Hepatitis C: who is at risk and how do we identify them?
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SUMMARY. The transmission of, and screening for, HCV infection varies considerably throughout the world; differences between resource-poor and resource-rich countries are particularly pronounced. The perspective of this review, principally, is that of resource-rich countries. The UK, particularly Scotland, experience is drawn on.

Keywords: hepatitis C virus, HCV testing, injecting drug user, Scotland, screening, transmission.

WHO IS AT RISK?
Table 1 lists the ways in which HCV is transmitted and the populations at risk. While, technically, everyone is at risk of acquiring HCV, the risk to an individual will range from very high to negligible. Appreciating the spectrum of HCV risk, however, is important in considering the question ‘How do (and should) we identify them’. The factors influencing the probability of a person acquiring HCV are shown in Table 2.

The inoculation of contaminated blood through the skin
Having received a blood/blood product transfusion
In resource-rich countries, the HCV risk conveyed to individuals by the receipt of a blood transfusion since late 1991, when an HCV antibody test became available and the HCV screening of donors was introduced, has been extremely low. HCV antibody screening of donors detects nearly all viraemic ones but infections can be missed if the donor acquired his or her HCV during the 10-week period prior to testing; in the great majority of newly infected persons, antibodies appear within 5–10 weeks though, occasionally, the time to seroconversion is longer [1]. Many blood transfusion services, particularly those in the UK, have introduced HCV nucleic acid testing, an approach which has reduced the ‘window period’ to 17 days [2]. The chances of a UK blood transfusion causing HCV infection are now estimated to be 1 in 2 000 000. The risk of infection among persons who received a blood transfusion predonor screening was much greater; most victims, however, will have died of non-HCV related causes though some who were transfused at a young age, for example following pregnancy, will still be alive. In many resource-poor countries, HCV donor screening is not performed. Accordingly, people who have a history of receiving a transfusion in such settings are at appreciable risk.

Heat treatment of blood factor in 1985 and 1986 eliminated this product as a source of HCV [3].

Having sustained an injury from a sharp implement within or outwith the healthcare setting
No instance of HCV transmission following an accidental needlestick injury outwith the healthcare setting has been documented.

Within the healthcare setting, the probability of an HCW acquiring HCV following percutaneous injury with a sharp implement previously used on a known HCV-infected patient is 1.9% [4]. This rate does not take into account factors such as the type of injury sustained (e.g. deep hollow-bore needle injury is more likely to inoculate blood than a shallow suture-needle one) and the viral burden of the source patient. As at December 2003, three occupational transmissions among HCWs in the UK had been identified.

Having undergone tattooing or body piercing
It is plausible that the receipt of a tattoo in an unlicenced or unregulated setting where sterile techniques might be suboptimal conveys a risk of contracting HCV. In many parts of the UK, for example, a tattooist can become established without acquiring a licence. The evidence, however, for tattooing being a risk factor for HCV is limited. Epidemiologists from the Centers for Disease Control and Prevention (CDC Atlanta, USA) believe that the risk is not appreciable as case control studies, generally, reveal no increased risk; and less than 1% of acute HCV cases, reported to CDC since 1980, occurred in someone with a tattoo [5,6]. The most

Abbreviations: ALT, alanine transferase; EEP, European Education Partnership; GUM, genitourinary medicine; HCV, hepatitis C virus; HCW, healthcare worker; HIV, human immunodeficiency virus; IDU, injecting drug user; QALY, Quality Adjusted Life Year; STI, sexually transmitted infection.
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Inoculation of contaminated blood through the skin
Having:

i. received a blood or a blood product transfusion
ii. sustained an injury from a sharp implement
   within or outwith the healthcare setting
iii. undergone tattooing or body piercing
iv. undergone invasive medical procedures including
   haemodialysis
v. injected drugs

Exposure of mucous membranes to contaminated blood or genital secretions
Having:

vi. been born
vii. had unprotected sexual intercourse
viii. exposed one’s broken skin or mucous membranes
to someone else’s blood (i.e. household contact)
ix. having received a tissue or organ transplant

Exposure of the internal body to infected tissue (not blood)

Having:

Table 2 Factors influencing HCV transmission

| i | the number of exposures to body fluids |
| ii | the types of exposure and, for each, |
| iii | the probability of the aforementioned body fluid being infected |
| iv | the amount of virus in the body fluid |

compelling evidence for tattooing conveying an HCV risk was generated by Haley and Fischer [7]: the causal inference was supported by the risk of HCV increasing in a dose-related fashion.

Having undergone invasive medical procedures including haemodialysis

In resource-poor countries, where the adequate sterilization of equipment used for invasive procedures is often never, or only sometimes, practised, the risk of iatrogenic HCV infection is high [8].

Although the risk of iatrogenic HCV in resource-rich countries is extremely low, several instances have been detected. In the UK, for example, two gynaecologists, three cardiothoracic surgeons and one orthopaedic surgeon were shown to have transmitted HCV to their patients [4,9].

Instances of patient-to-patient transmission of HCV, involving the contamination of dialysis machines [10], multidose vials [11], endoscopes [12] and other devices, have been documented. These appear to have been 'one-off' incidents that occurred as a consequence of a breakdown in infection control procedure. The most recent instance of a serious episode of iatrogenic HCV infection involved an anaesthesiologist who used unsterile needles on his patients in Israel; around 30 became infected [13].

In the context of the overall numbers of invasive medical/dental procedures undertaken on patients, however, the risk of a single one resulting in HCV transmission is likely to be less than one in several million (i.e. negligible); nevertheless, it is possible that the risk of iatrogenic HCV infection among people who visit resource-poor countries and undergo invasive medical management while there, is appreciable and on the increase.

Having injected drugs

The association between the illicit injection of drugs and the acquisition of HCV is incontrovertible. Prevalences of HCV among IDU populations throughout the world range from 20 to 90% [14,15]; in 2000, the prevalence among Scotland’s IDUs was 60%, a 1000-fold greater rate than that observed among the country’s blood donors [16].

During the pre-HIV awareness era (1975–85), when the incidence of IDU in Western countries increased dramatically, chaotic needle and syringe sharing was rife and the great majority of IDUs became infected within 12 months of their injecting debuts [16]. During the HIV awareness era of 1986–95, interventions to reduce the sharing of needles and syringes led to the reduction, but not control, of HCV among this population; in contrast, the incidence of HIV among IDUs in most parts of the Western world declined to low levels. During the post-HIV awareness era – after 1995 – there have been several examples of increases in the incidence of injecting equipment sharing [17] and HCV infection among IDUs [18–22] despite continuing improvements in interventions such as needle and syringe exchange and methadone maintenance therapy.

Among populations of IDUs, a gradient of HCV risk exists [21,23]. Key determinants of risk include: the frequency of injecting with used needles and syringes: the numbers of different sharing partners from whom used needles and syringes are obtained to inject; and the frequency of injecting in a shooting gallery setting where numerous IDUs share the same equipment. Those who never inject with used equipment have no injecting-related HCV risk; there is growing evidence, however, that persons who only share injecting paraphernalia other than needles and syringes, i.e. filters, spoons and water, are at risk of infection [23,24].

The environment in which the IDU resides, may also influence risk: for example, those who inject in prison will invariably share (often ‘home-made’) injecting equipment [25] because, other than in a few prisons in Western Europe, supplies of sterile needles and syringes are unavailable in this setting [26]. Some IDUs, on imprisonment, reduce their HCV risk because they stop injecting altogether.
Exposure of mucous membranes to contaminated blood or genital secretions

Having been born

For babies born to HCV viraemic mothers, the risk of transmission is 5% [27]; this may increase to almost 9% if the mother is known to have injected drugs and 19% if she is also HIV-infected. Breastfeeding is not considered to convey a risk [27]. For babies born to mothers of unknown status, their risk of HCV acquisition is the product of the prevalence of anti-HCV in the pregnant population (0.1–2.4%) [28–30]; the probability of the anti-HCV positive mother being viraemic (70%); and the probability of transmission if the mother is viraemic (as above). In Scotland during 2000, an estimated 1 in 5000 babies became HCV-infected. In most resource-rich countries, the majority of HCV-infected pregnant women have injected drugs; accordingly, the HCV risk of a baby born to a non-IDU mother is extremely low.

Currently, no effective intervention to reduce the probability of mother to child transmission of HCV exists. Ribavirin, one of the key components of combination therapy for those infected with HCV, is contraindicated for use in pregnancy because of its potential teratogenicity and there is, as yet, no compelling evidence to indicate that elective caesarean section can reduce transmission [27].

Having had unprotected sexual intercourse

HCV, indisputably, is transmitted through unprotected sexual intercourse: between 1995 and 2000 in the USA, 18% of acute HCV cases, reported to the CDC, declared sexual contact with an HCV antibody-positive individual in the previous 6 months (12%) or multiple sexual partners (6%) as their only risk factor for HCV acquisition [31]. Cohort studies of monogamous couples discordant for HCV indicated an HCV incidence of about 2 (range 0–6) per 1000 years of sexual contact [32,33]; the corresponding incidence for those at risk of STIs is estimated to be approximately 10 [4–18] per 1000 years [34].

The low efficiency of transmission by the sexual route is borne out by UK data which indicate that, unlike for HIV, the prevalence of HCV among homosexual or bisexual male attenders of genitourinary medicine clinics is the same, or only slightly greater, than that for heterosexual males (0.6%) [35]. Further, a cohort study of couples discordant for HIV/HCV coinfection revealed considerable HIV, but no HCV, sexual transmission over a median follow-up of 44 months [36].

However, because most adults engage in unprotected sexual intercourse, a large proportion are at risk of STIs and the size of HCV-infected populations is so considerable (e.g. 2.7 million in the USA), sexual transmission probably makes an appreciable contribution to the number of new cases. If condoms are used, the risk of transmission, almost certainly, is infinitesimal.

Having exposed one’s broken skin/mucous membranes to someone else’s blood (i.e. household contact)

Instances of possible HCV transmission as a consequence of broken skin/mucous membranes being exposed to someone else's contaminated blood in the context of, for example, shaving with equipment previously used by someone else [37], have been reported but are rare. The pooling of HCV prevalence data among siblings and household contacts of HCV-infected patients with chronic liver disease revealed that, when compared with controls, they had an increased risk of infection [38]; however, the investigators could not be certain that the contacts had not injected drugs nor were they able to ascertain if contacts acquired their infection from the index cases or how they became infected.

The exposure of the internal body to infected tissue

Having received a transplant

The HCV implications of transplantation are similar to those for blood transfusion recipients; all donors will have been HCV tested since late 1991.

HOW DO WE IDENTIFY THEM?

Before considering how to identify HCV infected persons, the question ‘Why should we identify them’ needs to be answered. There are four reasons why HCV case finding might be promoted.

1. To promote harm reduction among HCV-infected individuals

Excessive alcohol consumption increases the rate of HCV disease progression [39] and, occasionally, acute hepatitis A virus infection in an HCV carrier causes a particularly virulent illness [40]. Accordingly, advice and vaccine can be given as prophylaxis.

2. To inform people of their HCV infection status so that behaviour to reduce the probability of acquiring or transmitting infection can be promoted.

Only four, methodologically weak, investigations to determine the impact of HCV status knowledge on behaviour have been reported but none provided compelling evidence that HCV testing influenced behaviour, either positively or negatively [41–44]. It cannot be concluded, however, that testing does not promote harm-reducing behaviour. Longitudinal studies of individuals, probably IDUs, to gauge their behaviour pre- and post-HCV testing are required.

3. To identify persons who might be eligible for therapy

Infected persons, treated with pegylated interferon and ribavirin, have a 50–60% chance of permanently clearing their virus [45]. In many countries, including the UK, it is recommended that those with moderate or severe HCV-related liver disease should be administered such cost-effective antiviral
treatment unless there is a contraindication (e.g. current IDU) [46]. Thus the benefit of identifying HCV infected persons, eligible for therapy, is evident.

4. To monitor HCV infected persons who are currently ineligible for therapy but might become eligible in the future.

In resource-rich countries, the majority of ineligible HCV-infected individuals are current IDUs. The experience, in Scotland, of diagnosing, referring (to specialists) and following up such persons is a salutary one. Many fail to attend their initial specialist appointment and, thereafter, attrition from follow-up is extremely high. Since HCV disease progression is slow, particularly among those such as current IDUs who become infected when young [47,48] (see below), the benefits of detecting and then monitoring this infected population are questionable. Since past IDUs have an extremely high chance of being infected, targeting this group for testing would suffice.

Disbenefits of case finding
Lack of benefit/cost effectiveness, as might apply to infected current IDUs as above is probably the principal consideration. Psychological morbidity, including stigma, as a consequence of knowing one’s HCV positive status is a recognized, though not necessarily common, outcome.

Prioritizing HCV screening
Fully appreciating the benefits of offering people an HCV test is crucial in deciding who should be targeted and how testing effort should be prioritized. The spectrum of approach to screening can vary from a mandatory test in the context of blood or tissue donation to the offer of a test conveyed in written (e.g. posters or leaflets) or broadcast format. Organizations can indicate that they engage in screening but the effectiveness of their approach may be suboptimal. Most HCV testing guidelines list risk groups who should be offered an HCV test but few, if any, provide guidance as to which might benefit most from testing or how those most at risk might be identified [49–53]. Such guidelines, however, were drawn up in the mid to late 1990s, before the recent advances in treatment; in the context of these and the latest understanding of HCV risk, as above, the following prioritization to the HCV screening of risk groups is afforded. (Table 3): Individuals belonging to the category of Very High Priority would undergo testing as a requirement; those who were Intermediate Priority would be offered and recommended a test; those who were Low Priority would not be offered a test but could have one if they wanted.

Very High Priority should be afforded to individuals if they pose an infection control hazard in the healthcare setting. High Priority should be given to those who have a higher probability of infection and, if infected, are eligible for therapy. Intermediate Priority should be bestowed on people who

### Table 3 Prioritizing HCV testing

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<th>Priority Level</th>
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| **Very High Priority (testing required)** | - Haemodialysis patients  
- Blood or blood product, tissue or organ donors  
- Healthcare workers about to enter an exposure prone procedure training slot or post* |
| **High Priority (verbal offer and recommendation of test)** | - Patients with a persistently elevated ALT  
- Past injecting drug users  
- Children of a known HCV antibody positive mother†  
- HIV positive persons‡  
- Recipients of blood clotting factors prior to 1987.  
- Healthcare workers after percutaneous or mucous membrane exposure to HCV infected blood |
| **Intermediate Priority (offer (verbal or in the form of literature) but not recommendation, of test)** | - Recipients of blood products before 1991  
- Current injecting drug users  
- People who have had tattoos or body piercing in circumstances where infection control procedure was suspected to be suboptimal  
- Persons who have a history of multiple sexual partners, sexually transmitted infections or an HCV positive sexual partner/household contact |
| **Low Priority (no offer of test but available if wanted)** | - Everyone else including pregnant women not in any of the above categories |

*Because of recent HCW to patient transmission of HCV, UK guidance now requires such testing. HCV viraemic HCW cannot enter EPP training or posts until they have achieved sustained viral clearance.
†If a mother knows her HCV status it would be wise to have the child tested at some stage; since disease progression is slow in childhood, this need not occur in infancy.
‡Coinfection with HIV increases the rate of HCV disease progression.

have a lower, but not negligible, chance of infection or a higher probability of infection and, if infected, are ineligible for therapy. Low Priority should be given to those whose probability of infection is extremely low or negligible.

Thus, those in the High Priority category include persons with persistently elevated ALT (indicative of chronic hepatitis) and past IDU. The case for offering and recommending an HCV test to past IDUs is compelling. In most resource-rich countries the incidence of IDU increased dramatically in the 1970s and early 1980s; most IDUs who began to inject then and became HCV infected shortly after, have either died (20%) or stopped injecting. HCV disease progression is slow in people who are infected between ages 15–30 (5% develop cirrhosis within 25 years); 60%, however, develop moderate hepatitis within 17 years [47,48,54]. Accordingly, most past IDUs would be eligible for therapy.
Such prioritization would not deny anyone the right to have an HCV test. It would, however, impart a sense of purpose and focus to HCV case-finding.

**Screening past IDUs: cost-effectiveness, clinical setting and age**

The only group belonging to the Very High or High Priority categories that presents a major case-finding challenge is the past IDU one. A few cost-effectiveness investigations of HCV screening have been undertaken but only one was performed recently enough to apply to the era of interferon and ribavirin antiviral therapy [55–57]. The cost-effectiveness of HCV screening of past IDUs attending drug services or GUM clinics in England was estimated to be approximately £27 500 per QALY. The QALY for universal screening in GUM clinics was estimated to be £85 500. The main problem with the estimate for the past IDU group is that many key assumptions were based on flimsy, conservative data; the assumptions included rates of 32% for HCV prevalence, 49% for HCV test uptake, 77% for biopsy acceptance and 50% for the detection of moderate disease followed by the acceptance of treatment. Further, the impact of the more effective pegylated interferon/ribavirin combination was not accounted for and the cost of HCV test counselling was estimated to be £17.00. A cost per QALY of £27 500 is considered a modestly cost-effective one; this could be improved, however, if the rates of HCV prevalence (in global terms, the 32% rate is likely to be low), test acceptance and moderate disease yield were increased, and the cost of the counselling reduced. The former, likely, would be achieved if only past IDUs exceeding a certain age – say 35 – were targeted; the great majority would have been infected for a period, sufficient for progression to moderate, but insufficient for progression to severe, disease. The latter would be achieved if the discussion process surrounding the test could be kept to a minimum.

In some areas of extremely high IDU prevalence, it is possible that the screening of all middle-aged (35–55) general practice attendees would be cost-effective. Alternatively, general practitioners might identify their patients who they knew had either stopped injecting or ever had injected and had reached an age when the likelihood of them having stopped was considerable. Another possible site for targeting past IDUs is the prison setting; because such a high proportion of prisons harbour past and current IDUs – many of whom might not wish to identify themselves as such – offering and recommending a test to those exceeding a particular age might achieve a high yield.

**Screening Intermediate Priority populations**

As the screening of past IDUs and all GUM clinic attendees is considered moderately and not cost-effective, respectively, the screening of other ‘clinic’ populations is unlikely to be cost-effective. It is possible, however, that applying an age threshold to universal screening within the GUM clinic setting in certain areas might allow the cost-effective detection of individuals with moderate HCV disease who belong to either the High Priority group as past IDUs or the Intermediate Priority group as, for example, sexual contacts of IDUs.

Although the HCV risk of persons belonging to the Intermediate Priority group is relatively low, it is important that they appreciate their risk and that HCV testing can be performed if they wish; poster literature explaining this should be visible in, for example, waiting areas in healthcare settings and in prison recreation rooms.

If the above initiatives to identify those eligible for therapy are implemented, Virology, Hepatology and Infectious Disease services must have the resources to respond to the increased clinical demand.

**Declaration of interests:**

D. Goldberg and E. Anderson have a grant from Schering-Plough to undertake study of HCV testing among general practice attendees.

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