Effectiveness of interventions to increase hepatitis C testing uptake among high-risk groups: a systematic review

Lisa Jones¹, Geoff Bates¹, Ellie McCoy¹, Caryl Beynon¹, James McVeigh¹, Mark A. Bellis²

1 Centre for Public Health, Faculty of Education, Health and Community, Liverpool John Moores University, 15-21 Webster Street, Liverpool L3 2ET, UK
2 Public Health Wales, Haydn Ellis Building, Maindy Road, Cardiff CF24 4HQ, UK

Correspondence: Lisa Jones, Centre for Public Health, Faculty of Education, Health and Community, Liverpool John Moores University, 15-21 Webster Street, Liverpool L3 2ET, UK, tel: +151 231 4452, fax: +151 231 4552, e-mail: l.jones1@ljmu.ac.uk

Background: People who inject drugs are at the greatest risk of acquiring hepatitis C virus infection in many high-income countries, including those in Europe. Our review examined the effectiveness of interventions aimed at increasing hepatitis C virus testing uptake. Methods: We undertook a systematic review of controlled studies. Searches of 13 databases were supplemented with citation searching, and manual searches of reference lists and websites. Studies of interventions that aimed to increase testing uptake among high-risk groups were included. Testing uptake was our primary outcome measure of interest and secondary outcomes were engagement in follow-up services and treatment. A narrative synthesis was undertaken. Results: Eight controlled studies were included. Three studies examined interventions in primary care; one examined dried blood spot testing as an alternative method of testing, and two examined outreach provision. Two further studies examined interventions to improve hepatitis C management. Targeted case finding in primary care, support and training for primary care practitioners, offering alternative testing and provision of outreach testing all increased uptake of testing; however, intervention effects were variable. Conclusions: Evidence from the available studies suggests that increases in testing uptake can be achieved. Careful attention needs to be paid to the resource implications associated with implementation of interventions in primary care settings and also of the potential for interventions to improve outcomes once a positive diagnosis has been made. Further research on the cost-effectiveness of the intervention approaches examined in this review is required.

Introduction

Hepatitis C virus (HCV) infection represents a major public health problem worldwide. Within the World Health Organization European region, approximately 9 million people are chronically infected with the HCV, and as in other high-income regions, people who inject drugs (PWIDs) are at greatest risk of acquiring infection. Despite the burden associated with HCV, it is still a neglected disease in many countries in Europe. A Call to Action for the EU and Member States on hepatitis B and C was launched in 2011 with the goal of making viral hepatitis a public health priority. Within the past decade, calls for action have also been launched in individual European countries, but with differing levels of success. So far, government-led sustainable improvements in screening of high-risk groups have only been made in France and Scotland. Whereas effective antiviral therapies for HCV have become available within the past decade, coordinated and robust responses to the broader public health issues associated with tackling transmission of the virus have lagged behind. In many European countries, problems persist in the effective diagnosis and referral of patients, and although knowledge of HCV status is critical for preventing transmission and for initiating early treatment and care, the European Liver Patients Association found that many people are unaware of their HCV status at the time of infection. Furthermore, although an increasing number of studies have shown that PWIDs who have acquired HCV can be successfully treated, very few go on to receive HCV treatment.

European countries are therefore facing a major challenge to improve identification of individuals at high risk of HCV. To inform policy and practice responses, we carried out a systematic review of the effectiveness of interventions aimed at increasing uptake of case finding and testing among high-risk groups and health professionals involved in the promotion or provision of HCV testing.

Methods

This study was conducted as part of a series of extensive systematic reviews to inform policy recommendations on ways of offering hepatitis B virus and HCV testing in the UK by the National Institute for Health and Clinical Excellence (NICE). We conducted our systematic review in accordance with NICE methods and followed the PRISMA statement for transparent reporting. Accordingly, a protocol documenting the background, objectives and methods was prepared in advance of the review (available on request from the authors).

Search strategy

A comprehensive search approach was taken. Searches were conducted in 13 databases (Figure 1), with additional, citation searching, searches of the reference lists of retrieved studies and searches of relevant websites. Searches were limited to articles published since 1990 and were conducted in July 2011. Search strategies were developed for each database using a combination of free text and thesaurus terms. As this work was conducted as part of a broader review on hepatitis B virus and HCV testing, search terms relating to both types of hepatitis (e.g. by exploding the MeSH term ‘Hepatitis C’) and testing (e.g. case find, test) were combined with relevant terms for intervention, outcome and evaluation, professional role, setting, population or professional education.
Study selection and eligibility criteria

Titles and abstracts were initially screened by one reviewer from a team of three (L.J., E.M.C. and G.B.), and the lead reviewer (L.J.) independently second-screened 30% of the references. Titles and abstracts of any potentially relevant articles identified at this stage were then rescreened by two reviewers from the same team. Relevant articles identified after this stage were retrieved as full-text publications and screened by two reviewers independently (again from the same team) to determine whether the study met the inclusion criteria. Although studies of any design were eligible for inclusion...
in the broader review for this article, we focused on the findings from controlled studies, further limiting inclusion to randomized controlled trials (RCTs), controlled non-randomized controlled trials (NRCTs), and controlled before-and-after studies that compared an intervention against no intervention or another type of intervention (e.g., continuation of current testing practice). Fourteen uncontrolled studies (e.g., case series) were identified through our searches, but were excluded from the main analyses presented here. We included studies of any type of intervention that aimed to raise awareness of, or engagement in, HCV testing among high-risk groups. HCV infection is highly prevalent among PWIDs, and although they are the population primarily targeted for HCV testing, studies of interventions that targeted non-PWID high-risk populations were also included. Studies that focused on changing behaviors in relation to injection or sharing practices among PWIDs, but without reference to HCV testing, were not eligible for inclusion. Change in testing uptake was the primary outcome measure of interest. We defined this broadly, including changes in the number of participants: (i) requesting or accepting a test, (ii) undergoing testing, (iii) receiving a positive test or (iv) referred to treatment. Changes in the number of participants testing positive who engaged in follow-up services and/or treatment were examined as secondary outcomes.

Data extraction and quality assessment

Data relating to study design and quality were extracted by one reviewer from a team of two (E.M.C. and G.B.) and independently checked for accuracy by a second reviewer (L.J.). Disagreements were resolved through consensus, and when necessary, a third reviewer consulted. Data were extracted from the included studies on author, publication year, country, research funding source, study objectives, study design/characteristics (e.g., eligibility criteria), participants (e.g., age and gender), intervention, analysis/outcomes measured and results. Two reviewers independently undertook quality assessment using NICE checklist criteria,14 a revised version of the Graphical Appraisal Tool for Epidemiological studies.15

Data analysis and synthesis

We summarized the outcomes of data extraction and quality assessment in tables and as a narrative summary. Studies were grouped according to the type of intervention examined and the possible effects of study quality on the effectiveness data and review findings discussed. Where possible, intervention effectiveness was investigated by examining the difference between pre- and post-intervention changes in testing uptake. Otherwise, effectiveness was investigated by examining the difference in post-intervention testing uptake between intervention and control groups. To provide a comparison of effect sizes across the interventions examined, we used Wilson’s Effect Size Calculator16 to calculate Cohen’s d and corresponding 95% confidence intervals (CIs) using the logit method based on the proportion of intervention and control participants completing a HCV test. We chose not to pool effect sizes due to heterogeneity across the studies in the populations, settings and interventions examined. We developed a logic model to guide the narrative synthesis and to explore potential relationships between the interventions identified and outcomes. The logic model (Figure 2) depicts the links between the types of interventions identified, the settings in which they are delivered and the intended change in outcomes.

Results

We retrieved 12,656 references and assessed 299 full-text articles (Figure 1). Eight controlled studies, from the UK, France, The Netherlands, Ireland and the USA, met our inclusion criteria (Table 1). This included five RCT and three NRCTs. Three studies examined interventions designed to enhance case finding and testing in primary care.17,18,20 One study examined interventions designed to increase access to testing services based on offering alternative methods of testing,16 and two studies11,24 examined HCV testing in outreach settings. Two studies22,23 examined interventions designed to improve management of HCV among health professionals.

Raising awareness and encouraging use of testing services

A French study20 examined the impact of assistance with HCV screening for general practitioners (GPs). GPs receiving the intervention were assisted with the screening programme through the provision of information (posters/leaflets) in surgery waiting rooms. Two UK studies17,18 evaluated opportunistic case finding in general practices in areas of high injecting drug use and HCV prevalence. Both interventions targeted individuals aged 30–54 years, and the intervention examined by Cullen and colleagues18 was also limited to individuals with indicators of past injecting drug use. All patients meeting the inclusion criteria and attending for non-urgent appointments were offered screening and given an information leaflet; individuals accepting the offer could immediately attend, or return for, an appointment.

In the French study,20 provision of patient information was associated with a significantly higher number of post-intervention patient requests for testing compared with GPs receiving training only. HCV tests were undertaken at the request of the patient in 35.7% of cases in intervention practices compared with 19.5% of cases in control practices (P < 0.001 for comparison).20 However, although this demonstrated the value of providing information to patients, there was no significant impact on the overall number of tests requested per GP in intervention and control practices (net difference in post-intervention tests requested per GP = –0.5 tests). Two UK studies17,18 found that targeted case finding in primary care had a positive impact on the number of patients offered and accepting a test. In one study,17 the proportion of eligible patients tested increased from pre- to post-intervention by 9.9% in the intervention practice compared with a decrease of 0.1% in the control practice. Intervention was associated with low diagnostic yield, with 12.8% of intervention patients (n = 15/117) testing HCV positive. No control patients were tested during the intervention period.17 Among intervention practices that implemented a case finding intervention specifically targeting former PWIDs, 0.8% of the practice population aged 30–54 years were tested for HCV compared with 0.3% of the control practice population.18 The proportion of patients who were tested and received a positive (antibody) test was 70.5% in intervention practices compared with 22.2% in control practices.

Opportunistic case finding in primary care was found to have had a mixed impact on the number of patients starting HCV treatment after referral.17,18 Although referral rates were relatively high (Table 2), both studies found a high rate of failure to attend, and dropout from, follow-up services (around 70% and 50%18 in the two studies, respectively). Neither study examined reasons for non-attendance or dropout.

Increasing access to testing services

One cluster RCT19 examined the impact of offering dried blood spot (DBS) testing as an alternative to venepuncture in substance misuse services, drug clinics and prisons. Hickman and colleagues19 randomized services to offer DBS testing undertaken by drugs workers or testing as usual. The internal validity of the study was potentially affected by inconsistency in exposure to the intervention, and the authors questioned whether the study was adequately powered to detect an intervention effect. Two RCTs, based on
Figure 2: Logic model to explore relationships between interventions and intended outcomes.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Target population (number of patients in intervention/control)</th>
<th>Setting, (number in intervention/control)</th>
<th>Intervention phase</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2009</td>
<td>NRCT</td>
<td>Practice population aged 30–54 years (n = 1165/914)</td>
<td>General practices (n = 1/1)</td>
<td>Opportunistic age criterion-based screening</td>
<td>Before</td>
<td>Requesting or accepting a test</td>
</tr>
<tr>
<td>Cullen 2006</td>
<td>RCT</td>
<td>Health professionals (n = 104/92)</td>
<td>General practices (n = 13/12)</td>
<td>Implementation of clinical guidelines</td>
<td>Before</td>
<td>Completing testing</td>
</tr>
<tr>
<td>Cullen 2011</td>
<td>NRCT</td>
<td>Former PWIDs (n = 13037/14189)</td>
<td>General practices (n = 8/8)</td>
<td>Targeted, age-based screening</td>
<td>During</td>
<td>HCV positive test</td>
</tr>
<tr>
<td>Helser 2010</td>
<td>NRCT</td>
<td>Health professionals (NR)</td>
<td>Primary care services (n = 110/109)</td>
<td>Support programme</td>
<td>Before</td>
<td>Requesting or accepting a test</td>
</tr>
<tr>
<td>Hickman 2008</td>
<td>RCT</td>
<td>PWIDs (n = 6650/58000)</td>
<td>Drug treatment clinics and prisons (n = 14/14)</td>
<td>DBS testing</td>
<td>During</td>
<td>Completing testing</td>
</tr>
<tr>
<td>Rosenberg 2010</td>
<td>RCT</td>
<td>Co-occurring mental health/substance use disorders (n = 118/118)</td>
<td>Mental health programme (NR)</td>
<td>Direct provision of BBV services</td>
<td>During</td>
<td>HCV positive test</td>
</tr>
<tr>
<td>Roudot-Thorval 2000</td>
<td>RCT</td>
<td>GPs</td>
<td>General practices (n = 94/90)</td>
<td>Posters and leaflets in waiting room</td>
<td>During</td>
<td>Requesting or accepting a test</td>
</tr>
<tr>
<td>Sahajian 2011</td>
<td>RCT</td>
<td>Refugees and asylum seekers (n = A 222; B 243/811)</td>
<td>Homeless shelters (n = A 6; B 6/6)</td>
<td>A Testing by referral</td>
<td>During</td>
<td>Completing testing</td>
</tr>
</tbody>
</table>
individual\textsuperscript{21} and cluster\textsuperscript{24} randomization, respectively, examined whether provision of testing in non-specialist community services increased access to testing and follow-up services. One study examined an intervention targeting refugees and asylum seekers housed in shelters\textsuperscript{24} and the other, patients at mental health treatment sites with co-occurring mental health and substance abuse disorders.\textsuperscript{23}

Increases in HCV testing uptake were found in drug services and prisons offering DBS testing alongside other means of testing, compared with services offering venepuncture only.\textsuperscript{19} An overall significant positive effect of introducing DBS testing was found when all intervention sites were compared with control sites (weighted absolute increase in testing uptake = 10.8\%; 95\% CI: 0.5 to 69.4\%). Although reasons for variation in the treatment effect were not clear, the authors noted that the two sites with the highest difference in treatment effect attributed the increase ‘simply to an interest in HCV’.\textsuperscript{19}

Integration of testing services within non-specialist community settings also had a positive effect on testing uptake. Participation in the Screen, Test, Immunize, Reduce risk, and Refer (STIRR) programme\textsuperscript{21} within mental health treatment sites was associated with significantly higher acceptance of HCV testing among patients compared with control sites, in which patients were directed to off-site services (STIRR, 86.4\% vs. control, 14.5\%; \(P < 0.001\)). Outreach testing\textsuperscript{24} also improved testing acceptance and uptake, with testing completion significantly higher among participants who received either intervention approach compared with control [on-site testing vs. control group: odds ratio (OR) 98.5, 95\% CI 51.9–200.8; testing by referral vs. control group: OR 49.8, 95\% CI 26.1–102.1; provision of on-site testing vs. testing by referral OR 2.0, 95\% CI 1.3–2.9]. However, despite the positive intervention effects, 30\% of participants accepting a test did not complete one, with the authors finding that participants changed their minds because of a fear of having blood taken.

**Aimed at professionals**

Two studies\textsuperscript{22,23} examined interventions designed to improve health professionals’ management of HCV testing and treatment. Both studies\textsuperscript{22,23} evaluated complex interventions, comprising educational materials and education sessions for GPs in support of a public awareness campaign in an NRCT, and a nurse-led 6-month intervention to support the implementation of guidelines on the management of HCV in primary care in a cluster RCT.\textsuperscript{23}

The intervention supporting implementation of clinical guidelines improved HCV screening rates among patients on methadone maintenance treatment. In intervention practices, 49.0\% of patients were screened compared with 27.2\% of the control group (adjusted OR: 3.76, 95\% CI 1.3–11.3).\textsuperscript{23} Educational materials and education sessions for primary care practices also had positive intervention effects on testing uptake.\textsuperscript{22} The post-intervention testing uptake in the intervention region was 2.2 times (95\% CI 1.5–3.3) as high as in the control region, and the intervention was associated with a 2.6\% (95\% CI 0.7–5.8\%) increase in the number of positive tests. However, the clinical significance of these comparisons was not clear, and the intervention was associated with a low diagnostic yield.

Effects on referral and treatment outcomes were explored in one study.\textsuperscript{23} The intervention supporting clinical guideline implementation was associated with an increase in referrals for assessment at a hepatology clinic. However, after correction for clustering, the corresponding adjusted OR was no longer statistically significant (OR 3.15; 95\% CI 0.9–10.7). The authors suggest that this finding may be explained by the short duration of the study or by this outcome being subject to a clustering effect.

**Comparison of effect sizes across studies**

Data were available to calculate effect sizes for six of the eight studies included in the review (Table 2). The effect sizes (Cohen’s \(d\)) calculated ranged from 0.54 to 2.52. The largest effect sizes were associated with interventions based on the delivery of services in non-specialist community settings.\textsuperscript{21,24}

**Discussion**

**Main findings**

We conducted a systematic review of all available controlled studies of interventions aimed at increasing uptake of voluntary HCV testing among high-risk groups. Although we found relatively few controlled studies, a range of approaches were examined, including interventions designed to enhance case finding and testing uptake in primary care.\textsuperscript{17,18,20} Offer alternative methods of testing,\textsuperscript{19} deliver services in non-specialist community settings,\textsuperscript{21,24} and improve HCV management among health professionals.\textsuperscript{22,23}

Based on current evidence, it appears that targeted case finding, support and training for primary care practitioners, offering DBS testing and the provision of outreach testing may increase HCV testing uptake among high-risk groups. However, the effects of these interventions on testing uptake were variable, as shown by the comparison of effect sizes. It is also important to consider the limitations of the interventions examined for improving outcomes once a positive HCV diagnosis has been made. Although this review focused primarily on testing uptake, as the primary aim of testing should be to identify positive individuals and to offer them appropriate management and treatment, it is important to note that high-risk groups, and in particular PWIDs, may encounter further
barriers to care after diagnosis. These include problems with accessing referral and counselling,\textsuperscript{25} poor attendance at follow-up services,\textsuperscript{6,27} being denied opportunities to access treatment and receiving a lack of information on treatment options.\textsuperscript{26,28} Further research on how to increase engagement in HCV care and treatment after a positive diagnosis is needed to ensure that such barriers are reduced. Furthermore, there needs to be a greater awareness of the potential for treatment to substantially reduce the prevalence of HCV infection, particularly among PWIDs.\textsuperscript{29} Primary care services are an important setting for identification of HCV infection, and five of the included studies examined intervention approaches in this setting.\textsuperscript{17,18,20,22,23} Targeted case finding increased testing uptake and case yield in general practices in areas of high HCV prevalence,\textsuperscript{16,17} but in other studies, increases in diagnostic yield were low.\textsuperscript{22} Although a cost-utility study\textsuperscript{30,31} found it was likely that case finding for HCV in primary care among one of the key high-risk groups, in this case former users of injecting drugs, would be considered cost-effective, there were substantial uncertainties in the estimates used. The authors of two UK studies\textsuperscript{17,18} noted that GPs had found the process of offering a test and obtaining a sample time-consuming, and that sometimes multiple appointments were required to complete the testing process. The time and resource implications associated with primary care-based interventions therefore need to be considered, and further research on the cost-effectiveness of this and the other intervention approaches examined in this review is required.

Uncontrolled studies

We identified six uncontrolled studies through our searches that examined intervention approaches of relevance to our review. Although the results of uncontrolled studies should be treated with great caution, they provide some further context to the intervention approaches examined in controlled studies. The potential to improve testing uptake by broadening access to HCV services within community settings was shown in four studies.\textsuperscript{32-35} Two studies of particular relevance found that targeting current drug users through multidisciplinary or shared care approaches to HCV testing and treatment was associated with good uptake of follow-up services, and treatment outcomes considered comparable with those seen in non-drug-using populations.\textsuperscript{34,35} Drawing on qualitative research undertaken with PWIDs, convenient and opportunistic testing and location of HCV services, including treatment, in one setting appears to be an important facilitator of testing and management.\textsuperscript{32,33} For interventions aimed at improving professional practices, a study of a French national awareness campaign demonstrated that without support, offers of testing by primary care professionals may increase but not within the desired high-risk groups.\textsuperscript{37} Another study\textsuperscript{38} found that the number of clients tested for HCV was nearly six times greater after DBS testing was introduced compared with the number tested off-site by venepuncture in the previous year. The authors noted that the increase in uptake may have been attributable to the increased availability of on-site testing rather than solely to the introduction of an alternative method of testing.

Scope and limitations of the review and published literature

The scope of the review was broad and covered a range of intervention approaches and settings. The search strategy developed was comprehensive but resulted in the retrieval of a large number of irrelevant references, indicating high sensitivity, but low precision. It is possible that some relevant studies were missed, but including multiple strategies minimized this likelihood. Although limiting inclusion to controlled studies excluded a number of studies of relevant approaches, including uncontrolled studies in the main analyses would have introduced the potential for bias in determining effectiveness and risking overestimation of intervention effects. Alongside this consideration, there were uncertainties as to whether potential sources of bias had been minimized in the included controlled studies. Limitations were identified using the checklist quality criteria; in three RCTs,\textsuperscript{20,21,24} there were reservations about whether selection bias had been minimized, and across all studies, follow-up times were generally 6 months or less and consequently not long enough to fully assess the long-term harms or benefits of intervention. The internal validity of one RCT was also potentially affected by whether the study was adequately powered to detect an intervention effect.\textsuperscript{19} In addition, effect size estimates were not reported or calculable for two studies based on non-random allocation.\textsuperscript{17,18} A further limitation of the published literature was the differences in the types of outcomes reported across the included studies. Although all studies reported a measure of the number of participants completing testing, only three studies reported the proportion of participants testing HCV positive (Table 1).

Conclusions

In conclusion, despite a number of methodological limitations, evidence from available studies of interventions aimed at increasing uptake of HCV testing with high-risk groups suggests that increases can be achieved. However, careful attention should be paid to the resource implications associated with implementation of the interventions examined in this review and of the potential for interventions to improve outcomes once a positive HCV diagnosis has been made.

Funding

This study was funded by the UK National Institute for Health and Care Excellence as part of a series of extensive systematic reviews undertaken for the purposes of informing public health guidance. The interpretation, analysis and views expressed are those of the authors and not necessarily those of the National Institute for Health and Care Excellence.

Conflicts of interest: None declared.

Key points

- Existing evidence on the effectiveness of interventions aimed at increasing engagement in testing among groups at risk of HCV infection, and health professionals involved in the promotion or provision of testing, is limited.
- Eight controlled studies were identified that examined a range of approaches aimed at increasing engagement in HCV testing among high-risk populations.
- Our review indicates that targeted case finding in primary care, support and training for primary care practitioners, offering DBS testing and the provision of outreach testing may increase uptake of HCV testing among high-risk groups; however, the effects of these interventions are variable.
- The interventions examined had a limited impact on referral and treatment outcomes after a positive HCV diagnosis.

References
