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Identification and optimisation of evidence-based HCV prevention in Europe for young drug users at risk

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Scientific evidence for effective HCV prevention

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Content

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Abbreviations

BBI	Brief Behavioural Intervention
DCR	Drug Consumption Room
ECDC	European Centre for Disease Prevention and Control
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EPC	Enhanced Prevention Councelling
HCV	Hepatitis C Virus, Hepatitis C
IDU	Injecting Drug User, Injecting Drug Use
NSP	Needle and Syringe Programmme
OST	Opioid Substitution Treatment
RCT	Randomized Controlled Trial

1 Introduction

Hepatitis C is a major global health problem. Requiring widespread interventions for its prevention and control, it has been considered one of the major challenges in the third millennium (Friedrich, 1999; Lavanchy, 2011). The hepatitis C virus (HCV) is mainly acquired through percutaneous contact with infectious blood and can lead to severe hepatic complications like liver cirrhosis or cancer (ECDC, 2007).

Currently, a global HCV prevalence of 2.35 % is estimated, affecting approximately 160 million individuals (Lavanchy, 2011). Rates in the general population vary from < 1 % in several European, American or South-East Asian countries, up to over 10 % in some African or Asian countries and show considerable variations within continents and regions (Lavanchy, 2011). Also in Europe, there are notable differences in HCV prevalence. In a recent systematic review of HCV epidemiology in Europe, the lowest rates (< 0.5 %) were found in northern European countries, whereas the highest rates in the general population (≥ 3 %) were from Romania and rural areas in Greece, Italy and Russia (Cornberg et al., 2011). In 2007, 26.840 confirmed new cases of hepatitis C were reported by 27 EU and EEA/ EFTA Member States, which results in an overall incidence rate of 6.87 per 100.000 population (EMCDDA, 2009).

In industrialised countries, injection drug use (IDU) is considered as the main mode of transmission. Notably in countries with lower prevalences in the general population and well-established HCV screening programmes for blood products, more than half of HCV-infected patients (e.g. Norway 67 %, Sweden 65 %, UK 90 %) report a history of IDU (Cornberg, et al., 2011).

Among current injection drug users in Europe, midpoint prevalence of hepatitis C antibodies ranges between 21 % (Finland) and 91 % (Estonia) (Nelson et al., 2011). In most EU member states, prevalence among IDUs is between 50 % and 80 %, though there are some countries with rates of below 30 % (Czech Republic, Hungary, Finland, Slovenia) as well as states where above 80 % (Estonia; Lithuania, Denmark, Italy; Luxembourg, The Netherlands, Portugal) (ECDC, 2010; Nelson, et al., 2011).

Moreover, HCV rates are increased in the incarcerated population. According to a meta-analysis of Vescio et al. (2008), HCV antibodies were found in approximately 30 % to

40 % of inmates in most studies. However, there was a high variability in prevalence rates (from 2 % up to 58 %), which resulted from the different proportion of inmates with a history of IDU. Furthermore, in samples collected during detention, prevalence was higher than in samples assessed upon incarceration, which suggests an intra-prison transmission of HCV (Vescio, et al., 2008).

The acquisition of HCV usually occurs early in the drug career of IDUs (Hagan et al., 2007). Like the human immunodeficiency virus (HIV), HCV can be transmitted via sharing of injection equipment, especially needles and syringes but, unlike HIV, also by lower-dose or indirect blood exposure such as spoons, cotton filters and other paraphernalia (EHRN, 2010). Other risk factors are skin piercing and tattooing procedures, clinical injuries, such as needle stick injuries, medical procedures, vertical (materno-fetal) and sexual transmission, though the evidence base regarding the latter is limited. There are still large gaps in our knowledge, regarding the contribution of the various routes of transmission (Lavanchy, 2011). Compared with HIV, HCV infection is characterised by higher concentrations of the virus in the blood, not only during the primary infection phase, but also in those who become chronically infected, so that a high proportion of HCV infected patients become infectious carriers (ECDC & EMCDDA, 2011a). In contrast, knowledge of HCV serostatus among HCV-positive IDUs is shown to be rather low (approximately 30 % - 40 %) so that many infectious IDUs are not aware that they can transmit HCV (Kwiatkowski, Fortuin Corsi, & Booth, 2002).

Approximately 20 % of acutely infected people clear the virus within several months after acquisition, whereas around 80 % develop chronic infection (defined as continuous persistence of virus RNA in the blood after 6 months) which can lead to the development of fibrosis, cirrhosis, and, in some cases, hepatocellular carcinoma (Thomas & Seeff, 2005). In general, the course of chronic hepatitis C develops over decades, during which time HCV infection does not cause symptoms, until liver failure or end-stage liver disease become clinically apparent. The probability to develop cirrhosis within 20 years after infection is estimated between 5 % and 25 %. Among persons with HCV-related cirrhosis, it is assumed that hepatocellular carcinoma occurs at rates of 1 % to 7 % annually (Thomas & Seeff, 2005).

The current standard antiviral therapy can achieve cure rates between 45 % and 85 %, depending on virus genotype (Hadziyannis et al., 2004; Sheperd et al., 2007). In many countries, it is recommended for all patient groups (including IDU) and is considered cost-effective (Sheperd, et al., 2007). Though current evidence suggests that response rates

and treatment adherence are comparable to non- or ex-IDUs (Hellard, Sacks-Davis, & Gold, 2009), physicians are still reluctant to treat IDUs due to concerns about re-infection or compliance (Myles, Mugford, Zhao, Krahn, & Wang, 2011).

To reduce the spread of HCV, a variety of prevention and harm reduction strategies has been established during the last two decades. These comprised mainly the distribution of sterile needles and syringes, safer injecting advice and counselling, other behavioural interventions like peer-based approaches, and opioid substitution treatment (OST). These strategies have been successful in the control of HIV, but are not as effective for HCV, as prevalence and incidence rates of HCV infections are continuously high. However, some interventions might be more promising than others, which is why the available evidence for their effectiveness needs to be reviewed. A systematic compilation of the different approaches will allow generating recommendations for optimised HCV prevention strategies.

This report is a qualitative synthesis of the current evidence for the effectiveness of different interventions, which aim to prevent HCV transmission among IDUs.

2 Methods

This synthesis is based on a systematic literature review. For this purpose the major electronic peer-review databases Medline, Embase and Psychinfo were screend for articles on review-level as well as primary studies. Included literature had to meet the following criteria:

- Type of report: evidence reports, meta-analyses, systematic reviews. RCTs, observational studies
- Focus on HCV
- Evaluation of effectiveness either in terms of biological outcome measures (HCV prevalence/incidence) or injection risk behaviour
- Time limit: 2002 – current
- English language

The latest search was conducted on the OVID platform on November 10, 2011, using the search algorithm described in table 1. However, relevant evidence reports which were published after that date were considered for the updated review (ECDC & EMCDDA, 2011b, 2011c).

After running the systematic search, 186 references were found. After reading the abstracts of these references, 169 papers were excluded as they did not meet the inclusion criteria (step 14 to 15 in the search strategy).

In detail, the following number of references had been excluded:

- 95 articles without evaluation of effectiveness
- 34 epidemiological articles
- 18 guidelines, policies, conference procedures or opinion papers
- 16 articles on HIV
- 6 unsystematic overviews/ commentaries

After this procedure 17 studies were identified and included in this evidence report.

Among the 95 studies excluded due to lack of an effectiveness evaluation, some of them were considered as they provide additional information on e.g. the feasibility, acceptance or barriers for a successful implementation of HCV prevention, or as they include cost-effectiveness analyses.

Table 1: Search algorithm in Embase, Medline, PsychInfo

	Key Words	Results
1	(hepatitis c or hcv).ti	81.129
2	(hepatitis c or hcv).ab.	97.649
3	1 or 2	115.563
4	(substance disorder or addiction or substance abuse or IDU or drug user$).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tc, id, tm]	228.363
5	(evidence or evident or effective$ or effectiveness).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tc, id, tm]	4.817.593
6	3 and 4 and 5	1.390
7	prevention.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tc, id, tm]	950.631
8	(harm reduction or needle exchange or consumption room or safer injecting facilities or substitution treatment or maintenance treatment).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tc, id, tm]	24.301
9	7 or 8	971.220
10	6 and 9	462
11	limit 10 to English language	433
12	limit 11 to human	392
13	limit 12 to yr="2002 -Current"	329
14	remove duplicates from 13	186
15	after exclusion by hand search	17

3 Findings

Table 2: Overview on the included studies

Study design	Number	Studies	Country
Randomized controlled trial (RCT)	3	(Abou-Saleh et al., 2008)	UK
		(M. D. Stein, Herman, & Anderson, 2009)	USA
		(Tucker et al., 2004)	Australia
Observational studies (incl. prospective cohort, serial cross-sectional)	4	(Aitken, Kerger, & Crofts, 2002)	Australia
		(Knittel, Wren, & Gore, 2010) (uncontrolled before and after study)	USA
		(Leonard et al., 2008)	Canada
		(Van Den Berg et al., 2007)	Netherlands
Systematic reviews	5	(Gillies et al., 2010)	UK
		(Hagan, Pouget, & Des Jarlais, 2011)	USA
		(Jones, Pickering, Sumnall, McVeigh, & Bellis, 2010)	UK
		(Palmateer et al., 2010)	UK
		(Wright & Tompkins, 2006)	UK
Overview	2	(Birkhead et al., 2007)	USA
		(Hunt & Saab, 2009)	USA
Mathematical modelling	3	(Kwon, Iversen, Maher, Law, & Wilson, 2009)	Australia
		(Martin et al., 2011)	UK
		(Zeiler, Langlands, Murray, & Ritter, 2010)	Australia
Total	17		

Some of the included reviews assessed a number of different interventions. For this reason they are recorded multiple times according to the number of interventions they cover. In table 3 the available number of studies for each intervention is presented.

Table 3: Interventions evaluated in the included studies and reviews

Intervention	Number of studies
Behavioural interventions	5
Provision of sterile (injection) equipment	
Needle- and syringe exchange programmes (NSP)	9
Provision of injection paraphernalia	2
Provision of sterile crack smoking material	1
Provision of bleach	2
Opiate substitution treatment (OST)	4
HCV-testing	1
HCV-treatment	2
Drug consumption rooms	1
Interventions in prison	1

Effectiveness in HCV prevention is either defined as an improvement in biological outcome measures, or defined as reduction of risky injection behaviour, e.g. the sharing of needles or syringes. The largest evidence base was found for needle- and syringe programmes, whereas it was hard to find literature examining the HCV-related preventive effects of drug consumption rooms, the provision of sterile crack smoking material, and HCV testing.

3.1 Behavioural interventions

The term “behavioural interventions” covers a variety of different approaches, which aim to raise awareness for HCV transmission risks among drug users and to reduce unsafe injection practices. Their content is highly variable and may range from basic knowledge transfer to enhanced, multi-session counselling, motivational interviewing or peer-education approaches. Mostly, these interventions are provided within the framework of drug treatment facilities or syringe exchange programmes.

Through the systematic search four randomized controlled trials (RCTs) (Abou-Saleh, et al., 2008; Garfein et al., 2007; M. D. Stein, et al., 2009; Tucker, et al., 2004) and two systematic literature reviews were identified (Hagan, et al., 2011; Wright & Tompkins, 2006), which examined the effectiveness of behavioural interventions.

In their RCT, Tucker et al. (2004) compared individually tailored brief behavioural interventions (BBI) with the simple distribution of educational literature. They included 145 adult

IDUs, who were recruited at a specialist drug treatment facility (Tucker, et al., 2004). Primary outcome criterion was the change in HCV risk practices as measured by the BBV-TRAQ (Fry, Rumbold, & Lintzeris, 1998). At a one month follow up, both groups equally showed significant reductions in HCV-related risk behaviour, compared with baseline. Thus, the behavioural intervention was not superior in reducing risk behaviour, although participants in the BBI condition reported a higher overall satisfaction (Tucker, et al., 2004).

A peer-education intervention intended to motivate IDUs to change their own risk behaviours, by teaching them how to educate peers about the risks of HIV and HCV transmission (Garfein, et al., 2007). This approach was also evaluated by means of a RCT. A number of 853 HIV- and HCV antibody negative young IDUs (15-30 years) were recruited in five United States cities through street outreach, advertising, and coupon based participant referrals. A time-equivalent control intervention comprised the discussion of videos addressing social issues or other health-related topics. Participants in both groups were given the same HCV-related written educational material, and they all received HCV-testing before enrolment, including pre- and posttest counselling (Garfein, et al., 2007). At 6-month follow up, a significant decrease in injection risk behaviour compared with baseline was found in both groups, but participants in the peer-education group showed a significantly greater decline than in the control group. Though this indicates, that the peer-based intervention was effective in reducing risk behaviour, groups did not differ in their rates of HCV-seroincidence (Garfein, et al., 2007).

Abou-Saleh et al. (2008) evaluated a 4-session manual-guided, enhanced prevention counselling intervention (EPC), which was implemented in several drug services in UK. All of the 95 enrolled HCV-negative IDUs were in substitution treatment and randomized either to EPC or to a control condition. The control intervention was a single ten-minute session, during which advice on prevention strategies was given and information about HCV risk factors was provided. 12-months after baseline, only 62 out of 95 patients were available for follow-up. Eight of them had seroconverted, three out of 33 in the EPC group and five out of 29 in the control group. However, among the patients in the EPC group who seroconverted, none of them had actually attended the EPC sessions. Inversely, all patients who effectively attended at least one session of EPC, stayed HCV seronegative until follow-up. Consequently only patients were considered for analysis, who effectively attended at least one intervention session. Though this analysis suggests a positive effect of EPC, results are lacking significance due to low rates of recruitment and treatment adherence. Further, both groups improved in many secondary outcome measures: e.g.

injection risk behaviour was reduced, and alcohol use as well as medical or psychiatric symptoms decreased. EPC participants and controls did not significantly differ in their amount of improvement. Thus, no superiority of EPC compared with standard counselling, could be determined, but results suggest beneficial effects of the overall treatment (Abou-Saleh, et al., 2008).

Stein et al. (2009) tested if a four-session motivational intervention would reduce HCV seroincidence in injecting and non- injecting drug users. Participants (n = 277) were recruited via advertisement and word of mouth. Those who were randomized to the control condition only received a written informational handout about local treatment resources, which was also provided to the intervention group. After a 2-year follow-up period, no significant group differences in HCV rates were found. However, injection drug use emerged as the main factor for seroconversion, as higher incidence rates were found among injectors compared to non-injectors. Among those who had never injected at baseline, significantly fewer participants in the intervention group transitioned to injection drug use. This may indicate a beneficial effect of the motivational intervention, though in further measures of risk behaviour (frequency of sharing, number of injection drug use days), no differences were found between intervention participants and controls. For injectors, frequency of injection drug use decreased between baseline and follow-up (M. D. Stein, et al., 2009).

In addition to these four primary studies, there are two systematic reviews addressing behavioural interventions. The review of Wright & Tompkins (2006) considered three observational studies conducted in the 1990, which reported effects of “advice”, “counsellors” or “outreach workers”, but provided no separate evaluation of these behavioural interventions. Two of these studies demonstrated a statistically significant reduction in HCV rates due to the overall programme (Smyth, Keenan, & O'Connor, 1999; Van Ameijden, Vandenhoek, Mientjes, & Coutinho, 1993; as cited by Wright & Tompkins, 2006). The third study stated a reduction in HIV, but not in HCV prevalence after the introduction of safer injecting advice and the distribution of condoms (Hernandez-Aguado et al., 2001; as cited by Wright & Tompkins, 2006). As none of these studies did separately evaluated the behavioural components, the authors assumed that no reliable conclusions on the effectiveness of behavioural approaches should be drawn from these data (Wright & Tompkins, 2006).

A recent review and meta-analysis of Hagan et al. (2011) only included studies which reported results on HCV seroconversion. As a consequence of this relatively strict inclusion

criterion, the authors identified only two studies on behavioural interventions, namely the above described trials from Garfein et al. (2007), evaluating a peer-education approach and from Stein et al. (2009), evaluating a four-session motivational intervention. As none of both studies reported a reduction in HCV seroincidence, a pooled relative risk of 1.18 (95% CI .76-1.81) emerged, indicating a lack of effect (Hagan, et al., 2011). It should be noticed, that the above mentioned trial of Abou-Saleh et al. (2008), which provided a non-significant result in favour of the behavioural intervention, was also identified for that review. However, it was categorised as "multicomponent intervention" instead of "behavioural intervention", because all enrolled IDUs were receiving OST. Consequently, the authors interpreted the small but positive effect as a result of the multicomponent approach and not of the behavioural intervention alone. Accordingly they recommended multicomponent strategies for HCV prevention (Hagan, et al., 2011).

To summarise, the evidence of the effectiveness of behavioural intervention on risk behaviour and HCV seroincidence is equivocal. Concerning risk behaviour, only one out of four RCTs, namely the one with the largest sample, reported a significant effect in peer-education intervention participants (Garfein, et al., 2007). Another study reported lower rates of transition to injection drug use in the intervention group (M. D. Stein, et al., 2009). The remaining two trials failed to determine superiority of the behavioural intervention, compared to the control condition. However, all studies reported significant reductions in risk behaviour between baseline and follow-up, which were equal for intervention participants and controls and therefore indicate a positive effect of the overall treatment. HCV seroincidence was used as an outcome criterion in three studies. Only one RCT reported a reduction in the intervention group, which was however not significant. In accordance to this paucity of data and the small number of controlled trials, both systematic reviews show reluctance in concluding evidence for the effectiveness of behavioural interventions. This reflects the difficulty in assessing the behavioural components separately, as they are usually provided within a framework of other harm reduction components like OST or syringe exchange programmes. On the other hand, it could be exactly this multi-intervention framework which enhances effectiveness. Current evidence suggests that behavioural and counselling interventions are effective within other components like OST or NSP (Abou-Saleh, et al., 2008; Hagan, et al., 2007), though this needs to be further investigated.

3.2 Provision of sterile (injection) equipment

The most important and widely used strategies to provide sterile (injection) equipment are needle and syringe programmes (NSPs), which can be implemented in different settings (e.g. distribution by pharmacies, mobile vans or vending machines), and which may differ in their underlying distribution policies (e.g. “one-by-one” exchange vs. free distribution). Further, paraphernalia other than needles or syringes such as sterile water, “cookers” (e.g. spoons), and cotton are distributed, as well as crack smoking material and bleaching agents for syringe disinfection.

3.2.1 Needle and syringe programmes (NSPs)

In the following, the term NSP is used for all programmes which provide needles and/or syringes, independent from their distribution policy. Thus, it subsumes the older terms “syringe exchange programme” (SEP) and “needle exchange programme” (NEP). As current programmes usually distribute both needles and syringes, and do not necessarily “exchange” them, the term “needle and syringe programme” is more appropriate.

Due to the criteria of the search strategy, only a small number of primary studies on NSPs were identified. This was mainly because studies published before 2002 were excluded. Moreover, this review is explicitly focussed on HCV, but the majority of NSP studies were conducted in the framework of HIV prevention. As a consequence, most of the literature considered consists in systematic reviews or meta-analyses. Besides, three primary studies with different designs and purposes were included. One uncontrolled before and after study evaluated a peri-urban needle exchange programme on a small sample (Knittel, et al., 2010). The prospective “Amsterdam Cohort Studies” investigated the association between participation in harm reduction programmes and HCV/HIV seroconversion (Van Den Berg, et al., 2007). The third study is based on a mathematical model, which simulates the effects of increasing syringe distribution on HCV and HIV incidence (Kwon, et al., 2009).

The evaluation of a small US peri-urban needle-exchange programme provides very limited data due to its small sample size. Only 14 out of 88 clients of the baseline sample completed both baseline and 6-month follow-up assessment. The overall follow-up sample comprised 31 IDUs due to inclusion of new clients. However, significant reductions in risk behaviour from baseline to follow-up as well as non-significant trends were detectable. For example, individuals at follow-up were less likely to reuse syringes or to give another IDU

a previously used syringe. Follow-up respondents were more likely to clean their skin with alcohol when injecting, or to exchange syringes for another individual. Moreover, the data revealed that most clients were heavy drug users, injecting several times per day. This study corroborates a large body of evidence regarding a reduction of risk behaviour, but has a low impact by itself due to its small sample size and poor data quality. However, it demonstrates the feasibility and acceptability of NSP also in rural areas which are not covered by larger urban drug services (Knittel, et al., 2010).

The open, prospective Amsterdam Cohort Study was initiated in 1985. Recruitment is still ongoing and participation is voluntary. From clients enrolled in the study, detailed information on participation in harm reduction programmes has been collected, as well as data on risk behaviour, sociodemographic characteristics and HIV/HCV prevalence. In an analysis published in 2007, the authors determined the impact of NSP and methadone maintenance on HIV and HCV seroincidence (Van Den Berg, et al., 2007). They included drug users at risk for HIV/HCV at baseline, and assessed protective and risk factors for seroconversion. Participation in NSP and methadone maintenance was quantified by means of five categories, ranging from “full participation” (≥ 60 mg methadone per day, injecting drug use and all needles exchanged) to “no participation” (injecting drug use in the past 6 months but no needles exchanged, no OST in the past 6 months). The main result of the study was that only the defined “full participation” had significant effects on HCV incidence, with a six- to sevenfold reduction in the risk of seroconversion. Incomplete participation both NSP and OST had no effect on HCV rates. When separately regarding the effectiveness of NSP, no evidence for a reduction in HCV prevalence was found. NSP alone was even associated with a higher risk of seroconversion. However, this was found to have resulted from a selection bias, in the way that NSP clients were predominately current and heavy injectors. The authors concluded that neither NSP nor OST alone would be sufficient to prevent the spread of blood-borne infections in drug users, and recommended the extension of comprehensive programmes (Van Den Berg, et al., 2007).

Based on data obtained from Australian epidemiological studies, as well as biological and behavioural parameters taken from previous research, Kwon et al. (2009) developed a mathematical model of HCV and HIV transmission among IDUs. The model simulated the impact of NSPs on the spread of both viruses and aimed to determine the optimal level of coverage for either an effective prevalence reduction or long-term eradication of the virus. Key parameters in the model were e.g. the number of actually distributed syringes per year, the average frequency of injections (per syringe), the average size of a sharing group, transmission probabilities, etc. The model was based on the assumption that in-

creased syringe coverage would decrease the number of times each syringe (shared and non-shared) is used. Results of the Australian simulation show that if syringe distribution was doubled, the expected annual HCV incidence would decrease by ~50 %. In contrast, even a moderate reduction in the provision of syringes (one third) would increase the annual incidence by a factor of ~1.5. The model also shows that current NSP coverage in Australia has succeeded in controlling the spread of HIV, but nevertheless HCV incidence is expected to remain high, due to its higher background prevalence and increased infectivity. The authors concluded that their model provides supportive evidence for the effectiveness of NSP, and recommended to close current gaps in NSP coverage (Kwon, et al., 2009).

Four articles were identified, which investigated the effectiveness of NSP in terms of HCV seroconversion or injection risk behaviour (i.e. sharing of needles or syringes). One of them was a "review of reviews", summarising the results of the available systematic reviews and meta-analyses for this intervention. Further, there is one short overview on the implementation of harm reduction in New York State. In this overview the authors stated that a decline in HCV incidence in the 1990s has been due to the implementation of NSP (Birkhead, et al., 2007). This corresponds to similar observations in Europe.

In their review, Wright and Tompkins (2006) summarise the results of several long-term prevalence studies conducted in Scotland (Hutchinson et al., 2002), Australia (MacDonald et al., 2000), Sweden (Mansson, Moestrup, Nordenfelt, & Widell, 2000) and Switzerland (Broers et al., 1998; Somaini et al., 2000). All studies showed a reduction in HCV prevalence after the implementation of NSPs in their respective countries, which was between the late 1980s and late 1990s. The Swiss study reported a greater decline after both syringes and needles were available, compared with the period before 1991, when needles but not syringes were provided. In contrast, three North-American studies, using prospective cohort or case control designs, had equivocal results: Whereas one case control study revealed a seven-fold greater risk for HCV in non-users of NSP compared to users (Hagan, Jarlais, Friedman, Purchase, & Alter, 1995), a Canadian study failed to determine a significant effect due to lack of statistical power (Patrick et al., 2001; as cited by Wright & Tompkins, 2006). In the third study, which used a prospective cohort design, NSP use was even associated with an increase in HCV, though this was not statistically significant (Hagan et al., 1999). Concerning risk behaviour, the authors identified two large observational US studies, demonstrating that the introduction of NSPs led to a self-reported reduction in the sharing of needles or syringes, when this was associated with an increasing availability of these items (Wright & Tompkins, 2006).

The recent meta-analysis of Hagan et al. (2011) included seven observational studies, which used HCV seroconversion as an outcome criterion. All studies were conducted in North America and predominately assessed NSP participation as “any use” compared with “no use” during a defined period. In five studies, no significant association between NSP attendance and seroconversion was found. Only one case-control study, which was also included in the review of Wright et al. (2006), found a significant result in favour of NSP (Hagan, et al., 1995). A Canadian study, however, revealed an elevated risk of HCV infection in frequent NSP attendees compared with other IDUs (Patrick, et al., 2001). This study was also considered by Wright and Tompkins, who drew different conclusions from its results (see Wright & Tompkins, 2006). In contrast to the review of Wright & Tompkins (2006), Hagan et al. (2011) concluded that no effect of NSP on HCV incidence could be demonstrated. Comparing both reviews, Hagan et al. (2011) only included studies, which had an individual approach by assessing pre- and post intervention incidence rates, whereas Wright & Tompkins (2006) focused on studies assessing prevalence rates in large samples over years, which may explain their different conclusions. However, Hagan et al. (2011) assumed that individual-level comparisons are prone to volunteer bias: As NSPs particularly attract and retain higher-risk IDUs, this may explain the difficulty in demonstrating an effect on HCV incidence (Hagan, et al., 2011).

Another review, published in 2010, compared the effectiveness of different NSP approaches as a function of site, setting and distribution policy (Jones, et al., 2010). Also, the impact of additional harm reduction services and the provision of NSP alongside OST were investigated. The overall effectiveness of NSP on risk behaviour was not explicitly assessed, as the authors focused on the comparison of different settings. Based on 11 studies, which examined different types of NSPs, only marginal effects of site, setting, and distribution policy were found. There was some impact of distribution policy on syringe re-use, indicating that participants in distributive programmes, which provided more syringes and were open more days and hours, were less likely to re-use syringes than IDUs in programmes with more restrictive policies. However, distribution policy did not influence the amount of sharing. Moreover, there were no differences regarding site and setting (e.g. pharmacy vs. hospital-based or mobile access), though mobile NSP and vending machines seemed to attract high-risk and younger IDUs in particular. Regarding additional harm reduction services (e.g. counselling, testing), no reliable conclusions could be drawn due to several limitations in study design and reporting. In this context, Jones et al. (2010) included two studies on the provision of OST alongside NSPs. A Canadian study, which assessed the effect of OST delivered via NSPs, found that the combined approach led to

a significant reduction in the proportion of injectors; however, those who were still injecting at follow up showed no important reduction in risk behaviour (as cited by Jones, et al., 2010; Millson et al., 2007). The study of van den Berg et al. (2007) revealed that full participation in OST and NSP was associated with lower HIV and HCV incidence. In their conclusions, Jones et al. refer to this study as the most promising indication of benefit (Jones, et al., 2010).

A review of reviews from Palmateer et al. (2010), summarised the evidence of all relevant systematic, narrative or meta-analytic reviews conducted between 2000 and 2007, with respect to biological outcomes (HCV prevalence/ incidence) and self-reported risk behaviour. The authors distinguish between fixed-site NSPs, alternative modes of provision (i.e. pharmacy distribution, vending machines and outreach work) and the distribution of other injection paraphernalia. As to (fixed-site) NSPs, they concluded that the current evidence regarding biological HCV outcomes is not sufficient to either support or discount their effectiveness. By judging the review of Wright & Tompkins (2006), they argue that their results, which speak in favour of NSPs, were mainly derived from studies with weaker design (ecological observations), whereas the more robust studies on an individual level (case control or prospective cohort) provided only equivocal evidence. However, concerning behavioural outcomes Palmateer et al. (2010) stated that the evidence base is sufficient to support the effectiveness of (fixed-site) NSPs as consistent evidence emerged from multiple robust studies; 39 out of 43 primary studies reported reductions in self-reported risk behaviour. Regarding syringe provision through pharmacies no reviews were identified that examined effects on HCV incidence or prevalence. Tentative evidence however, is assumed for an effect in reducing risk behaviour, as seven weaker studies on pharmacy-based distribution consistently report positive effects. For vending machines no reviews regarding HCV transmission were identified, and only one study provided evidence for a reduction of risk behaviour. Regarding outreach NSP there were no reviews on HCV rates, and inconsistent evidence for a reduction in risk behaviour emerged from four studies (2 positive, 2 without association). The authors summarised that for all modes of needle and syringe distribution there is a lack of evidence regarding HCV seroincidence. Although there is sufficient evidence to support a reduction in risk behaviour for fixed-site NSPs and tentative evidence of an additional impact of pharmacy NSP, this might not be effectively enough to reduce HCV transmission (Palmateer, et al., 2010).

To summarise: There is solid evidence that NSPs lead to a reduction in injection risk behaviour like the sharing or re-use of syringes. Fixed-site NSPs are the most often evaluated provision mode. Currently there is no evidence to assume neither specific

advantages nor disadvantages of other distribution modalities like pharmacy access or vending machines. With respect to biological HCV outcomes, results are equivocal: Although a series of large observational studies, conducted in the 1980s and 1990s, have revealed a marked reduction in HCV prevalence after the implementation of NSPs, a number of more recent studies on an individual level (e.g. prospective cohort studies) provided less encouraging results. This might be explained by two reasons: First individual-level studies are more vulnerable to selection bias as NSP clients are mainly high-risk users who inject more often. Secondly, many studies did not assess the coverage of NSP and the frequency of its use, although these may be crucial factors. If there is only an occasional NSP use, this is less likely to effectively prevent HCV. It does therefore not appear useful to compare "any NSP use" with "no NSP use" as it was done in several studies (Hagan, et al., 2011). Also the results of the Amsterdam Cohort Study support the view that the quantity of NSP use is an important factor: combined with OST, only full participation in NSP (100% of needles exchanged) led to a reduced HCV risk, whereas occasional needle/syringe exchange had no effect (Van Den Berg, et al., 2007). However, a reduction in the number of times a syringe is used may lead to a long-term reduction of HCV-prevalence, as demonstrated by means of a mathematical model (Kwon, et al., 2009). As there is compelling evidence that NSPs reduce injection risk behaviour, NSP presents a key component in HCV prevention. However, either their current amount of coverage and/ or the frequency of their utilisation do not seem to be sufficient. It can be supposed that further improvement of NSP coverage is appropriate to overcome gaps (e.g. in rural areas), and if part of a multicomponent strategy effects may increase.

3.2.2 Distribution of other injection material/crack smoking material

The effectiveness of distributing other consumption equipment is assessed in one serial cross-sectional study investigating the distribution of sterile crack-smoking material in NSP sites in Ottawa (Leonard, et al., 2008) and two systematic reviews evaluating the provision of injection paraphernalia (sterile water, spoons etc.) (Gillies, et al., 2010; Palmateer, et al., 2010).

To investigate if the distribution of sterile crack-smoking material would result in a reduction of injection risk behaviour, Leonard et al. (2008) conducted a serial cross-sectional study in several NSP sites in Ottawa. They included active, street-recruited IDUs who also smoke crack, and assessed frequency of injections and of crack smoking. Prior to implementation and at three follow-up time points (1 month, 6 months and 12 months), anti-HCV prevalence was determined by means of saliva testing. Results indicate a good

acceptance of the programme, as 87 % of all NSP users welcomed the initiative. However, no significant difference in saliva-tested HCV incidence emerged, but a slight decline in injection frequency and in crack smoking was observed. According to the participants this was due to the availability of crack smoking equipment, but also a result of the higher availability of crack (Leonard, et al., 2008).

In a recently published systematic review, 13 studies were identified, which evaluated the provision of non-needle/syringe drug injection paraphernalia (Gillies, et al., 2010). None of these studies reported biological measures of HCV incidence. In one study, self-reported HCV status was assessed, and results showed that those who frequently used sterile cookers and water were more likely to report being HCV negative. Behavioural outcomes, such as self-reported risk behaviour, suggested a reduction in the sharing of injection paraphernalia when these items were provided. In most studies, however, this was confounded with NSP attendance in general which makes it difficult to determine, if the provision of paraphernalia has any additional impact. Due to the reduced number and quality of studies, the authors stated that robust conclusions cannot yet be drawn. In their review of reviews Palmateer et al. (2010) identified only one core review, which provided inconsistent evidence from a small number of studies. Thus, the authors also concluded that the level of evidence for the provision of paraphernalia is not sufficient to determine an effect of these interventions.

In conclusion, current evidence regarding the distribution of sterile injection paraphernalia is not sufficient either to support or to discount an effect on HCV transmission. No study was identified that reported biological outcomes. As to self-reported risk behaviour, results are equivocal and it remains unclear to which extent this decline can be attributed to NSP use in general. Concerning the provision of sterile crack-smoking material only one study was found, which observed a slight decline in injection frequency and an increase in crack smoking.

3.2.3 Distribution of bleach (syringe disinfection)

Two systematic reviews were identified that assessed the HCV prevention strategy of using syringe disinfectants (Hagan, et al., 2011; Wright & Tompkins, 2006). Wright & Tompkins (2006) identified only one primary study which reported a non-significant reduction in HCV prevalence for those who used bleach before every infection, compared to those who used it less often (Kapadia et al., 2002). In the more recent review of Hagan et al. (2011), four primary studies were cited that examined the effect of HCV seroincidence.

However, none of these studies could determine a significant effect on HCV transmission and also their pooled effect was not significant. As in all four studies measurements were consistent, the authors considered the level of evidence as sufficient to assume that bleach distribution has no effect on HCV transmission (Hagan, et al., 2011).

3.2.4 Needle and syringe programmes in prison

There is one summary of several HCV prevention strategies in prison, which gives a short résumé of the experiences made with NSP in the correctional setting, Results indicate, that these programmes have been effective in reducing injection risk behaviour and do not compromise safety of correctional staff or inmates (Hunt & Saab, 2009). Effects on biological outcome measures were not reported.

3.3 Opioid substitution treatment (OST)

There is already a consistent evidence base from multiple studies, predominately conducted in the context of HIV prevention, that OST successfully reduces injecting risk behaviour and the frequency of injections (Amato et al., 2005; Gowing, Farrell, Boremann, Sullivan, & Ali, 2008). As the focus of this review is on HCV-related outcomes, no studies on other aspects of OST were included. With respect to HCV two systematic reviews, one overview on the experiences in the correctional setting and one primary study on OST were considered for this review.

The above described Amsterdam Cohort Study suggests that the combination of two key prevention strategies, NSPs and OST, is an effective approach to reduce HCV incidence (Van Den Berg, et al., 2007). When the effectiveness of OST on HCV seroincidence was assessed separately, the authors found no evidence for a reduction in HCV rates. Though OST was associated with lower HCV incidence, this result failed to reach statistical significance. Another aspect of this study concerned the “dependence on harm reduction”: Persons who reported not to inject drugs and not to participate in OST in the previous six months were categorised as “not dependent on harm reduction”. In contrast, “limited dependence on harm reduction” was used to describe clients without injection drug use but enrolled in OST, with a methadone dosage up to 59 mg/day. Results revealed that persons categorised as limited dependent were at a slightly lower risk than the “no dependence” group. Though this difference failed to reach statistical significance, the authors suggested a possibly protective role of social and medical care networks that are associated with OST (Van Den Berg, et al., 2007).

The review of Wright & Tompkins (2006) included one case control study, two prospective cohort studies and three observational studies, which assessed the effect of OST on HCV incidence rates. Results were not encouraging, as none of these studies found statistically significantly results. At best, the results of the case control study were of borderline significance: IDUs not enrolled in OST during six months prior to testing were at slightly higher risk to contract HCV (Rezza et al., 1996; as cited by Wright & Tompkins, 2006). Further, one prospective cohort study found a non-significant decline in HCV incidence among IDUs who continued OST, compared to those who interrupted treatment or left (Van Ameijden, et al., 1993; as cited by Wright & Tompkins, 2006). Wright & Tompkins (2006) argued that the absence of a marked effect might partly be due to the insufficient consideration of substitution dosage in most studies, and under-dosing is likely to reduce the effectiveness of OST. Another point, which particularly concerns observational studies (as prospective studies generally included HCV negative users at baseline), is that drug users usually become infected in their early years of drug use, which is often years before they enter OST (Wright & Tompkins, 2006).

The meta-analysis and review of Hagan et al. (2011) provides similarly results. The pooled relative risk of eight included studies was at .60 (95 % CI: .35-1.03), which indicates a positive effect of OST in HCV reduction on trend level. However, this effect reached statistical significance when only studies without “interrupted” OST in the comparison groups were considered (RR: .52, 95 % CI: .34-.79). This result suggests that continuous OST is more effective in reducing HCV incidence compared to no OST, but not compared to irregular or interrupted OST, which may also have a small effect in HCV prevention. Further, the authors stated that seroconversion in these studies was rather low. This could result from the fact that most drug users become infected early in their drug career. As a consequence, IDUs enrolled in OST are either already HCV positive, or they have been succeeded in staying negative for a couple of years. The latter group may have developed strategies for safer drug use, and thus are probably less likely to seroconvert. A further explanation for the lack of a clear effect could be that OST does not completely eliminate injection risk behaviour. The authors concluded that control of one’s injection behaviour may be a key factor in HCV reduction, which is however not entirely assured by OST alone (Hagan, et al., 2011).

The overview of Hunt & Saab (2009) evaluated OST in prison. According to this overview OST effectively reduces HCV infection, drug use and drug injection, as well as reimprisonment rates and mortality. OST was shown to be most effective when sufficiently high

doses were provided, and when treatment covered the whole period of incarceration (Hunt & Saab, 2009).

To summarise: The evidence for the effectiveness of OST in reducing HCV incidence is not yet compelling. This may be related to several reasons: Often substitution dosage was not sufficiently assessed, and methods on how to consider interrupted OST in the analysis differed between studies. As low-dose and/or discontinuous treatment are likely to be less effective in preventing HCV, these methodical limitations may made it difficult to determine an effect. Further studies should therefore better quantify the amount to which participants receive or make use of OST, in order to investigate a possible dose-response relationship. In addition, it may play a role that most IDUs get infected in their early years of drug use, which is usually before they get enrolled in OST. Nevertheless, there is evidence that OST might be a key factor embedded in a multicomponent prevention approach (Van Den Berg, et al., 2007), as it effectively reduces risk behaviour and the frequency of injections (ECDC & EMCDDA, 2011c; Gowing, et al., 2008). Further, the social and medical network provided with OST may play an important protective role and may also provide a framework to initiate antiviral HCV treatment.

3.4 HCV testing

Through the systematic search there were no many studies identified that investigated the effects of regular HCV testing and counselling. There is one systematic review addressing this topic, and only one primary study which examined the effects of HCV testing on risk behaviour.

Aitken et al. (2002) evaluated a NSP in western Melbourne providing free hepatitis C testing and counselling, offered by a peer outreach worker. For the study sample of 47 IDUs, who have not been tested during the previous 12 months, testing was combined with an assessment of risk behaviour and HCV-related knowledge. Reasons why not previously being tested were explored, and participants were invited for a second interview. 28 of 47 IDUs returned for this second assessment. Regarding HCV-related knowledge, the number of correct responses was higher in the second interview, and participants gave more detailed and accurate answers (Aitken, et al., 2002). It should be considered, however, that these results may have been subject to a selection bias, as it is reasonable to assume that mainly persons who were interested in the issue of HCV were willing to be interviewed a second time. Self-reported risk behaviour improved in some participants in terms of less needle sharing and higher frequency of hand-washing. These improvements

were not observed for those IDUs who usually injected in street settings. No differences in behaviour change were observed between IDUs having received positive vs. negative test results (Aitken, et al., 2002). As main reasons for not previously being tested participants stated to be unaware of risks and to lack an appropriate testing situation (fear of stigma). Those who had previously been tested, reported the absence of an pre- and posttest counselling. From their experiences the authors concluded, that a demand exists for peer-delivered hepatitis c testing and counselling located at an NSP, and that this intervention is effective in improving the ability of IDUs to avoid harm (Aitken, et al., 2002).

A review of Stein et al. (2002) included studies published up to 2001. No compelling evidence was found that knowledge of HCV status had an impact on risk behaviour. However, there were some important methodological shortcomings: three of the four included studies were correlative designs, and based on self-reported testing results. The only longitudinal study determined no effect on risk behaviour, and the three correlative studies found either no association or equivocal results (K. Stein, et al., 2002).

In conclusion there is a notable lack of studies investigating the effects of HCV testing and counselling on risk behaviour of IDUs. In the only primary study results have to be regarded with caution due to the small sample size and many losses to follow-up. One systematic review (K. Stein, et al., 2002) also stated the lack of a reliable evidence base. Further research should also examine potential effect of receiving a positive versus a negative test result on behaviour, and clarify if receiving a positive result would e.g. result in an abandon of any caution, or, in contrast, would raise the responsibility for others and decrease the amount of needle/syringe sharing. To date, the evidence base is not sufficient to support or discount any effects.

3.5 HCV treatment

The current standard treatment of chronic hepatitis C with pegylated interferon alfa and ribavirin leads to cure rates (sustained viral response, SVR) of 45-80 %, depending on virus genotype (Hadziyannis, et al., 2004; Sheperd, et al., 2007). Though few active IDUs have been treated to date, a review suggests that their response rates and treatment compliance are comparable to non- or ex-IDUs (Hellard, et al., 2009).

In this evidence report, studies on response rates or treatment feasibility among IDUs were not included. Instead, studies are considered which examined HCV treatment as prevention strategy, by assessing its impact on prevalence or incidence rates in the IDU

population. In this respect two studies were identified which provided mathematical models for the UK and for Australia.

A British working group recently conducted a modelling analysis for the UK to assess possible long-term effects of antiviral treatment on HCV prevalence in the population of active IDUs (Martin, et al., 2011). Model parameters such as SVR rates, genotype distribution, treatment duration or rate of leaving IDU population (due to cessation or death) were obtained from literature. Average SVR was defined at 62.5 %, weighted half genotype 1 and genotype 2/3. The possibility of re-infection was considered. In the baseline scenario of their model, Martin et al. (2011) made rather conservative assumptions as neither re-treatment after treatment failure was assumed nor spontaneous clearance resulting in immunity. The simulation was run for different baseline HCV prevalence rates (20 %, 40 % or 60 % in the IDU population) as well as for different treatment rates (either 5, 10, 20 or 40 per 1000 IDUs annually). Results show that even a low treatment rate of 10 per 1000 active IDUs per year would result in a relative prevalence reduction of 7 %, 13 % or 31 % after 10 years, given baseline prevalences of 60 %, 40 % or 20 %, respectively. In contrast, a higher rate of treating 40 per 1000 IDUs per year would result in considerably higher prevalence reductions, of about 60 % over 10 years, given a baseline prevalence of 40 %. Relevant prevalence reductions remained even in the "reduced SVR scenario", when SVR rates were assumed to be at only 45 % (Martin, et al., 2011).

A similar modelling analysis was conducted for Australia (Zeiler, et al., 2010). The authors proposed two alternative models: the first one regarding the IDU population as a whole, the second one differentiating between IDUs enrolled vs. not enrolled in OST. Based on data from Australian clinical trials, zero injecting was not assumed for OST patients, but IDUs in OST were regarded to inject approximately 8-fold less. This resulted in a lower probability of equipment sharing and a lower probability to transmit the virus or to become (re-)infected. Rates of cycling in and out OST were also considered (Zeiler, et al., 2010). A prevalence rate of 60 % was assumed, and treatment success (SVR) was defined as 50 %. In contrast to Martin et al. (2011), who calculated with fixed numbers of annually treated IDUs, Zeiler et al. (2010) used percentages of treated IDUs and determined the resulting endemic steady state levels. For example, if the current Australian treatment rate of 1 % was maintained, the model predicts that HCV would remain endemic at the current level of 60 % prevalence. In contrast, if treatment rate was increased to 56.6 % of all infected IDUs, the endemic steady state would reach zero, suggesting that an eradication of the disease in the IDU population would be possible. In this condition, prevalence for chronically infected numbers would take 3.3 years to halve and 11.1 years for numbers of

acute infection (Zeiler, et al., 2010). However, as these projections are only valid if current rates of needle/ syringe sharing do not increase, the authors emphasised the important role of NSPs. In the second model, which splits the IDU population into those enrolled in OST and those who are not, results reveal that if equal adherence to therapy is assumed for OST and non-OST IDUs, the majority of treatment should be directed to those not in OST. Only if adherence of non-OST IDUs falls below 44 % of those in OST, then treatment should preferentially be targeted to those in OST (Zeiler, et al., 2010). In part, the authors attributed this at first sight contraintuitive finding to the high rates of switching in and out of OST. Calculations with longer duration in OST would shift the optimal treatment allocation more to the OST group (Zeiler, et al., 2010). The authors therefore concluded that any measures that can lead to more sustained OST will have a double effect: reducing the likelihood of injecting and offering greater effectiveness of HCV treatment (Zeiler, et al., 2010).

The abovementioned British working group around Martin, Vickerman and colleagues responded to this Australian modelling study in a recently published commentary (Vickerman, Martin, & Hickman, 2011). They argued that the projections of Zeiler et al. (2010) under-estimated the prevention effect of HCV treatment. They criticised that the baseline prevalence rate assumed for Australia was too high, and due to the way how Zeiler et al. (2010) implemented different treatment lengths depending on success and failure, the resulting model equations effectively led to only 33,3 % SVR instead of the assumed 50 % (Vickerman, et al., 2011). By replicating the model of Zeiler et al. (2010) with both assumptions changed (using a baseline prevalence of 45 % and a treatment efficacy of 50 %), the theoretical treatment rate to eradicate HCV decreases from 56.6 % (Zeiler, et al., 2010) to approximately 20 % (Vickerman, et al., 2011). When simulating more achievable treatment rates, e.g. 5 % or 10 % of IDUs per year, a relative reduction of 16 % or 32 %, respectively, could be expected. Vickerman et al. (2011) doubt in the finding that HCV treatment should preferentially be targeted to IDUs not enrolled in OST. Though SVR rates appear to be comparable for opiate-substituted and non-substituted IDUs (Hellard, et al., 2009), the authors argued for primarily treating IDUs in OST because of their regular contact with services (Vickerman, et al., 2011). Overall, the authors concluded that both the Australian model (Zeiler, et al., 2010) and their own additional sub-analyses (Vickerman, et al., 2011) demonstrate a substantial prevention effect of HCV treatment in IDUs. By considering various ranges of HCV prevalence scenarios (from 20 % up to 75 %), results are of relevance in further settings and countries with a similar genotype distribution and duration of injecting (Vickerman, et al., 2011).

Hunt & Saab (Hunt & Saab, 2009) reviewed the literature on HCV treatment in prison and concluded that the correctional setting provides favourable conditions for initiation of antiviral treatment. A cost-effectiveness analysis demonstrated that antiviral treatment would be cost-saving for most patient subgroups, and further, in the prison setting, low rates of discontinuation due to psychiatric and other side effects were reported. However, they also identified barriers for treatment such as the absence of secure post-release follow-up and the lack of available specialists (Hunt & Saab, 2009).

The current literature suggests that antiviral HCV treatment of (ex-) IDUs is a promising measure to prevent the further spread of HCV. It should be noticed, however, that the available evidence of HCV treatment of HCV prevention is obtained from mathematical modelling projections, as an evaluation of the treatment effect in larger prospective or epidemiological studies in the IDU population have not yet been conducted. Although the mathematical models have to be treated with caution as to the proposed treatment rates, the prognoses obtained from these models seem to be realistic projections. The model parameters were obtained from current data and were carefully adapted to country-specific settings. The authors of the Australian model (Zeiler, et al., 2010) recommend interventions that enhance the duration in substitution treatment. Further, the important role of NSPs is emphasised, as the proposed mathematical models are only valid if the rate of equipment sharing will not increase. Furthermore HCV treatment in prison appears to be a feasible option.

3.6 Drug consumption rooms

Though there is evidence that drug consumption rooms (DCRs) improve injecting hygiene and reduce risk behaviour (for a review, see Hedrich, Kerr, & Dubois-Arber, 2010), there is a lack of studies investigating their impact on HCV prevention. In our database search, no primary study has been identified, which systematically assessed the effects of DRC on HCV incidence. Wright and Tompkins (2006) also stated this gap in their systematic review as they found only one time series analysis from an early DCR evaluation in Australia, which examined anti-HCV conversion as an outcome but only presented descriptive data. They found no change in HCV incidence among local users, but an increase in HCV notifications in neighbourhood areas. However, the low population prevalence of HCV in Australia may make it difficult to detect significant changes and to deduce a relevant effect from these results. However, as several studies reveal that drug consumption rooms are frequented in particular by high-risk users, the authors assumed that DCRs might contrib-

ute to a reduced HCV incidence (Wright & Tompkins, 2006). Thus, further research is needed to investigate the effects of DCRs on the incidence of HCV and other infectious diseases.

4 Conclusions

The review is based on current literature investigating the effectiveness of a variety of interventions that aim to prevent the spread of HCV among IDUs. These interventions comprise behavioural interventions, the provision of sterile (injection) material, opiate substitution treatment (OST), HCV-testing, HCV-treatment and drug consumption facilities.

Regarding behavioural interventions, the evidence for their effectiveness is ambiguous, which is partly due to the absence of controlled studies. As behavioural interventions are usually implemented within other harm reduction programmes (e.g. NSP, OST) it is difficult to assess their specific effects. Also in RCTs, effect assessment is difficult as control interventions often contain similar components such as provision of information HCV-testing and pre- and posttest counselling. For this reason it can be assumed that these control interventions, which are partly "behavioural" as well, have a similar prevention effects. Behavioural components might have an effect on risk behaviour, even if the effect is small and not clearly to identify. As available studies often comprised NSP and/or OST, multicomponent interventions seem demonstrate the best success in prevention of at least risk behaviour in IDUs.

Concerning NSP there is a solid evidence base supporting the effectiveness of this intervention in reducing the sharing or re-use of syringes. At the same time there is only weak evidence that NSP has a relevant impact on HCV incidence rates. As NSP clients are mainly high-risk users who inject more often, most important factors would probably be the coverage of NSPs and the frequency of drug users making use of these services. Occasional needle/syringe exchange was shown to have no effect on HCV, while full participation in both NSP (100% exchange of needles) and OST had an effect on HCV incidence (Van Den Berg, et al., 2007). Recently, these findings were confirmed by Turner el al. (2011) on British samples, supporting the combination of NSP, when provided in sufficient coverage, and OST.

As regards the distribution of non needle/syringe injection paraphernalia and the distribution of sterile crack smoking equipment, the lack of studies currently does not allow draw-

ing conclusions on the effectiveness of these interventions. At present the level of evidence regarding the provision of paraphernalia and crack smoking material is not sufficient. Furthermore, current literature suggests that the distribution of syringe disinfectants is not effective in preventing HCV.

There is a solid evidence base that OST contributes to risk reduction by reducing the frequency of injections. However, results on biological HCV outcomes are not compelling, as there is no clear evidence for the reduction of HCV prevalence due to OST. This may partly be due to an insufficient consideration of treatment duration, treatment interruption and dosages in many studies. A second explanation for the unclear evidence is that many IDUs become infected long before they receive OST. Current evidence suggests, that OST might be a key intervention when combined with NSP and/or behavioural interventions (Hagan, et al., 2011; Van Den Berg, et al., 2007). Further, OST is supposed to provide a supportive framework to initiate antiviral treatment.

For the effectiveness of HCV testing and counselling there is a lack of well-designed studies. One primary study and one literature review provided ambiguous results. Further research is needed to investigate HCV testing and it effect on risk behaviour and prevention of acquiring HCV. As well the different consequences on behaviour related to a positive or negative test result needs further investigation. As to HCV treatment, mathematical modelling projections provide optimistic prognoses that relevant prevalence reductions could be obtained over the next 10 years, if a moderate rate of about 10 % of IDUs were treated per year. However, if these rates are realistic remains unclear.

Studies systematically examining the impact of DCRs on HCV prevention are currently lacking. Though there is evidence for an improvement in hygiene and reduction in risk behaviour, no definite statements on the role of DCRs in HCV prevention can be made.

If regarding each intervention separately, their impact on HCV prevention is rather discouraging as there is no evidence that any of these interventions are effective to prevent the spread of HCV. Though some of these interventions have been shown to be successful in controlling the spread of HIV, they fail to control infections with HCV as prevalence and incidence rates are continuously high. On the other hand there encouraging results for the combination of different interventions. In this respect optimistic findings were obtained in the Amsterdam Cohort Studies, revealing that OST in sufficient dosage, combined with full participation in NSP had a relevant impact in the prevention of new HCV infections (Van Den Berg, et al., 2007). Hagan et al. (2011) also supported the concept of multicomponent strategies in their meta-analysis: the pooled effect of the

Amsterdam study and of another combination approach (Abou-Saleh, et al., 2008) resulted in a reduction of HCV transmission risk by 75 % (Hagan, et al., 2011). In addition, a recent meta-analysis (Turner, et al., 2011), which also distinguished between different levels of harm reduction ("full", "partial" and "minimal harm reduction", depending on the coverage of OST and NSP), confirmed the results of Van den Berg et al. (2007) and came to the same conclusion:

> *"Uptake of opiate substitution therapy and high coverage of needle and syringe programmes can substantially reduce the risk of hepatitis C virus transmission among injection drug users" (Turner, et al., 2011, p. 1978).*

The importance of sufficient NSP coverage as well as continuous OST is also emphasised in recent mathematical modelling studies on the long-term impact of antiviral treatment. Continuity in OST and utilisation of NSP both reduce the frequency of possible transmissions (Vickerman, et al., 2011; Zeiler, et al., 2010). In addition, OST might provide support an increased retention in antiviral treatment (Vickerman, et al., 2011).

The evidence for the effectiveness of multicomponent interventions, as indicated in the conclusions of Van den Berg et al. (2007), Hagan et al. (2011), Turner el al. (2011), has also been confirmed in the recent technical reports and guidelines of ECDC and EMCDDA (ECDC & EMCDDA, 2011a, 2011b, 2011c). Combinations of key interventions, in particular OST and NSP, but also behavioural interventions and antiviral treatment are promising strategies in future prevention efforts. However, as the extent of their utilisation by drug users at risk seems to be a crucial factor, the sufficient amount of coverage needs to be determined. Further, it needs to be clarified if higher coverage would automatically lead to increased utilisation by IDUs or if there are other barriers that need to be resolved.

5 Discussion

By reviewing the current literature, the most important conclusion is that there are some key interventions that promise to be effective when combined, in particular OST and NSPs. However, their appropriate implementation and coverage is a crucial point. Best results were shown with a combination of continuous OST in sufficient dosage, and a high coverage of NSPs. Though the role of behavioural interventions, HCV testing and counselling is not yet clear, it can be assumed that a combination of these components with OST and NSP could have an improved impact. Based on the evidence it can be concluded that there are already interventions having the potential to be effective in prevent-

ing HCV, but these are not sufficient in their current amount, coverage, or implementation within multicomponent strategies.

To increase the coverage of NSP it has to be considered to further implemented NSPs and/or vending machines in some regions such as in the periphery of larger cities or in rural areas. In a recent evidence report published by ECDC and EMCDDA (2011b) facilitators for the use of NSPs were geographical proximity, low prices, encouraging staff attitudes and the possibility to receive additional services. The main barriers for NSP use were a fear of being caught by the police, long access routes, limited opening hours or a lack of privacy (ECDC & EMCDDA, 2011b).

Due to the highly infectious hepatitis C virus it is important to continue addressing risk behaviour in drug users. The role of transmission routes apart from needles and syringes is not yet fully clear. Research should further address this aspect. There is no clear knowledge how frequent infections occur due to sharing of paraphernalia (spoon, water), crack pipes or razorblades.

As a long-term option to reduce HCV prevalence in the IDU population, an increased treatment rate among IDUs is discussed. Despite, there is still some reluctance in treating IDUs, as it was demonstrated in a recent Canadian survey (Myles, et al., 2011). According to the results only 19 % of the interviewed practitioners in this survey were likely to treat a current IDU who regular attends an NSP. But also the attitudes of drug users towards antiviral HCV treatment are reluctant. Munoz-Plaza et al. (2008) conducted face-to-face and focus group interviews with 164 patients from 14 US drug treatment programmes. Their findings demonstrated that peers have an important role in shaping the perception of HCV treatment. The main reason not to initiate HCV treatment was the fear of side effects and “horror stories” reported by other drug users. In contrast, the interviewees were more likely to initiate therapy if they were in contact with person who successfully underwent treatment. Another aspect was the lack of any symptoms and the tendency to downplay the risks of HCV.

In addition, patients reported having received comprehensive pre-and posttest counselling for HIV, but only short communications on their HCV results. Thus, HCV testing and treatment referral procedures need to be improved. However, some practitioners and larger clinics have been successfully implemented models of integrated HCV prevention and treatment services within the setting of OST. Based on current literature and their own experiences in an Australian clinic Hallinan et al. (2007) proposed a HCV-specific harm reduction model, which should contain regular HCV-testing, clinical assessment of need

for treatment referral using broader inclusion criteria. During therapy flexibility in opioid substitution dosing is recommended. In future studies the long-term effect of HCV treatment needs to be examined, also in the light of currently upcoming treatment options, which promise better success rates and shorter treatment duration (Dore, Matthews, & Rockstroh, 2011). Improvement of harm reduction strategies is also needed for the prison population, including antiviral HCV treatment. An intensifying of HCV treatment in the correctional setting and the resolving of the respective barriers should be considered (Hunt & Saab, 2009).

Facing the importance of behaviour change and awareness raising among IDUs the role of counselling and other behavioural interventions as components within comprehensive intervention strategies need to be discussed. Though it is not yet clear to which extent these interventions contribute to risk reduction, there are encouraging results that they are effective within multicomponent approaches (Abou-Saleh, et al., 2008). Counselling, motivational interviewing or peer-based approaches could have a positive impact on the therapeutic alliance between drug service workers and clients (Davis & Abou-Saleh, 2008; Mayor, Fernandez, Colon, Thomas, & Hunter-Mellado, 2010; Purcell et al., 2007).

HCV acquisition predominately occurs early in the drug using career. Consequently it is of particular importance to target prevention intervention to new IDUs, and to people at risk to start injecting. IDUs are especially hard to reach in their early stages of their drug using career, when most of them are still integrated in society and do not show up in drug services or treatment programmes (Newmeyer, 2002). In his recommendations Newmeyer argued for an education of middle and high school youth on blood-borne transmission, injection risks, and also on drug treatment programmes in order to reach young people, even though only a minority of them might become injecting drug users (Newmeyer, 2002).

The study of Jost et al. (2010) reported many gaps in knowledge among new drug injectors. The risks of HCV are rarely discussed among peers, and those IDUs who were better informed reported that they received information from treatment programmes or NSP sites, which emphasises the importance of counselling in these services. Drug users expressed lower levels of HCV concern compared to HIV, and past or current risk behaviour was downplayed (Jost, et al., 2010). A similar picture emerged for IDUs enrolled in OST (Cohen-Moreno et al., 2010). It needs to be considered, which strategies work best to raise the awareness for HCV among drug users and probably also in a broader public.

In HIV prevention, this has shown to be successful by means of larger public health campaigns.

However, knowledge on HCV is not only lacking among drug users, but also among drug service workers (Strauss et al., 2006). This is a crucial point, because a comprehensive knowledge on HCV risk factors, prevention strategies and treatment options is a necessary prerequisite for giving adequate information to clients. By assessing the HCV-related knowledge among staff in different US drug treatment programmes, lack of information was found particularly among non-medically staff employed in drug-free programmes, whereas staff in OST programmes were better informed (Strauss, et al., 2006).

There are still barriers in coverage and utilisation of harm reduction. Such barriers exist as concerns the availability of syringes in the periphery or in rural areas, but may also consist in a the drug users lack of confidentiality or fees for HCV tests, as described by Curth et al (2009) who examined the situation in Eastern Europe. The issue of fees for HCV testing may also reflect the low public health awareness for HCV as the provision of HIV tests is more likely to be financially supported and to be offered for free (Curth, et al., 2009).

Overall, scientific knowledge needs to be extended in some points. As the combination of key interventions is recommended (ECDC & EMCDDA, 2011a), research should help determining the appropriate level of coverage for each component. These should also comprise interventions of which the evidence base is rather poor such as for HCV testing and counselling, provision of paraphernalia or crack smoking equipment, and supervised drug consumption facilities.

Limitations of this review

One important limitation for the review was probably the exclusion of articles in other than English language. Studies from European countries available in national language have been missed through language limitation. This may particularly concern findings from smaller, local harm reduction services, whose members usually do not publish in English language journals.

The main limitation is probably our rather restrictive search strategy which had a clear focus on HCV. For this reason a number of primary studies might be missed which are on injection risk behaviour and conducted in the context of HIV. Secondly grey literature has not been considered due to the search for peer-reviewed literature databases. The findings in this review might be - to a certain extent - subject of a publication bias. On the other hand not only primary studies but also systematic reviews and meta-analyses are

included in this review, and thus it can be assumed to have included all HCV-relevant evidence.

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