DRUG & ALCOHOL FINDINGS *Hot topic*

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GO Hepatitis C 'giant' still growing

In 1993 what was at the time Britain's magazine for the drug misuse sector alerted readers to an invisible "sleeping giant" – hepatitis C. Foreseeing that injectors "are unlikely to mount the same political lobby for funding hepatitis C prevention and treatment that the gay and heterosexual community have mounted for HIV," the authors warned that nevertheless government should prioritise these programmes to avoid a "longer term cost that is considerably greater, both in terms of finance and human suffering. It may be wise to let sleeping dogs lie, but not sleeping giants."

The term "giant" was warranted because at that time a staggering 85% of injectors in Glasgow and 61% in West Suffolk were known to have been infected. Before in 1989 a test was available to identify it, the virus had already infected a much larger fraction of drug injectors than HIV ever would, making it more difficult to achieve the same proportionate reduction than if the starting point had been lower. Since then it has been a case of playing catch-up against a rapidly moving target: high prevalence means a high probability that anyone who passes on their used injecting equipment is infected, and the robustness and transmissibility of the virus mean a high probability (relative to HIV) of that infection being transmitted through even a small chink in the protective barriers erected by harm reduction services and practices.

Hepatitis C: time to wake up

Like HIV, hepatitis C can be deadly; unlike HIV, it is already widespread among British injectors

The consequences of widespread hepatitis C infection among drug injectors could be staggering

by Tom Waller & Roger Holmes

In 1993 "Hepatitis C: time to wake up" sounded a warning to Britain about the consequences of ignoring the "sleeping giant" of injecting-related infection.

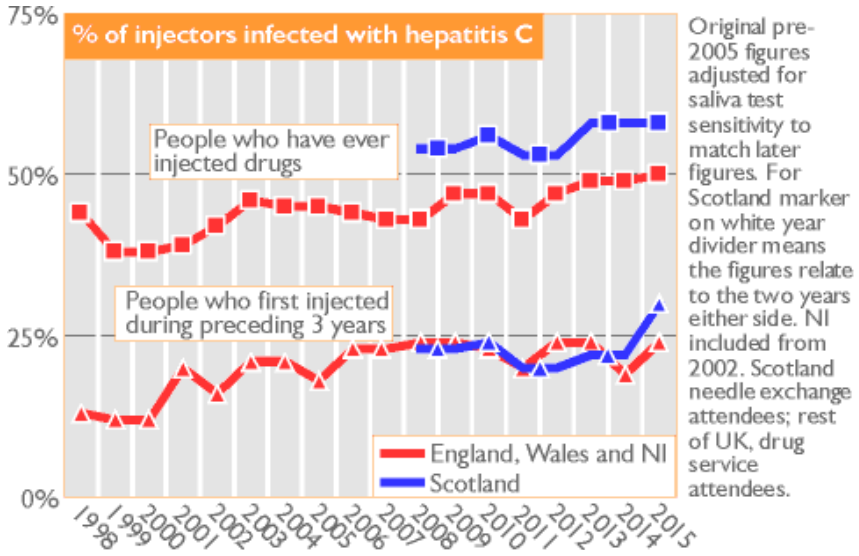
It is not that the UK's measures have been *in*effective; studies and simulations have calculated that the virus would have spread even further without harm reduction services, but over the last two decades infection figures suggest no further ground has been gained. Despite fewer drug users injecting, fewer sharing injecting equipment, more being tested and treated for hepatitis C infection, and more starting treatment for their addiction, hepatitis C has continued to spread extensively among injectors. Substantial reversal of the epidemic will require a more determined, widespread and multi-pronged attack. As comprehensively analysed in a four-part Findings series, coverage is the key. Rather than a reluctantly funded trickle, only a "flood" of harm reduction services will bring the virus under greater control, supplemented by treatment of injectors already infected both for their own sakes and to prevent them infecting others.

This hot topic describes the different components of hepatitis C control, including diagnosis, treatment and prevention. It reviews the place of harm reduction, which up to now has been the mainstay of hepatitis C control, and what could be game-changing additions to this armoury in the form of new treatments for the infection.

Anti-epidemic progress stalled ...

Since 2003 the annual *Shooting Up* reports from the UK's national public health authorities have documented infections among drug users in the UK, a barometer of the success of harm reduction efforts. Due to its transmissibility, the most sensitive barometer reading is the spread of hepatitis C, recorded for drug service attendees since at least 1998 in England and Wales, figures joined from 2002 with those from Northern

Ireland, and from 2008 supplemented by national figures from Scotland's needle exchanges. The figures show that though they have curtailed the epidemic, services have not been sufficiently abundant, with the result that by 2015 hepatitis C was spreading more rapidly than in the early 2000s, infecting a quarter of injectors within three years of their starting to inject.



Since 1998 the hepatitis C virus has continued to infect a large proportion of UK injectors

The report covering 2015 admitted that the "overall level of hepatitis C transmission among people who inject psychoactive drugs in the UK appears to have changed little in recent years". Arguably things are a little worse. Infection among people who have ever injected may have been acquired many years ago; infection among those relatively new to injecting is more indicative of how rapidly the virus is currently spreading. In England, Wales and Northern Ireland, within three years of starting to inject, 24% of injectors tested in 2015 were infected and in Scotland, 30%. For England and Wales an earlier report takes us back to 1998 to 2000, when the corresponding figures were just 12% or 13%. In Scotland a fairly stable infection rate among sub-three year injectors since 2008 of between 20% and 24% jumped to 30% in 2015/16 ▸ chart.

More sophisticated test procedures can narrow down the infection time-window, leading to an estimate that in 2015/16 in Scotland, during the equivalent of a year of injecting 11 to 12 out of every 100 injectors had become infected, and in the rest of the UK in 2015, between 4 and 13. In England the best estimate for 2015 was 7.4, substantially down from a peak of 19.1 in 2012 but about the same as the 8.1 registered the year before.

The result of past and continuing rapid spread is that by 2015, UK-wide around half of those who had injected psychoactive drugs and been tested at drug services or needle exchanges had been infected with hepatitis C – 58% in Scotland, 53% in Wales, 52% in England, and 27% in Northern Ireland. Around a quarter will already have naturally rid themselves of the virus, its presence detectable as only as an antibody legacy, leaving in 2015 about two in five injectors living with active and chronic hepatitis C infection.

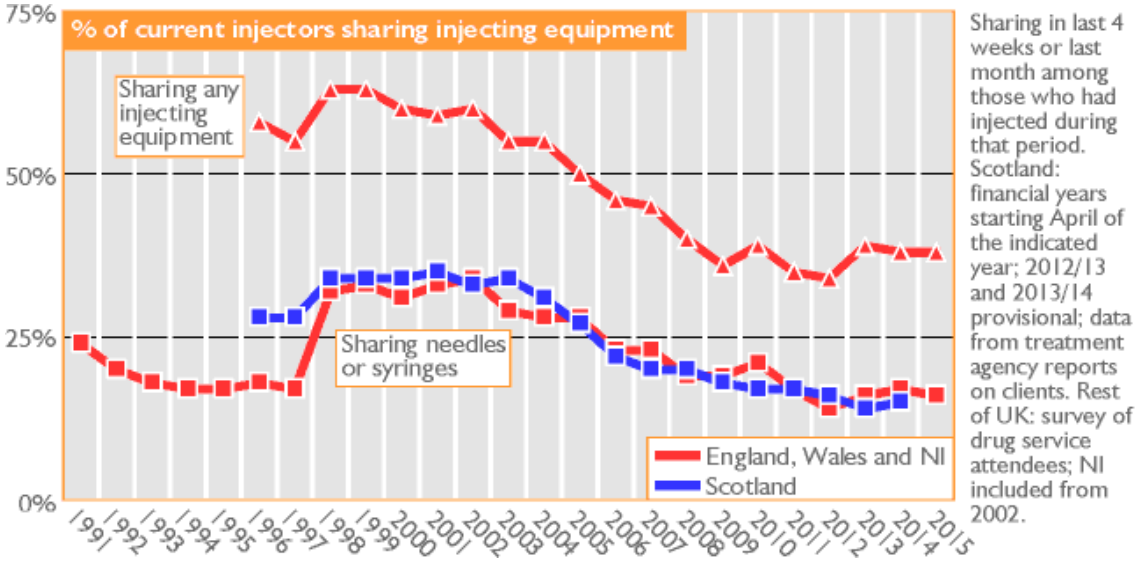
… even though behaviour risking infection has become less common

New infections among injectors will largely reflect the degree to which (without adequate disinfection measures) they inject using equipment previously used by someone else who may have been infected with hepatitis C. 'Sharing' is the shorthand for this behaviour, and with hepatitis C, often it means sharing infection as well as equipment. The term can mean both receiving and passing on used equipment.

Based on figures up to 2015, "Overall, the level of needle and syringe sharing (either borrowing or lending a used needle or syringe) among those currently injecting psychoactive drugs has fallen across the UK," was the welcome message from public health authorities. By 2014–15, across the UK 16–17% of people who had injected in the last four weeks had shared their needles and syringes, down from peaks of 34–35% in the early 2000s. Among those who had injected with used equipment, 29% surveyed in England, Wales and Northern Ireland in 2015 said they had attempted to clean it – for hepatitis C, often not done to an adequate standard.

Hepatitis C may also be spread (1 2) by the re-use or joint use of other items employed during the injection process such as water, spoons and filters. When these were included, in 2015 38% of current injectors surveyed in England, Wales and Northern Ireland had shared equipment in the past four weeks, again, well down on the roughly 60% of the early 2000s ▸ chart.

An apparent puzzle is that the reduction in sharing since the early 2000s has not been accompanied by a similar reduction in the spread of hepatitis C. The most likely reason is that when hepatitis C is already very common among injectors, the degree to which it spreads further is relatively unresponsive to *how widely* the infection-risk door is left open, as long as there is a small chink sufficient to let the

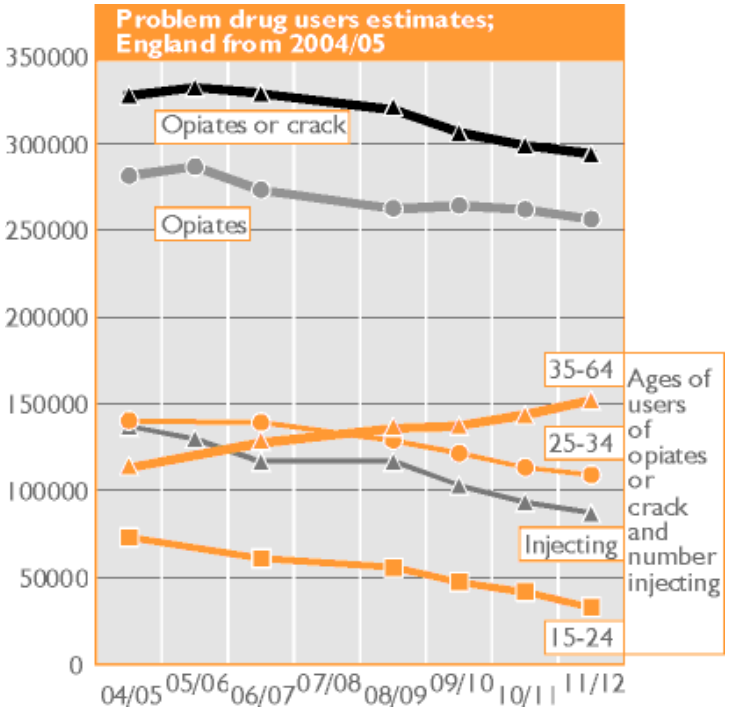


Since the early 2000s rates of sharing of injecting equipment among injectors have tended to fall in the UK but have been roughly stable since 2010

virus through (1 2). Britain has experienced a 'natural experiment' in the relationship between sharing levels and the spread of hepatitis C which might shed some light on whether this explanation is sufficient. Unfortunately, interpretations differ.

The opportunity to test the relationship came about because between 1997 and 1998 there was a sharp increase in the proportion of current injectors who had recently shared needles and syringes in England and Wales ▸ chart. That this was no artefact of methodology or sampling was confirmed by an analysis of the figures and by reports from patients new to or returning to drug addiction treatment.

A contrast to an increase in hepatitis B prevalence, at first analysts highlighted the fact that between 1998 and 2000 hepatitis C prevalence had remained at about 8% among injectors who had started injecting in the past two years, a sign that spread of this virus was unresponsive to the degree of sharing. Led by the same scientist, a few years later another analysis associated later increases in the acquisition of new HIV and hepatitis C infections with the persistence of the 1997 to 1998 increase in levels of sharing. Yet in respect of hepatitis C, if this was the explanation, by the same token, *decreased* sharing since around the year 2000 can be expected to have reduced the rate of new infections – an expectation for which there is no evidence.



Possibly another reason why hepatitis C levels did not fall as sharing levels fell was the countervailing influence of an upsurge in the injecting of crack cocaine since 2010. That year 31% of current injectors sampled at drug services in England had injected crack in the past four weeks. By 2015 the proportion was 51%. Used on its own or by heroin users this short-acting stimulant leads on average to more frequent injecting, and is a marker and perhaps too a generator of a more chaotic lifestyle than solely injecting opioid drugs like heroin, processes thought to increase risk of infection.

Most of the preceding figures have been expressed as proportions of injectors seen at drug services of various kinds. It is, however, worth reminding ourselves that these are proportions

drawn from a diminishing pool of people using the most commonly injected drugs and the pool actually injecting – in England, figures shrinking since at least 2004 ▸ chart. An estimated 137,141 drug users injecting opiates and/or crack in England in 2004/05 had by 2010/11 fallen to 87,302 (1 2). All else being equal, the result should be fewer people exposed to hepatitis C infection via the most efficient and common transmission route.

Harm reduction the 'cornerstone' of hepatitis C infection control

For people who inject drugs, infection with hepatitis C is one potential negative consequence among many, including other blood-borne viruses such as HIV and hepatitis B. Generated in its modern guise by the threat of injecting-related HIV, 'harm reduction' is a strategy which prioritises the reduction of such harms over the attempt to reduce drug use *per se*.

Dr Mary Ramsay from Public Health England's National Infection Service described harm reduction, including provisions for safer injecting and non-injecting drugtaking practices, as the "cornerstone of hepatitis C infection control". A *Consensus Statement on Best Practice* published by three leading organisations in harm reduction – the National Needle Exchange Forum, UK Harm Reduction Alliance, and Exchange Supplies – identified the essential elements of harm reduction as the provision of sterile injecting equipment, facilities for the safe disposal of used equipment, and substitute prescribing. Together, these pillars of harm reduction can they said help reduce injecting-related harms, including infection with hepatitis C.

The methadone pillar

In studies methadone maintenance and allied substitute prescribing treatments for opiate addiction have usually been associated with reduced spread of hepatitis C. A synthesis of results from UK studies estimated that when injectors were engaged in these treatments for at least half of a 12-month follow-up period, the chances of their becoming infected with hepatitis C were less than half those of other injectors – substantial, but still not a statistically significant difference. In Scotland a study based on needle exchange attendees found that compared to patients who had left methadone treatment in the last six months, those still on methadone had about 70% lower odds of having recently become infected, though these results again missed statistical significance.

Recently an analysis of three Canadian surveys of drug users found that the prevalence of hepatitis C was significantly lower among methadone maintenance patients (24%) than among other participants (76%). More to the point, methadone patients were also half as likely to *become* infected over the next two years, and less likely still the longer they had been in treatment during that time.

Another eight studies gathered together in a review cumulated to the near-significant estimate that the chances of becoming infected among injectors who received opioid substitution treatment were 40% less than those of comparison injectors.

Some of these associations between infection risk and treatment were very large, but with ethical and practical considerations prohibiting the randomised denial of substitute prescribing, the results might have been due to influences other than treatment. Studies do their best to compensate for known influences, but cannot compensate for those not measured. For example, in Canada very few survey respondents were in methadone treatment. The analysis adjusted for other influences on risk of infection including whether and which drugs respondents injected, but still this minority may have differed from the non-treatment majority in ways which would have reduced their risk of infection, regardless of treatment. Nevertheless, the evidence has been enough to convince European Union and UN authorities that substitute prescribing is a major component of effective anti-infection policies.

The exchange pillar

Research on services to promote safer injecting in the form of needle exchange programmes also largely relies on associations found in routine practice rather than randomised trials, making the findings vulnerable to extraneous influences the researcher cannot control or adjust for. In this case, these influences have loaded the dice against these services, making them look actually harmful.

The cause is almost certainly what we have termed the 'magnet effect': by attracting their intended caseload of injectors at high risk of infection, exchanges make themselves

look as if they are the cause of the high risk. The result is that overall, exchange attendance has been associated with a *greater* chance of becoming infected with hepatitis C.

Detailed examination of research from six case-study cities revealed that their exchanges often suffered from the 'magnet' illusion, but rarely was it the whole story. The deeper cause of poor results was that exchanges often chose or were forced to operate under what a Health Canada publication described as "restrictions that condemn the programmes to fall far short of the needs of the persons for whom they were designed". By under-resourcing and under-valuing this work and forcing exchanges to operate under crippling restrictions, sceptical authorities create the conditions which justify their misgivings.

> *By attracting injectors at high risk of infection, exchanges make themselves look as if they are the cause of the high risk*

One of the case study cities was the exception both in the evaluation's methodology and in its findings. For experts convened by the US National Academy of Sciences, studies in Tacoma in the USA 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. It was the one needle exchange study in the review cited above 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.

A distinctive methodology was not all which set the Tacoma study apart. Tacoma's exchange benefited from legal approval (the first in the USA), a well resourced and comprehensive service including effective referral to methadone maintenance, preparedness to supply unlimited quantities 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 spearheading 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. The study was imperfect, but the benefits of exchange attendance were so clear cut that only unrealistic assumptions would have rendered them insignificant.

Among British studies was one from Scotland based on needle exchange attendees which associated receiving at least twice the amount of injecting equipment equating to a fresh set each time with a near 70% lower chance of having recently become infected with hepatitis C. Data from Glasgow used in that study was fed into a synthesis of results from UK studies. It estimated that when injectors were engaged in needle exchange services sufficiently to obtain at least enough sterile injecting equipment to equate to a fresh set for each injection, the chances of their becoming (or having recently become) infected with hepatitis C were about half those of other injectors.

100% coverage not enough

As with substitute prescribing, despite the difficulty of providing definitive proof, the evidence has been enough for UN agencies and other authorities to promote needle exchange as a way to curb spread of the virus. Posed the question, "What level of coverage should needle and syringe programmes provide to keep HIV prevalence low and to reduce the prevalence of hepatitis C among people who inject drugs?", Britain's National Institute for Health and Care Excellence (NICE) called on commissioners to aim to provide *more* than enough needles and syringes for every injector to be able to use a sterile set each time they inject. Public Health England explained why simply equating the number of needles/syringes to the number of injections will not be enough: "some people receive more needles than they need … because they pass them on to partners or friends … Also, more than one needle is often required per injection, as needles may also be used during drug preparation and an injection may require several attempts (and therefore needles) to access a vein." Over 100% coverage is an ambitious target, but only a flood of injecting equipment has a chance of adequately containing the virus. Adequate coverage is important also to help prevent sharing of the other equipment used in injecting, suggested a study in Scotland.

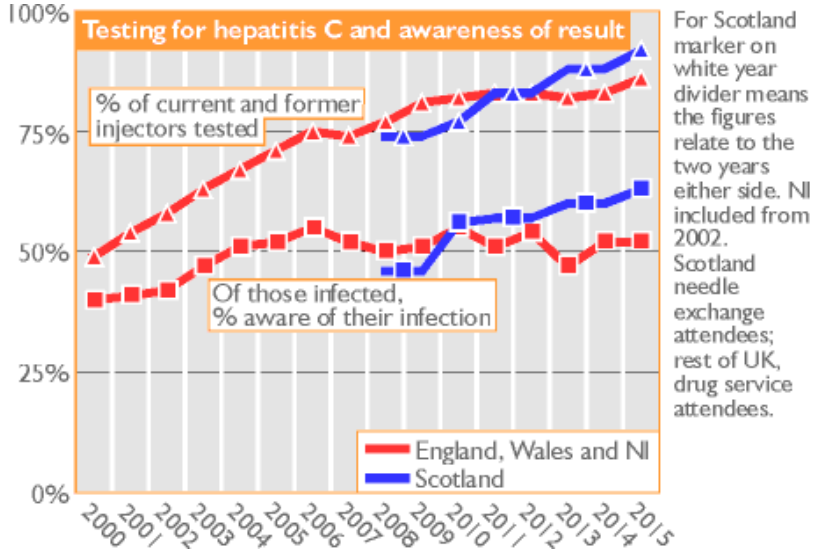
How far there is to go to exceed 100% coverage has been recorded in England since

2011. Since then just under half of current injectors surveyed at drug services have been estimated to have received sufficient needles/syringes to equate to a fresh set each time, varying only slightly from a high of 48% of injectors in 2011 and 2012 to a low of 45% in 2015. It means that slightly fewer than half the injectors *already* in contact with drug services reach the 100% coverage mark; include those not in contact and lift the bar to well over 100%, and the fraction is likely to be considerably smaller.

Where injectors do not (or cannot) obtain sterile needles and syringes, they may employ their own harm reduction techniques, including disinfecting used syringes and needles. The effectiveness of this tactic has been tested in a laboratory setting with readily available household products. Rinsing with bleach was found to be the most effective, eliminating hepatitis C in syringes with both fixed and detachable needles. Though promising, this practice is unlikely to safeguard all. Injectors may choose not to rinse their syringes with bleach for a number of reasons, including the fact that multiple rinses can damage the equipment.

Testing and treatment needs to be scaled up; half all infections undiagnosed

In high income countries hepatitis C is primarily transmitted through the sharing of contaminated injecting equipment, making drug users priority targets not just for harm reduction efforts but also for the treatment of infection. In the UK, around 90% of diagnosed hepatitis C infections have been acquired through injecting drug use. Estimates from Public Health England suggest that 3 in 4 people infected with hepatitis C will develop chronic infection (a total of 214,000 in the UK), a primary cause of cirrhosis and liver cancer. Treating hepatitis C not only saves individuals (already impacted by substance use) from these potentially fatal diseases, but by clearing the infection, it also helps prevents further spread of the virus. In the UK, the drive to extend treatment is starting from a very low base, though acceleration has been aided by the advent of new and less onerous treatment regimens.



Though proportions tested have increased, in England, Wales and NI awareness rates have not improved since the mid-2000s

One major barrier to extending treatment does not seem to be going away. Before treatment can help stem the spread of hepatitis C, the infection first has to be tested for and diagnosed. Among current or former injectors seen at drug services in the UK, from about half in the year 2000 the proportion at some time tested for hepatitis C rose to around 90% in 2015. Nevertheless, the infections of about half the injectors with hepatitis C remained undiagnosed, the worrying headline finding in Public Health England's latest report on infections among injectors ▸ chart.

The problem is that having been tested years ago is not enough – injectors who test clear can soon become infected or re-infected. In 2015 in England, Wales and Northern Ireland, 18% of injectors unaware they were infected said they had simply never been tested; 41% said they had, but over two years ago.

A positive test may need to be followed by treatment of the infection to prevent the disease progressing, a second weak link in the chain. Data from people initially tested at drug services between 2005 and 2014 indicated that only 3.7% of those who were currently infected had received hepatitis C treatment within a year of diagnosis, though the figures predate the newer and more acceptable treatments. Public Health England

has recommended (1 2) multiple strategies to raise uptake of testing and treatment, including employing a blood-borne virus nurse, distributing information about referral pathways to all staff in local drug and alcohol services, writing and re-writing to clients, offering appointments on a flexible and drop-in basis, and routinely testing unless injectors opt-out.

Elevating the current low treatment penetration base could intercept the virus's spread sufficiently to substantially reduce its prevalence among injectors. One study has mapped the prevalence of chronic hepatitis C across seven sites in the UK, and projected what the prevalence would be over the ten years from 2014 if we continued with the current approach to treating the infection versus a 'scaled-up' programme. The findings suggest that maintaining the status quo will not generate substantial reductions in hepatitis C. However, there would be a 15% reduction after 10 years by extending access to treatment to an annual 26 per 1000 people who inject drugs (upper limit of what may already have been achieved at two of the sites) and if new medications became available and used for all variants of the virus. The 15% figure is an absolute reduction from baseline rates of just over 50% or lower; in different areas this would amount to a 12% to 86% relative reduction in these proportions after 10 years, the biggest reductions predicted where prevalence levels start relatively low.

New medication regimens pave the way for expansion

A range of new oral drug treatments called 'direct-acting antivirals' have been developed which according to clinical trials reviewed in 2015 promised to be more effective, more easily tolerated and more acceptable to patients than existing treatment options, though also more expensive. Britain's National Institute for Health and Care Excellence (NICE) has directed several of these treatments to made available by the National Health Service as value-for-money lifesavers/improvers, though sometimes only if a discounted price is negotiated.

> *Treating those who are actively using drugs will dramatically reduce onward transmission of hepatitis C*

Writing in May 2017, for a leading London-based liver specialist these medications promised not just to revolutionise treatment of infection, but also its prevention. Previous treatments involved "a prolonged course of therapy with relatively ineffective, toxic drugs" which most patients refused, remaining infectious and leading to further spread of the virus. In contrast, "The new treatments require a short course of tablets … and are almost side effect free. The cure rates are in excess of 95% … treating those who are actively using drugs will dramatically reduce onward transmission of hepatitis C and many experts see treatment in those with on-going drug use as the key to control of the hepatitis C epidemic."

These expectations were questioned by a review published in 2017 with the cachet of the Cochrane collaboration behind it. It synthesised results from randomised clinical trials which had compared direct-acting antivirals (DAAs) to an alternative, generally an inactive placebo. The blunt conclusion was that "DAAs do not seem to have any effects on the risk of hepatitis C-related morbidity or all-cause mortality", though the reviewers acknowledged that lack of evidence rather than negative findings was the main contributor to these conclusions. More damaging still was their questioning of the importance of these drugs' ability to clear the virus from blood, known as a 'sustained virological response'. They accepted that the new medications seemed to promote clearance of the virus, "but all of the trial results were at high risk of systematic error ('bias'), and the clinical relevance of results on virological response is questionable". The lead author explained that "Sustained virological response is a surrogate outcome. From a patient perspective, it does not matter if virus cannot be detected in the blood if DAAs do not improve survival or lead to fewer hepatitis C complications." The review warned that "The lack of valid evidence and the possibility of potentially harming people with chronic hepatitis ought to be considered before treating people with hepatitis C with DAAs."

Clearing the virus from blood should mean the patient cannot spread the disease, but if it did not equate to a cure for the patient, then the major part of the justification for spending large sums of money on these treatments would be lost, and with it the potential for extended treatment to help curb spread of the virus. After its findings were reported in the *Guardian* newspaper, UK clinicians, scientists and patient groups criticised the Cochrane analysis as "fundamentally flawed". It had, they pointed out, analysed short-term clinical trials whose sole purpose was to evaluate the virological

efficacy of new antiviral drugs, trials "neither designed, nor powered, to assess mortality, so it is hardly surprising that the Cochrane review was unable to identify any impact on mortality." Far from being clinically irrelevant, "Regulatory authorities and clinicians all recognise that clearing hepatitis C virus reduces mortality." Writing in the *The Lancet*, US experts agreed: "DAA therapy is safe and effective in achieving [sustained virological responses] … [sustained virological responses] are durable in most patients … hepatitis C-induced liver damage improves after [sustained virological response], and … observational data show a large reduction in morbidity and mortality" – evidence which stacked up strongly in favour of treatment.

Among the evidence were observations in the 2017 report on hepatitis C from England's public health authority, which thought it may already be seeing the new treatments' lifesaving impacts which Cochrane's reviewers were unable to discern. Despite cases of relevant forms of liver disease remaining relatively stable, "an 8% fall in the number of deaths from these indications over the last year, suggests that increased treatment (around a 40% increase in 2015) with new direct acting antiviral (DAA) drugs, particularly in those with more advanced disease, may be starting to have an impact".

For maximal preventive impact, target treatment

Even if they cure the current infection, both the old and the new treatments do not prevent later reinfection. People who engage in high-risk behaviours, such as sharing used injecting equipment, are more likely to become re-infected (and infectious), leading to some reluctance to focus treatment on high-risk groups. But while it may seem counterintuitive to treat people at high risk of becoming re-infected, it might actually be the most effective preventive strategy at a population level.

Researchers in Australia have calculated that for maximum impact, treatment for hepatitis C should be focused on people who are still injecting frequently and not engaged in methadone treatment, a conclusion to some extent conditional on the likelihood that they will follow medical advice and complete their treatments for hepatitis C. Where completion levels are the same between injectors in versus out of methadone maintenance, the simulation model estimates that over 84% of hepatitis C virus treatment slots should be allocated to those outside treatment. Focusing on methadone patients only becomes preferential when (as it can do) being in a methadone programme raises completion rates. However, completion promises to be greatly enhanced by the newer medication regimens, possibly reducing whatever gap there is between methadone versus non-methadone injectors.

Similarly, in a simulation study researchers compared the preventive impact of treating high-risk injectors who share injecting equipment very frequently against the impact among less frequent sharers. They found that when more than half of all the shared syringes in a population of injecting drug users are contaminated with hepatitis C, the greatest preventive impact is gained by treating low-risk injecting drug users first. But below this threshold, it is most efficient to treat high-risk injecting drug users first.

The strategies described above require information about the level of risk of injectors and the likelihood of compliance with treatment. Based on injectors surveyed in the city of Melbourne in Australia, another study has suggested that information about the social networks of people who inject drugs should also be taken into account when prioritising treatment. Of those assessed in the study, the most effective strategy was to ask an injector being treated for infection who they injected with, and then to offer treatment to those among their injecting circle also infected with the virus, helping to prevent the focal injector becoming re-infected.

Combination of services will make the biggest impact

Signalling the dimensions of the challenge, a simulation model suggested that getting to the point where under 1 in 10 injectors in London are infected with hepatitis C would need injectors on average to cut their sharing of used syringes from 16 times a month to once or twice. Achieving this kind of step change seems to demand the synergistic impact of several harm reduction strands. Adequate opioid substitute prescribing and other successful treatments of addiction cut the number of injections and therefore the number of opportunities for the virus to be transmitted by sharing injecting equipment. In turn this should make it easier for needle and syringe provision programmes to supply enough equipment for a fresh set to be used for each remaining injection, while successful treatment of hepatitis C infection will render infected injectors non-infectious. In reverse, effective prevention will make it more possible to engage – and to be able to afford to engage – the reduced number of infected injectors in treatment for their

infection.

Simulation studies have modelled what the results might be (and might have been) of parts of such a strategy, calculating that consistent participation in methadone maintenance treatment plus adequate access to fresh injecting equipment has prevented thousands of hepatitis C infections. Given practical and ethical considerations, inevitably these models are based on *associations* between services and infections found in studies which could not securely establish what caused what. The results gain credibility from the face validity of the mechanisms linking service use to infection via rates of injecting and sharing, and from evidence that these mechanisms have actually been in play.

A synthesis of results from UK studies found that access to either opiate substitution treatment or needle and syringe provision to the degree set by the study (enough equipment for a fresh set for each injection; in treatment for at least six of the 12 months of the follow-up periods) is associated with a halving in the risk of infection, but that a combination of both would reduce risk by up to 80% compared to injectors who had used neither to that degree.

Those findings were fed into a simulation model for the UK (and other countries) which calculated that investment in methadone maintenance treatment and needle exchange services has already saved tens of thousands of lives from being blighted by infection. But the calculations also predicted that making further substantial progress will require comprehensive hepatitis C control integrating diagnosis, treatment and harm reduction, and a major commitment from both injectors and health service funders. For example, cutting prevalence from 40% to 30% over 10 years would require not just half, but at least 80% of injectors to be engaged in methadone maintenance *and* needle exchange services. Achieving this coverage means recruiting more injectors to these programmes and/or retaining those who do use them for longer. Without extended retention, the recruitment rate has to be much higher. For example, if retention averages eight months, to get 8 in 10 injectors into these programmes requires over half those not yet attending to join each month. If average retention doubles to 16 months, then just under 30% need to join each month.

In Scotland it has been estimated that the combination of needle exchange, methadone maintenance and a shift away from injecting meant that between 2008 and 2012, 1000 fewer injectors faced chronic infection than would have done had things remained as they were in 2008. Before them the authors had the results of an study based on needle exchange attendees in Scotland which combined being in opioid substitute prescribing treatment and having a supply of fresh injecting equipment into what was presumed to be an overall high, medium or low level of protection from becoming infected. Relative to the low level, both high and medium levels were associated with a halving in the chance of becoming recently infected. To different degrees, both UK-wide and Scottish analyses were able not just to link adequate service use to infection, but also to the intermediate links which connect the two via reduced frequency of injecting and a lower proportion of injectors continuing to share injecting equipment, constricting opportunities for the virus to be transmitted.

Treating the virus is also effective in reducing the overall prevalence of hepatitis C and reducing the risk of transmission. However according to an Australian study reported on above, resources must be allocated to harm reduction services as well as treatment in order to significantly reduce the risk of infection in the population. A synthesis of relevant studies by world-leading experts echoes that it is the combination of services and strategies which will make the biggest impact, and suggests that it has already substantially and significantly reduced transmission of hepatitis C by as much as 75% within populations who inject drugs.

We can ... but will we?

Even within existing resources, some further progress may be possible. Public Health England recommends that regular reviews of population needs be fed into strategies for controlling hepatitis C. Attention to the characteristics of the population reflects studies examined above which found better results when levels of risk, levels of compliance with treatment of infection, and the patient's injecting networks were factored into population-level treatment strategies.

However, better targeting of static or diminishing resources will not be enough. According to NICE, further increasing the coverage of syringe distribution and substitute prescribing programmes will not substantially curb hepatitis C. This will require a multi-

faceted programme, including early diagnosis and treatment of injectors already infected with hepatitis C, a strategy reflected in the Welsh Government's hepatitis action plan.

Based on data up to 2015, in 2017 Public Health England went further, warning that only a "radical change" in our response to hepatitis C among injectors will enable England to meet World Health Organization goals on reducing deaths related to the virus. New treatments for infection create a platform for further progress, but only if the proportion who know they need the treatment is increased, while preventive efforts in the form of needle/syringe provision are generally sub-optimal, reductions in the sharing of injecting equipment have stalled over the last five years, and there is little evidence of a fall in the number of new infections.

Not just increased, but sustained investment in services seems critical. UK studies referred to above predicted that expanded service access can further reduce the annual number of injectors who become infected with hepatitis C, but also that these reductions and the services underpinning them will need to be sustained for over a decade before the virus is substantially less common across the injecting population.

Public Health England's "radical change" call came in a policy-oriented report for England which drew in contributions from other experts and other agencies. In contrast, its latest corporately authored UK-wide report monitoring infections among injectors argued that "Provision of effective interventions needs to be maintained." Maintaining the status quo may not seem very ambitious and will not be enough to turn back the epidemic, but is perhaps a realistic aim in the era of austerity and of recovery as a national drug policy priority. NICE's Public Health Advisory Committee saw fit to caution that "a focus on recovery (that is, encouraging people to stop taking drugs completely) should not compromise the provision of needle and syringe programmes and any associated harm-reduction initiatives".

> *The extreme level of stigma routinely experienced by people who inject is a form of structural violence*

Like the problem drug use via which overwhelmingly the virus is transmitted, hepatitis C "disproportionately affects populations who are marginalised and underserved and have poorer access to healthcare and health outcomes". This observation from Public Health England begs the question of where the impetus will come from to radically reverse this relative exclusion, and *over*-serve the same populations with a flood of sterile equipment and universal testing for infection followed by treatment if required. In a similar vein, UN agencies surveying in 2017 the policy landscape for responding to hepatitis C and HIV among injectors itemised interventions, but were also aware of the broader political and social context and what that does to the chances of gaining adequate investment: "The extreme level of stigma routinely experienced by people who inject drugs is a form of structural violence. The language, policies and practices of legal, health and educational institutions and the media often create, reinforce and perpetuate this stigma. This makes it more difficult to reform harsh drug laws or properly resource HIV and [hepatitis C] prevention, diagnosis, treatment and care programmes for people who use drugs."

Though it may be unrealistic to expect a further major contribution to stemming the hepatitis C epidemic from greatly expanding services, it would help if current resources became less stretched because (aided or not by treatment) more drug users turn away from injecting and from the main injected drugs. Population estimates and trends in the treatment caseload indicate this has been happening (▸ above), but without knowing why, neither can we know whether these trends will stabilise, continue, or reverse.

Thanks for their comments on this entry to Andrew Preston of Exchange Supplies based in Dorchester, England. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

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