID; these individuals are more likely to have recently commenced injecting and are therefore less likely to be infected, but probably still engaging in high levels of risk behaviour, thereby diluting the strength of association between HCV and needle/syringe-sharing. That studies with a higher baseline prevalence have larger ORs also intuitively makes sense: in populations with a larger pool of infection, each injecting event would carry a higher risk of infection, therefore strengthening the association between HCV and needle/syringe-sharing. The finding of generally lower ORs among studies with increasing sample mean/median time since onset of injecting may be due to recall bias – i.e. if long-term injectors have more difficulty remembering their behaviour, as the recall period is longer. Another possibility is that, for long-term injectors, the cumulative effect of other unmeasured exposures over time (for example, sharing injecting paraphernalia, tattooing, etc) has diluted the strength of effect between needle/syringe-sharing and HCV.

Publication bias is one potential explanation for the funnel plot asymmetry observed in this meta-analysis; however, publication bias is less likely to be the case here because most of these studies were simply aiming to identify risk factors for HCV infection, rather than to examine needle/syringe-sharing and HCV specifically, and would therefore not necessarily have a vested interest in demonstrating a significant association with needle/syringe-sharing. Furthermore, by including non-English language studies (n=4), the potential for publication bias has been reduced even more. Additionally, although studies might have selectively reported adjusted outcomes (i.e. not reported the adjusted effect size if needle/syringe-sharing was not significant in a multivariate model), any impact of this selectivity will have been reduced because unadjusted effect sizes were also used (and most studies investigating risk factors for HCV infection will have examined needle/syringe-sharing). The influence of study-level characteristics (not shown) on the funnel plot were investigated, but no clear picture of any 'subgroups' of studies with asymmetry emerged. It is therefore likely that true heterogeneity in the effect size between studies is the most likely reason for the asymmetry. Finally, chance is another potential

reason for funnel plot asymmetry and is plausible in this case since there were relatively few studies.

Limitations of the methodology include the low power of meta-regression. Although a number of characteristics were statistically significant in univariable analysis, there was an insufficient number of studies to undertake multivariable analysis. Heterogeneity was explored at the study level by examining the effect of aggregate study characteristics on the pooled OR; sub-group analyses would have been preferable, but it was not possible to undertake these as the necessary data could not be extracted from the studies. Similarly, it would have been informative to explore a dose-response relationship between needle/syringe-sharing and HCV infection (i.e. the risk or odds of HCV by different frequencies of needle/syringe-sharing) but the majority of studies did not present an exposure gradient.

In this systematic review/meta-analysis, cross-sectional studies (of HCV prevalence), as well as longitudinal studies (of HCV incidence), were included. It is generally recognised that cross-sectional studies are limited with respect to measuring current risk of HCV transmission, since a prevalent HCV infection could have occurred at any time in the past. They were included here, however, as one of the objectives was to explore the correlation between HCV prevalence and self-reported needle/syringe-sharing (including the prevalence of HCV among those who reported never sharing needles/syringes), given a previous anecdotal observation that the latter varied between studies. It should also be noted that the RR and OR – although these were combined in the meta-analysis – do not measure the same thing. However, the sensitivity analyses showed that they were sufficiently similar to combine and, furthermore, the aim was not to measure a risk of infection per se.

Limitations of the studies themselves must also be considered, as individual study effect sizes that are biased will result in a biased pooled effect estimate. All of the studies included in this review were observational in nature (i.e. not randomised), therefore the association between needle/syringe-sharing and HCV infection may be subject to confounding by measured or unmeasured variables. Many of the studies either did not undertake adjusted analyses or did not include needle/syringe-sharing in the adjusted model(s), although the latter could be because they did not set out specifically to investigate the association between needle/syringe-sharing and HCV. However, sensitivity

analyses indicated that the pooled effect size did not differ substantially whether AORs or unadjusted ORs were used.

The included studies dated as far back as 1989; since then, there has been a general decline in IRB reported in many countries, which is generally accepted to be a result of introduction and expansion of harm reduction services (Palmateer et al., 2010). However, this decline should not affect the association between needle/syringe-sharing and HCV infection, provided that there have been no trends in reporting of risk behaviour over time. The finding that the year of study start did not impact on the pooled OR would seem to support the latter.

These findings may have implications for the use of IRB as a proxy for risk of BBV transmission. This inconsistency between self-reported IRB and BBV transmission has been seen in previous investigations of harm reduction interventions: for example, studies of NSP have found that provision of sterile needles/syringes has an impact on IRB, but not necessarily on HIV or HCV transmission (Palmateer et al., 2010). Therefore, if possible, the use of a biological measure is recommended if it is the actual outcome of interest. It will nevertheless remain important and desirable, in some studies, to measure IRB. Steps can be taken to reduce underreporting; for example, computer-assisted self-interviewing has been shown in some studies to yield a higher level of disclosure of sensitive behaviours (Des Jarlais et al., 1999a; Perlis et al., 2004) and may thus increase validity. In the study design phase, it is also very important to consider how other factors – for example, the privacy afforded by the setting and the impartiality of the interviewer – could influence the measurement of behaviours. Studies should also measure other risk factors for HCV – e.g. sharing non-needle/syringe paraphernalia, in addition to needle/syringe-sharing – as it is potentially the cumulative effect of these behaviours that accounts for most HCV transmission. Additionally, studies should define precisely what they mean by sharing: questions to elicit risk behaviour should distinguish between the receipt of used items of equipment and the passing on of used items of equipment.

In conclusion, the results suggest a higher risk of HCV infection among PWID who reported sharing needles/syringes relative to those who did not. Nevertheless, there were very high incidence/prevalence rates among those who did not report sharing needles/syringes during the risk period, which may be a result of a combination of unmeasured risk factors and reporting bias. Study design and population may be important modifiers of the size and strength of association between HCV and needle/syringe-sharing.

These findings have implications for the use of self-reported sharing of needles/syringes as a proxy for HCV risk.

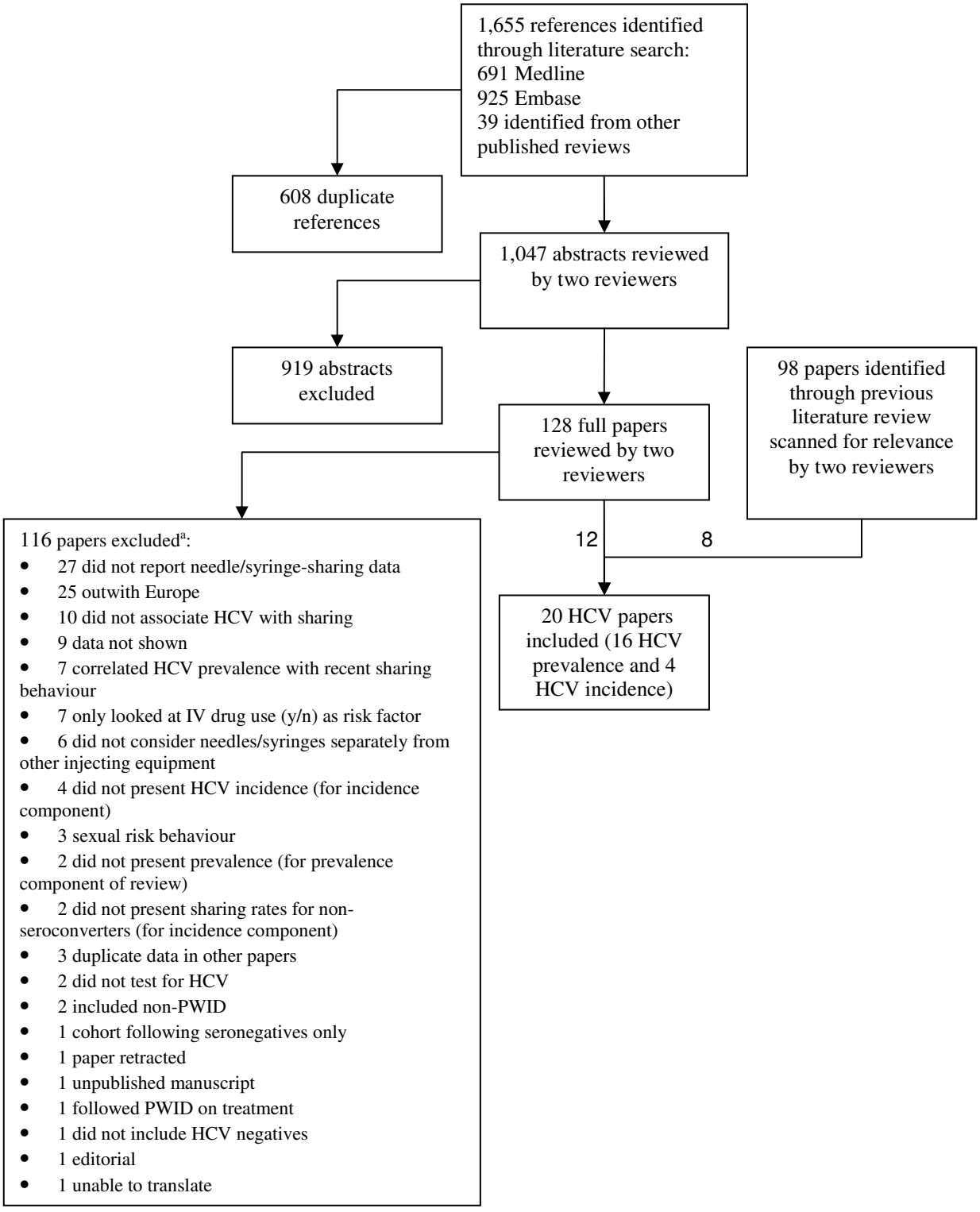


Figure 3-1. Papers identified in the systematic review of the association between self-reported sharing of needles/syringes and HCV prevalence/incidence among PWID in Europe
[a]Note that although the prevalence and incidence components of the review were carried out separately, the numbers are combined here for brevity. The excluded papers may therefore contain some duplicates; however, the reasons for exclusion are presented for the respective components of the review.

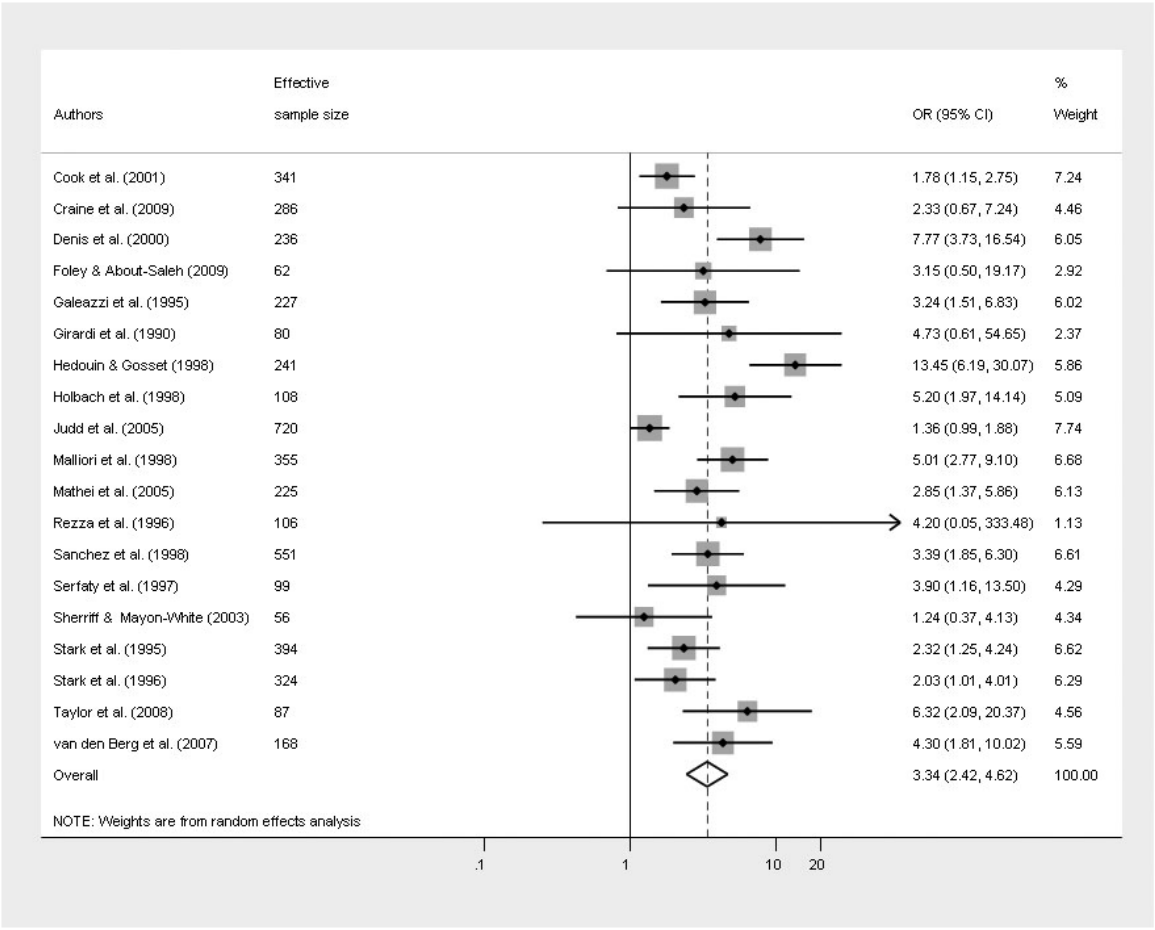


Figure 3-2. Forest plot of unadjusted ORs of the association between needle/syringe-sharing and HCV infection among PWID and the random effects (DerSimonian and Laird) pooled estimate. The size of the boxes represents the weight assigned to each study. The overall effect size estimate is indicated by a diamond, with the 95% CIs being indicated by its width.

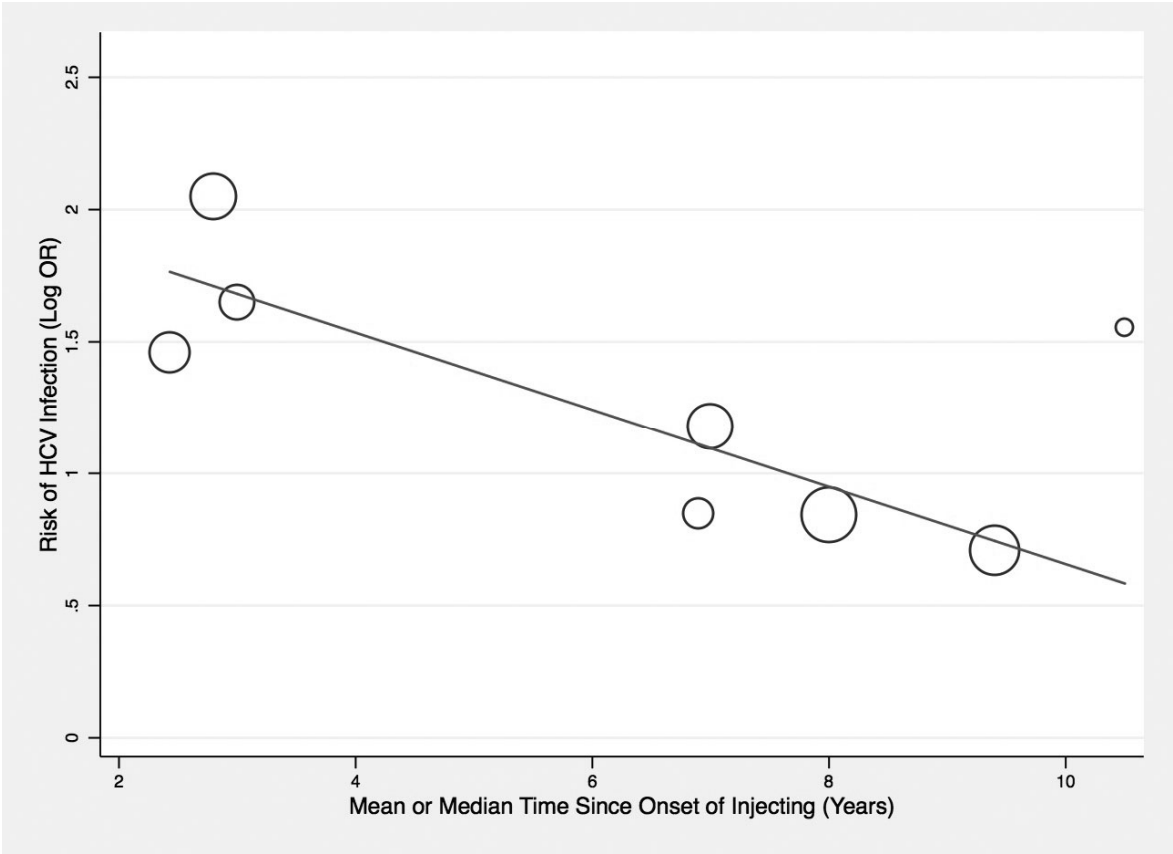


Figure 3-3. Plot of sample mean/median time since onset of injecting vs. the log OR for studies reporting this information (n=8) from the systematic review and meta-analysis of the association between self-reported sharing of needles/syringes and HCV prevalence/incidence among PWID in Europe

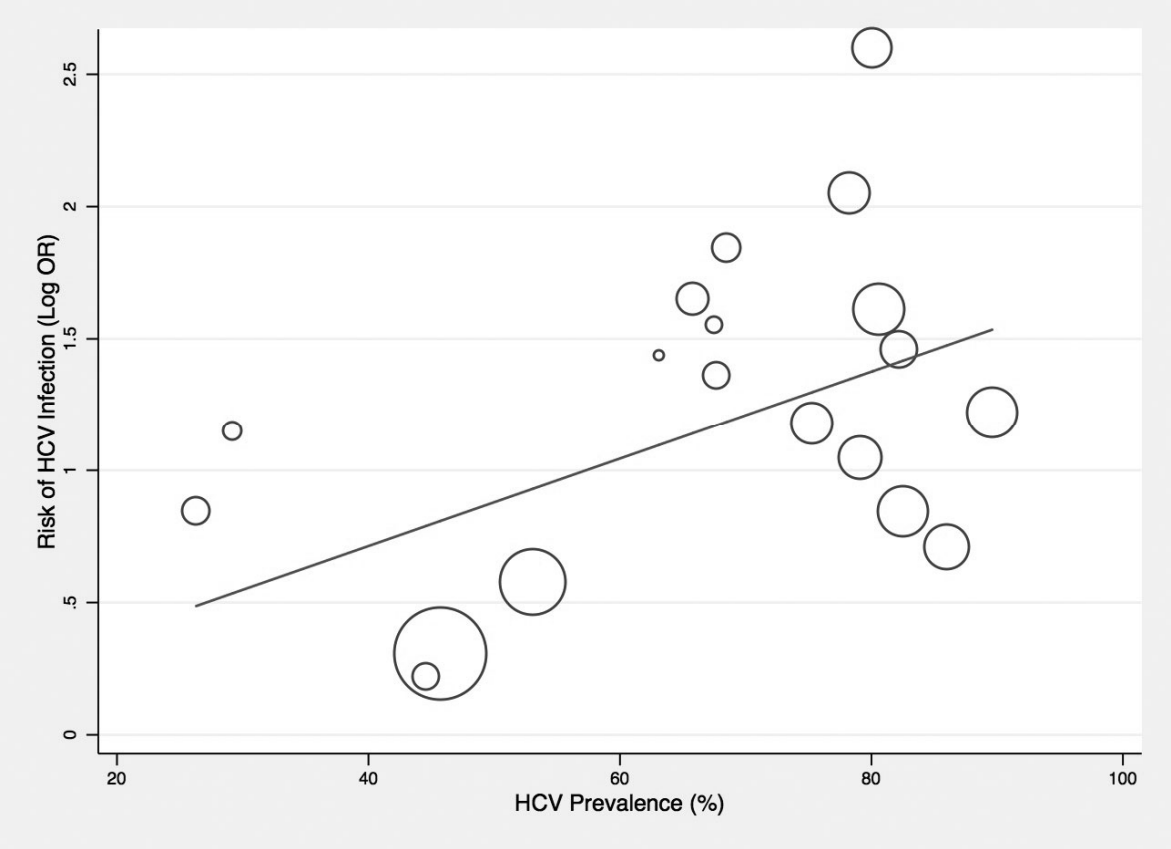


Figure 3-4. Plot of sample HCV prevalence vs. the log OR for studies reporting this information (n=19) from the systematic review and meta-analysis of the association between self-reported sharing of needles/syringes and HCV prevalence/incidence among PWID in Europe

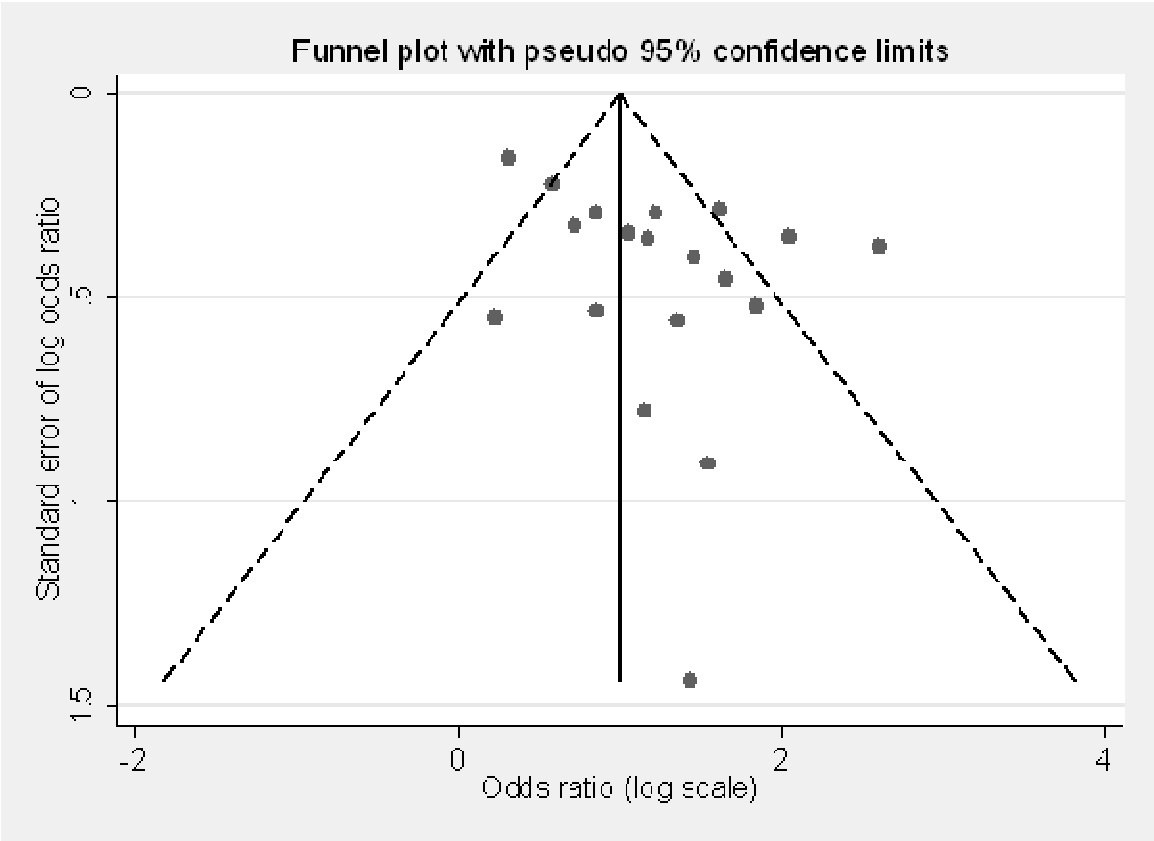


Figure 3-5. Funnel plot of the unadjusted OR (on the log scale) versus the standard error of the log OR for each of the included studies (n=19) from the systematic review and meta-analysis of the association between self-reported sharing of needles/syringes and HCV prevalence/incidence among PWID in Europe

Table 3-1. Description of studies included in the systematic review and meta-analysis of the association between self-reported sharing of needles/syringes and HCV prevalence/incidence among PWID in Europe

Reference	Design	Setting	Study population	Assessment of exposure	Assessment of outcome	Study limitations	Risk of bias[a]
Cook et al., 2001	Cross-sectional	Manchester and Wirral, UK; 1997-1999; recruitment at community drug teams, drug dependency units, rehabilitation centres, agency-based syringe exchange schemes, outreach	Convenience sample of those attending drugs agencies for the first time or specifically to request a test. Snowballing was also used to recruit 60 people. 360 completed questionnaires; 341 with HCV blood results. 72% male; mean age by recruitment group: 31.3 years at treatment sites; 29.1 at needle exchange; 30.0 self-presenters; and 28.6 not in contact with services.	'Direct sharing' not defined but this is presumed to refer to sharing of N/S; assessed via self-administered questionnaire	Anti-HCV positivity assessed through repeat reactive serum samples (all positives confirmed with second ELISA; remaining inconclusive samples tested with RIBA and PCR)	• No information on refusal rate (non-participation) • Self-complete questionnaire may reduce accuracy • Sharing N/S not included in adjusted analyses	Low
Craine et al., 2009	Longitudinal cohort	South Wales, UK; 2004-2006; recruitment at treatment services, NSP, homeless hostels	Convenience sample of 700 current PWID (had injected in past year) at baseline – 516 of whom were seronegative; 286 seronegatives followed-up. 71% male; mean age 28.5 years.	N/S sharing (not explicitly defined) in the year since baseline assessed via interviewer-administered questionnaire	HCV seroconversion, defined as someone who was HCV seronegative at baseline and seropositive at follow-up (one year later)	• Those lost to follow-up less likely to be on OST at baseline • Adjusted model included N/S sharing and any equipment sharing (which includes N/S) • Analysis included those who did not inject during follow-up (25/286) and therefore not at risk	Low
Denis et al., 2000	Cross-sectional	Charleroi, Belgium; 1995; recruitment at nine GP practices and a residential detoxification clinic for drug users	Convenience sample of past or current heroin users; 329 heroin users recruited, of which 244 were PWID. 73% male; mean age 26.3 years.	Ever/never sharing N/S assessed via interview	Anti-HCV positivity in serum assessed through 2nd or 3rd generation MEIA or ELISA; RIBA for confirmation	• PWID in treatment only • Questionnaire administered by GP – could result in underreporting of risk behaviour • No information on refusal rate	Moderate

Table 3-1 (continued).

Reference	Design	Setting	Study population	Assessment of exposure	Assessment of outcome	Study limitations	Risk of bias[a]
Foley and Abou-Saleh, 2009	Longitudinal cohort	London and Surrey, UK; dates not reported; recruitment at drug treatment centres	95 HCV seronegative PWID who had injected in the last six months, were aged 18-70 and had an ICD-10 diagnosis of mental and behavioural disorder due to the use of drugs. 62 individuals completed 12-month follow-up. 74% male; mean age 32 years.	Standardised self-completed questionnaire; N/S sharing refers to previous six months and is defined as 'accepting used needles and/or syringes'	HCV seroconversion defined as testing positive to anti-HCV in serum by the 12-month follow-up date; laboratory test not specified	• No adjusted analyses • 35% of sample lost to follow-up; no comparison of these with those retained in study • Small sample size • Risk behaviour is assessed for the six months prior to baseline interview, but period during which infection could have been acquired is 12 months after baseline interview • Analysis included those who did not inject during follow-up and therefore not at risk	High
Galeazzi et al., 1995	Longitudinal cohort (but only presents relevant data at baseline, therefore classified here as cross-sectional)	Veneto, Italy; 1992-1993; recruitment at drug dependence treatment centre in a hospital covering an area of about 138,000 inhabitants	Convenience sample of 227 PWID. 83% male; mean age 28 years.	Interview with physician (no details of questionnaire given); definition of N/S sharing not given	Anti-HCV positivity in serum assessed through 2nd generation ELISA; not specified whether confirmatory testing undertaken	• No adjusted analyses • If interviewing physician is involved in respondent's treatment, could bias responses • No information on sharing injecting paraphernalia • N/S sharing not defined • No information on refusal rate (non-participation)	High

Table 3-1 (continued).

Reference	Design	Setting	Study population	Assessment of exposure	Assessment of outcome	Study limitations	Risk of bias[a]
Girardi et al., 1990	Cross-sectional	Rome, Italy; 1989; recruitment at methadone treatment programme in a public assistance centre	Random sample of 80 IV heroin users attending the programme. 71% male; mean age 29.5 years.	Questionnaire – not clear if self or interviewer-administered; syringe sharing categorised as 'never', 'sometimes', or 'often'	Anti-HCV positivity in serum assessed through repeated reactivity to ELISA	• No adjusted analyses • No information on sharing injecting paraphernalia • N/S sharing not defined • No information on refusal rate (non-participation) • Small sample size (in particular, small number of never sharers)	High
Hedouin and Gosset, 1998	Cross-sectional	Loos-lez-Lille prison, France; 1995-1996; recruitment in prison	Convenience sample of 806 entering into prison during the period of study, 241 of whom were PWID. 91% male; mean age 22.5 years.	Interview by prison doctors; N/S sharing defined as 'exchange of injection material (needles and syringes) at least once in the past'	Anti-HCV positivity in serum assessed through repeated reactivity to 3rd generation ELISA	• No adjusted analyses • Interview by prison doctors may have biased responses • No information on sharing injecting paraphernalia • No information on refusal rate (non-participation)	Moderate
Holbach et al., 1998	Cross-sectional	Lohr, Germany; 1995-1997; recruitment at psychiatric hospital	Convenience sample of 120 individuals who had taken drugs intravenously in the past. 87% male; median age 24.5 years.	Standardised interview using questionnaire; N/S sharing not defined.	Anti-HCV or HCV-RNA positivity in serum assessed via ELISA/PCR	• No information on refusal rate (non-participation) • Recruitment at psychiatric hospital may have under-represented high risk users • Small sample size	Moderate

Table 3-1 (continued).

Reference	Design	Setting	Study population	Assessment of exposure	Assessment of outcome	Study limitations	Risk of bias[a]
Huntington et al., 2010	Cross-sectional	Catalonia, Spain; 2006; recruitment in the community	296 individuals who had injected drugs in the last six months. 78% male; 32% aged≤30 years.	Standardised questionnaire; sharing defined as ever having injected with used syringes	Anti-HCV positivity in saliva; test used/confirmation not specified	• No information on sharing injecting paraphernalia • No information on refusal rate (non-participation) • Laboratory methods not specified • Sampling method not explicitly described • Oral fluid instead of serum	Moderate
Judd et al., 2005	Cross-sectional	London and Glasgow, UK; 2001-2002; recruitment at drug treatment agencies, syringe exchanges and street setting	Convenience sample of 720 individuals who had begun injecting since January 1996 and had injected in the previous four weeks. 70% male; 37% aged <25 years.	Interviewer-administered questionnaire; sharing defined as having ever injecting with a previously used N/S	Anti-HCV positivity in saliva assessed using ELISA	• No information on refusal rate (non-participation) • Oral fluid instead of serum • Only presents recent sharing of injecting paraphernalia	Low
Malliori et al., 1998	Cross-sectional	Athens and Patra, Greece; 1994-1995; recruitment in prison	Prisoners convicted of/awaiting trial for drug-related offences who reported use of narcotic drugs (intravenous/mouth/nose/smoking) either currently or in the past, 375 of whom were PWID. 90% male; mean age 35 years.	Interviewer-administered questionnaire; exposure defined as 'ever shared needles'	Anti-HCV in serum, assessed via 2nd generation EIA	• No information on refusal rate (non-participation) • No information on sharing injecting paraphernalia	Low

Table 3-1 (continued).

Reference	Design	Setting	Study population	Assessment of exposure	Assessment of outcome	Study limitations	Risk of bias[a]
Mathei et al., 2005	Cross-sectional	Antwerp and Limburg, Belgium; 1999-2000; recruitment from patients attending a methadone programme at medico-social centres for drug users	Convenience sample of 310 drug users (out of 479 eligible who were approached); 225 PWID. 67% male; mean age of 33.0 and 34.5 years among participants from Limburg and Antwerp, respectively.	Standardised interview; exposure simply stated as 'N/S sharing'	Anti-HCV positivity in serum, assessed via 3rd generation EIA with confirmation by RIBA. Where RIBA was indeterminate, HCV-RNA testing was done.	• Interview by health personnel could have biased responses • Recruitment of PWID in treatment only, may under-represent high risk users • N/S sharing not entered into adjusted model	Moderate
Rezza et al., 1996	Longitudinal cohort	Naples, Italy; 1991-1993; recruitment from three drug treatment centres	746 PWID were eligible; 713 had data on HCV available. Among the 263 anti-HCV negative PWID, 106 completed follow-up. 97% male; 79% aged≤28 years.	Interviewer-administered questionnaire at baseline and 6-monthly intervals; exposure simply defined as 'needle-sharing' and referred to the six month period preceding interview	Anti-HCV seropositivity assessed by EIA and confirmed by RIBA.	• High loss to follow-up rate; no comparison provided of those followed up vs. not	High
Sanchez et al., 1998	Cross-sectional	Northeast Spain; 1994-1995; recruitment from seven prisons	All persons entering prison who remained for seven days or more; included 557 PWID. 85% male, mean age approximately 30 years.	Questionnaire administered by health personnel; exposure was 'syringe sharing'	Anti-HCV seropositivity assessed by EIA; positives confirmed by INNO-LIA	• No information on sharing injecting paraphernalia • No information on refusal rate (non-participation) • No adjusted analyses • Unclear if health personnel were affiliated to prisons – in which case responses could have been biased • Demographic information only presented for entire sample and not PWID subset	Moderate

Table 3-1 (continued).

Reference	Design	Setting	Study population	Assessment of exposure	Assessment of outcome	Study limitations	Risk of bias[a]
Serfaty et al., 1997	Cross-sectional	Newcastle UK; study dates not reported; recruitment in a regional drug and alcohol clinic	Eligible patients had a DSM-IV diagnosis of drug dependency/abuse and were either regular opioid users, receiving an opioid prescription, or had a history of past injecting. 202 patients were recruited; 194 with a history of injecting. 99 provided a blood sample for testing (2 of these had no history of injecting). 65% male; mean age 32.9 and 30.0 years among HCV positives and negatives, respectively.	Does not state how exposure data were collected or definition of 'needle sharing'.	Anti-HCV seropositivity assessed by 2nd generation ELISA and confirmed by RIBA	• Methods of ascertaining exposure not described • Sample includes two who had never injected • Analysis only adjusted for age • No information on sharing injecting paraphernalia	Moderate
Sheriff and Mayon-White, 2003	Cross-sectional	Oxford, UK; 2002; recruitment from sheltered accommodation and medical centre for homeless people	Convenience sample of 98 homeless individuals attending the recruitment sites, 56 of whom were past or current PWID. 90% male, mean age 30 years.	Interviewer-administered questionnaire; exposure simply stated as 'sharing needles'	Anti-HCV positivity in saliva (test not specified)	• No information on refusal rate (non-participation) • No adjusted analyses • Laboratory tests not specified • Oral fluid instead of serum • Demographic information only presented for entire sample and not PWID subset	High
Stark et al., 1995	Cross-sectional	Berlin, Germany; 1992-1993; recruitment at two drug treatment centres, an infectious disease hospital and a 'storefront agency' that provided syringe exchange	Sample of 405 individuals who had injected in the last three months. 71% male; median age 29.	Interviewer-administered questionnaire; exposure simply stated as 'syringe sharing'	Anti-HCV seropositivity in serum assessed with 2nd generation ELISA	• No information on sharing injecting paraphernalia • Adjusted analyses did not include N/S sharing • N/S sharing not defined	Low

Table 3-1 (continued).

Reference	Design	Setting	Study population	Assessment of exposure	Assessment of outcome	Study limitations	Risk of bias[a]
Stark et al., 1996	Cross-sectional	Berlin, Germany; 1994; recruitment at a treatment centre and 'storefront agencies'	Convenience sample of 324 PWID. 74% male; mean age 30.4 years.	Interviewer-administered questionnaire; exposure simply stated as "needle-sharing"	Anti-HCV seropositivity in serum assessed with 2nd generation ELISA	• No information on sharing injecting paraphernalia • Adjusted analyses did not include N/S sharing • N/S sharing not defined	Low
Taylor et al., 2008	Cross-sectional	Glasgow, UK; 1999; recruitment at a drop-in centre for sex workers	All women attending the centre during a four week period were approached (223); 114 agreed to participate; 99 had ever injected drugs, of which 89 had sufficient saliva sample. 0% male; mean age 26 years.	Self-completed questionnaire; exposure stated as 'ever shared needles for injecting'	Anti-HCV in saliva assessed using modified ELISA (85% sensitivity and 100% specificity)	• Oral fluid instead of serum and low sensitivity of antibody test • No information on sharing injecting paraphernalia	Moderate
van den Berg et al., 2007	Longitudinal cohort	Amsterdam, Netherlands; 1985-2005; recruitment from drug treatment centres, STD clinics and via word of mouth	Among 1640 DU enrolled, 1259 had at least two visits; 952 were ever injectors, of whom 168 were HCV seronegative. 67% male; median age 29 years.	Standardised questionnaire at baseline and at 4 to 6-month visits (questions refer to the previous six months at baseline and the time since last visit at follow-up visits)	Seroconversion defined as anti-HCV seropositivity detected by 3rd generation ELISA (in previous seronegatives); date of seroconversion was taken to be the midpoint between last seronegative and first seropositive visit	• Adjusted analyses did not include N/S sharing • No information on non-participation or loss-to-follow-up	High

ELISA: enzyme-linked immunosorbent assay; N/S: needle(s)/syringe(s); RIBA: recombinant immunoblot assay
[a]See the methods for a description of the risk of bias approach; 'high' refers to high risk of bias and/or poor precision

Table 3-2. Key findings of the cross-sectional (HCV prevalence) studies from the systematic review and meta-analysis of the association between self-reported sharing of needles/syringes and HCV prevalence/incidence among PWID in Europe

Study	Sample size[a]	Overall HCV prevalence	HCV prevalence among those ever shared N/S	HCV prevalence among those never shared N/S	Unadjusted OR (95% CI)[b]	AOR (95% CI)[c]	Variables adjusted for
Cook et al., 2001	341	53.1	NR	NR	1.8 (1.2-2.8)*	NR	N/A
Denis et al., 2000	236	78.3	90.2% (138/153)	54.2% (45/83)	7.8 (3.7-16.5)*	5.9 (2.4-14.2)*	"Cotton" sharing
Galeazzi et al., 1995	227	75.3	80.2% (146/182)	55.6% (25/45)	3.2 (1.5-6.8)*	NR	N/A
Girardi et al., 1990	80	67.5	70.2% (52/74)	33.3% (2/6)	4.7 (0.6-54.6)	NR	N/A
Hedouin and Gosset, 1998	241	80.1	92.2% (153/166)	46.7% (35/75)	13.5 (6.2-30.1)*	NR	N/A
Holbach et al., 1998	108	65.8	83.9% (52/62)	50% (23/46)	5.2 (2.0-14.1)*	5.2 (1.4-18.9)*	Age, total number of injections, borrowed syringes, borrowed spoons, intimate contact with risk person
Huntington et al., 2010	296	80.1	NR	NR	NR	3.1 (1.6-5.9)*	Front/backloading, age, drugs injected most frequently
Judd et al., 2005	720	45.7	48.4% (221/457)	40.8% (104/255)	1.4 (1.0-1.9)	1.0 (0.7-1.5)	Duration of injecting, frequency of injecting in last six months, no. of drugs mainly injected, cocaine and crack use, ever needlestick injury, ever in prison, recruitment setting and city of study
Malliori et al., 1998	355	80.6	89.2% (215/241)	62.3% (71/114)	5.0 (2.8-9.1)*	5.5 (2.7-10.9)*	Age, gender, no. of imprisonments, duration of injecting, injecting in prison
Mathei et al., 2005	225	79.1	84.4% (136/161)	65.6% (42/64)	2.8 (1.4-5.9)*	NR	N/A
Sanchez et al., 1998	551	89.6	94.0% (328/349)	82.2% (166/202)	3.4 (1.9-6.3)*	NR	N/A
Serfaty et al., 1997	99	67.7	73.2% (60/82)	41.2% (7/17)	3.9 (1.2-13.5)*	2.8 (0.99-7.95)[d]	Age
Sheriff and Mayon-White, 2003	56	44.6	47.8% (11/23)	42.4% (14/33)	1.2 (0.4-4.1)	NR	N/A
Stark et al., 1995	394	82.5	85.7% (264/308)	72.1% (62/86)	2.3 (1.2-4.2)*	NR	N/A
Stark et al., 1996	324	85.5	88.3% (203/230)	78.7% (74/94)	2.0 (1.0-4.0)*	NR	N/A
Taylor et al., 2008	87	68.5	85.1% (40/47)	47.5% (19/40)	6.3 (2.1-20.4)*	5.8 (2.0-16.5)*	Number of times in prison

NR: not reported; N/S: needle(s)/syringe(s)
* $p<0.05$.
[a]Sample size used in analysis
[b]As reported in paper if no HCV prevalence among sharers/non-sharers reported; otherwise calculated from 2x2 data presented in paper, with exact CIs
[c]As reported in paper
[d]CIs for AORs calculated from the standard error of the log OR, which was presented in the paper

Table 3-3. Key findings of the cohort (HCV incidence) studies from the systematic review and meta-analysis of the association between self-reported sharing of needles/syringes and HCV prevalence/incidence among PWID in Europe

Study	N[a]	HCV prevalence[a]	Effective N[b]	SC	PY	HCV Incidence	% seroconverted among those with recent[c] N/S sharing	% seroconverted among those with no recent[c] N/S sharing	Unadjusted OR (95% CI)[d]	Unadjusted RR (95% CI)	AOR (95% CI)[e]	Variables adjusted for
Craine et al., 2009	700	26.3%	286	17	287.33	5.9/100 PY	10.5% (6/57)	4.8% (11/229)	2.3 (0.7-7.2)	2.2 (0.8-5.7)	NR	N/A
Foley and Abou-Saleh, 2009	291	29.2%	62	8	NR	9.1/100 PY	23.5% (4/17)	8.9% (4/45)	3.2 (0.5-19.2)	2.6 (0.7-9.4)	NR	N/A
Rezza et al., 1996	716	63.1%	106	21	73.4	28.6/100 PY	50.0% (1/2)	19.2% (20/104)	4.2 (0.05-333.5)	2.6 (0.6-11.0)	3.7 (0.1-129.1)	Age, years injecting, injecting outside Naples, daily use of heroin, injecting cocaine, sharing of paraphernalia, PWID sexual partner, >1 sexual partners, methadone (all variables refer to last six months)
van den Berg et al., 2007	952	82.2%	168	58	NR	NR	42.1% (16 SC/38 PY)[f]	14.4 % (23 SC/159 PY)[f]	4.3 (1.8-10.0)*[g]	2.9 (1.7-4.9)[g]	NR	N/A

N/A: not applicable; NR: not reported; N/S: needle(s)/syringe(s); PY: person-years; SC: seroconversions.
* $p<0.05$.
[a]Sample size at baseline, i.e. before exclusion of anti-HCV positives
[b]Sample size used in analysis
[c]See Table 3-1 for definitions of recent sharing in the respective studies
[d]Calculated from data presented in paper
[e]As reported in paper
[f]Incidence rates of HCV seroconversion per person-years of observation
[g]OR and RR were calculated by taking the person-years of observation as a proxy for the number of individuals at risk

Table 3-4. Results of sensitivity analysis comparing pooled effect measures of the association between needle/syringe-sharing and prevalent/incident HCV infection

Study or model characteristic			No. of studies[a]	Pooled effect size[b]	95% CI		Test of overall effect	Test for heterogeneity	I^2
Analysis scale	All studies	OR	19	3.34	2.42	4.62	Z=7.35, p<0.001	X^2=66.1 (d.f.=18), p<0.001	72.8%
	Cross-sectional	OR	15	3.36	2.33	4.85	Z=6.50, p<0.001	X^2=64.5 (d.f.=14), p<0.001	78.3%
	Longitudinal	OR	4	3.43	1.95	6.05	Z=4.27, p<0.001	X^2=0.9 (d.f.=3), p=0.830	0.0%
	Longitudinal	RR	4	2.70	1.78	4.10	Z=4.67, p<0.001	X^2=0.3 (d.f.=3), p=0.966	0.0%
Adjustment for confounding	All studies	OR	19	3.34	2.42	4.62	Z=7.35, p<0.001	X^2=66.1 (d.f.=18), p<0.001	72.8%
	Studies reporting adjusted ORs	AOR	8	3.46	1.77	6.76	Z=3.63, p<0.001	X^2=35.4 (d.f.=7), p<0.001	80.2%
Risk of bias	All studies	OR	19	3.34	2.42	4.62	Z=7.35, p<0.001	X^2=66.1 (d.f.=18), p<0.001	72.8%
	Studies with low/moderate risk of bias	OR	13	3.46	2.34	5.14	Z=6.18, p<0.001	X^2=61.9 (d.f.=12), p<0.001	80.6%

[a]Unadjusted analyses are based on 19 studies since Huntington et al. (2010) did not present an unadjusted effect size
[b]Calculated using random effects (DerSimonian and Laird)

Table 3-5. Results of stratified analyses and meta-regression of study variables on the association between needle/syringe-sharing and HCV prevalence/incidence

Study characteristics		No. of studies	Stratified pooled ORs (95% CI)	Test for heterogeneity	I^2	Univariable meta-regression	
						Ratio of ORs (95% CI)	p-value
Study region	S and E Europe	5	3.93 (2.81-5.50)	X^2=1.3 (d.f.=4), p=0.856	0.0%	Ref	
	N Europe	14	3.21 (2.16-4.78)	X^2=59.0 (d.f.=13), p<0.001	78.0%	0.81 (0.39-1.68)	0.571
Year of study start	1995-2006	9	3.40 (1.91-6.04)	X^2=55.8 (d.f.=8), p<0.001	85.7%	Ref	
	1985-1994	8	3.24 (2.52-4.16)	X^2=6.5 (d.f.=7), p=0.486	0.0%	0.99 (0.50-1.94)	0.974
Recruitment setting	Drug treatment	13	2.72 (1.97-3.76)	X^2=30.1 (d.f.=12), p=0.003	60.1%	Ref	
	Prison	3	5.92 (2.83-12.40)	X^2=8.7 (d.f.=2), p=0.013	77.1%	2.13 (1.04-4.36)	0.038
	Other	3	3.53 (1.36-9.20)	X^2=5.6 (d.f.=2), p=0.060	64.4%	1.30 (0.56-3.03)	0.536
Recruitment method	Non-outreach	16	3.93 (2.94-5.27)	X^2=30.2 (d.f.=15), p=0.011	50.4%	Ref	
	Outreach[a]	3	1.53 (1.20-1.95)	X^2=1.7 (d.f.=2), p=0.435	0.0%	0.42 (0.23-0.76)	0.004
Current or past injectors[b]	Current only	5	2.24 (1.38-3.63)	X^2=9.5 (d.f.=4), p=0.051	57.7%	Ref	
	Current and past	11	4.15 (2.69-6.40)	X^2=35.0 (d.f.=10), p<0.001	71.4%	1.79 (0.90-3.56)	0.098
Mean or median time since onset of injecting of sample	(continuous)	8				0.86 (0.78-0.95)	0.003
Proportion of sample that are male	<72%	8	2.80 (1.82-4.31)	X^2=18.3 (d.f.=7), p=0.011	61.8%	Ref	
	≥72%	10	3.76 (2.30-6.17)	X^2=36.5 (d.f.=9), p<0.001	75.3%	1.31 (0.69-2.51)	0.408
Baseline HCV prevalence of sample	(continuous)	19				1.02 (1.00-1.03)	0.037
Risk behaviour questionnaire type	Interviewer-led	13	3.31 (2.19-4.99)	X^2=57.7 (d.f.=12), p<0.001	79.2%	Ref	
	Self-administered	3	2.98 (1.25-7.13)	X^2=5.3 (d.f.=2), p=0.072	62.0%	0.90 (0.35-2.30)	0.825
HCV test	Serum	16	3.67 (2.72-4.95)	X^2=36.2 (d.f.=15), p=0.002	58.5%	Ref	
	Oral fluid	3	2.08 (0.82-5.22)	X^2=8.2 (d.f.=2), p=0.017	75.6%	0.54 (0.25-1.15)	0.107

[a]Defined as any method to recruit individuals outside of services, e.g. street recruitment
[b]Where a current injector is someone who has injected recently; the definition of recently varies by study

4 Risk of transmission associated with sharing drug injecting paraphernalia: analysis of recent HCV infection using cross-sectional survey data

4.1 Introduction

In Chapter 3, it was concluded that the observed high incidence/prevalence rates among those who did not report sharing needles/syringes during the relevant risk period were likely a result of a combination of unmeasured risk factors and reporting bias. One of the unmeasured risk factors that may explain some of the HCV infection is sharing injecting paraphernalia. As described previously, the preparation of drugs for injection also involves several other items of equipment: spoons – on which the drugs are dissolved and heated – and filters – through which the drugs are drawn up into a needle/syringe (for removing particles). Water is also used to make a drug solution and/or to flush out a needle/syringe after injecting. These additional items are henceforth collectively referred to as injecting paraphernalia.

The evidence that direct percutaneous exposure to contaminated blood from a needle/syringe transmits HCV is generated from studies of needle-stick injuries in healthcare settings (Gerberding, 1995; Tomkins et al., 2012; Yazdanpanah et al., 2005). There is thus evidence that sharing needles/syringes in the recreational drug injecting setting has the potential to transmit HCV, although the actual risk of transmission would differ from the former setting based on a number of factors, such as the quantity of blood inoculated and the viral load. There is no equivalent evidence to demonstrate conclusively that sharing paraphernalia can transmit HCV infection. However, paraphernalia items may become contaminated with HCV in several ways, for example: if an individual draws up drug solution from a spoon and/or through a filter with a used needle/syringe (and these items are subsequently shared); or if someone flushes out his/her used needle/syringe with water (that is subsequently reused by someone else for flushing or for mixing with drugs) (Taylor et al., 2004).

Epidemiological studies have sought to quantify the risk of HCV transmission associated with sharing paraphernalia. Two previous reviews/meta-analyses have synthesised the evidence for the association between paraphernalia-sharing and incident HCV among PWID (De et al., 2008; Pouget, Hagan, and Des Jarlais, 2012), the latter of which concluded that there was an increased risk. These reviews included only two studies from

Europe (Lucidarme et al., 2004; Rezza et al., 1996), both of which were conducted more than a decade ago and neither of which specifically aimed to study paraphernalia-sharing. Furthermore, while the prevalence of paraphernalia-sharing has been fairly well described in the United States (Hagan et al., 2001; Hagan et al., 2010; Hahn et al., 2002; Kapadia et al., 2002; Roy et al., 2007a; Thorpe et al., 2002), these behaviours have not been extensively examined among PWID in Europe (Folch et al., 2012; Health Protection Agency, 2011b; University of the West of Scotland, Health Protection Scotland, and West of Scotland Specialist Virology Centre, 2010). Given the risk of HCV from paraphernalia-sharing observed in other studies (Pouget, Hagan, and Des Jarlais, 2012), this issue merits investigation in a European context.

This chapter therefore aims to address the third thesis objective of determining the association between sharing injecting paraphernalia and incident HCV infection among PWID in Scotland. As part of the Hepatitis C Action Plan for Scotland and the Sexual Health and Blood Borne Virus Framework (see sections 1.5.1 and 1.5.3), national cross-sectional surveys to monitor risk behaviour and HCV among Scottish PWID were implemented. Here, data from these surveys are used to examine the prevalence of sharing paraphernalia, and to examine the associations between incident HCV infection and (i) sharing needles/syringes (with or without paraphernalia) or paraphernalia only and (ii) sharing spoons, filters or water among those who report not sharing needles/syringes. This is the first study to apply a cross-sectional approach to the analysis of the relationship between paraphernalia-sharing and incident HCV.

4.2 Methods

4.2.1 Data collection

The Needle Exchange Surveillance Initiative (NESI) is a voluntary anonymous cross-sectional survey of PWID undertaken across mainland Scotland. Three sweeps of this survey have been undertaken to date: in 2008-09 (recruitment during June 2008 through June 2009), in 2010 (recruitment during January through November 2010) and in 2011-12 (recruitment during March 2011 through March 2012).

Participants were recruited from agencies and pharmacies that provide sterile injecting equipment, although many of these sites also provide other harm reduction interventions, such as OST. The number of sites at which recruitment was conducted exceeded 100 in each survey sweep, comprising more than 40% of all IEP services in Scotland (Information

Services Division, 2012c). Within logistical constraints (service manager agreement and a private room where the interviews could take place), services were selected to be broadly geographically representative.

The inclusion criteria for participation in the study were (i) having injected drugs at least once in the past and (ii) not having participated in the study during the current survey sweep. Current injectors (defined as having injected in the last six months) were oversampled, if necessary, so that the proportion of the sample comprised by this group was at least 75% in each recruitment area. Trained interviewers conducted the recruitment and interviewing of participants. The recruitment strategy simply involved approaching all potentially eligible individuals, although this was not always possible if the interviewer was occupied with an interviewee. If someone met the inclusion criteria, the purpose of the study and study procedures were explained to him/her and his/her consent was obtained. For those who were unwilling to participate, the reason for refusal, approximate age and gender of each person were recorded. After obtaining informed consent, the interviewer administered a questionnaire based on a longer questionnaire that has been employed in community surveys of PWID in Glasgow since the early 1990s (Taylor et al., 2001). The questions were designed to elicit information on socio-demographics, injection history, drug use practices, imprisonment, uptake of healthcare and harm reduction services and testing history for HCV. The same set of core questions were asked in all three surveys (2008-09, 2010 and 2011-12); with certain supplementary questions applied in some of the surveys (the 2011-12 questionnaire is attached in Appendix E). Forename and surname initial, date of birth, gender and first part of postcode were the only items of potentially identifying information collected.

Participants were also asked to provide a blood spot sample for HCV testing: capillary blood from a participant's finger was obtained by means of a single-use disposable lancet and then spotted onto Whatman Protein Saver cards. Individuals who completed the questionnaire were provided with a £5 voucher. So that the results of serological testing remained anonymous, a participant's dried blood spot (DBS) was linked to his/her questionnaire via a unique study number. Ethical approval for this research was obtained from the West of Scotland Research Ethics Service.

4.2.2 Laboratory methods

The DBSs on the absorbent cards were extracted and tested in a modification of the Ortho Save 3.0 EIA (Judd et al., 2003). Samples with optical densities of <0.4, 0.4-0.79 and ≥0.8 were classified as negative, weak reactive and positive for anti-HCV, respectively. HCV-RNA testing was undertaken on anti-HCV negative samples using an 'in house' PCR assay: the bioMerieux extraction protocol for DBSs on the Easymag and a real-time PCR (Bennett et al., 2012). The assay detects to 1000 IU/ml in DBSs. The testing was carried out in pools of five; samples in positive pools were then tested individually.

4.2.3 Analysis

The analysis presented in this chapter involves the NESI 2008-09 and 2010 surveys.

4.2.3.1 Outcome measure

The measure of incident HCV infection used here exploits the features of the immune response to the virus. As described in section 1.1.4, in the very early stages of HCV infection, individuals have high levels of viraemia prior to developing antibodies (seroconverting); this has been referred to as the viraemic pre-seroconversion window period and has been estimated to be of relatively short duration (Page-Shafer et al., 2008). Individuals who are anti-HCV negative and HCV-RNA positive have therefore acquired their infection recently. This outcome (anti-HCV negative and HCV-RNA positive) is henceforth referred to as recent HCV infection.

4.2.3.2 Measures of exposure

The exposures of interest were sharing needles/syringes and/or paraphernalia in the last six months. This information was elicited by the following questions: "how many times have you injected with a needle/syringe that had already been used by someone else?'; "have you used spoons or containers for mixing which had previously been used by someone else?"; "have you used filters or cottons which had previously been used by someone else?"; and "have you prepared drugs or rinsed your works with water that had already been used by someone else?"

4.2.3.3 Statistical analysis

Duplicate interviews (i.e. from individuals who participated more than once in either survey year or across both survey years) were identified based on initials, gender, date of birth and NHS Board of interview and were removed.

Two analyses were undertaken. In the first, a variable was created combining the exposures into the following categories: 'did not share in the last six months', 'shared needles/syringes with or without paraphernalia', or 'shared paraphernalia only'. The second analysis was limited to those who had not shared needles/syringes in the last six months, and examined the sharing of each item of paraphernalia individually. Analyses were restricted to anti-HCV negatives who reported injecting in the past six months. The association between the measures of exposure and recent infection was examined using logistic regression: univariable associations were initially determined; multivariable models were then built by entering suspected confounders and considering their contribution to the model. The confounding variables considered were: homelessness in the last six months (yes/no), stimulant injection in the last six months (yes/no), frequency of injection in the last six months (less than daily/daily or more frequently), time since onset of injecting (<5 years/≥5 years) and excessive alcohol consumption in a typical week during the past year (yes/no; where excessive is defined as >21 units per week for men and >14 units per week for women). Analyses were undertaken in SPSS version 17.

4.3 Results

A combined total of 5,355 unique respondents participated in the surveys, of whom 4,138 (77%) had reported injecting in the last six months (Figure 4-1). Of those with sufficient DBS samples for testing, 2,168 (53%) were found to be positive for anti-HCV. Among the 1,839 antibody negatives with sufficient sample for testing, 35 (1.9%) tested positive for HCV-RNA and were classified as recent infections.

Among the antibody negatives, 12% reported sharing needles/syringes and 40% reported sharing any paraphernalia in the last six months. The majority of those who reported sharing needles/syringes also reported having shared paraphernalia: 26 respondents reported sharing needles/syringes only (1.4% of the sample, Figure 4-2). In the last six months, 35% of the sample reported sharing spoons, 26% reported sharing filters and 26% reported sharing water. There were very large overlaps between these behaviours (Figure 4-3).

Table 4-1 presents characteristics of the study sample, according to self-reported sharing in the last six months. The proportions reporting sharing needles/syringes (with or without other paraphernalia) and paraphernalia only were significantly lower in 2010 (10% and 26%, respectively) than in 2008/09 (15% and 33%, respectively). Significantly more females than males reported sharing needles/syringes (with or without paraphernalia) and paraphernalia only. The mean age of those who reported sharing needles/syringes (with or without paraphernalia) was lower (29.4) than the mean age of those who reported sharing paraphernalia only (31.5) and not sharing (32.6). A higher proportion of those who had been homeless in the last six months, who had commenced injecting within the last five years, who had injected stimulants, who had injected more than daily in the last six months and who had consumed excessive alcohol, reported sharing both needles/syringes (with or without paraphernalia) and paraphernalia only.

The group that reported sharing needles/syringes with or without paraphernalia experienced the highest proportion of recent HCV infections (5.7%) as compared with those who reported sharing paraphernalia only (2.6%) or not sharing in the last six months (0.7%) (Table 4-2a). In univariable analyses, relative to those who had not shared any injecting equipment in the last six months, those who had shared needles/syringes with or without paraphernalia had the highest odds of recent infection (OR 9.1, 95% CI 3.6-23.0), followed by those who shared paraphernalia only (OR 4.0, 95% CI 1.6-9.9). The OR for needles/syringes with or without paraphernalia-sharing was lower after adjustment (AOR 6.7, 95% CI 2.6-17.1), as was the OR for sharing paraphernalia only (AOR 3.0, 95% CI 1.2-7.5). Unadjusted RRs for sharing needles/syringes with or without paraphernalia and sharing paraphernalia, relative to not sharing, were also calculated for comparison with the unadjusted ORs: they were very similar (RR 8.6, 95% CI 3.5-21.3 and RR 3.9, 95% CI 1.6-9.6, respectively).

The associations between sharing individual paraphernalia items and recent HCV infection among those who reported not sharing needles/syringes are given in Table 4-2b. Sharing spoons and sharing filters in the last six months were both significantly associated with recent infection in multivariable analyses (AOR 3.1, 95% CI 1.3-7.8 and AOR 3.1, 95% CI 1.3-7.5, respectively). Sharing water was not significantly associated with recent infection (AOR 1.2, 95% CI 0.5-3.3).

4.4 Discussion

This analysis showed that PWID who reported sharing needles/syringes (with or without paraphernalia) and sharing paraphernalia (only) had approximately seven and three times, respectively, the odds of recent HCV infection of those who did not share in the last six months. Although it was not possible to isolate the risk associated with needle/syringe-sharing due to too few participants reporting solely this behaviour, the fact that the majority of individuals who reported sharing needles/syringes also reported sharing paraphernalia suggests that the risk from the latter could be higher than the OR of three that was observed.

The effect size for sharing paraphernalia is consistent, if slightly higher, than effect sizes reported in previous studies (Hagan et al., 2010; Hahn et al., 2002; Lucidarme et al., 2004; Rezza et al., 1996; Roy et al., 2007a). These studies reported RRs ranging from 1.1 to 2.7, although the CIs for most of these included the estimate derived here. In addition, previous studies found a significant association with water (Kapadia et al., 2002; Maher et al., 2006; Thorpe et al., 2002), which was not replicated in this analysis. It is of note that ORs, rather than RRs, were presented here; however, RRs in univariable analyses were also calculated and these were comparable to the ORs.

In the sample presented in this study (NESI 2008-09 and 2010 combined), 7% reported sharing needles/syringes in the previous month, which is relatively low in comparison with other countries with comparable IEP services: 17% of PWID surveyed at specialist services in England, Wales and Northern Ireland in 2011 (Health Protection Agency, 2012) and 16% of PWID surveyed at IEP sites in Australia in 2011 (Iversen and Maher, 2012). In contrast, 30% of the NESI study population reported sharing paraphernalia in the last month; the comparable figures for England, Wales and Northern Ireland and Australia are 20% and 16%, respectively. The risk associated with paraphernalia-sharing determined in this analysis, combined with the high prevalence of this behaviour among Scottish PWID, means that it could potentially account for a substantial number of new HCV infections in this population. Previous studies have suggested that the proportion of infections attributable to paraphernalia-sharing could be in the region of 19% to 51% (Hagan et al., 2010).

During the Hepatitis C Action Plan for Scotland, there were approximately six-fold and four-fold increases in the provision of filters and spoons, respectively, between 2008/09

and 2009/10 (financial years) (Information Services Division, 2012c; Scottish Government, 2008a). Given these increases, the finding that the prevalence of sharing paraphernalia was significantly lower in 2010 than in 2008-09 is notable. Further NESI surveys will provide data to determine trends in this risk behaviour (see Chapter 6).

This study is the first to examine the association between paraphernalia-sharing and recent HCV infection using a cross-sectional design. This study design is generally considered inferior to a longitudinal design since the former usually cannot measure incident infection, a limitation that was overcome with the approach to detecting recent infections. Another frequently cited limitation of cross-sectional studies is that it is not known whether the exposure precedes the outcome. This limitation may apply here, as injecting equipment sharing (the exposure) relates to the six months prior to interview and it is not known exactly when in that six-month interval the behaviour occurred. However, this uncertainty presents no disadvantage in comparison with longitudinal studies of risk behaviour and BBVs, for which establishing the temporal association can also be a problem: these studies often follow up individuals at six-month intervals – the infection could have been acquired at any time during the interval and the exact timing of the risk behaviour is similarly not known. Although cross-sectional studies may be subject to sampling bias, they avoid bias from participant attrition that can arise in longitudinal cohort designs (DiFranceisco et al., 1998; Maher et al., 2006). Previous studies of paraphernalia-sharing and incident HCV have lost substantial numbers of participants to follow-up (De et al., 2008; Hagan et al., 2001; Hagan et al., 2010; Hahn et al., 2002; Maher et al., 2006), and although a description of dropouts was not always provided, in some cases they tended to engage in riskier behaviour than those who remained in the study (Maher et al., 2006). The result could be an underestimate of the association between sharing paraphernalia and incident infection.

To determine the independent effects of paraphernalia-sharing with regard to incident HCV, it is important to adjust for needle/syringe-sharing. Although many previous studies adjusted for needle/syringe-sharing, not all have done so (Brunton et al., 2000; Kapadia et al., 2002; Roy et al., 2007a). Furthermore, few studies have undertaken a stratified analysis (i.e. restricted the analysis to individuals who did not share needles/syringes) (Hagan et al., 2001; Lucidarme et al., 2004), as was done here, which can be a more reliable method of eliminating confounding from needle/syringe-sharing than simply adjusting for it in a multivariate model (Cook and Goldman, 1988).

In the study population, there were large overlaps between sharing of different paraphernalia items and thus the models examining individual items could not be adjusted for the other items. It therefore cannot be stated that the effect size associated with sharing filters is independent of sharing spoons or water, and vice versa. Despite this limitation, an association between recent HCV infection and sharing water was not detected. A few epidemiological studies have detected significant associations between sharing water (for rinsing) and HCV transmission (Kapadia et al., 2002; Maher et al., 2006; Thorpe et al., 2002), and a recent laboratory study demonstrated that HCV can survive for up to three weeks in bottled drinking water and remain infective (depending on the initial dose) (Doerrbecker et al., 2013). Water can become contaminated when it is used to flush/rinse out a syringe; it poses a transmission risk when it is subsequently reused by someone else for making a drug solution or rinsing out a needle/syringe (which is then used for injection). Twenty-six percent of the sample reported sharing water in the last six months, but it is not known which of the two behaviours (making a drug solution or rinsing out a needle/syringe) this refers to. It is plausible that the sharing of water for mixing is less risky, because a small volume of water is used, and the subsequent heating of the drug solution may deactivate some of the virus (Doerrbecker et al., 2011). The concentration of virus in the contaminated flush/rinse water may be correlated with the volume of residual blood left in the syringe after an injection, corresponding to the syringe's 'dead space' (Zule and Bobashev, 2009). The relative proportion of high/low dead space syringes used by the study population might therefore influence the transmission risk associated with water sharing. The NESI study did not collect information on syringe type, therefore it was not possible to examine this risk factor.

Limitations of this study include the use of self-reported measures of exposure. Evidence from studies that have compared computer-assisted self-interviewing with interviewer-administered questionnaires suggests that PWID underreport 'sensitive' behaviours, such as sharing needles/syringes and other equipment (Des Jarlais et al., 1999b; Metzger et al., 2000). Although there may be a degree of underreporting, the NESI surveys have taken steps to reduce this underreporting, including: employing independent, trained interviewers, undertaking the interviews in a private area and collecting the information anonymously. Corroboration of the behavioural data collected in the NESI surveys is provided by the strength of the association between sharing needles/syringes and recent infection seen here, which is larger than previous studies in which inconsistencies have been observed (Palmateer et al., 2013), and by the dose-response relationship that was observed between risk behaviour and recent HCV infection, such as increasing odds of

recent infection corresponding with increasing reported frequency of needle/syringe-sharing (e.g. ORs of 3.9 and 5.4 among those who shared once/twice and ≥3 times, respectively, in the last six months, relative to those who reported not sharing).

The pre-seroconversion window period for detection of recent HCV infection – with an estimated mean duration of six to eight weeks (Glynn et al., 2005; Netski et al., 2005; Page-Shafer et al., 2008) – has implications for this study. The studies that generated these window-period estimates mostly involved plasma donors as study subjects and therefore the validity of the estimates for PWID is less certain. Many factors can influence the duration of this acute phase of infection, including demographics and exposure frequency (Page-Shafer et al., 2008). However, the accuracy of the actual duration of the window period is perhaps less important in this study, where the aim is not to estimate incidence per se. Nevertheless, the short duration of the window period means that the outcome is rare: in this study, the 35 recent infections limited the statistical power.

Misclassification of the outcome must also be considered. A small number of recent infections may have been false positives in the case of delayed seroconversion among immunocompromised persons (i.e. chronic infections that are misclassified as recent) (Thomson et al., 2009). Similarly, because of fluctuating viraemia among a small proportion of acutely infected individuals, a recent infection could have been misclassified as being HCV-RNA negative during a low viraemic phase (Page-Shafer et al., 2008; Thomson, Smith, and Klenerman, 2011). Both of these sources of misclassification could result in a biased estimate of the association between the exposure and outcome. While re-infections among individuals who had previously cleared the virus would ideally be included in the outcome, they would not be captured by the measure of incident infection used here, because of the presence of antibodies from previous exposure to HCV among these individuals. This type of misclassification could result in a dilution of the exposure-outcome association as these individuals would likely be positive for the exposure (sharing injecting equipment) but negative for the outcome. Finally, a further source of misclassification could be the laboratory tests to detect anti-HCV and HCV-RNA in DBSs. Although these tests have high sensitivities (99% and 100%, respectively) and specificities (100% and 96%, respectively) (Bennett et al., 2012; Judd et al., 2003), there is nevertheless the possibility of false antibody negatives and false RNA positives.

There is the possibility that other unmeasured risk factors (for example, tattooing) may account for some of the risk of HCV infection. There may also be a role for other items

used in the injecting process (for example, swabs) in the transmission of HCV, but no information on the sharing or reuse of items was collected, other than the ones presented here (Thibault et al., 2011). It is also notable that the ORs presented here are not related to a 'per event' risk, since no information on the frequency of paraphernalia-sharing was available; however, an attempt was made to address this issue by adjusting for variables related to frequency of injecting in the models.

In conclusion, this analysis has demonstrated that a cross-sectional design generates results that are similar to those from longitudinal studies of the association between sharing injecting paraphernalia and incident HCV infection. This study is the first European study to examine this association, and confirms that, as has been observed in other western countries (Pouget, Hagan, and Des Jarlais, 2012), the prevalence of paraphernalia-sharing is high and represents significant potential for HCV transmission among PWID.

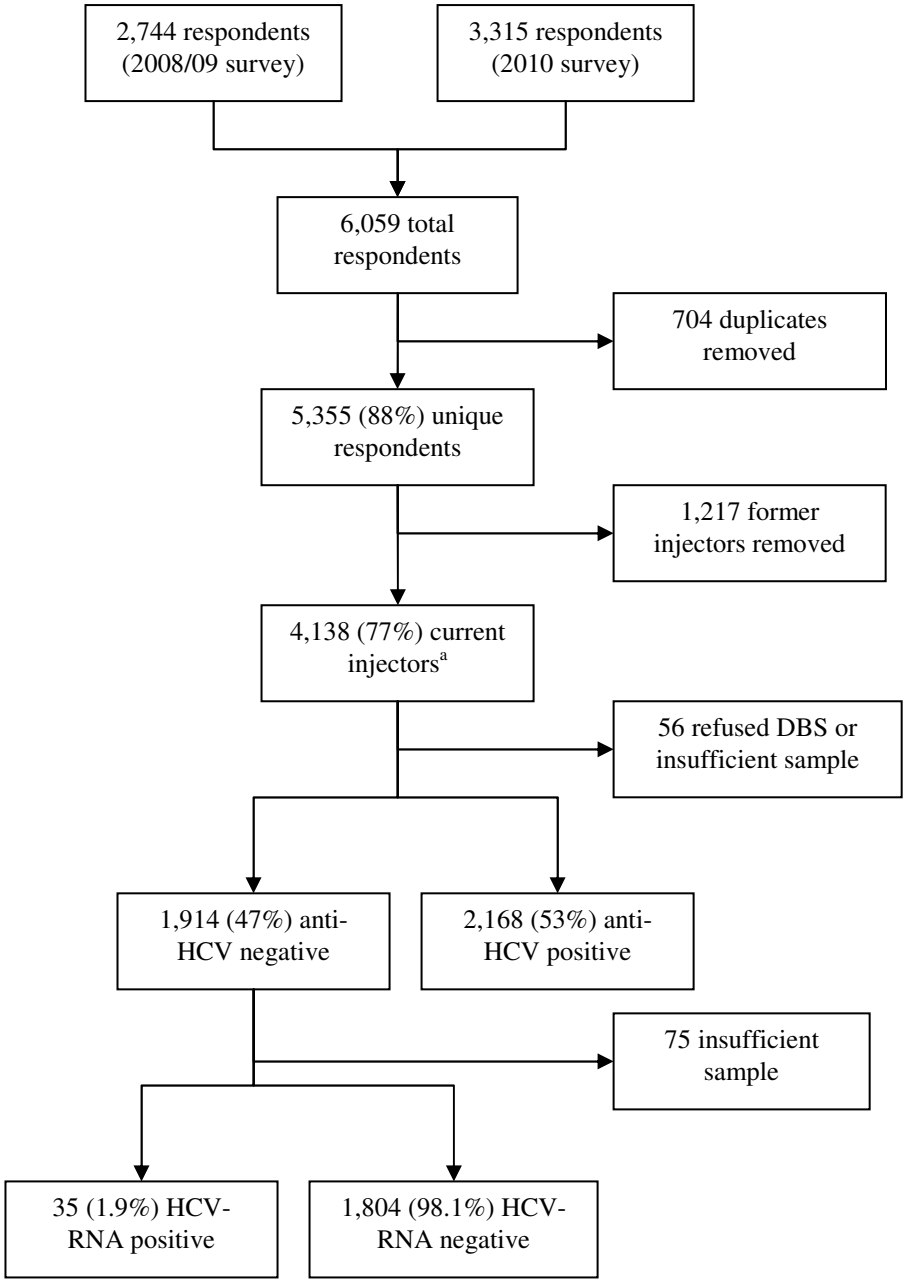


Figure 4-1. Flowchart of respondents in the 2008-09 and 2010 surveys of PWID recruited from IEP sites across Scotland and laboratory results of anti-HCV and HCV-RNA testing
[a]Injected in the last six months.

Figure 4-2. Venn diagram of overlap between self-reported sharing of needles/syringes and paraphernalia in the last six months among 1,821 anti-HCV negative PWID recruited from IEP sites in Scotland in 2008-09 and 2010 (excludes 18 missing responses)

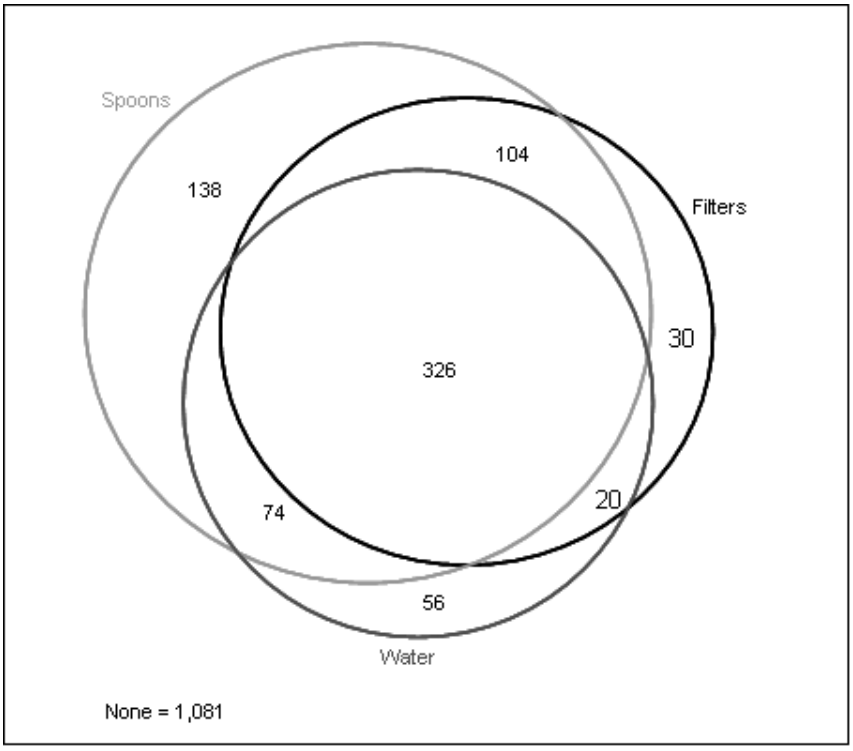


Figure 4-3. Venn diagram of overlap between self-reported sharing of paraphernalia items in the last six months among 1,829 anti-HCV negative PWID recruited from IEP sites in Scotland in 2008-09 and 2010 (excludes 10 missing responses)

Table 4-1. Characteristics of 1,820 anti-HCV negative PWID recruited from IEP sites in Scotland in 2008-09 and 2010, by self-reported sharing behaviour in the last six months

Characteristic	Categories	N	% who shared N/S (+/- paraphernalia)	% who shared paraphernalia only	% who did not share	p-value[a]
Survey year	2008-09	921	15%	34%	52%	<0.001
	2010	899	10%	26%	64%	
Gender (7 NR)	Male	1347	11%	28%	61%	<0.001
	Female	466	17%	34%	49%	
Age	Mean (SD)	1825	29.4 (6.9)	31.5 (7.0)	32.6 (6.8)	<0.001
Homeless in the last six months (2 NR)	No	1384	11%	27%	62%	<0.001
	Yes	434	18%	38%	44%	
Time since onset of injecting (5 NR)	<5 years	781	14%	33%	53%	0.001
	≥5 years	1034	11%	28%	61%	
Injected stimulants in the last six months	No	1610	12%	29%	60%	<0.001
	Yes	210	20%	38%	43%	
Frequency of injecting in last six months	<daily	786	8%	25%	67%	<0.001
	≥daily	1034	16%	33%	51%	
Excessive alcohol consumption (8 NR)[b]	No	1410	11%	29%	61%	<0.001
	Yes	402	18%	34%	47%	

NR: non-response; N/S: needle(s)/syringe(s); SD: standard deviation

[a]p-value for age was calculated using one-way ANOVA; p-values for all other variables were calculated using Chi-square test

[b]Refers to consumption in an average week during the last year where excessive is defined as >14 units/wk for women and >21 units/wk for men

Table 4-2. Logistic regression analyses of the association between sharing injecting equipment and recent HCV infection among anti-HCV negative PWID recruited from IEP sites in Scotland in 2008-09 and 2010

		No. anti-HCV negatives (N)	No. recent infections (n)	% (n/N)	Univariable			Multivariable[a]		
					OR	95% CI	p-value	AOR	95% CI	p-value
(a) Combined sharing variable (last six months)										
								(n=1,813)		
No sharing in last six months		1051	7	0.7	1			1		
Needles/syringes +/- paraphernalia		227	13	5.7	9.06	3.57-22.98	<0.001	6.65	2.58-17.13	<0.001
Paraphernalia only		542	14	2.6	3.96	1.59-9.86	0.003	2.95	1.16-7.48	0.023
(b) Individual sharing variables (restricted to those who did not report N/S sharing in last six months)										
								(n=1,594)		
Shared spoons in the last	No	1146	8	0.7	1			1		
six months	Yes	455	13	2.9	4.18	1.72-10.16	0.002	3.14	1.26-7.80	0.014
								(n=1,593)		
Shared filters in the last	No	1294	11	0.9	1			1		
six months	Yes	306	10	3.3	3.94	1.66-9.37	0.002	3.07	1.26-7.49	0.013
								(n=1,587)		
Shared water in the last	No	1290	15	1.2	1			1		
six months[b]	Yes	304	6	2.0	1.71	0.66-4.45	0.270	1.21	0.45-3.26	0.702

N/S: needle(s)/syringe(s)

[a]Adjusted for homelessness in last six months, stimulant injection in last six months and time since onset of injecting

[b]Refers to sharing water for flushing N/S or mixing with drugs

5 Measuring HCV incidence and determining the association between self-reported harm reduction intervention uptake and recent HCV infection

5.1 Introduction

The Scottish Government's Hepatitis C Action Plan for Scotland (section 1.5.1) recognised: (i) the need for augmentation of harm reduction interventions (principally IEP) to prevent HCV transmission and (ii) that monitoring of HCV transmission among PWID is essential to establish the impact of increases/changes in interventions. The monitoring of HCV among PWID in Scotland, and indeed in other countries, has often involved measuring the prevalence of anti-HCV – an indicator of past infection (Hutchinson et al., 2002; Roy et al., 2007b). Although examining long-term trends in HCV prevalence can inform on the effectiveness of interventions, measures of incidence of HCV are much more useful in determining short term impact. The traditional method of measuring incidence of HCV has been to establish seroconversion (i.e. development of antibodies to HCV) through follow-up and repeat testing of a cohort of individuals. This approach can, however, be logistically difficult (compared with other observational study designs) and suffers from attrition of participants over the course of follow-up, which can lead to bias (Mann, 2003).

In Scotland, the only study of HCV incidence applying a prospective approach was undertaken in a prison (Champion et al., 2004). A retrospective cohort approach, whereby the residual blood from PWID who had presented for at least two voluntary HIV tests was tested for anti-HCV, has also been applied (Roy et al., 2001). While the latter approach is relatively inexpensive and easy to undertake, disadvantages may include that: (i) the retrospective nature of the study is not useful if one is wanting to determine current incidence rates, (ii) the potentially long periods between last negative and first positive antibody test can make it difficult to estimate the exact date of seroconversion, (iii) many years of data can be required to generate a sufficient sample size and (iv) the sampling frame may not be representative of PWID at risk of HCV acquisition.

Another 'indirect' method of measuring HCV incidence that has been utilised in Scotland involved using, as a proxy for incidence, HCV prevalence among PWID who had recently commenced injecting. This approach assumes the date of seroconversion occurred midway

through their exposure period, which began at the commencement of injecting (Roy et al., 2007b). This approach also has obvious limitations, including the inaccuracy of the estimated date of seroconversion. It is also notable that all of the incidence estimates discussed here have been restricted to regional populations within Scotland (Roy et al., 2007b).

A measure of incident infection not only provides information about the rate of acquisition of new infections, but it is also essential for the evaluation of the effectiveness of interventions to prevent HCV. As determined in Chapter 2, the foremost harm reduction interventions – OST and IEP – have been shown to reduce self-reported IRB, but there was a dearth of evidence with respect to their impact on HCV transmission among PWID (at the time of undertaking this analysis) (Palmateer et al., 2010). As discussed in Chapter 2, rather than being an indication of the ineffectiveness of these interventions, the lack of evidence may result from limitations of the studies that had been conducted, such as employing ecological study designs and using crude measures of intervention uptake (for example, users vs. non-users of IEP services). Furthermore, few studies had measured the 'coverage' or intensity of interventions (e.g. the amount of injecting equipment distributed) (Lurie, 1997; Turner et al., 2011; Van Den Berg et al., 2007).

This chapter therefore aims to address the fourth and fifth thesis objectives, which are to measure the incidence of HCV and to determine the association between the (self-reported) uptake of harm reduction interventions and incident HCV infection among PWID in Scotland. The analyses in this chapter are based on a series of cross-sectional Scotland-wide surveys of PWID. At the time of conducting this analysis, it represented the first large-scale, national application of a novel method designed to determine incidence of HCV using a cross-sectional design (Hope et al., 2011; Page-Shafer et al., 2008).

5.2 Methods

5.2.1 Data collection and laboratory methods

The analysis in this chapter is based on data from NESI; the data collection and laboratory methods for the series of surveys have been described in greater detail in Chapter 4 (see sections 4.2.1 and 4.2.2).

5.2.2 Analysis

At the time of analysis, only the 2008-09 data were available and therefore this chapter relates to the analysis of this survey sweep. Chapter 6 presents an analysis of all three survey sweeps.

5.2.2.1 Outcome measure

The outcome of interest in this analysis is recent HCV infection. Recent infections were defined in Chapter 4 as individuals who were anti-HCV negative and HCV-RNA positive on DBS testing.

5.2.2.2 Intervention measures

The harm reduction interventions considered were IEP and OST. Although it will be referred to as OST, it should be noted that, for the purposes of the NESI study, this abbreviation designates methadone maintenance, which is the most commonly prescribed opioid substitute in Scotland. (In the 2008-09 NESI survey, methadone accounted for 97% of the respondents who reported receiving pharmacological treatment for opioid addiction in the last six months.)

Variables representing two types of IEP coverage were generated: needle/syringe coverage and injecting paraphernalia coverage were determined by dividing the reported number of obtained sterile needles/syringes and items of paraphernalia (i.e. spoons, filters or water ampoules), respectively, by the self-reported number of injecting events in the previous six months. The distribution of the latter variables was examined and, given a very large proportion of individuals who reported receiving at least one needle/syringe for every injection (i.e. 100% coverage), it was suspected that respondents may have over-reported the numbers of needles/syringes obtained. The threshold separating high and low needle/syringe coverage was therefore set at 200% (i.e. two needles/syringes for every injection).

Because the 2008-09 survey contained no questions to ascertain methadone dosage, individuals were simply categorised according to whether they were currently receiving OST, had received OST in the last six months (but were not currently receiving it), or had not received OST in the last six months.

A combined measure of intervention coverage was created with categories low, medium and high: the combinations of needle/syringe coverage and OST that were used to create these categories are listed in Box 5-1. Respondents who were not receiving OST and had not injected in the last six months were excluded.

Box 5-1. Categories of needle/syringe coverage and OST used to create combined intervention coverage

		Needle/syringe coverage		
		<200%	>=200%	Did not inject in last six months
OST	Currently	Medium (n=267)	High (n=275)	High (n=183)
	In the last six months (not currently)	Low (n=21)	Medium (n=12)	High (n=0)
	Not in the last six months	Low (n=218)	Medium (n=140)	Excluded (n=24)

5.2.2.3 Statistical analyses

5.2.2.3.1 Calculation of HCV incidence

A measure of incidence can be derived from the number of recent infections by multiplying them by a factor proportional to the duration of the window-period state (Hope et al., 2011; Page-Shafer et al., 2008). The following calculation was used to generate an estimate of incidence:

$$I = \frac{(365/T)n}{(N-n)+(365/T)n}$$

where I is the incidence, T is the estimated duration of the viraemic pre-seroconversion window period, n is the number of recent infections and N is the number of susceptibles (i.e. anti-HCV negative individuals) (Hope et al., 2011). Estimates of the duration of the pre-seroconversion window period (28 to 65 days) were obtained from the published literature. The window-period estimates used here were derived from the two largest studies (Glynn et al., 2005; Page-Shafer et al., 2008), as well as the only study of this kind involving PWID (Netski et al., 2005). These three studies presented different measures of spread of the window-period data: one presented a 95% CI, one presented an overall range and one presented a range capturing 75% of the data (Glynn et al., 2005; Netski et al., 2005; Page-Shafer et al., 2008). To be conservative, the smallest lower bound (28 days)

and the largest upper bound (65 days) were chosen from the latter reported ranges. Ninety-five percent CIs around the incidence estimates were not calculated as the uncertainty in the window period duration generated a wide range of potential values.

5.2.2.3.2 Association between harm reduction intervention uptake and recent HCV infection

Respondents who participated in the study more than once (duplicates) were identified in the database using initials, date of birth, gender and NHS Board of interview: either the first interview, or the interview with valid laboratory results, was retained for analysis. Out of a total of 2,749 respondents, 115 duplicates were identified (Figure 5-1). Anti-HCV weak reactives (representing only 2.7% of those with DBS results) were treated as anti-HCV positive.

Logistic regression was undertaken to examine associations between recent HCV infection and self-reported uptake of harm reduction interventions (OST and IEP). The reference group for comparison consisted of anti-HCV negative, HCV-RNA negative individuals. Associations between other variables and recent HCV infection were also explored. Univariable associations between each variable and recent infection were examined in turn. Multivariable models were subsequently built by including known or suspected confounders of the relationship between OST/IEP and recent HCV infection; IRB variables and injecting frequency variables were not considered because they are on the causal pathway. Where there was a theoretical reason to suspect potential effect modification between two variables, the presence of interactions was assessed by entering interaction terms into the model individually and examining the p-values (based on the Wald test), as well as the effect sizes when the analysis was stratified by the effect modifier. Additionally, sensitivity analyses were undertaken to assess the robustness of the final model(s) to: (i) the exclusion of unexpected results (incident infections who reported not injecting in the last six months) and (ii) restriction to current PWID (i.e. those who had injected in the last six months). All analyses were undertaken in SPSS version 14.

5.3 Results

A total of 2,629 respondents completed the questionnaire; comprising 63% of potentially eligible clients that were approached. Non-participants were slightly younger than participants (mean of 29 vs. 34 years); however, both participants and non-participants had the same gender distribution (72% male).

Among the 2,555 respondents who provided a sufficient DBS, 1,367 (54%) were anti-HCV positive (including weak reactives) (Figure 5-1). Twenty-four of the 1,140 anti-HCV negatives (with sufficient sample) were found to be positive for HCV-RNA. This generated incidence rate estimates ranging from 10.8 to 21.9 per 100 person-years, corresponding to viraemic pre-seroconversion window period estimates of 28 to 65 days.

In univariable analyses (Table 5-1), the following variables were found to be significantly associated with increased odds of recent HCV infection: homelessness in the last six months, imprisonment in the last six months and excessive alcohol consumption. The following factors were significantly associated with reduced odds of recent HCV infection: age >30 years, receipt of prescribed OST, ≥200% needle/syringe coverage (where sterile needles/syringes had been obtained from IEP services or from other people) and high coverage of combined interventions. Longer time since onset of injecting (≥5 years) was also associated with reduced risk and was marginally statistically significant (p=0.059).

Table 5-2 presents two alternative adjusted models: (i) with OST and IEP entered as separate variables in the model and (ii) with a combined measure of OST and IEP. In model (i), those who had ≥200% needle/syringe coverage had a nearly 70% reduction in odds of recent HCV (AOR 0.3, 95% CI 0.1-1.0), relative to those with <200% coverage, after adjustment for region, gender, homelessness, imprisonment, time since onset of injecting and excessive alcohol consumption. The results were also suggestive of reduction in risk among both those on OST currently and those not on OST in the last six months, relative to the baseline group of those who had been on OST in the last six months, although neither association was statistically significant.

In model (ii), the reduced risk of recent infection among those with high coverage, as compared with low coverage, observed in univariable analysis (OR 0.3, 95% CI 0.1-1.0) was no longer statistically significant after adjustment (AOR 0.5, 95% CI 0.2-1.5, p=0.203).

Suspected interactions between variables were investigated and there was some evidence that geographical region modifies the effect of OST. Table 5-3 shows the AORs for OST, stratified by region: in Greater Glasgow and Clyde there were marginally significant (p=0.055) reduced odds of recent HCV infection among those currently on OST, relative to those who had been prescribed OST in the last six months but not currently (AOR 0.04, 95% CI 0.001-1.1). This association was not seen in other Scottish regions.

Sensitivity analyses were undertaken to examine the robustness of the main effects model (Table 5-2, model (i)). The effect sizes were robust to the exclusion of those who had not injected in the last six months and the four incident infections who had not injected in the last six months. There was a loss of precision; however, this was expected because of the corresponding reduction in sample size.

5.4 Discussion

This analysis generated an estimated HCV incidence rate of 11 to 22 per 100 person-years in this population of Scottish PWID. This is higher than a recently reported incidence rate of 5.9 per 100 person-years among a cohort of PWID in Wales (Craine et al., 2009) but lower than rates (38 to 47 per 100 person-years) reported in England (Hope et al., 2011; Judd et al., 2005a). These variations may be attributable to differences in risk behaviour among regional injecting populations and/or study designs/recruitment approaches. Two of these studies employed prospective cohort designs (Craine et al., 2009; Judd et al., 2005a) and one recruited participants using respondent-driven sampling (RDS) (Hope et al., 2011). Notably, the RDS study may have overestimated HCV incidence due to detection of a transmission cluster; the authors note that exclusion of this cluster would result in an incidence rate of 18 to 25 per 100 person-years. Historically, regional incidence rate estimates among PWID in Scotland have ranged from 10 to 29 per 100 person-years (McDonald et al., 2012; Roy et al., 2007b). However, whereas the foregoing estimates were generally confined geographically, the estimate generated in this chapter applies to all of mainland Scotland.

A subset (Greater Glasgow and Clyde region) of the data presented here was included in a previous analysis that examined the effect of harm reduction interventions by pooling data from UK studies (Turner et al., 2011). Turner et al. demonstrated an independent effect of needle/syringe provision on incident HCV infection, a finding for which this analysis provides further evidence using data collected from across mainland Scotland. These studies are the first to observe a significant independent association between needle/syringe provision and recent HCV infection (European Centre for Disease Prevention and Control and European Monitoring Centre for Drugs and Drug Addiction, 2011a; Palmateer et al., 2010); possible reasons are likely to be the larger sample sizes (for example, in comparison with Van Den Berg et al. (2007)) and the use of more sensitive measures of exposure to needle/syringe provision. Because cross-sectional studies are generally cheaper and easier to undertake than prospective cohort studies, this analysis was

able to achieve a large sample size through the application of a method to determine incidence using a cross-sectional design. This analysis is also the first to look at sterile needles/syringes obtained from both IEP services and from other PWID, which may have further increased the sensitivity of this measure of exposure (because PWID who obtain sufficient sterile needles/syringes from others may have otherwise been misclassified as having low coverage and resulted in a dilution of the exposure-outcome association). This observation is an important finding that suggests secondary distribution may play a role in preventing HCV transmission (Bryant and Hopwood, 2009; Lenton, Bevan, and Lamond, 2006).

In contrast to Turner et al., the analysis in this chapter did not find a significant independent effect of OST, nor a significant combined intervention effect, when considering Scotland overall. This discrepancy could be a result of statistical power: although this analysis had a larger sample size than that in the Turner et al. paper (by approximately 200), there were fewer recent infections (24 vs. 40) than in the Turner et al. paper. Nevertheless, as demonstrated by Turner et al. and confirmed in this analysis (although a different measure of OST was used here), current OST was associated with reduced odds of recent HCV infection in the Greater Glasgow and Clyde region. The finding that the reduced odds of those currently receiving OST, when compared to those who had received OST in the last six months (but not currently), suggests that individuals coming off opioid substitution are at increased risk of HCV infection. This pattern was not seen in the other Scottish regions: regional variations in the effectiveness of OST may reflect differences in local delivery policies and practices. However, it is of note that the NESI study applies the same design and questionnaire across all areas, whereas the Turner et al. study pooled data from studies which employed a mixture of different designs (RDS, cohort, cross-sectional) and questionnaires.

No significant associations between the provision of filters or spoons and recent HCV infection were found: again, this lack of association is possibly attributable to insufficient statistical power. Additionally, this analysis was undertaken prior to the substantial changes in IEP services associated with the Hepatitis C Action Plan in Scotland, one of which was an approximately five-fold increase in the provision of filters and spoons between 2008/09 and 2009/10 (Information Services Division, 2011).

Non-intervention variables that were found to be associated with recent HCV infection in these analyses (age, homelessness, imprisonment) are also consistent with previous studies

(Champion et al., 2004; Craine et al., 2009; Maher et al., 2006; Thorpe et al., 2002). There are no studies that have found an association between alcohol consumption and recent/incident HCV infection; however, previous studies have suggested a link between alcohol consumption and injecting risk behavior (Arasteh and Des Jarlais, 2009; Sander et al., 2010; Vidal-Trecan et al., 1998). The finding that those with shorter injecting histories (<5 years) had a higher odds of recent HCV infection, suggests that interventions targeted at new initiates to injecting may be important in reducing HCV incidence.

The analysis presented in this chapter has a number of limitations. First, it was not specifically designed to examine OST as an intervention. The 2008-09 NESI survey did not collect information on methadone dosage from participants and, furthermore, methadone dosage remains a problematic measure of methadone coverage since an 'adequate' dosage can vary greatly from person to person.

Secondly, selection bias, which has been well documented in other studies of IEP programmes (Lurie, 1997; Palmateer et al., 2010), may be present here. Because recruitment was from sites that provide sterile injecting equipment (some of which will also dispense OST) rather than dedicated drug treatment sites, the NESI study is more likely to have sampled individuals who were receiving both OST and needles/syringes. The NESI survey will also have oversampled those on OST who continue to inject, since the proportion of non-current injectors (i.e. had not injected in the last six months) was confined to 25% of the sample. The survey may thus have been more likely to sample individuals receiving inadequate methadone dosages, because such individuals are likely getting injecting equipment in order to 'top up' with heroin; measures of OST effectiveness may therefore be underestimated. Recruitment at solely IEP sites may also bias the sample away from high risk injectors who are not in contact with services. Previous community-wide surveys undertaken in Glasgow showed that 90% of PWID recruited from street sites had visited IEP services in the past six months (Taylor et al., 2000); however, exclusion of individuals not in contact with services may still lead to underestimation of the impact of interventions.

Four recent infections among those who reported not injecting in the last six months were detected. Two of these four individuals reported receiving an HCV-positive result from a previous test. Possible reasons for this discrepancy could be false positive PCR results or false negative anti-HCV results. It is also plausible that the respondents were dishonest or incorrectly recalled their behaviour; however, other risk factors cannot be discounted, such

as tattooing, about which no information was collected in the questionnaire. Self-reported risk behaviour among PWID may be subject to social desirability or recall biases; however, it is unlikely to differ systematically between those who received/did not receive interventions or those with/without the outcome of interest. Respondents may have overestimated self-reported uptake of clean needles/syringes but the effect of this overestimation is likely to be non-differential. Thus, the 200% threshold is not meaningful in itself, except as an indicator of those with a higher ratio of clean needles/syringes to injections. However, it is recognised that the appropriate ratio of sterile needles/syringes to injections is important for policy-makers and injecting equipment providers, and therefore further work is required to elucidate this ratio.

The approach to calculating incidence applied in this analysis is heavily dependent on accurate estimation of the duration of the pre-seroconversion window period, around which there is uncertainty (Glynn et al., 2005; Netski et al., 2005; Page-Shafer et al., 2008). Intervention uptake in the six months prior to interview was examined: because this time frame is longer than the upper estimates of the duration of the window period, this may contribute to some inaccuracy in the results.

As stated in section 4.4, the laboratory test to detect antibodies to HCV on DBSs has been validated and has very high sensitivity and specificity (99% and 100%, respectively) (Judd et al., 2003); the respective values for the PCR test on DBSs are 100% and 96% (Bennett et al., 2012). Recent infections could have been missed if the sample was taken during a 'dip' – a phase of undetectable viral load during a period of fluctuating viraemia that is observed, in some individuals, in the acute phase of HCV infection (Thomson, Smith, and Klenerman, 2011). Conversely, a small proportion of the recent infections might have been false positives. There is also a chance that chronic infections could have been misclassified as recent infections in the case of immunosuppressed individuals (for example, those infected with HIV (Thomson et al., 2009), who may have delayed seroconversion). Given the low HIV prevalence in the Scottish injecting population (Health Protection Scotland and University of the West of Scotland, 2008), this type of misclassification is unlikely to be a significant factor; however, other lifestyle factors may contribute to immunosuppression, including the use of opiates themselves (Vallejo, de Leon-Casasola, and Benyamin, 2004).

In conclusion, this analysis utilised a method of generating incidence using a cross-sectional design and demonstrated that high coverage of needles/syringes is associated

with a reduction in recent HCV infection among PWID in Scotland. Despite the large sample size, statistical power was nevertheless an issue, given that only 24 recent infections were detected among a sample of more than 1100 anti-HCV-negatives. Additional sweeps of this survey will increase the cumulative sample size (and therefore power to detect associations) and allow the examination of the impact of the increase in interventions delivered by the Hepatitis C Action Plan for Scotland.

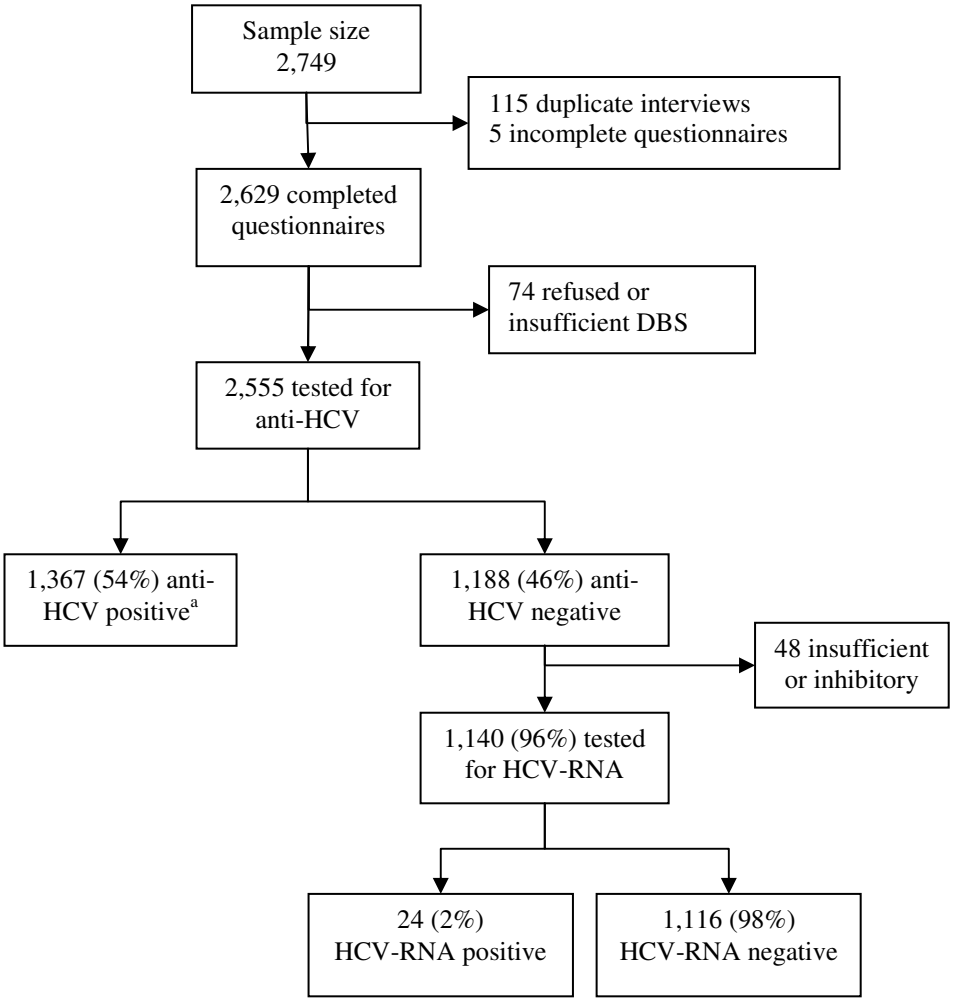


Figure 5-1. Flowchart of respondents in the 2008-09 survey of PWID recruited from IEP sites across Scotland and laboratory results of anti-HCV and HCV-RNA testing
[a]Includes anti-HCV weak reactives

Table 5-1. Descriptive characteristics of 1,140 anti-HCV negative PWID recruited from IEP sites across Scotland in 2008-09 and univariable logistic regression analyses of associations with recent HCV infection

Characteristic	Categories	No. anti-HCV negatives (N)	No. recent infections[a] (n)	% (n/N)	Univariable OR	95% CI	p-value
Gender (5 NR)	Male	835	17	2.0	1		
	Female	300	7	2.3	1.15	0.47-2.80	0.759
Age	16-30	573	17	3.0	1		
	>30	567	7	1.2	0.41	0.17-0.99	0.048
Region	Greater Glasgow and Clyde	294	5	1.7	1		
	Elsewhere	846	19	2.2	1.33	0.49-3.59	0.576
Homeless in last six months	No	886	10	1.1	1		
	Yes	254	14	5.5	5.11	2.24-11.65	<0.001
Prison	Never	641	9	1.4	1		
(2 NR)	In the last six months	142	6	4.2	3.10	1.09-8.85	0.035
	In the past but not last six months	355	9	2.5	1.83	0.72-4.64	0.206
Excessive alcohol consumption	No	863	11	1.3	1		
(last 12 months)[b] (6 NR)	Yes	271	13	4.8	3.90	1.73-8.82	0.001
Time since onset of injecting	<5 years	447	14	3.1	1		
(2 NR)	≥5 years	691	10	1.4	0.45	0.20-1.03	0.059
Stimulant injection in last six	No	1008	19	1.9	1		
months	Yes	132	5	3.8	2.05	0.75-5.58	0.161
Received OST	In the last six months (not currently)	33	3	9.1	1		
	Currently	725	13	1.8	0.18	0.05-0.68	0.011
	Not in the last six months	382	8	2.1	0.21	0.05-0.85	0.028
N/S coverage[c,d]	<200%	506	16	3.2	1		
	≥200%	427	4	0.9	0.29	0.10-0.87	0.028
Combined intervention coverage	Low	239	9	3.8	1		
(N/S and OST)[c,e]	Medium	419	8	1.9	0.50	0.19-1.31	0.157
	High	458	6	1.3	0.34	0.12-0.97	0.043
Filter coverage[c,d]	<200%	804	19	2.4	1		
	≥200%	129	1	0.8	0.35	0.05-2.65	0.307
Spoon coverage[c,d]	<200%	811	19	2.3	1		
	≥200%	122	1	0.8	0.36	0.05-2.70	0.318

NR: non-response; N/S: needle(s)/syringe(s)
[a]Anti-HCV negative and HCV-RNA positive individuals
[b]As defined by UK Royal College of Physicians: >14 units/week for women and >21 units/week for men
[c]See methods for definitions of coverage
[d]Among individuals who reported injecting in the last six months
[e]Excludes 24 respondents who reported not injecting and not receiving OST in last six months

Table 5-2. Multivariable logistic regression models examining the association between recent HCV infection and (i) OST and needle/syringe coverage as separate variables and (ii) combined OST and needle/syringe coverage among anti-HCV negative PWID recruited from IEP sites across Scotland in 2008-09

			Univariable			Multivariable[a]		
			OR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**
						(n=1,131)		
Model (i)	Received OST	In the last six months	1			1		
		Currently	0.18	0.05-0.68	0.011	0.29	0.07-1.19	0.086
		Not in the last six months	0.21	0.05-0.85	0.028	0.28	0.06-1.22	0.089
	N/S coverage[b]	<200%	1			1		
		≥200%	0.29	0.10-0.87	0.028	0.32	0.10-1.00	0.050
		Did not inject	0.60	0.20-1.83	0.372	1.30	0.38-4.43	0.674
						(n=1,107)		
Model (ii)	Combined intervention coverage (N/S coverage and OST)[b]	Low	1			1		
		Medium	0.50	0.19-1.31	0.157	0.50	0.18-1.35	0.170
		High	0.34	0.12-0.97	0.043	0.48	0.16-1.48	0.203

N/S: needle(s)/syringe(s)
[a]Adjusted for region, gender, homelessness, imprisonment, time since onset of injecting and excessive alcohol consumption
[b]See methods for definitions of coverage

Table 5-3. Adjusted ORs for the association between interventions and recent HCV infection among anti-HCV negative PWID recruited from IEP sites across Scotland in 2008-09, stratified by effect modifying variables (n=1,131)

						Multivariable[a]		
			N	Recent HCV (n)	Recent HCV (%)	AOR	95% CI	p-value
Prescribed OST stratified by Scottish region	GG&C	Last six months	9	2	22.2	1		
		Currently	205	1	0.5	0.04	0.001-1.07	0.055
		Not in the last six months	77	2	2.6	0.16	0.01-2.55	0.193
	Other Scottish regions	Last six months	24	1	4.2	1		
		Currently	515	12	2.3	0.73	0.08-6.64	0.777
		Not in the last six months	301	6	2.0	0.59	0.06-5.67	0.647

GG&C: Greater Glasgow and Clyde

[a]Adjusted for gender, homelessness, imprisonment, time since onset of injecting and excessive alcohol consumption

6 Scale-up of sterile injecting equipment and opioid substitution treatment among people who inject drugs in Scotland: evidence of impact on HCV transmission

6.1 Introduction

The review of the literature described in Chapter 2 highlighted that there is insufficient evidence demonstrating the effectiveness of certain harm reduction interventions – particularly IEP – on HCV transmission among PWID (Palmateer et al., 2010). This review was updated in 2011 (see section 2.4.1) and, although some of the evidence statements were strengthened in light of additional evidence, there was nonetheless only tentative evidence – at most – for the effectiveness of any of the interventions in preventing HCV transmission (Macarthur et al., 2014). These reviews also highlighted emerging evidence of a potentially synergistic impact of combined interventions, in that the combined effect may be greater than the impact of any of the interventions alone. Few studies have, however, examined the impact of combined harm reduction interventions (Turner et al., 2011; Van Den Berg et al., 2007) – including the analysis in Chapter 5 (Allen et al., 2012) – and there remains a need to strengthen understanding of the effectiveness of OST and IEP, to inform public health policy (Smith-Spangler and Asch, 2012; Vickerman et al., 2012). Furthermore, previous studies of the impact of IEP on HCV incidence have focused solely on sterile needle/syringe provision; no studies to date have directly examined the impact of providing injecting paraphernalia (primarily spoons and filters) in the prevention of HCV transmission (Gillies et al., 2010).

The analysis in Chapter 5 found a significant association between sterile needle/syringe coverage and recent infection, but did not demonstrate an association with the other interventions (OST or paraphernalia). The absence of an association may have resulted from a lack of statistical power. The latter analysis utilised data from the first sweep (2008-09) in a series of national cross-sectional surveys of PWID. This chapter examines the results of all three survey sweeps (2008-09, 2010 and 2011-12), presenting two advantages. First, these data allow the examination of trends in uptake of harm reduction interventions, risk behaviour and HCV incidence contemporaneous with a period of major service development in Scotland. Secondly, the pooling of these surveys helps to resolve sample size issues and generates the largest sample to have explored HCV transmission in relation to the combined effects of IEP and OST.

6.2 Methods

In addressing the thesis objectives of determining HCV incidence and determining the association between uptake of harm reduction interventions and HCV transmission, this chapter builds on, and is informed by, the analysis in Chapter 5. Section 6.2.2.1 describes how these two approaches differ.

6.2.1 Data collection and laboratory methods

The data collection and laboratory methods for the NESI study have been described in detail in Chapter 4 (see sections 4.2.1 and 4.2.2). Briefly, PWID were recruited at sites that provide sterile injecting equipment (and usually other harm reduction interventions, such as methadone) across mainland Scotland in three cross-sectional surveys undertaken in 2008-09, 2010 and 2011-12. People who had injected drugs in the past were eligible to participate, although the majority of participants were currently injecting (defined as having injected in the last six months). Individuals who consented to participate were asked to complete an interviewer-administered questionnaire and to provide a blood spot for laboratory testing for HCV markers.

In addition to data from the NESI study, data on the provision of OST and IEP in Scotland were collated from routine reports published in the grey literature (Information Services Division, 2012b; Information Services Division, 2013; Public Health England et al., 2013).

6.2.2 Analysis

The hierarchy of epidemiological study designs in relation to the investigation of public health interventions was discussed in section 1.8. The difficulties in undertaking what would traditionally be considered ‘robust’ study designs to evaluate such interventions have been well documented. Indeed, the review of reviews (Chapter 2) found that most study designs that have been undertaken to investigate the impact of harm reduction interventions were non-randomised, with the exception of a few RCTs investigating OST. It is perhaps, then, unsurprising that a randomised evaluation of the impact of the scale-up of harm reduction interventions in Scotland was not feasible. Nevertheless, some common themes that have emerged from evaluations of public health interventions, in relation to causal attribution, are the need to understand processes/theories of change and the combination of evidence generated from different non-experimental study designs. The analytical approach applied in this chapter borrows from these themes.

First, drawing on the theme of theories of change, an analytical framework was produced to guide the analysis (Figure 6-1). Strictly speaking, a theory of change or process evaluation for these interventions might go even further back than provision, perhaps seeking to understand exactly how each of the elements of the National Needle Exchange Guidelines were implemented in the NHS Boards. For example, training of needle exchange staff, if well implemented, might influence uptake of interventions and risk behaviour of clients. It was not possible to undertake such an evaluation for the purposes of this thesis; however, this framework nevertheless highlights the comprehensive approach being taken here, given that previous analyses of the impact of NSP and OST have generally focussed on one or two associations (Turner et al., 2011; Van Den Berg et al., 2007). The objective here was to describe each of the elements of the framework, as well as the relationships between them, in order to build an overall picture of the potential mechanisms between provision of interventions and HCV transmission. The framework is divided into interventions (boxes 1 to 3), intermediate determinants (boxes 4 to 9), outcome (box 10) and relationships (represented by letters A to M). The sources of evidence to populate the framework are indicated in Table 6-1: unless otherwise indicated, most of the evidence was derived from analysis of NESI data, described further below. All of the information was collated and summarised in a table, as a means of capturing the evidence for the framework.

Secondly, in relation to combining evidence from different study designs, the approach taken here is similar to that proposed by Kirkwood et al. (1997), who advocate the use of three comparisons: (i) the pre- vs. post-intervention comparison, (ii) the intervention vs. control comparison and (iii) the (post-intervention) adopters vs. non-adopters comparison. The major difference here, as compared to the analyses of the association between harm reduction interventions and recent HCV in Chapter 5, is obviously the addition of two survey sweeps. This serial aspect permits the examination of time trends in the data and therefore enables a pre- vs. post-intervention comparison (henceforth referred to as an ‘ecological’ or ‘group-level’ analysis). It was not possible to generate an intervention vs. control comparison; however, an adopters vs. non-adopters comparison was undertaken on the pooled data from all three surveys (henceforth referred to as the ‘individual-level’ analysis).

6.2.2.1 Outcome measure

As previously described, recent infections were defined as individuals in the 'viraemic pre-seroconversion window period', i.e. individuals who were anti-HCV negative and positive for HCV-RNA. Incidence was derived using the same formula applied in Chapter 5. The formula generates a rate per person-years of time and will be referred to as the 'derived' HCV incidence throughout this chapter. In Chapter 5, the uncertainty range surrounding the derived HCV incidence was generated by using the lower and upper pre-seroconversion window period bounds reported in the literature. In this chapter, one of these estimates of the duration of the window period (mean 51 days) (Page-Shafer et al., 2008), and its variance (56 days), was applied. Ninety-five percent CIs for the incidence rates were generated by: (i) sampling 1,000 values from each of the binomial and normal distributions relating to the number of recent infections and the window period, respectively; (ii) using the sampled values from (i) in the formula to generate a distribution for the incidence rates; and (iii) taking the 2.5th and 97.5th percentile values from (ii) to generate the lower and upper confidence limits. This process was undertaken for each survey year using R (2.8.1) statistical software.

In order to validate the derived HCV incidence estimates, HCV prevalence among those who commenced injecting within the last 12 months was also examined, based on the assumption that HCV infection will have been acquired since initiation of injecting.

6.2.2.2 Intervention measures

Variables categorising participants into high and low 'coverage' of each injecting equipment item were created by dividing the self-reported number of items (needles/syringes, spoons, filters, or water ampoules) obtained in the last six months, by the self-reported number of injections undertaken in the last six months. The threshold for high coverage (≥200%) was chosen as described in Chapter 5. Further work was also done to examine the association between needle/syringe coverage and recent HCV infection. With the additional sample size afforded by the pooled dataset (2008 to 2012), it was possible to calculate the odds of recent HCV infection for a large number of needle/syringe coverage groups: the findings from this approach provided further support for the choice of 200% as the threshold (results presented in Appendix F).

The spoon and filter coverage variables were further combined into a single variable called paraphernalia coverage, such that those who reported high coverage of both spoons and

filters were classified as having high paraphernalia coverage, with the remaining falling into the low category. Water coverage was not considered in this chapter since self-reported sharing of water (for mixing with drugs or rinsing needles/syringes) was not found to be associated with recent HCV infection in the analyses of NESI data described in Chapter 4.

Participants were also categorised by whether they reported being on OST at the time of the survey (yes or no). These categories were different from the categories chosen in Chapter 5, but ensured a more even distribution of the sample across the categories. (The categories in Chapter 5 involved using the 'in the last six months but not currently' group as the comparator; however, there were only 84 people in this group[5].) A simplified measure of OST was therefore preferable for increasing power when stratifying by additional variables and for combining OST with other interventions. Those who reported not injecting in the last six months and no uptake of any interventions were excluded from the analyses (n=157, 2.2% of the pooled sample).

For the purposes of comparing trends over time at the group-level, an additional coverage measure was calculated by dividing published numbers of injecting equipment items distributed (Information Services Division, 2013) by estimates of the total number of injections annually among Scottish PWID (the latter generated by multiplying the estimated mean annual number of injections per PWID from NESI by estimates of the size of the injecting population (Overstall et al., 2014)).

6.2.2.3 Group-level and ecological analysis

Ecological analysis refers to the derivation of conclusions regarding the association between interventions and outcomes that occur contemporaneously, where the unit of analysis is the population rather than the individual (Coggon, Rose, and Barker, 2009). Here, the ecological analysis simply involved examining the group-level statistics and considering the plausibility of associations between them. For the associations between provision and uptake of interventions (relationships A, B and C in Figure 6-1), only ecological analysis is possible since provision, as measured here, is a group-level variable.

[5] The analyses in Chapter 5 were re-run on the pooled (2008 to 2012) dataset (see Appendix G): the updated multivariable analysis produced very similar effect sizes and essentially resolved the issue of lack of power, as evidenced by reduced p-values.

Group-level refers to the statistics (proportions or means) that describe the interventions, intermediate determinants and outcomes (i.e. the boxes in Figure 6-1), and any changes therein. The following were compared across the three surveys: (i) harm reduction intervention uptake, (ii) risk behaviour, (iii) HCV prevalence and (iv) HCV incidence. Statistical significance was assessed using either the Mantel-Haenszel test for trend (called the linear-by-linear association in SPSS output) for categorical variables or analysis of variance (ANOVA) for continuous variables. In the ecological analyses, 'adequate' coverage was defined as at least one sterile item per injection (i.e. ≥100%). With regard to risk behaviour, 'sharing' was defined as the use of an item of injecting equipment after it had previously been used by someone else.

Respondents who had participated multiple times (duplicates) were identified using forename and surname initials, date of birth, gender and NHS Board of interview. The first interview was retained for analysis, unless more complete laboratory results were available from a subsequent interview. Duplicates were identified from within each survey (i.e. only individuals who participated more than once in a given survey were removed). There were 115 (1.4%), 147 (1.8%) and 40 (0.5%) duplicates identified within the 2008-09, 2010 and 2011-12 surveys, respectively.

6.2.2.4 Individual-level analysis

Individual-level analysis refers to the derivation of the associations between interventions and outcomes at the individual level, i.e. the intervention and outcome pair is known for each individual in the study sample. Analysis was conducted on the pooled dataset generated from combining the three surveys. Duplicates were identified using the criteria described above, except that individuals who participated more than once across the entire period, 2008 to 2012, were removed. Out of a total of 8,253 questionnaires, 5,966 (72%) were from individuals who participated only once across the period, with the remaining 2,287 questionnaires corresponding to 1,022 individuals who had participated two or more times. As described above, the first interview was retained for analysis unless more complete laboratory results were available from a subsequent interview, leading to the exclusion of 1,265 (15%) out of the 8,253 questionnaires. However, given that this approach would generally result in the exclusion of more interviews undertaken in the later surveys (131 in 2008-09 as compared with 587 in 2010 and 547 in 2011-12), sensitivity analyses were undertaken to examine the effect of preferentially including interviews from the latter years (see section 6.2.2.5 for details of sensitivity analyses).

Logistic regression was used to investigate the associations D through M (Figure 6-1). Univariable analyses were undertaken to explore the associations between the dependent and independent variables in each relationship of interest (i.e. the respective associations between intervention uptake and risk behaviour, between risk behaviour and HCV and between intervention uptake and HCV). Confounding variables that were considered included survey year, gender, age, homelessness and stimulant injection (in the last six months), time since onset of injecting, imprisonment (ever) and alcohol consumption (last 12 months). The general approach to model-building involved inclusion of the independent, dependent and all potential confounding variables in a model and subsequently removing confounding variables on the basis of having the largest p-value of the Wald statistic, until a model with only statistically significant variables was reached. Where it was felt that a variable should be included irrespective of statistical significance – for example, survey year – that variable was forced into the model(s). Logistic regression analyses were undertaken in SPSS version 21.

For the investigation of the association between intervention uptake and HCV, five multivariable models were built to examine the association with recent HCV of (self-reported): (i) needle/syringe coverage, (ii) paraphernalia coverage, (iii) OST, (iv) needle/syringe coverage and OST and (v) all three interventions combined. Weighted versions of the models were subsequently run in Stata version 9. Sampling weights (pweights in Stata) were set to be equal to the number of times that a respondent reported injecting in the six months prior to interview. Thus, observations from individuals who reported injecting more times counted more heavily in the analysis than those who reported injecting fewer times. All sampling weights were increased by one, such that individuals who reported not injecting in the last six months would be included in the analysis (with a weight equal to one).

6.2.2.5 Sensitivity analysis

A sensitivity analysis was undertaken to examine the effect of varying several parameters in the multivariable model examining combined needle/syringe coverage, paraphernalia coverage and OST (model (v) above). The aspects of the model that were varied were: (i) inclusion of continuous rather than categorical confounding variables or vice versa (for survey year and time since onset of injecting) and (ii) use of different criteria for the identification of duplicates (i.e. where a respondent participated multiples times across the surveys, the last interview was included).

6.2.2.6 New infections and infections averted

The number of new chronic HCV infections was estimated for each calendar year from 2008 to 2012 by combining the derived incidence rates with published estimates of the size of the PWID population (Overstall et al., 2014), estimates of anti-HCV prevalence from NESI and published estimates of the proportion of HCV-infected individuals who develop chronic infection (Micallef, Kaldor, and Dore, 2006). It was assumed that the size of the PWID population remained stable during this period. The method for generating a distribution of values for the incidence rates was described above. Additionally, posterior distributions for (i) the size of the PWID population, (ii) the proportion anti-HCV negative and (iii) the proportion that develop chronic infection, were generated. One thousand values were sampled from each of these distributions. The sampled values for the number of PWID were multiplied by those for the proportion anti-HCV negative, to generate a distribution for the number of susceptible PWID (i.e. number of anti-HCV negatives). The latter were then multiplied by the sampled incidence values and the sampled values for the proportion developing chronic infection, to generate a distribution (and 95% CIs, as also described above) for the number of new chronic HCV infections. An estimate of the number of HCV infections (all and chronic) potentially averted by harm reduction interventions over the period from 2008 to 2012 was calculated by subtracting the sum total of the calculated yearly estimates from that which would have been observed assuming the number of infections in 2008 had remained constant.

6.3 Results

Table 6-2 summarises the demographic characteristics of the study population by survey sweep. More than 2,000 participants were recruited in each sweep. Nearly three quarters of the sample were male and this proportion was consistent across the surveys. Significant differences in several variables were noted between the surveys: mean age increased from 33.6 in 2008-09 to 35.3 in 2011-12 ($p<0.001$), as did mean time since onset of injecting, with respective figures of 10.5 and 11.6 years ($p<0.001$). The proportion of respondents who reported homelessness in the last six months decreased slightly from 27% to 22% ($p<0.001$), as did the proportion who reported injecting stimulants (23% to 15%, $p<0.001$).

A summary of the evidence for each of the elements of the framework is provided in Table 6-3, and discussed in more detail below.

6.3.1 Group-level analysis

The major changes in provision of interventions (boxes 1, 2 and 3 in Figure 6-1) that took place over the period of study were increases in the provision of filters and spoons by six-fold and four-fold, respectively, between 2008/09 and 2009/10 financial years (Table 6-4). By contrast, provision of needles/syringes remained approximately stable over the period, hovering at around 4.7 million distributed annually, albeit with minor relative fluctuations. The number of methadone prescriptions dispensed in Scotland increased only slightly up until 2010/11 and then declined by 4% in 2011/12.

With regard to harm reduction intervention uptake (boxes 4 to 6 in Figure 6-1), the proportion who reported currently receiving OST increased from 50% to 64% ($p<0.001$) between 2008-09 and 2011-12 (Table 6-5). Despite the slight decline in the median number of sterile needles/syringes obtained (based on self-reported survey data), the proportion of individuals with adequate needle/syringe coverage was more or less stable (ranging from 75% to 79%) because of simultaneous declines in the frequency of injecting. The proportion of individuals with adequate coverage of filters and spoons increased between 2008-09 and 2011-12 (from 24% to 69% and from 20% to 70%, respectively, both $p<0.001$). Using the measure of IEP coverage based on service provision data, the proportion with adequate needle/syringe, filter and spoon coverage increased from 53% to 74%, 4% to 40% and 6% to 39%, respectively. These changes were mostly attributable to declines in the frequency of injecting.

The proportion of respondents reporting various risk behaviours in the last six months declined across the surveys (Table 6-5): injecting daily or more frequently (from 63% to 49%, $p<0.001$), sharing needles/syringes (from 15% to 8%, $p<0.001$), reusing one's own needles/syringes (64% to 45%, $p<0.001$), sharing spoons (42% to 20%, $p<0.001$), sharing filters (33% to 17%, $p<0.001$) and sharing water (31% to 21%, $p<0.001$).

The results of laboratory analysis of DBS samples are presented in Table 6-6. Across all the surveys, a total of 53 recent infections were detected among 3,459 susceptible (i.e. anti-HCV negative) individuals. The prevalence of anti-HCV ranged from 53% to 56% but did not differ significantly across the surveys. The proportion with recent HCV infection decreased from 2.1% (95% CI 1.4%-3.1%) in 2008-09 to 0.9% (95% CI 0.4%-1.7%) in 2011-12 (X^2 test for trend: $p=0.02$). The derived incidence rates per 100 person-years (among PWID, current) reduced from 13.6 (95% CI 8.1-20.1) in 2008-09, to 7.3 (3.0-12.9)

in 2011-12. HCV prevalence rates among those who commenced injecting within the last year were comparable to the derived incidence rates for the respective years (Figure 6-2), declining from 20.1% (95% CI 13.9%-27.6%) in 2008-09 to 8.2% (95% CI 3.4%-16.2%) (p=0.030).

6.3.2 Individual-level analysis

The individual-level associations between uptake of the interventions and IRB (relationships D, E and F) are presented in Tables 6-7, 6-8 and 6-9 and summarised in Table 6-3: high coverage (≥200%) of needles/syringes, spoons and filters was significantly associated with approximately 55%, 35% and 20% reductions, respectively, in the odds of having shared these items in the last six months. Currently being on OST was associated with a nearly 80% reduction in the odds of injecting daily or more frequently in the last six months (Table 6-10).

With regard to the associations between sharing injecting equipment and recent HCV infection (relationships H and I), in Chapter 4 the odds of recent HCV infection were estimated to be seven-fold and three-fold for sharing needles/syringes and sharing paraphernalia in the last six months, respectively, as compared with no sharing. The analysis of the association between frequency of injecting and recent HCV infection (relationship J) is presented in Table 6-11: it was not statistically significant after adjustment for potential confounders (AOR 1.45, 95% CI 0.80-2.63, p=0.218). Because this association is an indirect one, i.e. the effect of injecting frequency on HCV transmission is mediated through sharing injecting equipment, the associations between frequency of injecting and sharing injecting equipment were also examined. This analysis showed that the risk of sharing either needles/syringes, spoons or filters was three times higher among those who injected daily or more frequently than among those who did not (Tables 6-12 to 6-14).

Table 6-15 presents the univariable and multivariable analyses of the associations between uptake of harm reduction interventions and recent HCV infection (relationships K, L and M in Figure 6-1). The full models, including covariates, are included in Appendix H. The findings indicated that individuals with high needle/syringe or high paraphernalia coverage had lower proportions of recent HCV infection (0.9% and 0.7%, respectively) as compared with those on low coverage of these interventions (2.4% and 2.0%, respectively). Individuals on OST at the time of survey had a lower proportion recently infected (1.3%)

as compared with those not on OST (2.5%). The effect of the weighting was generally to amplify the differences in incidence between the high and low coverage groups.

In multivariable unweighted analyses, both high needle/syringe and paraphernalia coverage were associated with reduced risk of recent HCV (AOR 0.39, 95% CI 0.19-0.83, p=0.014 and AOR 0.39, 95% CI 0.14-1.12, p=0.081, respectively) relative to those with low coverage. In weighted analyses, both AORs moved farther away from null (weighted adjusted odds ratio [AOR_w] 0.14, 95% CI 0.04-0.48, p=0.002 for needle/syringe coverage and AOR_w 0.11, 95% CI 0.03-0.44, p=0.002 for paraphernalia coverage). Current OST, alone, was not statistically associated with recent infection in either unweighted or weighted analyses (AOR 0.63, 95% CI 0.35-1.12; and AOR_w 0.52, 95% CI 0.23-1.18, respectively).

Model (iv) examined the combined effects of needle/syringe coverage and OST. With the exception of those who did not inject in the last six months (the last category), there was a general downward gradient in incidence with increasing coverage of interventions, and this trend was more apparent in the weighted incidence. In the unweighted analyses, those with high needle/syringe coverage had significantly lower odds of recent infection, whether also on OST or not (AOR 0.28, 95% CI 0.08-0.96 and AOR 0.29, 95% CI 0.11-0.74). This pattern was also true for the weighted analyses, although there was a slight difference between the effect sizes, with those on high needle/syringe coverage and current OST exhibiting a greater reduction in risk (AOR_w 0.05, 95% CI 0.01-0.18) as compared to those on high needle/syringe coverage and no OST (AOR_w 0.18, 95% CI 0.04-0.87).

Model (v) further stratifies the results by intervention uptake. Figure 6-3 presents the unweighted and weighted proportions recently infected with HCV for the different strata. As above, a general downward trend in incidence with increasing coverage is seen, which is more pronounced in the weighted data. The highest incidence of HCV (3.5% unweighted and 3.9% weighted) was among the baseline group of those on the lowest coverage of all three interventions.

Among PWID with low coverage of both needles/syringes and paraphernalia, the results were suggestive of a reduction in risk of approximately 40% for those on current OST (this can be also seen by the difference in the height of the two left-hand bars in Figures 6-3a and 6-3b); although, as before, it was not statistically significant after adjustment for covariates (AOR 0.55, 95% CI 0.27-1.11; AOR_w 0.58, 95% CI 0.25-1.34). There were no

recent infections in the 'low needle/syringe, high para' groups, due to very small numbers (approximately 50 in both groups combined), and therefore it was not possible to calculate ORs for these groups (and they are excluded from Figure 6-3 and Table 6-15). Moving from low to high needle/syringe coverage was associated with lower HCV incidence, although the larger difference was seen among those not on OST (3.5% to 1.0% unweighted; 3.9% to 0.8% weighted) as compared to those on OST (1.7% to 0.9% unweighted; 2.0% to 0.1% weighted).

In unweighted analyses, those who were on the highest coverage of interventions (high coverage of needles/syringes, high coverage of paraphernalia and current OST) had significantly lower odds of recent infection relative to those on the lowest coverage of interventions (AOR 0.28, 95% CI 0.08-0.097, p=0.044). This effect size was not, however, substantially different from the group on high needle/syringe coverage and current OST, but low paraphernalia coverage (AOR 0.28, 95% CI 0.08-0.98, p=0.046). In weighted analyses, those who had high needle/syringe coverage and were on OST, regardless of paraphernalia coverage, had significantly lower odds of recent HCV (AOR_w 0.02, 95% CI 0.01-0.09 and AOR_w 0.07, 95% CI 0.01-0.35 for those with low and high paraphernalia coverage, respectively). Similar to the unweighted analyses, there was no appreciable difference in magnitude between the latter two effect sizes, or between the effect sizes for those in the 'high needle/syringe, low para, no OST' group vs. the 'high needle/syringe, high para, no OST' group; this can also been seen from Figure 6-3b.

6.3.3 Sensitivity analysis

The results of the sensitivity analysis are shown in Table 6-16, and demonstrate that the combined multivariable (unweighted) model is relatively robust with respect to variation in the use of continuous or categorical variables for survey year and time since onset of injecting. Varying the criteria for defining duplicate records changed the effect sizes marginally, as well as the p-values.

6.3.4 New infections and infections averted

The estimated number of new infections per year declined from 1063 (95% CI 591-1682) in 2008 to 566 (95% CI 205-1039) in 2012 (Table 6-17). With regard to new chronic infections, these have potentially declined from 787 (95% CI 441-1248) in 2008 to 419 (95% CI 152-774) in 2012. It is estimated that approximately 1,400 new infections and 1,000 new chronic infections may have been averted during 2008-2012.

6.4 Discussion

In this analysis of data from a series of cross-sectional studies undertaken during a period of major developments in harm reduction services in Scotland, a decline in HCV incidence among Scottish PWID was observed. This finding is corroborated by a similar trend observed in prevalence of HCV among recent initiates to injecting, which can be considered a proxy for incidence. Several factors are likely to have contributed to the declining incidence of HCV: determining the contributions of individual interventions is the challenge.

This analysis applied a framework approach in order to bring together evidence for all of the steps and relationships on the pathways from interventions to outcome. Considering first the ecological/group-level analysis: with regard to the provision of interventions, it would appear that the largest change was the increase in distribution of filters and spoons. The contemporaneous increase in the self-reported uptake of filters and spoons over the three surveys (both numbers of items and coverage) would appear to reflect this change in provision. Furthermore, the increases in uptake of paraphernalia were mirrored by significant declines in the self-reported sharing of these items over the period, as would be expected.

By contrast, the finding of a decline in the self-reported numbers of sterile needles/syringes obtained by individuals is apparently inconsistent with the relatively stable numbers of needles/syringes distributed, as reported in national service-level data. Stratifying the data by NHS Board reveals that this downward movement is mainly restricted to the Greater Glasgow and Clyde NHS Board, but is reflected in the overall results because of the large proportion of the overall sample constituted by this NHS Board (~45%). Rather than indicating a real decline in the numbers of needles/syringes obtained per individual, this observation could be a result of differences in the sampling frame in Greater Glasgow and Clyde – for logistic reasons, different recruitment sites were used in 2008-09 as compared with the subsequent surveys.

A further discrepancy lies between the numbers of needles/syringes and paraphernalia: while the self-reported data indicate that the uptake of paraphernalia is approximately the same as that of needles/syringes, the provision data show that the numbers of spoons and filters distributed annually remain substantially lower than the numbers of needles/syringes distributed. A potential explanation is that the NESI study population is biased toward

including individuals with a higher uptake of paraphernalia. This explanation is plausible because, again, such a large proportion of the study sample was recruited in Greater Glasgow and Clyde, where the service-level data do, in fact, indicate that spoons and filters are distributed in approximately equal quantities to needles/syringes (Information Services Division, 2013). Consequently, the proportion reporting high paraphernalia uptake in the NESI surveys may be an overestimate, but the observation of an upward trend is nevertheless valid.

Interestingly, the decrease in self-reported numbers of needles/syringes obtained by respondents is mirrored by a decline in the frequency of injecting, such that the proportion of PWID reporting high needle/syringe coverage across the three surveys remained more or less stable. This observation suggests that the finding of a lower self-reported uptake of sterile needles/syringes is perhaps explained by a lower need for them. By contrast, the alternative measure of coverage (based on needle/syringe provision figures) showed an increase from approximately half to three quarters of PWID with adequate coverage. Given that this measure was based on stable numbers of needles/syringes distributed, it was again the declining frequency of injecting that caused the change (from a mean of approximately 550 injections per PWID down to 400 in 2011-12). The observed reduction in reported needle/syringe-sharing is perhaps more consistent with increasing needle/syringe coverage. Otherwise, the decline in sharing might be explained by a potential improvement in the quantity/quality of education that is being provided during injecting equipment transactions, as recommended in the national guidelines (Scottish Government, 2010), leading to a greater awareness of the risks of injection. Thus, if PWID have usually been obtaining sufficient needles/syringes for their injections but not using all of them, coverage could feasibly stay the same while sharing goes down. A similar enigma was observed for water: self-reported sharing of water declined despite distribution of sterile water ampoules not having greatly increased.

The increase in self-reported uptake of OST among survey participants also occurred contemporaneously with more or less stable dispensation of methadone prescriptions. Speculatively, if the PWID population had decreased, this might explain how stable levels of prescriptions could translate into an increase in the uptake of OST. The increased uptake of OST was further mirrored by a decrease in the self-reported frequency of injecting across the three surveys.

From an ecological perspective, there is thus a situation whereby data on the provision of interventions, uptake of interventions and corresponding risk behaviour usually, but not always, paint a consistent picture. So, while ecological analyses can give an overview of trends, they generally do not provide insight into the relationships and, moreover, can highlight discrepancies in the findings that need to be further investigated using individual-level analyses.

The crux of the individual-level analyses was the examination of the associations between self-reported uptake of interventions and recent HCV, with the analysis of the other relationships on the pathway providing explanatory context. In the results of the unweighted multivariable analyses for the three interventions independently, both needle/syringe and paraphernalia coverage were associated with reduced risk of recent HCV infection, although these models were not adjusted for the other respective interventions. Notably, these associations represent risks per individual, and individuals may have injected few or many times. Several of the associations that were not statistically significant in unweighted analyses became significant in weighted analyses, and indeed many of the effect sizes also changed, indicating that the frequency of injecting of individuals in particular intervention/outcome groups is potentially obscuring some of the intervention impact in the unweighted models. For example, the AOR for high needle/syringe coverage reduced from 0.39 to 0.14; the reason for this reduction was that those with low needle/syringe coverage – in particular, the incident infections – reported injecting more frequently, whereas those with high needle/syringe coverage – also the incident infections in particular – reported injecting less frequently. The weighting therefore had the effect of amplifying the difference in the proportion of recent infections between the low and high coverage groups, moving the effect size further from null.

No significant association between uptake of OST, alone, and recent HCV was observed, in either unweighted or weighted analyses. It is possible that there was insufficient power to detect an effect – given that OST coverage is so high in this study population, the smaller sample in the lower coverage group reduces power, particularly when stratifying for other factors. A further consideration is that the association between OST and HCV is an indirect one, since OST affects frequency of injecting, which is not in itself a mode of HCV transmission (as is sharing needles/syringes). The theory is that higher OST uptake should reduce HCV risk, by reducing the frequency of injecting and, consequently, the probability of sharing injecting equipment. These analyses confirmed that OST was associated with a reduced frequency of injecting, and that lower frequency of injecting was

associated with less sharing of all types of equipment. From the unadjusted proportions with recent infection, it appeared that OST had a larger effect among those on low coverage of needles/syringes and paraphernalia, which would be expected, given that the impact of injecting frequency on HCV transmission would be augmented if insufficient sterile equipment was being used.

Despite there being no effect of OST alone, it was associated with recent HCV in combination with needles/syringes: being on OST and having high coverage of needles/syringes were associated with a greater reduction in risk of recent HCV (in weighted analyses, a 95% reduction in risk) as compared with either of the separate intervention effects, although the analysis was underpowered to demonstrate that the combined effect was statistically different from either independent effect.

In the combined interventions model stratified for paraphernalia, there was little difference in effect size between the groups with low and high paraphernalia coverage when the other interventions were kept the same, indicating that the association between paraphernalia coverage and HCV is likely confounded by needle/syringe coverage. The lack of association between paraphernalia coverage and recent HCV might be explained by relationships between the intermediate determinants on the pathways between interventions and HCV: the individual-level analysis found that uptake of paraphernalia is associated with a lower reduction in sharing as compared with uptake of needles/syringes (i.e. although PWID are obtaining paraphernalia from services, they are not using all of it). This finding is consistent with the observation from the group-level analyses that sharing of spoons and filters still remains higher than that of needles/syringes, despite coverage of spoons/filters having potentially reached the same level as needle/syringe coverage. For example, evidence suggests that residual drug can be retained in the filter after injecting (Keijzer and Imbert, 2011), thereby potentially encouraging their reuse even when sterile ones are available.

Further down the pathway, the evidence presented here suggests that there is potentially a lower risk (per individual) of HCV transmission associated with sharing paraphernalia (as compared with the risk associated with sharing needles/syringes), such that a reduction in sharing paraphernalia might have less of an effect on transmission as compared to a reduction in needle/syringe-sharing. Thus, these two elements – the weaker association between paraphernalia-uptake and paraphernalia-sharing, and the weaker association between paraphernalia-sharing and HCV transmission – may act to ‘dilute’ the association

between paraphernalia-uptake and recent HCV. In other words, providing sterile needles/syringes is likely more efficient in preventing HCV transmission than providing sterile paraphernalia.

The findings regarding paraphernalia coverage do not necessarily mean that providing paraphernalia is ineffective with regard to preventing HCV transmission. To evaluate the impact of sterile paraphernalia, one would ideally compare the incidence rates between high and low paraphernalia coverage groups solely among those with low needle/syringe coverage. This comparison was not possible here because there were too few people in these groups, as a result of the fact that uptake of paraphernalia generally goes hand-in-hand with uptake of needles/syringes. It is possible that these analyses are underpowered to detect an effect and that pooling further sweeps of NESI would enable this comparison with a larger sample size. A further consideration is that, for sharing paraphernalia to pose a risk of HCV transmission, it must first become contaminated with blood from a used needle/syringe. Thus, the risk from sharing paraphernalia is dependent on the rates of reuse or sharing of needles/syringes, both of which have declined over the period of study. Regardless, there have been no harms from distributing paraphernalia and, furthermore, sterile paraphernalia may have had an impact with regard to preventing bacterial infections: that sharing rates have gone down indicates that the injecting hygiene message is reaching PWID. If the rates of needle/syringe-sharing or reuse in Scotland were to rise, the availability of sterile paraphernalia might become more critical in preventing HCV transmission.

6.4.1 Comparability of these results with other published findings

Scotland is one of few countries in the world to have a surveillance system, with national coverage, that generates serial measures of HCV incidence. While one-off studies have been done to measure incidence in regional populations of PWID in the UK (Craine et al., 2009; Hope et al., 2011; Judd et al., 2005a), it is not known whether the decline in HCV incidence observed here has been replicated elsewhere in the UK. Internationally, others have reported reductions in HCV incidence among PWID; however, these reductions have tended to be over very long periods of time (often decades), restricted to regional populations, involving smaller sample sizes than the sample size used in this chapter and/or involving lower coverage of interventions as compared with Scotland (Iversen et al., 2013; van den Berg et al., 2007). Furthermore, it is notable that the declines in HCV observed elsewhere occurred within the context of major shifts away from heroin and/or injecting

(de Vos et al., 2013; Iversen et al., 2013). Although this analysis observed a reduction in frequency of injecting (related to increased prescribed methadone), Scotland continues to have a large heroin-injecting population. Thus, other countries with persistent injecting populations can draw inferences on the potential impact of high coverage IEP and OST from these findings.

The findings presented here regarding OST are in contrast to other reports in the literature, which have found a significant association between OST uptake and HCV. In a synthesis of UK data, Turner et al. (2011) found that receiving OST was associated with an approximately 60% reduction in odds of incident HCV (AOR 0.41, 95% CI 0.21–0.82). However, another meta-analysis of studies of OST and HCV incidence found a broadly similar result to the findings of this analysis, with a pooled RR of 0.60 (95% CI 0.35-1.03) (Hagan, Pouget, and Des Jarlais, 2011).

Turner et al. also found that high needle/syringe coverage was associated with a reduced risk of recent HCV (AOR 0.48, 95% CI 0.25–0.93). This finding was very similar to the adjusted (unweighted) effect size reported in this analysis of 0.39 (95% CI 0.19-0.83). In contrast, the effect size for needles/syringes calculated by Hagan, Pouget, and Des Jarlais (2011) actually suggested an increased risk (pooled RR 1.62, 9% CI 1.04-2.52), as they found only one study (of a total of seven) that demonstrated a reduction in risk of HCV associated with needle/syringe use.

Finally, Turner et al. determined that ‘full’ harm reduction (i.e. on OST plus high needle/syringe coverage) reduced the odds of new HCV infection by nearly 80% (AOR 0.21, 95% CI 0.08–0.52), which is similar to the (unweighted) AOR for combined coverage of 0.29 (95% CI 0.11-0.74) derived in this chapter. Hagan, Pouget, and Des Jarlais (2011) derived a similar effect size of 0.25 (95% CI 0.07-0.83) for combined interventions, although this pooled RR was based on the meta-analysis of only two studies.

6.4.2 Strengths and limitations

Whereas most analyses take either an ecological or an individual-level approach, this analysis has attempted to consider both types of evidence in conjunction. Constructing a coherent narrative from the ecological data can be a puzzle in itself – particularly when trying to reconcile data from different sources, such as service provision and selected population samples. The limitations of drawing inferences solely from ecological analysis

are also apparent from this analysis: for example, one might assume – given the observed declines in all three types of risk behaviour (needle/syringe-sharing, paraphernalia-sharing and frequency of injecting) – that all three interventions played a significant role in contributing to the reduction in HCV incidence. On the other hand, considering just the individual-level evidence does not give an overview of trends in provision, uptake, risk behaviour and HCV incidence. Although these types of evidence will never provide the same level of confidence, with regard to a causal association between intervention(s) and outcome, as an RCT, the triangulation of evidence generated by different study designs is understood to increase confidence (Kirkwood et al., 1997).

The difficulty with conducting ecological analyses is that that there is little certainty when attributing the changes in outcome to the intervention(s). Other contemporaneous interventions or factors could potentially have been responsible for some of the observed changes. In this study, the individual analyses provide validation for some of these associations. For example, that the uptake of interventions is associated with reduced risk behaviour at the individual-level, means one can therefore be more confident that the changes in risk behaviour observed across the surveys were a result of the provision of the interventions. There are nevertheless factors that were outwith the scope of these analyses that could have had an impact on HCV incidence; for example, HCV antiviral treatment. The number of PWID aged under 30 years (those who are most likely to be injecting) initiated onto HCV treatment has doubled from around 50 to 100 per year over the Action Plan period (Sharon Hutchinson, Glasgow Caledonian University, personal communication). Despite this increase, treatment rates remain low in this population group (in the order of 6 per 1,000 PWID annually, assuming a population of 16,000 active PWID) and so treatment, alone, is unlikely to account fully for the reduced HCV incidence. However, the potential impact of HCV treatment has been demonstrated in mathematical models (Martin et al., 2011; Martin et al., 2013a) and it is possible that, in combination with IEP and OST, it contributed to the reduction in HCV transmission observed here.

Selection bias is an issue that always needs to be considered in non-randomised studies. The NESI studies recruited participants at services that provide sterile injecting equipment (and often dispense methadone as well); this approach may have excluded ‘high risk’ PWID who are not in contact with services. This potential exclusion might have resulted in an underestimate of HCV incidence (if one assumes that those not using services are at greater risk of HCV infection) and an underestimate of intervention impact (if one assumes

those not using services would have contributed to the group with recent infection and low coverage of interventions and thereby strengthened the effect size). However, a decline in incidence among those using services is nevertheless an important finding in itself, and is indicative that these services are having an impact among service users. There is also the issue of the comparability of the consecutive NESI surveys. While an attempt was made to maximise consistency in recruitment across surveys, it was not always possible to recruit from the same services year-on-year for logistical reasons.

There are indications that the PWID population in Scotland is an ageing cohort: an increase in the average age and time since onset of injecting has been observed in the study sample over the years. One could postulate that older PWID are less likely to engage in risk behaviour and that this may explain some of the downward trends in risk behaviour and incidence. However, it is unlikely that the ageing population alone would be sufficient to explain the sharpness of the downward trends observed, and furthermore the finding of a declining prevalence among those who had commenced injecting within the previous year provides evidence that this decline in HCV is also occurring among newer PWID.

One of the strengths of this analysis is the large sample size that was obtained by pooling data from three surveys. However, one result of large sample sizes is that relatively small changes can become statistically significant, as was the case with some of the variables examined in the group-level analyses. Nevertheless, despite the large sample size, only just over 50 recent infections were detected in the pooled analysis: thus, the opposite problem was the case with the individual-level analyses. The lack of statistical significance in some cases – particularly when examining interventions classified into multiple strata – may have been a result of lack of power. In a scenario of declining HCV incidence, increasingly large sample sizes will be required to detect increasingly small numbers of recent infections.

The derived incidence estimates are reliant on an accurate figure for the duration of the pre-seroconversion window period, around which there is uncertainty (Glynn et al., 2005; Netski et al., 2005; Page-Shafer et al., 2008). This analysis will not have captured persons who had recently seroconverted at the time of interview; however, the incidence calculation used here takes this underestimation into account. The incidence estimates could nevertheless be underestimates, as re-infections would not have been detected: people who had already been infected in the past would have anti-HCV and would be classed as prevalent infections in this analysis. This may affect the individual-level

analysis, but the general trends observed in the group-level analyses are still valid, as one would expect any underestimation to apply equally to each survey year. The other issues in relation to potential misclassification of the outcome were described in the discussion sections of Chapters 4 and 5, and also apply here (false HCV-RNA positives, fluctuating viraemia during acute HCV infection and delayed seroconversion among immunocompromised individuals).

In relation to OST, one of the limitations of this study is that it is not specifically designed to measure the impact of this intervention. Questions on methadone dosage have not been asked consistently across the survey years, and therefore it was not possible to examine the association between dosage and recent HCV; moreover, dosage itself is a problematic measure, as what constitutes an adequate dosage can vary greatly from person to person. At the provision level, the absence of available data on persons receiving methadone mixture meant that numbers of methadone mixture prescriptions were presented instead: these could be misleading because a single prescription can indicate that a single dose or multiple doses are to be dispensed at a given visit. However, assuming that prescribing practices have not changed drastically over the period of study, then the observed upward trend is still likely to be valid.

Finally, the self-reported nature of the risk behaviours and uptake of harm reduction interventions is a limitation. While the self-reported data likely contains an element of inaccuracy because of difficulty with respondents' ability to recall events, the consistency of the associations between self-reported behaviour and biological markers (both HCV prevalence and incidence) is high, lending credence to the validity of the data.

6.5 Conclusions

These data provide evidence of a downward trend in HCV incidence among PWID in Scotland. The two different approaches used in this analysis strengthen the inference that the changes in HCV incidence are attributable to harm reduction interventions – particularly high coverage of needles/syringes and OST combined. There is currently insufficient evidence to conclude that the increase in provision of paraphernalia contributed significantly to the decline in HCV incidence. Future monitoring of PWID will be required to establish whether the downward direction in HCV transmission among PWID in Scotland is sustained.

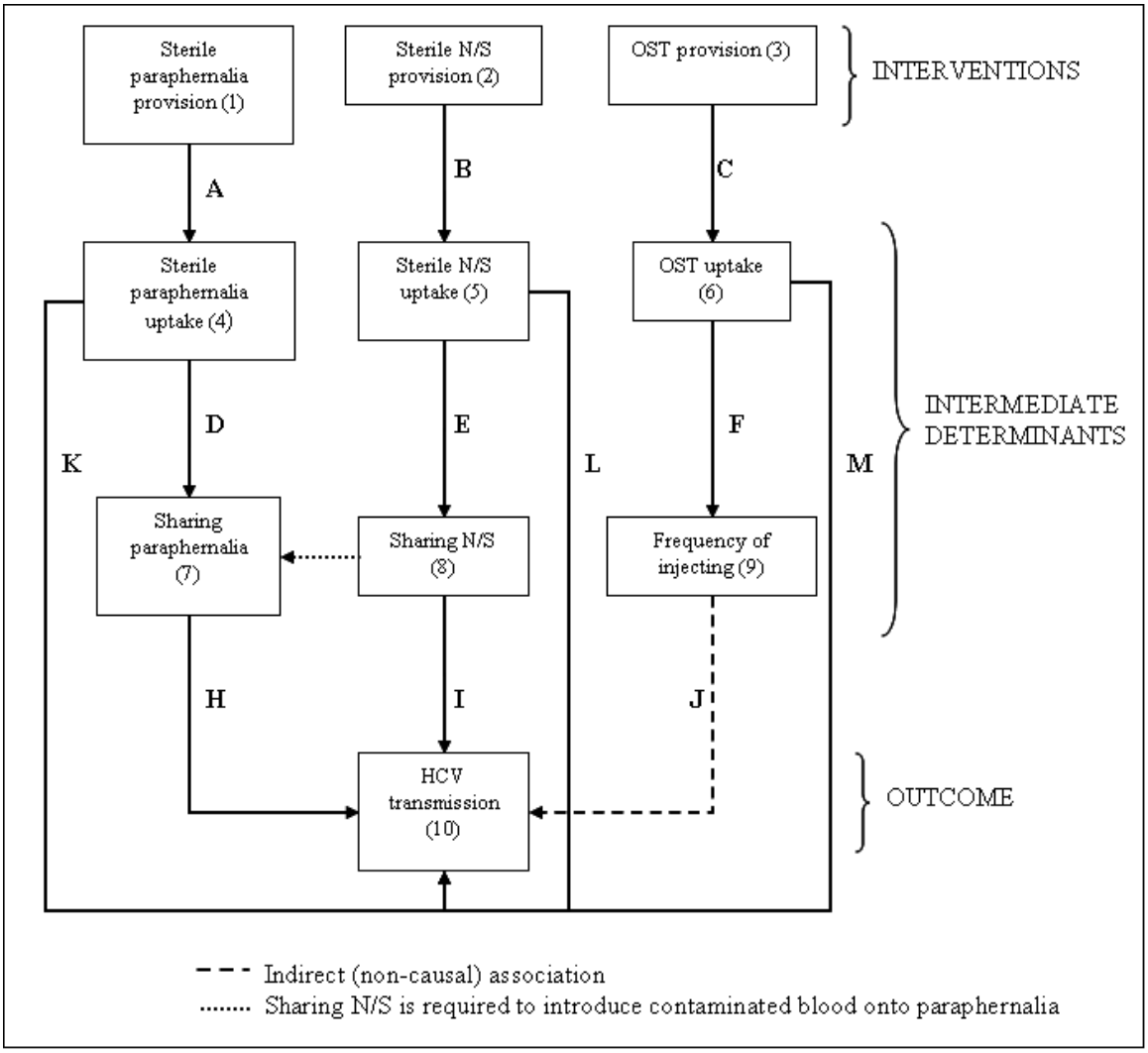


Figure 6-1. Analytical framework of potential associations between harm reduction interventions and HCV transmission

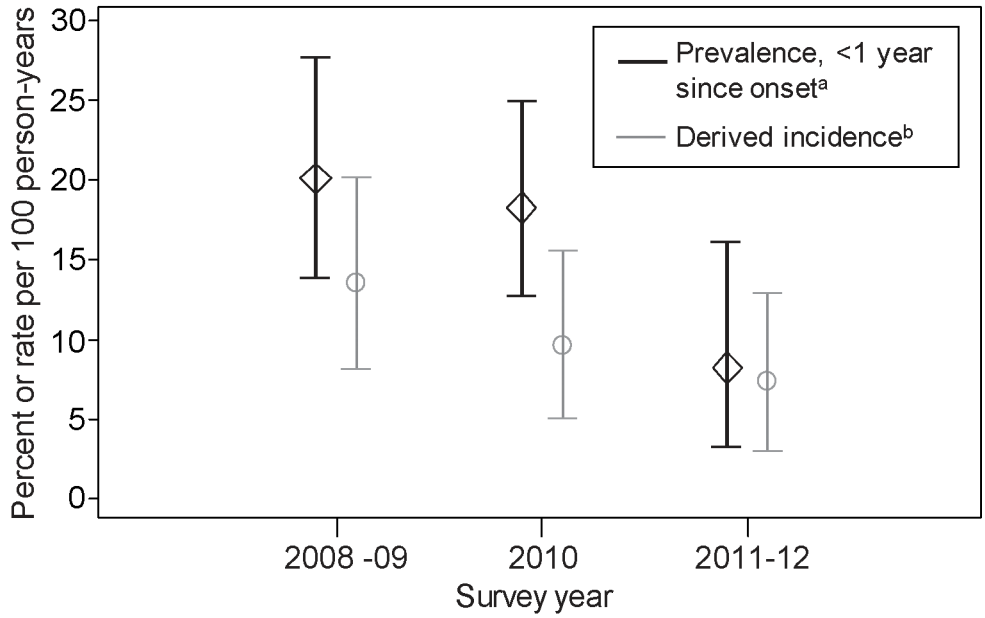


Figure 6-2. Prevalence (among recent onset injectors) and derived incidence of HCV among PWID recruited at IEP sites across Scotland, by survey
The diamonds/circles represent the point estimates and the bars represent the upper and lower 95% CIs.
[a]anti-HCV prevalence among those who commenced injecting within the past 12 months
[b]Determined by applying the estimated pre-seroconversion window period durations to the observed number of anti-HCV negative and HCV-RNA positive individuals (see methods for details)

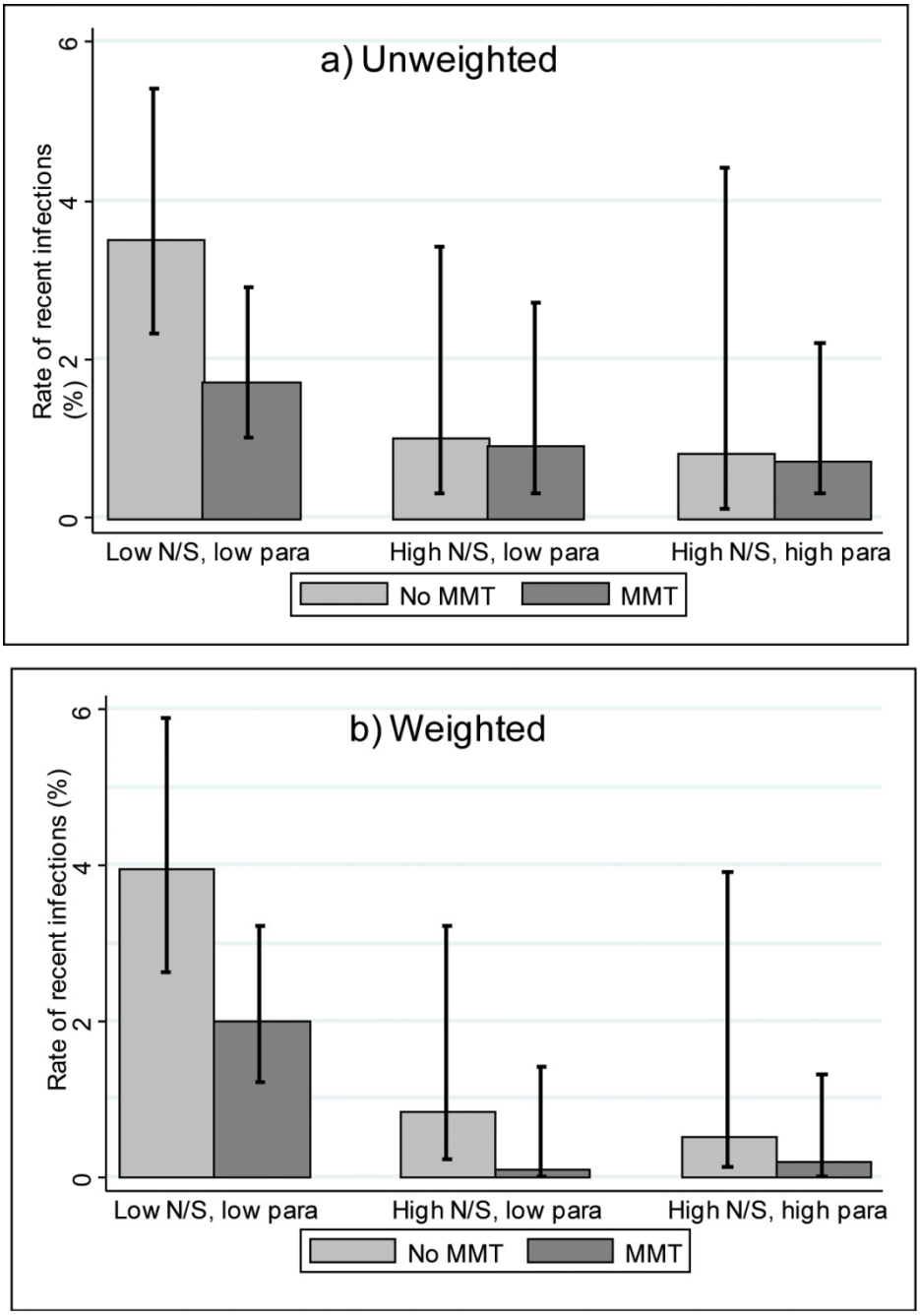


Figure 6-3. (a) Unweighted and (b) weighted proportions of PWID with markers of recent HCV infection, by harm reduction intervention coverage, using pooled data from surveys of PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12
95% CIs are indicated by the black bars.

Table 6-1. Sources of evidence to populate the analytical framework

Item	Reference to Fig.1	Source
Changes in provision of interventions	Boxes 1, 2, 3	Information Services Division Scotland (ISD) reports (Information Services Division, 2012b; Information Services Division, 2013)
Changes in uptake of interventions	Boxes 4, 5, 6	NESI data (group-level analysis)
Changes in injecting risk behaviour	Boxes 7, 8, 9	NESI data (group-level analysis)
Changes in outcome	Box 10	NESI data (group-level analysis)
Associations between provision and uptake of interventions	Relationships A, B, C	Ecological analysis of ISD reports and NESI data (group-level)
Associations between uptake of interventions and risk behaviour	Relationships D, E, F	NESI data (individual-level analysis of pooled data)[a]
Associations between risk behaviour and outcome	Relationships H, I, J	NESI data (individual-level analysis of pooled data); and evidence generated in Chapter 4 using NESI data [a]
Associations between uptake of interventions and outcome	Relationships K, L, M	NESI data (individual-level analysis of pooled data) [a]

[a]Where pooled data refer to the dataset generated by combining the 2008-09, 2010 and 2011-12 survey data

Table 6-2. Demographic and other characteristics of PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12, by survey

	2008-09 (N=2,629)	**2010 (N=3,168)**	**2011-12 (N=2,154)**	**X^2 test (trend) or ANOVA**	**p-value**
Male gender	72%	72%	73%	0.086	0.770
Mean age in years (SD)	33.6 (7.1)	34.6 (7.3)	35.3 (6.9)	F=35.465	<0.001
Aged <25 years	14%	12%	9%	37.000	<0.001
Homeless in last six months	27%	22%	22%	21.370	<0.001
Injected stimulants in last six months[a]	23%	13%	15%	45.416	<0.001
Ever in prison	59%	61%	61%	2.213	0.137
Excessive alcohol consumption[b] (last 12 months)	27%	24%	26%	0.572	0.449
Mean time since onset of injecting in years (SD)	10.5 (7.4)	11.2 (7.7)	11.6 (7.4)	F=15.247	<0.001
Commenced injecting within the last five years	26%	24%	21%	11.970	0.001

[a]Among those who reported injecting in the last six months
[b]Defined as >14 units/week for women and >21 units/week for men

Table 6-3. Summary of evidence for the analytical framework

Type of evidence	Category	Reference to Fig.6-1	Description	Needles/syringes	OST	Paraphernalia
Group-level	Intervention	1, 2, 3	Changes in provision of intervention over time	Minor fluctuations but relatively stable number of N/S distributed at approximately 4.7 million annually (Table 6-4)	More or less stable, if very slight increase, in number of methadone mixture prescriptions dispensed (Table 6-4)	Several-fold increase in number of spoons and filters distributed, up to approximately 2.5 million each annually (Table 6-4)
	Intermediate determinant	4, 5, 6	Changes in uptake of intervention over time	Decline in self-reported uptake of N/S but, given the concurrent declines in frequency of injecting, this translates into either a relatively stable or increasing proportion of PWID with adequate (≥100%) N/S coverage, depending on which measure of coverage is used (Table 6-5)	Increase in those reporting currently being on OST (Table 6-5)	Increase in reported numbers of spoons and filters obtained, as well as increase in reported proportion with high filter and spoon coverage – reaching almost equal coverage to that of N/S (Table 6-5)
	Intermediate determinant	7, 8, 9	Changes in risk behaviour over time	Reduction in proportion who reported sharing N/S in last six months (Table 6-5)	Decline in the proportion that reported injecting daily or more frequently in the last six months (Table 6-5)	Decline, for both spoons and filters, in proportion who reported sharing in last six months (Table 6-5)
	Outcome	10	Changes in HCV incidence over time	Decline in estimated HCV incidence between 2008-09 and 2011-12; validated by a parallel decline in the prevalence of anti-HCV among those who commenced injecting within the last 12 months (Table 6-6)		
Individual-level	Relationship	D, E, F	Association between uptake of intervention and risk behaviour	Approx 55% reduction in the odds of having shared N/S in the last six months among those with high N/S coverage (Table 6-7)	Nearly 80% reduction in the risk of injecting daily or more frequently in the last six months associated with current uptake of OST (Table 6-10)	~35% reduction in the odds of having shared spoons in the last six months among those with high spoon coverage. High filter coverage associated with ~20% reduction in odds of sharing filters (Tables 6-8 & 6-9)
	Relationship	H, I, J	Association between risk behaviour and HCV incidence	Approx 7-fold increased risk of recent HCV infection associated with sharing N/S in the last six months (Chapter 4)[a]	No direct association between frequency of injecting and recent HCV infection (Table 6-11); but, injecting at least daily is associated with 3-fold increased risk of sharing (each of) N/S, spoons and filters (Tables 6-12 to 6-14)	Approx 3-fold increased risk of recent HCV infection associated with sharing spoons or filters in the last six months (Chapter 4)[a]
	Relationship	K, L, M	Association between uptake of intervention and HCV incidence	Strong association between high coverage N/S and recent HCV in unweighted analyses (AOR 0.4, 95% CI 0.2-0.8, p=0.01) and weighted analyses (AOR_w 0.1, 95% CI 0.04-0.5, p=0.002) (Table 6-15, Appendix H)	No evidence for an association between current OST and recent HCV, in either weighted or unweighted analyses (Table 6-15, Appendix H)	High paraphernalia coverage associated with recent HCV in unweighted analyses (AOR 0.4, 95% CI 0.1-1.1, p=0.08) but more so in weighted model (AOR_w 0.1, 95% CI 0.03-0.4, p=0.002) (Table 6-15, Appendix H)
				Evidence of a strong association between the combined effects of N/S & OST and a reduced risk of recent HCV (AOR 0.3, 95% CI 0.1-0.8, p=0.02; and AOR_w 0.05, 95% CI .01-0.19, p<0.001). Combined effects of N/S, OST, & paraphernalia (AOR 0.3, 95% CI 0.1-1.1, p=0.06 and AOR_w 0.07, 95% CI 0.01-0.4, p=0.002) are not substantially different from that of N/S and OST combined. (Table 6-15, Appendix H)		

N/S: needle(s)/syringe(s)

[a]As stated in Chapter 4, it was not possible to separate the effects of needles/syringes due to few individuals who reported sharing only needles/syringes. It is, however, assumed that the potential AOR for needles/syringes could be even higher than that detected for needles/syringes +/- paraphernalia.

Table 6-4. Numbers of items of injecting equipment distributed and methadone mixture prescriptions dispensed in Scotland, by financial year, 2008/09 to 2011/12

		2008/09	2009/10	2010/11	2011/12	Factor increase between 2008/09 and 2009/10	Factor increase between 2009/10 and 2010/11	Factor increase between 2010/11 and 2011/12
Injecting equipment items distributed	Needles/syringes[a]	4,736,700	4,699,600	4,626,700	4,722,500	0.99	0.98	1.02
	Filters	355,872	2,224,259	2,500,147	2,534,289	6.25	1.12	1.01
	Water ampoules	62,229	77,352	71,575	68,984	1.24	0.93	0.96
	Spoons	508,515	2,142,740	2,438,381	2,527,480	4.21	1.14	1.04
Methadone mixture prescriptions dispensed		493,767	510,063	534,674	515,897	1.03	1.05	0.96

Modified from Injecting Equipment Provision in Scotland Survey 2011/12 (Information Services Division, 2013) and Drug Misuse Statistics Scotland 2011 (Information Services Division, 2012b)

[a]Figures have been adjusted by the proportion of total services providing data for respective financial years

Table 6-5. Group-level analyses: risk behaviour and harm reduction intervention uptake among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12, by survey

		2008-09 (N=2,629)	2010 (N=3,168)	2011-12 (N=2,154)	X^2 test (trend) or ANOVA	p-value
(i) Intervention uptake (last six months)						
Proportion currently on OST	All PWID[a,b]	50%	60%	64%	48.442	<0.001
	PWID, current[a,b]	49%	60%	64%	50.564	<0.001
Median no. obtained in typical week in last six months	Needles/syringes (SD)[b]	15 (25)	10 (17)	10 (18)	113.493	<0.001
	Filters (SD)[b]	0 (8)	8 (20)	10 (19)	794.167	<0.001
	Spoons (SD)[b]	0 (5)	7.5 (19)	10 (18)	1026.638	<0.001
Proportion with adequate coverage (≥100%) based on self-reported survey data	Needle/syringe coverage[b]	75%	79%	77%	3.271	0.071
	Filter coverage[b]	24%	58%	69%	817.385	<0.001
	Spoon coverage[b]	20%	58%	70%	972.267	<0.001
Proportion with adequate coverage (≥100%) based on service provision data[c]	Needle/syringe coverage	53%	62%	74%	-	-
	Filter coverage	4%	34%	40%	-	-
	Spoon coverage	6%	33%	39%	-	-
(ii) Risk behaviour (last six months)						
Injected at least daily[b]		63%	54%	49%	73.712	<0.001
Shared N/S[b]		15%	11%	8%	51.497	<0.001
Mean no. times shared N/S (SD)[b]		0.89 (4.0)	0.69 (4.2)	0.46 (4.0)	F=5.357	0.005
Mean no. times shared N/S among those who shared (SD)[b]		5.9 (8.7)	6.5 (11.4)	6.0 (13.0)	F=0.209	0.812
Reused own needle/syringe[b]		64%	59%	45%	131.952	<0.001
Shared spoons[b]		42%	33%	20%	217.652	<0.001
Shared filters[b]		33%	28%	17%	123.088	<0.001
Shared water[b]		31%	29%	21%	48.740	<0.001

N/S: needle(s)/syringe(s)
[a]Among those who cited needle exchange as the reason for visit on day of recruitment
[b]Among those who reported injecting in the last six months
[c]p-values have not been calculated for the second measure of IEP coverage – because of the large numbers, very small changes would be statistically significant

Table 6-6. Group-level analyses: HCV incidence/prevalence among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12, by survey

		2008-09	2010	2011-12	X^2 test (trend)	p-value
HCV prevalence						
HCV prevalence[a]	N % 95% CI	2,629 54% 52-55%	3,168 56% 54-58%	2,154 53% 51-55%	0.004	0.951
HCV incidence						
HCV prevalence among those injecting <1 year	N % 95% CI	144 20.1% 13.9-27.6%	169 18.3% 12.8-25.0%	85 8.2% 3.4-16.2%	4.711	0.030
Proportion with recent HCV infection (all PWID)[b]	N % 95% CI	1,140 2.1% 1.4-3.1%	1,323 1.5% 0.9-2.3%	996 0.9% 0.4-1.7%	5.092	0.024
Proportion with recent HCV infection (PWID, current)[b,c]	N % 95% CI	933 2.1% 1.2-3.3%	1,024 1.5% 0.8-2.4%	831 1.1% 0.5-2.0%	3.224	0.073
Derived HCV incidence (all PWID)	95% CI	13.3 8.4-19.8	9.9 5.5-14.8	6.1 2.5-11.1	-	-
Derived HCV incidence (PWID, current)[c]	95% CI	13.6 8.1-20.1	9.6 5.1-15.5	7.3 3.0-12.9	-	-

[a]Numerator includes anti-HCV positives and weak reactives; the denominator is all PWID
[b]Where recent infection is defined as anti-HCV negative and HCV-RNA positive; the denominator is all anti-HCV negative PWID
[c]Among those who reported injecting in the last six months

Table 6-7. Univariable and multivariable models of the association between needle/syringe coverage and sharing needles/syringes (in the last six months) among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled), including model covariates

		No. who shared			Univariable			Multivariable (n=5,409)		
		Total (N)	N/S (n)	% (n/N)	OR	95% CI	p-value	AOR	95% CI	p-value
Needle/syringe coverage	**<100%**	**1274**	**227**	**18**	**1**			**1**		
	100-199%	**1913**	**234**	**12**	**0.64**	**0.53-0.78**	**<0.001**	**0.64**	**0.52-0.79**	**<0.001**
	≥200%	**2264**	**195**	**9**	**0.44**	**0.35-0.53**	**<0.001**	**0.44**	**0.35-0.54**	**<0.001**
Survey	2008-09	2046	310	15	1			1		
	2010	2063	229	11	0.70	0.58-0.84	<0.001	0.77	0.64-0.93	0.008
	2011-12	1379	120	9	0.53	0.43-0.67	<0.001	0.59	0.47-0.74	<0.001
Gender	Male	4035	453	11	1			1		
	Female	1430	201	14	1.29	1.08-1.55	0.005	1.35	1.12-1.63	0.002
Homeless in last six months	No	4067	425	10	1			1		
	Yes	1413	231	16	1.68	1.41-1.99	<0.001	1.34	1.12-1.61	0.002
Injected stimulant in last six months	No	4552	495	11	1			1		
	Yes	935	164	18	1.74	1.44-2.11	<0.001	1.58	1.29-1.94	<0.001
Alcohol consumption in the last 12 months[a]	Not excessive	4047	414	10	1			1		
	Excessive	1412	239	17	1.79	1.51-2.12	<0.001	1.68	1.40-2.01	<0.001
Current OST	No	1716	256	15	1			1		
	Yes	3771	403	11	0.68	0.58-0.81	<0.001	0.80	0.67-0.96	0.014
Age (years)	<25	761	147	19	1			1		
	≥25	4724	512	11	0.51	0.42-0.62	<0.001	0.59	0.47-0.73	<0.001

N/S: needle(s)/syringe(s)

Models are restricted to those who reported injecting in the last six months

[a]Excessive is defined as >14 units/week for women and >21 units/week for men

Table 6-8. Univariable and multivariable models of the association between spoon coverage and sharing spoons (in the last six months) among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled), including model covariates

		No. who shared			Univariable			Multivariable (n=5,419)		
		Total (N)	spoons (n)	% (n/N)	OR	95% CI	p-value	AOR	95% CI	p-value
Spoon coverage	**<100%**	**2945**	**1165**	**40**	**1**			**1**		
	100-199%	**1196**	**329**	**28**	**0.58**	**0.50-0.67**	**<0.001**	**0.72**	**0.62-0.85**	**<0.001**
	≥200%	**1320**	**326**	**25**	**0.50**	**0.43-0.58**	**<0.001**	**0.63**	**0.54-0.74**	**<0.001**
Survey	2008-09	2052	868	42	1			1		
	2010	2063	694	34	0.69	0.61-0.79	<0.001	0.87	0.76-1.00	0.055
	2011-12	1380	266	19	0.33	0.28-0.38	<0.001	0.42	0.35-0.50	<0.001
Gender	Male	4035	1281	32	1			1		
	Female	1437	538	37	1.29	1.14-1.46	<0.001	1.35	1.18-1.55	<0.001
Homeless in last six months	No	4069	1217	30	1			1		
	Yes	1418	608	43	1.76	1.55-1.99	<0.001	1.50	1.32-1.72	<0.001
Injected stimulant in last six months	No	4557	1405	31	1			1		
	Yes	937	423	45	1.85	1.60-2.13	<0.001	1.63	1.40-1.90	<0.001
Alcohol consumption in the last 12 months[a]	Not excessive	4051	1190	29	1			1		
	Excessive	1415	628	44	1.92	1.69-2.17	<0.001	1.79	1.57-2.05	<0.001
Current OST	No	1717	636	37	1			1		
	Yes	3777	1192	32	0.78	0.70-0.88	<0.001	0.90	0.79-1.02	0.094
Age (years)	<25	762	336	44	1			1		
	≥25	4730	1491	32	0.58	0.50-0.68	<0.001	0.66	0.56-0.78	<0.001

Models are restricted to those who reported injecting in the last six months

[a]Excessive is defined as >14 units/week for women and >21 units/week for men

Table 6-9. Univariable and multivariable models of the association between filter coverage and sharing filters (in the last six months) among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled), including model covariates

		No. who shared			Univariable			Multivariable (n=5,413)		
		Total (N)	filters (n)	% (n/N)	OR	95% CI	p-value	AOR	95% CI	p-value
Filter coverage	**<100%**	**2882**	**871**	**30**	**1**			**1**		
	100-199%	**1235**	**306**	**25**	**0.76**	**0.65-0.89**	**<0.001**	**0.90**	**0.76-1.06**	**0.211**
	≥200%	**1344**	**297**	**22**	**0.66**	**0.56-0.76**	**<0.001**	**0.81**	**0.69-0.95**	**0.011**
Survey	2008-09	2055	671	33	1			1		
	2010	2063	576	28	0.80	0.70-0.91	0.001	0.94	0.81-1.09	0.390
	2011-12	1380	233	17	0.42	0.35-0.50	<0.001	0.50	0.42-0.60	<0.001
Gender	Male	4037	1036	26	1			1		
	Female	1438	434	30	1.25	1.10-1.43	0.001	1.40	1.21-1.62	<0.001
Homeless in last six months	No	4073	967	24	1			1		
	Yes	1417	511	36	1.81	1.59-2.06	<0.001	1.53	1.34-1.76	<0.001
Injected stimulant in last six months	No	4558	1124	25	1			1		
	Yes	939	356	38	1.87	1.61-2.16	<0.001	1.67	1.43-1.95	<0.001
Imprisoned	Never	2188	540	25	1			1		
	Ever	3302	938	28	1.21	1.07-1.37	0.002	1.21	1.06-1.38	0.006
Alcohol consumption in the last 12 months[a]	Not excessive	4052	958	24	1			1		
	Excessive	1417	511	36	1.82	1.60-2.08	<0.001	1.65	1.44-1.89	<0.001
Current OST	No	1718	529	31	1			1		
	Yes	3779	951	25	0.76	0.67-0.86	<0.001	0.81	0.71-0.93	0.002
Age (years)	<25	763	258	34	1			1		
	≥25	4732	1221	26	0.68	0.58-0.80	<0.001	0.79	0.66-0.94	0.008

Models are restricted to those who reported injecting in the last six months

[a]Excessive is defined as >14 units/week for women and >21 units/week for men

Table 6-10. Univariable and multivariable models of the association between OST and injecting daily or more frequently among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled), including model covariates

			No. injected at		Univariable			Multivariable (n=6,776)		
		Total (N)	least daily (n)	% (n/N)	OR	95% CI	p-value	AOR	95% CI	p-value
Current OST	**No**	**1724**	**1263**	**73**	**1**			**1**		
	Yes	**5104**	**1869**	**37**	**0.21**	**0.19-0.24**	**<0.001**	**0.22**	**0.20-0.25**	**<0.001**
Survey	2008-09	2552	1295	51	1			1		
	2010	2666	1123	42	0.71	0.63-0.79	<0.001	0.84	0.74-0.94	0.003
	2011-12	1611	715	44	0.78	0.68-0.88	<0.001	0.89	0.78-1.02	0.088
Homeless in last six months	No	5214	2209	42	1			1		
	Yes	1607	920	57	1.82	1.63-2.04	<0.001	1.50	1.33-1.69	<0.001
Injected stimulant in last six months	No	5887	2527	43	1			1		
	Yes	941	606	64	2.41	2.09-2.78	<0.001	2.22	1.90-2.58	<0.001
Imprisoned	Never	2722	1181	43	1			1		
	Ever	4094	1946	48	1.18	1.07-1.30	0.001	1.27	1.14-1.41	<0.001
Age (years)	<25	836	496	59	1			1		
	≥25	5988	2636	44	0.54	0.47-0.63	<0.001	0.70	0.60-0.83	<0.001

Models exclude individuals who reported not currently being on OST and also not injecting in the last six months

Table 6-11. Univariable and multivariable models of the association between frequency of injecting (in the last six months) and recent HCV infection among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled)

			No. recent HCV		Univariable			Multivariable (n=2,999)		
		Total (N)	infections (n)	% (n/N)	OR	95% CI	p-value	AOR	95% CI	p-value
Injected daily or more frequently	**No**	**1659**	**19**	**1.1**	**1**			**1**		
in the last six months	**Yes**	**1365**	**31**	**2.3**	**2.01**	**1.13-3.57**	**0.018**	**1.45**	**0.80-2.63**	**0.218**
Survey	2008-09	1116	23	2.1	1			1		
	2010	1130	19	1.7	0.81	0.44-1.50	0.507	0.92	0.49-1.72	0.795
	2011-12	778	8	1.0	0.49	0.22-1.11	0.088	0.56	0.25-1.27	0.166
Homeless in last six months	No	2392	25	1.0	1			1		
	Yes	629	25	4.0	3.92	2.24-6.87	<0.001	3.02	1.70-5.36	<0.001
Injected stimulant in last six	No	2731	39	1.4	1			1		
months	Yes	293	11	3.8	2.69	1.36-5.32	0.004	2.26	1.11-4.58	0.024
Time since onset of injecting	<5 years	1186	32	2.7	1			1		
	≥5 years	1826	18	1.0	0.36	0.20-0.64	0.001	0.39	0.22-0.71	0.002
Alcohol consumption in last 12	Not excessive	2383	31	1.3	1			1		
months[a]	Excessive	631	19	3.0	2.36	1.32-4.20	0.004	1.93	1.07-3.50	0.030

Models exclude individuals who reported not currently being on OST and also not injecting in the last six months

[a]Excessive is defined as >14 units/week for women and >21 units/week for men

Table 6-12. Univariable and multivariable models of the association between frequency of injecting in the last six months and sharing needle/syringes in the last six months among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled)

		No. who shared			Univariable			Multivariable (n=6,746)		
		Total (N)	N/S (n)	% (n/N)	OR	95% CI	p-value	AOR	95% CI	p-value
Injected daily or more frequently	**No**	**3687**	**180**	**4.9**	**1**			**1**		
in the last six months	**Yes**	**3119**	**479**	**15.4**	**3.54**	**2.96-4.23**	**<0.001**	**3.04**	**2.53-3.66**	**<0.001**
Survey	2008-09	2537	310	12.2	1			1		
	2010	2663	229	8.6	0.67	0.56-0.81	<0.001	0.80	0.66-0.97	0.020
	2011-12	1606	120	7.5	0.58	0.47-0.72	<0.001	0.68	0.54-0.85	0.001
Gender	Male	4903	453	9.2	1			1		
	Female	1879	201	10.7	1.18	0.99-1.40	0.069	1.21	1.01-1.46	0.042
Homeless in last six months	No	5197	425	8.2	1			1		
	Yes	1601	231	14.4	1.89	1.60-2.25	<0.001	1.36	1.14-1.63	0.001
Injected stimulant in last six	No	5870	495	8.4	1			1		
months	Yes	935	164	17.5	2.31	1.91-2.80	<0.001	1.75	1.42-2.14	<0.001
Time since onset of injecting	<5 years	1678	211	12.6	1			1		
	≥5 years	5107	447	8.8	0.67	0.56-0.79	<0.001	0.80	0.66-0.98	0.031
Alcohol consumption in last 12	Not excessive	5057	414	8.2	1			1		
months[a]	Excessive	1719	239	13.9	1.81	1.53-2.15	<0.001	1.75	1.46-2.09	<0.001
Age (years)	<25	833	147	17.6	1			1		
	≥25	5968	512	8.6	0.44	0.36-0.54	<0.001	0.58	0.46-0.73	<0.001

N/S: needle(s)/syringe(s)
Models exclude individuals who reported not currently being on OST and also not injecting in the last six months
[a]Excessive is defined as >14 units/week for women and >21 units/week for men

Table 6-13. Univariable and multivariable models of the association between frequency of injecting in the last six months and sharing spoons in the last six months among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled)

			No. who shared		Univariable			Multivariable		
		Total (N)	spoons (n)	% (n/N)	OR	95% CI	p-value	AOR	95% CI	p-value
Injected daily or more frequently in the last six months	**No**	**3845**	**612**	**15.9**	**1**			**1**		
	Yes	**3125**	**1216**	**38.9**	**3.37**	**3.01-3.77**	**<0.001**	**3.02**	**2.68-3.39**	**<0.001**
Survey	2008-09	2603	868	33.3	1			1		
	2010	2724	694	25.5	0.68	0.61-0.77	<0.001	0.81	0.71-0.92	0.001
	2011-12	1643	266	16.2	0.39	0.33-0.45	<0.001	0.42	0.35-0.49	<0.001
Gender	Male	5020	1281	25.5	1			1		
	Female	1926	538	27.9	1.13	1.01-1.27	0.040	1.21	1.07-1.38	0.004
Homeless in last six months	No	5310	1217	22.9	1			1		
	Yes	1652	608	36.8	1.96	1.74-2.21	<0.001	1.47	1.30-1.68	<0.001
Injected stimulant in last six months	No	6032	1405	23.3	1			1		
	Yes	937	423	45.1	2.71	2.35-3.12	<0.001	2.11	1.80-2.46	<0.001
Time since onset of injecting	<5 years	1709	544	31.8	1			1		
	≥5 years	5240	1279	24.4	0.69	0.61-0.78	<0.001	0.78	0.68-0.90	<0.001
Alcohol consumption in last 12 months[a]	Not excessive	5167	1190	23.0	1			1		
	Excessive	1773	628	35.4	1.83	1.63-2.06	<0.001	1.80	1.59-2.05	<0.001
Age (years)	<25	848	336	39.6	1			1		
	≥25	6116	1491	24.4	0.49	0.42-0.57	<0.001	0.68	0.57-0.81	<0.001

Models exclude individuals who reported not currently being on OST and also not injecting in the last six months

[a]Excessive is defined as >14 units/week for women and >21 units/week for men

Table 6-14. Univariable and multivariable models of the association between frequency of injecting in the last six months and sharing filters in the last six months among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled)

			No. who shared		Univariable			Multivariable (n=6,772)		
		Total (N)	filters (n)	% (n/N)	OR	95% CI	p-value	AOR	95% CI	p-value
Injected daily or more frequently in the last six months	**No**	**3689**	**484**	**13.1**	**1**			**1**		
	Yes	**3127**	**996**	**31.9**	**3.10**	**2.74-3.50**	**<0.001**	**2.77**	**2.44-3.14**	**<0.001**
Survey	2008-09	2546	671	26.4	1			1		
	2010	2663	576	21.6	0.77	0.68-0.88	<0.001	0.93	0.81-1.07	0.308
	2011-12	1607	233	14.5	0.47	0.40-0.56	<0.001	0.54	0.45-0.64	<0.001
Gender	Male	4905	1036	21.1	1			1		
	Female	1887	434	23.0	1.12	0.98-1.27	0.092	1.22	1.07-1.40	0.004
Homeless in last six months	No	5203	967	18.6	1			1		
	Yes	1605	511	31.8	2.05	1.80-2.32	<0.001	1.59	1.39-1.82	<0.001
Injected stimulant in last six months	No	5876	1124	19.1	1			1		
	Yes	939	356	37.9	2.58	2.23-2.99	<0.001	1.98	1.69-2.32	<0.001
Alcohol consumption in last 12 months[a]	Not excessive	5062	958	18.9	1			1		
	Excessive	1724	511	29.6	1.81	1.59-2.05	<0.001	1.68	1.47-1.92	<0.001
Age (years)	<25	835	258	30.9	1			1		
	≥25	5976	1221	20.4	0.57	0.49-0.67	<0.001	0.72	0.61-0.86	<0.001

Models exclude individuals who reported not currently being on OST and also not injecting in the last six months

[a]Excessive is defined as >14 units/week for women and >21 units/week for men

Table 6-15. Individual-level analyses: unweighted and weighted models of the association between self-reported uptake of harm reduction interventions and recent HCV infection among PWID recruited at IEP sites across Scotland in 2008-09, 2010 and 2011-12 (pooled)

					Univariable		Multivariable[a]		Weighted multivariable[a]	
Model	Intervention	Categories	Recent infection %	Weighted recent infection %	OR (95% CI)	p-value	AOR (95% CI)	p-value	AOR_w (95% CI)	p-value
(i)	N/S coverage[b]						(n=2,481)		(n=2,481)	
		Low	2.4	2.9	1		1		1	
		High	0.9	0.4	0.36 (0.17-0.75)	0.006	0.39 (0.19-0.83)	0.014	0.14 (0.04-0.48)	0.002
(ii)	Paraphernalia coverage[b,c]						(n=2,481)		(n=2,481)	
		Low	2.0	2.7	1		1		1	
		High	0.7	0.2	0.33 (0.12-0.94)	0.037	0.39 (0.14-1.12)	0.081	0.11 (0.03-0.44)	0.002
(iii)	OST						(n=3,008)		(n=3,008)	
		Not current	2.5	3.0	1		1		1	
		Current	1.3	1.3	0.51 (0.29-0.90)	0.020	0.63 (0.35-1.12)	0.111	0.52 (0.23-1.18)	0.119
(iv)	N/S coverage and OST combined[d]						(n=2,993)		(n=2,993)	
		Low N/S, no OST	3.4	3.8	1		1		1	
		Low N/S, OST	1.6	2.0	0.48 (0.24-0.95)	0.035	0.55 (0.27-1.11)	0.093	0.59 (0.26-1.35)	0.209
		High N/S, no OST	0.9	0.7	0.26 (0.08-0.88)	0.030	0.28 (0.08-0.96)	0.043	0.18 (0.04-0.87)	0.034
		High N/S, OST	0.8	0.1	0.24 (0.10-0.60)	0.002	0.29 (0.11-0.74)	0.009	0.05 (0.01-0.18)	<0.001
		Did not inject, OST	1.4	1.4	0.39 (0.17-0.94)	0.035	0.62 (0.24-1.59)	0.324	0.61 (0.21-1.80)	0.370
(v)	N/S coverage, paraphernalia coverage and OST combined[d]						(n=2,992)		(n=2,992)	
		Low N/S, low para, no OST	3.5	3.9	1		1		1	
		Low N/S, low para, OST	1.7	2.0	0.48 (0.24-0.96)	0.037	0.55 (0.27-1.11)	0.095	0.58 (0.25-1.34)	0.202
		High N/S, low para, no OST	1.0	0.8	0.27 (0.06-1.15)	0.076	0.29 (0.07-1.26)	0.098	0.18 (0.03-1.34)	0.095
		High N/S, low para, OST	0.9	0.1	0.26 (0.08-0.89)	0.031	0.28 (0.08-0.98)	0.046	0.02 (0.01-0.09)	<0.001
		High N/S, high para, no OST	0.8	0.5	0.22 (0.03-1.65)	0.141	0.25 (0.03-1.90)	0.180	0.16 (0.02-1.25)	0.081
		High N/S, high para, OST	0.8	0.2	0.21 (0.06-0.71)	0.012	0.28 (0.08-0.97)	0.044	0.07 (0.01-0.35)	0.001
		Did not inject, OST	1.4	1.4	0.38 (0.16-0.90)	0.028	0.60 (0.24-1.54)	0.292	0.59 (0.20-1.75)	0.343

N/S: needle(s)/syringe(s); para: paraphernalia

[a]All models adjusted for survey year, homelessness in last six months, stimulant injection in last six months and time since onset of injecting

[b]Restricted to those who reported injecting in the last six months; see methods for definition of high and low coverage

[c]Paraphernalia refers to spoons and filters

[d]Where 'no OST/OST' refers to no current/current receipt of OST, 'low' refers to low coverage and 'high' refers to high coverage

Table 6-16. Results of sensitivity analysis of varying parameters in model (v)

		Main effects model[a,b]			Survey year included as a continuous variable[a,c]			Time since onset of injecting as a categorical variable[a]			Different duplicates excluded[a,d]		
		AOR	95% CI	p-value	AOR	95% CI	p-value	AOR	95% CI	p-value	AOR	95% CI	p-value
N/S coverage, paraphernalia coverage and OST combined	Low N/S, low para, no OST	1			1			1			1		
	Low N/S, low para, OST	0.55	0.27-1.11	0.095	0.60	0.30-1.20	0.149	0.60	0.30-1.21	0.154	0.64	0.30-1.39	0.263
	Low N/S, high para, no OST	-	-	-	-	-	-	-	-	-			
	Low N/S, high para, OST	-	-	-	-	-	-	-	-	-			
	High N/S, low para, no OST	0.29	0.07-1.26	0.098	0.28	0.06-1.24	0.093	0.29	0.07-1.27	0.100	0.37	0.08-1.65	0.193
	High N/S, low para, OST	0.28	0.08-0.98	0.046	0.32	0.09-1.11	0.073	0.33	0.10-1.13	0.076	0.43	0.12-1.51	0.187
	High N/S, high para, no OST	0.25	0.03-1.90	0.180	0.25	0.03-1.86	0.173	0.24	0.03-1.84	0.170	0.30	0.04-2.28	0.242
	High N/S, high para, OST	0.28	0.08-0.97	0.044	0.31	0.09-1.08	0.066	0.31	0.09-1.07	0.064	0.36	0.10-1.28	0.114
	Did not inject, OST	0.60	0.24-1.54	0.292	0.84	0.33-2.13	0.713	0.84	0.33-2.13	0.709	0.89	0.2-2.48	0.825

N/S: needle(s)/syringe(s); para: paraphernalia

[a]All models adjusted for survey year, homelessness in last six months (binary), stimulant injection in last six months (binary) and time since onset of injecting

[b]In main effects model, survey year is categorical and time since onset of injecting is continuous

[c]A continuous variable was created with the first interview conducted in 2008-09 serving as the baseline (time zero) and taking on values equivalent to the days since baseline that the respective interviews were carried out

[d]Where a respondent had participated in multiple surveys, the last interview was retained for analysis (as opposed to the first, as was done in the main effects model)

Table 6-17. Estimated number of new infections and new chronic infections per calendar year 2008-2012 based on derived incidence rates

	Estimated incidence per 100 PY (95% CI)	Proportion anti-HCV negative (95% CI)	No. new infections (95% CI)	No. new chronic infections (95% CI)[a]
2008	13.6 (8.1-20.1)	0.48 (0.46-0.50)	1063 (591-1682)	787 (441-1248)
2009	13.6 (8.1-20.1)	0.48 (0.46-0.50)	1063 (591-1682)	787 (441-1248)
2010	9.6 (5.1-15.5)	0.45 (0.43-0.47)	697 (336-1240)	516 (251-908)
2011	7.3 (3.0-12.9)	0.47 (0.44-0.49)	566 (205-1039)	419 (152-774)
2012	7.3 (3.0-12.9)	0.47 (0.44-0.49)	566 (205-1039)	419 (152-774)

Number of PWID assumed to be stable during 2008-2012 at 16,000 (95% CI 11,782-20,334)
[a]26% (95% CI 22-29%) were assumed to spontaneously clear acute infection (Micallef, Kaldor, and Dore, 2006)

7 Summary and future work

7.1 Summary of chapter findings in relation to thesis objectives

To recap, the overall aim of this thesis was to investigate the impact of harm reduction interventions on the transmission of HCV among PWID in Scotland. The sections in this chapter present a summary of the findings in relation to this overall aim, as well as the secondary objectives of the thesis, which were:

i. To review the international literature on the effectiveness of IEP and OST in preventing HCV transmission among PWID;

ii. To determine the association between self-reported sharing of needles/syringes and incident/prevalent HCV infection among PWID;

iii. To determine the association between sharing non-needle/syringe injecting paraphernalia and incident HCV infection among PWID in Scotland;

iv. To determine the incidence of HCV among PWID in Scotland; and

v. To determine the association between self-reported uptake of harm reduction interventions (IEP and OST) and incident HCV infection among PWID in Scotland.

7.1.1 International evidence for the effectiveness of IEP and OST in preventing HCV transmission among people who inject drugs: a review of reviews

Chapter 2 addressed the first objective of reviewing the international literature for evidence of effectiveness of OST and IEP in the prevention of HCV transmission. The outcomes were also expanded to include HIV and IRB, yielding important insights with regard to differences in the evidence base for the respective outcomes. Applying a review of reviews approach, the findings with regard to NSP were: insufficient evidence for an impact on HCV, tentative evidence for an impact on HIV and sufficient evidence for an impact on IRB. For OST, there was insufficient evidence for an impact on HCV and sufficient evidence for an impact on both HIV and IRB. For the remaining IEP interventions (pharmacy NSP, vending machines, outreach NSP, sterile injecting paraphernalia

provision) there was generally no or insufficient evidence with respect to any of the outcomes.

The review of reviews was updated to include reviews published until March 2011 (Macarthur et al., 2014) (the original work for Chapter 2 included reviews published up until March 2007). Only four evidence statements were changed as a result of additional evidence identified. The evidence statement for the effectiveness of outreach NSP with respect to HIV was upgraded from none to insufficient, as was the evidence statement for injecting paraphernalia with respect to HCV. Additionally, the evidence statement for the effectiveness of injecting paraphernalia with regard to IRB was upgraded from insufficient to tentative; as was the evidence for OST with regard to HCV. Thus, despite updating the evidence base with an additional four years of published literature, many interventions are still lacking evidence.

It is, however, important to emphasise that lack of evidence does not equal evidence for lack of effectiveness. For the interventions other than NSP and OST, this lack of evidence resulted from an absence of reviews that had been undertaken and likely reflects a corresponding lack of primary studies investigating these interventions. For NSP and OST, the limitations of the primary studies that investigated these interventions may have played a role where there was less than sufficient evidence. RCTs were generally absent from the evidence base, with the exception of a few that had been undertaken to examine OST. The next most robust design in the evidence hierarchy, for the purposes of this review, was the longitudinal cohort study; most of the studies employing this design had negative findings (i.e. a change in the outcome in the opposite direction of the intended effect) or showed no association. Ecological studies were more likely to report positive findings (i.e a reduction in the outcome associated with the intervention) than individual-level studies, but were accorded less importance in the framework for deriving evidence statements (because ecological studies generally did not control for confounding, there was a high risk that any changes in the outcome observed could have been a result of other factors). The lack of positive findings in cohort studies may have been partly attributable to limitations and/or bias in the measurement of exposure to the intervention, as a result of selection bias, lack of distinction between exposed and unexposed groups and not measuring intervention intensity or ‘coverage’.

In comparing the relative levels of evidence for the different outcomes, the evidence was slightly stronger for HIV than for HCV, but it was particularly notable that it was much

stronger for IRB than either of HIV or HCV. In other words, there was better evidence for behavioural, than for biological, outcomes. Explanations for this observation are potentially three-fold: (i) the limitations of the self-reported nature of IRB, (ii) that IRB is more prevalent and therefore studies had more power to detect any differences (as compared with HIV or HCV, for which one generally requires a substantial duration of follow-up and/or a large sample size in order to observe seroconversions) and (iii) that there is a non-linear relationship between IRB and HIV/HCV (i.e. a reduction in IRB does not necessarily lead to a proportional reduction in BBV transmission).

7.1.2 Systematic review and meta-analysis of the association between self-reported sharing of needles/syringes and HCV prevalence and incidence

Following on from the finding of apparent inconsistencies between self-reported needle/syringe-sharing and biological markers of HCV infection observed in Chapter 2, Chapter 3 summarised and explored factors that could explain the variation in the measure of association between self-reported sharing of needles/syringes and HCV prevalence/incidence (addressing the second thesis objective). A systematic review and meta-analysis of European studies published from January 1990 through September 2011 was undertaken. The pooled prevalence of HCV was 59% among PWID who reported never sharing needles/syringes and the pooled incidence of HCV was 11% among PWID who reported not recently sharing needles/syringes. Random effects meta-analysis generated a pooled OR of 3.3 (95% CI 2.4-4.6), comparing HCV infection among those who ever (or recently) shared needles/syringes with HCV infection among those who reported never (or not recently) sharing. There was substantial heterogeneity between the study effect sizes (I^2=72.8%). Differences in pooled ORs were found when studies were stratified by recruitment setting (prison vs. drug treatment sites), recruitment method (outreach vs. non-outreach), sample HCV prevalence and sample mean/median time since onset of injecting. This analysis found high incidence/prevalence rates of HCV among those who did not report sharing needles/syringes during the risk period, which may be attributable to a combination of unmeasured risk factors (for example, sharing injecting paraphernalia) and reporting bias. It was concluded that study design and population are likely to be important modifiers of the size and strength of association between HCV and needle/syringe-sharing.

7.1.3 Association between sharing injecting paraphernalia and recent HCV infection

Chapter 4 addressed the third objective of determining the association between sharing injecting paraphernalia (spoons, filters and water) and incident HCV infection using data from the 2008-09 and 2010 sweeps of the NESI survey. Logistic regression was applied to examine the association between recent HCV infection (individuals in the pre-seroconversion window period, i.e. anti-HCV negative and HCV-RNA positive) and self-reported measures of injecting equipment sharing in the six months preceding the interview. Twelve percent of the sample reported sharing needles/syringes and 40% reported sharing paraphernalia in the previous six months. The AORs for sharing needles/syringes (with or without paraphernalia) and sharing only paraphernalia in the last six months were 6.7 (95% CI 2.6-17.1) and 3.0 (95% CI 1.2-7.5), respectively. Among those who reported not sharing needles/syringes, sharing spoons and sharing filters in the last six months were both significantly associated with recent HCV infection (AOR 3.1, 95% CI 1.3-7.8 and 3.1, 95% CI 1.3-7.5, respectively); sharing water was not. This study is the first to apply a cross-sectional approach to the analysis of the association between sharing paraphernalia and incident HCV infection and demonstrates consistent results with previous longitudinal studies. The prevalence of paraphernalia-sharing in the study population is high, representing significant potential for HCV transmission.

7.1.4 Determining HCV incidence and measuring the association between harm reduction intervention uptake and recent HCV infection

The fourth and fifth thesis objectives were addressed in Chapters 5 and 6. Chapter 5 used data from the 2008-09 sweep of NESI: twenty-four recent HCV infections were detected. By extrapolating from the estimated duration of the window period, incidence rate estimates ranging from 10.8-21.9 per 100 person-years were derived. Logistic regression analysis of the association between self-reported needle/syringe coverage and recent infection illustrated that, after adjustment for confounders, those with high coverage (defined as at least two sterile needles/syringes per injection) had reduced odds of recent infection, with an AOR of 0.32 (95% CI 0.10-1.00, p=0.050). With regard to OST and recent HCV infection, the overall effect size for Scotland was not statistically significant. In the Greater Glasgow and Clyde region, however, there was a reduced odds of recent infection among those currently receiving OST, relative to those on OST in the last six months but not currently (AOR 0.04, 95% CI 0.001-1.07, p=0.055). The effect of

combined uptake of OST and high needle/syringe coverage was only significant in unadjusted analyses (OR 0.34, 95% CI 0.12-0.97, p=0.043; AOR 0.48, 95% CI 0.16-1.48, p=0.203).

Chapter 6 addressed the same objectives of determining HCV incidence and the association between uptake of harm reduction interventions and recent HCV infection; however, the analysis involved data generated from three sweeps of the NESI survey, undertaken in 2008-09, 2010 and 2011-12. The analyses in Chapter 5 were used to inform and refine the analytical strategy; the additional two surveys allowed the examination of trends over this time period. A framework to triangulate the different types of evidence – 'group-level/ecological' and 'individual-level' – was created and applied. Most of the evidence to populate the framework was derived from the cross-sectional surveys; they were supplemented with service data on the provision of injecting equipment and OST. Ecological analyses examined changes in intervention provision, self-reported intervention uptake, self-reported risk behaviour and HCV incidence across the surveys; individual-level analyses investigated relationships within the pooled survey data. The approach to deriving estimates for incidence, and associated uncertainty ranges, was modified from that in Chapter 5.

A decline in HCV incidence, per 100 person-years, from 13.6 (95% CI 8.1-20.1) in 2008-09 to 7.3 (95% CI 3.0-12.9) in 2011-12 was observed, a period during which increases in the coverage of OST and IEP, and decreases in the frequency of injecting and sharing of injecting equipment, were also seen.

Individual-level evidence demonstrated that combined high coverage of needles/syringes and OST were associated with reduced risk of recent HCV in analyses that were unweighted (AOR 0.29, 95% CI 0.11-0.74) and weighted for frequency of injecting (AOR_w 0.05, 95% CI 0.01-0.18). There was no additional effect found for high paraphernalia coverage. The number of new HCV infections and new chronic HCV infections that may have been averted between 2008 and 2012 as a result of the combination of harm reduction interventions was estimated to be 1,400 and 1,000, respectively.

7.2 Considering the thesis findings within the historical context of HCV prevention in Scotland

In analysing the impact of harm reduction interventions in Scotland, this thesis considers the relatively narrow period from 2008 to 2012; however, it is important to recall that the scale-up of harm reduction interventions had been happening since the late 1980s/early 1990s (see section 1.4.4 and Figures 1-3 and 1-4). It is only since the introduction of DBS collection/testing and the pre-seroconversion window period method of determining incidence that it has really been possible to examine the impact of interventions on HCV incidence.

Historically, data on HCV prevalence in Scotland were derived from the UAT system, as described in section 1.3.2. This system covered the four largest Health Board areas and showed declines in HCV prevalence among all PWID and among PWID aged <25 in three of these four areas during the 1990s (see Figures 1-1 and 1-2). Although the data from UAT were comparable across years due to the consistent approach applied, the samples were associated with limited epidemiological information (only age, gender and NHS Board) and it was not known whether they related to people who were currently injecting or had injected in the past.

Another source of historical data on HCV prevalence was a series of cross-sectional community surveys of PWID that began in 1990, although they covered only Glasgow, and inconsistent inclusion criteria across the different surveys make the data less comparable. Nevertheless, overall HCV prevalence in these surveys ranged between 66% and 79%[6] during 1990 to 1996 (Taylor et al., 2000); these figures compare with 64% to 68% during 2008 to 2012 in Greater Glasgow and Clyde (from the NESI data), suggesting that HCV prevalence among all PWID has not changed greatly (certainly, in this NHS Board) after approximately two decades of harm reduction.

Examining trends in disease prevalence as an indicator of the effectiveness of interventions is not as simple as examining incidence, since prevalent infections could have been acquired at any time in the past. Ecological trends in HCV prevalence are difficult to interpret because there are a large number of potentially contributing factors, including the initiation and cessation of injecting drug use. Studies nevertheless attributed the early

[6] These figures have been adjusted for the 85% sensitivity of the saliva test in detecting HCV antibodies.

reductions in HCV prevalence (seen in the UAT data during the early to mid-1990s) to the initial scale-up of interventions (Hutchinson et al., 2002). It could be that the latter reductions were achieved because interventions were increasing from virtually nothing and therefore any increase was bound to have an impact. It has been suggested that the subsequent plateau in HCV prevalence (seen in both the UAT and community survey data in the late 1990s/early 2000s) may indicate that coverage of interventions had to surpass a threshold in order to make further inroads (Hutchinson et al., 2002).

By contrast, HCV prevalence among those with <5 years since onset of injecting was 70% in 1990 (Glasgow community surveys, unpublished data) as compared with the respective figures of 25 to 40% derived from the recent NESI surveys. Given that HCV prevalence among people who recently started injecting could be considered a proxy for incidence, the decline in prevalence among recent initiates to injecting would suggest that incidence has declined. The changes in IRB over time are also consistent with declining incidence: 27% to 43% of Glasgow PWID interviewed in community surveys during 1990 through 1999 reported injecting with a previously used needle/syringe in the last six months (Taylor et al., 2001) as compared with 8% to 15% observed during 2008 through 2012 from NESI; and 70% to 90% of Glasgow PWID (1990 through 1996) reported injecting drugs at least daily (Taylor et al., 2000) as compared with 49% to 63% during 2008 to 2012.

What explains the consistently high overall HCV prevalence among PWID, given the evidence above? One potential explanation might be that there has been an increase in incidence in longer term injectors. While there is no direct evidence to verify this possibility historically, there is no evidence to support it if one compares the proportion of recent infections across the NESI surveys among those with shorter vs. longer injecting careers (in fact, the data seem to suggest the opposite, although statistical power is an issue[7]). Possibly, a more likely explanation is related to the evidence suggesting that PWID in Scotland are an ageing cohort: this is supported by data from NESI (see Table 6-2) and earlier community surveys of Glasgow PWID indicating that the average age and time since onset of injecting of the sample have been increasing over time (Taylor et al., 2000). Recent onset injectors, therefore, seem to be forming an ever-decreasing proportion of the PWID population. Further evidence from capture-recapture modelling suggests a decline in the size of the PWID population between 2006 and 2009 (see Table 1-5). Hypothetically,

[7] For example, the proportion recently infected declined from 2.7% to 2.3% during 2008-09 and 2011-12 among those with <3 years since onset of injecting, as compared with 1.9% to 0.5%, respectively, among those with ≥3 years since onset of injecting

supposing there had been no changes in HCV incidence, one might expect HCV prevalence to increase if fewer new (uninfected) PWID were entering the population (i.e. diluting the existing HCV prevalence among longer term injectors, assuming that those leaving the population through cessation or death are equally likely to be anti-HCV positive or negative). Thus, in the scenario of declining HCV incidence that has been observed in Scotland, one could potentially expect HCV prevalence to remain stable (i.e. fewer new uninfected PWID entering the population, but declining incidence among existing PWID to counterbalance this).

A mathematical modelling study suggested that, in a scenario of 40% prevalence of chronic infection (which is approximately the situation in Scotland), 60% coverage of both OST and high coverage NSP (i.e. 60% of the PWID population receiving OST and 60% of the population receiving at least one sterile needle/syringe per injection) would need to be sustained for a 15-year period in order to reduce prevalence by a third (Vickerman et al., 2012). The most recent NESI figures suggest that OST and needle/syringe coverage are approximately 65% and 75%, respectively, and that the 60% 'threshold' for both interventions may have been surpassed only in 2010 (depending on the measure of needle/syringe coverage used). Thus, it may be the case that it will take many years of a sustained reduction in HCV transmission before any changes in overall HCV prevalence are observed.

7.3 Policy and practice implications

7.3.1 Influence on current policy and guidelines

Because the work for this thesis was undertaken over a period of years, some of the chapters – the review of reviews (Chapter 2), primarily – have already influenced policy within Scotland and elsewhere.

7.3.1.1 Local

The review of reviews was a key document that informed the evidence base for Phase II of the Hepatitis C Action Plan for Scotland (Scottish Government, 2008a). During Phase I (2006-2008) of the Action Plan, working groups relating to three areas (testing, treatment and care; education, training and awareness-raising and; prevention) were established. Their mandate included the generation of evidence and the translation of evidence into proposed 'issues' and 'actions'. A workshop of the Prevention Working Group was

convened, at which the results of the review of reviews, among other evidence, were presented. The Prevention Working Group developed a series of issues and actions; these were shared with various stakeholders, who were given an opportunity to comment, primarily through the forum of a consultation event attended by nearly 200 individuals. The issues and actions that resulted from this process have been described in section 1.5.1. Principally, the review of reviews informed the evidence base that led to the derivation of Action 15 (Services providing injection equipment will be improved in accordance with the Guidelines). The review of reviews also informed the need to develop 'Information Generating Initiatives to Monitor the Performance of Actions', specifically: the development of a data collection system to monitor the provision of injection equipment and national annual surveys of HCV prevalence and incidence among PWID (i.e. the Needle Exchange Surveillance Initiative).

Concurrently with the development of the Action Plan Phase II, the Advisory Council on the Misuse of Drugs produced a report to advise the UK government entitled 'The Primary Prevention of Hepatitis C among Injecting Drug Users', which cited the review of reviews among its sources of evidence, and which made recommendations to increase NSP coverage, to ensure the implementation of combination interventions (i.e NSP and OST) and to undertake studies to directly test the effectiveness of NSP and OST in reducing HCV incidence (Advisory Council on the Misuse of Drugs, 2009).

7.3.1.2 International

The updated review of reviews (described in section 2.4.1, although covering a wider range of interventions than are discussed here) (European Centre for Disease Prevention and Control and European Monitoring Centre for Drugs and Drug Addiction, 2011a; Macarthur et al., 2014) was commissioned to provide evidence to inform guidance on preventing infectious diseases among PWID in Europe (European Centre for Disease Prevention and Control, 2011).

7.3.2 Policy recommendations

In contrast to clinical interventions, public health interventions have, historically, required much less of an evidence base prior to implementation. This implementation despite a lack of evidence has been true of IEP interventions: for example, Chapter 2 found that the evidence was weak for many interventions that had already been implemented. Another example is the Hepatitis C Action Plan for Scotland, which advocated the scale-up of

interventions, including the distribution of injecting paraphernalia, despite a weak evidence base. A certain level of pragmatism regarding the epidemiological evidence required to underpin decision-making, given the difficulties in designing and undertaking studies of this nature, is therefore required. With these difficulties in mind, it is important to recognise that this thesis, and the existing body of literature to which it adds, is the best and strongest evidence that has existed to date on the effectiveness of interventions in preventing HCV transmission. Although the study designs used to generate the evidence in this thesis could be criticised from a purist epidemiological viewpoint, the evidence is nevertheless sufficiently compelling to justify, at least, the maintenance of current harm reduction services and certainly the consideration of further scale-up, given that promising signs in the direction of movement of HCV incidence have been observed and it is likely that the level of interventions will need to be sustained for a number of years before any changes in HCV prevalence are seen.

Although this thesis did not consider the cost-effectiveness of the prevention investment, a 'back-of-the-envelope' calculation indicates that the prevention investment could be much less than the potential costs of treating the infections that would otherwise have occurred. The costs of the direct-acting antivirals that will be available from 2015 have yet to be confirmed, but have been estimated to be in the region of £30,000 to £80,000 per treatment course (Sharon Hutchinson, Glasgow Caledonian University, personal communication). If the prevention interventions are estimated to have averted 1,000 chronic infections during the period 2008 through 2012 (Chapter 6), and if even half of them had gone on to receive therapy, then this would result in saved treatment costs of £15 million to £40 million. These potential savings compare to the Scottish Government prevention investment of approximately £11 million during 2008 to 2012 (£8 million over the course of the Action Plan Phase II (Scottish Government, 2008a) and a further £3 million in the first year of the Sexual Health and Blood Borne Virus Framework (Nicola Rowan, Health Protection Scotland, personal communication)).

The further scale-up of interventions, however, may not simply be a political decision (i.e. securing funding), because there are issues surrounding the saturation of interventions. In Scotland, services have attained very high coverage of both OST and IEP (although there is perhaps more scope to increase the provision of injecting paraphernalia). There have been anecdotal reports from services that PWID do not want to take away any more equipment than the amount they are currently getting (John Campbell, Glasgow Addiction Services, personal communication). It could be that the 'easy-to-reach' PWID are now

covered by existing interventions and that increasing the coverage of interventions will require innovative ways to target and reach the more 'hard-to-reach' PWID. Getting these individuals into treatment, maintaining them in treatment and ensuring that they use a sterile set of equipment for every injection, remain a challenge.

Modelling studies have examined the impact of HCV therapy as a preventive intervention, (Martin et al., 2013a; Martin et al., 2013b). These studies suggest that scaling up HCV therapy (in addition to the existing harm reduction interventions) is necessary if substantial reductions in HCV prevalence over the next decade or two are to be made. It has been suggested that the new direct-acting antivirals have the potential for much higher rates of uptake because of their improved effectiveness, lower toxicity and reduced treatment times (Martin et al., 2013c); however, the cost of direct-acting antivirals may prohibit scaling up HCV treatment even among high-income countries, let alone low- to middle-income countries (Anonymous, 2014). Nevertheless, the future of HCV therapies may have implications for HCV prevention in the long term: the patents for many of the direct-acting antivirals will run out by 2030 and there are therefore cheaper drugs on the horizon (David Goldberg, Health Protection Scotland, personal communication). Some might argue that the widespread access to affordable therapy would obviate the need for preventive interventions such as IEP. However, widespread therapy would first require a number of challenges to be overcome, including increasing the uptake of therapy among PWID (which involves the challenges of both case finding, and educating clinicians and the health workforce to offer testing and treatment to active PWID). In the meantime, given that this scenario of inexpensive HCV therapy is probably at least 15 years away, the need for OST and IEP remains (and the speed with which HCV can spread in the absence of harm reduction interventions should not be forgotten).

It merits mention that, with regard to harm reduction interventions, there are policy considerations beyond just HCV prevention. While OST has other obvious benefits – reduced risk of overdose, reduced criminal activity and increased employment potential (Bell and Zador, 2000) – policymakers also need to take a holistic view of IEP services. Although chiefly aimed at preventing BBVs, other benefits of IEP that have not been considered in this thesis should be taken into account: for example, the prevention of bacterial infections. In many cases, IEP services often serve as a first point of contact for someone who has recently commenced injecting, therefore providing an opportunity to 'capture' PWID and refer them onto other services, such as treatment for their addiction.

A further consideration with regard to harm reduction interventions, particularly IEP, is the potential evolution of a new virus. The past epidemics of BBVs among PWID in Scotland were not discovered until very large proportions of the population had become infected. HIV and HCV found a suitable niche among PWID because of the prevalence of risk behaviours in this population group that permitted their efficient transmission given that, at the time, preventive interventions did not exist, or existed only at very low levels of coverage. Thus, there is a strong argument for maintaining harm reduction to prevent future, as-yet-unknown outbreaks of infection among PWID.

7.4 Recommendations for future research

The next sections address pertinent outstanding questions and suggest methods through which answers might be generated.

7.4.1 Are there other ways to measure recent HCV infection using cross-sectional designs?

Given that HCV among PWID has not yet been controlled, it will remain important to continue to monitor HCV transmission in this population. As described earlier, although the 'pre-seronversion window period' approach to measuring HCV incidence has benefits over a traditional cohort approach, one of its limitations is that large sample sizes are required in order to detect relatively few recent infections.

Another measure of recent infection, involving the avidity of anti-HCV, has been under development. Avidity is a term that is used to refer to the affinity or binding capacity of an antibody for an antigen (Abbas, Lichtman, and Pillai, 2014; Shepherd et al., 2013): in this case, the affinity of anti-HCV Immunoglobulin G for the HCV virus. Briefly, the assay involves treating a sample with a dissociation agent (which removes antibodies that are weakly bound to antigens) and comparing the treated sample with an untreated sample. The comparison generates an avidity index: the higher the index value, the greater the affinity or binding of the antibody.

It has been demonstrated that avidity increases with the time elapsed since infection – reflecting that the affinity of an antibody for a particular antigen 'matures' over time (Shepherd et al., 2013) – and several studies have shown distinct differences in the average avidity index between samples taken from individuals with new/acute infection as compared with current/chronic infection (Gaudy-Graffin et al., 2010; Kanno and

Kazuyama, 2002; Klimashevskaya et al., 2007). One study found that, when using an avidity threshold of 43, the assay distinguished new from current/chronic infections with 98% sensitivity and 100% specificity (Gaudy-Graffin et al., 2010). Another study used a threshold of 42 and found that all avidity index values for new/acute infections and current/chronic infections were lower and higher, respectively, than this threshold (Klimashevskaya et al., 2007). Studies have also demonstrated that, although avidity among people with past/cleared infection is (on average) lower than those with current/chronic infection and higher than those with new/acute infection, the index values can fall below the threshold that might be used to distinguish new/acute and current/chronic infection. Thus, the avidity index, alone, has been shown to be insufficient to distinguish between a new infection and a past/cleared infection; the individual's HCV-RNA status would also need to be known in order to make this distinction (Klimashevskaya et al., 2007).

While the development of the avidity test may have been driven by clinical considerations, there are promising epidemiological applications. Work in Scotland has been undertaken to validate an avidity assay on plasma and DBS: this study demonstrated that avidity index results on DBS samples (that had been mocked up from plasma) were generally lower than the corresponding avidity index results on plasma. They derived an algorithm, which included HCV-RNA status, that generated 100% sensitivity (95% CI 73.5-100%) and 98.3% specificity (95% CI 93.9-99.8%) from DBSs (a combination of mocked up and 'real' samples), but this was based on only 12 new/acute infections (Shepherd et al., 2013). Being able to undertake the avidity test on DBSs would open up epidemiological possibilities, because sero-surveillance studies among PWID are increasingly utilising DBSs for their ease and relative cost as compared with venepuncture (Hope et al., 2011). It is important to remember, however, that, because the avidity assay is possible only on individuals who have anti-HCV, it does not capture all recent infections (as it will miss those in the pre-seroconversion window period). Epidemiological studies might consider applying both avidity and window period approaches in order to maximise the number of recent infections detected, and consequently maximise statistical power.

For most HCV-infected individuals, the avidity index will increase from the date of infection, although not necessarily in a linear fashion. Thus, the avidity index in itself cannot be used as a measure of time since infection. The Scottish work indicates that a low avidity result suggests the infection has occurred within the previous four to five months (Shepherd et al., 2013); however, the duration of this state needs to be better elucidated,

particularly if the intention is to use avidity to estimate incidence per 100 person-years, using a similar approach to that applied in Chapters 4 and 6.

7.4.2 Are there alternatives to self-reported information when measuring harm reduction intervention uptake?

The reliance on self-reported information is a recurring limitation in this thesis. In Chapters 5 and 6, the exposure to the intervention was based on self-report. Although most published studies of harm reduction interventions have used self-reported information to determine exposure status, there have been a few instances where this was not the case. For example, follow-up studies of PWID in treatment have recorded the dosage of OST administered to participants; however, these studies have mostly been conducted in clinical settings. Additionally, a few studies have assigned exposure status based on whether a participant had attended a needle exchange (or not) during a defined time period; however, this approach has limitations that were discussed in Chapter 2.

In Scotland, data on the provision of IEP have been routinely reported and collated centrally since 2007 (Information Services Division, 2009). While these data were originally collected by means of a survey sent out to the NHS Boards to complete and return, recent steps have been taken to implement an electronic system, which will have nearly universal coverage across the NHS Boards in Scotland (Boards are currently in different stages of implementation). Data are collected in the service at the point of transaction with a client. At a minimum, the type and amount of injecting equipment given to the client are recorded. The identifying items of information collected from clients are initials, date of birth and sex, permitting the linkage of records both within the injecting equipment database itself and to external databases. This future national repository of data on injecting equipment provision presents the opportunity to undertake data linkage with the NESI data in order: (i) to compare provision data with self-reported data on the uptake of sterile injecting equipment in order to validate the self-reported data, and (ii) to examine the association between uptake of sterile injecting equipment using provision data and HCV infection status.

7.4.3 What is the relationship between needle/syringe coverage and HCV incidence?

In this thesis, the threshold defining high coverage of IEP was set at 200% (i.e. two sterile needles/syringes for every injection) for analysis purposes; however, there were indications

that PWID had overestimated the amount of equipment that they obtained from services, and thus the threshold might not be accurate. Although it has been suggested that the relationship between IEP and HCV incidence is not a dose-response relationship (Chapter 2), further work to determine the nature of this relationship – for example, to elucidate the actual coverage 'threshold' above which reductions in HCV incidence are realised – would be helpful to inform policy and practice. Statistical power to examine this threshold may present a challenge, given that the current analysis had only just enough power to examine two coverage groups (<200% and ≥200%), by the time other confounding variables were taken into account. A potential method to overcome this issue of power is through a pooled analysis. The pooling of data can be a useful tool when multiple studies examining the same intervention(s) and outcome(s) have been undertaken and when the variables are sufficiently similar to combine. Pooled analysis is generally preferable to meta-analysis when the data from these studies can be accessed. A pooled analysis of UK studies has already been undertaken and was able to demonstrate the combined impact of interventions, when individual studies had been unable to do so (Turner et al., 2011).

7.4.4 To what extent do PWID transition into and out of high coverage of interventions?

While the evidence presented here gives a cross-sectional 'snapshot' of the proportion of PWID on OST or with high coverage of needles/syringes, it is known that PWID do not remain consistently in these categories – for example, individuals' methadone dosages are often adjusted and it is well known that individuals in receipt of OST can drop out of treatment (Peters and Reid, 1998). What is not known is the frequency with which they transition into and out of high coverage of interventions. As stated in Chapter 6, more than 1,000 individuals participated two or more times across the three NESI surveys. Data linkage across these datasets would therefore offer the opportunity: (i) to examine how individuals change intervention 'states' over time, and (ii) to examine the factors that are associated with sustained high coverage of interventions.

7.4.5 Can the specific contributions of harm reduction interventions to the HCV prevalence and incidence landscape be elucidated?

There is a wealth of historical data available (mainly for Glasgow) on HCV prevalence, IRB and uptake of harm reduction interventions from community surveys of PWID undertaken regularly since 1990. To understand which interventions contributed to the

observed reduction in HCV incidence, a mathematical modelling study is planned, that will model the changes in OST, IEP and antiviral therapy over time to explore whether these models are consistent in generating the levels of HCV prevalence and incidence that have been observed in Scotland. The findings from these models would support or refute the evidence for a reduction in HCV transmission associated with the changes in coverage of interventions as a result of the Hepatitis C Action Plan. The projected impact of various scenarios of future harm reduction intervention coverage in Scotland will also be examined: for example, maintaining current coverage levels, further scale-up, or a decline in existing coverage. This study will help to identify the combinations of interventions that are needed to reduce HCV transmission effectively.

7.4.6 Can harm reduction interventions be further scaled up?

Can harm reduction interventions be scaled up or has a saturation point been reached? The answer to this question is likely dependent on the local context. In Scotland as a whole, the numbers of needles/syringes distributed has more or less reached a plateau; however the picture differs if separate NHS Board areas are examined (Information Services Division, 2013). There also appears to be more scope for scaling up paraphernalia distribution, which has not yet reached levels on a par with needle/syringe distribution in certain areas. As mentioned above, anecdotally, service providers have said that PWID already feel they are taking enough equipment for their needs (John Campbell, Glasgow Addiction Services, personal communication). Qualitative research would be helpful to identify reasons why PWID take away as much equipment as they do: for example, do they feel it is sufficient for their needs? Is it too much to carry? Do other barriers to taking away injecting equipment exist? Shedding light on these issues may help to tailor interventions if the intention is to bolster existing levels of IEP coverage.

7.5 Conclusions

The body of work in this thesis represents a novel contribution to the evidence base: it was the first large-scale, national application of a method designed to determine incidence of HCV using a cross-sectional design, and the first study to apply a framework to triangulate the evidence from different designs in order to investigate the association between harm reduction interventions and HCV transmission. This thesis does not propose to be able to establish a definitive causal link between IEP/OST and the prevention of HCV transmission. It does, however, provide sufficiently plausible evidence that the scale-up of

a combination of harm reduction interventions in Scotland between 2008 and 2012 contributed to the reduction in HCV incidence observed. Components of the thesis have already influenced existing policy and practice in Scotland and internationally. Regarding future policy in this area, the evidence generated and presented here supports, at least, the maintenance of the HCV prevention investment in Scotland, and certainly the consideration of further scale-up.

Appendix A: Review of reviews of opioid substitution treatment

OST is the provision of agonist pharmacotherapy for the treatment of opioid dependence. OST prevents withdrawal symptoms, reduces cravings associated with illicit opioid use and diminishes the effects of illicit opioids with a view to reducing both illicit opioid use and the frequency of injection. The most commonly prescribed forms of OST are methadone maintenance treatment (MMT) and buprenorphine maintenance treatment (BMT). In this review we refer primarily to evidence relating to MMT but the findings can be largely taken to refer to OST generally. OST is widely prescribed in the UK.

Three of the core review papers met the critical appraisal criteria related to OST and were primarily drawn upon for the evidence of effectiveness of this intervention:

- Tilson, H., Aramattana, A., Bozzette, S., Celentano, D., Falco, M., Hammett, T., Kozlov, A., Lai, S., Mahal, A., Scotthenfeld, R., and Solomon, S., 2007. *Preventing HIV Infection among Injecting Drug Users in High-Risk Countries: An Assessment of the Evidence*. Washington D.C.: Institute of Medicine.

- Gowing, L., Farrell, M., Bornemann, R., and Ali, R., 2004. Substitution treatment of injecting opioid users for prevention of HIV infection. *The Cochrane Library*, 4(Oct 18).

- Sorensen, J.L., and Copeland, A.L., 2000. Drug abuse treatment as an HIV prevention strategy: A review. *Drug Alcohol Depend,* 59(1), pp.17-31.

In the absence of any core review addressing the impact of OST on HCV incidence and prevalence, the evidence from one supplementary review paper was also considered:

- Wright, N.M., and Tompkins, C.N., 2006. A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users. *Harm Reduct J,* 3(6 Sep), p.27.

Supplementary reviews on the effectiveness of OST in prisons and young people are also referred to:

- World Health Organization, UNAIDS, and United Nations Office on Drugs and Crime, 2007. *Effectiveness of interventions to manage HIV in prisons - Opioid substitution therapies and other drug dependence treatment*. Geneva: World Health Organization.

- Hopfer, C.J., Khuri, E., Crowley, T.J., and Hooks, S., 2002. Adolescent heroin use: a review of the descriptive and treatment literature. *J Subst Abuse Treat,* 23(3), pp.231-7.

Finally, one review which examined the cost-effectiveness of OST and a key modelling study on the cost-effectiveness of OST in preventing HIV and HCV, were identified:

- Connock, M., Juarez-Garcia, A., Jowett, S., Frew, E., Liu, Z., Taylor, R.J., Fry-Smith, A., Day, E., Lintzeris, N., Roberts, T., Burls, A., and Taylor, R.S., 2007. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess,* 11(9), pp.1-171.

- Pollack, H.A. and Heimer, R., 2004. The impact and cost-effectiveness of methadone maintenance treatment in preventing HIV and hepatitis C. In: J. Jager, W. Limburg, M. Kretzschmar, M. Postma, and L. Wiessing., eds. *Hepatitis C and injecting drug use: impact costs and policy options.* Luxembourg: European Monitoring Centre for Drugs and Drug Addiction.

A summary of the papers described above can be found in Table A-1.

A1.1 Effects on HCV Incidence/Prevalence

The supplementary review by Wright and Tompkins (2006) refers to the results of five[8] studies which examined the relationship between OST and HCV incidence (Tables A-2 and A-3a). A nested case-control study and a prospective cohort study found lower but statistically non-significant HCV incidence among those in OST compared to those who are not in treatment (Rezza et al., 1996) or those who have left treatment (Thiede, Hagan, and Murrill, 2000), respectively. Another cohort study found OST (in combination with

[8] One study is erroneously quoted by Wright et al. as comparing HCV incidence between those in MMT/not in MMT, but the study in fact compared HCV with HIV and HBV incidence, and is therefore not included in the latter table (Chamot et al., 1992).

NSP) was not associated with any decreases in annual HCV incidence over four years (van Ameijden et al., 1993). Finally, two cohort studies did not find any significant differences in HCV incidence between those in OST and those not in OST (Crofts et al., 1997; Selvey, Denton, and Plant, 1997). The findings of these studies are summarised in Table A-3.

Based on the available evidence Wright and Tompkins (2006) concluded that: "As regards methadone maintenance therapy, whilst it has been successful in reducing the incidence of HIV, the evidence for its effectiveness in reducing HCV incidence is less convincing." (p.5)

The findings from primary studies examining OST and HCV incidence published *since* the Wright and Tompkins review are mixed (Table A-3b). Two community-based OST studies suggested a positive impact of OST: HCV incidence was considerably (although non-significantly) lower among those in continuous OST compared with those with interrupted OST (Hallinan et al., 2004); and OST in the past six months was protective against HIV/HCV infection among mono-infected or non-infected IDUs (Miller et al., 2004). While Maher et al. (2006), albeit using a less categorical measure of exposure to OST, found no difference in risk of HCV seroconversion among IDUs recruited from OST clinics and IDUs recruited from NSP sites. From two linked prison-based OST studies, Dolan and colleagues found no difference in HCV incidence between the prison OST and waitlist control groups at five month follow-up (Dolan et al., 2003); however, in a subsequent four year follow-up, retention in OST was associated with reduced HCV infection, while short OST episodes (less than five months) were significantly associated with greater risk of HCV (Dolan et al., 2005). Finally, in addition, a prospective cohort study of IDUs in South Wales showed that, at 12-month follow-up, HCV incidence was similar among individuals who were not in OST during follow-up or in OST for up to six months, but was lower amongst individuals in treatment for seven to 12 months. Moreover, among homeless IDUs, HCV incidence of those not in OST was more than twice that of those in OST (Craine et al., 2009).

Drawing on Wright and Tompkins (2006) and the above-mentioned primary studies, we see: three studies have shown a significant positive association between retention in OST and reduced HCV incidence (all cohort studies); and eight have reported no association (one RCT, one case-control and six cohort studies).

We conclude that the level of evidence is insufficient, given the absence of a statement from a core review and inconclusive evidence from multiple robust studies (showing a few positive associations, but predominantly no association).

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness in reducing HCV transmission among PWID.

A1.2 Effects on HIV Incidence/Prevalence

All of three of the core OST reviews assessed the evidence with respect to HIV incidence outcomes (Gowing et al., 2004; Sorensen and Copeland, 2000; Tilson et al., 2007). The focus is primarily on the Tilson et al. (2007) and Gowing et al. (2004) reviews as these are the most recent and rigorous (note: Tilson et al. draws heavily on Gowing et al.). In total the three reviews draw on seven primary studies which relate to the impact of OST on HIV incidence or prevalence and there was high overlap between studies included in the reviews (Table A-2). These comprised one RCT (Dolan et al., 2003), four cohort studies (Hartel and Schoenbaum, 1998; Metzger et al., 1993; Moss et al., 1994; Williams et al., 1992); one case-control study (Serpelloni et al., 1994) and one cross –sectional study (Novick et al., 1990).

The odds of HIV seroconversion were found to be many times greater for untreated individuals or those with interrupted OST compared to those who remained continuously in OST (Metzger et al., 1993; Moss et al., 1994; Williams et al., 1992), although the latter study was statistically non-significant. Lower daily dose and more time out of OST was also associated with higher risk of HIV seroconversion (Hartel and Schoenbaum, 1998; Serpelloni et al., 1994). Dolan and colleagues' RCT of OST in prison found no difference in HIV incidence between those in OST and waitlist controls; however, this was in the context a short period of follow-up and low prevalence of HIV and reduced injection prevalence (Dolan et al., 2003). The findings from these studies are summarised in Table A-4.

The conclusions from all three core reviews allowed that continuous OST is associated with lower rates of HIV seroconversion but that self selection bias, that is patients who resist treatment or engage in risky behaviours may leave treatment while those with fewer HIV risk behaviours may stay in treatment longer, cannot be ruled out:

Tilson et al. (2007) concluded that:

"Modest evidence from prospective cohort and case-control studies shows that continuous opioid agonist maintenance treatment is associated with protection against HIV seroconversion. This association persists after controlling for many confounders. These studies also show that the risk of HIV seroconversion is inversely related to length of time in treatment. However the possibility of bias in these findings from self selection cannot be ruled out." (p.92)

Gowing et al. (2004) concluded that:

"Few data and variability in the means of reporting limit the conclusiveness of any analysis, but these studies consistently indicate lower rates of [HIV] seroconversion associated with substitution treatment. This suggests that reductions in risk behaviour do translate into actual reduction in cases of HIV infection." (p. 16)

Finally, Sorensen and Copeland (2000) concluded that:

"Four out of the six studies reviewed…provided firm evidence for the protective effect of OST against HIV seroconversion. These findings are more convincing because they are based on biologically verified outcomes rather than participant self-report…[but] nearly all the studies are inherently limited by a self-selected treatment sample…in most of the studies the in-treatment and out-of treatment groups differ on demographics and that there may be other unidentified differences in these groups that may account for the differences found in HIV seroconversion". (p.27)

Evidence statement: There is sufficient review-level evidence to support the effectiveness of continuous OST in reducing HIV incidence but self-selection bias cannot be ruled out.

A1.3 Effects on injecting risk behaviour

In total the three core reviews draw on 37 primary studies which relate to IRB, 22 of which are included in more than one review (A-2). There was considerable heterogeneity in the measurement of IRB in the primary studies. The measurement of IRB can be categorised into three domains: prevalence and frequency of injection; sharing of injecting equipment; and scores of drug-related risk. The studies are summarised in Table A-5.

A1.3.1 Prevalence and frequency of injection

Tilson et al. (2007) and Gowing et al. (2004) reviewed six studies that reported on prevalence of injecting drug use before and after OST (Camacho et al., 1996; Chatham et al., 1999; Dolan et al., 2003; Gossop et al., 2000; King et al., 2000; Magura et al., 1991); eight studies that reported on frequency of injection at baseline and follow-up (Batki et al., 1989; Brooner et al., 1998; Camacho et al., 1996; Chatham et al., 1999; Dolan et al., 2003; Kwiatkowski and Booth, 2001; Simpson et al., 1995; Strang et al., 2000); and two studies that examined both the proportion and frequency of injection (Camacho et al., 1996; Chatham et al., 1999). The studies varied in design, follow-up periods (range 3 to 12 months) and measurement of frequency of injecting, but all studies showed statistically significant decreases in IRB from baseline to follow-up (Gowing et al., 2004; Tilson et al., 2007).

Additionally, Sorensen and Copeland (2000) refer to a further nine studies with data on injection prevalence and frequency: five longitudinal studies of in treatment samples showed retention in OST was associated with decreases in injection frequency (Abbott et al., 1998; Ball et al., 1988; Iguchi, 1998; Saxon, Calsyn, and Jackson, 1994; Shore et al., 1996); and four studies comparing those in treatment with non treatment samples found OST associated with fewer injections (Baker et al., 1995; Greenfield, Bigelow, and Brooner, 1995; Meandzija et al., 1994; Stark et al., 1996b).

A1.3.2 Sharing of injecting equipment

Tilson et al. (2007) and Gowing et al. (2004) reviewed seven studies that examined the proportion of participants who reported sharing equipment before and after a period of OST. Six out of seven (Camacho et al., 1996; Chatham et al., 1999; Dolan et al., 2003; Gossop et al., 2000; Grella et al., 1996; Margolin et al., 2003) found a significant reduction in sharing between baseline and follow-up. The seventh study (King et al., 2000), found a non-significant reduction in reported sharing.

Sorensen (2000) additionally reported on four longitudinal studies of in-treatment samples which showed that retention in OST was associated with decreases in sharing of injecting equipment (Camacho et al., 1996; Magura et al., 1991; Rhoades et al., 1998; Saxon, Calsyn, and Jackson, 1994) and one study that showed no differences in sharing between new treatment entrants and the rest of the sample (Calsyn et al., 1991). Five studies

comparing those in treatment with non treatment samples found OST was associated with decreased sharing (Caplehorn and Ross, 1995; Greenfield, Bigelow, and Brooner, 1995; Klee et al., 1991; Longshore et al., 1993; Stark et al., 1996b) and one study found no differences in sharing (Baker et al., 1995).

A1.3.3 Scores of drug related risk

Tilson et al. (2007) and Gowing et al. (2004) report on five studies which provided data on drug-related HIV risk scores before and after OST (Abbott et al., 1998; Avants et al., 1998; Baker et al., 1995; Chatham et al., 1999; Sees et al., 2000). Abbott et al. and Avants et al. used the Risk Assessment Battery (Navaline et al., 1994), Baker et al. used the HIV-Risk Taking Behaviour Scale (Ward, Darke, and Hall, 1990), Sees et al. used the Risk of AIDS Behaviour Scale (Metzger et al., 1992) and Chatham et al. calculated a Risky Needle Exposure Index (based on the number of persons with whom injecting equipment had been shared pre and post OST). For all of these scales, a higher score indicates higher levels of risk behaviour. Three of the five studies (Abbott et al., 1998; Avants et al., 1998; Chatham et al., 1999) found significant decreases in drug-related HIV risk behaviour scores before and after OST. Sees et al. (2000) found a non-significant reduction in mean risk scores between intake and six month follow-up between the methadone maintenance and methadone detoxification groups. Finally Baker et al. (1995) compared risk scores for cohorts of PWID who currently, previously or never received OST and found the current OST group had significantly reduced risk scores compared to the other groups.

The conclusions from all three reviews were conclusively that OST was associated with reductions in self-reported prevalence and frequency of injection, sharing of injecting equipment and injecting risk scores: Tilson et al. (2007) concluded that:

“Moderate to strong evidence from one RCT and a number of observational studies show that patients receiving methadone maintenance treatment report reductions in several drug-related HIV risk behaviours, including frequency of injecting and sharing of injecting equipment. These patients also had lower summary scores of drug-related risk behaviour compared with pre-treatment levels”. (p.89)

Gowing et al. (2004) concluded that:

"Substitution treatment is associated with a significant decrease in the proportion of participants reporting injecting drug use and in the frequency of injection…[and] a significant decrease in the sharing of injecting equipment…[drug risk scores] data were consistent with the findings in relation to injecting drug use and sharing of injecting equipment in that the studies that reported scores also showed a significant reduction is risk associated with substitution treatment." (pp.14-15)

Finally Sorensen (2000) concluded that:

"26 out of 28 studies showed positive results in reducing HIV risk behaviours…In this review both longitudinal studies of in-treatment samples and studies comparing treatment patients with other samples found very strong evidence that drug abuse treatment decreases the risk of HIV infection by decreasing needle-use. The evidence is less strong, but still substantial, that drug abuse treatment changes the needle use patterns of participants (e.g. less needle-sharing, more use of sterile needles)." (pp. 27-28).

Evidence statement: There is sufficient review-level evidence to support the effectiveness of OST in reducing IRB by reducing the frequency of injection, the sharing of injecting equipment and injecting risk scores.

A1.4 Prison

None of the core reviews specifically examined the impact of prison-based OST on HCV/ HIV incidence/prevalence or IRB. We refer to a recent supplementary review of the effectiveness of OST to manage HIV in prison (World Health Organization, UNAIDS, and United Nations Office on Drugs and Crime, 2007). The evidence was reviewed using the Bradford Hill criteria as per other reviews in the World Health Organization (WHO) Evidence for Action series (e.g. Wodak and Cooney, 2004). The primary question in this review, as relates to the outcomes being examined in this review, was whether prison-based OST leads to a reduction in illegal drug use and associated risk behaviours in prison. This review, however, provided very little detail on individual study quality, characteristics or findings.

A1.4.1 Effects on HCV Incidence/Prevalence

Two studies included in the WHO (2007) review examined prison OST and HCV incidence and have already been described (Section 8.1). Briefly, in their RCT, Dolan and colleagues found no difference in HCV incidence between the prison OST and waitlist control groups at five month follow-up (Dolan et al., 2003). However at four year follow-up, retention in OST was associated with reduced HCV infection, while short OST episodes (less than five months) were significantly associated with greater risk of hepatitis C (Dolan et al., 2005).

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness OST with respect to HCV transmission in prison settings. One RCT suggests that retention in OST from prison to community settings is associated with reduced HCV incidence.

A1.4.2 Effects on HIV Incidence/Prevalence

Only one study included in the WHO (2007) review examined the effects of prison OST on HIV incidence. Dolan et al. (2003) found no difference in HIV incidence between treatment and control groups. As mentioned earlier, however any impact on HIV incidence may not have been detectable given the low prevalence of HIV in the Australian context and the short period of follow-up (Dolan et al., 2003).

Evidence statement: There is insufficient review-level evidence to draw any strong conclusions regarding the effectiveness OST with respect to HIV transmission in prison settings. Data from one RCT in a jurisdiction with low HIV prevalence found no difference in HIV incidence between those receiving OST and controls.

A1.4.3 Effects on injecting risk behaviour

WHO (2007) referred to seven studies of prison-based OST programmes ('four controlled trials and three descriptive studies'). On closer examination however, it appears that several of these publications are reporting very similar findings from the same data set ((Heimer et al., 2005; Heimer et al., 2006) and (Dolan, Hall, and Wodak, 1996; Dolan, Wodak, and Hall, 1998)).

They reported that all included studies found that opioid using IDUs who receive OST in prison inject significantly less frequently than those not receiving OST (Bayanzadeh, 2004;

Boguna, 1997; Dolan, Hall, and Wodak, 1996; Dolan et al., 2003; Dolan, Wodak, and Hall, 1998; Heimer et al., 2005; Heimer et al., 2006).

WHO (2007) concluded:

"Prison-based OST programmes appear to be effective in reducing the frequency of injecting drug use and associated sharing of injecting equipment, if a sufficient dosage is provided and treatment is provided for longer periods of time. The risk of transmission of HIV and other BBVs among prisoners is also likely to be decreased. In addition, there are other benefits, both for the health of prisoners participating in the programmes, and for prison systems and the community" (p.9)

Evidence statement: There is tentative review-level evidence to support the effectiveness of OST in reducing IRB among IDUs in prison settings by reducing heroin and other opioid use.

A1.5 Young IDUs

None of the core reviews specifically examined the impact of OST on young people's HCV/ HIV incidence/prevalence or IRB. We refer to one supplementary review of drug treatment (including OST) in young people (Hopfer et al., 2002). 'Young' was defined as a mean age of 21 years or less. We also identified a Scottish systematic literature review of services for young problem drug users (aged less than 16 years) but it did not include any studies that demonstrated the effects of OST for young drug users (Elliott et al., 2002). Clinical guidelines and other advisory material suggest that the decision to prescribe OST to under-16s should be a highly unusual occurrence, and that is only undertaken in the most extreme circumstances (Effective Interventions Unit, 2003).

A1.5.1 Effects on HCV Incidence/Prevalence

We did not identify any reviews that examined the effects of OST on HCV incidence or prevalence among young people.

Evidence statement: There is no review-level evidence to either support or discount the effectiveness of OST with respect to HCV transmission among young people.

A1.5.2 Effects on HIV Incidence/Prevalence

We did not identify any reviews that examined the effects of OST on HIV incidence or prevalence among young people.

Evidence statement: There is no review-level evidence to either support or discount the effectiveness of OST with respect to HIV transmission among young people.

A1.5.3 Effects on injecting risk behaviour

Hopfer et al. (2002) refer to three observational studies of OST and young people which examined OST retention. The limited data reported on drug use suggest that, for those retained in OST, heroin use decreased (DeAngelis and Lehmann, 1973; Rosenberg and Patch, 1972; Sells and Simpson, 1979).

Evidence statement: There is insufficient review-level evidence to either support or discount the effectiveness of OST with respect to injecting-related risk behaviour among young people.

A1.6 Other factors affecting OST outcomes

Several factors have been shown to impact on OST outcomes: duration of treatment, dosage and the provision of adjunctive psycho-social services.

As highlighted previously, continuous OST is associated with lower HIV incidence than interrupted OST or no OST. The impact of treatment duration/continuity of treatment on drug use and IRB is addressed by Tilson et al. (2007) and Gowing et al. (2004):

In relation to duration or length of treatment, Tilson et al. (2007) concluded:

"Strong evidence from several large randomized clinical trials shows that continuous agonist maintenance therapy is associated with longer treatment retention – and reductions in illicit opioid use and relapse to opioid dependence – than short term use of these agents. Furthermore, modest evidence from quasi-experimental studies also suggests that discontinuation of agonist maintenance therapy is associated with higher rates of re-addiction and criminal behaviour. Agonist maintenance therapies are effective while they are provided and no evidence suggests a benefit to early termination. Thus, reasonable clinical guidance is to continue such therapies as long as they are associated with positive effects" (p.94).

In relation to the impact of OST on IRB after cessation of OST, Gowing et al. (2004) concluded:

"The duration of effect of substitution treatment is unclear. Relapse to illicit opioid use is common following cessation of substitution treatment but it is not clear to what extent injecting risk reduction strategies are practised following cessation of substitution treatment" (p.16).

In relation to dosage, Tilson et al. (2007) concluded:

"Strong evidence from randomized, double-blind clinical trials, shows that buprenorphine and methadone maintenance treatment have greater efficacy at higher doses. Thus reasonable clinical guidelines would recommend raising the dose until optimal effects occur, rather than setting arbitrary limits. Studies systematically examining dosing show greater efficacy up to 100 milligrams per day of methadone, and up to 16 milligrams per day of buprenorphine" (p.96).

Finally, in relation to OST in combination with psycho-social treatment, Tilson et al. (2007) concluded:

"Few studies have specifically examined the impact of adjunctive psychosocial interventions on HIV risk behaviour among patients on opioid agonist maintenance therapy. Weak evidence from several studies suggests that some psychosocial interventions for patients enrolled in such therapy can be effective in reducing sexual and drug-related HIV risk behaviour, but more research is needed" (p.100).

Evidence statement: There is sufficient review-level evidence to support the effectiveness of continous and higher dose OST in reducing opioid use and injection frequency. There is insufficient review-level evidence to either support or discount the impact of adjunctive psycho-social treatment in combination with OST treatment in reducing IRB.

A1.7 Cost-effectiveness

Connock et al. (2007) reviewed eleven economic evaluations of OST effectiveness in managing opioid dependence (Barnett, 1999; Barnett, Zaric, and Brandeau, 2001; Dijkgraaf et al., 2005; Doran et al., 2003; Goldschmidt, 1976; Harris, Gospodarevskaya, and Ritter, 2005; Masson et al., 2004; Sheerin, Green, and Sellman, 2004; Sirotnik and

Bailey, 1975; Zaric, Barnett, and Brandeau, 2000; Zaric, Brandeau, and Barnett, 2000; Zarkin et al., 2005). The economic methods and findings of these studies are summarised in Table A1-6. They concluded:

"With respect to retention in treatment and reductions in opioid use, both flexible-dose MMT and BMT are more clinically effective and more cost-effective than no drug therapy in opioid-dependent users. In direct comparison, flexible-dose MMT (daily equivalent dose from 20 or 30 to 60 or 120 mg) was found to be somewhat more effective in maintaining individuals in treatment than BMT (daily equivalent dose from 2 or 4 to 8 or 16 mg) and was therefore associated with a slightly higher health gain and lower costs. However, this needs to be balanced by the more recent experience of clinicians in the use of buprenorphine, the possible risk of higher mortality of MMT and individual opioid-dependent users' preferences" (Connock et al., 2007).

Pollack and Heimer (2004) used a random mixing modelling approach to examine the cost-effectiveness of OST in preventing HCV and HIV, inputting parameters drawn from the US literature (Alter and Moyer, 1998; Centers for Disease Control and Prevention, 1998; Kaplan, 1989; Kaplan and Heimer, 1992a; Vlahov et al., 1995; Zaric, Barnett, and Brandeau, 2000). They drew five main conclusions:

"MMT appears to be highly cost-effective as a means of HIV prevention in high risk populations. Even if MMT did not bring any improvement in other outcome domains (e.g. mental health and physical well-being, criminal offending, social integration), it would remain highly cost-effective based solely upon its ability to reduce HIV infection;

Typical MMT programmes appear less effective and thus less cost-effective in the control of HCV. As HCV is so efficiently transmitted MMT has a smaller impact on HCV incidence. This highlights the reality that harm reduction interventions effective for HIV may be less effective against HCV;

MMT treatment quality is more important to the success of HCV prevention than to the prevention of HIV. Given the efficiency of HCV transmission, the impact and cost-effectiveness of MMT are especially sensitive to treatment quality. The rate of treatment-related exits and the proportion of treatment adherent MMT clients play critical roles in the impact and cost-effectiveness of MMT;

MMT is most cost-effective when applied to a large fraction of active IDUs. Because many current and former MMT clients share (or would share if active injectors) syringes with other IDUs, broad coverage creates substantial benefits, even for active drug injectors who are not currently in treatment. Treatment on request provides substantial protection against HIV;

Effective harm reduction interventions can increase the impact and cost- effectiveness of concomitant interventions. Costs per averted injection of MMT are proportional to the reproductive rate of infection. Interventions that reduce steady-state prevalence (e.g. bleach provision, shortening of drug users careers), augment the cost-effectiveness of MMT. The converse also holds, broad availability of MMT to slow the spread of blood-borne disease increases the cost-effectiveness of harm reduction interventions." (p.360)

Evidence statement: There is sufficient review-level evidence to support the cost-effectiveness of OST in HIV prevention but insufficient evidence to support its cost-effectiveness in HCV prevention. There is also sufficient review-level evidence to support the cost-effectiveness of OST in reducing illicit opioid use.

A1.8 Discussion and conclusions

There is a relatively large body of evidence of reasonable quality in relation to OST outcomes. We identified several core reviews which reported largely consistent findings that allow us to make confident conclusions about the impact of OST on HIV transmission and IRB. However the review-level evidence leaves us uncertain about the impact of OST on HCV transmission.

A1.8.1 What we know

- The available evidence for the impact of OST on HCV incidence is not compelling. We did not identify any core level reviews. The evidence from a supplementary review and subsequently published primary studies is mixed and suggests any impact will be greatest among those in continuous OST.

- There is consistent evidence from three core reviews that OST is effective in reducing HIV seroconversion, especially among those in continuous treatment. However, a key bias highlighted in the evidence base which cannot be discounted is

self-selection, whereby those with fewer risk behaviours may be more likely to both engage in and be retained in OST.

- There is consistent evidence from three core reviews that OST reduces frequency of drug injection, sharing of injecting equipment and scores of drug related risk.

- There is evidence from two core reviews that highlights that the impact of OST on reduced HIV seroconversion and IRB is associated with continuous treatment and is dose dependent.

- There is good evidence that OST is highly cost-effective in reducing opioid use and in HIV prevention but not as cost-effective in HCV prevention.

A1.8.2 Gaps and inconsistencies in the evidence

- There was insufficient evidence to make conclusions about the role of adjunctive psycho-social treatment on blood borne viral incidence and IRB outcomes.

- It is not clear from these reviews to what extent the reduction in sharing behaviour after entering OST is due to overall reductions in the prevalence of injecting and to what extent injecting risk reduction strategies are practised following cessation of OST.

- It is not clear from these reviews to what extent treatment service models and quality impact on OST blood borne viral incidence and IRB outcomes.

Table A-1. Summary of core and supplementary reviews on OST

Author and date	Title	Dates covered	Scope	Critical assessment	No. studies
Tilson et al., 2007	Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence	Up to Jan 2006	OST and NSP	Core review	0 HCV 4 HIV 21 injecting-risk
Gowing et al., 2004	Substitution treatment of injection opioid users for prevention of HIV infection	Up to July 2003	OST	Core review	0 HCV 5 HIV 24 injecting-risk
Sorensen and Copeland, 2000	Drug abuse treatment as an HIV prevention strategy: a review	1988-1998	MMT and other drug treatments (e.g. inpatient, outpatient, drug free, residential)	Core review	0 HCV 6 HIV 19 injecting-risk
Wright and Tompkins, 2006	A review of the evidence for the effectiveness of primary prevention interventions for Hepatitis C among injecting drug users	Up to April 2003	MMT, NSP, behavioural interventions, bleach, DCRs	Supplementary review	6 HCV 0 HIV 0 injecting risk
WHO, 2007	Effectiveness of Interventions to Manage HIV in Prisons – Opioid substitution therapies and other drug dependence treatment	Not specified. Publication dates up to 2006	Prison settings: OST, therapeutic communities, counselling, 'boot camp'.	Supplementary review	2 HCV 1 HIV 8 injecting-risk
Hopfer et al., 2002	Adolescent heroin use: a review of the descriptive and treatment literature	Not specified. Publication dates up to 1998	Heroin using youth: MMT, drug free treatment, therapeutic communities	Supplementary review	0 HCV 0 HIV 3 injecting-risk
Connock et al., 2007	Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation	Up to August 2005	OST	Core review	10 Economic
Pollack and Heimer, 2004	The impact and cost-effectiveness of methadone maintenance treatment in preventing HIV and hepatitis C	Not specified. Publication dates up to 2002	Modelling study	Supplementary economic paper	NA

Table A-2. Primary studies included within the core review papers (OST)

	Tilson et al (2007)	Gowing et al (2004)	Sorensen and Copeland (2000)	Wright and Tompkins (2006)
HCV incidence				
Crofts et al., 1997				✓
Rezza et al., 1996				✓
Selvey et al., 1997				✓
Thiede et al., 2000				✓
Van Ameijden et al., 1993				✓
Total	0	0	0	5
HIV incidence				
Dolan et al., 2003		✓		
Hartel and Schoenbaum, 1998			✓	
Metzger et al., 1993	✓	✓	✓	
Moss et al., 1994	✓	✓	✓	
Novick et al., 1990			✓	
Serpelloni et al., 1994	✓	✓	✓	
Williams et al., 1992	✓	✓	✓	
Total	4	5	6	0
Injecting-risk behaviour[a]				
Abbott et al., 1998	✓	✓	✓	
Avants et al., 1998	✓	✓		
Baker et al., 1995	✓	✓	✓	
Ball et al., 1998			✓	
Batki et al., 1989	✓	✓		
Bellis 1993			✓	
Britton 1994		✓		
Brooner et al., 1998	✓	✓		
Camacho et al., 1996	✓	✓	✓	
Caplehorn and Ross, 1995			✓	
Caslyn et al., 1991			✓	
Chatham et al., 1999	✓	✓		
Dolan et al., 2003	✓	✓		
Gossop et al., 2000	✓	✓		
Grella et al., 1996	✓	✓		
Gottheil 1993			✓	
Greenfield et al., 1995			✓	
Iguchi, 1998			✓	
King et al., 2000	✓	✓		

[a]Includes prevalence and frequency of injecting, sharing and scores of drug related risk

Table A-2 continued.

	Tilson et al (2007)	Gowing et al (2004)	Sorensen and Copeland (2000)	Wright and Tompkins (2006)
Klee et al., 1991			✓	
Kwiatkowski et al., 2001	✓	✓		
Longshore et al., 1993			✓	
Maddux 1997	✓	✓		
Magura et al., 1991	✓	✓		
Magura et al., 1998			✓	
Margolin et al., 2003	✓	✓		
Meandzija et al., 1994		✓	✓	
Metzger et al., 1993	✓	✓		
Rhoades et al., 1998			✓	
Saxon et al., 1994			✓	
Sees et al., 2000	✓	✓		
Shore et al., 1996			✓	
Simpson et al., 1995	✓	✓		
Stark et al., 1996	✓	✓	✓	
Strang et al., 2000	✓	✓		
Thiede et al., 2000	✓	✓		
Williams et al., 1992			✓	
Total	21	23	19	0

Table A-3a. Results of primary studies of the effectiveness of OST with respect to HCV prevalence/ incidence

Author and year	Study design and setting	Finding[a]	Results
Crofts et al., 1997	MMT clinic cohort Australia N=73	No association	HCV incidence was 22/100 py (95%CI 14.2-34.8). There was no significant difference in cumulative incidence between those in MMT (continuous or interrupted) and those not in MMT (f=.005).
Rezza et al. 1996	Nested case control study Naples, Italy N=746	No association	HCV incidence was 28.6/100py (95% CI 17.8–43.4). Increased risk of seroconversion associated with no MMT in the previous six months of borderline significance (AOR 2.9, 95% CI 0.9–9.7).
Selvey et al., 1997	Prospective cohort Brisbane, Australia N=106 MMT clinic	No association	HCV seroconversion was 11/100 py (95% CI 2-20). Univariately MMT was not associated with seronconversion (RR and CIs not reported).
Thiede et al., 2000	Prospective cohort Seattle, USA N=716	No association	No statistically significant reduction in HCV seroconversion among those who continued in MMT compared to those who left MMT (AOR = 0.4, 95% CI 0–4.2)
Van Ameijden et al., 1993	Prospective cohort MMT, NSP and information/education/counselling Amsterdam, Netherlands N=305	No association	No statistically significant reduction in annual HCV incidence rate/100 py over the four year study period (1986: 16.9; 1987: 4.0; 1988: 12.5; 1989: 11.2) chi-squared test for trend, P=0.79)

[a]Positive, negative, or no association refers to overall direction of association with HCV prevalence/seroconversion.

Table A-3b. Results of primary studies of the effectiveness of OST with respect to HCV prevalence/ incidence published since Wright and Tompkins (2006) review

Author and year	Study design and setting	Finding[a]	Results
Craine et al., 2009	Prospective cohort South Wales, UK	Positive	At 12-month follow-up, HCV incidence was similar between those not in OST and OST up to six months, but wassignificantly lower among those in OST for 7 to 12 months. Among homeless IDUs, HCV incidence of those not in OST was more than twice that of those in OST.
Dolan et al., 2003	RCT New South Wales, Australia N=67 (anti-HCV negatives at baseline)	No association	There was no difference in HCV incidence between heroin-using prisoners randomised to receiving MMT (24.3 per 100 py, 95% CI 7-62) vs. the waitlist control group (31.7 per 100 py, 95% CI 9-81)
Dolan et al., 2005b	Prospective cohort New South Wales, Australia N=382	Positive	4 year follow-up found among those in MMT in prison, increased risk of HCV seroconversion was associated with MMT episodes less than five months [AHR 4.2 (95% CI, 1.4-12.6; P = 0.01)].
Hallinan et al., 2004	Retrospective cohort Sydney, Australia N=54	No association	Overall HCV incidence was 3.8/100 py (95% CI 1.2-8.9). Of the five seroconversions, four were in the interrupted OST group (n=20), incidence of 7.4/100 py (95% CI 2.0-18.9), compared with one seroconversion in the continuous OST group (n=34), incidence of 1.3/100 py (95% CI 0.03-7.3). The difference between the groups was not statistically significant.
Maher et al., 2006	Prospective cohort Multi-site, Australia N=368 (anti-HCV negatives at baseline)	No association	Study recruitment from a MMT clinic was associated with no difference in risk of seroconversion [AOR 1.92 (0.66–5.62)] compared to recruitment from NSP sites.
Miller et al., 2004	Prospective cohort Vancouver, Canada N=479 community recruited young IDUs (<30 years)	Positive	16% were co infected with HIV and HCV at baseline and a further 15% became co infected during the study. MMT in previous six months was associated with reduced time to HCV and/or HIVseroconversion (ARR = 0.23, CI 0.09, 0.59).

[a]Positive, negative, or no association refers to overall direction of association with HCV prevalence/seroconversion.

Table A-4. Results of primary studies of the effectiveness of OST with respect to HIV prevalence/ incidence

Author and year	Study design and setting	Finding[b]	Results
Dolan et al., 2003	RCT of MMT New South Wales, Australia N=253	No association	HIV prevalence was zero at both baseline and follow up for all subjects.
Hartel and Shoenbaum, 1998	Retrospective and prospective cohort New York. USA N=622	Positive	Reduced risk of HIV infection associated with MMT dose > = 80 mg (AOR = 3.07/yr, 95% CI 1.23-7.68) and last year entered MMT (AOR = 1.22/yr, 95% CI 1.06-1.41).
Metzger et al., 1993	Prospective cohort Philadelphia, USA N=205	Positive	HIV seroconversion greater among those not in MMT compared to those who remained continuously in MMT (OR 7.63, 95% CI 1.99-29.27; p<0.01).
Moss et al., 1994	Case-control San Francisco, USA N=681	Positive	HIV seroconversion greater among those who spent < 12 months in MMT compared with those who spent >= 12 months in MMT (AHR 4.0, p<0.002).
Novick et al., 1990	Cross sectional New York, USA N=58	Positive	Zero HIV prevalence among long term stable MMT clients (16.9 +/- 0.5 years MMT) on median dose of methadone was 60 mg (range 5 to 100 mg) with history of high risk PWIDbefore MMT (10.3 +/- 1.7 years IDU).
Rhoades et al., 1998	RCT Texas, USA N=150	No association	Four groups of 50 or 80 mg of MMT and clinic attendance two or five days per week. HIV infection rate at MMT entry was 9%. No seroconversions between baseline and six months.
Serpelloni et al., 1994	Nested Case-control Verona, Italy N=952	Positive	HIV seroconversion risk increased 1.5 times for every three months of the last 12 months spent out of MMT (OR 1.44, CI 0.89-2.32 , Wald statistic 1.55) and there was an inverse association between daily MMT dose and HIV incidence (OR 0.77, CI 0.53-1.13, Wald statistic -1.39).
Williams et al., 1992	Prospective cohort New Haven, USA N=98	No association	The seroconversion rate for the continuous MMT group was 0.7/100 py (95% CI 0.1-5.3) and 4.3/100 py (95% CI 2.2.-8.6) for the interrupted treatment group. Controlling for length of follow-up, the difference between seroconversion rates was not significant (Z=1.65; p=0.10).

[a]Positive, negative, or no association refers to overall direction of association with HIV prevalence/seroconversion

Table A-5. Results of primary studies of the effectiveness of OST with respect to IRB[a]

Author and year	Study design and setting	Finding[b]	Results
Abbott et al., 1998	RCT USA N=151	Positive	MMT with community reinforcement vs. standard MMT had significantly fewer positive urines at three weeks and lower drug use and risk scores (Addiction Severity Index) at six months.
Avants et al., 1999	RCT USA N=307	Positive	Among socially anxious IDUs, reductions in drug use and HIV risk behaviours and abstinence at end of treatment greatest in lower intensity MMT vs. intensive MMT day program group.
Baker et al., 1995	Cross-sectional Sydney, Australia N=260	Positive	MMT group had significantly lower injecting risk-taking behaviour scores (HIV Risk-taking Behaviour Scale) than previous MMT and non-MMT groups ($p<0.05$).
Ball et al., 1998	Cohort Multi-site USA N=388	Positive	MMT associated with reduced injecting and needle-sharing. Of those who remained in MMT for >= one year, 71% ceased injecting while 82 % who left MMT relapsed rapidly to injecting.
Batki et al., 1989	Cohort San Francisco, USA N=42	Positive	Significant reduction in mean number of days injected in past month between baseline (27.5) and 12 month MMT follow-up (6.3)
Bellis et al., 1993	Cohort California, USA N=41	Positive	61% retention of sex working female IDUs in free MMT program at 12 months. Total urinalyses positive for non-prescribed drugs decreased from 80% at baseline to 51% at 12 months.
Britton et al., 1994	Cohort San Francisco, USA N=96	Positive	PWIDwho ceased MMT due to funding cuts at 12 month follow-up had more days of heroin injecting ($F = 6.63$, $p = .01$) and needle-sharing ($F = 4.41$, $p = .04$) in the past six months than those who remained in MMT.
Brooner et al., 1998	Cohort Baltimore, USA N=325	Positive	Drug use was significantly reduced between baseline and 3-month MMT follow-up.
Camacho et al., 1996	Cohort Texas, USA N=327	Positive	IRB significantly reduced between baseline and three and six months of MMT treatment.
Caplehorn and Ross, 1995	Cross sectional Sydney, Australia	Positive	MMT clients half as likely as daily heroin users not in MMT to report IRB (OR 0.55, 95% CI 0.33 to 0.90).
Caslyn et al., 1991	Seattle, USA N=313	Not stated	Summary not available
Chatham et al., 1999	Cohort Texas, USA N=435	Positive	Reductions in illicit drug use and IRBs at one year MMT follow-up.
Dolan et al., 1996	Cross-sectional MMT in prison New South Wales, Australia N=185	Positive	IDUs receiving MMT in prison reported significantly fewer injections per week (mean 0.16 v 0.35; P=0.03 Mann-Whitney test) than those not in MMT but only when dose > 60 mg and MMT provided for the entire prison time.

Table A-5 (continued).

Author and year	Study design and setting	Finding[b]	Results
Dolan et al., 1998	Cross-sectional MMT in prison New South Wales, Australia N=185	Positive	IDUs in prison maintained on MMT reported a significantly lower prevalence of heroin injection and syringe sharing and scored lower on an HIV Risk-taking Behavioural Scale than IDUs who received counselling or time-limited MMT.
Dolan et al., 2003	RCT of MMT in prison New South Wales, Australia N=253	Positive	At five month follow-up, heroin use was significantly lower among MMT than control subjects and MMT subjects reported lower levels of drug injection and syringe sharing.
Gossop et al., 2000	Cohort London, UK	Positive	Significant reductions in illicit drug use for MMT and methadone reduction groups at one year follow-up,
Grella et al., 1996	Secondary follow up analysis of data from RCT of MMT Los Angeles, USA N=500	Positive	At follow-up clients had reduced their drug use and HIV-risk behaviours from baseline.
Gottheil et al.,1993	Cohort Philladelphia, USA N=229	Positive	Of those in MMT for less than 12 months, 35% were opioid free for a three month period, that value increased 71% for patients enrolled for >four years, and 85% for paients remaining in treatment for >10 years.
Greenfield et al., 1995	Cohort USA N=281	Positive	MMT group reported fewer drug injections and less needle-sharing and had fewer positive urinalyses for opioids and cocaine than the no MMT group.
Heimer et al., 2005 and Heimer et al., 2006	Follow-up prison MMT Puerto Rico N=60	Positive	Inmates enrolled in MMT reduced their heroin use by more than 94%. Good correlation between self-report and urine test results.
Iguchi et al., 1998	Cohort New Jersey, USA N=51	Positive	Decreases in frequency of opioid drug use during MMT. Also reductions in the frequency of sharing.
King et al., 2000	Cohort Baltimore, USA N=91	Positive	Decreases in overall IRB between baseline and six month MMT follow-up.
Klee et al., 1991	Cross-sectional UK	Positive	Long term MMT clients (>6 months) less likely to pass on needles compared to short term (< six months) MMT clients or IDUs not in treatment.
Kwiatkowski and Booth, 2001	Prospective cohort Denver, USA N=316	Positive for reduced heroin use not sharing	Those in MMT for >= 90 days before six month follow-up had a significantly greater reduction in heroin injections than those who did not enter/remain in MMT. No differences between groups in sharing needles or other injection equipment.
Longshore et al., 1993	Cross-sectional Los Angeles, USA	Positive	Those who continued to inject while in MMT reported less sharing than users not in MMT after controlling for injecting frequency and background characteristics.
Maddux et al., 1997	Prospective cohort San Antonio, USA N=610	Positive	MMT retention was 52% at 12 months. Among those in MMT at 12 months, injection frequency and sharing had decreased signicantly between baseline to 12 months.

Table A-5 (continued).

Author and year	Study design and setting	Finding[b]	Results
Magura et al., 1991	Retrospective cohort New York City, USA N=1206	Positve	Higher MMT dosage and less heroin and cocaine use during MMT were associated with longer treatment retention.
Margolin et al., 2003	RCT New Haven, USA N=90	Positive	HIV+ MMT clients randomised to HIV Harm Reduction Program (HHRP+) or a control that included harm reduction education, both showed reductions in IRB at nine month follow-up. The HHRP+ were less likely to use illicit opioids and and were less likely to have engaged in high risk behaviour.
Meandzija et al., 1994	Cross-sectional New Haven, USA N=424	Positive	MMT clients compared to other IDUs reported fewer injections in the last 30 days, reduced speedball injection frequency and reduced total cocaine and injected cocaine use.
Rhoades et al., 1998	RCT Texas, USA N=150	Positive	IRB declined between baseline and six months regardless of group/dose assignment (i.e. 50 or 80 mg MMT and clinic two or five days per week). Higher proportions of opioid-positive urines were associated with lower MMT dose. (F(Des Jarlais et al., 1998)=4.74).
Saxon et al., 1994	Cohort USA N=313	Positive	Among IDUs in MMT at baseline, sharing at 18 month follow-up was independently associated with less time in treatment.
Sees et al., 2000	Controlled clinical trial San Francisco, USA N=179	Positive	MMT group had greater treatment retention and lower rates of heroin use compared to detoxification group. MMT resulted in a lower rate of IRB (mean [SD] at 12 months, 2.17 [3.88] vs. 3.73 [6.86].
Shore et al., 1996	Cohort USA N=277	Positive	Decreases in injection frequency associated with consistent MMT enrollment and increases in injection frequency associated with inconsistent MMT enrollment ($p < .01$).
Simpson et al., 1995	Cross sectional Texas, USA N=557	Positive	Significant improvements in drug use behaviours and psychosocial functioning between baseline and three months MMT.
Stark et al., 1996	Cross-sectional Berlin, Germany N=612	Positive	MMT was protective against borrowing of syringes (AOR 0.36, 95% CI 0.2, 0.8)
Strang et al., 2000	RCT London, UK	Positive	The average number of days of illicit drug injection reduced from 25.7 to 10.8 days for the injectable MMT group and from 20.1 to 11.9 days for the oral MMT group.
Thiede et al., 2000	Prospective cohort Seattle, USA N=716		Cessation of injecting at follow up was significantly associated with continuing MMT (AOR = 0.1, 95% CI 0.1–0.2).

[a]Includes IRB (e.g. prevalence and frequency of injecting, sharing and scores of drug related risk) and treatment behaviours (levels of drug use, retention, duration, continuity of treatment).
[b]Positive, negative, or no association refers to overall direction of association with IRB or treatment behaviours .

Table A-6. Results of primary studies of the cost- effectiveness of OST[a]

Author and year	Drug regimen and comparator	Form of economic analysis	Perspective	Model used	Time horizon (years)	Outcome measure	ICER[b]
Barnett, 1999	MMT vs. drug free treatment	Cost effectiveness	US Healthcare System	Markov	Life-time	Cost per life year gained	US$5,250 (£3,904 2004) per life year gained
Barnett et al., 2001	BMT vs. MMT	Cost utility	US healthcare system	Dynamic	10	Cost per QALY[c] gained	5% HIV prevalence US$14,00-84,700 (£9,965-60,289 2004) cost per QALY gained 40% HIV prevalence US$10,800-66,700 (£7,687-47,477 2004) cost per QALY gained
Dijkgraff et al., 2005	MMT vs MMT+heroin	Cost-utility	Societal	None	1	Cost per QALY gained	MMT+heroin alone dominated
Doran et al., 2003	BMT vs.MMT	Cost effectiveness	Australian Health Service provider	None	1	Cost per heroin free day	Cost per heroin fee day MMT dominated BPN ICER MMT vs BMT (95% CI):$201 per heroin free day (-$2069 to $1809)
Goldschmidt, 1976	MMT vs. therapeutic community programme (TCP)	Cost effectiveness	Societal	None	1	Cost per 'effectiveness measure unit', 'Normabider cirterion' (successful patients) and 'heroin-free' patients.	Cost per successful patient: MMT US$147, TCP US$243 Cost per heroin free patient MMT US$61, TCP US$122
Harris et al., 2005	BMT vs MMT	Cost effectiveness and cost utility	Soceital	None	NA	Cost per heroin-free day, Cost per QALY gained	Cost per heroin-free day exlcudeding cost attributed to crime: MMT dominated BPN. Including costs attributed to crime: BMT had lower costs and less HFD than MMT. Cost per QALY Excluding costs attributed to crime: ICER for BMT vs MMT AUS$ 39,404 (£17,326 2004). Including costs attributed to crime: BPN dominated MMT
Masson et al., 2004	MMT vs MDT	Cost effectiveness and cost utility	US healthcare system	Markov	10	Cost per year of life gained and QALY gained	US$16,997 per life year saved US$46,217-19,997 per QALY gained

Table A-6 (continued).

Sheerin et al 2004	MMT vs five treatment options	Cost effectiveness	New Zealand Healthcare system	Markov	10	Cost per year of life saved	NZ$25,035-25,397 per life year saved (£8,737-8,864 2004)
Sirotnik and Bailey, 1975	MMT vs five modalities of care	Cost benefit	Societal	None	1	Dollar benefit to society	Total dollar benefit to society of US$3.4 millon
Zaric et al., 2000a	MMT vs four populations by HIV prevalence (5,10,20,40)	Cost utility	US healthcare system	Dynamic	10	Cost per life year gained and cost per QALY gained	US$9,700–17,200[a] per life-year gained (£6,904–12,243 2004) US$6,300–10,900[a] per QALY gained (£4,484–7,759 2004)
Zaric et al., 2000b	MMT vs. Expansion of 10% of those in MMT within high (40%) and low (5%) HIV prevalence populations	Costy utility	US healthcare system	Dynamic	10	Cost per life year gained and cost per QALY gained	US$8,200–10,900[b] per QALY gained (£5,837–7,759 2004)
Zarkin et al., 2005	MMT vs no MMT comparison of costs (criminal activity, earnings, healthcare use) within a simulated population of 1 millon	Cost-benefit	Societal	Monte-Carlo	Lifetime	Cost-benefit ratio	Benefit-cost ration (i.e MMT vs no MMT) over a lifetime was 37.72

[a]Based on Connock et al. (2007)
[b]Incremental Cost Effectiveness Ratio
[c]Quality Adjusted Life Year

Appendix B: Search terms used in the review of reviews

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

(1) MEDLINE

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

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

(2) EMBASE

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

18. *Substance Abuse/
19. (substance$ or drug$).ti,ab.
20. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
21. (inject$ or intravenous).ti,ab.
22. 18 or (19 and 20) or (19 and 21)
23. Harm Reduction/
24. Intervention Study/
25. Preventive Health Service/
26. Primary Prevention/
27. Infection Prevention/
28. 23 or 24 or 25 or 26 or 27
29. (needle$ or syringe$).ti,ab.
30. exchange$.ti,ab.
31. 29 and 30
32. outreach.ti,ab.
33. mobile.ti,ab.
34. backpack$.ti,ab.
35. (vending and machine$).ti,ab.
36. (29 and 32) or (29 and 33) or 34 or 35
37. (paraphernalia or equipment).ti,ab.
38. (distribu$ or provi$).ti,ab.
39. 37 and 38
40. *Methadone/
41. *Buprenorphine/
42. substitution or maintenance.ti,ab.
43. 40 or 41 or 42
44. (bleach and disinfect$).ti,ab.
45. (needle and disinfect$).ti,ab.
46. 44 or 45
47. Health Education/
48. Patient Education/
49. Counseling/
50. Attitude to Health/
51. Health Promotion/
52. 47 or 48 or 49 50 or 51
53. outreach.ti,ab.
54. peer intervention.ti,ab.
55. peer education.ti,ab.
56. 53 or 54 or 55
57. Human Immunodeficiency Virus Infection/di
58. Hepatitis C/di
59. (HCV test$ or hepatitis c test$ or HIV test$).ti,ab.
60. Diagnostic Test/
61. 57 or 58 or 59 or 60
62. ((HCV or hepatitis c) and treatment).ti,ab.
63. drug consumption rooms.ti,ab.
64. (safe$ inject$ and (site or facility)).ti,ab.
65. 63 or 64
66. (structural and intervention).ti,ab.
67. (environment$ and intervention$).ti,ab.
68. 66 or 67
69. crack pipe.ti,ab .
70. 28 or 31 or 36 or 39 or 43 or 46 or 52 or 56 or 61 or 62 or 65 or 68 or 69

71. 5 and 17 and 22 and 70

(3) CINAHL
1. "Systematic Review"/
2. "Literature Review"/
3. “Program Evaluation"/
4. "Meta analysis"/
5. ((review$ or overview$ or evaluation$) and (systematic or methodologic$ or quantitative$ or literature$)).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. "Hepatitis C"/
8. (hepatitis c or HCV).ti,ab.
9. HIV Infections/
10. HIV.ti,ab.
11. transmission.ti,ab.
12. seroconver$.ti,ab.
13. Risk Taking Behavior/
14. risk behav$.ti,ab.
15. Health Behavior/
16. Needle Sharing/
17. 7 or (8 and 11) or (8 and 12) or 9 or (10 and 11) or (10 and 12) or 13 or 14 or 15 or 16
18. Substance Abuse, Intravenous/
19. Intravenous Drug Users/
20. (substance$ or drug$).ti,ab.
21. (abuse$ or depend$ or use$ or misus$ or addict$).ti,ab.
22. (inject$ or intravenous).ti,ab.
23. 18 or 19 or (20 and 21) or (20 and 22)
24. Harm Reduction/
25. Experimental Studies/
26. Preventive Health Care/
27. Community Health Services/
28. 24 or 25 or 26 or 27
29. (needle$ or syringe$).ti,ab.
30. exchange$.ti,ab.
31. Needle Exchange Programs/
32. (29 and 30) or 31
33. outreach.ti,ab.
34. mobile.ti,ab.
35. backpack$.ti,ab.
36. (vending and machine$).ti,ab.
37. (29 and 33) or (29 and 34) or 35 or 36
38. (paraphernalia or equipment).ti,ab.
39. (distribut$ or provi$).ti,ab.
40. 38 and 39
41. Methadone/
42. BUPRENORPHINE/
43. (substitution or maintenance).ti,ab.
44. 41 or 42 or 43
45. (bleach and disinfect$).ti,ab.
46. (needle and disinfect$).ti,ab.
47. 45 or 46
48. Health Education/

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

(4) PsycInfo

1. Evidence Based Practice (DE)
2. Intervention (DE)
3. Program Evaluation (DE)
4. Meta analysis (ME)
5. 1 or 2 or 3 or 4
6. Intravenous Drug Usage (DE)
7. Drug abuse (DE)
8. Drug addiction (DE)
9. At risk populations (DE) or Developing countries (DE)
10. 6 or 7 or 8 [or 9] for EU review only
11. HIV ((KW)
12. Hepatitis C (KW)
13. Infectious Disorders (DE)
14. transmission (KW=)
15. seroconvert* (KW)
16. Needle Sharing (DE)
17. Risk Taking (DE)
18. Risk Management (DE)
19. Risk behavio?r (KW)
20. Treatment outcomes (DE)
21. Drug overdoses (DE)
22. Death and dying (DE)
23. Health care seeking behaviour (DE)
24. Health care utilization (DE)
25. Crime (DE)
26. Costs and cost analysis
27. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. AIDS Prevention (DE)
29. Harm reduction (DE)
30. Preventative Medicine (DE)
31. 28 or 29 or 30
32. Needle Exchange Programs (DE)
33. (needle* or syringe*) (KW)
34. exchange* (KW)
35. 32 or (33 and 34)
36. outreach (KW)
37. mobile (KW)
38. backpack* (KW)
39. (vending and machine*) (KW)
40. (32 and 36) or (32 and 37) or 38 or 39
41. (paraphernalia or equipment) (KW)
42. (distribu* or provi*) (KW)
43. 41 and 42
44. Methadone Maintenance (DE)
45. Buprenorphine (KW)
46. substitution or maintenance (KW)
47. 44 or 45 or 46
48. (bleach and disinfect*) (KW)
49. (needle and disinfect*) (KW)
50. 48 or 49
51. Naloxone (DE)
52. overdose prevention (KW)
53. (peer or take-home or prescription) (KW)
54. (51 and 53) or 52
55. Health Education (DE)
56. Health Promotion (DE)
57. Client Education (DE)
58. Counselling (DE)
59. Health Knowledge (DE)
60. 55 or 56 or 57 or 58 or 59
61. Outreach Programs (DE)
62. outreach (KW)
63. peer intervention (KW)
64. peer education (KW)
65. 61 or 62 or 63 or 64
66. HIV testing (DE)
67. (HCV test* or hepatitis c test* or HIV test*)(KW)
68. 66 or ((11 or 12) and 67)
69. ((HCV or hepatitis c) and treatment) (KW)
70. Safe* inject* and (site or facilit*) (KW)
71. Drug consumption rooms (KW)
72. 70 or 71
73. (structural and intervention) (KW=)
74. (environment* and intervention) (KW=)
75. 73 or 74
76. crack pipe(KW)
77. 31 or 35 or 40 or 43 or 47 or 50 or 54 or 60 or 65 or 68 or 69 or 72 or 75 or 76
78. 5 and 10 and 27 and 77

(5) IBSS

1. Intervention (DE)
2. Evaluation (DE)
3. Meta analysis TI or AB
4. Literature review (DE)
5. Systematic review TI or AB
6. 1 or 2 or 3 or 4 or 5
7. Drug-users (DE)
8. Drug-abuse (DE)
9. Inject* drug use* TI or AB
10. Drug-addiction (DE)
11. Developing countries (DE)
12. 7 or 8 or 9 or 10 or 11 or 12
13. HIV (DE)
14. Hepatitis (DE)
15. Hepatitis C TI or AB
16. transmission TI or AB
17. seroconvert* TI or AB
18. Risk (DE)
19. Needle Sharing TI or AB
20. Risk behavio?r TI or AB
21. Inject* frequency TI or AB
22. Inject* behavio?r TI or AB
23. Treatment outcomes TI or AB
24. Drug-overdose (DE)
25. Health seeking behaviour TI or AB
26. Health care utilization TI or AB
27. Access to health care (DE)
28. Crime or drug-related crime TI or AB
29. Cost benefit analysis (DE)
30. 13 or 14 or 15 or 16 or 17 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. Prevention (DE)
32. Harm reduction TI and AB
33. Public health (DE)
34. 31 or 32 or 33
35. needle and program* TI and AB
36. (needle* or syringe*) TI and AB
37. exchange* TI and AB
38. 35 or (36 and 37)
39. outreach TI and AB
40. mobile TI and AB
41. backpack* TI and AB
42. (vending and machine*) TI and AB
43. (38 and 39) or (38 and 40) or 41 or 42
44. (paraphernalia or equipment) TI and AB
45. (distribu* or provi*) TI and AB
46. 42 and 43
47. Methadone Maintenance TI and AB
48. Buprenorphine TI and AB
49. substitution or maintenance TI and AB
50. 47 or 48 or 49
51. (bleach and disinfect*) TI and AB
52. (needle and disinfect*) TI and AB

53. 51 or 52
54. Naloxone TI and AB
55. overdose prevention TI and AB
56. (peer or take-home or prescription) TI and AB
57. (54 and 56) or 55
58. Health Education TI or AB
59. Health Promotion (DE)
60. Counseling (DE)
61. Knowledge (DE)
62. 58 or 59 or 60 or 61
63. outreach TI and AB
64. peer intervention TI and AB
65. peer education TI and AB
66. 63 or 64 or 65
67. (HCV test* or hepatitis c test* or HIV test*) TI and AB
68. 67or ((13 or 14) and 68)
69. ((HCV or hepatitis c) and treatment) TI and AB
70. Safe* inject* and (site or facilit*) TI and AB
71. Drug consumption rooms TI and AB
72. 71 or 72
73. (structural and intervention) TI and AB
74. (environment* and intervention) TI and AB
75. 74 or 75
76. crack pipe TI and AB
77. 34 or 38 or 43 or 46 or 50 or 53 or 57 or 62 or 66 or 68 or 70 or 73 or 76
78. 6 and 12 and 30 and 77

(6) Cochrane Library
1. (HCV):ti,ab,kw or (hepatitis c):ti,ab,kw
2. (HIV):ti,ab,kw
3. (risk NEXT behav*):ti,ab,kw
4. (substance*):ti,ab,kw or (drug*):ti,ab,kw
5. (inject*):ti,ab,kw or (intravenous):ti,ab,kw
6. (#1 OR #2 OR #3)
7. (#4 AND #5)
8. (#6 AND #7)

Appendix C: Critical appraisal of supplementary reviews

Table C-1. Summary of critical appraisal of supplementary reviews not included in the evidence base[a]

Appraisal criteria	Bastos et al., 2000	Coffin et al., 2000	Delgado et al., 2004	Dolan et al., 2005	Hagan et al., 2005	Hoffmann et al., 2006	Hunt et al., 2003
Type of review	Narrative	Systematic	Narrative	Systematic	Narrative	Systematic	Narrative
Does the paper have a clearly focused aim or research question?	Yes	Yes	No	Yes	Yes	Yes	Yes
Study identification							
Are details given of:							
Databases and years searched	No	Yes	No	No	No	Yes	No
Grey literature searched	No	No	No	Yes	No	Yes	No
Search terms used	No	Yes	No	No	No	No	No
Inclusion criteria used	No	No	No	Yes	No	Yes	No
What materials were excluded	No	No	No	No	No	Yes	No
Critical appraisal							
Do the authors address the quality (rigour) of the included studies?	No	No	No	Yes	No	No	No
Data presentation							
Are sufficient data from individual studies included to mediate between data and interpretation/conclusions?	No	No	No	Yes	No	No	No
Synthesis and interpretation							
Does the review make clear what steps have been taken to deal with potential bias?	No	No	No	No	No	No	No
Do the authors consider whether the results could be due to chance (*p*-values and confidence intervals)?	No	No	No	No	No	No	No
Do the authors acknowledge any other limitations to the research, including weakness in their own approach?	No	No	No	No	No	Yes	No
Has more than one assessor been involved?	Not reported	No	No	Not reported	Not reported	Not reported	Not reported
For meta analyses:							
Are the studies addressing similar research questions?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Are the studies sufficiently similar in design?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Are the results similar from study to study (test of heterogeneity)?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Are the reasons for any variation in the results discussed?	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table C-1 continued.

Appraisal criteria	Hunt et al., 2005	Ksobiech et al., 2003	Ksobiech et al., 2006	Loxley et al., 2004	Rhodes et al., 2004	Rich et al., 2000	Strathdee et al., 2006
Type of review	Narrative	Meta-analysis	Meta-analysis	Systematic	Systematic	Narrative	Narrative
Does the paper have a clearly focused aim or research question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study identification							
Are details given of:							
Databases and years searched	No	No	No	Yes	Yes	No	No
Grey literature searched	No	No	Yes	Yes	Yes	No	No
Search terms used	No	No	Yes	No	Yes	No	No
Inclusion criteria used	No	Yes	Yes	No	No	No	No
What materials were excluded	No	Yes	Yes	No	No	No	No
Critical appraisal							
Do the authors address the quality (rigour) of the included studies?	No	No	No	Yes	No	No	No
Data presentation							
Are sufficient data from individual studies included to mediate between data and interpretation/conclusions?	No	No	No	No	No	No	No
Synthesis and interpretation							
Does the review make clear what steps have been taken to deal with potential bias?	No	No	No	Yes	No	No	No
Do the authors consider whether the results could be due to chance (*p*-values and confidence intervals)?	No	No	No	No	No	No	No
Do the authors acknowledge any other limitations to the research, including weakness in their own approach?	No	Yes	Yes	No	Yes	No	No
Has more than one assessor been involved?	Not reported	Yes	Yes	Yes	Not reported	No	Not reported
For meta analyses:							
Are the studies addressing similar research questions?	N/A	Yes	Yes	N/A	N/A	N/A	N/A
Are the studies sufficiently similar in design?	N/A	Yes	Yes	N/A	N/A	N/A	N/A
Are the results similar from study to study (test of heterogeneity)?	N/A	No	No	N/A	N/A	N/A	N/A
Are the reasons for any variation in the results discussed?	N/A	Yes	Yes	N/A	N/A	N/A	N/A

[a]Based on the critical appraisal tool developed by the Health Development Agency

Appendix D: Proformas for assessing risk of bias and precision in cross-sectional and cohort studies

Adapted from: Viswanathan M, Berkman ND. Development of the RTI item bank on risk of bias and precision of observational studies. J Clin Epidemiol 2012; 65(2): 163-78.

Code each item as high, moderate or low (where high = high risk of bias or low precision). If no information is provided, code as high.

Cross-sectional studies

Sample definition and selection (Selection bias)	Was the strategy for recruiting participants into the study the same across study groups? (i.e. sharers and non-sharers)	
	Consider rate of non-response and whether those who don't participate might be different to those recruited	
	Is the selection of the comparison groups appropriate?	
	Are the individuals selected to participate in the study likely to be representative of the target population?	
Measurement of Interventions/Exposure (Detection/ Information bias)	Are exposures assessed using valid and reliable measures and implemented consistently across all study participants?	
	Are outcomes assessed using valid and reliable measures and implemented consistently across all study participants?	
	What is the level of detail in describing the intervention or exposure?	
Analysis	Were the important confounding and effect modifying variables taken into account in analysis (e.g. through stratification, interaction terms, multivariate analysis, etc)?	
	Are the statistical methods appropriate?	
Sample size	Was the sample size likely to be sufficiently large to detect a statistically significant difference in the main outcome?	
Other comments		

Cohort studies

Sample definition and selection (Selection bias)	Was the strategy for recruiting participants into the study the same across study groups? (i.e. sharers and non-sharers)	
	Consider rate of non-response and whether those who don't participate might be different to those recruited	
	Is the selection of the comparison groups appropriate?	
	Are the individuals selected to participate in the study likely to be representative of the target population?	
Measurement of Interventions/Exposure (Detection/ Information bias)	Are exposures assessed using valid and reliable measures and implemented consistently across all study participants?	
	Are outcomes assessed using valid and reliable measures and implemented consistently across all study participants?	
	How was an incident case defined? How was follow-up time calculated	
	What is the level of detail in describing the intervention or exposure?	
Follow-up	Is the length of time following the exposure sufficient to support the evaluation of primary outcomes?	
	What was the attrition rate?	
	Did attrition differ between groups by more than 20 percent? How did those lost-to-follow-up differ from those retained in the study?	
Analysis	Were the important confounding and effect modifying variables taken into account in analysis (e.g. through stratification, interaction terms, multivariate analysis, etc)?	
	Are the statistical methods appropriate? (for the purposes of this review)	
Sample size	Was the sample size likely to be sufficiently large to detect a statistically significant difference in the main outcome?	
Other comments		

Appendix E: Needle Exchange Surveillance Initiative 2011-12 questionnaire

UWS UNIVERSITY OF THE WEST of SCOTLAND

Health Protection Scotland

Needle Exchange Surveillance Initiative

NESI 2011

E1	Have you ever injected drugs?	Yes ☐ 1 No ☐ 2	→ If no, REJECT
E2	Have you participated in this study before?	Yes ☐ 1 No ☐ 2	→ If yes when was the last time you participated in this study? M M Y Y Y Y If interviewed during April – December 2011 REJECT
E3	What is the reason for your visit today? ***(Please tick all that apply)***	Needle exchange ☐ 1 Methadone ☐ 1 Other ☐ 1	→ Please specify
	Time interview started:	H H : M M	

Attach sticker here

Site No: ☐☐☐ Interviewer code: ☐☐ Date: D D M M Y Y

V19/03/10

I am first going to start by asking you some general questions about you			
1	What are your initials?	☐☐	
2	Sex	Male ☐ 1 Female ☐ 2	
3	What is your date of birth?	D D M M Y Y	
4	In which area are you living at the moment?		
5	What is the first part of your post code?	☐☐☐☐	
6	**a)** Have you ever lived in a hostel for the homeless, had no fixed abode or lived on the streets?	Yes ☐ 1 No ☐ 2	→ *If no, go to Q7*
	b) Has this been in the last 6 months?	Yes ☐ 1 No ☐ 2	

I am now going to ask you about drug services and healthcare you may have received			
7	Have you ever been vaccinated for Hepatitis B (Hep B jag)?	Yes ☐ 1 No ☐ 2 DK ☐ 8888	→ *If no/don't know, go to Q10*
8	How many Hep B jags have you had?	1 ☐ 1 2 ☐ 2 3+ ☐ 3 DK ☐ 8888	
9	Where did you receive the vaccinations for Hepatitis B? *(tick all that apply)*	GP ☐ 1 Drug treatment centre/Counselling service ☐ 1 GUM clinic ☐ 1 Hospital ☐ 1 In prison ☐ 1 Needle exchange ☐ 1 Other *(please specify below)* ☐ 1 ☐	

10	**a)** Have you ever been prescribed methadone?	Yes ☐ 1 No ☐ 2	→ *If no, go to Q11*
	b) Are you currently on methadone?	Yes ☐ 1 No ☐ 2	
	c) For how many of the last 6 months have you been prescribed methadone?	☐ months	→ *If 0, go to Q11*
	d) What is the highest dose you have been prescribed in the last 6 months?	☐☐☐ mls	
	e) For how long were you on this dose?	☐ months	
	f) What is the lowest dose you have been prescribed in the last 6 months?	☐☐☐ mls	
	g) For how long were you on this dose?	☐ months	
11	**a)** Have you ever received any other drug treatment (excluding methadone)? **(Show prompt card)**	Yes ☐ 1 No ☐ 2	→ *If no, go to Q12*
	b) In the last 6 months, have you received any other drug treatment (excluding methadone)?	Yes ☐ 1 No ☐ 2	→ *If no, go to Q12*
	c) In the last six months, what treatment have you received (excluding methadone)? **(Show prompt card)**	☐	

I would now like to ask you some questions about your alcohol and drug use. The first few questions are about alcohol

12	In the past 12 months, how often did you have a drink containing alcohol? ***Show prompt card***	Never ☐ 0 Once a month or less ☐ 1 Twice a month ☐ 2 Once a week ☐ 3 2 - 3 times a week ☐ 4 4 - 5 times a week ☐ 5 6 - 7 times a week ☐ 6	→ ***If never go to Q15***

13 On a typical day when you drink, what do you drink?

Drink	Size and Number	Units*
A ☐ Beer/lager/cider/shandy		
B ☐ Strong beer/lager/cider (>6%)		
C ☐ Wine		
D ☐ Strong wine (>15%) e.g. Buckfast		
E ☐ Spirits and liqueurs		
F ☐ Alcopops		
G ☐ Other		

14	**Total number of Units** ***To be completed by interviewer after the interview**	

I am now going to ask you about your injecting drug use			
15	How old were you when you first injected drugs?	☐☐ years	
16	When did you last inject drugs?	M M Y Y Y Y	
17	Was this in the last 4 weeks?	Yes ☐ 1 No ☐ 2	→ *If yes, go to Q19*
18	Have you injected in the last 6 months?	Yes ☐ 1 No ☐ 2	→ *If no, go to Q25*
19	In the last 6 months, which of the following drugs have you injected? ***(tick all that apply)***	Heroin ☐ 1 Cocaine ☐ 1 Heroin and cocaine together (Speedball) ☐ 1 Crack ☐ 1 Speed ☐ 1 Temazepam or Valium ☐ 1 Bodybuilding drugs e.g. steroids, HCG ☐ 1 Other ***(please specify below)*** ☐ 1 ☐	
20	In the last 6 months, which drug have you injected most often?	☐	

21	In how many of the last 6 months did you inject drugs? ***Please fill in the number of months***	☐ months	
22	**a)** In the months when you injected drugs how often on average did you inject them?	1 to 3 times a month ☐ 1 About once a week ☐ 2 2 to 6 times a week ☐ 3 Once a day ☐ 4 2 to 3 times a day ☐ 5 4 or more times a day ☐ 6	
23	Of all the needles and syringes that you have used to inject in the last 6 months, how many were new and unused (i.e. from a packet) on a scale of 0 to 10 (where 0 is none and 10 is all) ***Tick one box***	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	
24	In the last 6 months, did someone inject you after injecting themselves or others?	Yes ☐ 1 No ☐ 2	

Reminder to the interviewer: Complete using the respondent's answers to Q17 and Q18. Has the respondent injected in the...			last 6 months? *(see Q18)* Yes ☐ 1 No ☐ 2 *If no skip column B* ↓	last 4 weeks? *(see Q17)* Yes ☐ 1 No ☐ 2 *If no skip column C* ↓
		A - Ever	**B - In the last 6 Months**	**C - In the last 4 Weeks**
25	Have you ever injected with a needle/ syringe that had already been used by someone else (including your partner)? How many times have you injected with a needle/syringe that had already been used by someone else (including your partner)? (Ask about the last 6 months and the last 4 weeks)	**a)** Yes ☐ 1 No ☐ 2 *If no, go to Q28b* ↓	**b)** ☐ times *If 0, go to Q26a then Q28*	**c)** ☐ times
26	Have you shared needle/syringes with someone you knew had Hepatitis C? If yes, was this in the last 6 months/last 4 weeks?	**a)** Yes ☐ 1 No ☐ 2 *If no, go to Q27* ↓	**b)** Yes ☐ 1 No ☐ 2 *If no, go to Q27* ↓	**c)** Yes ☐ 1 No ☐ 2
27	**From** how many different people, in total, have you received used needles/ syringes (including your partner)?		**b)** ☐ people *If 0, go to Q28*	**c)** ☐ people
28	**To** how many different people, in total, have you passed on used needles/ syringes (including your partner)?		**b)** ☐ people *If 0, go to Q29*	**c)** ☐ people
29	Have you ever injected with the same needle/syringe more than once before discarding it? In the last 6 months, how many times, on average, did you use the same needle/ syringe before discarding it?	**a)** Yes ☐ 1 No ☐ 2 *If no, go to Q30* ↓	**b)** Never ☐ 0 Once or twice ☐ 1 3 to 5 times ☐ 2 5+ times ☐ 3	
30	Have you ever injected with a used needle/syringe that you were not sure was your own? In the last 6 months, how many times did you inject with a used needle/syringe that you were not sure was your own?	**a)** Yes ☐ 1 No ☐ 2 DK ☐ 8888 *If no or DK, go to Q31* ↓	**b)** Never ☐ 0 Once or twice ☐ 1 3 to 5 times ☐ 2 5 to 19 times ☐ 3 20+ times ☐ 4	

		A - Ever	B - In the last 6 Months	C - In the 4 Weeks
Have you:				
31	Used spoons or containers for mixing which had previously been used by someone else?	Yes ☐ 1 No ☐ 2 *If no, go to Q32* ↓	Yes ☐ 1 No ☐ 2 *If no, go to Q32* ↓	Yes ☐ 1 No ☐ 2
32	Used filters which had previously been used by someone else?	Yes ☐ 1 No ☐ 2 *If no, go to Q33* ↓	Yes ☐ 1 No ☐ 2 *If no, go to Q33* ↓	Yes ☐ 1 No ☐ 2
33	Prepared drugs or rinsed your works with water that had already been used by someone else?	Yes ☐ 1 No ☐ 2 *If no, go to Q34* ↓	Yes ☐ 1 No ☐ 2 *If no, go to Q34* ↓	Yes ☐ 1 No ☐ 2
34	Shared filters, spoons, cookers or water with someone who you knew had Hepatitis C?	Yes ☐ 1 No ☐ 2 *If no, go to Q35* ↓	Yes ☐ 1 No ☐ 2 *If no, go to Q35* ↓	Yes ☐ 1 No ☐ 2
35	**a)** In the last year, on how many occasions were you present when someone injected for the first time?	☐		→ *If 0, go to Q36*
	b) On the last occasion, how many other injectors were present (not including yourself or the first time injector)?	☐		
	c) On the last occasion, what was the gender of the first time injector? ***(if more than one person was initiated, please tell us about the one that was injected last)***		Male ☐ 1 Female ☐ 2	
	d) What was the approximate age of this first time injector?		< 21 years ☐ 1 21 - 25 years ☐ 2 26 - 30 years ☐ 3 >30 years ☐ 1	
	e) Was this individual still injecting drugs 1 month after having injected for the first time?		Yes ☐ 1 No ☐ 2 DK ☐ 8888	
	f) Was this individual still injecting drugs 3 months after having injected for the first time?		Yes ☐ 1 No ☐ 2 DK ☐ 8888	

I would now like to ask you some questions about Hepatitis C and HIV			
36	**a)** Have you ever had a hepatitis C test?	Yes ☐ 1 No ☐ 2 DK ☐ 8888	→ *If no/don't know, go to Q41*
	b) In which year did you last have a hepatitis C test?	Y Y Y Y	
	c) Was that test in the last 12 months?	Yes ☐ 1 No ☐ 2	
37	Where were you last tested for hepatitis C?	GP ☐ 1 Drug treatment centre/counselling service ☐ 2 GUM clinic ☐ 3 Hospital ☐ 4 Prison ☐ 5 Needle exchange ☐ 6 Other *(please specify below)* ☐ 7 ☐	
38	Would you mind telling me the result of your last test?	Have hep C ☐ 1 Cleared hep C ☐ 2 Did not have hep C ☐ 3 Awaiting result ☐ 4 Did not get result ☐ 5 Do not want to say ☐ 6 DK ☐ 8888	→ *go to Q41*
39	Did you get a letter asking you to attend a hospital appointment for your hepatitis C?	Yes ☐ 1 No ☐ 2 DK ☐ 8888	→ *If no/don't know, go to Q41*

40	**a)** Did you attend the appointment?	Yes ☐ 1 No ☐ 2	→ *If yes, go to Q41*
	b) Why not?		
41	**a)** Have you ever had an HIV test?	Yes ☐ 1 No ☐ 2 DK ☐ 8888	→ *If no/don't know, go to Q43*
	b) In which year did you last have an HIV test?	Y Y Y Y	
	c) was that test in the last 12 months?	Yes ☐ 1 No ☐ 2	
42	Would you mind telling me the result of your last test?	Have HIV ☐ 1 Did not have HIV ☐ 2 Awaiting results ☐ 3 Did not get result ☐ 4 Do not want to say ☐ 5 DK ☐ 8888	

I would like to now ask about any time you may have spent in prison or a young offenders' institution			
43	How many times have you been in prison (or a young offenders' institution) since you first injected drugs?	☐	→ *If 0, go to Q49*
44	**a)** In the last year, approximately how long did you spend in prison *(Enter zeros if not in prison in last year)*	☐☐ mths ☐☐ wks ☐☐ days	
	b) When was the last time you were in prison? (Date of release)	M M Y Y Y Y	
45	Did you ever inject drugs when you were in prison (or a young offenders' institution)?	Yes ☐ 1 No ☐ 2	→ *If no, go to Q49*
46	When you ever injected in prison (or a young offenders' institution), did you ever use a needle and/or syringe that had already been used by a fellow prisoner?	Yes ☐ 1 No ☐ 2 DK ☐ 8888	
47	Did you inject drugs in prison in the last 6 months?	Yes ☐ 1 No ☐ 2 N/A (not in prison in the last 6 months) ☐ 7777	→ *If no or N/A, go to Q49*
48	When you injected in prison (or a young offenders' institution) in the last 6 months did you use a needle and/or syringe that had already been used by a fellow prisoner?	Yes ☐ 1 No ☐ 2 DK ☐ 8888	

Reminder to the interviewer: Has the respondent injected in the last 6 months	Yes ☐ 1 No ☐ 2	→ *If no, go to Q53*

And finally I would like to finish by asking a few quick questions about needle exchanges, but firstly I'd like to ask you about how frequently you inject

49	In an average injecting week during the last 6 months, how often did you inject drugs?	☐☐☐ times
50	In an average injecting week during the last 6 months, how many new and unused needles and syringes did you obtain <u>for yourself</u> from….	
	a) A pharmacy exchange	☐☐☐
	b) A fixed site, specialist needle exchange	☐☐☐
	c) A mobile/outreach/other exchange	☐☐☐
	d) Other people (e.g. friends, acquaintances, partners)	☐☐☐
51	In an average week during the last 6 months, how many new and unused needles and syringes did you obtain <u>for others</u>	☐☐☐
52	In an average week, during the last 6 months, how many of the following did you obtain from an exchange?	
	a) Filters	**i)** ☐☐☐
		ii) How many of these were for yourself? ☐☐☐
		iii) If you didn't get any filters, were they available at the exchange that you attended? Available ☐ 1 Not available ☐ 2 DK ☐ 8888
	b) Spoons/cookers	**i)** ☐☐☐
		ii) How many of these were for yourself? ☐☐☐
		iii) If you didn't get any spoons/ cookers, were they available at the exchange that you attended? Available ☐ 1 Not available ☐ 2 DK ☐ 8888
	c) Water ampoules	☐☐☐ If 0, were they available at an exchange that you attended? → Available ☐ 1 Not available ☐ 2 DK ☐ 8888

	In an average week, during the last 6 months, did you obtain any of the following from an exchange?	
	d) Citric acid or vit C sachets	Yes ☐ 1 — Available ☐ 1 No ☐ 2 — Not available ☐ 2 If no, were they available at an exchange that you attended? → — DK ☐ 8888
	e) Wipes/swabs	Yes ☐ 1 — Available ☐ 1 No ☐ 2 — Not available ☐ 2 If no, were they available at an exchange that you attended? → — DK ☐ 8888
	f) Sharps bins	Yes ☐ 1 — Available ☐ 1 No ☐ 2 — Not available ☐ 2 If no, were they available at an exchange that you attended? → — DK ☐ 8888
53	In the last four weeks, how have you disposed of your used needles/ syringes? ***Please tick all that apply***	Returned to the same Needle exchange/pharmacy ☐ 1 Returned to a different NE/pharmacy ☐ 1 Put in a cin/sharps bin in a public place (e.g. hostel) ☐ 1 Passed on to other injectors ☐ 1 Put in a cin/sharps bin before putting in the rubbish at home ☐ 1 Put directly into regular rubbish at home (i.e. not in a cin/sharps bin) ☐ 1 Discarded on the street or other public place ☐ 1 Elsewhere ***(please specify below)*** ☐ 1 ☐

54	**a)** Have you been prescribed take-home Naloxone in the past year?	Yes ☐ 1 No ☐ 2	→ *If no, go to end of questionnaire*
	b) Are you carrying take-home Naloxone with you today? ***(ask the respondent to show it)***	Yes ☐ 1 No ☐ 2	
	c) The last time you were prescribed take-home Naloxone, where did you get it from?	GP ☐ 1 Drug treatment centre/counselling service ☐ 2 Hospital ☐ 3 Prison ☐ 4 Needle exchange ☐ 5 Other ***(please specify below)*** ☐ 6 ☐	

Time interview finished: H H : M M

When we began this questionnaire, I asked if you would give a dried blood spot sample. Is that still OK with you?

Thank the respondent for their time and give them the Voucher envelope

Dried blood spot sample

Taken ☐ Sample labelled ☐

Refused ☐ → offer saliva sample

Saliva sample

Taken ☐ Sample labelled ☐

Refused ☐

N/A ☐

Questionnaire labelled ☐

Appendix F: Odds of recent infection by needle/syringe coverage group in the pooled NESI data

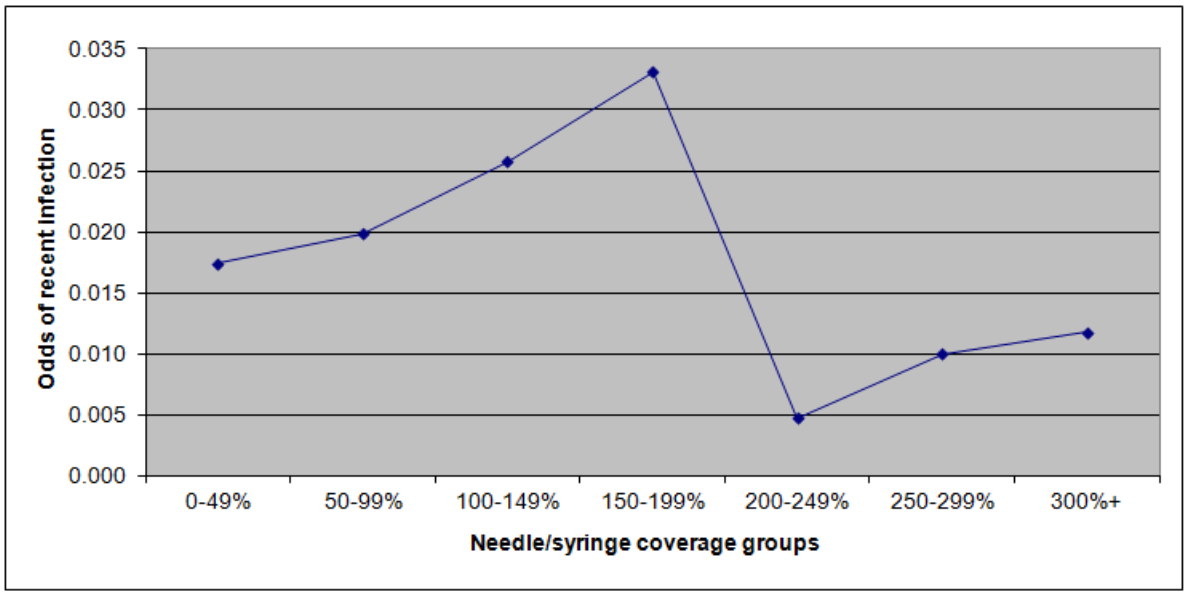


Figure F-1. Odds of recent infection by needle/syringe coverage group among respondents to the NESI survey interviewed in 2008-09, 2010 and 2011-12 (n=2,503)

Appendix G: Reproduction of analyses in Chapter 5 using additional NESI survey data

Table G-1. Multivariable logistic regression models examining the association between recent HCV infection (anti-HCV negative and HCV-RNA positive) and i) OST and needle/syringe coverage as separate variables and (ii) combined OST and needle/syringe coverage[a]

			2008-09 data			2008-09, 2010 and 2011-12 data		
			AOR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**
			(n=1,131)			(n=3,059)		
Model i)	Received OST	In the last six months	1			1		
		Currently	0.29	0.07-1.19	0.086	0.29	0.10-0.79	0.016
		Not in the last six months	0.28	0.06-1.22	0.089	0.33	0.11-0.93	0.036
	N/S coverage[b]	<200%	1			1		
		≥200%	0.32	0.10-1.00	0.050	0.38	0.18-0.81	0.012
		Did not inject	1.30	0.38-4.43	0.674	0.92	0.41-2.08	0.842
			(n=1,107)			(n=2,988)		
Model ii)	Combined intervention coverage (N/S coverage and OST)	Low	1			1		
		Medium	0.50	0.18-1.35	0.170	0.49	0.25-0.96	0.038
		High	0.48	0.16-1.48	0.203	0.44	0.21-0.91	0.028

N/S: needle(s)/syringe(s)

[a]Using the intervention categories and confounders described in Chapter 5. The results in the left-hand panel (2008-09) are those presented in Table 5-2. The results in the right-hand panel are applying the same analyses but including the additional data from the 2010 and 2011-12 NESI surveys.

Appendix H: Full models (i.e. including covariates) of the associations between intervention uptake and recent HCV infection (Chapter 6)

Table H-1. Model (i) including covariates[a]

		No. anti-HCV negatives (N)	No. recent infections (n)	% (n/N)	Univariable			Multivariable (n=2,481)			Weighted multivariable (n=2,481)		
					OR	95% CI	p-value	AOR	95% CI	p-value	AOR_w	95% CI	p-value
Needle/syringe coverage	**Low**	**1443**	**34**	**2.4**	**1**			**1**			**1**		
	High	**1051**	**9**	**0.9**	**0.36**	**0.17-0.75**	**0.006**	**0.39**	**0.19-0.83**	**0.014**	**0.14**	**0.04-0.48**	**0.002**
Survey year	2008-09	933	20	2.1	1			1			1		
	2010	907	15	1.7	0.77	0.39-1.51	0.443	0.84	0.42-1.66	0.616	0.96	0.40-2.29	0.919
	2011-12	669	8	1.2	0.55	0.24-1.26	0.159	0.58	0.25-1.33	0.196	0.31	0.12-0.81	0.017
Homeless in last six months	No	1925	21	1.1	1			1			1		
	Yes	581	22	3.8	3.57	1.95-6.54	<0.001	2.98	1.61-5.51	0.001	2.06	0.94-4.50	0.071
Injected stimulant in last six months	No	2216	32	1.4	1			1			1		
	Yes	293	11	3.8	2.66	1.33-5.34	0.006	2.50	1.22-5.09	0.012	2.03	0.85-4.85	0.112
Time since onset of injecting	(continuous)	-	-	-	0.95	0.89-1.01	0.081	0.96	0.90-1.02	0.155	0.94	0.84-1.04	0.209

[a]Restricted to those who reported injecting in the last six months

Table H-2. Model (ii) including covariates[a]

		No. anti-HCV negatives (N)	No. recent infections (n)	% (n/N)	Univariable OR	95% CI	p-value	Multivariable (n=2,481) AOR	95% CI	p-value	Weighted multivariable (n=2,481) AOR_w	95% CI	p-value
Paraphernalia coverage	**Low (<200%)**	**1914**	**39**	**2.0**	**1**			**1**			**1**		
	High (≥200%)	**580**	**4**	**0.7**	**0.33**	**0.12-0.94**	**0.037**	**0.39**	**0.14-1.12**	**0.081**	**0.11**	**0.03-0.44**	**0.002**
Survey year	2008-09	933	20	2.1	1			1			1		
	2010	907	15	1.7	0.77	0.39-1.51	0.443	0.94	0.47-1.86	0.851	1.06	0.44-2.55	0.901
	2011-12	669	8	1.2	0.55	0.24-1.26	0.159	0.68	0.30-1.58	0.374	0.38	0.15-0.97	0.043
Homeless in last six months	No	1925	21	1.1	1			1			1		
	Yes	581	22	3.8	3.57	1.95-6.54	<0.001	3.10	1.68-5.72	<0.001	2.07	0.94-4.56	0.071
Injected stimulant in last six months	No	2216	32	1.4	1			1			1		
	Yes	293	11	3.8	2.66	1.33-5.34	0.006	2.48	1.22-5.06	0.012	1.96	0.83-4.67	0.127
Time since onset of injecting	(continuous)	-	-	-	0.95	0.89-1.01	0.081	0.95	0.90-1.01	0.128	0.93	0.84-1.03	0.170

[a]Restricted to those who reported injecting in the last six months

Table H-3. Model (iii) including covariates[a]

		No. anti-HCV negatives (N)	No. recent infections (n)	% (n/N)	Univariable			Multivariable (n=3,008)			Weighted multivariable (n=3,008)		
					OR	95% CI	p-value	AOR	95% CI	p-value	AOR_w	95% CI	p-value
OST	**Not current**	**928**	**23**	**2.5**	**1**			**1**			**1**		
	Current	**2095**	**27**	**1.3**	**0.51**	**0.29-0.90**	**0.020**	**0.63**	**0.35-1.12**	**0.111**	**0.52**	**0.23-1.18**	**0.119**
Survey year	2008-09	1116	23	2.1	1			1			1		
	2010	1130	19	1.7	0.81	0.44-1.50	0.507	0.91	0.49-1.69	0.764	0.72	0.29-1.78	0.481
	2011-12	778	8	1.0	0.49	0.22-1.11	0.088	0.52	0.23-1.17	0.114	0.33	0.13-0.85	0.021
Homeless in last six months	No	2392	25	1.0	1			1			1		
	Yes	629	25	4.0	3.92	2.24-6.87	<0.001	3.56	2.00-6.31	<0.001	2.08	0.91-4.80	0.086
Injected stimulant in last six months	No	2731	39	1.4	1			1			1		
	Yes	293	11	3.8	2.69	1.36-5.32	0.004	2.18	1.08-4.38	0.029	2.08	0.85-5.10	0.110
Time since onset of injecting	(continuous)	-	-	-	0.99	0.95-1.04	0.703	1.01	0.96-1.06	0.742	0.94	0.85-1.05	0.283

[a]Excludes individuals who reported not currently being on OST and also not injecting in the last six months

Table H-4. Model (iv) including covariates[a]

		No. anti-HCV negatives (N)	No. recent infections (n)	% (n/N)	Univariable OR	Univariable 95% CI	Univariable p-value	Multivariable (n=2,993) AOR	Multivariable (n=2,993) 95% CI	Multivariable (n=2,993) p-value	Weighted multivariable (n=2,993) AOR_w	Weighted multivariable (n=2,993) 95% CI	Weighted multivariable (n=2,993) p-value
N/S coverage and OST combined	**Low N/S, no OST**	**590**	**20**	**3.4**	**1**			**1**			**1**		
	Low N/S, OST	**852**	**14**	**1.6**	**0.48**	**0.24-0.95**	**0.035**	**0.55**	**0.27-1.11**	**0.093**	**0.59**	**0.26-1.35**	**0.209**
	High N/S, no OST	**334**	**3**	**0.9**	**0.26**	**0.08-0.88**	**0.030**	**0.28**	**0.08-0.96**	**0.043**	**0.18**	**0.04-0.87**	**0.034**
	High N/S, OST	**717**	**6**	**0.8**	**0.24**	**0.10-0.60**	**0.002**	**0.29**	**0.11-0.74**	**0.009**	**0.05**	**0.01-0.18**	**<0.001**
	Did not inject, OST	**515**	**7**	**1.4**	**0.39**	**0.17-0.94**	**0.035**	**0.62**	**0.24-1.59**	**0.324**	**0.61**	**0.21-1.80**	**0.370**
Survey year	2008-09	1116	23	2.1	1			1			1		
	2010	1130	19	1.7	0.81	0.44-1.50	0.507	0.91	0.49-1.69	0.754	0.96	0.40-2.31	0.934
	2011-12	778	8	1.0	0.49	0.22-1.11	0.088	0.50	0.22-1.13	0.096	0.33	0.13-0.84	0.020
Homeless in last six months	No	2392	25	1.0	1			1			1		
	Yes	629	25	4.0	3.92	2.24-6.87	<0.001	3.47	1.93-6.22	<0.001	1.96	0.88-4.39	0.098
Injected stimulant in last six months	No	2731	39	1.4	1			1			1		
	Yes	293	11	3.8	2.69	1.36-5.32	0.004	2.27	1.11-4.64	0.025	2.04	0.85-4.89	0.109
Time since onset of injecting	(continuous)	-	-	-	0.99	0.95-1.04	0.703	1.01	0.96-1.06	0.734	0.94	0.85-1.04	0.250

N/S: needle(s)/syringe(s)

[a]Excludes individuals who reported not currently being on OST and also not injecting in the last six months

Table H-5. Model (v) including covariates[a]

		No. anti-HCV negatives (N)	No. recent infections (n)	% (n/N)	Univariable OR	Univariable 95% CI	Univariable p-value	Multivariable (n=2,992) AOR	Multivariable (n=2,992) 95% CI	Multivariable (n=2,992) p-value	Weighted multivariable (n=2,992) AOR_w	Weighted multivariable (n=2,992) 95% CI	Weighted multivariable (n=2,992) p-value
N/S coverage, paraphernalia coverage and OST combined	**Low N/S, low para, no OST**	**569**	**20**	**3.5**	**1**			**1**			**1**		
	Low N/S, low para, OST	**817**	**14**	**1.7**	**0.48**	**0.24-0.96**	**0.037**	**0.55**	**0.27-1.11**	**0.095**	**0.58**	**0.25-1.34**	**0.202**
	Low N/S, high para, no OST	**21**	**0**	**0.0**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
	Low N/S, high para, OST	**35**	**0**	**0.0**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
	High N/S, low para, no OST	**208**	**2**	**1.0**	**0.27**	**0.06-1.15**	**0.076**	**0.29**	**0.07-1.26**	**0.098**	**0.18**	**0.03-1.34**	**0.095**
	High N/S, low para, OST	**318**	**3**	**0.9**	**0.26**	**0.08-0.89**	**0.031**	**0.28**	**0.08-0.98**	**0.046**	**0.02**	**0.01-0.09**	**<0.001**
	High N/S, high para, no OST	**126**	**1**	**0.8**	**0.22**	**0.03-1.65**	**0.141**	**0.25**	**0.03-1.90**	**0.180**	**0.16**	**0.02-1.25**	**0.081**
	High N/S, high para, OST	**398**	**3**	**0.8**	**0.21**	**0.06-0.71**	**0.012**	**0.28**	**0.08-0.97**	**0.044**	**0.07**	**0.01-0.35**	**0.001**
	Did not inject, OST	**515**	**7**	**1.4**	**0.38**	**0.16-0.90**	**0.028**	**0.60**	**0.24-1.54**	**0.292**	**0.59**	**0.20-1.75**	**0.343**
Survey year	2008-09	1116	23	2.1	1			1			1		
	2010	1130	19	1.7	0.81	0.44-1.50	0.507	0.93	0.50-1.74	0.814	0.99	0.41-2.39	0.988
	2011-12	778	8	1.0	0.49	0.22-1.11	0.088	0.53	0.23-1.20	0.127	0.35	0.13-0.89	0.028
Homeless in last six months	No	2392	25	1.0	1			1			1		
	Yes	629	25	4.0	3.92	2.24-6.87	<0.001	3.46	1.93-6.21	<0.001	1.96	0.88-4.40	0.099
Injected stimulant in last six months	No	2731	39	1.4	1			1			1		
	Yes	293	11	3.8	2.69	1.36-5.32	0.004	2.22	1.09-4.55	0.029	2.01	0.84-4.82	0.119
Time since onset of injecting	(continuous)	-	-	-	0.99	0.95-1.04	0.703	1.01	0.96-1.06	0.759	0.94	0.85-1.04	0.238

N/S: needle(s)/syringe(s)

[a]Excludes individuals who reported not currently being on OST and also not injecting in the last six months

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