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Hepatitis C: interventions for patient case-finding and linkage to care

Evidence review

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Executive summary

This report summarizes the evidence for interventions to increase case-finding and linkage to care for hepatitis C-infected patients, in order to support commissioning and provision of evidence-based interventions as part of efforts to achieve hepatitis C (HCV) elimination as a major public health threat in the UK.

We conducted a rapid evidence review, with publications database searches and hand-searching of reference lists supplemented with evidence received through contact networks. Studies in English from the UK, Australia, North America, and Western Europe were included if they had a comparator group and evaluated interventions to increase uptake of testing and diagnosis for HCV, improve linkage to care and/or (re)engagement in treatment for those diagnosed with HCV, and/or increase retention in treatment and treatment completion for those diagnosed with HCV. Cost analyses and economic evaluations of studies meeting these criteria were also included. Studies were categorised by setting, target group (people who inject drugs (PWID), prisoners, men who have sex with men (MSM), homeless persons and migrants) and intervention type. Risk of bias in individual studies was assessed using validated tools (ROBINS-I for non-randomised studies and Cochrane collaboration for randomised studies) and tables were used to summarise the results of the included studies.

Evidence was largely from small or pilot non-randomised studies. Almost all randomised studies had at least 1 domain at high risk of bias, and most non-randomised studies were at critical risk of bias. Many took place in the interferon era when treatment uptake and outcomes were poorer than they are with current direct acting antiviral (DAA) drugs.

For PWID, facilitator or nurse-led coordination of dried blood spot (DBS) testing in drug treatment services (DTS) increased testing uptake. Care coordination interventions in DTS significantly increased referrals to, and uptake of, HCV treatment, with limited data on their effect on treatment outcomes. Findings on pharmacy testing and onsite DAA treatment for PWID were promising, but were from preliminary studies. The cost-effectiveness of testing PWID was well supported by the evidence, with higher treatment uptake increasing the cost-effectiveness of testing and treatment.

In primary care and General Practice, electronic medical records (EMR) alerts, usually implemented alongside other interventions such as staff education, increased testing, and staff education alone was associated with small but significant increases in implementation of recommended testing. Two recent randomised UK studies found EMR interventions which identified at-risk patients (via a risk algorithm or migrants) significantly increased testing and were cost-effective. Improved recording of risk factors, including migrant status, in EMR is required to improve the effectiveness of these interventions.

Provision of onsite treatment with DAA drugs was shown to be feasible in primary care and DTS, with similar outcomes to tertiary care, but no studies directly compared treatment uptake for PWID in primary care or DTS to tertiary referral, and 1 study of migrants found no difference in treatment uptake or completion in primary care compared to tertiary care. Multidisciplinary care coordination within HCV treatment, including for patients with comorbid substance misuse and/or mental illness increased treatment initiation and cure, with limited evidence suggesting that these interventions were cost-effective or even cost-saving.

Research in prisons was limited, and showed impacts of implementation considerations at each site. Opt-out testing evaluations showed testing rates remain below what would be expected from a true ‘opt-out’ implementation. Testing in prisons was cost-effective in more recent studies which took into account improved treatment uptake and completion possible with DAAs.

Research on interventions for homeless populations was very limited, although homeless outreach interventions are taking place. An understanding of injecting status is needed to ascertain whether homeless persons are likely to be picked up elsewhere in PWID interventions.

No studies which met inclusion criteria evaluated the effectiveness of interventions for MSM. Some of the learning from interventions to promote the uptake of HIV testing, such as rapid testing and counselling in community settings is likely to be transferrable to HCV testing in the MSM population.

Research on care pathway interventions including multicomponent, multidisciplinary approaches across different settings provided suggestive evidence that care pathway redesign and managed care programmes were effective.

Recommendations

Recommendations for commissioners and providers

1. Prioritise commissioning facilitator or nurse-led complex interventions for PWID, providing a multi-agency package of care to test patients and support them to access and complete treatment. This will require collaborative working across a range of organisations involved in the HCV treatment and care pathway.
2. Fully implement the opt-out screening programme in prisons, prioritising linkage to care and treatment outcome as the critical components of cost-effectiveness.
3. Commission incentivised combined HCV and hepatitis B screening in primary care for migrants, particularly in areas of high migrant density.
4. Improve recording of country of birth and risk factors on primary care and community drug service health information systems.
5. Commission primary care screening via electronic flagging using validated risk algorithms.
6. When assessing value for money of interventions focus on most recent cost-effectiveness models which have up to date assumptions about treatment efficacy, acceptability, uptake, duration and costs.
7. Horizon scan to obtain evidence from ongoing and emerging research, in particular participate in action research taking place as part of the evaluation of a national patient re-engagement exercise.

Recommendations for future research

1. Evaluate complex multi-component interventions covering the whole care pathway from testing to treatment completion in different settings, including cost-effectiveness analysis.
2. Update economic evaluations with current treatment efficacies and costs.
3. Further evaluate pharmacy interventions for testing and treatment of PWID where NSP services are provided.
4. Undertake further research on ways of improving uptake of screening of migrants in primary care.
5. Undertake implementation research in prisons on scalability and addressing challenges in embedding testing and treatment programmes in secure settings with community follow up.
6. Use economic modelling to guide the scale-up and prioritisation of case-finding interventions and minimise costs.
7. Develop a template to evaluate pilots and determine whether further large-scale studies or trials are required or interventions should proceed to phase IV post implementation evaluation.

Introduction

Purpose

This report provides a summary of the evidence for interventions to increase case-finding and linkage to care for hepatitis C-infected patients, including those who are already “diagnosed” but not in specialist care and treatment, with the aim of supporting commissioners and providers in making decisions on prioritisation of resources and commissioning of services. Increased and improved provision of appropriate services is essential to ensure the high levels of testing and treatment coverage needed to progress towards the World Health Organization (WHO) goal, which the UK Government has signed up to, of eliminating hepatitis C virus (HCV) as a public health threat by 2030 (World Health Organization 2016).

Background

Epidemiology

Modelling suggests that in 2018 around 113,000 (95% credible interval 94,900 to 132,400) individuals in England were chronically infected with HCV (Harris, Harris et al. 2019). Due to the asymptomatic nature of chronic HCV infection, a high proportion of those infected with HCV likely remain undiagnosed until late stages of liver disease, leading to morbidity and mortality from end stage liver disease (ESLD) and hepatocellular carcinoma (HCC). Furthermore, a low proportion of patients who were diagnosed in the past have received treatment, and an even lower proportion have gone on to be cured (Simmons, Ireland et al. 2018). Many of these people were diagnosed when the natural history of HCV-related disease was less certain and/or when treatment options were limited with sub-optimal outcomes. The current number of people diagnosed and yet to access treatment is difficult to establish, but a lower bound of 45,000 was estimated based on HCV positive tests reported to Public Health England (PHE) from NHS laboratories over time (Harris, Harris et al. 2019).

Overall HCV prevalence in the UK is low, and risk is concentrated among particular groups at higher risk of HCV infection:

- people who inject drugs (PWID)
- prisoners
- homeless people
- migrants from higher prevalence countries
- men who have sex with men (MSM)

People who inject drugs (PWID)

PWID are the major risk group for HCV infection in England, with injecting drug use cited as the key risk factor for over 90% of new diagnosed infections where risk factors were disclosed (Public Health England 2018). An estimated 40% of PWID are currently infected with HCV, and around half of these are undiagnosed (Public Health England 2017).

PWID experience barriers to accessing HCV testing and treatment, including poor knowledge of HCV infection and treatment options, low levels of trust in health professionals, and greater loss to follow-up along the care pathway. In addition, active PWID often have poor venous access, a barrier to testing if blood samples are acquired via venepuncture. Dried blood spot (DBS) testing is now the widely accepted and commonly implemented method of testing for this group.

National Institute for Health and Care Excellence (NICE) guidance recommends providing HCV testing in drug treatment, but implementation is varied (NICE 2012). Interventions aimed at PWID not in drug treatment are also needed, as not all those with injecting drug use as a risk factor will access drug treatment. In addition, an estimated 57% of the HCV-infected population are former PWID who have permanently ceased injecting (Harris, Harris et al. 2019). Although the risk factor for this group is the same as for current PWID, there are particular challenges in quantifying, identifying and testing this population as they may no longer be in contact with drug and alcohol services nor have opioid dependence/injecting history recorded in primary care notes.

Prisoners

Prisoners are at increased risk of HCV infection, with HCV antibody (anti-HCV) positivity among the England prison population between 5% and 8% in sentinel surveillance of blood-borne viruses (SSBBV) testing data from 2014-2016 (Public Health England 2015, Public Health England 2016, Public Health England 2017). Risk in prisoners is mainly due to injecting practices, but may also come from sexual exposure. Prisoners are a transient population, with over half having sentences of less than 6 months, during which time they may stay in more than 1 prison (Ministry of Justice 2019). A stay in prison represents a window of opportunity to test and start treatment, with prompt testing and linkage to care required to capitalise on this.

NICE guidance recommends that HCV testing should be offered in prisons (NICE 2012), and opt-out BBV testing on reception to English prisons began phased implementation in 2014 under a tripartite agreement between PHE, NHS England and the Prison and Probation Service (NHS England 2014). Despite this there are implementation challenges and although uptake is increasing it remains low, with only 26% of prisoners tested for HCV on reception in 2017/18 (Public Health England 2018).

Homeless

Homeless populations are at increased risk of HCV infection, with 1 small UK study finding a seroprevalence of 27%, although seroprevalence estimates among this group vary widely (Sherriff and Mayon-White 2003, Beijer, Wolf et al. 2012). Homeless populations are among the most marginalised populations in accessing health care and are less likely to access mainstream services than other populations. The homeless population is not clearly defined and an understanding of injecting status and service use is needed to ascertain whether HCV in homeless people is likely to be detected and managed elsewhere via interventions targeting PWID.

Migrants from higher prevalence countries

Migrants from higher prevalence countries, and black and minority ethnic populations who have close links to those countries are at increased risk of HCV (Uddin, Shoeb et al. 2010). Risk in these populations may be due to travel to country of origin, receiving medical treatment abroad and household exposure. Migrants face barriers to accessing BBV testing and treatment, and may face legal and bureaucratic obstacles to accessing healthcare, as well as barriers due to language, stigma and poor knowledge and understanding of the diseases (Guirgis, Nusair et al. 2012, Rechel, Mladovsky et al. 2013).

NICE guidance recommends primary care should offer HCV and hepatitis B (HBV) testing to migrants from higher prevalence countries, but evidence suggests that implementation of this guidance is low, with 1 study finding only 12% of eligible migrants were tested for HBV in primary care (NICE 2012, Evlampidou, Hickman et al. 2016).

MSM

MSM are at increased risk of HCV infection through sexual contact, particularly those living with HIV, and there are particular risk factors among MSM for HCV relating to group sex and ChemSex practices. Among HIV-uninfected MSM, those taking pre-exposure prophylaxis (PreP) due to their increased risk of HIV are likely to be at increased risk of HCV.

British Association for Sexual Health and HIV (BASHH) guidelines for testing in sexual health settings recommend offering HCV testing to PWID, HIV-positive individuals, MSM eligible for 3-monthly HIV testing and those taking or eligible for PrEP, but do not currently recommend testing in HIV-negative MSM without additional risk factors (BASHH 2017). MSM taking PrEP are likely to regularly attend services in order to obtain their prescriptions, and therefore may be considered more likely than other risk groups to undergo regular HCV testing.

Policy context

Viral hepatitis elimination goal

In 2016 the UK government committed to the WHO strategic goal of eliminating HCV (and HBV) globally as a public health threat by 2030. Achieving this goal in the UK will require system-wide concerted action to improve testing, diagnosis, referral to treatment, and treatment initiation and completion for those infected with HCV.

Prior to this, in 2002 the UK government published the Hepatitis C Strategy for England, which brought together existing initiatives and suggestions for how prevention, diagnosis and treatment of HCV could be improved (Department of Health 2002).

Progress on tackling HCV is monitored and reported by PHE in the annual Hepatitis C in England and Hepatitis C in the UK reports (Public Health England 2018, Public Health England 2018)

Commissioning and the patient pathway

The patient pathway from prevention, testing and diagnosis, to referral and treatment is funded by multiple commissioners and delivered by multiple providers (figure 1). These include both Local Authority (LA) and Clinical Commissioning Group (CCG) commissioned services as well as NHS and community services.

Testing and diagnosis

All anti-HCV positive test results should be followed by confirmatory testing for active HCV infection, as recommended by Standards for Microbiology Investigations (SMI) and NICE (NICE 2012, Public Health England 2017). SMI provide recommended laboratory testing algorithms for the diagnosis of HCV which state that all anti-HCV positive test results should be followed by either HCV RNA Nucelic Acid Amplification Tests (NAAT) or HCV core antigen testing on the same sample (known as ‘reflex testing’) to confirm active infection (Public Health England 2017). NICE guidelines recommend that commissioners ensure that laboratories automatically test anti-HCV positive samples for the presence of HCV RNA, or refer the sample to a laboratory which can perform this test (NICE 2012).

SSBBVT data indicate that between 2005 and 2014, 77% of anti-HCV positive patients were RNA tested, with 65% of these tests being performed within 7 days of the original test, indicating reflex testing (Simmons, Ireland et al. 2018). Cost analyses suggest that significant efficiencies would be gained if reflex testing was more widely implemented, due to reductions in unnecessary appointments and multiple anti-HCV tests (Ireland, Simmons et al. 2018).

There may also be a role in some contexts for direct HCV RNA testing, which would be cost-effective above a threshold prevalence and allow for faster diagnosis and linkage to care. This would need to be carefully considered in the context of prevalence in the target group and how linkage to care is planned to be achieved.

Treatment

The advent of direct-acting antiviral (DAA) drugs has enabled patients with HCV to be rapidly (12 to 16 weeks) and successfully (>95% sustained virological response (SVR)) cured, and made the elimination of HCV a realistic ambition. NHS England (NHSE) has implemented strategic agreements with industry that establish new levels of collaboration and significantly increase the level of investment from industry to both help find patients and make treatment more affordable. This in turn will enable significantly expanded treatment rates. As part of the agreement, NHSE has committed to invest up to £190 million per year in HCV treatments for a period of up to 5 years. This represents the NHS's single largest investment in treatment.

To coordinate treatment delivery NHSE has developed 22 Operational Delivery Networks (ODNs) to coordinate and lead local partnerships of relevant organisations involved in the HCV treatment and care pathway, including prisons, drugs services and patient organisations. Each ODN is led by a Lead NHS Provider Trust with a specialist hepatology or infectious disease Clinical Lead. NHSE made resources available to each ODN to purchase liver fibroscanners which rapidly and non-invasively assess liver health. ODN Clinical Leads report that those patients with the most advanced disease have now been treated. Case-finding is evolving into community based models, and patients with less advanced disease are being treated.

The NHSE Prescribed Services Commissioning for Quality and Innovation (CQUIN) scheme is seen as a key lever to incentivise NHS provider stewardship of NHS HCV resources, enabling them to play a leading role in delivering sustainable services. The HCV CQUIN scheme has been 1 of the largest schemes available between 2017-2020.

The current financial year (2019/2020) is the fifth year of treatment ramp-up at rates consistent with those set out by NICE in the costing template supporting their guidance. NHSE estimate that the number initiating treatment each year is currently around 11,000.

However, treatment is limited by the ability to find infected patients and link them to care, and then encourage treatment adherence and retention in care until SVR. Despite the various guidelines and programmes in place to test high risk populations, all have variable implementation success in practice. Making use of all available evidence on which interventions are most effective at identifying patients with HCV and engaging them in care is needed.

A national patient re-engagement exercise to help find and treat people who were previously diagnosed with HCV and may not have been treated was commenced in September 2018 by PHE and NHSE. PHE-held laboratory surveillance data on patients previously diagnosed with HCV (between 1996 and 2017) was released to ODNs, enabling ODNs to contact these patients to invite them for treatment. New interventions by ODNs to reach and encourage confirmatory testing in these patients are expected as a result of the re-engagement exercise and investment in finding patients.

Due to the complex commissioning and delivery environment across the patient pathway from prevention, testing and diagnosis, to referral and treatment, the ramping up of both case-finding and treatment services to reach elimination targets by 2030 is critically dependent on the capacity of a complex multi-disciplinary network of diverse clinical and other services (figure 1). In particular, case-finding will require commitments from NHSE, Local Government, community drug and alcohol services, primary care and health and justice to have the biggest impact.

Scope

This review includes interventions aimed at the groups at increased risk of HCV infection in England; PWID, prisoners, homeless people, migrants from higher prevalence countries and MSM.

As PWID are the major risk group for HCV infection in England the report begins by considering interventions aimed at PWID in drug treatment and pharmacies. It then reviews primary care interventions, which are aimed at several different population groups including PWID and migrants, followed by interventions aimed at prisoners, homeless populations and MSM and then reviews other interventions by setting. Care pathway interventions which take place across multiple settings, and psychosocial and care coordination interventions within HCV care are then considered separately, followed by a summary of cost analyses and economic evaluations.

UK studies are presented separately from overseas studies, as interventions are context and health-system specific and evidence from UK interventions are more likely to have direct applicability to the UK setting.

The review focusses on the evidence for specific interventions – the main types and settings of which are summarised in table 1. Soft system changes and adjustments to commissioning which may result in ‘quick wins’ through better implementation of strategies, which are also required to optimise the benefit from the range of elimination activities underway, are not considered here.

Figure 1. Commissioning pathway diagram (HCV Action 2018)

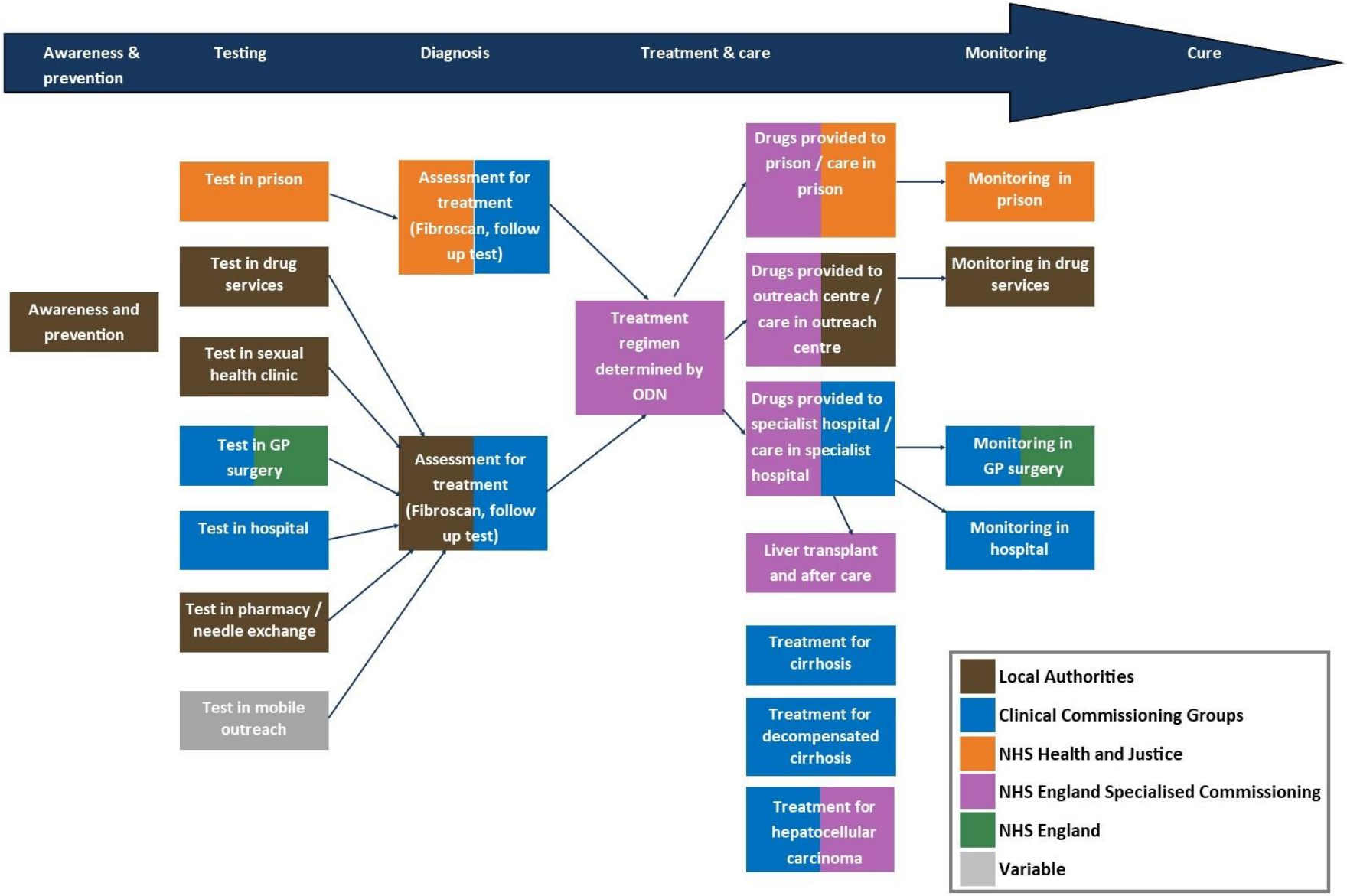

Table 1. Summary of main case finding and engagement in treatment intervention types

Intervention	Setting	Population targeted
Opt-out screening	Primary care, A&E, antenatal services, prisons	General population, prisons, A&E attendees, pregnant women, GP registered population
Electronic flagging of HCV diagnosed or at risk in health systems +/- invitation to testing or treatment	Primary or secondary care (GP, hospital, drug services)	PWID, migrants, past blood products recipients, positive for other BBV
Peer support and buddying	Drug services	PWID
POC and non-invasive testing (DBS)	Pharmacy, GP, drug services, community outreach, prison and probation	PWID accessing needle and syringe exchange, migrants
Dedicated and trained key worker/ BBV nurse support	Drug services, GP/other services in community	PWID
Brief interventions: assess risk and offer test and harm reduction advice or psychosocial support to access treatment	Drug services, GP, pharmacy	PWID
Inreach / outreach HCV treatment services in drug services, inreach in prisons	Community / prisons	PWID, prisoners
Health / prison / drug professional education and awareness raising	Primary care; drug service workers	GP registered population, PWID, prisoners
Patient education and awareness-raising campaigns	Primary care, drug services, secondary care	PWID, migrants, past blood products, positive for other BBV
Complex / multicomponent interventions and managed care	Primary care, drug services, secondary care	PWID, migrants, past blood products, positive for other BBV, any HCV infected
Financial incentives for treatment uptake/adherence	Primary care, drug services, secondary care	PWID, general HCV infected population

DBS – dried blood spot; CCG – clinical commissioning group; HCW – health care worker; IDPS – infectious diseases in pregnancy screening; LA – local authority; PHE – Public Health England; POC – point of care; PWID – people who inject drugs; NHSE – NHS England;

Methodology

Inclusion criteria

Studies were considered eligible for inclusion if they met the following criteria:

Population: people with or at risk of HCV, including but not restricted to PWID, prisoners, migrants, homeless people, and MSM.

Interventions to:

- increase uptake of testing and diagnosis for HCV
- improve linkage to care and/or (re)engagement in treatment for those diagnosed with HCV
- increase retention in treatment and treatment completion for those diagnosed with HCV

Comparison: a comparison group of participants allocated to no intervention or receiving care as usual. This includes historical comparisons and before and after interventions.

Outcomes: testing uptake, positivity, referral to treatment, treatment uptake, treatment adherence, treatment outcomes (treatment completion, SVR), cost effectiveness.

Studies from the UK, Australia, North America, and Western Europe are included. UK case studies and evaluations of interventions / service reports are included where they provide comparator data. Data from unpublished studies was used where available from conference abstracts and presentations.

A rapid evidence review methodology was used, with searches in publications databases and searching of reference lists supplemented with evidence received through contact networks and professional forums. Searches were conducted in Embase and Medline in March 2019, and reference lists from systematic reviews obtained through these searches were obtained (see Appendix 1 for search terms). A call for projects was put out through PHE Viral Hepatitis Leads Group and research networks. Contacts undertaking ongoing research shared preliminary results and information on study design. Data on service evaluations and case studies were also obtained through this route.

Risk of bias in individual studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins, Altman et al. 2011), and for non-randomised studies the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) assessment tool (Sterne, Hernán et al. 2016). Cost analyses and economic evaluations have not been assessed using a validated tool but represent a summary of

existing evidence. Tables are presented to summarise the the key characteristics and results of the included studies.

This report provides a summary of the evidence available which met the inclusion criteria at the time of the review. To keep up to date with the rapidly increasing body of evidence on interventions and research activity being generated as a result of the global hepatitis elimination agenda, horizon scanning is needed. Increased activity and new interventions are expected as part of the re-engagement exercise following the PHE historical laboratory diagnoses data release to ODNs, which will vary by ODN. Capturing and using emerging evidence from these interventions will be essential to translate evidence into effective action within the limited timeframe of the elimination goal. This report is being converted into a systematic review for peer reviewed publication to broaden reach.

Drug treatment services (DTS) interventions

Results presented here are mainly from a recent systematic review of interventions to increase HCV testing, linkage to care and treatment uptake among PWID (Bajis, Dore et al. 2017), and a review of interventions to improve the care continuum for viral hepatitis (Zhou, Fitzpatrick et al. 2016). Additional data are presented from UK case studies, service evaluations and more recently published research studies.

HCV testing in DTS

Two randomised (1 UK and 1 international), 5 non-randomised (3 UK and 2 international) studies and 2 UK case studies/service reports evaluated interventions to increase HCV testing in DTS (table 2).

In the UK

A UK randomised controlled trial (RCT) evaluated a HCV testing intervention which compared DBS testing to usual care involving venepuncture in 28 DTS and 6 prisons (Hickman, McDonald et al. 2008). In DTS significantly higher testing was demonstrated in intervention sites. However, only 9% of intervention patients were tested compared to 3% in control sites and there was considerable variability between sites, with the paired difference between intervention and control sites ranging from -0.5% to 65.2%.

A non-randomised UK pilot complex intervention in 3 DTS with 3 control sites aimed to increase engagement in HCV therapy (The Hepatitis C Awareness Through to Treatment (HepCATT) study) and demonstrated a significant increase in testing uptake associated with the intervention (interaction odds ratio (OR) 3.9 (95% CI 2.7–5.5, p<0.001),17 percentage-point increase in testing overall (95% CI 7-26) at intervention sites, compared to a 2 percentage point decrease (95% CI -8-+4) at control sites) (Harrison, Murray et al. 2019).This intervention had multiple components, with some variations between sites. All sites had a half-time HCV nurse facilitator to coordinate the intervention, DBS testing, staff training, use of IT systems to identify patients, actively contacting identified patients for testing, and increased communication with keyworkers of HCV positive clients and at-risk clients who needed to be tested.

A non-randomised study evaluated the impact of introducing DBS testing in non-statutory and community drug services and needle and syringe programes (NSP) alongside improved referral pathways (Abou-Saleh, Rice et al. 2013). Self-administered DBS testing was also offered as an option to some patients. The rate of testing

increased from 1.75 patients per 3 months prior to the intervention to 52 patients per 3 months after the intervention.

A non-randomised study evaluated the introduction of DBS testing in multiple settings including 11 DTS during Scotland's HCV Action Plan (McLeod, Weir et al. 2014). Testing in DTS increased from an average count of 67 per year in the 7 years before the action plan to 973 per year during the 5 years of the action plan, with anti-HCV positivity in those tested also increasing from 19% to 38%.

A case study of a service development in DTS in Bristol which employed a specialist hepatitis nurse and offered all PWID and MSM service users HCV testing at initial assessment and repeatedly afterwards if they initially refused testing and provided outreach testing reported that testing increased from 12% of eligible patients before the intervention to 95% in 2016 (Wolf and HCV Action 2016). No denominator data were available to assess statistical significance and no data on positivity were reported.

An evaluation of a programme of peer education and workforce development delivered in DTS in the South West of England indicated that an increased number of DBS tests were done in the month after peer education workshops had been held compared to the previous month. These services already had DBS infrastructure in place and no denominator data were available to assess what proportion of clients had been tested, nor were the longer term effects of the intervention assessed (The Centre for Public Innovation 2017).

International testing in DTS

A pilot RCT in Belgium evaluated an intervention combining formal and peer HCV education for DTS clients and off-site Fibroscan with transport support provided (Arain, De Sousa et al. 2016). Although this study had low numbers and was not adequately powered to detect a difference, a non-significant increase in HCV testing from 7% to 20% of participating clients was reported.

A non-randomised evaluation of an intervention in France to educate clients in harm reduction centres about their injecting practices found a non-significant decrease in self-reported testing in unadjusted analysis, but after adjusting for factors associated with HCV testing (crack and buprenorphine use) participants that had been exposed to the intervention at least once were more likely to report having been tested for HCV (adjusted OR 4.13 (95% CI 1.03-16.60)) (Roux, Rojas Castro et al. 2016).

A non-randomised evaluation of a US programme which added HCV & HBV testing to routine blood testing on intake to DTS and scheduled all patients to attend a 'healthy liver' educational session 3 to 4 weeks after intake reported that 98% of the 67% who attended the education session had been tested on intake, compared to 72% of clients

overall prior to the intervention. No data were provided on testing among those that had not attended the educational session, so the effect of the intervention on testing rates could not be evaluated (Hagedorn, Dieperink et al. 2007).

HCV linkage to care in DTS

Seven randomised studies (6 international and 1 UK) and 4 non-randomised studies (2 UK and 2 international) evaluated interventions to improve HCV linkage to care within DTS (table 3).

In the UK

A UK cluster RCT evaluated the impact of a nurse-initiated pathway onsite in drug treatment compared to the standard pathway of attending an offsite appointment before initiating PEG-IFN/RBV treatment (Lewis, Kunkel et al. 2016). The study found no difference in treatment initiation (10% vs 9%, p=0.53), adherence, or SVR (6% vs 4%).

HepCATT, the pilot HCV nurse-led complex intervention in 3 DTS with 3 control sites significantly increased engagement in treatment (interaction OR 29.2 (95% CI 11.9-71.8, p<0.001), referrals to hepatology (interaction OR 16.0 (95% CI 8.0-32.2)) and treatment initiation associated with the intervention (interaction OR 21.4 (95% CI 8.2-56.1, p<0.001)) (Harrison, Murray et al. 2019). Elements of this intervention which aimed to support engagement in treatment included streamlining referral pathways, peer support and direct interaction from the facilitator to encourage attendance at appointments and engagement with treatment.

A non-randomised study evaluated a multi-agency pathway intervention in Scotland which included nurse-led clinics in hospital and outreach clinics in DTS and prisons, along with interventions to encourage attendance by sending patients and referrers a letter if patients did not attend (Tait, McIntyre et al. 2010). An increased proportion of referrals came from DTS during the intervention, from 2.5% to 18.3% of all referrals, but the proportion of DTS eligible clients that were referred was not reported. Details of the programme's overall results are presented in the Care Pathway section.

International linkage to care in DTS

Four studies evaluated interventions to facilitate referrals to treatment:

A US RCT evaluated a care coordination intervention involving motivational interviewing, counselling and case management to facilitate referrals for patients receiving opioid substitution therapy (OST) in 2 methadone maintenance programmes (Masson, Delucchi et al. 2013). Attendance at an off-site HCV evaluation appointment

within 6 months of referral was significantly higher in the intervention group (65% vs 37% of anti-HCV positive patients, p<0.001).

The Belgian pilot RCT combining formal and peer HCV education for DTS clients and off-site Fibroscan to increase testing and treatment did not report on positivity but reported that 1 of the 5 intervention group patients who were tested were referred to the hepatologist and started treatment, while none of the 2 tested in the control group did (Arain, De Sousa et al. 2016).

A non-randomised French study evaluated onsite HCV care provided by a multidisciplinary team, which included Fibroscan, psychiatric evaluation and motivational interviewing to encourage treatment initiation (Moussalli, Delaquaize et al. 2010). A higher proportion of HCV RNA positive clients entered treatment compared to before the intervention (38% vs 2%, p<0.001) and 43% of these achieved SVR (no comparator data).

The non-randomised study of a US programme which added HCV & HBV testing to routine blood testing on intake to drug treatment and scheduled all patients to attend a ‘healthy liver’ educational session 3 to 4 weeks after intake, followed by an individual nurse consultation and referral if needed reported that 100% of new diagnoses were referred to hepatology during the intervention compared to 50% before the intervention, and 78% of referrals initiated treatment (Hagedorn, Dieperink et al. 2007).

One study evaluated a multidisciplinary care coordination intervention to provide treatment to patients in a hospital that had co-located drug treatment and HCV care:

A non-randomised Italian study evaluated a multidisciplinary care coordination intervention for OST patients receiving PEG-IFN/RBV treatment (Curcio, Di Martino et al. 2010). The multidisciplinary team included drug treatment, hepatology, mental health and social workers. Intervention patients were given weekly counselling, 3-monthly psychiatric evaluation, and allocated a case manager to communicate with other professionals about their care. Intervention patients had higher treatment adherence (93% vs 41%, significance not reported) and higher SVR (68% vs 34%, significance not reported). Included patients had a mixture of genotype 1 and 3, stratified analysis by genotype was not reported.

Four studies evaluated the provision of directly observed HCV treatment (DOT) in DTS:

A randomised US pilot compared DOT with pegylated interferon and ribavirin (PEG-IFN/RBV) provided onsite to OST patients in a methadone clinic to self-administered treatment (SAT) at home (Bonkovsky, Tice et al. 2008). This study found no significant differences in treatment completion (83% in DOT patients vs 71% in SAT, p=0.3) or SVR (54% vs 33% respectively) between the 2 groups, with an adjusted analysis finding

that SVR was not significantly associated with being in the DOT group (OR 3.27, 95% CI 0.90-11.91, p=0.073).

A US RCT compared modified DOT (mDOT) (PEG-IFN/RBV) provided to OST patients in a methadone maintenance programme with an onsite HCV clinic to treatment as usual (Litwin, Arnsten et al. 2011). Both arms received weekly IFN injections onsite, the mDOT arm took their RBV daily onsite while the control arm self-administered this at home. RBV pill count adherence at 12 weeks was higher in the intervention group (88% vs 80%, p=0.02), but there was no significant difference in SVR (44% vs 40%, p=NS), which was attributed to both arms receving the same weekly provider-administered IFN injections.

A US pilot RCT compared mDOT (PEG-IFN/RBV) provided onsite to OST patients in a methadone maintenance programme to SAT in tertiary care (Bruce, Eiserman et al. 2012). Patients randomised to mDOT received a morning dose of RBV along with their methadone dose, and were given an evening dose to self-administer 12 hours later. If they earned take-home methadone doses then they would be given doses of RBV to take home. PEG-IFN was administered weekly by a nurse or other health worker. Patients in the SAT arm were taught to self-administer their PEG-IFN and RBV doses at the Liver Centre and continued to receive their methadone separately at the methadone maintenance centre. This study was not powered to demonstrate a statistical difference, however 100% of patients randomised to receiving mDOT started treatment, compared to 44% patients receiving SAT. 50% of intervention patients completed treatment and achieved SVR, whereas only 11% of the control group (1 patient, who had not completed treatment) achieved SVR.

A US RCT compared DOT, a group medical visit, and treatment as usual for OST patients receiving DAA treatment onsite in methadone maintenance (Litwin, Agyemang et al. 2017). Of 136 patients who had reached 12 weeks after the end of treatment SVR was higher in the DOT (98%) and group medical visit (93%) groups than the control (88%), but the difference was not significant and rates were high in all groups.

One study evaluated an education intervention to improve treatment adherence:

A non-randomised controlled trial evaluated the impact of an educational intervention for patients in OST receiving PEG-IFN/RBV treatment (Reimer, Schmidt et al. 2013). Univariate analysis showed no significant difference in treatment completion (OR 1.66, 95% CI 0.82-3.36, p=0.156) or SVR (OR 1.18, 95% CI 0.63-2.19, p=0.613) and this was also the case in adjusted analysis (OR 0.05, 95% CI 0.01-33.95, p=0.370 and OR 0.01, 95% CI 0.01-7.77, p=0.183 respectively). However, among genotype 1 and 4 patients who had attended at least 5 education sessions the differences were significant, suggesting that attendance supported continuation of treatment for this longer duration (48 weeks) treatment.

One study compared provision of DAA treatment in DTS for NSP patients to those receiving OST:

A non-randomised US study provided DAA treatment for PWID engaged in OST and those enrolled through NSP and compared both to a community standard of patients (conference abstract, interim results (Seaman, Witkowska et al. 2018)). Patients in the NSP arm had lower enrolment into the study than those in OST (20/25 vs 25/25) and lower treatment adherence (65% vs 92%). Patients in the OST arm had SVR rates that were similar to the community standard (89% vs 94%), whereas this was lower for patients recruited through NSP (59%, P<0.001).

One randomised US study evaluated the impact of financial incentives and peer mentors on treatment uptake:

A conference presentation provided interim results from a US RCT evaluating the impact of cash incentives or peer mentors to improve uptake and completion of DAA HCV treatment among HIV coinfected PWID (Sulkowski, Ward et al. 2017). Cash incentives started at $10 and increased by $5 each week contingent on attendance, up to a maximum of $220. Peer mentors were HIV-coinfected patients who had been cured of HCV, who contacted patients by phone and in person to engage in structured interactions. Treatment uptake was significantly higher in the peer mentor group (88%, p=0.01) and non-significantly higher in the cash incentive group (72%, p>0.05) compared to usual care (66%). Treatment adherence was not reported, and SVR was 90% overall for patients who had reached 12 weeks after the end of treatment.

Risk of bias

All 10 randomised studies were at high risk of performance bias, as it was not possible to blind participating staff to the interventions. Other than the UK DBS testing RCT and the UK nurse-initiated treatment pathway which were cluster randomised, the randomised studies were at high risk of recruiting a non-representative group due to consent processes, such that the recruited group was likely to include those more willing to engage with services. The DBS testing RCT was at unclear risk of attrition bias as the same denominator was used for the intervention and baseline periods (Hickman, McDonald et al. 2008). The nurse-led treatment initiation pathway was at unclear risk of bias in the randomisation process, moderate risk of measurement bias in assessing adherence but low risk in assessing SVR, and low risk of bias in other domains (Lewis, Kunkel et al. 2016). Two RCTs evaluating linkage to care were pilots and were not powered to detect a difference in outcomes (Bruce, Eiserman et al. 2012, Arain, De Sousa et al. 2016), and 1 of these, the Belgian pilot RCT of an educational intervention and Fibroscan was at high risk of detection bias, as outcome measures were obtained from reports from staff, who were not blinded to the intervention (Arain, De Sousa et al. 2016). The US RCT which evaluated a care coordination intervention was at low risk of

detection bias and attrition and at unclear risk of reporting bias (Masson, Delucchi et al. 2013). The randomised US study which evaluated DOT vs SAT in OST patients was at unclear risk of selection bias as randomisation was not described, and it was also unclear how adherence was measured, but there was low risk of bias in measurement of SVR and low risk of reporting and attrition bias (Bonkovsky, Tice et al. 2008). Three RCTs were conference abstracts only and so are at unclear risk, as methods were not fully described (Litwin, Arnsten et al. 2011, Litwin, Agyemang et al. 2017, Sulkowski, Ward et al. 2017).

Most of the non-randomised studies had at least 1 domain at critical risk of bias and were at critical risk of bias overall. Most did not adjust for or did not report confounding factors which could affect the outcome.Two were case studies which provided very limited comparator data on which to assess outcomes and were at critical risk of bias (Wolf and HCV Action 2016, The Centre for Public Innovation 2017). Two studies were at critical risk of time-varying confounding and serious risk of deviation from the intended interventions due to their long follow up periods (Tait, McIntyre et al. 2010, McLeod, Weir et al. 2014). One was at critical risk of bais due to deviation from the intended intervention as it introduced DBS testing along with an improved referral pathway, at critical risk of bias in selection of the reported result and at unclear risk in several other domains (Abou-Saleh, Rice et al. 2013). Several studies were at critical risk of selection bias, either due to selection criteria which led to an unrepresentative group of participants (as for the randomised studies) or to unclear descriptions of how participants were recruited to the study. Two studies which evaluated the effect of educational sessions analysed results as a proportion of those who had attended an educational session, rather than of all participants (Hagedorn, Dieperink et al. 2007, Roux, Rojas Castro et al. 2016). One study was a conference abstract/poster only which limited the risk of bias assessment, but similar to most other studies did not adjust for confounding factors, and was at serious risk of bias in selection of the reported result due to the limited data presented (Seaman, Witkowska et al. 2018). The non-randomised study of psychoeducation to improve adherence reported an adjusted analysis and was at moderate risk of bias overall (Reimer, Schmidt et al. 2013). The non-randomised study of multidisciplinary care for OST patients was at critical risk of confounding and at moderate risk of bias due to deviations from the intended intervention due to the complex nature of the intervention (Curcio, Di Martino et al. 2010).

Qualitative studies

Two qualitative studies were undertaken alongside the HepCATT UK nurse-led complex intervention. In-depth interviews, focus groups and observations were undertaken with 96 participants, comprising drug service and intervention providers and clients with an injecting history (Bonnington and Harris 2017, Harris, Bonnington et al. 2018).

One study explored the success of the intervention as a whole and its potential for transfer (Harris, Bonnington et al. 2018). Testing and treatment barriers identified at baseline included limited HCV knowledge, fear of diagnosis and treatment, precarious living circumstances and service-specific obstacles perceived by clients, including lack of availability of testing and of DAA treatment, and a lack of interest from GPs in them and in HCV in general. The nurse facilitator was seen as key to the intervention's success through implementing the intervention and innovating to respond to different clients' needs and site contexts. Multiple interrelated factors were perceived to help engagement in treatment, including intervention timeliness, improved communication structures, personalised care, streamlined testing and treatment pathways, and peer support.

The other study explored the peer support component of the intervention, which was set up by the Hepatitis C Trust (Bonnington and Harris 2017). Tensions in the role of peer/buddy were identified; while clients expected a peer/buddy to be someone who would 'just be there' and listen and who they could relate to, organisational expectations of boundaries and policies for who could become a peer/buddy were in tension with this. The recovery model was perceived as influencing the selection of 'recovery champions' as peers, who may be unrepresentative of many current PWID. Low visibility and poor integration of peers within the service was also identified, which affected opportunities for peers to relate to and build trust with clients. The authors recommended that peers should be integrated into the clinical team for HCV rather than kept as a separate service, and that organisational barriers should be lessened in order to facilitate acceptance of peers and their interactions with clients.

Summary

Testing

DBS testing among PWID in DTS is well-established and widely adopted and is supported by the evidence, but is insufficient in itself to obtain high rates of testing:

- there is moderate evidence that nurse-led complex interventions to coordinate DBS testing within DTS can increase HCV testing
- there is suggestive evidence that educational interventions aimed at drug service users increase testing.

None of the published studies include economic evaluations – the publication of HepCATT economic evaluation is awaited.

Linkage to care

There is moderate evidence that nurse-facilitated referrals (linked to onsite testing) can increase referrals to offsite treatment:

- there is moderate evidence that care coordination interventions in DTS involving a multidisciplinary approach and multiple components such as psychosocial support, and onsite treatment assessement and investigations (e.g. staging of liver disease with Fibroscan) can increase engagement in treatment
- there is moderate evidence that onsite HCV treatment in DTC has successful outcomes for OST patients, particularly when DAAs are used, but a lack of evidence on whether this increases treatment uptake compared to offsite care
- there is suggestive evidence that PWID engaged through needle exchange can achieve good levels of SVR with DAA treatment, although they have poorer follow up and SVR than those engaged in OST
- there is mixed evidence on whether DOT improves treatment adherence, and no evidence of a significant impact on SVR (both PEG-IFN/RBV and DAA studies)
- there is suggestive evidence that peer mentors help increase treatment initiation
- there is suggestive evidence that educational interventions may improve adherence to longer duration treatment, but no studies from the DAA era

None of the published studies include economic evaluations; the publication of the HepCATT economic evaluation is awaited.There are currently no published evaluations of onsite treatment in DTS in the UK, for example, a fully integrated pathway in a one-stop shop but it is likely that these are taking place.

Qualitative data from HepCATT

Engagement in treatment was helped by multiple interrelated factors, including intervention timeliness, improved communication structures, personalised care, streamlined testing and treatment pathways and peer support:

- the role of nurse facilitator to implement and innovate the intervention was perceived to be key to its success.
- peer support requires careful implementation; integration with HCV clinical team and a reduction of organisational barriers are required to facilitate the peer relationship

Pharmacy interventions for PWID

HCV testing within pharmacies for PWID

One randomised and 2 non-randomised studies evaluated testing interventions in community pharmacies which provided OST or OST and NSP, all were UK based (table 4). Two of the studies (1 randomised and 1 non-randomised) were aimed at patients receiving OST in the pharmacies, and 1 non-randomised study took place in NSP pharmacies and could be accessed by patients attending for NSP, OST or those who self-referred as a result of an awareness campaign.

In the UK

A Scottish RCT evaluated the feasibility of providing a full pharmacist-led pathway for OST patients, comprising DBS HCV testing and onsite DOT in 4 community pharmacies (Radley, Tait et al. 2017). Both arms provided DBS testing and a higher proportion of eligible patients were tested in intervention pharmacies (36% vs 24%, $p<0.003$), which was attributed to patients' awareness that they could be treated onsite if they were diagnosed.

A non-randomised Scottish quasi-experimental study provided DBS testing for OST patients in 6 community pharmacies and compared this to testing received elsewhere by OST patients who attended non-intervention pharmacies (Radley, Melville et al. 2017). A significantly higher proportion of eligible patients were tested at intervention sites compared to those who attended non-intervention pharmacies (30% vs 13%, OR 2.3 (95% CI 1.5-3.4) $p\leq0.0001$).

A pilot in the Isle of Wight trained pharmacists in 22 community pharmacies to offer DBS testing (Buchanan, Hassan-Hicks et al. 2016). Testing was offered to patients attending for NSP and OST, and to those who self-referred in response to an island-wide advertising campaign. Over 9 months, 88 DBS tests were done in the pharmacies of which 39 (44%) were for PWID, compared to 34 PWID tested in the island drug service. Of the 39 PWID tested in pharmacies, 17 were not engaged with the DTS and were significantly less likely to have been previously tested (77% vs. 41%, $p=0.04$).

HCV linkage to care for PWID in pharmacies

One randomised and 1 non-randomised study evaluated linkage to care in community pharmacies, both were UK based (table 5). One was in an OST-prescribing pharmacy and the other in a pharmacy which provided OST and NSP.

In the UK

In the Scottish RCT which evaluated the feasibility of providing a full pharmacist-led HCV treatment pathway in 4 community pharmacies (Radley, Tait et al. 2017) a significantly higher proportion of newly diagnosed anti-HCV positive patients attended for assessment appointments in intervention pharmacies than in control pharmacies (77% vs 27%, $p<0.002$). Treatment uptake was limited by the fact that only genotype 1 patients could be treated in the pharmacies – 7 out of 10 patients who attended for follow up blood tests were genotype 3 and were unable to be treated on this pathway. The remaining 3 patients all completed treatment. The study estimated that costs for the pharmacy treatment pathway were £695 less per patient than in the traditional setting.

In the Isle of Wight pilot, hepatologists attended intervention pharmacies for a point of diagnosis consultation for patients diagnosed positive (Buchanan, Hassan-Hicks et al. 2016). 100% of the 6 patients diagnosed HCV positive in pharmacies attended a point of diagnosis consultation, had baseline investigations and remained engaged in treatment at the time of the evaluation, whereas 0 patients referred from drug treatment had yet been seen by hepatology.

Risk of bias

The randomised study was at serious risk of performance bias, as participating pharmacies could not be blinded to the intervention (Radley, Tait et al. 2017). This study had biased selection of participants to treatment; only genotype 1 patients were recruited as only they could be treated on the pathway, but there was low risk of selection bias in patients recruited to testing, and low risk of bias in other domains.

The non-randomised studies were both at critical risk of confounding and therefore at critical risk of bias overall, as they did not adjust for confounding factors which could affect the outcome. The Scottish non-randomised study was at serious risk of selection bias as intervention clients were those notified as having no previous HCV test, whereas the control group included all OST prescribed patients attending the pharmacies (Radley, Melville et al. 2017). The Isle of Wight pilot did not provide denominator data for testing, so it was not possible to make a direct comparison of testing rates (Buchanan, Hassan-Hicks et al. 2016).

Qualitative studies

Both Scottish pharmacy studies undertook qualitative process evaluations through semi-structured interviews with staff and patients (Radley, Melville et al. 2017, Radley, Tait et al. 2017). Patients had positive perceptions of pharmacy testing and treatment, valued their relationships with pharmacy staff, and perceived that travelling to hospital would be a barrier to attending clinics due to the costs involved. Staff felt that strong

leadership and the involvement of the whole team were essential for successful implementation of interventions. Staff stated that it often took time for patients to come around to the idea of being tested and entering treatment, and positive relationships with clients were a key factor for acceptance of testing and treatment. The need for off-site phlebotomy for those found anti-HCV positive was recognised as a weakness of the pharmacist-led testing and treatment pathway.

Summary

Testing

There is moderate evidence that provision of DBS testing in pharmacies can significantly increase testing and achieve moderate rates of testing among OST patients:

- there is moderate evidence that providing an onsite treatment pathway within a pharmacy also increased testing
- there is suggestive evidence that providing DBS testing in a needle exchange pharmacy accessed patients who were not in drug treatment and were less likely to have been previously tested

A number of pharmacy intervention studies are ongoing and results are awaited.

Linkage to care

There is moderate evidence that providing onsite treatment or hepatologist consultations in pharmacies increased attendance for initial assessment appointments:

- there is limited evidence of an effect on treatment uptake and completion – more robust data are needed
- at the time of the DOT study the available DAAs could not treat genotype 3 – further studies and evaluations of providing onsite treatment in pharmacies using newer DAAs are needed

A number of pharmacy interventions are ongoing and results are awaited.

Qualitative

Strengths of pharmacies in providing care for PWID were identified as positive relationships with PWID and their location in the community, which reduced the barriers faced by PWID in travelling to hospital appointments.

Strong leadership and the involvement of the whole team were perceived by staff to be important for the success of interventions.

Primary care interventions

HCV testing in primary care

Four randomised studies (2 UK and 2 international), 26 non-randomised studies (3 UK and 23 international) and a UK service evaluation were included (table 6). In 2012, in response to a high prevalence of HCV infection identified among people in the 1945 to 1965 birth cohort, US Centers for Disease Control and Prevention (CDC) published guidelines supporting one-time HCV screening for all persons born 1945 to 1965, as this was estimated to be more cost-effective than risk-based screening (McGarry, Pawar et al. 2012, Rein, Smith et al. 2012, Moyer 2013). As a result, there is a large body of research from the US to support the implementation of these guidelines in primary care, which is summarised in the section on international studies.

In the UK

A cluster RCT evaluated a complex intervention to increase HCV case-finding and treatment in 22 intervention and 23 control GP practices (HepCATT in primary care (Roberts, Macleod et al. 2019)). The intervention consisted of staff HCV training within practices, raising patient awareness through posters and leaflets, and identifying at-risk patients to be invited for testing using an algorithm which searched the practice electronic medical records (EMR), and also flagged these patients for opportunistic testing if they attended a consultation. In control practices opportunistic HCV testing was undertaken as usual, with the electronic algorithm run retrospectively for comparison purposes. Testing in intervention practices increased from 5% to 16%, with a higher rate of testing in intervention practices than controls (adjusted risk ratio 1.59 (95% CI 1.18-2.09, p=0.002)). Anti-HCV positivity among those tested in intervention practices was slightly higher in intervention than control practices (6.2% vs 4.4%, p = 0.088).

A cluster RCT evaluated an intervention to increase HBV and HCV testing for migrants in 50 intervention and 8 control GP practices (HepFREE (Flanagan, Kunkel et al. 2018)). GPs were incentivised for testing by being paid £500 to set up EMR searches to identify patients, and £25 for each signed consent form returned. Intervention GPs were supported by a dedicated clinician (3 days a week over 50 practices). Patients were invited for testing by letter. In control practices, GPs were given a teaching session on viral hepatitis and told to test all registered migrant patients. Testing was significantly higher in intervention practices (20% vs 2%, p=0.01).

A non-randomised UK study compared 3 approaches to increase HBV and HCV testing for Pakistani/British Pakistani patients: (i) 5,000 leaflets were distributed to mosques advising patients to attend their GP for testing, (ii) opportunistic testing when patients attended GP appointments, (iii) 'opt-out' testing, where patients were contacted by letter and phone to invite them to attend the GP for testing (Lewis, Burke et al. 2011). No patients responded to the leaflets, 2% of patients were tested under the opportunistic approach, and 20% were tested in the 'opt-out' strategy ($p<0.0001$).

A non-randomised evaluation of an intervention in 1 GP practice in Scotland with a comparator practice offered opportunistic testing to patients aged 30 to 54 who attended GP appointments (Anderson, Mandeville et al. 2009). Testing was higher in the intervention practice, with 20% of eligible patients who attended tested, whereas none in the control practice were. The authors noted that case yield would have increased from 13% (15/117) to 83% (14/17) if only patients who identified as former PWID had been tested, with the loss of only 1 case.

Another non-randomised Scottish intervention used EMR to identify former PWID aged 30 to 54 for opportunistic testing during GP consultations (Cullen, Hutchinson et al. 2012). Testing of patients within the 30 to 54 age group was 3-times higher in intervention practices than control practices (0.8% vs 0.3%, PWID status of controls unknown) and positivity rates were also higher in the intervention group (70% vs 22% anti-HCV).

A pilot service development in Leeds aimed to offer opt-out BBV (HBV, HCV and HIV) testing to all newly registering patients at 29 GP practices (Leeds City Council Sexual Health Team, Elton John Aids Foundation et al. 2017). 18% of eligible patients were tested during the pilot, ranging from 0-67% in individual GP practices, representing a 250% increase in testing compared to 8 months prior to the intervention. Although overall positivity rates were low, at 0.29% HIV, 3% HBV and 0.8% HCV the pilot was assessed to be cost effective, with an estimated cost of £1,060 per diagnosis. The variable uptake of testing between practices was investigated and attributed to insufficient involvement of some practices in the pilot, some staff being unaware of the pilot due to high staff turnover, and the variable implementation of opt-out testing in places where it was offered.

International HCV testing

17 US studies, including 2 cluster RCTs evaluated the implementation of EMR best practice alerts (BPA) to remind staff to screen patients in the 1945-1965 birth cohort when they attended appointments (Shahnazarian, Karu et al. 2015, Tzarnas, Allen et al. 2015, Gemelas, Locker et al. 2016, Goel, Sanchez et al. 2016, Thuluvath, Feldman et al. 2016, Brady, Liffmann et al. 2017, Castrejon, Chew et al. 2017, de la Torre, Castaneda et al. 2017, Federman, Kil et al. 2017, Golden, Duchin et al. 2017, Karliner, Kobashi et al. 2017, Konerman, Thomson et al. 2017, Jain, Sanders et al. 2018, MacLean, Berger et al.

2018, Magaldi, Brown et al. 2018, Soo, Mukhtar et al. 2018, Teply, Mukherjee et al. 2018). All studies reported substantially increased testing rates in the birth cohort, and most reported small decreases in anti-HCV positivity in those tested.

Of the randomised studies, 1 was a cluster RCT in 10 hospital and community based primary care practices (Federman, Kil et al. 2017). Staff in both study arms had a brief education session introducing the CDC testing recommendations, and staff were blinded to the intervention. Intervention sites had increased testing (from 2% to 20% of eligible patient visits ($p< 0.0001$)) and higher positivity (from 1.1% to 3.1% of unique patients ($p<0.0001$)).

The other cluster RCT took place in 10 primary care practices and included an automatic test order with the EMR alert (Brady, Liffmann et al. 2017) and had significantly increased testing at intervention sites (from 4% to 31% of eligible patients, adjusted risk ratio (aRR) 13.2, 95% CI 3.5-48.6). This study also conducted RCTs of 2 other interventions in different sites; repeated mailing of eligible patients, and patient solicitation by approaching eligible patients after their medical visit. Both significantly increased testing, with patient solicitation having the largest effect of the 3 interventions (64% in intervention sites compared to 2%, aRR 32.9, 95% CI 19.3-56.1), while repeated mailing had the smallest (27% vs 1%, aRR 19.2, 95% CI 9.7-38.2).

The non-randomised US EMR studies were all before/after studies reporting the effect of the EMR intervention compared to a baseline period. Most included other co-interventions such as staff education, awareness raising posters, discussions with leadership, and workflow redesign to incorporate testing, while a few implemented EMR alerts alone. Reported testing rates after implementation range from 20% (baseline 7% (Tzarnas, Allen et al. 2015)) to over 70% in several studies, with the highest testing rate being seen in 1 study which implemented an automated test order as no consent for testing was needed under state law (Shahnazarian, Karu et al. 2015). One study conducted before the CDC recommendations came in assessed the impact of reminder stickers on paper notes rather than EMR alerts and also found an increase in testing associated with the intervention, from 6% before the intervention to 10% when birth cohort patients were flagged, and 13% when staff were reminded to test patients with risk factors ($p<0.001$)(Litwin, Smith et al. 2012).

Four non-randomised US studies assessed the effect of staff education alone to improve knowledge of the CDC guidelines and of HCV. All interventions provided training on a regular basis within existing clinical staff meetings, with or without additional awareness raising through posters in work areas and leaflets for patients. One study with 3 intervention and 4 control sites conducted continuous audit alongside staff education; testing of eligible patients increased from 6% to 18% in intervention sites, which was significantly higher than the increase in control sites from 5% to 10% ($p<0.001$) (Nitsche, Miller et al. 2018). The other 3 studies were before/after designs.

Two reported increased testing rates from 1% to 10% (Wong, Abdelqader et al. 2017) and 7% to 13% (Madhani, Aamar et al. 2017). Another reported screening rates increased from 46% to 69% (p<0.001) (Murphy, Triplett et al. 2016), however this was a conference abstract and it is unclear whether this refers to testing or screening assessment.

Outside the US, an Irish cluster RCT evaluated an intervention aimed at improving HCV care for current or former PWID in primary care by supporting staff in methadone-prescribing GP practices with the implementation of clinical guidelines (Cullen, Stanley et al. 2006). A liaison nurse worked across 13 practices to support and train staff, encourage the uptake of the guidelines and liaise with specialist hepatology and addiction treatment services, as well as holding individual patient consultations. HCV testing for OST patients significantly increased after 6 months of the intervention (34% of patients compared to 26% before, p=0.02).

A non-randomised controlled intervention study in the Netherlands evaluated the effect of a support programme for primary care staff as a supplement to a national public awareness campaign (Helsper, van Essen et al. 2010). HCV testing increased more in the intervention region than the control region (proportional increase in number of anti-HCV tests in intervention region 2.2 (95% CI 1.5-3.3) times as high as in control region), with no significant change in positivity.

HCV linkage to care within primary care

Four randomised studies (2 UK and 2 international) and 9 non-randomised studies (all international) evaluated linkage to care in primary care (table 7). Several of the testing studies reported on linkage to care but without comparator data, and so are not included here. Only 1 intervention was specifically aimed at linkage to care for PWID, an Irish RCT also described in the testing section.

In the UK

The cluster RCT evaluating a complex intervention to increase HCV case-finding and treatment using a risk-based algorithm in 22 intervention and 23 control GP practices (HepCATT (Roberts, Macleod et al. 2019)) found strong evidence that the intervention increased the number of referrals (aRR 5.78, 95% CI 1.55-21.61), although the absolute difference was small – 46% of 43 PCR positive patients (15 per 10,000 high-risk patients) referred in intervention practices, 23% of 13 PCR positive patients (3 per 10,000 high-risk patients) referred in control practices.

The cluster RCT of incentivised screening for migrants in 50 intervention and 8 control GP practices evaluated the impact of treating patients diagnosed with HBV and/or HCV in the study in the community, compared to standard hospital-based care (HepFREE

(Flanagan, Kunkel et al. 2018)). Patients were recruited into the study if they attended an initial hospital referral appointment after diagnosis. 68% of patients declined to be randomised at this point as they did not want to defer treatment until community care was available, and a further 8% did not attend for treatment. Among those who consented and attended the intervention made no impact on treatment uptake, with 100% adherence to therapy among HCV patients in both arms.

International linkage to care within primary care

The Irish RCT of supporting staff in a methadone-prescribing GP practices with clinical guidelines on HCV management reported a non-significant increase in referrals; from 32% to 60% of OST patients diagnosed anti-HCV positive, a significant increase in hepatology clinic attendance (from 22% to 51%, p=0.04), and a non-significant increase in treatment initiation (3% to 7%, p=0.2)(Cullen, Stanley et al. 2006).

Two of the non-randomised US EMR and staff education birth cohort interventions assessed linkage to care associated with the intervention:

One implemented an EMR automated test order with reflex RNA testing along with the EMR alert staff education (Magaldi, Brown et al. 2018). Interim results were presented as patients were still progressing through the care pathway, but showed that RNA testing of anti-HCV positive patients had increased to almost 100% (358 out og 359 patients) compared to 81% before the intervention. A similar proportion of patients attended their first appointment (76% vs 76%) but treatment initiation was higher after implementation of the intervention (33% vs 14%, no significance reported).

The other consisted of an EMR best practice alert and staff education ((Jain, Sanders et al. 2018). RNA testing significantly increased from 54% to 75% of anti-HCV positive patients (aOR 2.38, 95% CI 1.95-2.90) but there was no significant increase in the proportion of RNA positives who were linked to care (45% vs 43%, aOR 1.61, 95% CI 0.88-1.54).

Six studies evaluated the provision of HCV treatment in primary care:

An Australian RCT evaluated the impact on the care cascade of prescribing DAAs in primary care compared to tertiary care (Wade, Doyle et al. 2018). More patients completed assessment in the intervention arm (87% vs 64%, significance not reported) and of patients assessed as eligible, a significantly higher proportion initiated treatment (75% vs 34% p<0.001), however SVR was not significantly higher in the intervention group (47% vs 30% p=0.065). 48% of recruited patients were active PWID, and for this group the difference in treatment uptake was greater than for the overall cohort (72% in primary care compared to 26% in tertiary care).

A non-randomised Australian study evaluated an intervention to support GPs to prescribe DAAs in primary care by creating a pathway to refer patients for remote consultation before prescribing, a requirement at that time in Australia for GPs not experienced in HCV management (Wade, McCormack et al. 2018). GPs initiated treatment for 40% of anti-HCV positive patients during the first year of the intervention, compared to 8% before. DAAs were available the quarter before the intervention was launched and in this quarter GPs initiated treatment for 12 patients, compared to an average of 45 per quarter after the launch. 73% of patients eligible for assessment of SVR at the time of the study had achieved SVR, the rest were lost to follow up.

A non-randomised US study evaluated a telementoring intervention to support primary care providers in underserved areas with no previous experience of providing HCV treatment to deliver HCV care (PEG-IFN/RBV) through Project ECHO (Extension for Community Healthcare Outcomes (Arora, Kalishman et al. 2010, Arora, Thornton et al. 2011)). Primary care providers attended weekly HCV video- or teleconferences with specialists from hepatology, infectious diseases, psychiatry and pharmacology and were also given short educational presentations by experts. SVR was 58% in intervention sites and not significantly different from 58% in the state secondary care clinic, which met the study aims of demonstrating non-inferior care.

A non-randomised Australian study initiated telementoring through the Project ECHO model to support primary care and community clinicians, including in those in drug services, to prescribe DAA treatment, and compared outcomes to treatment in tertiary care (Mohsen, Chan et al. 2018). Telementoring provided access to a multidisciplinary team, including a hepatologist, gastroenterology advanced trainee, clinic nurse consultant, pharmacist, administrative assistant and a social worker. Intervention patients were more commonly substance misusers (44% vs 17%, $p<0.0001$), including active PWID (32% vs 12%, $p=0.001$). A similar proportion of referred patients intitiated treatment in both arms (78% vs 81%), and SVR was also similar (60% vs 67%), despite the different patient group intake.

A non-randomised US study evaluated a state-wide community-based testing and treatment programme in over 40 sites and compared the cascade of care in community sites to tertiary care (Franco, Galbraith et al. 2018). Rates of viral load confirmation were lower in community sites (57% vs 72% of anti-HCV positives confirmed RNA+, $p<0.001$), but treatment uptake was similar (29% vs 29% of RNA positives, $p=0.97$). Of those with SVR data available, a similar proportion achieved SVR (95% in community sites vs 97% in tertiary care, $p=0.87$), however a greater proportion of patients were lost to follow up in the intervention arm (87% vs 66% lost to follow up).

A non-randomised US study compared a primary care treatment pathway using a patient navigator in a health centre for formerly incarcerated individuals with referral to tertiary care (Fox, Hawks et al. 2015). A greater proportion of referrals initiated were

completed in the intervention pathway (73% vs 33% of those referred completed, p=0.03) but there were no significant differences in treatment uptake (18% vs 8% of those referred, p=NS) or SVR (9% vs 8% of those referred, p=NS).

One study evaluated the impact of quality improvement interventions to increase RNA testing:

A non-randomised US study evaluated quality improvement interventions to improve the proportion of patients receiving timely RNA testing after receiving positive anti-HCV results (Hirsch, Lawrence et al. 2014). Phase 1 was establishing RNA testing at outpatient clinics and establishing a monitoring database for HCV patients. Phase 2 was implementing a reflex RNA testing policy, and phase 3 was assembling an improvement team to investigate and address continued failures in reflex testing. Each phase led to a significant increase in the proportion of patients receiving timely RNA testing, from 45% at baseline to 68% in phase 1, 96% in phase 2, and 100% in phase 3 ($p<0.001$ for each phase).

One study assessed the effect of POC testing on linkage to care for migrants:

A non-randomised Netherlands study compared the impact on linkage to care of community HCV and HBV testing for Asian (majority Chinese) migrants using POC tests compared to community venous sampling (Ho, Michielsen et al. 2018). HCV positivity was low in this study and linkage to care was reported for HBV and HCV cases together (40 HBV and 1 HCV positive cases). Patients tested on the POC protocol were more likely to be linked to care (86% vs 34% of HBV and HCV positive patients, p=0.02), and costs were also lower on this arm (€25.5 vs €54.0 per person screened).

Risk of bias

One US RCT of using EMR best practice reminders was at moderate risk of confounding due to differences in practice characteristics which were not adjusted for, and at low risk in other domains (Federman, Kil et al. 2017). All other RCTs were at high risk of performance bias as staff were not blinded to the interventions. The other US testing RCT was at unclear risk of detection and attrition bias as it was not clear how data were collected or how missing data were dealt with (Brady, Liffmann et al. 2017). The UK RCTs were at low risk in domains other than performance bias in their evaluation of testing interventions (Flanagan, Kunkel et al. 2018, Roberts, Macleod et al. 2019), however the evaluation of community based treatment for migrants was at critical risk of selection bias, as 68% of patients declined to be randomised to the study so recruited participants were unlikely to be representative of the cohort of eligible patients (Flanagan, Kunkel et al. 2018). The Irish RCT was at unclear risk of bias due to allocation concealment, and low risk in other domains (Cullen, Stanley et al. 2006). The

Australian RCT of providing DAAs in primary care was a conference abstract and poster and at unclear risk in several domains (Wade, Doyle et al. 2018).

Almost all of the non-randomised studies were at critical risk of bias from confounding as they did not report or adjust for factors which could affect the outcome and were therefore at critical risk of bias overall. Several of the EMR studies were at serious risk of bias in classification of interventions and deviation from intended interventions, due to co-occuring interventions which took place alongside the EMR alerts such as staff education and quality improvement activities, the impact of which it is not possible to separate from the effect of the EMR intervention (Tzarnas, Allen et al. 2015, Gemelas, Locker et al. 2016, Goel, Sanchez et al. 2016, Karliner, Kobashi et al. 2017, Konerman, Thomson et al. 2017, Jain, Sanders et al. 2018, Magaldi, Brown et al. 2018). One study conducted a plan-do-study-act (PDSA) cycle so deliberately altering the intervention throughout the study (Shahnazarian, Karu et al. 2015). Several studies were conference abstracts or presentations and so were at unclear risk in several domains (Tzarnas, Allen et al. 2015, Thuluvath, Feldman et al. 2016, Jain, Sanders et al. 2018, Magaldi, Brown et al. 2018, Soo, Mukhtar et al. 2018, Teply, Mukherjee et al. 2018). The UK PWID EMR study was at critical risk of selection bias, as the comparator was all patients in the age group, whereas the intervention recruited those with indicators of past injecting drug use on their EMR (Cullen, Hutchinson et al. 2012).

Two non-randomised studies which evaluated the impact of staff education were at moderate or serious risk of selection bias as they excluded patients with risk factors (Wong, Abdelqader et al. 2017), or only included patients who attended at least 2 times during the study period (Madhani, Aamar et al. 2017), and 2 were at serious risk of bias due to deviation from intended interventions, as the educational sessions were not standardised and may be variably implemented (Madhani, Aamar et al. 2017, Nitsche, Miller et al. 2018). One was a conference abstract and presented results from a 4-week period before and after the intervention so providing little evidence of its longer term impact (Murphy, Triplett et al. 2016).

Both non-randomised studies of migrants testing were conference abstracts and at unclear risk in several domains (Lewis, Burke et al. 2011, Ho, Michielsen et al. 2018). One was at serious risk of bias in selection of the reported result as no denominator data were presented to be able to assess test uptake (Ho, Michielsen et al. 2018). The other was at moderate risk of bias in classification of interventions as individuals approached for opt-out or opportunistic testing may also have received the other intervention of leaflets at the mosque, however this is unlikely to significantly affect the outcomes of the study (Lewis, Burke et al. 2011).

Two studies which implemented testing at multiple sites were at serious risk of bias due to misclassification of interventions and deviation from intended interventions, due to varied implementation at different sites (Leeds City Council Sexual Health Team, Elton

John Aids Foundation et al. 2017, Franco, Galbraith et al. 2018). However, these reflect the reality of variability of implementation at scale.

Non-randomised studies evaluating interventions to provide HCV treatment in primary care are at critical risk of selection bias, as primary care treatment may increase access for harder to reach persons, including PWID, however these patient characteristics were only reported in 1 study (Mohsen, Chan et al. 2018), while the others reported little or no data on differences between patients seen in each pathway (Arora, Thornton et al. 2011, Fox, Hawks et al. 2015, Wade, McCormack et al. 2018). One of study was at serious risk of bias due to missing data, as patients who did not receive any dose of PEG-IFN/RBV treatment were excluded from the analysis (Arora, Thornton et al. 2011). Another was a conference abstract and was at unclear risk in all domains (Fox, Hawks et al. 2015).

Qualitative

Three UK studies reported qualitative data on hepatitis testing in primary care. After the Scottish EMR PWID testing intervention interviews were conducted with patients and staff to determine the acceptability of the intervention (Cullen, Hutchinson et al. 2012).Two other UK studies explored GP's views on HCV testing (Datta, Horwood et al. 2014) and how social and cultural influences may affect hepatitis testing and treatment for migrants (Sweeney, Owiti et al. 2015) through semi-structured interviews with GPs and focus groups with representatives from migrant populations.

GPs' experiences of HCV infection were mostly with PWID, with many interviewees saying they would test patients who used drugs (not just PWID), and fewer saying they would test migrant patients from higher prevalence countries (Datta, Horwood et al. 2014). Most didn't routinely question patients about HCV risk factors. Perceived barriers to testing included difficulties in raising the subject and remembering to offer the test, in the context of other more pressing issues and time pressured appointments, particularly if patients had previously declined testing. Interviewees highlighted the importance of developing a rapport with patients, and the difficulties in doing this with PWID who often infrequently attend. Difficulties in finding previous test results were also identified, particularly where tests had been done elsewhere, for example in drug services.

Patients interviewed after the PWID testing intervention perceived it positively, although those who agreed to be interviewed were a self-selecting group. Staff again identified barriers to testing former PWID in GP practices as many rarely consulted their GP, presenting limited opportunities for testing. Limitations within the clinical administration system and poor venous access were also cited. Some staff were hesitant to test former PWID, who they saw as less likely to complete treatment and more likely to be negatively impacted by the news of a diagnosis, and perceived that opportunistic HCV

testing for former PWID in this setting was often inappropriate or too time consuming due to the multiple health and social problems faced by former PWID.

Barriers for migrant patients to access testing included language, fear of diagnosis, fear of the testing process involved, trust and confidence in primary care (Sweeney, Owiti et al. 2015). Screening letters were perceived by migrants as likely to be ignored, and a need for reassurance and verbal explanations of the process from primary care staff was identified, with staff working alongside community groups to communicate verbal information about hepatitis and testing and provide support to patients during treatment.

GPs suggested that raising their awareness of who to test and getting better access to test results would help them to increase testing. Primary care are likely to need support to undertake screening and treatment due to workload implications.

Summary

Testing

There are limited studies on primary care interventions to provide HCV testing for PWID:

- US birth cohort studies provide a good body of evidence that interventions to flag patients for testing through electronic medical records (EMR) are successful in increasing testing
- there is moderate evidence from the UK that identifying patients for testing by risk-factors (including migrant status) on EMR is effective and cost-effective
- there is good evidence that staff education and support can lead to small increases in implementation of recommended testing in primary care
- there is moderate evidence from the UK that incentivising GP practices to test migrant patients increases testing for this group
- there is suggestive evidence that community awareness raising alone does not lead to increased testing for migrants
- the Leeds pilot study is an example of variable offer of opt-out testing and considerations when implementing interventions in multiple sites.

Linkage to care

There is suggestive evidence that community care compared to tertiary care does not increase treatment uptake for migrants diagnosed in GP practices:

- there is suggestive evidence that POC testing can increase linkage to care for migrants compared to community venous sampling
- there is suggestive evidence that system-wide automated RNA testing increases linkage to care.
- there is moderate evidence that HCV care can be delivered in primary care with telementoring support
- there is moderate evidence that providing treatment in primary care increases the proportion of uptake from PWID and achieves similar outcomes as for non-PWID when DAAs are used
- there is moderate evidence that nurse-led support and education for staff increases referrals and hepatology clinic attendance

Qualitative

- GPs identified difficulties in offering opportunistic testing based on risk factors and perceive barriers to testing former PWID in primary care.
- migrant patients identified a need for for verbal and face to face support to access testing.
- GPs are likely to need additional support to implement testing recommendations and to treat in primary care

Prisons

Results here are from a recent systematic review of interventions to increase HCV testing, linkage to care and treatment in prisons (Kronfli, Linthwaite et al. 2018). Four additional studies (3 UK and 1 US) on the implementation of opt-out testing are also included.

HCV testing in prisons

Two randomised (both UK) and 4 non-randomised studies (3 UK and 1 international) evaluated HCV testing interventions in prisons (table 8).

In the UK

A cluster RCT evaluating DBS testing introduced in 8 DTS and 3 prisons found that the intervention non-significantly increased HCV testing in the prison sites by 24.8% (95% CI 10.9-60.5) (Hickman, McDonald et al. 2008).

A later stepped-wedge cluster RCT evaluated the introduction of DBS testing in 5 UK prisons compared to venepuncture as usual care and found that the intervention did not increase HCV testing (OR 0.84, 95% CI 0.68-1.03) and concluded that DBS as a stand-alone intervention was not enough to increase testing (Craine, Whitaker et al. 2015). Four of the 5 prisons in this study had no pre-existing HCV testing service, so implementing DBS testing was challenging and required significant staff training.

A non-randomised study evaluated the impact of introducing DBS testing in 1 prison in the South East alongside improved referral pathways (Abou-Saleh, Rice et al. 2013). The rate of testing increased from 0.5 patients per 3 months prior to the intervention, who were tested in prison GUM services, to 43 patients per 3 months after the intervention.

Three non-randomised studies evaluated the effect of implementing opt-out DBS testing following the inception of the national opt-out testing policy in England. One study in 14 East Midlands prisons found that in the year after implementation of opt-out testing, testing increased from 1,972 to 3,440 or 13.5% of prison entrants (no denominator data were available to assess the proportion tested before implementation) (Jack, Thomson et al. 2019). A study in 1 prison in the North East reported that testing increased from 2.3% of receptions before the intervention to 35% during the intervention (Morey, Hamoodi et al. 2019), and another study in 1 prison in Birmingham reported that testing increased from 0% to 7.6% of receptions in the year after implementing a service improvement plan, including opt-out DBS testing (Arif 2018).

A non-randomised study evaluated the introduction of DBS testing in multiple settings including prisons during Scotland's HCV Action Plan (McLeod, Weir et al. 2014). In prisons, DBS testing was offered alongside a package of interventions including improved accessibility of HCV testing and targeted activities to promote HCV testing. There was a small but significant increase in testing in prisons on introduction of the intervention (relative risk (RR) 1.32, 95% CI 1.00-1.74) and a similar increase in the trend in total yearly tests in prisons (RR 1.19, 95% CI 1.15-1.24).

International testing in prisons

A non-randomised study in Australia evaluated the introduction of an on-site nurse-led weekly clinic to offer BBV and sexually transmitted infection (STI) testing in 3 prisons (Winter, White et al. 2016). Using a convenience sample of 100 consecutive new prison inmates in each prison, HCV testing significantly increased from 13% to 25% ($p<0.001$) during the intervention.

A non-randomised US study evaluated the effect of offering opt-out HIV and HCV testing through venous sampling in 1 prison (de la Flor, Porsa et al. 2017). Testing increased from 118 inmates in the first month of the intervention to 269 in the final month, with acceptance of testing among those offered increasing from 12.9% to 80.5%, however the number offered testing decreased over the same time period and the overall proportion of receptions tested was not reported.

HCV linkage to care in prisons

One international randomised and 2 UK non-randomised studies evaluated linkage to care from prisons (table 9).

In the UK

A non-randomised study evaluated the effect of implementing a nurse-led inreach HCV clinic with telecare hepatology consultant consultations, alongside opt-out DBS testing in 1 prison in the North East (Morey, Hamoodi et al. 2019). Treatment initiation increased from 14% of RNA positive patients before the intervention to 71% of those seen in the clinic during the intervention, with 53% completing treatment within prison.

A retrospective cohort study in Scotland evaluated the impact of a multi-agency pathway intervention which included nurse-led clinics in hospital and outreach clinics in drug treatment and prisons, along with interventions to encourage attendance by sending patients and referrers a letter if patients did not attend (Tait, McIntyre et al. 2010). For prisoners, hepatology attendance increased from 4 to 75 people; as no data were presented on the number eligible for referral it is unknown whether this represents an increased proportion of participants being referred.

International linkage to care in prisons

An RCT in Spain evaluated the effect of providing DOT with PEG-IFN/RBV compared to SAT in prison (Saiz de la Hoya, Portilla et al. 2014). 252 patients in 25 prisons were individually randomised to DOT or SAT. PEG-IFN was administered by a nurse in both study arms, while in the DOT arm RBV was administered by a nurse and in the control arm was self-administered. Continuation in treatment (81% intervention, 84% control) and SVR (61% intervention, 66% control) were both similar in both arms, suggesting that DOT did not increase treatment completion, although both arms had high rates of completion and SVR.

Risk of bias

All 3 randomised studies were at high risk of performance bias, as participating staff could not be blinded to the intervention (Hickman, McDonald et al. 2008, Craine, Whitaker et al. 2015). The step-wedged RCT was at high risk of attrition bias due to imputation of missing data (Craine, Whitaker et al. 2015). The earlier DBS testing RCT was at unclear risk of attrition bias as the same denominator was used for the intervention and baseline periods, and at low risk of detection and reporting bias (Hickman, McDonald et al. 2008). The Spanish RCT was at moderate risk of selection bias as 9 patients moved from the DOT to the non-DOT arm at the start of the study and were analysed on a per-protocol rather than intention to treat basis (Saiz de la Hoya, Portilla et al. 2014). It was at unclear risk of detection bias as it did not describe how adherence was measured, and low risk in other domains.

All of the non-randomised studies were at critical risk of bias due to confounding as they did not report or did not adjust for confounding factors which could affect the outcome. Both of the Scottish non-randomised studies were at serious risk of bias due to time-varying confounding and deviations from the intervention due to their long study period and before and after study design (Tait, McIntyre et al. 2010, McLeod, Weir et al. 2014). The Australian study of a nurse-led weekly clinic was at moderate risk of bias due to missing data, as some data were missing from the selected files, but low risk in all other domains other than confounding (Winter, White et al. 2016). The South East England study was at critical risk of bias due to deviation from intended interventions as it introduced DBS testing along with an improved referral pathway, at critical risk of bias in selection of the reported result and at unclear risk in several other domains (Abou-Saleh, Rice et al. 2013). The North East England study was at unclear risk of bias due to missing data, measurement of outcomes and bias in the selection of reported result as it was not clear how testing data were collected, and was at critical risk of selection bias in the comparison of treatment uptake rates as these compared the proportion of RNA positive patients who started treatment before the intervention with the proportion of patients seen in the telemedicine clinic who accepted treatment during the intervention (Morey, Hamoodi et al. 2019). The Birmingham study was at serious risk of

bias due to deviations from the intended intervention as the study reported a service improvement plan with several areas of implementation, and at critical risk of bias in the measurement of outcomes, as testing data was compared to a historical control which may have been inadequately recorded (Arif 2018). The East Midlands study was at low risk in domains other than confounding (Jack, Thomson et al. 2019).

The non-randomised US study was at critical risk of selection bias as only data on individuals offered testing was reported, with no data on the overall prison intake (de la Flor, Porsa et al. 2017). As a result it was also at critical risk of bias due to deviation from intended interventions, as it was reported as opt-out testing but was unclear what proportion of inmates were offered testing. It was at unclear risk of bias in measurement of outcomes, as it was unclear how testing data were recorded, and low risk in other domains other than confounding.

Qualitative studies

A rapid realist review of opt-out testing in prisons identified implementation considerations which offer explanations for the varied and overall low uptake of testing in prisons (Francis-Graham, Ekeke et al. 2019). The review found that the proportion of intake offered testing was influenced by the timing of the test offer, with prisons which conducted testing during the first night health check achieving higher rates than those which left testing until later. However, the test offer was often delayed due to barriers to prisoner access. Prisoners' decisions to accept testing were influenced by concerns about confidentiality, fear of a positive diagnosis, personal interpretation of risk, fear of needles, institutional trust, and the fidelity of the opt-out offer. Challenges to fidelity of the opt-out offer were identified, originating from the conceptualisation of the offer by programme implementers, misinterpretation by those delivering the test offer, and/or contextual pressures. Depending on how consent was sought, offers ranged from those that were really 'opt-in,' to those where it was unclear that prisoners had a right to decline, bordering on a mandatory approach. A recommended set of words for health workers to use when discussing opt-out testing, originally conceived by NHSE and PHE was further developed through findings from the review and shared with partners to be implemented within London prisons.

One of the included UK opt-out testing studies investigated the low uptake of testing through staff interviews and attributed it to inadequate healthcare facilities to meet the volume of testing and constraints imposed by adherence to prison regimens (Jack, Thomson et al. 2019).

Summary

Testing

There is limited evidence on testing in prisons:

- three non-randomised evaluations of the implementation of opt-out testing in England show increases in testing, but testing rates remain low and below levels that would suggest true ‘opt-out’ implementation
- understanding of systemic barriers for interventions in prisons is important and should be considered when planning interventions.
- fidelity to the opt-out offer is varied and challenging; recommended wording for use by health care workers is available and should be considered

Linkage to care

There is limited evidence on linkage to care in prisons:

- there is suggestive evidence that a telemedicine clinic within prison increased treatment initiation.
- there is moderate evidence that DOT compared to SAT (PEG-IFN/RBV) in prison does not improve treatment adherence or SVR.

Homeless

Only 3 studies of interventions for current homeless populations were found. Several US studies of multidisciplinary HCV care report that their population includes former homeless people and are included in the multidisciplinary care section. Outreach interventions to provide homeless healthcare are taking place but none have published evaluations with a comparator group. HCV seroprevalence estimates among homeless populations vary (3.9% to 36.2% (Beijer, Wolf et al. 2012)) and the population is not clearly defined. An understanding of injecting status is needed to ascertain whether homeless persons are likely to be picked up elsewhere in PWID interventions.

HCV linkage to care for homeless populations

One randomised UK study and 2 non-randomised international studies evaluated linkage to care interventions for homeless populations (table 10).

In the UK

A UK RCT evaluated the impact of peer support for people attending outreach substance misuse and homelessness services to improve engagement in HCV care (Stagg, Surey et al. 2019). Patients were randomised after testing RNA positive for HCV. Standard of care was referral to treatment in a local hospital, the peer support intervention was given by formerly homeless peer advocates who supported patients to attend health appointments and promoted engagement by maintaining contact, following up appointments and supporting people to tackle other health issues. Individuals randomised to the intervention arm were more likely to engage with services at least 3 times, looking at absolute differences (37% vs 18%, p=0.04) and relative odds (ORs), although for the latter, statistical certainty was lower (OR 2.55, 95% CI 0.97-6.70, p=0.06). No individuals achieved SVR during the study period.

International linkage to care for homeless populations

A non-randomised US study evaluated an integrated medical, mental health and case management model in a community health centre for people who were homeless or at risk of being homeless (Hodges, Reyes et al. 2019). All patients included in the study attended at least 1 integrated care appointment, and some then opted to follow individual care and were used as the comparator group. Completion of treatment was non-significantly higher in patients who opted for the intervention arm (99% vs 88%, OR 10, 95% CI 0.99-101) and SVR was significantly higher (91% vs 69%, OR 6.33, 95% CI 2.09-19.2).

A non-randomised Canadian study evaluated HCV treatment outcomes for homeless PWID compared to those who were stably housed in a multidisciplinary care program which addressed medical, psychological, social and addiction-related needs (Singh, Alimohammadi et al. 2017). SVR was non-significantly lower in individuals who were homeless (88% vs 97%, p=0.19). Treatment type was not reported but assumed to be DAAs due to the high SVR achieved.

Risk of bias

The randomised study was at high risk of performance bias as staff and patients were not blinded to the intervention (Stagg, Surey et al. 2019). It was at moderate risk of reporting bias, as it reported created its own definition of engagement as 3 or more attendances, and did not report on adherence or treatment completion, and at unclear risk of bias due to recruitment of a non-representative cohort as it did not describe what proportion of patients consented to participate.

The non-randomised studies were both at critical risk of bias due to confounding, as they did not adjust for confounders which could affect the outcomes of the study. One was at critical risk of selection bias and bias in classification of interventions, as the comparator group consisted of patients who had declined to participate in the intervention (Hodges, Reyes et al. 2019). The other was a conference abstract and was at unclear risk in most domains (Singh, Alimohammadi et al. 2017).

Summary

Testing

There were no studies of testing in homeless populations with a comparator group.

Linkage to care

There were few studies evaluating linkage to care for homeless populations with a comparator group:

- there is moderate evidence that peer mentors increased engagement in treatment for homeless persons, but no evidence of an impact on SVR
- there is suggestive evidence that SVR is higher among homeless persons who attend integrated care than those who opt for individual appointments
- there is suggestive evidence that high rates of SVR can be achieved for homeless populations receiving multidisciplinary care, but these are lower than for those who are stably housed

MSM

No studies were identified which evaluated HCV testing or linkage to care interventions targeted at MSM. Although BASHH guidelines for testing in sexual health recommend testing for HIV-positive individuals, MSM eligible for 3-monthly HIV testing and those taking or eligible for PrEP, they do not currently recommend testing in HIV-negative MSM without additional risk factors (BASHH 2017). HCV testing in sexual health clinics is low compared to HIV testing (18% vs 94% in 2 London clinics (Pasvol and Orkin 2017) although there are suggestions that it should be offered routinely to all MSM in the sexual health setting (Ward and Lee 2014).

Although some MSM are well engaged with sexual health services and routinely attend for testing, others may be less so. Evidence on interventions to promote the uptake of HIV testing among MSM is likely to be transferrable. A systematic review found evidence that rapid testing and counselling in community settings and intensive peer counselling can increase the uptake of HIV testing, whereas evidence in support of other approaches such as bundling HIV tests with other tests, peer outreach in community settings, and media campaigns was inconclusive (Lorenc, Marrero-Guillamón et al. 2011).

Emergency department (ED) interventions

HCV testing interventions in emergency departments (ED)

Two randomised (both international) and 2 UK non-randomised studies evaluated testing interventions in emergency departments (table 11).

In the UK

A non-randomised UK pilot of opt-out testing in 1 ED evaluated the effect of quality improvement interventions on the opt-out offer, including staff training, staff rewards, testing champions, and creating a common order BBV request set (Bradshaw, Rae et al. 2018). BBV testing significantly increased from a median 121 tests per week, 55% of which were BBV tests (vs standalone HIV test) during the first 10 weeks of the intervention to a median 180 tests per week, 96% of which were BBV tests during the final 10 weeks ($p<0.01$), however the proportion of patients tested overall was low at 24%.

A non-randomised study in 1 ED compared the offer of concomitant HCV and HIV POC testing with POC HCV testing alone and found that offering HCV testing alone was associated with higher uptake than when concomitant HIV testing was offered (47% vs 31%, OR 0.51, 95% CI 0.38-0.68, $p<0.001$) (Geretti, Austin et al. 2018). HCV positivity was 0.31%, while no cases of HIV were identified.

International HCV testing interventions in ED

A US RCT in 2 ED targeted patients with self-disclosed drug use in the past 3 months and compared the effect of providing a HIV/HCV risk assessment (control) with a brief intervention plus HIV/HCV risk assessment (intervention) on testing rates (Merchant, Baird et al. 2014). There was no increase in testing for patients that received the intervention. However, high rates of testing were achieved in both intervention and control arms with 65% in each arm accepting testing.

A subsequent US RCT evaluated a brief intervention in ED aimed at patients with higher levels of drug misuse which aimed to comprehensively address drug misuse, HIV and HCV risk-taking behaviours and need for HIV/HCV screening (Merchant, DeLong et al. 2015). In this study testing was significantly lower in the intervention arm (37% vs 43%, $p<0.04$).

A non-randomised US study evaluated the introduction of opt-out HCV testing to all patients aged over 13 years in ED (Schechter-Perkins, Miller et al. 2018). An EMR alert was added when any phlebotomy order was made to state that the patient was eligible

for HCV testing, and providers followed an opt-out script to standardise the offer. Testing increased from an average of 18 tests per month before the intervention to 1,269 per month in the 3 months of the intervention – 39% of patients who had blood taken.

HCV linkage to care in ED

There were no studies which evaluated linkage to care from emergency departments.

Risk of bias

Both of the randomised studies were at high risk of selection bias due to lengthy recruitment processes which required that patients disclosed their substance misuse and were willing to engage in responding to these questions (Merchant, Baird et al. 2014, Merchant, DeLong et al. 2015). Because of this, they were also at high risk of attrition and reporting bias, as data on those who did not consent to participate was not reported. The studies were also at high risk of performance and detection bias as testing was offered, conducted and recorded by research assistants not blinded to the intervention.

Two of the non-randomised studies were at critical risk of bias due to confounding as they did not adjust for factors which could affect the outcome (Bradshaw, Rae et al. 2018, Schechter-Perkins, Miller et al. 2018) while the other conducted comparator interventions over consecutive alternating time periods, so reducing the risk of confounding to moderate (Geretti, Austin et al. 2018). Two were at moderate risk of bias due to classification of interventions, 1 because the EMR alert did not fire in some cases, and the other because a PDSA cycle was used (Bradshaw, Rae et al. 2018, Schechter-Perkins, Miller et al. 2018).

Qualitative studies

A qualitative study conducted semi-structured interviews with staff and patients who were involved in an UK opt-out BBV testing pilot in 9 ED (Cullen, Grenfell et al. 2019). Patients viewed the routine and low-key nature of the opt-out testing offer positively and saw it as reducing negativity and anxiety around the idea of testing, and described feeling a social responsibility to test, particularly when offered in the ED context where it was seen as reciprocal to receiving the health service offered. All interviewed patients perceived themselves not to be at risk of HCV. Patients speculated that those at higher risk may be more reluctant to test due to anxiety about receiving a positive result, and staff noticed that younger and PWID patients were more reluctant to test, which suggests that routine testing in ED may be more problematic for those who are more anxious of the test outcome (and possibly more at risk, if PWID). Most patients and staff saw the intervention in this setting as taking advantage of a presented opportunity. Staff talked about the ease of taking an additional vial when taking bloods and said that the time to do this once it

was integrated into routine was minimal. A few patients questioned the appropriateness of the location, with 1 saying he did not want to risk a ‘double whammy’ of bad news, and another that testing conflicted with the emergency remit as it was not applicable to the emergency situation and should be dealt with elsewhere. Staff identified that the intervention presented the opportunity to test patients not immediately thought of by staff as high risk, who in some cases were diagnosed, as well as those who had disengaged from care and those reluctant to attend sexual health services.

Summary

Testing

There is suggestive evidence that quality improvement interventions such as staff training, staff rewards, testing champions, and creating a common order BBV request set can increase the offer of opt-out testing in ED:

- there is suggestive evidence that EMR reminders can increase testing in ER
- there is moderate evidence that brief interventions are not effective in increasing uptake of testing among drug users in ED.
- there is suggestive evidence that concomitant HIV test offer reduces uptake of HCV testing.

Linkage to care

No studies evaluated linkage to care from emergency departments with a comparator group.

Qualitative

- patients perceive the offer of testing in this setting positively and see a reciprocal responsibility to test.
- staff and patients perceive that testing in this setting is easy.
- patients at higher risk may be more anxious about testing in this setting.

Other settings

HCV testing in other settings

Two randomised and 2 non-randomised studies evaluated testing interventions in other settings, all were international (table 12). Two were in mental health settings, 1 was in sheltered accommodation and 1 was in inpatients in a community hospital.

International HCV testing in other settings

A US RCT evaluated HBV and HCV education, counselling, testing, referral and support into treatment for people with dual diagnosis (severe mental illness and substance misuse) in community mental health (Rosenberg, Goldberg et al. 2010). 88% of the intervention group were tested compared to 14% in the control group ($p<0.01$).

A cluster RCT in France compared the efficacy of 2 HBV and HCV screening strategies for people living in long-term shelters for underprivileged people including unemployed, social welfare recipients and asylum seekers (Sahajian, Bailly et al. 2010). Both strategies consisted of a group educational session followed by an individual consultation with a GP, 1 then offered testing onsite while the other referred patients to the local health centre for testing. Testing was significantly higher in shelters that offered onsite testing (19%), than those that referred for testing offsite (9%) and both were significantly higher than the control group (2%), $p<0.0001$.

A non-randomised study in Australia provided a program of HCV education and counselling to psychiatric inpatients, who were then approached individually to offer testing (Lacey, Ellen et al. 2007). Testing increased from 9% of patients in the 6 months before the intervention to 18% of patients during the intervention ($p<0.01$).

A non-randomised US study assessed an intervention to test birth cohort (born 1945-1965) inpatients in a community hospital (Jen and Nguyen 2016). Testing was coordinated by an interdisciplinary ward round including an associate medical director, 2 physicians, social worker, case manager, nurse manager. Testing increased from 4% to 28% of patients, with an anti-HCV positivity of 7.7%.

HCV linkage to care in other settings

In the US RCT of HBV and HCV testing, risk reduction, referral and support into treatment for people with dual diagnosis (severe mental illness and substance misuse) in community mental health self-reported referral to treatment was non-significantly

higher in the intervention group (81% vs 75% of those who self-reported HCV-positive) (Rosenberg, Goldberg et al. 2010) (table 13).

Risk of bias

Both randomised studies were at high risk of selection and reporting bias, as participants were recruited individually into the studies and results were reported as a proportion of those who consented to participate, who are unlikely to be representative of all eligible patients / residents (Rosenberg, Goldberg et al. 2010, Sahajian, Bailly et al. 2010). One had a high risk of performance bias as staff were not blinded to the intervention (Rosenberg, Goldberg et al. 2010), and the other was unclear on whether those offering testing were aware of allocation (Sahajian, Bailly et al. 2010). The US RCT had a high risk of detection bias because it used self-reported outcomes on testing (Rosenberg, Goldberg et al. 2010).

The non-randomised studies were both at critical risk of confounding as they did not adjust for confounding factors which could affect the outcome (Lacey, Ellen et al. 2007, Jen and Nguyen 2016). One was also at high risk of selection bias as individual patients were approached to participate in the study and only 24% consented, who are unlikely to be representative of the entire population, however the results were presented as a proportion of all patients (Lacey, Ellen et al. 2007). It was also at moderate risk of bias due to deviation from intended interventions as the pre- and post-test counselling was adapted to individual clients' needs. The other was a conference abstract and was at unclear risk in all domains other than confounding due to the limited details presented (Jen and Nguyen 2016).

Summary

There is moderate evidence that counselling and education to promote testing in settings including mental health, community hospital wards and supported housing increases testing in these settings; these may provide suitable settings to access higher risk patients:

- there is limited evidence on linkage to care from these settings, evidence from other settings is likely to be transferrable

Care pathway interventions

Studies which assessed integrated care models to move patients diagnosed with HCV along the care pathway, or specific interventions to improve treatment uptake or retention were often across multiple settings or were not setting specific, and were not targeted at 1 specific population group, and so are presented together here.

Multicomponent interventions across the care pathway

Three non-randomised UK studies evaluated changes to the care pathway which took place across multiple settings and providers (table 14).

In the UK

A non-randomised study evaluated an integrated multidisciplinary care intervention to address alcohol and drug use problems, social circumstances and general health along with HCV specialist care in the Tayside region of Scotland (Tait, McIntyre et al. 2010). A half-time nurse specialist was employed to run clinics in hospital and outreach clinics in DTS and prisons, and non-medical referrals were implemented, along with interventions to encourage attendance by sending patients and referrers a letter if patients did not attend, and a database of HCV positive patients was established. Referrals to hepatology increased from 35% to 87% of anti-HCV positive patients during the intervention, and hepatology attendance significantly increased from 66% to 82% of those referred ($p<0.0001$). There were non-significant increases in treatment completion (74% vs 66%, $p=0.2$) and SVR (61% vs 51%, $p=0.2$). SVR was similar in patients who had injected drugs in the past 12 months (57%) to those who had not (61%), and an increased proportion of referrals came from DTS during the intervention, from 2.5% to 18.3% of all referrals.

The same research team assessed the subsequent implementation of routine DBS testing in DTS and needle exchanges, a full-time nurse specialist, and an increase in outreach clinics in the same region (Tait, Wang et al. 2017). DAAs also began to be used in the treatment regimen during this time. The proportion of patients who were tested in DTS increased from 10% when the managed care network was in place to 36% after DBS testing was introduced, and referrals from DTS increased from 18% to 39% over the same time period. SVR increased to 77% for patients who tested anti-HCV positive after 2009 compared to 69% among those tested positive between 2004-2009.

A non-randomised UK study evaluated the implementation of a care pathway redesign in the Nottingham healthcare region, including reflex RNA testing, annotation of

laboratory results to recommend referral of actively infected patients to specialist clinics, education for primary care staff, and establishment of clinics in DTS (Howes, Lattimore et al. 2016). In 2000-2002 prior to the new pathway 27% were RNA tested; this increased to 94% in 2010-2011 after the implementation of reflex testing. Among those diagnosed as RNA positive, 80% were referred compared to 35% of anti-HCV positives referred before the intervention, with the greatest increase seen in primary care (92% compared to 66% before the intervention). Treatment initiation (38% of RNA positives vs 10% of anti-HCV positive patients) was also higher after implementation of the intervention.

Risk of bias

All 3 non-randomised UK studies are at critical risk of bias due to time-varying confounding due to the long follow up periods, and were also at serious risk of deviation from the intended interventions due to the long follow up period and implementation across multiple settings.

Summary

Linkage to care

- There is suggestive evidence that pathway changes, including staff education, community DBS testing, non-medical referrals, reflex RNA testing, and annotation of laboratory results to recommend referrals can increase referrals of HCV-infected patients to care and treatment initiation, however more robust studies with control groups are needed.

Multidisciplinary care coordination

Two randomised (both US) and 3 non-randomised (1 UK and 2 international) studies evaluated multidisciplinary care coordination to support patients in HCV treatment (table 15). Two further studies which evaluated support specifically for the side-effects of interferon-based treatment have been excluded.

In the UK

A non-randomised UK study evaluated the implementation of a multidisciplinary care service in a hospital in Grimsby to support compliance with PEG-IFN/RBV treatment (Ahmed, Habibi et al. 2013). The team comprised a specialist nurse, hepatologist, community support team and psychological support worker. Patients were given education and written information about treatment, involved in treatment decisions, had comorbidities and substance misuse issues addressed and psychological support throughout treatment, and given appointment reminders and frequent opportunities for

communication with healthcare providers. Side effects were managed with adjunctive therapies and patients were given feedback on treatment efficacy. Patients had higher treatment initiation (92% vs 82%, significance not reported) and completion (88% vs 39%, significance not reported), and significantly higher SVR (69% vs 20%, p=0.001) after implementation of the intervention compared to before the intervention.

International multidisciplinary care coordination

A US RCT evaluated a care coordination and case management intervention for people with substance misuse and/or psychiatric comorbitities in 3 HCV clinics (Ho, Bräu et al. 2015). The intervention was delivered in partnership with mental health providers and consisted of multidisciplinary care coordination, case management and brief psychological interventions to support participants to start and complete HCV treatment. Treatment with both PEG-IFN/RBV and DAAs was used during the time of the study. Treatment initiation was significantly higher in the intervention group (32% vs 19%, p=0.0054) and so was SVR (16% vs 8%, p=0.018).

A US RCT evaluated an integrated care intervention including case management and psychological brief interventions for patients with psychiatric comorbities or substance misuse attending a HCV clinic (Groessl, Liu et al. 2017). DAA treatment was used. Treatment initiation was significantly higher in the intervention group (45% vs 23%, p=0.032) and SVR was non-significantly higher (30% vs 13%, p=0.07).

A non-randomised Spanish study evaluated a multidisciplinary support programme to improve adherence to PEG-IFN/RBV treatment for patients identified as HCV RNA positive in a Liver Unit (Carrion, Gonzalez-Colominas et al. 2013). The multidisciplinary support group included 2 hepatologists, 2 nurses, a pharmacist, a psychologist, an administrative assistant and a psychiatrist. Adherence to treatment was significantly higher in patients in the intervention (95%) compared to the control group (79%) (p<0.001). SVR was also significantly higher in the intervention (77%) group than the control group (62%) (p<0.05), although an analysis of responses for each genotype found that the differences were not significant for patients with genotypes 2 or 3, where SVR was >80% in both intervention and control groups.

A US intervention with a propensity-score-matched comparator group evaluated a care coordination intervention for patients identified as HCV RNA positive on surveillance systems (Deming, Ford et al. 2018). DAA treatment was used. Patients were assigned a care coordinator who helped them navigate the health system, accompanied to medical appointments, counselled on medication adherence, conducted health promotion and self-sufficiency coaching and intake assessments which were used to tailor support and treatment plans to patients' individual needs. Uptake of treatment was higher in the intervention group (72% vs 36%) (p<0.001), and so was SVR (65% vs 47% of those who initiated treatment, p<0.001, or 47% vs 17% by intention to treat).

Risk of bias

Both RCTs were at high risk of performance bias, as staff could not be blinded to the interventions (Ho, Bräu et al. 2015, Groessl, Liu et al. 2017). They were also at high risk of selection bias, due to consent processes which mean those participating are unlikely to be representative of all clients and likely to be those more willing to engage.

The non-randomised UK study was at critical risk of bias due to confounding as it did not adjust for potential confounders (Ahmed, Habibi et al. 2013). Both this and the Spanish study were likely to be at serious risk of bias due to deviation from intended interventions due to the before-after designs with potential for other changes to occur during this time (Ahmed, Habibi et al. 2013, Carrion, Gonzalez-Colominas et al. 2013). The US study of care coordination was at moderate risk of bias due to confounding as it used a propensity-score matched analysis, and at moderate risk of selection bias as intervention participants were recruited from a different subset of the population than controls (Deming, Ford et al. 2018).

Summary

There is moderate evidence that an integrated, coordinated and holistic approach to care for patients receiving HCV treatment significantly increases treatment initiation and also increases SVR, including among patients with comorbid substance misuse and/or mental illness, including in the DAA era.

Psychosocial and educational interventions to improve adherence and treatment uptake

One randomised and 5 non-randomised international studies evaluated interventions to promote treatment uptake or adherence among patients (table 16).

International

An RCT evaluated the impact of a structured 4-session nurse-led behavioural intervention for HIV/HCV coinfected patients which addressed barriers to initiation of DAA HCV treatment (The Psychosocial Readiness Evaluation and Preparation for hepatitis C treatment (PREP-C) (Weiss, Aaronson et al. 2017)). Patients in the intervention group were significantly more likely to be prescribed HCV medication in the 6 months post-randomisation (59% vs 27%, p=0.018) and were also non-significantly more likely to start treatment in this time (48% vs 23%, p=0.052).

A non-randomised study evaluated the impact of offering a $15 gift card to patients in HCV treatment for attending their appointments (Lee, Quintiliani et al. 2018). During the

intervention period 73% of appointments were attended, compared to 61% the year before the intervention (p=0.005). Treatment adherence was not specifically mentioned.

Four studies evaluated the impact of patient education on adherence to PEG-IFN/RBV treatment:

A non-randomised US study evaluated the implementation of an education session for HCV-infected patients on adherence to PEG-IFN/RBV treatment (Lubega, Agbim et al. 2013). Overall treatment rates were similar before and after the implementation of the intervention (24% vs 19%, p=0.1). Among those who initiated treatment, adherence to clinical visits (86% vs 88%, p=0.79) and SVR (68% vs 50%) were both similar in those who had and had not received the educational intervention, but an adjusted analysis found that SVR was significantly associated with receiving the intervention (OR 3.0, 95% CI 1.1-1.79, p=0.031). It was not clear, however, what proportion of patients had accepted the referral to the education class.

A non-randomised French study evaluated the impact of therapeutic education on treatment outcomes (Renou, Lahmek et al. 2009). Patients were given an initial psychology assessment and monthly follow up by a therapeutic education nurse and a hepatologist. Multivariable analysis found that intervention patients had significantly higher rates of SVR (71% vs 53%, p=0.001), however when this was broken down by genotype the difference was only significant for genotypes 1, 4 and 5 which required 48 weeks of treatment and was not significantly different for genotypes 2 and 3 (24 weeks of treatment).

A non-randomised French study evaluated the impact of nurse-led education on treatment adherence and outcomes (Larrey, Salse et al. 2011). Patients who received the intervention had higher treatment adherence (74% vs 63%) and higher SVR overall (38% vs 25%; p<0.02), however when broken down by genotype the difference was only significant for patients with genotypes 1, 4 or 5 who received 48 weeks of treatment and was not significantly different for patients with genotypes 2 and 3 (24 weeks of treatment).

A non-randomised US study evaluated the impact of a nurse-led support for patients receiving PEG-IFN/RBV treatment using a propensity-score matched comparator group (Hussein, Benner et al. 2010). Intervention patients could choose a support level based on their needs; all had 24/7 access to a nurse, and could choose to have in addition support phone calls and motivational and educational mailings. Adjusted analysis found that intervention patients refilled 1.2 (95% CI 0.52-1.83, p<0.001) more injections in the first 12 weeks than control patients and were more likely to fill 12 or more injections within 12 weeks of initiation (72% vs 64%, p<0.001).

Risk of bias

The US RCT was a conference abstract and poster and was at unclear risk in most domains as the study methods were not fully described (Weiss, Aaronson et al. 2017). Three of the non-randomised studies were conference abstracts so at unclear risk in several domains (lee, renou, larrey). The study of financial incentives was at serious risk of bias due to selection of reported results, as it only reported on appointment attendance and not on adherence, treatment completion or SVR (Lee, Quintiliani et al. 2018). It was at moderate risk of confounding as it presented an adjusted analysis, and moderate risk of bias due to deviation from the intended intervention due to the before/after study design. The evaluation of nurse-led education was at critical risk of bias due to confounding, as confounding factors were not adjusted for in the analysis (Larrey, Salse et al. 2011).

The US study of an educational intervention adjusted for confounders and so was at moderate risk of bias due to confounding, however it did not present clear denominator data on the number that had been referred to the educational intervention and accepted, but instead compared those who had attended to those who had not, thus making it difficult to assess the efficacy of the intervention overall as those who attended are likely to be more motivated patients (Lubega, Agbim et al. 2013).

The US study of nurse-led support used a propensity-score matched comparator group and so was at moderate risk of confounding, however it was at critical risk of bias due to missing data and selection of the reported result, as it presented adherence to injections among those who could be followed up at 12 weeks, but did not report on the proportion lost to follow up (Hussein, Benner et al. 2010).

Summary

- one study provided suggestive evidence that providing financial incentives to attend treatment appointments increases attendance, but no evidence on treatment completion or SVR

- one study provided suggestive evidence that a brief intervention to address psychosocial barriers to treatment uptake can be effective in increasing treatment uptake, however this study was at unknown risk of bias

Evidence for educational interventions to support adherence was all from the interferon era. Although there was some evidence that these interventions improved adherence for longer-duration therapies, the effect was limited when considering short duration treatment, which may limit the transferability of these findings when considering adherence to DAA treatments.

Economic evaluations and cost analyses

Results from 2 systematic reviews of HCV screening interventions are included here (Geue, Wu et al. 2015, Coward, Leggett et al. 2016). Ten additional studies are included which were not in either review, including studies evaluating the cost-effectiveness of linkage to care interventions.

Coward and colleagues undertook a systematic review of economic evaluations of HCV screening in 2016 and found 30 eligible studies (Coward, Leggett et al. 2016). The review included studies in English of any type of economic evaluation (cost minimisation, cost-effectiveness (CEA), cost utility (CUA) or cost benefit) of population or risk group HCV screening or comparison to opportunistic, high-risk group or no programme. Abstracts or commentaries were excluded, as were economic evaluations of blood donor testing, diagnostic tests, screening for HCV coinfection (HCV and HIV) versus HCV alone, and HCV treatments. Databases were searched from inception until May 2016. The Coward review used the Consensus Health Economic Criteria list to evaluate the quality of studies based on a checklist of 24 recommended items, with a point allocated for each of the items included (Evers, Goossens et al. 2005). Studies were deemed high quality if they scored >20 points, average if 17-20 and poor if they scored <11.

Geue and colleagues undertook a systematic review of existing modelling techniques for cost-effectiveness of HCV and HBV screening in 2015 and found 31 eligible studies for HCV screening (Geue, Wu et al. 2015). The Geue review included economic evaluations incorporating cost-effectiveness analysis which evaluated testing strategies in Organisation for Economic Co-operation and Development (OECD) countries for the general population and selected subpopulations (pregnant women, MSM, migrants, PWID, recipients of blood transfusion and healthcare workers (HCW)), and which measured and reported both costs and benefits. Databases were searched from inception until July 2015. The Geue review critiqued studies using guidelines for assessment of decision-analytic models developed by Phillips and colleagues (Philips, Bojke et al. 2006) and guidelines for authors and peer reviewers of economic submissions to the British Medical Journal developed by Drummond and colleages (Drummond and Jefferson 1996).

Studies from the 2 reviews which did not meet the inclusion criteria for this report (not in English; countries outside Western Europe, North America and Australia; screening for HCW) have been excluded.

Some studies include expected value of perfect information (EVPI) analyses. These estimate the value of obtaining perfect information for the model, which can be interpreted as the maximum amount that should be paid for further research given a

threshold value of cost per additional unit of health (e.g. cost per quality-adjusted life year (QALY)). EVPI is subject to a number of factors including the ability of research to change policy (e.g. to move a cost-effectiveness estimate over a threshold value such as £20,000 to £30,000 per QALY) and the size of the population who could benefit. EVPI can either be reported for the whole model, or by disaggregating in order to identify which aspects of the model would benefit most from further information, known as the expected value of partially perfect information (EVPPI).

Interventions were considered to be cost-effective if they met the NICE willingness to pay (WTP) threshold of £20,000 to £30,000 per QALY gained. International currencies have been converted to UK pounds using current exchange rates.

Studies were grouped by target population, first for the high risk populations considered in the first part of the report: PWID, prisoners, migrants, and MSM (there were no studies relating to homeless populations), and then for other groups and settings: antenatal, sexual health, risk-based, birth cohort, general population and emergency department.

PWID

There were 19 studies which evaluated the cost-effectiveness of testing interventions for PWID, 15 were CUA, 1 CEA and CUA, 2 CEA and 1 was a cost analysis of a pharmacy testing intervention included elsewhere in this report. Ten were UK studies (including the cost analysis) and 9 were international (table 17).

In the UK

A 1999 UK CUA used a decision tree analysis to estimate the cost-effectiveness of a single round of screening for PWID in contact with drug services in the South and West of the UK and found an incremental cost-effectiveness ratio (ICER) of £9,300 per QALY (Leal, Stein et al. 1999). At the time of the study little was known about the natural history of HCV and progression rates were modelled on those for HBV. Liver biopsy was required before treatment to assess moderate-severe disease to be considered suitable for treatment with IFN. There was a high degree of uncertainty in the estimate, with results sensitive to discount rates, acceptance of liver biopsy, acceptance of treatment, and continuation of treatment.

A 2003 UK CUA used a Markov model to estimate the cost-effectiveness of HCV screening for GUM clinic attendees who were former PWID compared to no screening and found an ICER of £27,138 per QALY (Stein, Dalziel et al. 2003). Liver biopsy was required before treatment to assess moderate-severe disease to be considered suitable for treatment with IFN. The model was sensitive to prevalence, acceptance of testing, acceptance of liver biopsy, and acceptance of treatment.

A 2004 UK CUA used a simple epidemiological model of screening and diagnosis with a Markov model of treatment to estimate cost-effectiveness of one-time screening for PWID in drug treatment followed by treatment with either IFN/RBV or PEG-IFN/RBV (Stein, Dalziel et al. 2004). An ICER of £28,000 per QALY was found for treatment with IFN/RBV, and £14,000 per QALY for PEG-IFN/RBV due to the higher response rates and lower RBV dose rates required. The model was sensitive to acceptance of liver biopsy, acceptance of treatment, treatment response, disease staging of the population, mortality rate of biopsy complications, and utility assumptions for chronic hepatitis and successful drug treatment.

A 2006 UK CUA used a decision tree plus Markov model to evaluate the cost-effectiveness of offering HCV testing to former PWID in drug and alcohol services and in general practice (Castelnuovo, Thompson-Coon et al. 2006). The drug and alcohol service intervention had an ICER of £17,515 per QALY. The general practice intervention identified former PWID from their medical records and invited them for screening with a letter and found a cost per QALY of £16,493 (also reported in (Thompson Coon, Castelnuovo et al. 2006)). The model was sensitive to discount rates, utility assumptions, and distributions of disease severity in the population, with increased cost-effectiveness associated with treating individuals with more severe disease. Probabilistic sensitivity analysis showed considerable uncertainty, including a small number of cases where screening was dominated. EVPI analysis (assessed for the ‘general case’) showed a population EPVI of £16.9 million at a WTP threshold of £30,000 per QALY, with partial EVPI analysis showing that the only parameters with an associated value of information were the utilities.

A 2013 UK CUA evaluated DBS testing in DTS compared to venepuncture as usual care and found it to be cost-effective, with an ICER of £14,600 (Martin, Hickman et al. 2013). This study used a dynamic-transmission model which included the population-level benefits of prevention of HCV. Cost-effectiveness was sensitive to discount rates, treatment rates and assumptions on the disutility of diagnosis, which was not included in the base case. If a disutility of diagnosis of 0.1 was included the intervention resulted in negative incremental QALYs due to the low assumed treatment rates and was dominated. Increasing treatment to 50% of those referred initiating treatment within 2 years would result in an ICER of £20,100 per QALY with the disutility included.

A 2015 UK CUA used a dynamic transmission model to evaluate the long-term impact of treatment uptake and efficacy on future infections and resulting cost-effectiveness (Bennett, McEwan et al. 2015). In a population of 4,240 PWID, if treatment were increased to 250 per 1,000 PWID with an SVR of 90%, discounted gains of 300 life years (LY) and gains of 1,700 QALYs would be made, with and discounted cost savings of £5.4 million over the period 2015 to 2027.

A 2017 UK RCT of a pharmacist-led treatment pathway in community pharmacies for HCV with DOT using DAAs estimated that the costs for the pharmacy treatment pathway were £695 less per patient than in the traditional setting (Radley, Tait et al. 2017).

A 2017 UK CUA evaluated the effect of increased treatment uptake on the cost-effectiveness of providing DAA treatment to PWID using a dynamic transmission model and found that treatment uptake of 10-100% in chronically HCV-infected PWID who had not previously been treated had an incremental net monetary benefit of £29,188 to £90,559 respectively per patient treated at a £20,000 WTP threshold, with a 30 to 79% decrease in the ICER of DAA treatment strategies, depending on genotype and treatment uptake rate (Bennett, Gordon et al. 2017). In addition to treatment uptake, the model was sensitive to the time horizon with shorter time horizons capturing fewer transmissions and therefore having a smaller impact on cost-effectiveness.

A 2017 UK CUA used a Markov model to evaluate the cost-effectiveness of a programme delivering testing and treatment in a drug treatment unit (Selvapatt, Ward et al. 2017). Using 3 years of data from the programme, the intervention was found to have an average cost saving compared to no screening and treatment and so dominated. A hypothetical scenario where all DAA treatment was used had an ICER of £1,029 per QALY gained. Sensitivity analysis found that the base case remained cost saving under the majority of scenarios, which was only sensitive to increasing the discount rate to 6%, reducing health state costs and increasing treatment costs by 20%. Both scenarios remained cost-effective under all scenarios in sensitivity analysis, with ICER ranging from -£2,291 to £1,430 per QALY for the base case and -£1,542 to £3,892 per QALY for the all DAA case.

International PWID analysis

A 2003 French CEA used a decision tree and Markov model to evaluate the cost effectiveness of a strategy of screening PWID using 2 enzyme immunoblot assay (EIA) tests, or EIA then PCR, compared to no screening and no treatment (Loubiere, Rotily et al. 2003). The 2 EIA tests was the most cost-effective option with a cost of €3,825 (£3,302) per LY gained.

A 2007 US CEA evaluated the cost of offering HCV counselling, testing and referral to PWID sexual health clinic attendees (Honeycutt, Harris et al. 2007). Included costs were staff time for pre- and post-test counselling and performing the blood test, and laboratory costs. The cost per true positive client who returned for results was $54 (£43). This was sensitive to estimates of the cost of testing, but all results under sensitivity analysis were highly cost-effective.

A 2008 Italian CUA used a Markov model to estimate the cost-effectiveness of screening PWID in a population in north-east Italy, with an aim of identifying cases of acute HCV as this had more successful treatment outcomes with PEG-IFN/RBV (Tramarin, Gennaro et al. 2008). The ICER for this intervention was -€3,132 (-£2,814) per QALY as the intervention cost less and was more effective (dominated) no screening. The model was sensitive to the prevalence of genotypes 1 and 4, as these were more difficult to treat under the treatment regime.

A 2012 Netherlands CUA used a Markov model to estimate the cost-effectiveness of a campaign in Rotterdam targeted at hard drug users, in particular PWID which aimed at increasing their knowledge and their willingness to test for HCV (Helsper, Borkent-Raven et al. 2012). The resulting ICER was €7,321 (£5,804) per QALY. The model was primarily sensitive to the age at testing, and also to costs and disease progression parameters. Uncertainty analysis indicated that the probability of the intervention not being cost-effective was negligible.

A 2012 US CEA and CUA used a whole population dynamic transmission model to assess the cost-effectiveness of various strategies for screening individuals in OST for HIV, HCV or both with an aim of identifying acute infections (Cipriano, Zaric et al. 2012). This study found that strategies which included HCV screening were less cost-effective than those which screened for HIV alone, with ICERs in excess of $100,000 (£78,740) per QALY. The model was sensitive to assumptions on the disutility of HCV diagnosis, as people diagnosed were likely not to access testing for some time, and on behaviour change resulting from a known diagnosis, with a reduction in needle sharing on knowledge of HCV diagnosis improving the cost-effectiveness of HCV screening.

A 2015 US CUA used a decision tree plus Markov model to assess the cost-effectiveness of providing rapid onsite HCV and HIV testing in drug treatment (one-third PWID or former PWID) and found that this was cost-effective compared to no testing at a cost of $18,300 (£14,173) per QALY, and dominated referral for offsite testing (Schackman, Leff et al. 2015). Results were similar whether PEG/RBV/sofosbuvir (SOF) (genotype 1) or SOF/RBV (genotypes 2/3), or interferon-free regimens were used, and results were consistent in sensitivity analyses.

A 2017 Netherlands CUA used a Markov chain model to estimate the cost-effectiveness of a national campaign to increase testing for PWID in DTS, finding an ICER of €9,056 (£7,813, 95% CI £5,205-£11,668) per QALY, indicating that the probability of the intervention not being cost-effective was negligible. The model was sensitive to the proportion of PWID who chose to be treated and the cost of treatment. If DAAs were used instead of predominantly PEG-IFN/RBV treatment, the ICER increased to €11,035 (£9,521) per QALY which was still cost-effective (Helsper, Janssen et al. 2017).

A 2018 French CUA used a stochastic dynamic model to assess the cost-effectiveness of different scenarios to improve harm reduction and the cascade of care for PWID treated with DAAs: i) current practice, ii) improved access to NSP and OST, iii) treatment initiation at earlier fibrosis stage (F0 vs F2), iv) improved testing and linkage to care, v) (iii) and (iv) combined, vi) (ii)-(iv) combined (Cousien, Tran et al. 2018). Scenarios (ii) to (iv) all had at least 1 more expensive scenario that was more cost-effective, such as extended dominance. Scenario (v) was the most cost-effective with an ICER of €5,300 (£4,574) per QALY compared with scenario (i). Scenario (vi), although more effective than scenario (v) was not cost-effective, with an ICER of €105,600 (£91,129) per QALY. The model was sensitive to treatment costs, incidence, and connectivity of the social network.

A 2018 US CUA used a decision analytic model to evaluate the cost-effectiveness of a care-coordination intervention in methadone maintenance ((Schackman, Gutkind et al. 2018), intervention results presented in (Masson, Delucchi et al. 2013)). Compared to no intervention the intervention of HCV screening, education and care coordination had an ICER of $24,600 (£18,771) per QALY, and had extended dominance (cost more but more effective) over the control intervention of HCV screening and education only. This result was consistent to sensitivity analyses and an analysis using the societal perspective.

Summary

Almost all studies show that screening for PWID is cost-effective, although 1 study showed it was not – this was due to disutility of diagnosis followed by treatment delay, plus likely reinfection included in the model:

- care coordination and onsite treatment in drug treatment services were both cost-effective in analyses of real life interventions
- there is evidence that increasing treatment uptake increases the cost-effectiveness of DAA drugs
- results were sensitive to disease progression rates, treatment uptake, and prevalence, particularly of difficult to treat genotypes

PWID in prisoners

Six studies evaluated the cost-effectiveness of interventions for prisoners – a UK CEA, 4 UK CUA and a US CUA (table 18).

In the UK

A 2006 UK CEA used a Markov model to compare the cost-effectiveness of 4 verbal screening strategies applied to casefinding on reception into prison (Sutton, Edmunds et al. 2006). Prisoners attended a 1-hour lecture on risk factors for BBVs and then were verbally screened for i) past positive HCV test and ever PWID ii) past positive HCV test only iii) ever PWID only or iv) no verbal screening before being offered testing. Incremental costs per case were £2,102, £16,625 and £6,388 for scenarios i), iii) and iv) respectively compared to no screening and no testing, while scenario ii) was dominated. The model was sensitive to the number of prisoners that attended the lecture on reception into prison and the proportion of prisoners accepting testing.

A 2006 UK CUA used a decision analytic model to evaluate the cost effectiveness of 2 interventions aimed at all new prisoners aged 25-39 years, 1 which gave a general lecture on BBV during induction (population approach), and the other gave a lecture with a specific focus on injecting drug use as a risk factor for HCV (targeted PWID approach), both followed by opt-in testing (Castelnuovo, Thompson-Coon et al. 2006). The first scenario resulted in an ICER of £20,083 per QALY, and the second had an ICER of £16,484 per QALY. Sensitivity analysis was conducted for the 'general case' (not specifically for this population) and was sensitive to discount rates and distributions of disease severity in the population, with increased cost-effectiveness associated with treating individuals with more severe disease. Probabilistic sensitivity analysis showed considerable uncertainty in the estimate, including a small number of cases where screening was dominated. EVPI analysis showed a population EPVI of £16.9 million given a WTP threshold of £30,000 per QALY, with partial EVPI analysis showing that the only parameters within the model with an associated value of information were the utilities.

A 2008 UK CUA evaluated screening plus an educational session for those who disclosed as current or former PWID on reception into prison, followed by subsequent treatment and found that HCV screening compared with no screening cost £54,852 per QALY and was not cost-effective (Sutton, Edmunds et al. 2008). There was extensive uncertainty around this estimate, with the model sensitive to assumptions on chronic HCV progression rates, discount rates, and rates of re-presentation for testing in the community. Re-presentation was assumed to increase after release for those exposed to the screening programme due to increased awareness of HCV, but if those individuals did not re-present, the intervention was dominated, likely due to the negative impact on quality of life of a HCV diagnosis followed by lack of successful treatment in prison. There were a number of cases under probabilistic sensitivity analysis where screening was dominated.

A 2013 UK CUA evaluated DBS testing compared to venepuncture as usual care for PWID in prisons and calculated an ICER of £59,400 assuming no linkage to treatment on release from prison which was not cost-effective (Martin, Hickman et al. 2013). This

study used a dynamic-transmission model which included the population-level benefits of prevention of HCV. Cost-effectiveness was sensitive to parameters on rates of treatment initiation and continuity of care, as many of the IFN/RBV treatments were discontinued due to short incarceration times and long duration of treatment. If 50% of PWID referred initiated treatment within 2 years the ICER would be below £30,000 per QALY, and if continuity of care was greater than 40% the ICER would fall below £20,000.

A 2016 UK CUA evaluated the effect of increased case-finding from DBS testing combined with DAA treatment using a dynamic transmission model and calculated an ICER of £19,850 if currently available treatments were used and £15,090 if DAAs were used (Martin, Vickerman et al. 2016). The increased cost-effectiveness in this model was due to the increased treatment rates in prison which were possible due to the availability of therapies with shorter durations. This model was sensitive to changes in the cascade of care and could be highly cost-effective (ICER <£13,000) if treatment rates after referral in prison were increased from 2.5% (base case) to 10%.

International PWID in prisoners

A 2016 US CUA used a Markov model to estimate the cost-effectiveness of 5 different screening scenarios followed by treatment with DAAs in prison if diagnosed compared to no screening. ICER ranged from $19,600 (£15,539) per QALY gained for 1-year risk-based to $29,200 (£23,150) per QALY gained for a 10-year universal screening program (He, Li et al. 2016). Patients with fibrosis scores 3 and 4 would be eligible for treatment and receive treatment at a rate of 4.1% per month in prison, or 2.6% per month in the community. Treatment as prevention was included in the model and had a substantial effect. Results were sensitive to the cost of treatment and timeliness of treatment initiation in relation to diagnosis and disease stage.

Summary

There was mixed evidence on the cost-effectiveness of screening in prisons:

- ability to link patients to treatment is an important factor in cost-effectiveness of prison interventions; studies which assumed that patients were linked to treatment in prison were cost-effective.

Migrants

Two UK CUA evaluated the cost-effectiveness of screening for migrants in primary care (table 19).

In the UK

A 2014 UK CUA used a decision tree plus Markov model to evaluate the impact of inviting South Asian immigrants for 'opt-out' screening with a letter compared to background testing rates and reported an ICER of £23,200 which was potentially cost-effective, although there was a high degree of uncertainty around the estimate (Miners, Martin et al. 2014). Cost-effectiveness was sensitive to prevalence, the intervention effect, cost of the intervention and treatment uptake. EVPI analysis found that if the intervention remained a viable option for 10 years it would produce a total population EVPI of around £4 million at a WTP threshold of £30,000. This figure was described as conservative as it considered net rather than gross immigration and only included migrants from the Indian subcontinent over a 10 year time span, whereas immigration from HCV endemic countries is more widespread and is likely to continue for longer than 10 years. Partial EVPI analysis suggested that research into probability of treatment uptake, utility of SVR health states and the cost of the intervention would be of most value.

A 2018 UK CUA analysis undertaken alongside an RCT evaluating the impact of incentivising GPs to identify and test first and second generation migrants from countries >2% prevalence for HCV and HBV found the intervention to be cost-effective, with an ICER of £8,540 in the base case (Flanagan, Kunkel et al. 2018). If HCV treatment was with pure DAA regimes the intervention was cost-effective with ICER of between £6,935 and £18,185 per QALY, depending on pricing and the regime/treatment duration applied. The intervention was not cost-effective for cohorts with mean age >56. Screening based on ethnic background was cost-effective for Pakistani ethnicity with an ICER of >£9,523 per QALY. Probabilistic sensitivity analysis found that the intervention was likely to be cost-effective in almost all scenarios.

Summary

Although limited, the available evidence suggests that primary care screening interventions for migrants are cost-effective:

- results were sensitive to prevalence, intervention effect, costs of treatment and treatment uptake.

MSM

One study evaluated the cost-effectiveness of screening for MSM; a US CUA (table 20).

International

A 2012 US CUA used a Monte Carlo simulation model to evaluate the cost-effectiveness of several different screening strategies for acute HCV in HIV-positive MSM (Linas, Wong et al. 2012). Screening using 6-monthly liver function tests (LFTs) and a 12-month anti-HCV test had an ICER of $43,700 (£34,388) per QALY compared to symptom-based screening with IFN+RBV treatment. If protease inhibitors were added to the treatment the ICER increased to $57,800 (£45,483) per QALY.

Summary

There was limited evidence for cost-effectiveness of screening for MSM; the 1 available study suggests that screening HIV-positive MSM using 6-monthly LFTs and 12-month anti-HCV test was the most cost-effective method, however this was not cost-effective at UK WTP thresholds.

Antenatal screening for HCV

Three studies evaluated the cost-effectiveness of antenatal screening for HCV, a UK CUA, a US CUA and a Netherlands CEA (table 21).

In the UK

A 2015 UK CUA used data from a 10 year antenatal screening programme in a general population in London to estimate cost-effectivenes using a Markov model (Selvapatt, Ward et al. 2015). This study considered the impact on the pregnant women only and identified 3 separate scenarios, all of which were cost-effective: £2,400 per QALY for treatment with RBV only, £9,139 per QALY for SOF only and £3,105 per QALY for RBV then SOF. Results were sensitive to prevalence of HCV and treatment uptake (assumed to be 50% in the base case), with increases in either increasing cost-effectiveness.

International antenatal screening

The 2005 US CUA used a decision tree with Markov model to assess the cost-effectiveness of antenatal screening including the lifetime of the infant in addition to the mother and found that HCV screening compared with no screening in a general population cost £802,984 per QALY gained; for the infant screening and treatment had

an ICER of £7,039 per QALY and the addition of a Caesarean section to each woman diagnosed had an ICER of £2,125 per QALY (Plunkett and Grobman 2005).

In this model treatment (PEG-IFN/RBV) was only available to those with moderate hepatitis, of which 70% were treated in the base case. Screening alone caused a net decrease in QALYs due to the disutility of knowledge of infection with no treatment for several years, as this population are relatively young and healthy. The addition of a Caesarean to prevent transmission to the infant led to a net increase in QALYs, but was still not cost-effective at $1,170,000 (£927,926) per QALY. The model was robust to all cost, probability and utility variables and the discount rate.

A 2013 Netherlands CEA considered the pregnant woman only, and used a Markov model to assess screening in the general population of pregnant women and found a cost of £39,138 per life year gained, which was deemed not to be cost effective (Urbanus, van Keep et al. 2013). The same study assessed a population of first-generation non-Western pregnant women and found this to be more cost-effective (although still not cost-effective at a UK WTP threshold) at a cost of £35,140 per life year gained due to the higher prevalence in this group.

This study also assumed a 50% treatment rate, with PEG-IFN/RBV (genotype 2 to 4) or PEG-IFN/RBV+PI (genotype 1), but differed from the UK study in that the costs of screening and treatment were higher in the Netherlands, and did not include the value of improved quality of life associated with completing treatment. The model was sensitive to treatment costs, treatment outcome, costs of testing, discount rates, disease state transition and treatment uptake, with disease state transition having the largest impact on both the whole population and non-Western screening.

Summary

There is mixed evidence on the cost-effectiveness of antenatal screening interventions:

- cost-effectiveness is sensitive to prevalence and assumptions on linkage to care.

Sexual health

Two studies evaluated the cost-effectiveness of interventions in sexual health settings; a UK CUA of screening for GUM clinic attendees, and a US CEA of counselling, testing and referral for sexual health clinic attendees (table 22).

In the UK

A 2003 UK CUA used a Markov model to estimate the cost-effectiveness of HCV screening for all GUM clinic attendees compared to no screening and found that this was

not cost-effective with an ICER of £85,000 per QALY (Stein, Dalziel et al. 2003). At the time of this study treatment required disease propression to moderate hepatitis which was assessed by liver biopsy. Baseline treatment was not stated but if PEG-IFN was used the ICER decreased to £46,389 per QALY. The model was sensitive to prevalence, acceptance of testing, acceptance of liver biopsy, and acceptance of treatment.

International sexual health settings

A 2007 US CEA evaluated the cost of offering HCV counselling, testing and referral to 3 groups of sexual health clinic attendees – non-PWID men aged 40+ with fewer than 100 sexual partners, non-PWID men aged 40+ with 100 or more sexual partners, non-PWID women aged 40+ (Honeycutt, Harris et al. 2007). Included costs were staff time for pre- and post-test counselling and performing the blood test, and laboratory costs. Costs per true positive client who returned for results were $179 (£142) for non-PWID men aged 40+ with 100 or more sexual partners, $1,386 (£1,098) for non-PWID men aged 40+ with fewer than 100 sexual partners, and $2,986 (£2,367) for non-PWID women aged 40+. Results were sensitive to prevalence estimates, particularly for women as prevalence was lowest in this group.

Summary

Limited evidence suggests that HCV screening is not cost-effective for general UK GUM attendees:

- cost-effectiveness is sensitive to prevalence in this group

Risk-based screening

Six studies evaluated the cost-effectiveness of screening based on risk factors; a UK CUA, a UK financial option appraisal and commissioning model for purchasers, a US CEA, a French CEA, an Italian CUA and a US CUA (table 23).

In the UK

A 2001 financial option appraisal and commissioning model for purchasers in West Kent district health authority was included in the Coward review, although this study was not a formal CEA (Batra 2001). The model compared providing opportunistic testing and treatment to people with risk factors with the cost of liver transplantation and calculated a net present value of -£25,407 to -£32,471 for opportunistic screening of high-risk individuals to prevent 1 patient developing cirrhosis in 10 to 20 years, which was deemed not to be cost-effective. This study was not a formal CEA and did not include utility, and used testing data from 1998 to 1999 when HCV prevalence was lower.

A 2019 UK CUA used a Markov model to assess coct-effectiveness alongside an RCT of a complex intervention in GP practices which included staff HCV training, raising patient awareness through posters and leaflets, and using an electronic algorithm on practice systems to identify at-risk patients to be invited for testing and flag them for opportunistic testing if they attended a consultation (HepCATT in Primary Care (Roberts, Macleod et al. 2019)). An ICER of £7,507 per QALY was found for the base case, with probabilistic sensitivity analyses finding an 89.7% probability of the intervention being cost-effective at the £20,000 per QALY threshold. The intervention remained cost-effective when parameters on linkage to care, test yield, utility and drug costs were varied.

International risk based screening

A 1998 US CEA reported a cost per case ranging from £247 and concluded that risk-factor based screening was cost-effective (Lapane, AF et al. 1998).

A 2004 French CEA evaluated the cost-effectiveness of screening for people who received blood transfusions before 1991 and current or former drug users (injection or inhalation) in primary care (Josset, Torre et al. 2004). Costs per positive test ranged from €654 (£590) to €2,182 (£1,970) depending on which costs were included. Strategies including other risk groups (history of gastroscopy, contact with an infected person, active or former imprisonment, history of invasive procedures, history of colonoscopy, history of surgery) were compared and all were less cost-effective than the base case. The model was sensitive to prevalence and the proportion of practice population in the risk groups; if this was lower cost-effectiveness decreased rapidly.

A 2008 Italian CUA used a Markov model to estimate the cost-effectiveness of screening people who had surgery in a population in north-east Italy, with an aim of identifying cases of acute HCV as this had more successful treatment outcomes with PEG-IFN/RBV (Tramarin, Gennaro et al. 2008). The ICER for this intervention was €918,147 (£727,907) per QALY as there was a low incidence of infection in this group. The model was sensitive to the prevalence of genotypes 1 and 4, as these were more difficult to treat under the treatment regime.

A 2013 US CUA used a decision tree plus Markov model to estimate the cost-effectiveness of risk-factor based screening and did not report an ICER but concluded that risk-based screening was not cost-effective (Liu, Cipriano et al. 2013).

A 2017 Netherlands CUA used a Markov chain model to estimate the cost-effectiveness of a nationwide public and health professional awareness raising campaign to test at-risk groups, including migrants, blood product recipients before 1992, travellers who had their skin pierced in endemic countries and family members of HCV positive individuals (Helsper, Janssen et al. 2017). The intervention was cost-effective with an ICER of

€18,421 (£15,882) per QALY, and a 34% probability of being below the Netherlands £11,668 per QALY threshold. The model was primarily sensitive to the number of additional HCV positive patients identified and was also sensitive to the costs of the campaign. This intervention became more cost-effective if DAA treatment was used instead of the predominant PEG-IFN/RBV, with the ICER decreasing to €14,471 (£12,485) per QALY.

Summary

Results for risk-based screening are variable and depend on population and which risk factors are included.

Evidence from 1 recent UK RCT suggests that risk-based screening in GPs is cost-effective – further evaluations are needed.

Birth cohort screening interventions

Twelve studies evaluated the cost-effectiveness of birth cohort screening interventions – 2 UK CUA, 7 US CUA, a US CUA and CEA, a Italian CUA and a Canadian CUA (table 24).

In the UK

A 2006 UK CUA used a decision tree plus Markov model to evaluate the cost-effectiveness of opportunistic HCV screening offered to people aged 30 to 54 years in general practice in an areas of assumed high HCV prevalence (Castelnuovo, Thompson-Coon et al. 2006) using data from the Anderson et al intervention described in the primary care interventions section (Anderson, Mandeville et al. 2009) and found a cost per QALY of £15,493. Sensitivity analysis was conducted for the ‘general case’ (not specifically for this population) and was sensitive to discount rates and distributions of disease severity in the population, with increased cost-effectiveness associated with treating individuals with more severe disease. Probabilistic sensitivity analysis showed considerable uncertainty in the estimate, including a small number of cases where screening was dominated.

A 2016 UK threshold CUA assessed the cost-effectiveness of testing a birth cohort of patients born 1950-1980, assuming 52.4% treatment uptake. To meet the cost-effectiveness threshold of £20,000 per QALY £24.52 per patient could be spent on the intervention, which increased to £41.31 if DAAs were used. The model was sensitive to treatment uptake and HCV prevalence. The intervention was deemed unlikely to be cost-effective.

A UK CUA (not yet published) evaluated the cost-effectiveness of HCV screening as an add-on to the NHS Health Check for people born between 1950 and 1979 and found that it had a low probability of cost-effectiveness for all birth cohorts in the UK population, with ICER ranging from £31,695 to £105,568 (Williams, Miners et al. 2019). This was sensitive to parameters on disease progression, probability of referral, probability of receiving treatment and prevalence. EVPI analysis across all birth cohorts was £7.8 million at £20,000 per QALY, with the partial EVPI analysis (performed for the 1970 to 1974 cohort) identifying that linkage to care and utility of achieving SVR had the highest values, and other parameters having no value at this threshold.

International birth cohort screening

A 2012 US CUA used a decision analytic model for screening and a Markov model for disease progression to estimate the cost-effectiveness of offering one-time screening for the population born between 1945 and 1965 with PEG-IFN/RBV treatment in addition to risk-based screening, compared to risk-based screening for the whole population and found a cost of $5,400 (£4,281) per QALY which dominated general population screening (Coffin, Scott et al. 2012).

A 2012 US CUA used a Markov model to estimate the cost-effectiveness of one-time screening for the population born between 1945 and 1965 followed by either PEG-IFN/RBV, or by treatment with DAAs for patients with genotype 1 and PEG-IFN/RBV for genotypes 2 and 3, compared to risk-based or no screening (Rein, Smith et al. 2012). ICERs of $15,700 (£12,452) per QALY for standard treatment and $35,700 (£28,314) per QALY for treatment with DAAs plus standard treatment were found. The model was most sensitive to assumptions of disutility from disease stages before liver disease, discount rates, and probability of SVR for genotype 1.

A 2012 US CUA and CEA used a decision tree plus Markov model to estimate the cost-effectiveness of providing screening to the population born 1946 to 1970 followed by treatment with DAAs (McGarry, Pawar et al. 2012). An ICER of $37,700 (£29,889) was found when comparing birth cohort to risk-based screening. This was sensitive to the time horizon over which costs and benefits were assessed, and uptake and efficacy of treatment.

A 2013 US CUA used a Markov model to estimate the cost-effectiveness of screening for people aged 40 to 74 and found ICER of $60,590 (£48,036) for treatment with IL-28B guided triple-therapy and $65,749 (£52,126) if universal triple therapy was used (Liu, Cipriano et al. 2013). The model was sensitive to fibrosis stage of diagnosed patients, disutility of knowledge of diagnosis, healthcare costs resulting from knowledge of HCV status (to manage condition and due to anxiety about health), treatment uptake, treatment adherence and reduction in non-liver related mortality from treatment.

A 2013 US CUA used a Markov model to compare risk-based and universal screening for the cohort born between 1945 and 1965 (McEwan, Ward et al. 2013). In the risk-based strategy those with risk factors of former PWID, blood clotting factor recipients prior to 1978, blood transfusion or organ transplantation prior to 1992, long-term dialysis and children of HCV-infected mothers were tested. An ICER of $28,602 (£22,685) was found for the universal over risk-based strategy. This was sensitive to treatment uptake, timing of treatment initiation and prioritisation of treatment by disease staging, with treatment prioritised to patients with more advanced disease being more cost-effective.

A 2012 Italian CUA used a decision tree plus Markov model to estimate the cost-effectiveness of offering one-time screening to the 35+ age group compared to no screening with only symptomatic cases identified, with PEG-IFN/RBV treatment (Ruggeri, Coretti et al. 2013). An ICER of €5,171 (£4,101) per QALY was found, which was sensitive to the age of the target population (older age groups had increased costs per QALY), the time horizon, with decreasing ICERs at longer time horizons, and prevalence. Probabilistic sensitivity analysis showed the intervention was cost-effective at a WTP threshold of £30,000 per QALY in 88% of scenarios, with more than 85% of scenarios under the £20,000 threshold.

A 2015 Canadian CUA used a Markov model to assess the cost-effectiveness of one-time screening for people aged 25-64 or 45-64 years, comparing no screening to screening with various treatment strategies: i) PEG-IFN/RBV; ii) simeprevir-based combination therapy (genotype 1 patients), SOF-based combination therapy (genotype 2 and 3 patients), or PEG-IFN/RBV (other genotypes); iii) as in ii) but genotype 1 patients treated with DAA (ABT-450–based interferon-free combination therapy) (Wong, Tu et al. 2015). For the 25-64 years age group, ICER were $38,117 (£30,231) per QALY for strategy i), $42,398 (£33,626) per QALY for strategy ii), and $34,783 (£27,587) per QALY for strategy iii). For the 45-64 years age group, ICER were $34,359 (£27,250) per QALY for strategy i), $35 562 (£28,205) per QALY for strategy ii) and $44,034 (£34,924) per QALY for strategy iii). This was sensitive to assumptions about the costs (excluding treatment costs) and utilities of HCV infection, prevalence, acceptance of screening, costs of screening, and rate of known infections.

A 2017 US CUA estimated the cost-effectiveness of conducting one-time testing on the entire population aged 18+, compared to testing the 1945-1964 birth cohort and to risk-based screening as baseline (Rein, Wittenborn et al. 2017). This was a conference abstract and model type was not reported. Testing the entire adult population had an ICER of $48,998 (£37,513) per QALY compared to risk-based testing, and dominated birth cohort testing. The model was sensitive to drug costs, treatment uptake, and testing uptake.

Summary

International studies (mainly US) broadly show that birth cohort screening is cost-effective, largely due to high HCV prevalence in this birth cohort in the US:

- there was mixed evidence from UK studies; most recent study suggests it is not cost-effective in any birth cohort in the UK

Results were sensitive to utility assumptions, treatment uptake and prevalence

General population screening

Five studies evaluated the cost-effectiveness of general population screening – a UK cost analysis, 3 US CUA and a Netherlands CUA (table 25).

In the UK

A 2017 UK pilot study which implemented incentivised opt-out testing in GP practices in an area of high HIV prevalence estimated a cost per BBV diagnosis of £1,060, where included costs were sign up and incentive payments made to practices, laboratory payments, promotion and a GP advisor fee (Leeds City Council Sexual Health Team, Elton John Aids Foundation et al. 2017).

In the US

A 2001 US CUA used a decision tree plus Markov model to estimate the cost-effectiveness of screening for a hypothetical cohort of 35 year old average risk adults presenting in primary care for routine checkups, comparing ELISA then PCR testing, only PCR testing, and no screening with IFN/RBV treatment and found that both strategies were dominated by no screening (Singer and Younossi 2001). The model used a societal perspective which included days lost from work due to treatment effects. The model was sensitive to treatment uptake, disease progression rate, and the disutility associated with knowledge of HCV diagnosis, but when this was altered from 0.02 to 0.01, not screening was still the more cost-effective strategy. The authors concluded that the disutility of knowledge outweighed the benefits as few were treated, and few would go on to develop cirrhosis later on.

A 2012 US CUA used a decision tree for screening and a Markov model for disease progression to estimate the cost-effectiveness of offering one-time screening to the population aged 20-69 with PEG-IFN/RBV treatment and found a cost of $7,900 (£6,243 per) QALY (Coffin, Scott et al. 2012). The intervention remained cost-effective in all

one-way sensitivity analyses, although the ranges used were small, with a prevalence range of 1.3-2% which is higher than the prevalence in the UK.

A 2013 US CUA used a decision tree plus Markov model to estimate the cost-effectiveness of population screening followed by treatment with boceprevir compared to no screening and found an ICER of $47,276 (£37,364) per QALY (Eckman, Talal et al. 2013). The higher cost of this model was likely due to the higher costs of DAA treatment used. Probabilistic sensitivity analysis showed that screening was preferred over not screening 100% of the time. The model was sensitive to prevalence, disease progression, proportion with genotypes 2 and 3, quality of life associated with receiving treatment, age at time of infection, treatment cost, test characteristics, and treatment efficacy.

A 2012 Netherlands CUA used a Markov model to estimate the cost-effectiveness of a general publicity campaign in a region of the Netherlands, and an additional support programme for primary care, consisting of voluntary courses for GPs and the employment of 2 practice facilitators who visited GP practices to provide information regarding HCV and the campaign (Helsper, Borkent-Raven et al. 2012). The general publicity campaign led to no extra cases being diagnosed, but the additional support campaign was cost-effective with an ICER of €11,297 (£10,136) per QALY. The model was most sensitive to parameters on the number of cases identified during the campaign and the rate of referral to treatment.

Summary

There is mixed evidence from international studies on the cost-effectiveness of general population screening:

- limited UK evidence suggests screening in a high HIV-prevalence area was cost-effective, but this did not include linkage to care or utility
- results were sensitive to prevalence, treatment uptake and disease progression rates

Emergency department

Three UK studies assessed the cost-effectiveness of ED interventions – 2 cost analyses and a threshold CEA (table 26).

In the UK

A 2016 UK ED opt-out testing pilot evaluated a cost per case of HCV identified of £988, assuming a cost per diagnosisof £7 which was deemed to be cost-effective (Orkin, Flanagan et al. 2016).

A 2018 UK ED opt-out testing pilot found a cost per HCV diagnosis of £4,682 (Bradshaw, Rae et al. 2018). Both studies only included laboratory costs, the higher costs in the second study were due to a lower prevalence of HCV and inclusion of the higher costs of RNA testing (£68 per test) to confirm current infection.

A 2019 UK threshold CEA found that ED opt-out testing would be cost-effective at a £20,000 WTP threshold at 0.26% HCV RNA prevalence (Williams, Vickerman et al. 2019). This was sensitive to the costs of diagnostic tests, treatment costs, proportion of patients contacted, proportion of patients requiring linkage to care and proportion accepting treatment.

Summary

There is limited evidence on the cost-effectiveness of ED interventions:

- threshold analysis suggests 0.26% HCV RNA prevalence is needed for ED screening to be cost-effective at £20,000 WTP threshold

Care pathway interventions

Four international studies evaluated the cost-effectiveness of other care-pathway interventions – 2 CUA and 2 cost analyses (table 27).

A Spanish study conducted a CUA alongside an RCT of multidisciplinary support for patients receiving PEG-IFN/RBV treatment, using a Markov model (Carrion, Gonzalez-Colominas et al. 2013). The intervention cost less per patient (£11,505 vs £13,977) and achieved greater QALYs (16.3) than the control (15.8) and so dominated.

A US study conducted a cost analysis of an intervention to provide hepatitis education, counselling, testing, referral and support into treatment for people with dual diagnosis (severe mental illness and substance misuse) in community mental health ((Slade, Rosenberg et al. 2013). Results from this intervention are presented earlier (Rosenberg, Goldberg et al. 2010)). The intervention cost $399 (£305) more per patient than treatment as usual, with a cost of $706 (£541) per additional patient HVC tested.

An Australian cost analysis evaluated the costs of an intervention to provide rapid access to treatment by providing Fibroscan and immediate hepatologist consultation in a hospital

liver clinic, compared to a historic comparator where patients were assessed by liver biopsy (Whitty, Tallis et al. 2014). Patients who received the intervention had on average AU$3,040 (£1,660) lower healthcare costs per patient and shorter time to treatment.

A US CUA used a decision tree and Markov model to evaluate the cost-effectiveness of a project ECHO telementoring intervention to support primary care to test and treat HCV, compared to usual care with patients referred to tertiary care for treatment (Rattay, Dumont et al. 2017). An ICER of $10,351 (£7,923) per QALY was found, with a probabilistic sensitivity analysis finding that 95.6% of the iterations fell below a $50,000 (£38,280) per QALY WTP threshold. The model was sensitive to age of patients treated and the discount rate, with a more favourable ICER if younger patients were treated.

Summary

There are limited studies on care pathway interventions, and studies do not reflect the range of possible interventions:

- one study found a multidisciplinary care pathway reduced the cost of the patient pathway overall
- one study of telementoring to support primary care testing and treatment found that this was cost-effective

Discussion

Of 63 studies which evaluated the costs of interventions, 49 were CUA, 10 were CEA, and 4 were cost analyses or comparisons. Among the CUA, 40 evaluated HCV screening, covering a range of populations, interventions and model approaches. In contrast, only 6 studies evaluated the costs of a linkage to care intervention, and only 4 of these were full CUA. Nevertheless, the importance of linkage to care in influencing cost-effectiveness was highlighted in several studies (Bennett, McEwan et al. 2015, Martin, Vickerman et al. 2016, Bennett, Gordon et al. 2017, Cousien, Tran et al. 2018). The least cost-effective studies were those where a low proportion of the diagnosed population were likely to be treated, either due to poor linkage to care in prisons (Sutton, Edmunds et al. 2008, Martin, Hickman et al. 2013), or a low proportion of the diagnosed population likely to reach the threshold of disease progression required to initiate treatment (Plunkett and Grobman 2005, Cipriano, Zaric et al. 2012).

In these cases, screening interventions had the potential to result in a net disutility due to the disutility of awareness of infection lived with for many years without the prospect of accessing treatment. Due to the current availability of treatment through the ODNs these situations are now less likely to occur, a factor which should increase the cost-

effectiveness of all screening interventions, but also highlights the importance of ensuring linkage to care in order for screening interventions to be cost-effective.

The other parameters that cost-effectiveness results were most sensitive to were prevalence in the target population, in particular prevalence of difficult to treat genotypes, progression rates from chronic HCV to cirrhosis, and utilities. Cost-effectiveness in the models was overall relatively insensitive to variations in most of the input parameters, such as costs of screening and treatment, although 1 study showed that adding protease inhibitors to standard treatment changed the conclusions about cost-effectiveness (Urbanus, van Keep et al. 2013). Screening which identified people at an older age and with more advanced disease was generally more cost-effective, a factor which influences the cost-effectiveness of birth cohort screening in the US, although 3 studies identified that interventions were less cost-effective for older populations due to the reduced time horizon to obtain benefits from treatment (Ruggeri, Coretti et al. 2013, Rattay, Dumont et al. 2017, Flanagan, Kunkel et al. 2018).

The Coward review noted that none of the studies included the costs associated with implementing a screening programme, and that further evaluations of implementation methods were needed. The Coward review reported that overall studies were high quality, representing a robust body of evidence. The Geue review identified that more recent studies performed better when assessed by a performance matrix. Correct assumptions about treatment efficacy, acceptability and uptake, duration and costs are needed to make accurate cost-effectiveness estimates. Only the most recent of the included studies used IFN-free DAAs as treatment, and therefore these most recent studies are more likely to provide accurate cost-effectiveness estimates for the current environment.

Summary

There is a substantial body of evidence which shows that testing PWID is cost-effective, with degree of cost-effectiveness being sensitive to disease progression rates, treatment uptake, and prevalence, particularly of difficult to treat genotypes:

- there is mixed evidence for screening prisoners, with estimates sensitive to the uptake of screening and treatment and the inclusion of the effects of treatment as prevention

- screening birth cohorts was found to be cost-effective in US studies, however a UK study indicated that it was unlikely to be cost-effective in the UK population as a stand alone intervention, but may be cost-effective if done alongside other existing screening programmes

- there was mixed evidence on the cost-effectiveness of general population and antenatal screening, with cost-effectiveness being dependent on prevalence in the population group
- two UK studies provided evidence that inviting migrants for screening in primary care was cost-effective.
- three UK studies provided limited evidence that ED testing may be cost-effective depending on local HCV prevalence in ED attendees, but did not consider utility or linkage to care
- there was limited evidence on the cost-effectiveness of linkage to care interventions, with 2 evaluations of care coordination interventions finding them to be cost-effective
- three evaluations of interventions which provided onsite treatment in DTS, pharmacy or primary care found them to be cost-effective compared to referral to tertiary care

Models have highly variable inputs, particularly in relation to treatment regimes; more recent models which have the correct assumptions on treatment efficacy and uptake are more likely to provide accurate cost-effectiveness estimates.

Conclusions

This review describes the characteristics and yield of interventions to increase the uptake of testing and diagnosis for HCV, improve linkage to care and increase retention in treatment and treatment completion for those diagnosed with HCV. Evidence is largely from small or pilot non-randomised studies. Almost all randomised studies had at least 1 domain at high risk of bias, and the majority of the non-randomised studies were at critical risk of bias.

Studies had heterogeneous outcomes, both between similar studies and within individual studies which implemented interventions in multiple sites. These demonstrate the multiple factors which affect the implementation and outcome of interventions, and the need to tailor interventions to individual populations and settings.

Cost-effectiveness studies had highly variable inputs, and consideration of the different assumptions around treatment efficacy and linkage to care in all but the most recent studies is needed. More recent models which have up to date assumptions on treatment efficacy, costs and uptake with DAAs are more likely to provide accurate cost-effectiveness estimates. There is a lack of evidence on the cost-effectiveness of complex interventions and interventions to link patients to care. More cost-effectiveness evaluations undertaken alongside interventions, as have been undertaken in some

recent studies, are needed to provide up to date and relevant cost-effectiveness information.

For PWID, DBS testing alone was insufficient to substantially increase testing, whereas nurse-led interventions to coordinate the provision of DBS testing in DTS were associated with greater increases in testing. There is evidence that multidisciplinary or nurse-led care coordination interventions in DTS can significantly increase referrals to treatment and treatment uptake, but there are limited data on their effect on treatment outcomes. Onsite HCV treatment with DAAs has been shown to be feasible for OST patients in DTS, with SVR >88% in 2 studies which evaluated this, but neither compared this to an offsite treatment pathway for the same patient group. One study provided suggestive evidence that needle exchange clients could also be successfully treated onsite in DTS, but had lower adherence and SVR. Findings from pharmacy interventions for PWID, both for testing and onsite treatment were also promising, but these were from preliminary studies and more evaluations are needed. There was a good body of evidence which supported the cost-effectiveness of testing interventions for PWID, with higher treatment uptake increasing the cost-effectiveness of testing and treatment.

Multidisciplinary care coordination interventions were effective in supporting patients to complete HCV treatment and achieve SVR, both for patients with mental health and substance misuse comorbidities and for general patients. Where evaluated, these were found to be cost-effective. Further evaluations are needed of cost-effectiveness and of the effectiveness of these interventions in supporting adherence when prescribing newer DAAs.

Research in prisons, where the population is assumed to be at risk from past or current injecting drug use, is challenging due to the difficulties in access to and delivering healthcare programmes in this secure setting. Findings from studies in other settings may be transferrable with consideration of what is known about the implementation challenges for this particular setting, but many of the issues are specific and unique to the prison estate. Although evidence on the cost-effectiveness of testing interventions in prisons was mixed, more recent studies which took into account improved treatment uptake and completion in prisons now possible with the shorter course treatments demonstrated cost-effectiveness. The available evidence suggests that interventions in prisons can be effective and cost-effective, but that implementation considerations at each site have substantial impacts on what can be achieved.

In primary care, there is a good body of evidence from the US to support the effectiveness of EMR based alerts in increasing testing for patients based on their birth cohort. There is also evidence from 2 randomised UK studies that using the EMR to identify at-risk patients, either through a risk algorithm or identifying migrants, significantly increases testing for those with risk factors recorded on the EMR and is

cost-effective. For migrants, the intervention was more likely to be cost-effective if linked to HBV screening (as more prevalent in migrant populations in the UK).

A weakness of these interventions is that risk factors are often not recorded on the EMR. As such, complete reporting and recording of protected characteristics, including country of birth or origin and ethnicity, in primary care health information systems is required to improve the effectiveness of interventions targeting migrants. There is moderate evidence that staff education interventions lead to small but significant increases in implementation of recommended testing in primary care, and that they improve referral rates for diagnosed patients. Few studies assessed testing or treatment specifically targeted at PWID in primary care. There is evidence that patients can be successfully treated in primary care with DAA treatment, with similar outcomes to tertiary care, and suggestive evidence that this increases access from PWID, but no direct comparisons of the impact primary care compared to tertiary referral on treatment uptake or outcomes for HCV-infected patients in general or for PWID. A study of migrants found there was no difference in treatment uptake or completion when provided in primary care compared to tertiary care.

There is a paucity of evidence for interventions for MSM and homeless populations. For MSM, findings from interventions to promote HIV testing and linkage to care for this group are likely to be transferrable and are available. The only available evidence on cost-effectiveness was for screening HIV-positive MSM, which is already undertaken as part of HIV care in the UK. Further cost-effectiveness evaluations would be needed to support the development of screening interventions for MSM. Research with homeless populations is challenging due to the transience of the population and difficulty in defining the study population. The few studies which were found supported the role of peers in promoting engagement with treatment, and provided suggestive evidence that multidisciplinary care coordination also leads to successful treatment outcomes for this population. There was no evidence relating to the cost-effectiveness of interventions for homeless populations.

The review identified a number of research gaps. There were fewer studies focussing on linking patients to care than there were for testing, and where treatment initiation and uptake were reported in testing studies (usually without comparator data), levels were low. This supports what is already known about the high proportion of previously diagnosed patients who are not engaged in care, and demonstrates the need for further research on interventions to improve linkage to care and treatment retention.

Overall, most of the studies were small pilots or non-randomised studies with limited evidence of scalability and transformation of delivery. However, they do reflect the importance of implementation evaluation in real-world situations. The report does not include the many studies in progress. Horizon scanning to obtain evidence from ongoing

studies as well as action research interventions initiated as part of the national patient re-engagement exercise will be required to build upon the evidence within this report.

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