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► **A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs.**

Hagan H., Pouget E.R., Des Jarlais D.C.
Journal of Infectious Diseases: 2011, 204(1), p. 74–83.

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Despite the challenges, review confirms that hepatitis C infection can be prevented among injectors, but it takes multi-component strategies with elements such as substitute prescribing to reduce or eliminate drug injection, treatment of infection, and enabling safe injection practices by providing sterile injecting equipment and behaviour-change counselling.

SUMMARY Preventing infection with hepatitis C in people who inject drugs is a tremendous public health challenge. The virus is very efficiently transmitted through injecting practices which expose the injector to infectious blood, and typically 40% to 90% of injectors are infected. Together this means each time injectors share injecting equipment, there is high risk that one will be infected and transmit it to the other. This systematic review and [meta-analysis](#) synthesised results of research on the degree to which interventions to prevent such transmission are actually associated with fewer new infections, as demonstrated by biological tests for the seroconversion which marks transition from not being to being infected.

Though the search included reports in other languages, all the 26 studies found were reported in English and were from high-income countries. All tested for seroconversion in individuals who had versus had not (or not to the same degree) accessed a preventive intervention or set of interventions. No population-level studies (eg, comparison of infection rates among injectors across an area before and after the opening of needle exchanges) were found which used seroconversion as an outcome measure, and none reported on seroconversion in relation to supervised injection facilities or pharmacy sales of syringes. Four of the studies randomly allocated injectors to the intervention versus the comparator; the remainder tracked what happened when people did or did not (at least to the same degree) access the intervention in the normal way [meaning their results may be due to some extent to pre-existing differences between the groups or other influences rather than to the intervention].

Main findings

Behavioural interventions Two studies examined psychosocial interventions. [One](#) tested a six-session training programme to enable injectors to educate other injectors. It made no significant difference to the seroconversion rate. The same was true in [another study](#) of four sessions of motivational interviewing, and when the results of both studies were pooled.

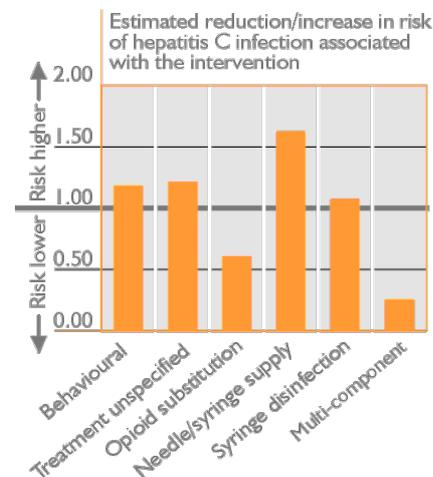
Substance use treatment Five studies assessed treatment (variously defined, including being in it at the start of the study, ending up in it, staying in it, or being retained for a certain period) for problem substance use without specifying what the treatment was. The relationship between treatment and seroconversion differed substantially: in two studies, higher rates with treatment; in two, lower. With such variation, the statistically insignificant estimate from pooling the results should be interpreted with caution [because it seems that like is not being combined with like].

Opioid substitution therapy Eight studies evaluated programmes like methadone maintenance which substitute another opiate-type drug for the one(s) the patient is dependent on. 'Treatment' was variously defined as being in treatment at the start of the study, ending up in it, or having stayed in it throughout, and was compared to not being in treatment at all or not continuously. Six of the eight studies found that proportionately fewer of the treatment group became infected with hepatitis C, [one](#) the reverse. Pooled results indicated that the chances of becoming infected among injectors who (as defined in the study) received opioid substitution therapy were 40% less than those of comparison injectors, [a reduction in risk which [only narrowly missed](#) being statistically significant according to the conventional criterion].

Needle and syringe programmes Seven studies – all from North America – evaluated programmes which distribute sterile injecting equipment to injectors. All but one compared seroconversion rates among injectors who used the service to any degree versus those who had never used it during the period assessed by the study. [One study](#) used a case-control design to evaluate the needle exchange in Tacoma in the USA, [calculating whether (versus injectors who had not become infected) newly infected injectors were disproportionately common among those who had never used the needle exchange]. It found exchange use associated with a substantially and significantly reduced risk of infection. On the contrary, a [Canadian study](#) of Vancouver's needle exchange found the risk of infection significantly greater in frequent exchange attendees compared to other injectors. All other studies reported no significant association. Pooled findings from all the studies indicate there is a significantly greater chance that exchange attendees will become infected with hepatitis C, [but the findings differed so much that like may not be being combined with like].

Syringe disinfection Disinfecting syringes with bleach (defined as always using bleach or disinfecting all syringes) was evaluated in four US studies. Though the studies' estimates ranged from substantial risk reduction to much greater risk, none were statistically significant, and the pooled estimate too was non-significant and very close to the risk being the same whether or not bleach was used.

Multi-component programmes Among patients being prescribed methadone or buprenorphine, a [UK randomised trial](#) evaluated four sessions of enhanced counselling aimed at preventing hepatitis C infection versus a brief, non-interactive hepatitis C information/advice session. The seroconversion rate after counselling was nearly half that after the briefer intervention, but this difference was not statistically significant, so could not be securely attributed to the counselling. [In Amsterdam](#) injectors prescribed at least 60mg daily of methadone and who had either stopped injecting or used only equipment from needle exchanges, were substantially and significantly less likely (equivalent to 3.5 per 100 people per year versus 23.9) to become infected than those less adequately engaged in either or both types of service. Pooling the results of the UK and Dutch studies led to a statistically significant risk-education estimate equivalent to one person becoming infected with the combined interventions versus four without.



The authors' conclusions

Despite the challenges, infection with hepatitis C can be prevented among drug injectors; combined results from the two studies of multi-component programmes show risk reduced by about 75%. The extra impact of combining interventions is consistent with hepatitis C transmission being facilitated by an array of factors, including the large disease reservoir of already infected injectors, the ease with which the virus can be transmitted via several practices related to injecting, and the chaotic and rushed atmosphere of the injection setting. Given this context, multi-component programmes which promote a range of strategies (such as substitute prescribing to reduce or eliminate drug injection, and promoting safer injection practices through the provision of sterile syringes and drug preparation equipment and/or behaviour-change counselling) would be expected to be more effective than single-focus programmes.

Both the reviewed multi-component interventions included opioid substitution treatment as an element. On its own this treatment has less substantial and more inconsistent impacts on seroconversion, so cannot be assumed to be the sole active ingredient in the multi-component interventions. What may be important is the degree to which (together with other elements) it helps patients stop or greatly reduce their injecting.

The findings of this review are consistent with the conclusions of other reviews supporting packages of harm reduction interventions. [Another meta-analysis](#) from the same parent project as the featured review found that the expansion of syringe access and opioid substitution programmes in high-income countries was associated with a lengthening in the time from onset of drug injection to infection with hepatitis C. Findings are also consistent with those of a [study](#) of long-term injectors in areas where hepatitis C was common, but who nonetheless remained uninfected. They told researchers that they used a combination of strategies to avoid withdrawal symptoms and practice safe injection.

Among the limitations of the studies on which the featured review was based is that in some the definition of the intervention could have allowed for sporadic and ineffective degrees of engagement. However, in respect of opioid substitution treatment, studies which defined this as unbroken treatment found no more robust a link with reduced infection rates than other studies. All the studies of syringe disinfection with bleach stipulated 100% use, so the pooled findings strongly support the conclusion that even this degree of implementation has no effect on the transmission of hepatitis C. Also, the source studies were commonly unable to eliminate influences other than the evaluated intervention which might have accounted for the findings. In particular, needle exchanges attract and retain injectors who are already at a higher risk of infection, so comparisons with injectors who do not use exchanges can lead to the mistaken conclusions that exchange participation increases the risk of infection.

FINDINGS COMMENTARY Transmissibility of the hepatitis C virus, and the fact that any time you do let down your defences, the other injector whose blood you come in to contact with is likely to be infected, mean there is at the moment no easy solution to preventing its spread. It takes a fusillade of complementary anti-infection practices and interventions to substantially impede the virus's progress. At the heart of current strategies are methadone maintenance and allied treatments to reduce the number of injections, making it easier for needle and syringe programmes to ensure each remaining injection is with uncontaminated equipment.

The reviewers' conclusion in favour of the parallel deployment of several risk-reduction interventions is supported by a [synthesis of results](#) from UK studies. It found that when injectors were protected by consistent participation in methadone maintenance treatment or adequate access to fresh injecting equipment (a fresh set for each injection) the chances of their becoming infected were halved relative to the risk faced by injectors who had not adequately participated in either type of service. But when they were protected by both interventions, their risk of infection was just a fifth of that faced by injectors who had used neither to the degree set by the study.

Such findings contributed to [guidance](#) from the UK's National Institute for Health and Clinical Excellence, which also called for multi-strand prevention featuring adequate syringe distribution, substitute prescribing programmes and early detection and treatment of injectors already infected with hepatitis C.

Other factors cannot be ruled out

However, the reviewers' caution that the studies are compromised by non-randomisation is no methodological nicety. Their estimates of the link between interventions and infections would only correspond to the *impact* of the interventions if we assume real-world selection processes have not weighted the balance for or against the interventions. Commonly these processes take the form of injectors who choose versus choose not to engage in interventions being at unequal risk of infection. It has meant that needle exchanges which (as intended) attract high-risk injectors, for that reason look as if they are generating infections – the 'magnet effect' identified by Drug and Alcohol Findings in its [case studies](#) of Vancouver and other cities. In fact, the [main lesson of Vancouver](#) and other cities is that 'trickle feed' supply of injecting equipment, with more of an eye on public reaction and minimising supply than preventing infection, cannot curb hepatitis C infection, and may not even dent spread of the easier-to-control HIV virus.

What seems a clear if unusual example of selection processes making an intervention seem counterproductive comes from the [one study](#) in the featured review to find methadone maintenance associated with *more* injectors becoming infected with hepatitis C. It was set in a general practice in Melbourne, Australia, which did not routinely re-test its continuing methadone patients for the virus. Probably, say the researchers, many patients were not re-tested because the clinic saw no reason to do so. Those who were re-tested would tend to be the higher risk cases – hence the impression that methadone treatment generated infections.

Tacoma shows needle exchange can prevent hepatitis C

For experts convened by the US National Academy of Sciences, studies in Tacoma, including the [one highlighted](#) in the featured review, [constituted evidence](#) of a "powerful retardant effect of needle exchange program attendance on infection with [hepatitis B and C]". This judgment from 1995 remains valid, and the Tacoma hepatitis study [remains](#) a rare convincing demonstration that exchanges can intercept the spread of hepatitis C among injectors. It was the one needle exchange study in the featured review which found a significantly reduced risk of infection, and the only one to use a case-control methodology based on identifying new cases of infection and establishing whether they had used the exchange, then comparing these figures with injectors who remained uninfected.

Among the factors which set Tacoma's exchange apart was legal approval (the first in the USA), what became a well resourced and comprehensive service including effective referral to methadone maintenance, unlimited supplies of injecting equipment, encouragement for service users to act as mini-exchanges for other injectors not directly using the exchange, and an engaged set of service users [who saw themselves](#) as part of an activist-led fight to establish exchanges in a hostile national environment. Against a background where little else was on offer, the exchange's anti-infection impacts [became visible](#) in ways not seen elsewhere. Although selection processes might have biased Tacoma's [hepatitis C study](#), the benefits of exchange attendance were so clear cut that only unrealistic assumptions would have rendered them insignificant.

See this [hot topic entry](#) for more on controlling the hepatitis C epidemic.

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