University of Dundee

DOCTOR OF MEDICINE

HEPATITIS C: PATHWAYS FOR DIAGNOSIS AND TREATMENT

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Award date:
2023

University of Dundee

HEPATITIS C: PATHWAYS FOR DIAGNOSIS AND TREATMENT

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Thesis presented for the degree of
Doctorate of Medicine
University of Dundee
24th May 2023

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LIST OF ABBREVIATIONS

CI	Confidence Interval
CoC	Cascade of care
DAA	Direct acting antivirals
DBS	Dried blood spot
GP	General practitioner
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICER	Incremental cost effectiveness ratio
IDU	Injecting drug use
IEPS	Injecting equipment provision sites
LFTs	Liver function tests
MoC	Model of Care
MSM	Men who have sex with men
NHS	National health service
NMB	Net monetary benefit
NOS	Newcastle-Ottawa Scale
OAT	Opiate agonist therapy
OST	Opiate substitution therapy
PCR	Polymerase chain reaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWID	Person who injects drugs
QALY	Quality adjusted life years
RCT	Randomised controlled trial
RR	Risk ratio
SIC	Supervised injection centres

SIMD	Scottish index of multiple deprivation
SMS	Substance misuse service
SVR	Sustained virologic response
WHO	World Health Organisation
WTP	Willingness to pay
WWID	Women who inject drugs

ACKNOWLEDGEMENTS

I would like to acknowledge gratefully the assistance of many people who supported me during my doctoral studies and contributed to the development of this thesis.

Sincere thanks to my supervisor Professor John Dillon for his unwavering support and belief throughout my doctorate.

I would like to thank my colleagues in the Gut Group at the University of Dundee for their kind support and advice, especially Shirley Cleary, Linda Johnston, Madeleine Caven and Cassandra Baiano.

I am thankful to the nursing and support staff of the HCV multidisciplinary team, I am in awe of their commitment and enthusiasm; Jan Tait, Brian Stevenson and Christian Sharkey, to name just a few.

Thank you to my co-authors for their input into each manuscript, with particular thanks to Francesco Manca, Andrew Radley and Esther Aspinall.

I am grateful to Petra Wright at the Hepatitis C trust who generously donated her time and knowledge.

I wish to extend special thanks to my friend Jacqui Paterson for proof reading my thesis.

Finally I would like to thank my family and friends, without whom I could not have completed this thesis albeit from half a world away.

DECLARATION

I hereby declare that this dissertation entitled “Hepatitis C pathways for diagnosis and treatment” has been prepared by me under the direct guidance of Professor J.F. Dillon as part of my study for the award of Doctorate of Medicine Degree at the University of Dundee, Dundee, Scotland.

I have not submitted this dissertation previously for the award of any degree or diploma at any other institution.

This thesis includes chapters from which three original papers were published in peer-reviewed journals. I have revised and expanded on sections of the published papers in order to generate a consistent presentation within the thesis.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 2, 3 and 5 my contributions to the work involved are described at the beginning of the respective chapters.

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student’s and co-authors’ contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Date

02/06/2022

Signature

SUMMARY

Scotland has committed to eradicating Hepatitis C (HCV) by 2030. In order to achieve this goal, rates of HCV diagnosis, treatment and cure need to be escalated. Given that those most at risk of HCV infection e.g. people who inject drugs (PWID) often belong to a marginalised part of society and find it difficult to engage in conventional hospital based medical care, it is important that diagnosis and treatment initiatives are accessible for all.

The aim of the thesis was to determine the efficacy and cost-effectiveness of HCV diagnosis and treatment pathways in Tayside. A scoping review (Chapter 2) assessed models of care (MoCs) utilising direct acting antivirals (DAAs) to identify the key concepts underpinning their success, especially in underserved populations. Findings from a systematic review and meta-analysis (Chapter 3) demonstrated the feasibility of decentralising care and providing local services with reach into communities of people infected with HCV.

The study presented in Chapter 4 analysed a number of specialised pathways for testing and treatment of HCV amongst the most at-risk populations. Diagnostic pathways targeting populations most at risk of HCV are more effective at yielding new HCV diagnoses than standard pathways. A subsequent cost-effectiveness evaluation of the pathways (Chapter 5) found that testing in injecting equipment provision (IEPS) and in primary care were most cost effective.

These tailored diagnostic pathways will also resolve some of the health inequalities around drug use and provide methods of ensuring entry to treatment. We believe using targeted testing will find the majority of our undiagnosed population. This will help us to direct resources and achieve our aim of elimination by 2030.

CHAPTER 1 – INTRODUCTION

1.1 HEPATITIS C

Hepatitis C is a blood-borne infectious disease that is caused by Hepatitis C virus (HCV). Despite only being discovered in 1989 it has had worldwide impact and is considered a major public health threat. This is due in the most part to the associated liver morbidity and mortality, with liver cirrhosis, hepatocellular carcinoma, liver transplantation and liver disease related death being consequences of untreated infection. Viral hepatitis is the 7th leading cause of death worldwide. HCV has become the target of World Health Organisation (WHO) strategy to eliminate the virus as a global public health threat by 2030.(1)

The virus is transmitted through percutaneous exposure to infected blood although vertical and sexual transmissions have also been described. In developed countries the most common risk factor for HCV infection is injecting drug use and therefore individuals and communities most affected by HCV are amongst the most deprived and marginalised.(2)

The advent of highly effective all oral antiviral treatment for HCV with direct acting antivirals (DAAs) offering cure rates of over 95% has revolutionised the landscape of HCV treatment. Previous modelling studies have demonstrated that it may be possible to eliminate HCV within the next 15-20 years if we combine curative therapy with increased diagnosis rates and prevention of new infections.(3,4) This knowledge has enabled health policy makers to set ambitious treatment targets, which modelling has suggested will make HCV elimination possible.

The challenge therefore is to identify people at risk, test and diagnose HCV infection and then engage affected individuals in care to provide treatment and cure. This is no easy feat in a population who are widely stigmatised and wary of health professionals.(5–7)

This thesis explores some of the original strategies and models of care used in a health board in Scotland seeking to re-balance the health inequalities by delivering testing and treatment to those most at risk.

1.2 EPIDEMIOLOGY

1.2.1 Globally

Current figures suggest that 71.1 million people worldwide are chronically infected with HCV,(1) which equates to approximately 1% of the world's population. Annual mortality rates are approximately 400,000 due to HCV related liver disease.(1,8)

There are wide geographical variations of Hepatitis C infection rates, with Central and East Asia, North Africa and the Middle East estimated to have high prevalence (>3.5%); South and Southeast Asia, sub-Saharan Africa, Central and Southern America, the Caribbean, Australasia, and Europe having moderate prevalence (1.5%-3.5%); whereas Asia Pacific and North America have low prevalence (<1.5%).(9) Historically Egypt has had the highest prevalence due to a widespread anti-schistosomal campaign using injectable anthelmintics therapy from 1950 to 1980. In 2015 Egypt had a seroprevalance of 10% and viral prevalence of 7%.(10)

In high-income countries (HIC) the prevalence is generally below 2%. Transmission of the HCV virus most commonly occurs through injecting drug use or the transfusion of unscreened blood or blood products. Less commonly transmission due to tattooing, vertical transmission and sexual transmission also occurs. It is estimated that 8.5% of global infections (6.1 million), are due to recent injecting drug use. However, this figure does not include those who have contracted HCV through historical injecting drug use.(11,12)

In low to middle income countries (LMIC) the HCV prevalence is higher. The primary sources of HCV infection are the iatrogenic use of non-sterilized medical injection equipment and infusion of inadequately screened blood and blood products.(13) In addition ritual scarring and circumcision traditional in some cultures also carries a risk of HCV transmission if the equipment is re-used or unsterilized.

Approximately 2.3 million people are co-infected with HIV and HCV infections. Co-infection in predominantly seen in men who have sex with men (MSM) and people who inject drugs (PWIDs).(14)

1.2.2 UK

80% of HCV infection in UK is due to intravenous drug use as a consequence of high risk practices such as sharing needles and other injecting paraphernalia. The remaining 20% is accounted for by blood transfusion (occurring prior to screening by the National

Blood Service in the early 1990's), tattoos, body piercing, immigration from high prevalence countries, and sexual or vertical transmission.

The relative importance of these various risk factors has changed since the virus was originally identified 20 years ago. Due to the development of effective HCV screening by the National Blood Service, availability of recombinant clotting factors and the use of erythropoietin (EPO), rates of new transmission due to transfusion of blood or blood products in the UK are nearly eliminated. Recent data suggesting the risk estimates of new HCV infections due to UK given transfusions of blood or blood products range between 0.1 and 2.33 per million donations.(15) However infection rates amongst IV drug users continues to remain high.

1.2.3 Scotland

Recent estimates suggest 21,000 people in Scotland are living with chronic HCV infection.(16) 90% of infections were acquired through injecting drug use.(17) Approximately half (10,500) have been diagnosed to date. Diagnosis rates have fallen in recent years, despite high levels of testing. 1423 people were newly diagnosed as HCV antibody positive during 2018-2019, which is the lowest number since 1996.(18) Among PWIDs the rate of recent infections (i.e. acute HCV infection) was 2.3% for the year 2017-18.(19)

1.2.4 NHS Tayside health board region

As of December 2018, the total number of people ever diagnosed with HCV in the NHS Tayside health board area was 3624. 76% (2771/3624) were thought to be alive and resident in Tayside. Of the 2771, it was estimated that 750 people were living with chronic HCV and as in the rest of Scotland the predominant risk factor was injecting drug use. 105 new patients were diagnosed in 2018 (a reduction from previous years with diagnosis rates of 125, 127, and 195 for the years 2017, 2016 and 2015 respectively) which directly reflects the increased treatment and HCV prevention activity in the region over this time period.(19)

1.3 NATURAL HISTORY

1.3.1 Virology

HCV is a single stranded, positive-sense, ribonucleic acid (RNA) virus of the Flaviviridae family.(20) There are seven known genotypes with sixty seven sub types identified with further sub types as yet unclassified.(21) Genotypes vary in their

geographical distribution mostly due to viral evolution, but also due to the effect of migration and in the case of Genotype 4 in Egypt, the unintended consequence of mass schistosomiasis eradication attempts. Genotype 1 is the most prevalent both worldwide and within the UK, followed by genotypes 2 and 3. Genotypes 4, 5 and 6 are rarely encountered in the UK. Until the introduction of pan-genotypic treatment regimes, HCV treatment was genotype specific, requiring confirmation of genotype before treatment was prescribed. For economic reasons this remains the case for the majority of infected individuals.(22)

There are two phases of HCV infection; acute and chronic. The incubation period for the virus ranges between 15-150 days before onset of clinical symptoms. Symptoms in acute hepatitis C infection are typically mild and non-specific.(23) It is rare that the symptoms of malaise, nausea, abdominal pain and flu-like symptoms are recognised as being due to hepatitis C. Only 20% present with clinical jaundice. On average 15-25% of patients clear the virus within these first 6 months of acute infection.(24) Studies have shown that female sex, symptomatic infection and high bilirubin levels are all positive indicators for spontaneous clearance of the virus in the acute phase and correspond to a clearance rate of up to 45%.(25) The remaining 80-85% who have viral persistence beyond 6 months are deemed to have chronic Hepatitis C infection.

People may remain undiagnosed until end stage liver disease occurs with complications such as cirrhosis, decompensated liver disease and hepatocellular carcinoma.(26) Once in the chronic phase, the rate of liver disease progression varies among patients. It is generally a slowly progressive disease characterised by persistent hepatic inflammation leading to the development of cirrhosis in approximately 20–30% of patients over 20–30 years of HCV infection.(24)

Once cirrhosis has developed there is a 1–5% annual risk of HCC and a 3–6% annual risk of hepatic decompensation.(23) HCV accounts for 40% of all chronic liver disease and is a leading cause of transplantation worldwide.(27) Historically up to 21% of all liver transplants in the UK occurred in patients with chronic HCV infection.(28)

Transplantation has some inherent shortcomings including; high costs, limited access, and 10 year post transplant survival rates of approximately 67.9% in patients with liver failure secondary to HCV infection.(28,29) A recent Japanese study showed that liver transplantation for HCV related complications was associated with a poorer outcome

compared to other indications with a 10 year survival of 50.8% for HCV infected recipients compared with 87% for non HCV infected recipients.(30)

Factors that influence the rate of HCV disease progression include increasing age, male sex, higher amounts of alcohol consumption, and co-existent steatosis. HIV co-infection is associated with a markedly increased rate of disease progression over and above other risk factors.

The future burden of the disease is uncertain however, as the population of undiagnosed people infected with HCV is aging. In Europe the seroprevalence of HCV increases with age to a peak of 55-64 years.(9) This is particularly pertinent as it is likely that the HCV transmission was historical and they will therefore be at risk of cirrhosis, HCC and liver related death. Given the historical risk factor, they may be unaware of their "at risk" status and will potentially present to medical services with advanced disease.

The sexual health and blood borne virus framework collects data on patients with advanced liver disease at diagnosis in Scotland who either die or are hospitalised. This number fell for the first time in 2017 with 139 new diagnoses, in contrast to 171 and 169 in previous years. A further drop was noted in 2018 with 103 cases. This is an indication that the landscape of HCV is changing with interventions such as enhanced testing enabling earlier diagnosis and treatment and avoidance of the long term complications.(19)

1.4 DIAGNOSIS

Diagnosis of chronic HCV infection is mostly incidental or through targeted testing as the condition is asymptomatic in up to 80% of cases due to non-specific symptoms at the time of infection as previously discussed.

1.4.1 Screening and diagnostic tests

1.4.1.1 Antibody testing

The detection of antibodies to HCV is the initial test to determine whether someone has active HCV infection. A positive anti-HCV test indicates that the person may be actively infected, may have spontaneously cleared the infection, or the result may be a false positive. It is typically performed on venous blood obtained via venepuncture by a trained healthcare professional. In NHS Tayside, samples are processed via the detection of HCV antibodies (anti-HCV) by enzyme-linked immunoassays (EIA). By the third generation of an enzyme-linked immunoassay (EIA) the window period

between infection and ability to identify the infection was 2-3 weeks. Immunocompromised individuals may not develop antibodies.(31)

1.4.1.2 RNA testing

Following HCV antibody positivity, active infection is confirmed using RNA testing. This is also used as a screening test for patients who are known to be antibody positive to detect the presence of subsequent infections. Nucleic acid testing for HCV RNA is standard of care. This involves conducting a Polymerase Chain Reaction (PCR) test to determine presence of viral RNA, indicating an active infection. It also quantifies the viral load (i.e. number of copies of the virus present in the blood sample), which can be useful in formulating treatment decisions. Viral RNA can be detected within one to two weeks of infection.(31)

1.4.1.3 Dried blood spot (DBS) testing

DBS testing involves fingertip capillary sampling, using a lancet, which is a relatively non-invasive method of sampling. The blood is dropped onto specialist filter paper (Whatman 903 Protein Saver), which enables stable, easy storage and transport. The paper can then be analysed for both anti-HCV antibody using EIA (sensitivity and specificity approaching 100% (32)) and HCV RNA. In order to conduct an anti-HCV antibody test, three of the five circles on the filter card must be filled. To conduct a HCV RNA test, all five circles must be filled. Each circle holds approximately 75µl of sample. In NHS Tayside, the laboratory infrastructure enables antibody testing of DBS samples across multiple BBVs including HCV, but if a HCV PCR test is requested via this testing method it must be sent to a remote laboratory for analysis. NICE guidelines recognise that HCV testing using DBS may be more acceptable to the target population particularly if obtaining venous bloods through venepuncture is difficult or the individual is needle phobic. DBS has high sensitivity and specificity, so is a good alternative in non-hospital settings as non-clinical persons can be taught to safely utilise DBS testing.(33)

1.4.1.4 Genotyping

If active infection is confirmed, it is current practice to genotype the infection. As previously mentioned genotypes 1, 2 and 3 are the most common in Scotland. Treatment course and length currently depends on the genotype isolated. Pangenotypic antivirals are now available but are more expensive than the genotype specific antiviral regimens. Economic considerations often mean that genotype specific treatment is used and the pangenotypic regimens are currently saved for situations where waiting for a

genotype result will cause an unacceptable delay in starting treatment and/or risk non engagement.

1.4.1.5 Oral fluid testing

The sensitivity and specificity of oral fluid testing is reduced compared to the gold standard venepuncture or DBS. However it does offer a viable alternative in individuals who are needle phobic or difficult to obtain venous samples from. As oral fluid testing will only give an anti-HCV results, positive tests need to be followed up with venepuncture for PCR.

1.4.1.6 Point of care testing with Cepheid GeneXpert

Point of care testing allows HCV testing using only a capillary blood sample without the need for a remote laboratory to process samples. The Cepheid GeneXpert utilises automated reverse transcriptase polymerase chain reaction (RT-PCR) using fluorescence to detect and quantify RNA. It can detect and quantify HCV genotypes 1–6 over the range of 10 to 100,000,000 IU/mL. It has a 105 minute run time for sample processing. It has a sensitivity of 95%.(34,35) It is useful in non-hospital settings such as Prisons, drug treatment centres and community based clinics where a one-stop-shop approach could be utilised thereby reducing people lost to follow up.

1.5 ASSESSMENT

After an individual is diagnosed with chronic hepatitis C infection they should undergo assessment to ascertain the presence and degree of liver fibrosis. Additional blood sampling should also be performed to detect any associated conditions or consequences of HCV infection. These include screening for other blood borne viruses such as Hepatitis B and HIV infection and sexually transmitted infections if sexual transmission is suspected. Kidney function should be assessed by measuring urea and electrolytes. Indication of underlying fibrosis and cirrhosis might be seen with a prolonged prothrombin time and elevated liver blood tests. A low platelet count is an indication of portal hypertension, a recognised complication of cirrhotic liver disease. Individuals with advanced fibrosis or cirrhosis may be asymptomatic and have normal blood tests. The staging of fibrosis is a vital component of the assessment as it impacts upon treatment options, treatment length and cure rates. Detection of fibrosis will also determine whether additional evaluation is required such as variceal and hepatocellular carcinoma screening.

Modalities of assessing liver fibrosis have evolved since HCV was first discovered. These include invasive and non-invasive methods.

1.5.1.1 Invasive fibrosis scoring

The gold standard for assessing presence and degree of fibrosis is the liver biopsy. Severity of fibrosis is reported using the METAVIR scoring system.(36)

Table 1.1. The METAVIR fibrosis scoring system. Biopsy samples are assessed for degree of activity (inflammation) and fibrosis.

Activity	**A0**	**A1**	**A2**	**A3**	
	No activity	Mild activity	Moderate activity	Severe activity	
Fibrosis	**F0**	**F1**	**F2**	**F3**	**F4**
	No fibrosis	Portal fibrosis without septa	Portal fibrosis with few septa	Numerous septa without cirrhosis	Cirrhosis

However liver biopsy has some significant drawbacks including: complications such as bleeding, pain and rarely death; unacceptability to some individuals; small sample size can result in sampling variation and over or underestimation of fibrosis; inter- and intra-observer variability. These different factors and serious complication risks make serial liver biopsies to determine progression of fibrosis or response to HCV treatment impractical.

1.5.1.2 Non-invasive fibrosis scoring

In recent years non-invasive methods of measuring liver fibrosis have been used more widely. The various methods give an approximation of liver fibrosis based on the METAVIR fibrosis score, although as non histological methods degree of fibrosis is an approximation. Degree of fibrosis is reported as F0 (no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis) F3 (advanced fibrosis) and F4 (cirrhosis).

Serological tests have the benefit of being widely available and can be repeated to enable longitudinal evaluation of liver fibrosis in the context of HCV infection. The FIB4 score uses indirect markers of hepatic fibrosis and consists of a combination of platelet count, AST, ALT and age. Studies have shown it demonstrates good predictability of excluding advanced fibrosis in individuals with HCV.(37,38)

The European Liver Fibrosis panel (ELF score) measures direct markers of hepatic fibrosis including hyaluronic acid level, amino-terminal propeptide of type III collagen level, and Tissue inhibitor of metalloproteinases-1 (TIMP-1). This propriety panel of serological tests has demonstrated good sensitivity and specificity of detecting advanced fibrosis.

Transient elastography (TE / FibroScan) is a method of determining liver stiffness using shear wave imaging. As shear waves move through the liver their propagation is measured. Increased liver stiffness correlates with increased fibrosis. TE is relatively quick, painless and has a high patient acceptance.

In Tayside all three methods of fibrosis assessment have been used over the years. Initially only liver biopsies were available, then transient wave elastography (FibroScan) and more recently a combination of FibroScan and the FIB4/ELF scores have been used. This combination of serological tests and elastography assessment has helped to reduce the number of patients with indeterminate fibrosis scores.

1.5.1.3 Treatment

The goal of treatment of chronic HCV infection is eradication of the HCV virus, regression of fibrosis and a reduction in the development of liver related (hepatic decompensation and portal hypertension) and non-liver related complications (improved quality of life, removal of social stigma, and prevention of onward transmission) resulting in longer and symptom free survival.(39)

Current international guidelines recommend treatment for all people with hepatitis C infection, if they are willing to be treated and taking into account any life-limiting non-liver related conditions, which may negate anti-HCV therapy.(39,40)

The aim of therapeutic intervention in Hepatitis C is a viral eradication or sustained virologic response. A sustained virologic response (SVR) is defined as an absence of detectable (<10IU/mL) HCV RNA using PCR 12 weeks after cessation of antiviral treatment.

Successful viral eradication improves the morbidity and mortality associated with HCV infection and aims to improve quality of life.

1.5.2 Therapies pre-direct acting antivirals

Prior to 2015 Interferon therapy was the mainstay of HCV treatment. Initially as a solitary agent, then later as Pegylated Interferon (PegINF) in combination with Ribavirin (RBV).

PegINF/RBV has a wealth of adverse effects up to 85% of patients experience “flu-like” symptoms and 25-30% report neuropsychiatric symptoms. Other common symptoms include fatigue, irritability, depression and anxiety.

Historically treatment guidelines excluded PWIDs from treatment due to concerns about treatment engagement, adherence and risk of re-infection. Latterly clinical studies showed that PWIDs treated with PEG interferon/ribavirin achieved equivalent SVRs to non-PWIDs.(41)

1.5.3 Direct acting antiviral era of treatment

Greater understanding of the Hepatitis C virus structure, lifecycle and enzymes led to the discovery of Direct Acting Antivirals (DAAs).(42) Initially the first generation protease inhibitors were combined with PEGylated Interferon and Ribavirin to improve SVR rates. Latterly second generation DAA's were combined to form Interferon free regimes. The combination regimens of DAAs provide cover across genotypes, increase SVR rates and reduce viral resistance. Currently there are many DAAs approved for HCV treatment, which are classified according to their chemical structure: protease NS3 inhibitors (boceprevir, glecaprevir, grazoprevir, paritaprevir, simeprevir, telaprevir, voxilaprevir), NS5A serine protease inhibitors (daclatasvir, elbasvir, ledipasvir, pribrentasvir, velpatasvir), NS5B RNA-dependent RNA nucleoside polymerase (sofosbuvir), and non-nucleoside polymerase inhibitors (dasabuvir).(43)

The safety profile and tolerability of DAAs has greatly widened their scope of use. DAA's have also proved to be effective in people with cirrhosis (16)., those who are treatment experienced and those co-infected with HIV, which historically have been difficult to treat populations. With clinical studies consistently showing SVR rates >95% and real world data matching this efficacy, the possibility of eradicating HCV has a chance of being realised.(44)

1.6 HCV VACCINE

An effective vaccine for Hepatitis C does not currently exist. It is clear that a successful vaccine would prevent transmission and significantly reduce the burden of HCV liver disease. A partially effective vaccine would also convey benefit by improving immune response to reduce the transmission rate or boost the proportion of people able to clear the virus after initial infection.(45) There is evidence to suggest that PWIDs who clear the infection are less likely to become re-infected(46,47) and spontaneous clearance rates are higher following a second infection than a primary infection suggesting there is some acquired immunity after initial HCV infection.(48)

Although there has been significant interest in developing a HCV vaccine the complexity of the HCV virus is a major challenge which has not yet been overcome. Scotland is dedicated to clearing the HCV virus through treatment. There may be a place for a HCV vaccine in prevention of re-infection for those at highest risk or in those countries who do not achieve HCV elimination through treatment.

1.7 POLICY

In 2016, the World Health Organisation promoted a global hepatitis strategy to eliminate viral hepatitis as a public health threat by 2030. In order to achieve this, ambitious targets were set including: a 90% reduction in incident cases of hepatitis C and a 65% reduction in mortality.(49) To reach these targets, 80% of treatment-eligible individuals with chronic HCV need access to be engaged in care and commenced on treatment.

Phase 1

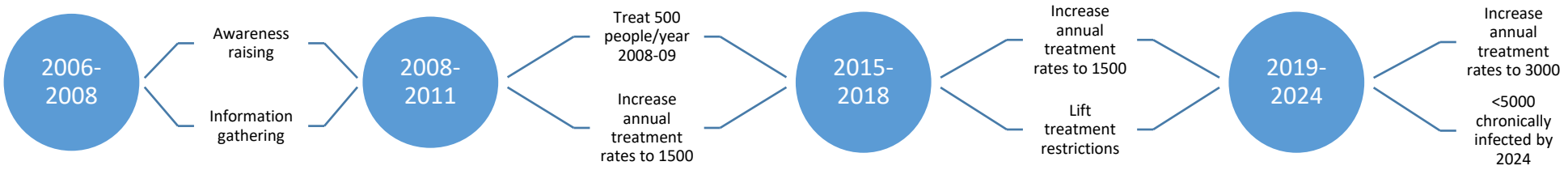


Figure 1.1. The Scottish Government invested in the hepatitis C action plan in 2008 to direct the countries HCV elimination strategy.

In 2006, the Scottish Government developed a Hepatitis C action plan as detailed in Figure 1.1, to direct national HCV elimination efforts. During 2018-19 NHS Scotland exceeded the target to treat more than 1500 people annually (2609 treated), and the Scottish health secretary has made a commitment to increase annual treatment numbers to 3000 by 2021.(16,50) By outstripping the number of new infections with people treated and cured this enables significant headway towards reducing the pool of infected people and eventually eradication.

1.8 HEPATITIS C CASCADE OF CARE

A cascade of care (CoC) refers to the movement of patients infected with an illness between stages of an infection. For example, in HCV most CoCs will depict disease prevalence, diagnosed persons, those who have accessed treatment and those cured.

It is expected that there will be a degree of attrition as people move through the cascade: As not all people with the illness will be aware of their risk factors or attend for testing; not all with a positive diagnosis will engage with services or comply with treatment and even if everyone infected access treatment, not everyone will achieve cure.

Analysing cascade of care for specific areas can be useful in determining where health and social services can direct efforts: to improve rates of disease detection, improve access to care, increase drug availability for treatment or improve concordance with treatment to yield a cure.

In Tayside, we have analysed our cascade of care and can see the benefit of previous interventions in improving the proportion of people moving through the cascade, for example streamlining and simplifying the referral and assessment processes prior to starting treatment and making treatment available in both the community and secondary care settings and these interventions are examined later in this thesis. The cascade of care also continues to inform points in the pathway where there are systematic shortfalls and additional input is required. As we move towards achieving elimination of HCV on-going analysis of our strategies is vital to ensure we remain on target.

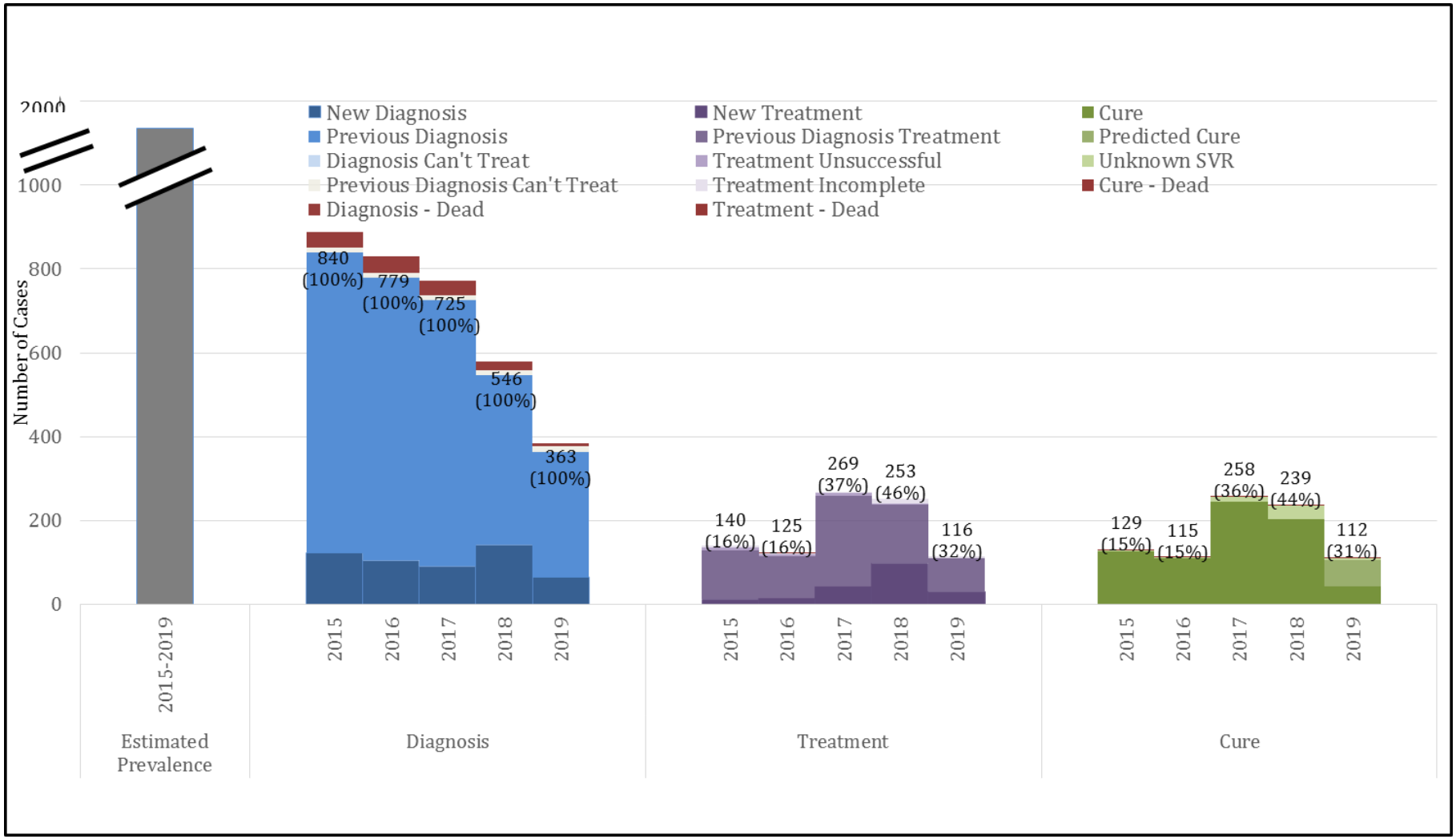


Figure 1.2. A cascade of care for NHS Tayside between 2015 and 2019.

Figure 1.2 depicts NHS Tayside's cascade of care between 2015 and 2019. The prevalence figure is an estimate assuming 0.55% positivity rate for the Tayside population. The cascade shows a reduction in patients diagnosed with Hepatitis C over the 5 year stretch. The year on year rate of new diagnosis varies slightly, but does not account for the reduction in overall diagnoses. The light blue colour represents individuals with an existing diagnosis and the dark blue colour represents individuals who were newly diagnosed that year. The treatment column shows the proportion of those with a HCV diagnosis who were treated each year. The light purple colour (previous diagnosis treatment) represents individuals who had been diagnosed in preceding years, whereas the dark purple colour (new treatment) shows those who were treated in the same year of diagnosis. It is important to note that both newly diagnosed individuals and people with a previous diagnosis were started on treatment suggesting that the treatment pathways are accessible for both new and previously diagnosed individuals. The proportion of people with HCV who achieve cure closely maps those started on treatment. This is both a reflection of the efficacy of the DAAs and the concordance with treatment exhibited by the individuals cured. As the numbers of patients diagnosed with HCV and awaiting treatment falls we will move closer to elimination.

1.9 BARRIERS TO CARE

There are significant barriers to care at patient, provider and system levels for PWID.

Individual-level barriers included:

- perceived lack of need
- limited knowledge of HCV and potential complications
- competing priorities (e.g., avoiding opioid withdrawal, securing shelter beds).

Interpersonal-level barriers included:

- stigma
- perceived low quality of care for PWID.

Systemic-level barriers included:

- difficulty navigating healthcare systems
- limited number of sites for testing and treatment delivery

- inadequate transportation

These barriers are illustrative of what can prevent the undiagnosed population having access to testing and, if required, treatment. People who engage in substance misuse are often amongst the most marginalised in society and are subject to the on-going negative effects of stigma, discrimination and criminalisation related to their lifestyles, which can both cause and exacerbate multiple complex health and social needs.

The World Health Organisations' guidelines for the care and treatment of persons diagnosed with chronic HCV denote good practice principles for health service delivery. These include strategies to strengthen linkage from testing to care, simplified service delivery models, integration with other services, decentralised services supported by task-sharing and community engagement.(40) These guiding principles were considered carefully when designing the interventions put in place in NHS Tayside since committing to HCV elimination by 2030. The implementation of these strategies were premised on the understanding that they should improve access to testing and care, as well as lessen the adverse effects of health and social inequalities that PWID experience.

With the availability and reliable efficacy of DAAs we have the necessary tools to treat HCV. Outdated diagnosis and treatment pathways do not adequately serve the majority of people living with HCV who require treatment. We need to focus on treatment accessibility and delivery rather than drug effectiveness to make a meaningful impact on the HCV epidemic.

1.10 THESIS AIMS

As recognised by the World Health Organisation, Hepatitis C is now eminently treatable and healthcare systems should be devising strategies to treat and cure those individuals with Hepatitis C infection.

Scotland has devised an action plan with clear aims for the numbers treated and cured of the infection in order to reach elimination targets within the next 5 years.

This thesis aims to explore the strategies required to find and diagnose all those infected with HCV in the Tayside Health Board.

There are four main aims:

- Review of the relevant literature to identify the aspects of HCV models of care that promote diagnosis, treatment and cure
- Review the relevant literature to evaluate the efficacy of community and primary care based HCV testing and treatment services using direct acting antivirals
- Evaluate the different testing and treatment pathways currently in use in NHS Tayside with a view to establishing the most effective pathways
- Identify the most cost effective pathway(s) in NHS Tayside providing testing and treatment for HCV positive individuals

CHAPTER 2 – SCOPING REVIEW OF MODELS OF CARE

This chapter is a revision of a paper entitled "We know DAAs work, so now what? Simplifying models of care to enhance the Hepatitis C cascade" published in the Journal of Internal Medicine in 2019.(44) I, along with two co-authors carried out the literature search for models of care and prepared the tables. All authors contributed to the final manuscript, reviewed the full draft of the article, subsequent revisions and approved the final version for submission.

I revised the published paper including an updated literature search for this chapter.

2.1 SUMMARY

Several models of care (MoCs) and service delivery interventions have the potential to improve outcomes across the HCV cascade of care (CoC), but much of the relevant research was carried out when interferon-based therapies were the standard of care. Often it was not practical to scale up these earlier models and interventions because the clinical care requirements for patients taking interferon-based regimens would have imposed significant financial and human resource burdens upon healthcare systems. In addition, low rates of treatment uptake and cure with interferon based regimens would not have been addressed with expansion of existing models of care.

Despite the adoption of highly effective, all-oral direct-acting antiviral (DAA) therapies in recent years, approaches to HCV testing and treatment have evolved slowly and often remain rooted in earlier health service delivery models. The effectiveness of DAAs allows for simpler models of care and has encouraged countries where DAAs are widely available to set their sights on the ambitious World Health Organization (WHO) HCV elimination targets. Since a large proportion of chronically HCV-infected people are not currently accessing treatment, there is an urgent need to identify, evaluate and implement existing simplified MoCs. Particularly those MoCs, which address specific sub-populations' needs. The goal of this scoping review was to assess the evidence on MoCs utilising DAAs and identify the key concepts underpinning the simplification of pathways and explore how these are deployed in the different contexts of the provision of HCV therapy. Elucidation of these issues, resulted in the development of a road map enabling stakeholders to simplify the path taken by chronically HCV-infected individuals from testing to cure and subsequent care and monitoring.

2.2 INTRODUCTION

Although HCV became a highly curable disease with the introduction of all-oral direct-acting antiviral agents (DAAs) in 2013, most countries have been slow to provide unrestricted access to these life-saving drugs(51–53) and thus decrease the disease's spread(54) and reduce its prevalence.

In reality, global elimination of HCV will require major increases in services for all affected populations along the entire cascade of care, including testing, linkage to care, retention in care, treatment, chronic care and prevention of primary infection and reinfection.

In 2013, Bruggmann and Litwin found that, whilst HCV treatment had been successfully delivered to many people, through various multidisciplinary models, few treatment settings were adapted to the needs of people who inject drugs (PWID).(55) PWID who have previously engaged with services, e.g. with drug treatment services or are established on opioid substitution therapy, are often those who are most motivated to seek out health services. PWIDs without this history of engagement and who are more marginalised find accessing healthcare difficult. In order to deliver HCV treatment to all those who require it, especially PWID and other marginalised high-burden populations, such as migrants and the homeless, distinct models of care (MoC) for are required for each setting. These MoCs should specifically target at risk populations whilst taking advantage of the ease of use that characterises DAA therapy. This is a rapidly changing field as the ease of use of DAAs combined with high cure rates has greatly expanded the repertoire of treatment delivery options.

There is a wide range of community sites and care providers detailed in this review, and even more community based models of care that did not meet the inclusion criteria. This heterogeneity is actually desirable as it indicates that care providers are utilising a wide variety of measures to treat this global problem affecting mostly marginalised communities.

In this scoping review, we use MoC to signify a setting-specific framework that outlines how to provide the relevant services and interventions throughout the HCV cascade of care. A MoC should address four key questions: *where* to provide the services, *what* services to provide, *who* to provide them and *how* to integrate them.

Selection of new models of hepatitis C care presented in this review

- Nurse-led
- Telemedicine
- Multidisciplinary (including non-medical personnel in the core team, e.g. social workers, case managers or psychologists)
- Pharmacist-led
- Mobile van units

Figure 2.1. List of the different types of new models of hepatitis C care explored and presented in this review.

2.3 METHODS

This scoping review was conducted according to the scoping review methodological framework as described by Arksey & O'Malley.(56) The framework consists of six key steps; 1. Identify the research question, 2. Identify relevant studies, 3. Study selection, 4. Chart data, 5. Collate, summarize, and report results. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

2.3.1 Identifying the research question

In this review, our research aim was to answer the question of how to provide HCV infected PWIDs with relevant services and interventions throughout the HCV cascade of care. We wanted to evaluate existing MoCs to identify setting-specific frameworks that demonstrate these services and interventions. The aim was to address four key questions: where to provide the services, what services to provide, who to provide them and how to integrate them. This research question was refined using PICOS criteria and was intended to provide a broad overview to allow extensive coverage of the MoCs in use globally and explored comparisons between interventions, programs and approaches in delivery of Hepatitis C care.

Study populations of people with chronic Hepatitis C were included, those co-infected with other blood borne virus infections were excluded as their additional care needs were likely to add complexity to MoCs and therefore not be broadly applicable to individuals living with chronic HCV infection. Studies published after 2014 were included to capture literature on MoCs utilising DAAs. MoCs including interferon and ribavirin-based treatment regimens as the primary intervention were also excluded for this reason. Studies were restricted to the English language since study resources

precluded any translation activities. Published studies were utilised including conference abstracts, in order to capture results from early studies when the first DAAs were introduced into practice.

Outcomes were wide ranging and included studies which demonstrates awareness raising and prevention, testing and diagnosis, treatment, linkage to care and access to medications to ensure coverage of the cascade of care.

Sources included electronic databases, reference lists, hand searches, and gray literature including conference abstracts and presentations.

The PICOS elements for this review were as follows:

Table 2.1. Elements of the PICOS question defined for this review.

	Inclusion	Exclusion
Population	Infected with chronic hepatitis C Studies published after 2014	Studies published pre 2014 Co-infection with other blood borne virus’
Intervention	Provision of hepatitis C treatment in any Model of Care Treatment using any direct acting antiviral therapy Care provider could be any health care provider.	Treatment with ribavirin / interferon regimes as the primary intervention Solitary interventions
Comparison	Care in any hospital or secondary care environment or no comparison group.	
Outcome	Awareness and prevention, testing and diagnosis, linkage to care, access to medications,	
Study design	Observational studies, retrospective or prospective cohort studies, randomised trials; conference abstracts; systematic reviews	Case studies; qualitative and mixed methods studies

2.3.2 Identifying the relevant studies

The models of HCV care were selected by reviewing the peer-reviewed literature in the PubMed/Medline database. The following search terms were used:

(HCV[All Fields] OR ("hepatitis c"[MeSH Terms] OR "hepatitis c"[All Fields] OR "hepacivirus"[MeSH Terms] OR "hepacivirus"[All Fields])) AND model[All Fields] AND s[All Fields] AND care[All Fields]

Abstracts and presentations from The Liver Meeting of the American Association for the Study of Liver Diseases (AASLD 2018); European Association for the Study of the Liver International Liver Congress (EASL ILC 2018 and 2019), and the International

Network on Hepatitis in Substance Users (2018) were also examined for the following terms:

"models of care", "hepatitis C", "HCV", "public health"

2.3.3 Study selection

The results were limited to studies in English, which were published between 2014 and 2019. References and associated bibliographies were also examined for further relevant articles.

The literature search was conducted by three independent reviewers (ER,JC,CP) who identified 71 abstracts that reported studies of new models of care to address HCV that had measurable outcomes. All three reviewers (CP, JC and ER) screened the results of the literature search. At the end of the initial screening process, the three reviewers discussed any conflicts or uncertainties. JL was with arbitrator for any conflicts/uncertainties that we were unable to resolve amongst the three reviewers.

An additional search through publications and recent conference abstracts was carried out independently by all three reviewers. Inclusion of additional studies was reviewed and verified by all three reviewers.

Tables were prepared to collate the outcomes from the included literature. All comparable aspects of the MOCs were identified and populated the tables. For example providers of MOCs, setting of MOCs and aspect of the cascade of care covered by the MOC.

We divided collation of the tables between us. Every table and its contents were assessed and reviewed by at least two reviewers to ensure agreement. The tables were then reviewed by JL and amended as required to ensure clarity.

Prior to the analysis all three reviewed re-assessed the tables to ensure there were no discrepancies or missing data.

2.3.4 Charting the data

The characteristics and findings of the included studies were summarised and structured using tables. Due to the heterogeneity of the topic data synthesis and interpretation a descriptive approach in place of a more systematic data extraction was used allowing for post-hoc development of inclusion/exclusion criteria and data synthesis in terms of the value yielded by qualitative or quantitative analysis of results. Utilising the completed tables, we were able to draw conclusions based on what aspect of the model

of care was demonstrated. When collating, summarising and reporting the results an analytic narrative account of existing literature was performed.

2.4 RESULTS

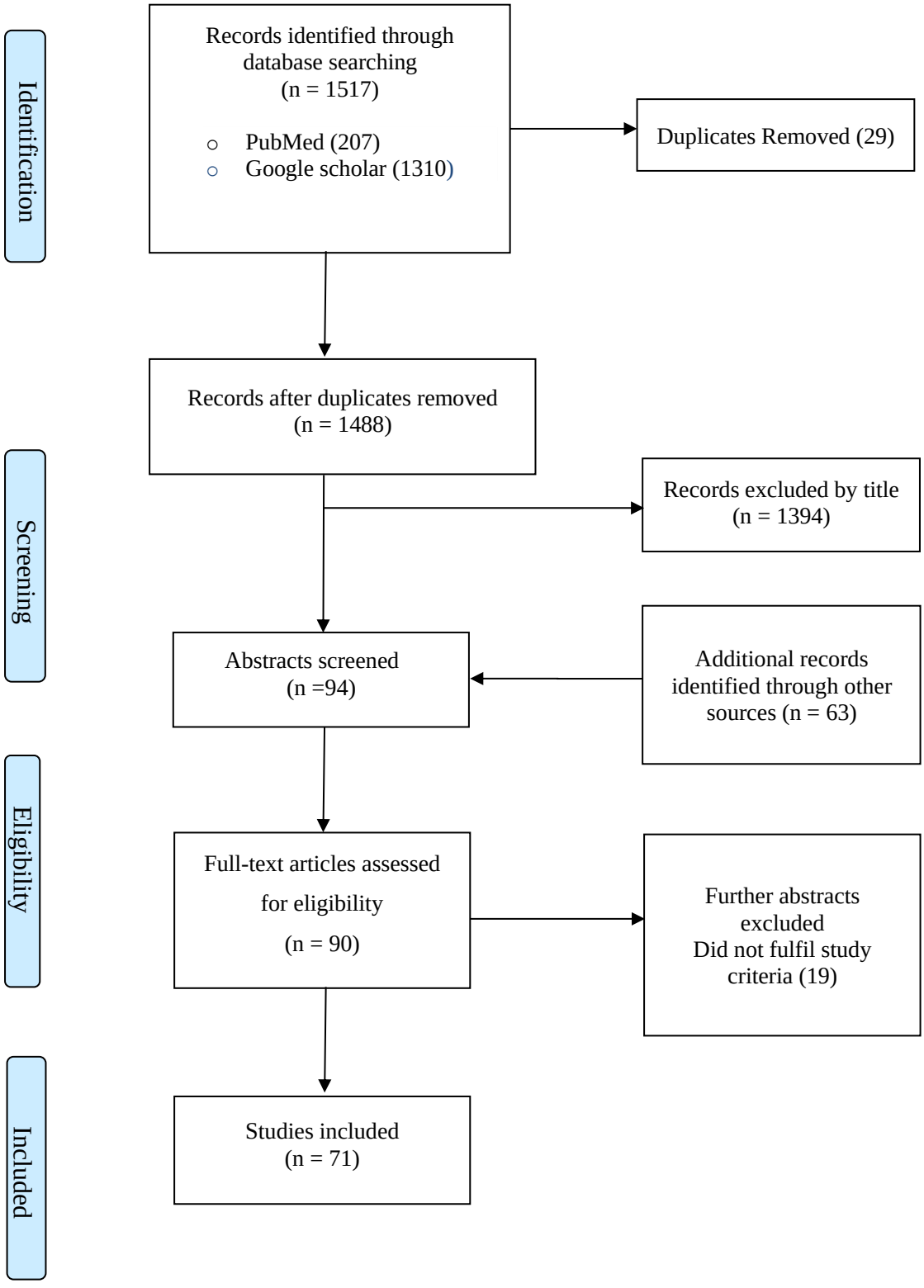


Figure 2.2. Flow chart of studies included in the scoping review.

Figure 2.2 shows the flowchart of studies initially identified through database searching, screened to select appropriate studies and then assessed for eligibility. 71 studies were deemed to fulfil the PICOS criteria and were analysed in this scoping review. Characteristics and findings of included studies are set out in Table 2.2.

2.4.1 Desirable elements in models of care

2.4.1.1 Simplicity

Simplicity is key to the scaling up of interventions and is widely considered a predictor of its success.(57–60) Fortunately, because DAAs have few side-effects and can be administered orally, MoCs designed to optimise DAA delivery are much simpler than those designed for PEGylated interferon treatment, which required more pre-treatment work up (e.g. pre-treatment liver biopsy, HCV genotyping, psychiatric assessment), as well as intensive monitoring and dose modification. Other elements that contribute to simplicity include effective linkage to care and the targeting and integration e.g. co-location of services.(61) Whilst having services co-located makes linkage and retention into care easier for patients, it often create more difficulties for health services to provide resources for testing and treatment especially if outwith a secondary care environment.

2.4.1.2 Population targeted

Targeting is also essential, delivering interventions to high prevalence or high-risk populations allows for economies of scale. Populations with identifiable risk factors may be accessible for testing and treatment in specific locations e.g. prisons and needle exchange centres. A concerted effort and often more resources are required to test members of hard-to-reach at-risk populations. Outreach has been used effectively to approach specific groups within their own milieu rather than waiting for them to present at healthcare facilities. Table 2.2 presents the ten populations identifies and addressed by the respective MoC studies identified in this scoping review. Of the 71 studies that we reviewed for this paper, 42 specifically targeted the PWID population.

Table 2.2. Categories of populations at risk of HCV infection addressed in the identified models of care.

Populations (n)	**Country**	**N. of study (see appendix)**
PWID/ on OST *(42/3)*	Australia; Belgium; Canada; Denmark; France; Georgia; Greece; Ireland; Norway; Portugal; Spain; Switzerland; UK; USA	Papaluca et al. (1), Alimohammadi et al. (2), Remy et al. (3). Bourgeois S et al. (4), Chronister KJ et al. (6), Valencia JA et al. (7), Liberal R et al. (8), Inglis SK et al. (10), Ford MM et al. (11), Borojevic M et al. (12), Peters L. (13), Williams B et al. (14), Saludes V et al. (15), O'Loan J et al. (16), Grebely J et al. (17), Norton et al. (30), Morris et al. (31), Schulkind J et al. (33), Saludes V et al. (34), Radley A et al. (35), Alam Z et al. (37), Sypsa V et al. (40), Kugelmas M et al. (42), Howell et al. (43), Kraichette N et al. (44), Greenan S et al. (45), Ryder N et al. (46), Doyle J et al. (47), Bielen R et al. (48), Stvilia K et al. (49), Mitchell S et al. (50), Thompson H et al. (51), Lamond S et al. (53), Sinan F et al. (54),Midgard H et al. (56), Berger SN et al. (57), Read P et al (60), Mason K et al (62), Hashim A et al (63), Treloar C et al (64), Chronister KJ et al (65), Linnet et al (65), Barror S et al. (66), Simoes D et al. (68), Nouch S et al (69), Scherer ML et al. (71) **Specifically OST**: Inglis SK et al. (10), Radley A et al. (35), Bielen R et al. (48)
General population *(20)*	Australia; Canada, Egypt; India; Mexico; Pakistan; USA	Balcomb A (5), Ford MM et al. (11), Trooskin et al. (18), Chiong F et al. (23), Cooper et al. (24), Capileno et al. (25), El-Akel et al. (26), Kattakuzhy et al. (29), Dhiman RK et al. (36), Shiha G et al. (38), Shiha G et al. (39), Greenan S et al. (45), Ryder N et al. (46), Thompson H et al. (51), Perez Hernandez JL et al. (52), Lamond S et al. (53), Naveed A et al. (55), Koren D et al. (59), Sokol et al (61), Nouch S et al (69)
Prisoners *(11)*	Australia; France; Ireland; Portugal; Romania; Spain; Sweden; UK	Papaluca, Remy AJ et al. (3), Liberal R et al (8), Cuadrado A et al (9), Inglis SK et al. (10), Vroling H et al. (20), Olsson A et al. (21), Bartlett SR et al. (22), Overton et al. (41), Barror S et al. (66), McDonald L et al. (70)
Homeless *(7)*	Australia; Canada, France; Romania; Scotland; Spain; UK	Alimohammadi A et al. (2), Remy AJ et al. (3), O'Loan J et al. (16), Grebely J et al. (17), Hashim A et al. (28), Macbeth K et al. (32), Barror S et al. (66)
Sex workers *(5)*	Australia; Ireland; Italy; Romania; Spain; Portugal; UK	Chronister KJ et al. (6), Read P et al. (60), Barror S et al. (66), Teti E et at. (67), Simoes D et al. (68)
Migrants *(3)*	France, Portugal	Remy AJ et al. (3), Saludes V etl al. (34), Simoes D et al. (68)
People with mental health issues *(2)*	Canada, France	Mason K et al (62), Remy AJ et al. (2)
Other (reviews) *(2)*	Multi-country reviews	Pourmarzi et al. (19), Wade et al. (27)
Veterans *(1)*	USA	Fleming BS et al. (58)
MSM *(1)*	Portugal	Simoes D et al. (68)

Abbreviations: PWID – Persons who inject drugs; OST – Opiate substitution therapy: MSM – Men who have sex with men.

2.4.1.3 Ease of testing

Among PWID and other vulnerable populations, rapid testing with quick turn around times e.g. point of care testing has been shown to substantially increase coverage and referral rates(62–64). To date, many services have not been developed for vulnerable populations such as the homeless, PWID and prisoners, which must accommodate the numerous social factors(65–68) that contribute to poor quality of life and poor social functioning(69,70) in addition to health inequalities(71).

2.4.1.4 Access to treatment

It should be emphasised that HCV treatment should be offered based on clinical rather than social factors or injecting-related behaviours.(72,73) It is necessary to remove obstacles which prevent HCV treatment delivery to PWID. In particular, several studies demonstrate that acceptable outcomes are achieved in people who continue to inject drugs whilst receiving HCV treatment, and outcomes that are just as good in people on opiate substitution therapy as in people who do not inject drugs.(74–76) At governmental level it is paramount that policies are supportive of these endeavours,(77) since restrictive drug policies and the criminalisation of drug use not only drive much of the HCV epidemic amongst PWID(78) but also discourage PWID from accessing, harm reduction services, HCV services and drug treatment services.(79) Harm reduction services can offer HCV testing, enabling testing to occur in community facilities and allowing PWID easy access to testing. Many PWID may not otherwise be able to access testing. Equally as OST clients can pick up their OST prescription daily, this offers an opportunity to dispense DAAs daily to this cohort and therefore support clients through their HCV treatment and encourage concordance with the treatment course. This daily support might also prove beneficial to other vulnerable individuals receiving treatment.(80)

2.4.1.5 Barriers to effective models of care

Globally the biggest obstacle to the scale-up of HCV services in many settings is affordability and availability, for both diagnostic tools and treatment. While the World Health Organisation's "Right to Health" suggests that anyone infected with HCV should have access to treatment, irrespective of disease stage and drug use,(81) some people must pay for DAAs themselves in those countries where high costs and/or discrimination have led to reimbursement restrictions. In most countries where DAA therapy is subsidised, there are restrictions to DAAs in terms of rules about who can prescribe DAAs and limitations on who can receive treatment dependent on disease

severity.(51) This is despite evidence that treatment is cost-effective at any disease stage when the long-term costs of morbidity, mortality and onward transmission are included in the calculations, and provided that harm reduction is widely available.(74,82–87) Strategies that have proven successful in bringing DAA costs down to a fraction of the list price include directly negotiating with pharmaceutical companies, licensing generic options and committing to scaling up treatment in order to secure bulk discounts and achieve economies of scale.(74)

Other obstacles also need to be overcome to scale up HCV treatment.(88,89) These include the heterogeneity of national policies,(90–92) a lack of appropriate infrastructure for HCV services in tertiary centres and addiction clinics,(55,93–96) stigma and discrimination(97,98) (including the reluctance of some physicians to treat PWID(99–101)), limited access to point of care diagnostics(102), and inadequate knowledge of HCV and HCV treatment and a generally deficient sense of urgency.(103–105)

Two other essential characteristics of successful MoCs that Bruggmann and Litwin emphasised in their MoC study,(55) were a multidisciplinary approach and integration of services, and are addressed below in the sections responding to the questions of who and how, respectively.

2.4.2 Where to provide services

The delivery of HCV services and interventions varies tremendously in practice. Table 2.3 identifies the diverse settings where they can be offered. The following sections draw on the scientific literature for recent experiences in implementing MoCs for HCV.

Table 2.3. Model of care setting in the identified studies (n=71).

Setting (n)	Country	N. of study (see appendix)
Low-threshold setting *(25)*	Australia; Belgium; Canada; Denmark; France; Georgia; Greece; Italy; Ireland; Norway; Portugal; Romania; Spain; UK; USA	Alimohammadi A et al. (2), Remy AJ et al. (3), Bourgeois S et al (4), Valencia JA et al. (7), Ford MM et al. (11), Williams B et al. (14), Saludes V et al (15), O'Loan J et al. (16), Grebely J et al. (17), Hashim A et al. (28), Morris et al. (31), Schulkind J et al. (33), Saludes V et al. (34), Sypsa V et al. (40), Howell et al. (43), Stvilia K et al. (49), Mitchell S et al. (50), Sinan F et al. (54), Midgard H et al. (56), Treloar C et al (64), Chronister KJ et al (65), Linnet et al (65), Barror S et al. (66), Teti E et al. (67), Simoes D et al. (69), Scherer ML et al. (72)
Primary care *(20)*	Australia, Canada, Ireland, Mexico, Pakistan, Romania, Scotland, Spain, UK, USA	Balcomb A (5), Chronister KJ et al. (6), Trooskin et al. (18) Capileno et al.(25), Kattakuzhy et al.(29), Norton et al. (30), Macbeth K et al. (32), Doyle J et al. (47), Thompson H et al. (51), Perez Hernandez JL et al. (52), Lamond S et al. (53), Naveed A et al. (55), Koren D et al. (59), Read P et al (60), Sokol et al (61), Mason K et al (62), Hashim A et al (63), Treloar C et al (64), Chronister KJ et al (65), Barror S et al. (66), Nouch S et al. (69)
Prison *(9)*	Australia, Ireland, Romania, Spain, Sweden, Portugal, UK	Papaluca et al. (1), Liberal R et al (8), Cuadrado A et al (9), Vroling H et al. (20), Olsson A et al. (21), Bartlett SR et al. (22), Overton et al. (41), Barror S et al. (66), McDonald L et al. (70)
High-threshold setting *(6)*	Belgium, Denmark, Switzerland, USA	Borojevic M et al (12), Peters L. (13), Alam Z et al. (37), Kugelmas M et al. (42), Bielen R et al. (48), Berger SN et al. (57)
Hospital *(4)*	Australia, Canada, India	Chiong F et al. (23), Cooper et al. (24), Dhiman RK et al. (36), Ryder N et al. (46)
Rural *(4)*	Canada, Egypt, France	Cooper et al. (24), Shiha G et al. (38), Shiha G et al. (39), Kraichette N et al. (44)
Regional setting *(3)*	Canada, Egypt, UK	Inglis SK et al. (10), El-Akel et al. (26), Greenan S et al. (45)
Pharmacy *(3)*	Scotland, USA	Radley A et al. (35), Fleming BS et al. (58), Koren D et al. (59)
Mobile van *(4)*	Australia, France, USA	Remy et al. (3), Trooskin S et al. (18), Kraichette N et al. (44), Doyle J et al (47)
Other *(2)*	Multi-country reviews	Pourmarzi et al. (19), Wade et al. (27)

As MoCs are setting-dependent, particular attention was directed to the question of which different environmental settings can provide the primary venue for HCV services. With reference to Table 2.3 low-threshold and high-threshold settings refer to harm reduction-based health care centres targeted towards people who use substances. "Low-threshold" programs are programs that make minimal demands on the patient, offering services without attempting to control their intake of drugs, and providing counselling only if requested. "High-threshold" programs, require individuals to accept counselling and cease all drug use as a condition of assistance. While a “one-stop shop” may be ideal, in that it provides continuity, it can be difficult to arrange financing for an integrated clinic offering a variety of health and social services in a system where funding comes from narrowly defined budgets. Moreover, clients often access services according to convenience, and provision of services at diverse sites may offer welcome flexibility and improve uptake. In such cases, it is critical to coordinate service provision so that clients receive consistent, seamless care regardless of location.

2.4.2.1 Hospitals

For decades, Hepatitis C has predominantly been managed by specialists in hospitals.(55,78) As evidence became available on the effectiveness of DAAs for treatment of HCV, it became clear that there was a for tailored care pathways, consequently new MoCs were developed. A systematic review of interferon-based treatment for PWID(106) found satisfactory results in the six studies analysing sustained virologic response (SVR) and in the five studies analysing re-treatment after reinfection(107–109) There appeared to be no clear advantage in outcomes when providing treatment to PWID in hospitals instead of community-based settings.(106) Most of the studies comparing HCV treatment in the two settings showed generally better uptake in the community based setting.(110) The main challenge is to provide simplified care at integrated centres and limit the hospital role in HCV treatment. While hospital specialists may continue to play a key role in integrated HCV care for marginalised populations, hospital referrals should ideally be necessary only in cases with severe complications, such as advanced liver disease and certain co-morbidities (which are expected to become much less common as DAA therapy becomes more widespread). However, in order to facilitate this shift to non-hospital setting the restrictions on DAA treatment in community settings(111) must be lifted.

2.4.2.2 Primary care facilities

The feasibility of successfully treating PWID receiving OST with interferon-based regimens has been broadly demonstrated in studies where general practitioners with a special interest in HCV work alongside nurses, social workers and other professionals in a primary care setting.(112–114) This model can also benefit from telehealth technology.(115) This ability to train non specialists to deliver HCV treatment outwith a secondary care environment can be capitalised upon when considering that DAA treatment delivery requires less expertise and oversight that interferon-based regimens.

The experience of the Australian Kirketon Road Clinic(116) in Sydney sheds light on the benefits of delivering DAA therapy in primary care (Table 2.4, Case 1). Among 242 marginalised PWID who started DAA therapy, overall 68% achieved SVR by week 12 (SVR12) and only 2 documented virological failures were observed, per protocol SVR12 was therefore 99%, with the remainder not attending for an SVR12 test. Seventy-nine of these people received enhanced support in the form of daily or weekly administration of DAAs. Homelessness was associated with a need for enhanced support (see Table 2.4), but reassuringly this support, ensured that virological outcomes and adherence were high. Further research is warranted on the impact of housing services on long-term outcomes for PWID.(117,118)

Multidisciplinary primary care facilities in the United States that provide training and support to professional staff have been found to provide high-quality assessment and treatment of PWID with HCV,(119–121) but these facilities are in the minority.(122) It is unclear if shifting from a MoC relying on infectious disease doctors working in primary care settings to an integrated-care pathway led by general practitioners or nurse-practitioners can be both productive and cost-effective. General practitioners are still prohibited from prescribing DAAs in most countries,(51) or are limited to delegated prescribing. In countries where they may prescribe DAAs freely, such as Australia, the proportion of general practitioners prescribing DAAs is high.(123)

2.4.2.3 Community health centres

These community-based facilities are not fully integrated into the healthcare system. The term is used here for centres whose primary focus is *not* drug addiction. There are several examples of community health centre MoCs from the interferon era.(110) In 2001–2005, the overall SVR for a Canadian treatment cohort, most of them PWID, was 61%, which was comparable to outcomes from contemporaneous randomised controlled trials.(124)

In one systematic review of community-based HCV treatment, most studies were undertaken at OST facilities, but none assessed DAA delivery in the community setting.(110) Studies in Toronto(125) and Philadelphia(126) (Table 2.4, Cases 2 and 3**)** provide evidence of the effectiveness of community-based MoCs involving OST and DAAs, and a project in Brighton, UK shows promising preliminary results.(127) A Melbourne trial is comparing a control group treated with DAAs and followed up in tertiary level care with an intervention group treated and followed up in community health centres.(128)

2.4.2.4 Addiction centres and harm reduction centres

Addiction centres include drug addiction treatment centres, primary addiction care units and facilities providing services to help PWID cope with medical and psychological issues related to addiction. Harm reduction centres include OST facilities, injecting equipment provision sites (IEPS) and supervised injecting centres (SIC) with many incorporating peer-based services with medical oversight and support.

A Danish project has provided important evidence of DAA therapy being delivered in addiction centres affiliated with hospital infectious disease departments. Preliminary results show that PWID can be tested and treated outside of hospitals, using specialists who prescribe DAAs without ever seeing the patient in person (Table 2.4, Case 4).(129) In an East London study, 83 of the PWID attending an outreach clinic, where a consultant hepatologist and a nurse reviewed client cases, expressed an interest in receiving antiviral therapy, 63 initiated treatment and 92% of those completed treatment. Compliance was greater than 80%; homelessness, active drug injection and pre-treatment antidepressant therapy were not associated with noncompliance.(130)

Emerging data are available from recent studies using DAAs in OST settings,(131) though an international trial from 2016 concluded that drug use ought not to be a barrier to DAA therapy in patients receiving opioid agonist therapy.(132) Further, acceptability and feasibility of dosing DAAs through an OST infrastructure has been demonstrated in Australia and Scotland.(133) In Tayside DAAs were successfully delivered alongside OST prescriptions and yielded superior treatment uptake rates.(80)

IEPS too have been shown to be effective and cost-effective in preventing both HIV(134) and HCV transmission amongst PWID.(135,136) They are essential for optimising linkage to care and testing, particularly among the younger PWID population,(137) and can serve as a venue for HCV treatment. A large Australian study

of PWID attending IEPS in 1999–2011 found that the proportion treated for HCV increased over time, although overall numbers never exceeded 10%.(138) A study in an IEPS in Tayside, Scotland demonstrated effective delivery of interferon and ribavirin based HCV treatment in PWID who continued to inject with SVR rates comparable to the non PWID population.(139) A further study in the same IEPS is assessing treatment update, concordance and outcomes in PWID who continue to inject who are treated with DAAs.(140)

There is also evidence for the effectiveness of supervised injecting centres (SIC) in preventing HCV and other blood-borne infections and avoiding other serious medical complications.(141,142) Assessment for liver disease has proven suitable in this setting.(143,144) However, beyond a survey of hepatitis C services offered at SIC globally,(145) there were no studies assessing the implementation of HCV treatment pathways through such centres. Moreover, models involving these centres, such as the "service model" used by the European Monitoring Centre for Drugs and Drug Addiction, rarely address HCV.(146) Basic work is still needed to conceptualise the role of supervised injecting centres within the HCV cascade.

2.4.2.5 Prisons

PWID, both former and current, form a large proportion of the prison population throughout the developed world.(147) A study involving 3126 HCV-infected individuals incarcerated in the United States showed that rates of linkage to care and treatment for adults were very low, with just 18% being evaluated for initiation of treatment while incarcerated, and a mere 10% initiating DAAs.(148) The high burden of HCV infection in prisons, together with the presence of other conditions such as HIV infection, HBV infection or drug use, creates a synergistic cluster that is difficult to address. On the other hand, surveillance and movement restrictions allow for straightforward implementation of diagnostic and therapeutic strategies. For instance, a recent modelling study concluded that incarceration contributes a 28% risk of HCV transmission among PWID in Scotland, but scaling up HCV treatment to 80% of chronically infected PWID with sufficiently long sentences (>16 weeks) upon entrance to prison was able to reduce both the incidence and prevalence of HCV by 46%.(149) Offering prisoners HCV services upon incarceration is quite rare, however. Another recent study using a prevention benefit analysis concluded that increasing HCV testing in United Kingdom prisons is marginally cost-effective compared to current voluntary risk-based testing, but it could be highly cost-effective if DAAs are broadly prescribed

and PWID treatment rates increased.(150) A comparable United States study drew similar conclusions.(151) Other authors have demonstrated that scaling up harm reduction services is a prerequisite to effectively tackling HCV, HIV and drug epidemics in prisons.(152) Another challenge is ensuring prisoners' uninterrupted treatment upon release. One study ensured prisoners who had begun DAA therapy while in prison but were released early were given their remaining medication to complete the treatment course in the community.(153) This same study also offered prisoners who were ineligible for treatment, due to short sentences, referrals to healthcare services for treatment in the community once released.

A systematic review of the effectiveness of MoCs for HCV in European prisons found that seven studies utilising second-generation DAAs in France, Italy and Spain achieved SVR rates of 85% to 98%, and one study that switched from interferon therapy to DAA therapy increased SVR rates from 62%–68% to 90%–98%.(154) An exemplary Spanish study demonstrated that HCV elimination is possible in a prison setting. Using a test-and-treat strategy, the prison tested 99.5% of its inmates, treated all who were infected and would be incarcerated more than 30 days, established a teleconsultation programme for those who were released, and achieved SVR in 97% of the treated prisoners (Table 2.4, Case 5).(155)

2.4.2.6 Pharmacies

Available evidence supports including pharmacies as essential service venues in MoCs for treating HCV in PWID (Table 2.4, Case 6).(156,157) Some pharmacies dispense OST and therefore have daily contact with people on opiate substation therapy, some also offer needle and syringe provision services. One study demonstrated the feasibility of implementing DAAs through a community pharmacy for PWID receiving OST.(75)

In addition, both rapid HCV testing using dried blood spot sampling(156) and injecting equipment provision(158) have been proven effective in community pharmacies. These findings suggest that any further development of MoC designs and policies to incorporate HCV services for PWID at pharmacies should be based on the use of standard community pharmacies rather than hospital or specialist pharmacies, which can pose barriers to PWID access.

2.4.2.7 Sexual health clinics

Sexual health clinics provide a good platform for linkage to the HCV cascade. Australian and United Kingdom studies have demonstrated that interferon-based

treatment in sexual health clinics, including follow-up and regular assessments, resulted in SVRs comparable to treatment at specialist clinics.(159–161) However, there were no studies assessing rapid point-of-care testing followed by DAA therapy in this setting. Other studies from Australia and the United Kingdom linking confirmed HCV infections in sexual health clinics to injecting drug use have shown that HCV and HIV screening is feasible there but probably insufficient.(162,163) It has not yet been determined whether HCV screening in this setting should be clinician-led, as with these studies (which showed an HCV incidence of around 3%), or whether universal routine HCV testing should be implemented instead. Guidelines on who to test for hepatitis C in sexual health services are available, and often risk-factor based.(164) In either case, in order to achieve elimination in high-risk populations such as men who have sex with men, primary prevention and the prevention of reinfection will play a major role.(165–167)

Table 2.4. Selected case studies by country and population addressed.

Case studies of interest were identified from the literature. Models of care which demonstrated a unique approach or targeted a hard to reach population were selected.

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
1. Read et al., 2019(116) Kirketon Road Centre (KRC), Sydney, Australia	Primary health care facility targeting PWID, sex workers and "at-risk" young people	Viral hepatitis testing, DAA therapy, hepatitis A and B vaccination, "healthy liver clinic" with specialized hepatitis service; sexual health services; drug and alcohol counselling, assessment and referrals; crisis intervention; housing, social service and welfare assistance; methadone access and case management; NSP; street van and bus outreach; HIV testing and counselling; general health services	GPs, nurses, social workers	Integrated primary health care model offering anonymous services to risk populations. DAAs can be provided through a community pharmacy, with a follow-up phone call to confirm treatment initiation, standard of care pathology. Enhanced adherence support includes phone calls or other contact at least weekly, flexible directly observed dispensing of the medications, with or without OST, linkage to partner organisations, DAA delivery to prisons, police cells, psychiatric units and general hospital wards.	242 PWID were included, 74% recent or current injectors, 44% enrolled in OST. 79 (32%) of clients chose enhanced daily or weekly dosing support options. Enhanced support was associated with homelessness, daily injecting, Aboriginality, mental health co-morbidity and poly-drug use (all $p<0.001$). Overall adherence was 86%, and 92% of patients missed one or more doses (median 10, IQR 4-24). The study confirms that PWID can be successfully treated for HCV in a real-world setting using an integrated primary health care model and demonstrates the feasibility of scaling DAA therapy up in high-risk PWID populations.
2. Mason et al., 2017(125) Toronto Community Hep C Program (TCHCP), Toronto, Canada	A partnership between three community health centres to provide underserved populations with low-threshold access to HCV care	Treatment assessment, DAA therapy, weekly pre- and post-treatment questionnaires, follow-up	Nurses, nurse-practitioners, family physicians	Integrated multidisciplinary specialist support on site	74 PWID initiated DAA therapy, achieving high adherence and SVR with appropriate support. Participants housing status and income increased significantly during the study.

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
3. Trooskin et al. 2015(126) Do One Thing, Philadelphia, United States	Community-based program in a medically underserved neighbourhood with high rates of HCV and HIV	Social marketing campaign, door-to-door outreach, rapid HIV and HCV screening in a mobile medical unit, immediate phlebotomy for confirmatory testing of reactive antibody tests, facilitation of client enrolment in health insurance, linkage to care and retention in care	Trained HCV test counsellors, phlebotomists, patient navigators, social workers; linkage to primary care physicians and HCV subspecialists	Developed and coordinated a local hospital and local university	Among 1301 people screened, 2.8% were chronically infected, half of whom were newly diagnosed. The biggest barrier to retention in care was obtaining referrals for subspecialty providers due to a lack of insurance. Some subjects started treatment, while many who were eligible were awaiting approval from insurance companies. This study illustrates how a good model of care can adapt to local circumstances.
4. SACC, 2017;(168) Linnet et al., 2017(129) Shared Addiction Care Copenhagen (SACC) Project, Copenhagen, Denmark	12 drug counselling and treatment centres; 1 hospital infectious disease department	Hepatitis and HIV counselling and testing; transient elastography, DAA therapy, management, follow-up; various drug and alcohol treatment and harm reduction services	GPs, hospital specialists, social service providers	Decentralised shared care model, in which hospital infectious disease department was responsible for prescription and monitoring the course of treatment, while the drug treatment staff were responsible for testing, assessment, dispensing and adherence support	More than 700 people were screened for viral hepatitis and HIV. The proportion of clients tested for HCV in the treatment centres increased by 50%, and 208 were diagnosed with chronic HCV infection; 25 of them ended up being treated and cured. The model permitted many more people to be diagnosed and cured than otherwise, despite little tradition of collaboration between the centres and the hospital.

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
5. Cuadrado et al., 2018(155) El Dueso Prison, Santoña, Cantabria, Spain	Prison healthcare facility	HBV, HCV and HIV screening and diagnosis; DAA therapy, teleconsultation; phylogenetic analysis of nonresponders, followed by targeted retreatment	Prison health team -physicians, nurses, pharmacist; addiction specialists; social service providers; hospital team - infectious disease specialists, hepatologists, specialized nurses, radiologists, ID specialists, pharmacists, psychologist; telemedicine expert	A video collaboration tool was used for consultations between prison and hospital teams, as well as between treatment recipients and a hospital hepatologist, also after any inmate release. Treatment was prescribed by the hepatologist and administered by the prison healthcare providers. Prisoners were consulted on study design, and their input contributed to the use of telemedicine and the choice of the quickest treatment regimen (non-ribavirin).	A test-and-treat strategy enabled the prison to screen 99.5% of its inmates for HCV, treated everyone who was infected and would be in prison more than 30 days, established a teleconsultation programme for those who were released. The programme achieved SVR in 97% of the treated prisoners. At the end of the programme, no inmate had any detectable HCV RNA.
6. Radley et al., 2017(75) Directly Observed Therapy for Hepatitis C (DOT-C), Dundee, Scotland, United Kingdom	Community pharmacies	Dried blood spot testing, OST, DAA therapy	Pharmacists, physicians	Community pharmacies referring patients who test positive for HCV to clinics for assessment and treatment	HCV testing and treatment is feasible in community pharmacies, especially for patients already receiving OST there. Compared to nurse-practitioners, pharmacists were much more likely to get patients to take a rapid HCV test, and for clients with reactive tests, the pharmacist were much more successful in getting them to attend a clinic for assessment and treatment.

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
7. Hashim(169) VALID (vulnerable adults liver disease) Study, Southeast England, UK	Hostels, Community clinics	Point of care testing, liver fibrosis assessment (Fibroscan), alcohol and substance misuse counselling/ social support (provided by primary care physician) and HCV treatment. A specialist registrar runs the clinics under the supervision of a Hepatologist.	General practitioner, medical specialist	One stop HCV clinic at two major homeless hostels in Southeast England.	72 attended the clinic, 71 (99%) were included in the program, 28 (39,4%) were anti-HCV positive, 26/28 consented to further testing, 20/26 were HCV RNA positive, 5/20 started DAA treatment. Results in 2019: 131 individuals approached, 127/131 individuals enrolled in the program, 59/127 were HCV Ab positive, 48/59 were HCV RNA posiitve, 28/48 initiated HCV treatment, 14/17 achieved SVR12, 13 still on treatment/waiting SVR results, 1 discontinued the treatment.
8. Shiha(170) HCV elimination in general population, Egypt	Rural setting	Point-of-care testing, liver fibrosis assessment, complete laboratory work, treatment initiation with DAAs	Multidisciplinary	Awareness raising campaign followed by HCV screening by using HCV antibody RDT a week later. Anti-HCV positive got tested for HCV RNA with GeneXpert IV, and on the same day the HCV RNA positive patients had the Fibroscan, abdominal ultrasound and basic laboratory work (liver function, renal function, CBC, AFP) and initiated treatment with DAA.	475 individuals were screened for anti-HCV antibodies by RDT, 56 had PCR HCV RNA, 43 positive for HCV RNA, 40 initiated the treatment, 3 were excluded due to focal hepatic lesion and pregnancy.

2.4.3 What services to provide

The latest HCV guidelines from WHO,(40,171) the European Association for the Study of the Liver (EASL),(172) the American Association for the Study of Liver Diseases (AASLD),(173,174) and the International Network on Hepatitis in Substance Users(175) all include concrete recommendations for providing HCV services to marginalised populations. The WHO guidelines specifically address the needs of low- and middle-income countries. In addition, several systematic reviews helpfully provide an overview of the evidence for various interventions for PWID in the DAA era.(63,64,176,177)

Simplicity, scalability and patient convenience should be the bywords in developing a MoC. They call for a test-and-treat model wherever possible, to eliminate the gaps between testing and treatment.(170,178–182) Strong referral links in all directions between testing, treatment, harm reduction and social services are of paramount importance. In countries with high diagnosis rates, attention should be paid to reengaging individuals who have been diagnosed in the past and bringing them into care. For a high-prevalence population like PWID, rapid antigen or RNA testing is appropriate, the latter providing results within an hour,(183–185) and it may be sensible to omit genotyping if there is no major price differential between pangenotypic DAAs and genotype-specific ones. If transient elastography is not readily available, it makes sense to use alternative easily available non-invasive fibrosis assessment tools such as FIB4 or APRI.(186) Figure 2.3 shows the Models of Care studies from the literature search organised by the stages in the cascade of care.

Some MoCs focussed on single stages of the cascade of care, for example testing and diagnosis, whilst others crossed multiple stages. Both have value, however those MoCs covering more than one stage of the cascade have the benefit of improving linkage or retention in care; 37 of the 71 studies covered awareness and prevention, linkage to care, access to treatment and monitoring and evaluation. 11 covered testing and diagnosis, linkage to care and access to medications. 7 covered testing and diagnosis and linkage to care. 5 covered testing and diagnosis. 2 covered testing and diagnosis. 3 covered access to treatment, 2 covered monitoring and evaluation. 1 study covered awareness and prevention, testing and diagnosis and linkage to care. 1 study covered awareness and prevention, testing and diagnosis, linkage to care, access to treatment and monitoring and evaluation. 1 study covered awareness and prevention, testing and

diagnosis, linkage to care and access to treatment. 1 study covered linkage to care and access to treatment.

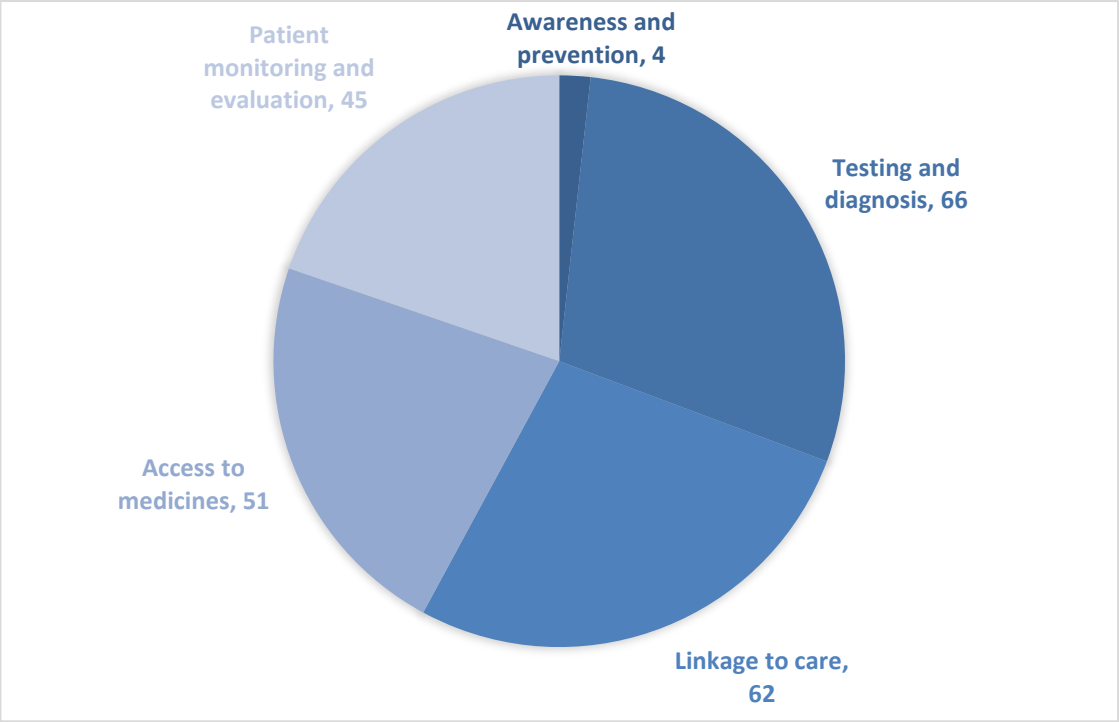


Figure 2.3. Summary of articles included (n=71). These articles were grouped according to the area or areas of the cascade of care their model of care covered. Some articles focused on one stage of the cascade e.g. testing and diagnosis, whilst others covered multiple stages.

DAA therapy is now the treatment of choice for all patients and everything should be done to ensure its availability.(74,187) Access to harm reduction services are critical, as discussed above, to reach key, high-burden populations. Finally, good patient follow-up and contact are essential to help ensure adherence and maximise cure rates. Appropriate peer support, as discussed in the next section, can be crucial in increasing service uptake and retention, particularly in working with marginalised populations.

2.4.4 Who should provide the services

Throughout the HCV cascade of care, multidisciplinary teams of healthcare and social service professionals can help ensure the best possible outcomes, which in turn will improve public health. That is why the International Network on Hepatitis in Substance Users recommends treating HCV in a multidisciplinary team setting.(175) Multidisciplinary approaches encompassing biomedical, psychoeducational and social interventions have been shown to improve engagement in care,(188) treatment uptake,(189,190) patient adherence and retention,(191–196) management of HCV/HIV coinfection(197) and of HCV in psychiatric patients,(198) stigma reduction and patient

well-being,(67,125) and reduction in mortality.(182) However, the creation of multidisciplinary teams or structures where existing structures are functioning effectively is not a requirement of a good MoC.

As previously mentioned, in evolving from MoCs designed around interferon-based treatment to MoCs designed around DAAs, HCV services should be provided in a variety of settings to facilitate scale-up. With DAA therapy, HCV assessment and treatment no longer require specialist training, so it makes sense to expand who may evaluate persons with HCV infection and prescribe treatment beyond specialists in tertiary care centres. With proper training, anyone can undertake assessment and prescribe DAAs competently, either as a delegated prescriber or a nonmedical prescriber – which again facilitates scale-up. Evidence has shown good results from the prescribing of DAAs by primary care providers, drug and alcohol service providers, nurse-practitioners, nurses, including nurse prescribers, and pharmacists.(199–202) Delegated prescribing may be a good option where prescribing is limited by statute. Table 2.5 presents the diversity of providers featured in the 71 recent MoC studies reviewed for this paper, including 18 studies highlighting the benefits of multidisciplinary teams.

Table 2.5 Categories of providers in the models of care identified in the literature search. N=71

Providers (n)	**Country**	**N. of study (see appendix)**
Multidisciplinary* (22)	Australia; Canada; Denmark; Egypt; France; Greece; Ireland; Portugal; Romania; Spain; Switzerland; UK; USA	Alimohammadi A et al. (2) Remy et al. (3), Balcomb A (5), Chronister KJ et al. (6), Valencia JA et al. (7), Cuadrado A et al (9), Inglis SK et al. (10), Ford MM et al. (11), Borojevic M et al (12), Peters L. (13), Trooskin S et al. (18), El-Akel et al. (26), Morris et al. (31), Macbeth K et al. (32), Shiha G et al. (39), Sypsa V et al. (40), Fleming BS et al. (58), Mason K et al (62), Chronister KJ et al (64), Linnet et al (66), Barror S et al. (66), Simoes D et al. (68)
Medical specialists^ (26)	Australia; Belgium; Canada; France; India; Norway; Pakistan; Portugal; Sweden; UK; USA	Papaluca et al. (1), Alimohammadi A et al. (2), Bourgeois S et al (4), Liberal R et al (8), Williams B et al. (14), Olsson A et al. (21), Bartlett SR et al. (22), Chiong F et al. (23), Hashim A et al. (28), Kattakuzhy et al. (29), Norton et al. (30), Dhiman RK et al. (36), Alam Z et al. (37), Overton et al. (41), Kraichette N et al. (44), Greenan S et al. (45), Ryder N et al. (46), Mitchell S et al. (50), Thompson H et al. (51), Lamond S et al. (53), Midgard H et al. (56), Berger SN et al. (57), Sokol et al (61), Hashim A et al (63), McDonald L et al. (70), Scherer ML et al. (71)
General practitioners (12)	Australia; Belgium; Canada; France; India; Norway; Pakistan; Portugal; Sweden; UK; USA	O'Loan J et al. (16), Chiong F et al. (23), Hashim A et al. (28), Kattakuzhy et al. (29), Thompson H et al. (51), Perez Hernandez JL et al. (52), Lamond S et al. (53), Naveed A et al. (55)*, Sokol et al (61), Mason K et al (62), Barror S et al. (66), Nouch S et al. (69) *Defined in manuscript as "doctors without speciality training"
Telemedicine (7)	Australia; Spain; Canada; Mexico; USA	Balcomb A (5), Cuadrado A et al (9), Vroling H et al. (20), Olsson A et al. (21), Cooper et al. (24), Perez Hernandez JL et al. (52), Komaromy M et al (67)
Nurse-led (14)	Australia; Belgium; Canada; Georgia; Sweden; UK; USA	Papaluca, Williams B et al. (14), Vroling H et al. (20), Olsson A et al. (21), Kattakuzhy et al. (29), Schulkind J et al. (33), Doyle J et al. (47), Bielen R et al. (48), Stvilia K et al. (49), Mitchell S et al. (50), Sinan F et al. (54), Berger SN et al. (57), Hashim A et al (63),McDonald L et al. (70)
Specialist nurse (but not nurse-led) (12)	Australia; Belgium; Canada; Norway; UK; USA	Bourgeois S et al (4), O'Loan J et al. (16), Bartlett SR et al. (22), Chiong F et al. (23), Cooper et al. (24), Radley A et al (35), Overton et al. (41), Greenan S et al. (45), Thompson H et al. (51), Naveed A et al. (55) Midgard H et al. (56), Fleming BS et al. (58)
Peer-support (3)	Australia; Belgium	Bourgeois S et al (4), Chronister KJ et al (6), Treloar C et al (64)
Pharmacists (3)	Pakistan; UK; USA	Radley A et al. (35), Fleming BS et al. (58), Koren D et al. (59)

Providers (n)	Country	N. of study (see appendix)
Non-governmental organization (1)	Pakistan	Capileno et al. (25)
Not reported/Not specified (8)	Australia; Egypt; Spain; USA	Saludes V et al (15), Grebely J et al. (17), Saludes V et al. 2 (34), Shiha G et al. (38), Kugelmas M et al. (42), Howell et al. (43), Read P et al (60), Teti E et al. (67)
Other (reviews) (3)	Multi-country reviews	Pourmarzi et al. (19), Vroling H et al. (20) Wade et al. (27)

In particular, when using non-specialist service providers, it is essential to invest in human resources i.e. hiring the best people for the job and providing them with thorough and regular training. One model that has proven useful in helping such providers serve vulnerable and dispersed populations is the model promoted by Project ECHO (Extension for Community Healthcare Outcomes).(203) By engaging frontline service providers with a continuous learning system and specialist mentors, it can dramatically increase the access of PWID to HCV care and treatment.(204,205)

A peer provider can use shared experience, as someone who has had chronic hepatitis C and/or someone who has been part of a target population, to connect with vulnerable people and help them through the cascade of care. They can also use their experience to help ensure that MoCs reflect client concerns. Limited data from both the interferon era(206) and the DAA era highlight(207,208) the potential benefit of including peer support workers in MoCs.

Countries with very broad community access to DAAs, such as Australia,(209) have been successful in mobilising the peer workforce and training them to provide services at different points in the cascade of care, where they have been crucial in building momentum towards HCV elimination.

2.4.5 How to integrate services

In the DAA era, as mentioned above, the ideal form for a successful MoC for PWID with HCV is either a one-stop-shop approach, in which all relevant services are integrated in locations where people are already accessing other services, or a flexible approach, in which various sites and services are well coordinated and strongly linked. The challenge in implementing the one-stop approach is to evolve towards comprehensive yet decentralised points of care,(210) for instance through single-visit diagnoses.(183) Multidisciplinary team working and integration go hand in hand, it is important MoC for marginalised populations to access MoCs within systems where these populations already access services, particularly OST and IEPS in the case of PWID.(211) The aim should be to bring services closer to the client, rather than expecting the client to seek them out. Secondly, it requires multidisciplinary and integrated training, which includes task-shifting, so fewer types of professionals are providing more services in the same settings, thereby necessitating fewer visits to access them.

In their seminal review on MoCs for HCV, Bruggmann and Litwin contrast various integrated MoCs with conventional secondary and tertiary care models.(55) Where it is feasible and affordable, we advocate integration: delivering integrated care in non-specialist settings that are better suited to the care of vulnerable individuals. In Scotland, where managed care networks exemplify integrated multi-agency MoCs, they have been shown to improve not only HCV outcomes, but also outcomes related to drug use.(182,212,213)

Although not exhaustive, the presented examples demonstrate that integrated MoCs are effective in addressing the entire HCV cascade of care (Figure 2.3), plus evidence that an integrated format might be particularly well suited to primary care, community health centres, addiction and harm reduction centres, prisons, sexual health clinics, pharmacies and other settings. Such models of care can successfully target both the typical young drug user and the veteran of addiction treatment,(214,215) thereby increasing overall eligibility for HCV treatment(216) while providing the appropriate counselling, peer support(188) and management of medical, mental health and social issues for both those on opioid substitution therapy and those who are not.(114,127,217,218)

2.5 CONCLUSION

Around the world, models of care for HCV need to be redesigned to reflect the recent widespread availability of DAAs if countries are to meet their commitments to eliminating HCV as a public health threat by 2030, as set out by WHO. In some countries, this will require major changes to established care pathways and systems. One immediate challenge for policymakers and researchers is to develop cost-effective, easily implemented mechanisms that incorporate health information and reimbursement systems, and interdisciplinary and multi-facility communication. Healthcare providers, affected populations and other key stakeholders should be involved in such development to ensure that the final mechanisms represent relevant perspectives and are mutually beneficial to all. While further research on the feasibility of different MoCs in specific settings is needed, much can be learned from examining the innovative MoCs reviewed here, which suggest that an effective model of care for HCV infection should be simple, targeted, multidisciplinary, scalable, integrated, patient-centred and affordable.

CHAPTER 3 – SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 A SYSTEMATIC REVIEW AND META-ANALYSIS OF COMMUNITY AND PRIMARY-CARE BASED HEPATITIS C TESTING AND TREATMENT SERVICES THAT EMPLOY DIRECT ACTING ANTI-VIRAL DRUG TREATMENTS

This chapter was published as "A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments" published in BMC Health Services Research in 2019.(219) I, along with my co-author carried out the literature search. I performed the meta analysis and prepared the accompanying tables and graphs. All authors reviewed the full draft of the article.

In keeping with the thesis aims I wished to explore the efficacy of community based models of care for HCV treatment. Where possible we looked for studies which had conventional secondary care led HCV services as a comparator.

3.2 SUMMARY

3.2.1 Introduction

Direct Acting Antiviral (DAAs) drugs have a much lower burden of treatment and monitoring requirements than regimens containing interferon and ribavirin, and a much higher efficacy in treating hepatitis C (HCV). These characteristics mean that initiating treatment and obtaining sustained virologic responses (SVR) on completion of treatment, in non-specialist environments should be feasible. We investigated the literature evaluating community and primary care-based pathways using DAAs to treat HCV infection. This was with a view to establishing which pathways would be most effective for our population with a view to optimising testing and treatment for HCV in NHS Tayside.

3.2.2 Methods

Databases (Cinahl; Embase; Medline; PsycINFO; Pubmed) were searched for studies of treatment with DAAs in non-specialist settings to achieve SVR. Relevant studies were

identified including those containing a comparison between community and specialist services where available. A narrative synthesis and linked meta-analysis were performed on suitable studies with a strength of evidence assessment (GRADE).

3.2.3 Results

Seventeen studies fulfilled the inclusion criteria: Five from Australia; two from Canada; two from UK; eight from USA. Seven studies demonstrated use of DAAs in primary care environments; four studies evaluated integrated systems linking specialists with primary care providers; three studies evaluated services providing care to people who inject drugs; two studies evaluated delivery in pharmacies; one study evaluated delivery through telemedicine. Sixteen studies recorded treatment uptake. Patient numbers varied from around 60 participants with pathway studies to several thousand in two large database studies. Most studies recruited less than 500 patients. Five studies reported reduced SVR rates from an intention-to-treat analysis perspective because of loss to follow-up before the final confirmatory SVR test. GRADE assessments were made for uptake of HCV treatment (medium); completion of HCV treatment (low) and achievement of SVR at 12 weeks (medium).

3.2.4 Conclusion

Services sited in community settings are feasible and can deliver increased uptake of treatment. Such clinics are able to demonstrate similar SVR rates to published studies and real-world clinics in secondary care. Stronger study designs are needed to confirm the precision of effect size seen in current studies.

3.3 INTRODUCTION

Rates of uptake of HCV testing, linkage to care and treatment remain low across many countries.(63) Barriers to treatment are both personal and systemic as discussed in Chapter 1: individuals may prioritise other needs and may be wary of the consequences of a diagnosis; health systems may present complex and rigid arrangements that must be navigated in order to access care.(220) The stigma associated with both injecting drug use and HCV infection is pervasive.(221) The concept of the care cascade has focussed attention on the performance of different pathways and the attrition of patients accessing testing, diagnosis, treatment and care.(222)

In many developed and developing countries, HCV treatment is delivered by specialist clinicians, often from hospital outpatient facilities.(223) As direct-acting antiviral drugs

(DAAs) have become widely available, treatment with these medicines is simple and well-tolerated.(187) The safety profile and high efficacy of DAAs means that HCV treatment can be delivered by a range of non-specialist clinicians including nurses, pharmacists and general practitioners.(110) Allowing treatment to be delivered in community and primary care environments, in essence taking treatment to those who need it, rather than expecting them to negotiate secondary care settings. Progress with implementing treatment pathways provided by non-specialists in community and primary care environments has been identified as one of the key steps in the elimination of HCV.(40) The World Health Authority's Guidelines for the care and treatment of persons diagnosed with chronic hepatitis c virus infection promote simplified service delivery models: integration with other services; decentralised services supported by task-sharing and community engagement, with the intention of reducing stigma and increase uptake of treatment.(40)

This review was undertaken to identify rates of treatment uptake, treatment completion and achievement of sustained virologic response for adults infected with hepatitis C using DAA-only treatment regimens in community and primary care-based care pathways, evaluated by studies using observational and experimental study designs. Studies that compared community-based treatment care pathways with specialist care were actively sought.

3.4 METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(224) Methods of analysis and inclusion criteria were specified in advance and documented in a protocol. The study was registered in PROSPERO (CRD42017069873).

The PICOS elements for this review were as follows:

Table 3.1. Elements of the PICOS question defined for this review.

	Inclusion	Exclusion
Population	Age 18 years and over Infected with chronic hepatitis C	Age less than 18 years Co-infection with Hepatitis B virus Co-infection with HIV.
Intervention	Provision of hepatitis C treatment in any primary care and community environments. Treatment using any direct acting antiviral therapy Care provider could be any health care provider.	Hepatitis C treatment in prison populations Treatment with ribavirin / interferon regimes as the primary intervention
Comparison	Care in any hospital or secondary care environment or no comparison group.	
Outcome	Treatment uptake, treatment completion and SVR outcomes	
Study Design	Observational studies, retrospective or prospective cohort studies, randomised trials; conference abstracts; qualitative and mixed methods studies.	Case studies; systematic reviews

The rationale for the inclusion of the above PICOS elements was the intention to address the WHO Guidance and its recommendations for simplified and decentralised treatment delivery models, integrated with other services in community and primary-care environments.(40) Therefore a population aged over 18 were selected, as being less likely to have gained their infection through vertical transmission. Co-infected individuals with other blood borne virus infections were also excluded as their care was likely to be more complex, requiring specialist rather than simplified care. Studies from prison populations were excluded since these individuals lived in contained communities. Studies that utilised interferon and ribavirin-based treatment regimens as the primary intervention were also excluded as the enhanced monitoring and patient management requirements made simplified and decentralised care less likely. Studies were restricted to the English language since study resources precluded any translation activities. Published studies were utilised including conference abstracts, in order to capture results from early studies when the first DAAs were introduced into practice.

3.4.1 Search strategy

Published research was identified by formal searches of five electronic databases (Cinahl, Embase, Medline, PsycINFO, PubMed) from January 2013 to December 2017, as well as Google Scholar. The last search was run on 11 December 2017. Search topics

included “hepatitis C”, “treatment” and “setting”. A comprehensive list of search terms related to each of the search topics was used to develop a search strategy for each electronic database. Search strings were formulated using a combination of keywords and indexed subject headings (MeSH and EMTREE terms). Primary care was defined using the World Health Organization accepted terminology that promotes Primary Care as a key process in the health system: It is first-contact, accessible, continued, comprehensive and coordinated care.(225)

The full search strategy is set out in Appendix 2/Chpater3. Reference lists of selected articles, citing articles and relevant review articles retrieved during the initial search were hand-searched and forward citation checks were performed to identify additional studies by AR and ER. Abstracts from the selected scientific conferences were screened for review eligibility by AR and ER. Any discrepancies or uncertainties were discussed between AR and ER. Where there was no resolution between reviewers, JD was called upon to arbitrate.

3.4.2 Study selection

Data retrieved through the search strategy were imported into EndNote X8 (Thomson Reuters, New York, NY, USA) and duplicates removed. Titles obtained from the initial search strategy were screened and irrelevant citations were removed. Abstracts were then assessed using the inclusion and exclusion criteria by two reviewers independently (AR and LT) to establish a relevant pool of evidence for further evaluation. Full-texts from all abstracts identified for further evaluation and were double-screened independently by two reviewers (AR and ER) to assess whether they met the defined inclusion and exclusion criteria. In the event of a disagreement, the senior investigator (JFD) determined final inclusion. Reasons for exclusion are reported. The AR contacted abstract authors to attempt to obtain further study results if available.

3.4.3 Data collection process and data items collected

Data from studies included for analysis were extracted by one reviewer author (AR) using a standardised data extraction form (Microsoft Excel 2010 Redmond, WA, USA). A second reviewer (ER) checked the extracted data, and disagreements were resolved by discussion until consensus was reached. The following variables were collected: first author, title, publication year, study design, study location, setting, intervention description, comparator description, sample size outcome description, number of participants achieving SVR12 (and percentage if applicable).

3.4.4 Risk of bias assessment in individual studies

Risk of bias in individual studies was assessed by two reviewers (AR and ER) independently using the "Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses"(226) and the Cochrane Collaboration's risk of bias tool for randomised studies.(227) Differences were reviewed and discussed until a consensus was reached. In the event of a disagreement, the senior investigator (JFD) determined final inclusion. The NOS measures three items; selection of cases and controls including their definition and representativeness; comparability of cases and controls in design and analysis; and exposure ascertainment. The scale has a minimum score of 0 and a maximum score of 9. Risk of bias was rated as high, medium or low according to the scores obtained by reviewing the selection, comparator and exposure categories. Risk of bias was rated low if studies scored 8 or 9 stars; medium risk if studies were scored as 6 or 7 stars. Studies were rated as having a high risk of bias if they were scored as having 5 or less stars or scored zero for the comparator category.(228)

For randomised studies, outcomes were evaluated along the six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The number of domains deemed as 'high risk' of bias for each study per outcome was identified. Outcomes of non-randomised studies were evaluated along seven domains: bias due to confounding, bias in selection of participants into study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. The overall risk of bias for each outcome was classified into five categories: low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias or no information.

We (AR and ER) assessed the strength of evidence using GRADE.(229) The scheme evaluates a required group of domains (study limitations, directness, consistency, precision and reporting bias) and enables grading of the strength of evidence as High; Moderate; Low or Insufficient. Use of this approach enabled us to summarise the outcomes and findings and make clear judgements about the effects of the interventions.

3.4.5 Data analysis

The characteristics and findings of the included studies were summarised and structured using tables and Forest plots. Studies evaluating similar service environments in community and primary care-settings were grouped together to facilitate comparison.

Study designs, participants, interventions and reported out-comes varied significantly, and a meta-analysis was unable to be performed on all included studies. Studies were excluded from the meta-analysis if the authors considered them to be sufficiently flawed so as not to contribute meaningfully to the body of evidence.(229)

The meta-analysis was conducted by ER. The characteristics and findings of studies amenable to meta-analysis were summarised using tables and forest plots. Risk ratio (RR) and corresponding 95% confidence interval (95% CI) was calculated for each study outcome, using the initial number of eligible participants included and the number achieving the outcome of interest in each arm. If the study reported more than one outcome e.g. treatment uptake and SVR, outcomes were derived separately. Outcomes were coded to treatment uptake (a), treatment completion (b) and SVR (c). Risk ratio and confidence interval were calculated using Microsoft Excel 2013 (Redmond, WA, USA) prior to data importation to STATA for analysis. STATA enables the results of multiple studies to be combined to estimate an overall effect size. Analyses were conducted using statistical package Stata v14.0 (College Station, TX, USA).

3.4.6 Data synthesis

3.4.6.1 Deriving pooled estimates of treatment uptake, treatment completion and SVR

Treatment uptake, treatment completion and SVR and their exact 95% confidence intervals (CIs) were calculated assuming a binomial distribution in Microsoft Excel. Pooled estimates were derived using random- or fixed-effects methods, according to whether significant heterogeneity (defined as $I^2 > 30\%$) was or was not present, respectively. Analysis was initially run with a fixed effect model, however if significant heterogeneity (defined as $I^2 > 30\%$) was detected a random effects model was used. Sensitivity analysis was used to assess the impact of study quality (restricting to studies with an NOS score ≥ 6) on the pooled estimate of SVR.

Further sensitivity analysis was used to assess the impact of conference abstracts on the pooled estimate of SVR. We identified studies using similar environments from which to deliver care and grouped them into categories. Factors identified as linking studies

within categories were examined as well as factors that differentiated studies from each other

3.5 RESULTS

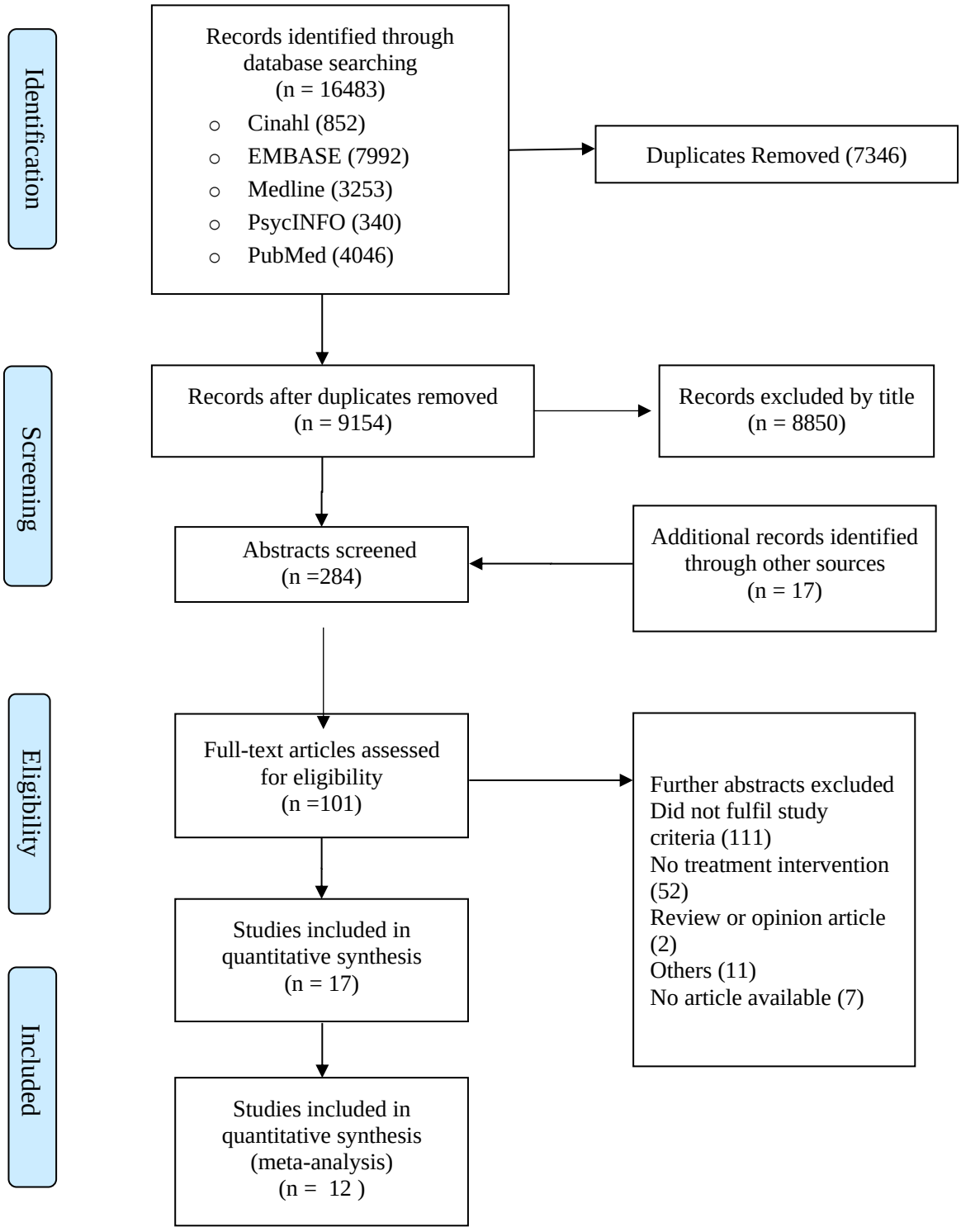


Figure 3.1. Flow diagram of search results.

3.5.1 Study selection

The flow diagram of the study analysis is shown in Figure 3.1. The searches yielded 9,154 publications after removal of duplicates. This resulted in 101 articles retrieved

for full text inspection and 17 included for analysis. Explanations for exclusion of studies at the full text stage are provided in Figure 3.1. These included "Did not fulfil inclusion criteria; no treatment intervention; review or opinion article; other (e.g. insufficient detail reported in conference abstract).

3.5.2 Study characteristics

Studies evaluated care pathways in:

- primary care(202,230–235)
- integrated health systems(236–239)
- places where people who inject drugs (PWIDs) are treated(240–242)
- pharmacies(75,243)
- using telemedicine(244)

Characteristics and findings of included studies are set out in Table 3.2. Eight of these studies originated from United States of America; five from Australia; two from the United Kingdom; two from Canada. The large proportion of identified studies published as conference abstracts reflected the length of time that DAAs have been widely available outside specialist environments. Seven from seventeen studies were only available as conference abstracts. There were two randomised controlled trials; four cohort studies, nine retrospective data analyses and two prospective non-experimental designs. Assessment of studies were described in terms of design and assessment of bias. Table 3.2 describes the outcomes from the meta-analysis of selected studies and Table 3.3 defines the Strength of Evidence Assessment for identified studies answering the PRISMA objective. Details of assessment of bias and design for studies are located in Appendix Table 1 (non-randomised) and Appendix Table 2 (randomised).

Table 3.2. Summary of key findings, outcomes and strength of evidence.

Outcome	**Study designs/No. Studies**	**Findings and Direction of Effect**	**GRADE**(229)
1. Uptake of HCV treatment	RCT* – 2 Cohort – 3 Observational – 5	Two RCTs assessed as having low risk of bias reported a positive effect on uptake with precision and a consistent positive direction of effect. One cohort study assessed as having medium-grade study limitations also reported a positive effect on uptake.	Medium
2. Completion of Treatment	Cohort - 1 Observational 2	One cohort study with medium study limitations reported a positive direction of effect on uptake.	Low
3. Sustained Viral Response at 12 weeks (%)(SVR12)	RCT -2 Cohort 4 Observational -11	Two RCTs assessed as having low risk of bias reported a positive effect on SVR but were imprecise in the estimate of effect size. Four cohort studies and 11 observational studies with over 10,000 participants all reported a consistent positive direction of effect, but with significant study limitations.	Medium

Abbreviations: RCT, randomised controlled trial; SVR, sustained virologic response.

3.5.3 Primary care

Seven studies evaluated interventions to enhance treatment uptake and achievement of SVR in primary care environments.(202,230–235) One paper was a randomised controlled trial (RCT), two papers were cohort studies and four were non-randomised studies. Four studies utilised nurses in delivery of the care pathway. Three papers included uptake of testing and assessment in their description of care and all papers discussed uptake of treatment and ascertainment of SVR. Two papers reported a reduction in potential SVR rates because of failure of participants to complete the confirmatory blood test at 12 weeks after completion of DAA treatment. All studies reported increased access to treatment in primary care environments and high rates of SVR attainment.

3.5.4 Integrated health systems

Four studies provided evaluations of care through integration of specialist centres with primary care delivery.(236–239) One study was a retrospective cohort study and three were non-randomised studies. Three of the studies utilised the ECHO care pathway in which hepatitis specialists support primary care providers through video-conferencing and collaboration on specific cases, with a defined curriculum and active mentorship.(204) None of the papers discussed uptake of testing amongst their treated

cohorts. All papers reported increased access to treatment and high rates of attainment of SVR.

3.5.5 Places where PWIDs are treated

Three studies evaluated care provision in dedicated settings where people with opioid addiction received harm reduction and treatment services.(240–242) All papers were non-randomised analyses of treatment data and assessed the uptake and completion of treatment by participants using these services. No assessment of the extent of testing of these populations was reported, which may introduce a selection bias. All papers reported high rates of treatment uptake and treatment completion in diagnosed individuals. All papers described problems with retention of participants in the service post-treatment with consequent reductions in uptake of confirmatory SVR testing.

3.5.6 Pharmacies

Two studies evaluated hepatitis C care provision by pharmacists in community and primary care settings.(75,243) One paper was a feasibility RCT that compared the delivery of a community pharmacy test and treatment pathway with standard hospital-based care. One study was a non-randomised data analysis. The RCT demonstrated an increase in testing uptake, when the participant received all care in a pharmacy environment and showed increased retention in care. Data from this study also demonstrates a marked loss of patients from the care pathway for those randomised to attend the local hospital for standard hospital-based care. The non-randomised study concluded that patients treated in pharmacist clinics achieve high rates of SVR similar to non-pharmacist clinics

3.5.7 Telemedicine

A single cohort database study(244) compared treatment uptake and SVR rates in participants cared for through a telemedicine pathway (n=157) with participants cared for through a standard care pathway (n=1,130). The study demonstrated increased access to care from under-served and remote areas and concluded that the telemedicine intervention achieved high rates of treatment initiation and SVR.

Table 3.3. Characteristics and findings of included studies.

Author	Year	Country	Design	Intervention	Comparator	Number	Uptake (%)	SVR (%)
Primary care								
Bloom(230)	2017	Australia	Prospective cohort study of treatment uptake and SVR	Adherence to DAA treatment protocols	Treatment by tertiary care provider	1044	503 (40.6)	253 (50.2)
Francheville(231)	2017	Canada	Prospective observational study design	Specialist nurse-led care	No comparator group	242	93(38.4)	82(88.2)
Kattakuzhy(202)	2017	USA	Non-randomised open label study	Treatment by primary care providers and nurse practitioners	Standard care - Treatment by secondary care clinic	NP 150 PCP 160		NP 134(89.3) PCP139(86.9)
McClure(232)	2017	Australia	Retrospective data analysis of SVR12	Nurse-led care and GP remote consultation	Specialist care in Tertiary centre	Nurse-led 70	50(74.3)	46(65.7)
Miller(233)	2016	USA	Retrospective observational study	Treatment by primary care providers	No comparator group	95		79(83)
Norton(234)	2017	USA	Retrospective cohort study of SVR	Treatment in urban primary care centre	SVR 12 in PWIDs and non_PWIDs	89		85(95.5)
Wade(128)	2018	Australia	Randomised controlled trial	Testing, assessment and treatment in primary care	Testing, assessment and treatment in tertiary care	59	31(52.5)	14(23.7)
Integrated Health Systems								
Abdulameer(236)	2016	USA	Retrospective data analysis of SVR 12	VA-Echo model supporting primary care providers	No comparator group	588		318 (54)
Beste(237)	2017	USA	Retrospective cohort study of treatment uptake and SVR	VA-Echo model supporting primary care providers	Standard care - Treatment by unexposed primary care providers	6431	1303 (21.4)	(58.2)
Buchanan(238)	2015	United Kingdom	Retrospective data analysis	Community-based outreach clinic	Standard care - Treatment by secondary care clinic	77	24 (31.2)	

Author	Year	Country	Design	Intervention	Comparator	Number	Uptake (%)	SVR (%)
Georgie(239)	2016	USA	Retrospective data analysis of SVR12	VA-Echo model supporting primary care providers	Treatment by sub-specialist providers	623		GT1 (99) GT2 (98) GT3 (79)
Places where PWIDs are Treated								
Butner(240)	2017	USA	Retrospective data analysis	Opioid treatment programme	No comparator group	75	75 (100)	64 (85.0)
Morris(241)	2017	Australia	Retrospective data analysis of treatment uptake and SVR	Treatment in a community-based harm reduction and treatment facility	No comparator group	127	122(96)	102(80.3)
Read(242)	2017	Australia	Retrospective data analysis of SVR12	Treatment of PWIDs in primary care setting	No comparator group	72		59(81.9)
Pharmacies								
David(243)	2017	USA	Retrospective data analysis of SVR12	Pharmacy-managed clinics	Treatment by non-pharmacist providers	204		170 (83.6)
Radley(75)	2017	United Kingdom	Pilot cluster RCT of treatment uptake and SVR	Treatment in community Pharmacy	Treatment by secondary care clinic	26	3(11.5)	3(11.5)
Telemedicine								
Cooper(244)	2017	Canada	Retrospective cohort study of treatment uptake and SVR	Use of telemedicine	Treatment by secondary care clinic	157	35 (22.2)	18(11.5)

3.5.8 Data synthesis

The 12 studies included in the meta-analysis examined treatment uptake, completion and SVR in a variety of primary care environments, these were; integrated systems that linked specialists with primary care providers; places where PWIDs are treated; Pharmacies; telemedicine and specialist hospital care. The remaining 5 studies were felt not to be suitable for meta-analysis due to non-reporting of the required outcomes, use of PEGylated interferon or insufficient follow up time to achieve SVR. Across 12 studies, the pooled estimate is shown in Table 3.4. Forest plots for suitable studies are set out in Figures 3.2, 3.3 and 3.4. These plots demonstrate that across the variety of community and primary care environments, a consistent direction of effect to improve treatment uptake, treatment completion and achievement of SVR is seen.

In this analysis, heterogeneity was noted to be high so a sensitivity analysis restricting to higher-quality studies (NOS score ≥6) was performed. Despite this the heterogeneity remained high. A further sensitivity analysis was performed restricting the meta-analysis to published studies only. See Table 1 in Appendix 2/Chapter 3. This had no impact on heterogeneity.

Table 3.4. Meta-analysis of studies examining treatment uptake, treatment completion and SVR among people with hepatitis C treated in a variety of community settings or specialist hospital care.

Inclusion Criteria	**Treatment Uptake**			**Treatment Completion**			**SVR**		
	No. Of studies	Heterogeneity[a] (I^2)	Pooled estimate (95% CI)	No. Of studies	Heterogeneity (I^2)	Pooled estimate (95% CI)	No. Of studies	Heterogeneity (I^2)	Pooled estimate (95% CI)
Places where PWIDs are treated				2	77.7%	91.9 (82.2-100)	3	0.0%	82.3 (77.8-86.8)
Integrated health system	1	Not applicable	75.6 (68.0-83.2)	1	Not applicable	96.8 (93.2-100)	2	84.6%	81.3 (66.9 -95.5)
Telemedicine	1	Not applicable	22.3 (15.8-28.8)				1	Not applicable	51.4 (34.8-68.0)
Primary care	1	Not applicable	67.4 (53.9 – 80.9)	1	Not applicable	100 (97.95-100)	5	94.9%	74.4 (60.3 – 88.5)
Pharmacy	1	Not applicable	66.67 (58.3 – 75.1)				2	89.0%	79.0 (79.2 – 98.9)
Specialist care	2	0.0%	34.5 (31.79 – 37.29)				5	96.8%	73.46 (60.9 – 85.9)

Abbreviations: CI, confidence interval; PWID, people who inject drugs; SVR, sustained virologic response.

a. Random-effects method used if $I^2 \geq 30\%$.

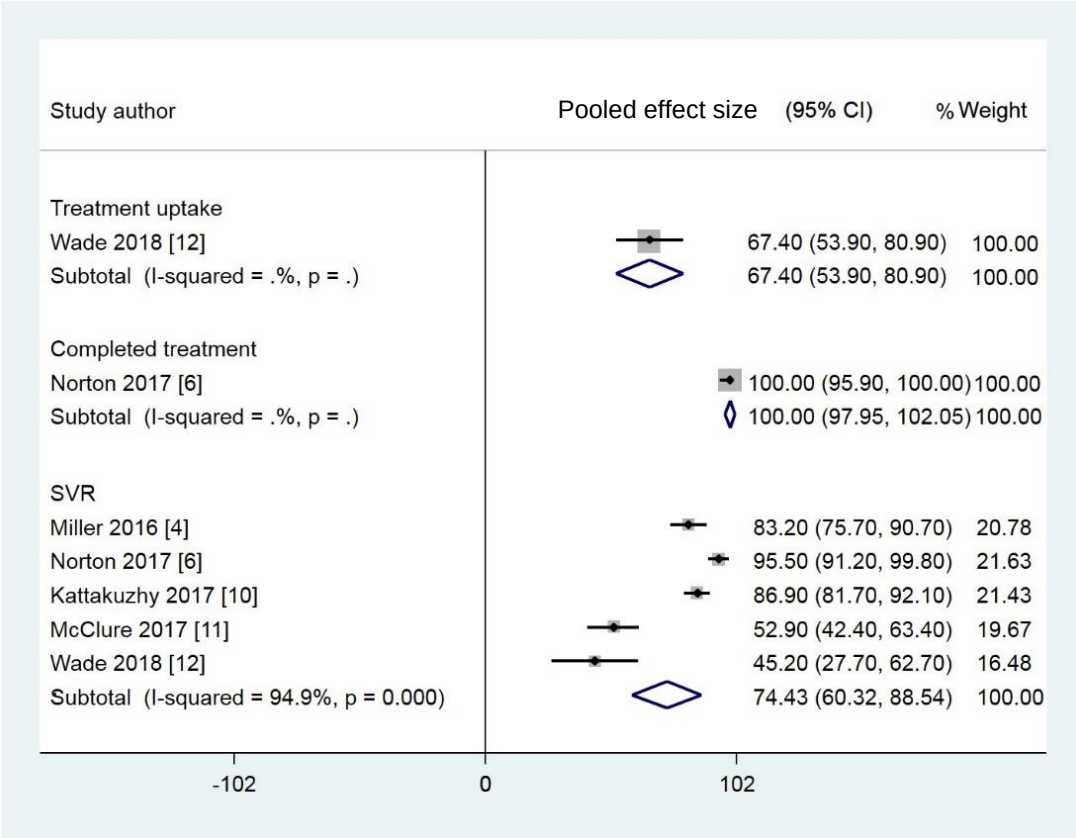


Figure 3.2. Forest plots of treatment uptake, completed treatment and SVR rates for selected studies in the primary care location.

Figure 3.2 demonstrates outcomes for studies where HCV care was delivered in the primary care setting. There is one study apiece demonstrating treatment uptake and treatment completion with five studies demonstrating SVR outcomes in the primary care location. The direction of effect is the same for all studies, although this was not statistically significant.

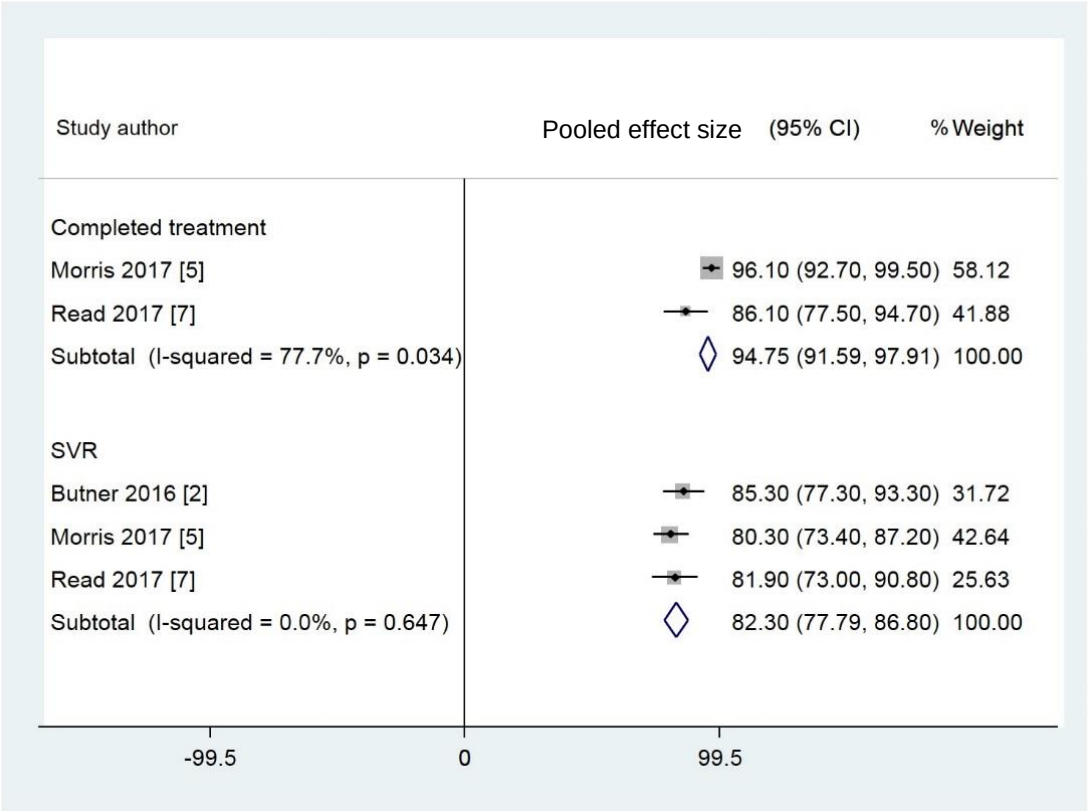


Figure 3.3 Forest plots of completed treatment and SVR rates for selected studies in the integrated health system location.

Figure 3.3 demonstrates outcomes for studies where HCV care was delivered in the integrated health system setting. There are two studies demonstrating treatment completion and three studies demonstrating SVR outcomes in the integrated health system location. The direction of effect is the same for all studies, although this was not statistically significant.

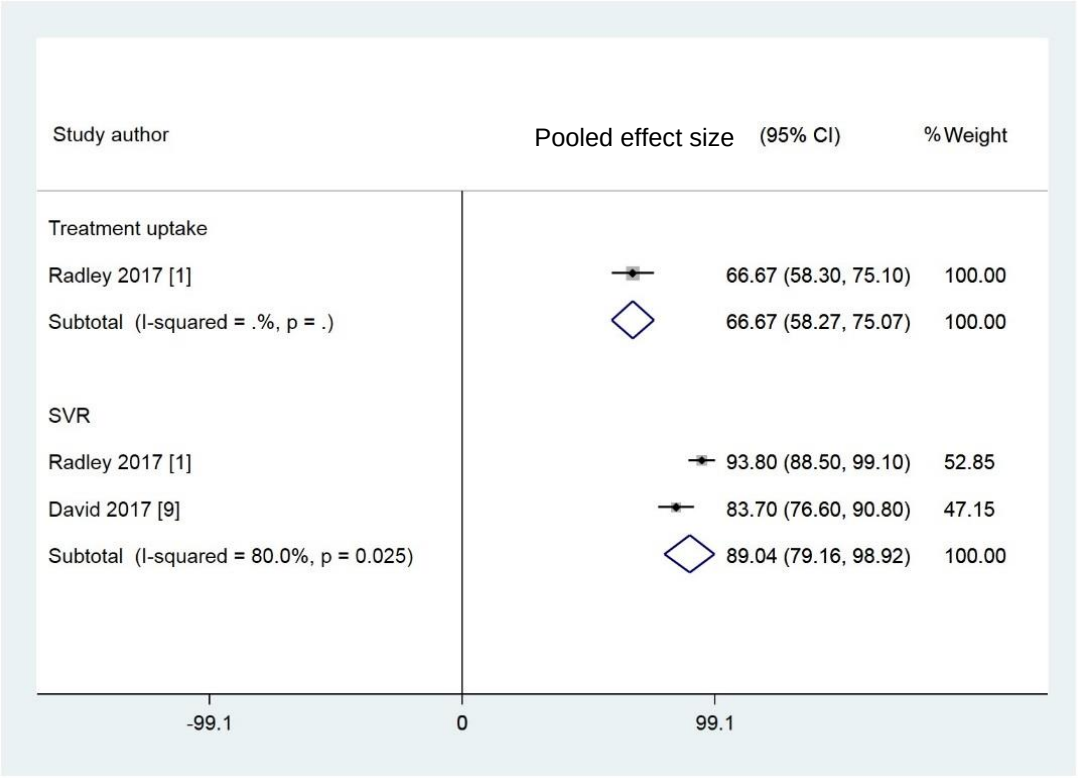


Figure 3.4. Forest plots of treatment uptake and SVR rates for studies in the pharmacy location.

Figure 3.4 demonstrates outcomes for studies where HCV care was delivered in the pharmacy setting. There is one study demonstrating treatment uptake and two studies demonstrating SVR outcomes in the pharmacy location. The direction of effect is the same for both studies, although this was not statistically significant. ‘

3.6 DISCUSSION

This chapter reviews outcomes of care pathways that utilise DAAs in a range of community and primary care settings. The WHO Guidelines on care and treatment of persons diagnosed with chronic HCV infection promote simplified service delivery models; integration with other services; decentralised services supported by task-sharing and community engagement to address stigma and increase reach.(40) The studies considered in this systematic review and meta-analysis therefore provide some real world evidence for the uptake and implementation of these guidelines.

The identified studies that met our inclusion criteria have been grouped according to location: primary care; integrated health care systems; places where PWIDs are treated; in pharmacies; and through telemedicine. These care pathways acknowledge the need to provide local services with roots in the communities and establishments where people with hepatitis C will have easy access to them.

Uptake of treatment, completion of treatment and attainment of SVR was demonstrated with a positive outcome reported by all identified studies. However, amongst the studies that met our inclusion criteria, there were a lack of studies using comparators to specialist centres. Data contained in these studies nevertheless demonstrated high uptake of treatment and high rates of attainment of SVR notably among populations of vulnerable people who normally struggle to access care. Studies that did include comparators showed no significant differences in uptake or SVR. Several of the studies reported an increased uptake of treatment, but most reported equivalence. Some studies reported lower rate of attainment of SVR because of study participants failing to undergo a confirmatory blood test post treatment, within the study timelines. With the use of DAAs, SVR rates of greater than 97% are achieved if patients adhere to treatment, therefore completion of therapy can be a surrogate for SVR.(245)

Previous systematic reviews have considered barriers and facilitators to care, as well as the views and experiences of people who inject drugs.(220,246) These studies concluded that the target groups for HCV often had poor levels of knowledge about the infection and of the processes involved with testing and treatment. A fear of stigma and discrimination and a reticence to discuss risk behaviours tended to prevent engagement. These barriers could be addressed through educating participants and integrating HCV treatment pathways into other services the target group are likely to access.

Increased uptake of testing has been seen when testing is offered at the same time as other routine care,(63) with positive outcomes seen when testing is offered along with services for opioid users and with mental health services. There are advantages to developing targeted services that address populations with a high predicted prevalence of HCV.(247) Provision of HCV treatment as part of a directly observed opiate substitution therapy (OST), increased attainment of SVR.(248) Utilising these pathways within established health systems needs to be commonplace in order to benefit from the increased treatment uptake, treatment completion and SVR effect in order for the WHO target for elimination is to be met.(249)

The results from this systematic review highlight the lack of well-controlled randomised controlled trials and comparative studies in this area of study, with just two randomised controlled trials identified and four cohort studies. While the publication of such studies is an important step in building confidence that decentralisation of hepatitis C treatment can be accomplished, the paucity of evidence reflects the difficulty in funding pathways to care studies and the relatively recent removal of the restrictions on the use of DAAs. Publication of three study protocols identify that further evaluations of interferon-free treatments in primary care environments are underway.(128,220,250)

As with any systematic review, the quality of the studies and the heterogeneity of the study populations included in the analysis present a limitation of this study. The sensitivity analyses performed for our analysis did not have any impact on heterogeneity, meaning that an unexplained source of heterogeneity is still present. These difficulties may reflect the variety of ways in which patients can access HCV treatment. This could be seen as a positive factor and may be explained by the development of diverse and more patient centred pathways. These factors prevented a meta-analysis being achieved for all of the studies identified as eligible through the PICO question definition for this review. Many of the studies that met the inclusion criteria were only available as conference abstracts, including one of the randomised controlled trials. Nevertheless, over 10,000 participants have been included in identified studies. All studies had a consistent direction of effect, as demonstrated in the Forrest plots (Figures 3.2–3.4). It is hoped that the addition of future studies will confirm this direction of effect and define the effect size that should be delivered by simplifying treatment pathways and decentralising them to primary care. In terms of further limitations, we acknowledge limitations in the chosen methods for the systematic review, including potential publication bias especially given that all included

studies showed the same direction of effect. We cannot overlook the possibility that studies which didn't have statistically significant results or clinically favourable results were not published, therefore leading to an imbalance in the available literature in this area. We excluded non-English language studies and may have unintentionally provided additional bias by our chosen inclusion and exclusion criteria.

3.7 CONCLUSION

This systematic review and meta-analysis identifies studies which demonstrate the feasibility of decentralising care and providing local services with reach into communities of people infected with HCV. Such pathways may increase uptake of treatment and can provide sustained virologic responses equivalent to those attained in specialist centres. The successful implementation of such pathways to deliver successful patient outcomes is a key requirement for a "treatment as prevention" strategy as a pathway to elimination of HCV.(251)

CHAPTER 4 – THE EVERYONES HCV STUDY

4.1 SUMMARY

NHS Tayside has instituted a number of specialised pathways for testing and treatment of HCV amongst the most at-risk populations, including people who inject drugs (PWID), those on opiate substitution therapy (OST) and prison inmates. Widespread testing occurs in injecting equipment provision sites (IEPS), community pharmacies and the prison service as part of a coordinated regional strategy. The aim of the data presented in this chapter was to analyse the effectiveness of these targeted diagnosis pathways compared with standard testing.

Data was collected retrospectively for every HCV antibody and PCR test ever done in NHS Tayside. Each test was attributed to a diagnosis pathway according to the testing source. Data was cross-referenced with clinical records including testing source and clinical outcome for every individual with positive antibody results.

Analysis of local data revealed testing in primary and secondary care has tripled (2364 to 7486 antibody tests/year) from 1999 to 2017, with PCR positivity falling from 2.3% to 0.7%, as more medium/low risk individuals have been tested. In contrast, testing in prisons yields a rate of 4%, IEPs a rate of 15% and community pharmacies 13.5%.

Diagnostic pathways targeting populations most at risk of HCV are more effective at yielding new HCV diagnoses than standard pathways. These tailored diagnostic pathways also resolve some of the health inequalities around drug use and provide methods of ensuring entry to treatment. The results suggest targeted testing will find the majority of Tayside's undiagnosed population, which would be challenging using only the standard testing pathway. However no single pathway is sufficient on its own, requiring multiple testing pathways to be deployed. This will help achieve the aim of HCV elimination within NHS Tayside by 2030.

4.2 INTRODUCTION

Scotland has taken the lead within the UK in tackling HCV with its Hepatitis C Action Plan,(252) published first in 2006, and the subsequent Sexual Health and Blood-borne Virus Framework, published in 2015.(19) One of the Hepatitis C Action Plan's key goals was to identify undiagnosed infections and identified that access to testing was a

significant obstacle in achieving this target. Nearly 75% of undiagnosed cases of HCV within Scotland (16,300) are individuals who were previously classified people who inject drugs (PWID) but who no longer inject.

Tayside is a geographically defined area covering approximately 3,000 square miles, with a mix of small villages, medium-sized towns and larger cities, representing a combination of population densities. The estimated population of Tayside on 30th June 2017 was 416 090 and is comprised of 3 main areas, Dundee city, Perth and Kinross and Angus,(253) all administered by different councils. Tayside has an unusually stable population that is confined by the geography of the region, and that co-locates a health service providing all health care for this area. As a single health board serves all of these council areas, the population has limited options in accessing health care outside this board. However, this unitary health provision, combined with the stable population and wide variety of settlements, makes Tayside an ideal area to conduct natural experiments at the population level to assess the effectiveness of health interventions.

Several pathways to diagnose and treat HCV-positive patients have been developed in Tayside and subsequently evolved over the years due to the changing disease and treatment landscape. There has been a particular focus on diagnosing and increasing access to care for PWID, given that this population represents both the biggest risk group in the region and also the highest risk category for onward transmission. Tayside is recognised to have a relatively high number of both drug-related hospital admissions and drug-related deaths compared to the rest of Scotland and the UK.(253)

In order to achieve HCV elimination, it is vital that diagnostic activity is optimised and is responsive to patient needs and social environment. In order to increase chances of engagement, cure and reduce risk of onward transmission it is imperative that individuals with chronic HCV are engaged in care, treated and cured, as soon as possible after contracting the infection. Evaluation of the relative benefit of being tested in one pathway or an alternative pathway in terms of diagnosis rate, access to treatment and retention in care is a vital task in order to allow the health board to continue to plan future HCV services which will galvanise activities designed to deliver elimination of Hepatitis C at a regional level.

4.3 AIMS AND OBJECTIVES

In line with Scottish Government targets, NHS Tayside is committed to eliminating the Hepatitis C virus (HCV) as a public health threat by 2024.(16) With an estimated

prevalence of 0.5-0.55% we anticipate that 2,000- 2,200 people are living with chronic HCV in Tayside. Currently 1800 individuals have been diagnosed, leaving 200-400 as yet undiagnosed.

4.3.1 Primary outcome

To demonstrate the most effective combination of existing pathways to diagnose HCV infection in a typical developed world population.

4.3.2 Secondary outcome

1. To define effectiveness of each pathway
2. To define rate of conversion of test-to-diagnosis and diagnosis-to-treatment for each pathway

4.4 MATERIALS AND METHODS

4.4.1 Approvals and trial registration

4.4.1.1 Ethical approval

The clinical trial received favourable ethical opinion from the West of Scotland Research and Ethics Committee 4 on 18th March 2018, reference number 18/WS/0035. Research and Development approval was granted for the study to proceed locally in Tayside on 12th March 2018 (Appendix 3).

4.4.1.2 Calidcott approval

Approval to access relevant clinic data for the trial was received from the Caldicott Guardian on 9th March 2018 (Appendix 3).

4.4.1.3 Trial registration

The trial was registered on clinicaltrials.gov on 27th March 2018. ClinicalTrials.gov Identifier: NCT03513796

4.4.2 Study setting

As already mentioned the Tayside region of Scotland has a population of approximately 416 090 people.(254) In Scotland the prevalence of hepatitis C antibodies is in the region of 1.0%,(255) and updated figures in NHS Tayside indicate an active infection prevalence of 0.5-0.6%, which would correspond to approximately 2100 - 2500 people living with HCV in the region. An overview of some of the milestone developments in HCV care, set against annualised figures for testing in NHS Tayside are displayed in Figure 4.1, whilst established pathways for viral hepatitis diagnosis and management in Tayside is shown in Figure 4.2.

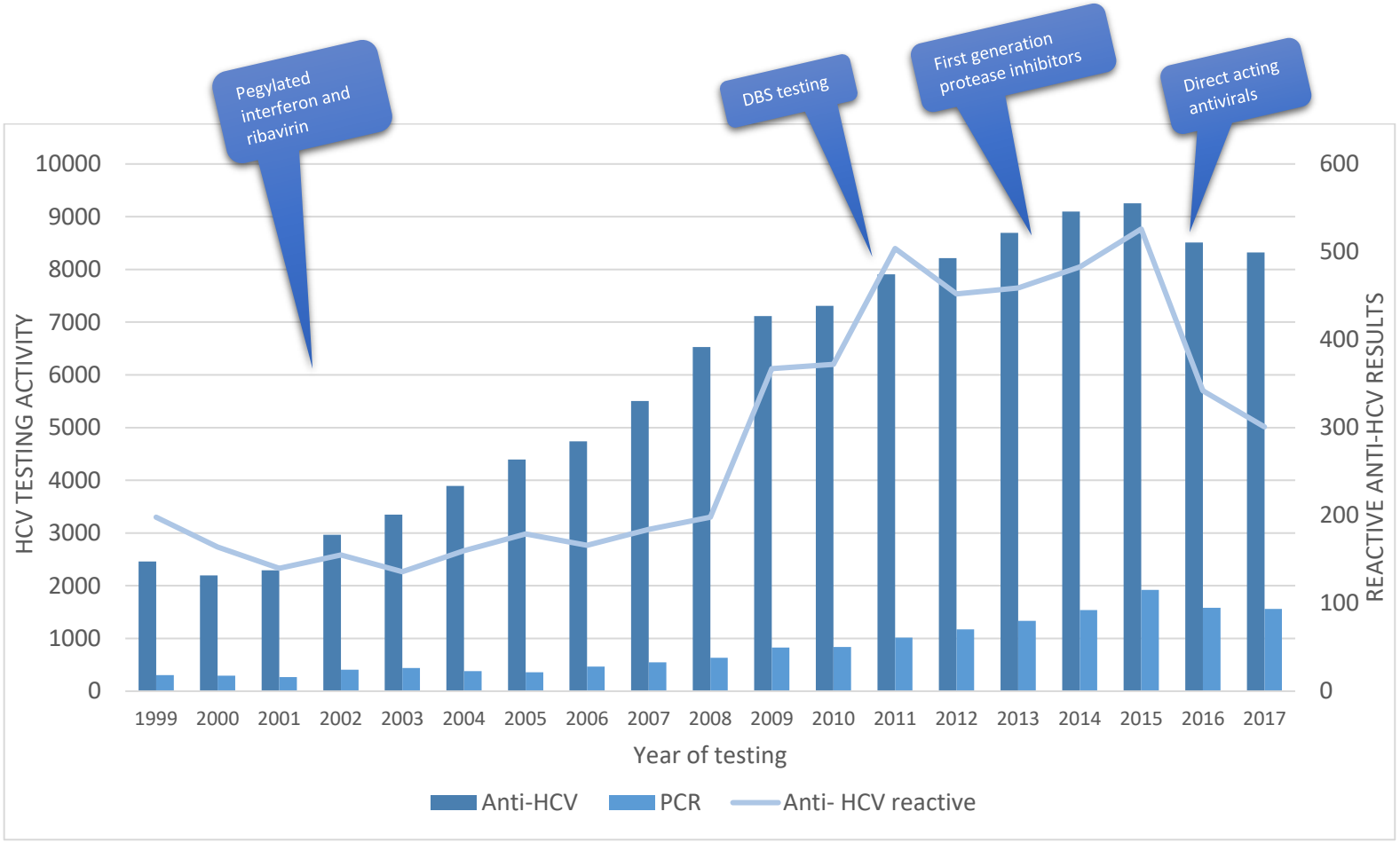


Figure 4.1. Graph demonstrating the testing activity in NHS Tayside from 1999–2017 with advances in treatments for hepatitis C noted at the specific time points. Anti-HCV relates to HCV antibody testing. PCR relates to confirmatory polymerase chain reaction tests to confirm HCV positivity. Levels of these are noted on the left Y axis denoting HCV testing activity. Anti-HCV reactive refers to positive HCV antibody tests and is represented by the pale blue line graph corresponding to the right Y axis.

Viral hepatitis specialist services for Tayside residents, including those who live in more remote towns and villages to the north and west of Dundee, are based in Ninewells Hospital and Medical School, which is a tertiary level, university-affiliated hospital based in Dundee. The hospital is well served by public transport links for those who are able to attend here, for those unable to attend there are multiple outreach clinics run by NHS staff with multidisciplinary team support from Ninewells as appropriate.

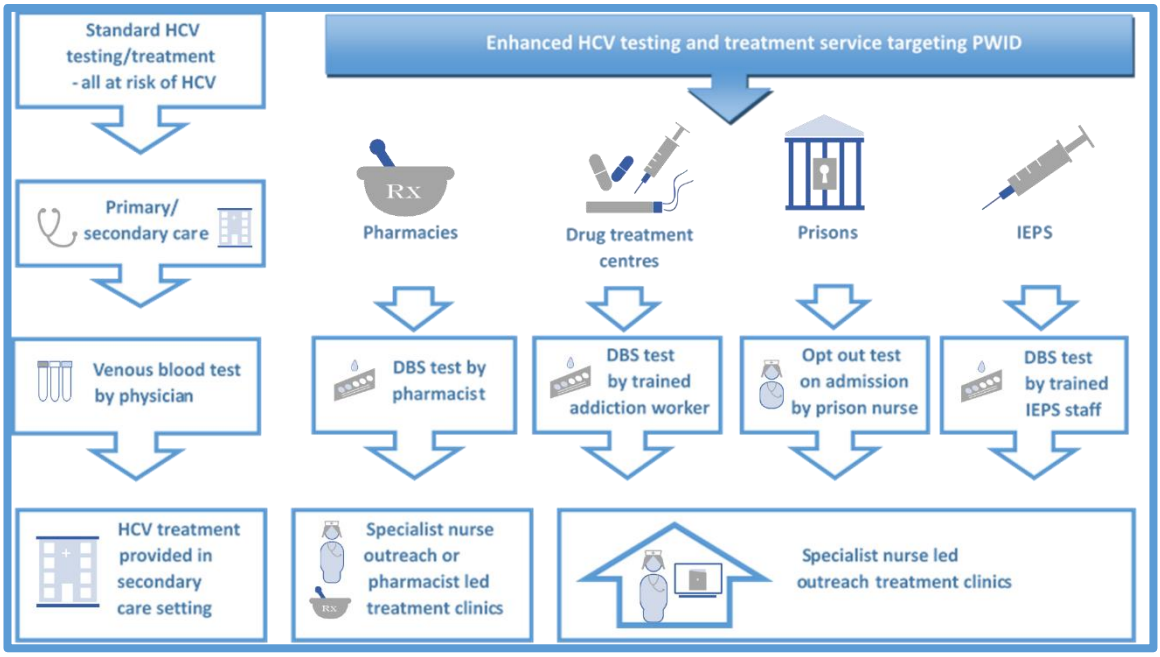


Figure 4.2. HCV diagnosis and treatment pathways in NHS Tayside.

Figure 4.2 shows the currently active NHS-based HCV diagnosis and treatment pathways which are discussed in detail in the next section. This figure does not include the research-led testing pathways or one-off interventions, which were also included in the analysis. These research-led pathways were primarily run through IEPS and community pharmacies around the health board.

4.5 Overview of included diagnostic pathways

4.5.1 Group 1 – Continuous care pathways for the duration of the epidemic

4.5.1.1 Pathway 1 – Standard pathway. Primary and secondary care

Following a clinical interaction in either primary or secondary care, there may be clinical suspicion that the patient has HCV, based on symptoms, risk factors or abnormalities detected via other investigations such as elevated liver blood tests. Following blood draw – either in Ninewells Hospital, general practice, phlebotomy services or in one of the outreach clinics serving the regional towns and villages – an anti-HCV antibody test is requested, with a HCV PCR often requested concurrently. If a

patient is positive for HCV antibodies, the HCV PCR test is performed to assess for active infection. This is known as reflex testing. If the result indicates that individual is HCV positive, this is fed back to the patient by the requesting healthcare worker and an onward referral to HCV specialist services is made.

Patients are reviewed at the HCV clinic in Ninewells Hospital or in a regional outreach clinic. The Ninewells-based team comprises a nurse-led assessment clinic and a specialist clinic staffed by gastroenterologists, infectious diseases physicians and hepatology nurses. The outreach clinics are staffed by specialist hepatology nurses, with weekly multidisciplinary team support. This outreach service provides HCV care for those who are unable or unlikely to travel for whatever reason to Ninewells Hospital for an appointment.

4.5.1.2 Pathway 2 – Opiate substitution pathway. Drug treatment services

PWID are the most significant risk group for HCV in the developed world.(256) On the road to recovery from opiate substance dependence many individuals will be placed on a programme of opiate substitution therapy. Those clients whose HCV status is unknown and are being assessed to commence opiate substitution therapy (OST) by the Tayside Substance Misuse Service (TSMS), or who are already on an opiate substitution programme, are opportunistically offered a HCV test when they engage with TSMS. Again, as in pathway 1 results are communicated by the requesting healthcare worker. If a test returns negative for HCV antibodies (i.e. HCV status is known), clients are offered annual HCV testing on an ongoing basis in line with prevailing recommendations on HCV case-finding in Scotland.(257)

A dried blood spot (DBS) test is taken by an addictions worker when the patient interacts with the TSMS, who then requests a blood-borne virus screen tests via the local laboratories in Ninewells Hospital. Tests which return antibody positive on DBS sampling are followed up by another panel of blood tests, obtained by a HCV outreach nurse, to assess for a confirmatory HCV PCR as well as safety and suitability of the patient for HCV treatment. If the individual is confirmed to have active HCV infection, treatment is either initiated by the individual's community pharmacist, who routinely dispenses their OST, or by the HCV specialist nurses in the community outreach clinics. The treatment venue is allocated according to patient preference.

4.5.1.3 Pathway 3 – Opiate substitution pathway. Community pharmacies

Clients attending community pharmacies to collect OST are typically either previous or current injecting drug users, meaning they are at high risk of infection with HCV. Similarly to testing through drug treatment services, at a number of community pharmacies in Tayside, OST clients are opportunistically offered a HCV test using a DBS if their status is not already known. If their test returns antibody negative, they are offered re-testing on an annual basis in line with the prevailing HCV case-finding guidelines.

Pharmacists and pharmacy workers have been trained by NHS Tayside to perform and respond to results for both HCV antibody and HCV PCR tests using DBS, and refer any patients with positive results to the core HCV care team in Ninewells Hospital for onward care if required. There is a linked payment for pharmacies conducting HCV testing for their OST clients, on a per-test fee basis, which incentivises pharmacists to maintain this referral pathway above and beyond the obvious clinical benefits for their clients, and their own professional practice.

If a non-complex case (bloods results within set parameters, supplied to pharmacists as part of their training) of HCV infection is confirmed, and the community pharmacist is an independent prescriber, the client can be initiated on DAA treatment and monitored by the community pharmacist. This practice is a continuation of a recently completed clinical trial (SuperDOTC (250)), which has now been embedded into clinical practice. In more complex cases of infection, individuals can be referred to the HCV specialist team in Ninewells Hospital for review, and appropriate treatment can then be commenced in a HCV community outreach clinic or the individual's community pharmacy.

4.5.1.4 Pathway 4 – Injecting equipment provision sites (IEPS)

In NHS Tayside, provision and clean injecting equipment and related paraphernalia, such as needles, pots, filters, sterile water, antiseptic wipes, citric acid, and so on, are provided to PWID at no cost in select community pharmacies and larger dedicated provision sites in collaboration with third-sector partners. People attending these provision sites are offered HCV testing via DBS by trained third-sector workers employed by the service provider, or via traditional phlebotomy by trained NHS staff, if they happen to be on site at the time of exchange.

If previously HCV positive, routine bloods (i.e. liver function tests, full blood count, coagulation, anti-smooth muscle antibody), a HIV and Hepatitis B (HBV) screen, and HCV RNA are taken. If the HCV RNA test is positive, patients are invited to attend a BBV outreach clinic situated in the IEPS to be started on HCV treatment, which is monitored via the clinic in the IEPS by specialist nurses with MDT support from Ninewells Hospital. The specialist nurses can offer this monitoring as they staff the clinic 9-5, five days a week, to provide a harm reduction and wound dressing service.

Additional services that are available for clients within the larger dedicated IEPS include wound care, dentistry, broader sexual health care, contraception clinics and social worker engagement. Substance recovery cafes are also co-located on site.

4.5.1.5 Pathway 5 – Prisons

PWID are frequently imprisoned, and estimates place HCV prevalence between 3-38% amongst prison inmates.(258) Modelling studies have confirmed the negative impact of incarceration on perpetuating the HCV epidemic.(259) National Scottish guidelines recommend opt-out HCV testing in prisons as the most appropriate model of care, and it is a required part of NHS service level agreements.(260)

On entry to prison, new inmates are offered HCV and HBV testing as part of the reception process by the prison staff. If the individual accepts a BBV test, they are appointed to the prison HCV clinic at the next available appointment and reviewed by the specialist HCV nurse. HCV testing is conducted by traditional phlebotomy or by DBS, depending on patient preference and clinical requirements (e.g. patient has difficult venous access). In late 2019, a Cepheid GeneXpert was introduced to the largest prison in NHS Tayside in order to provide point-of-care, rapid HCV testing. This platform enables staff to test for HCV PCR using only a capillary blood sample.

If the test results confirm an individual has active HCV, they are initiated on pan-genotypic DAA treatment. The prison pharmacist checks for drug interactions before the medications are dispensed from the prison dispensary, and inmates can choose to receive either a two-week dispense or to attend for daily observed therapy. If an individual is liberated prior to treatment completion, they are provided with the remaining DAA treatment course upon release and followed up in the community to ensure SVR.

4.5.2 Group 2 One off interventions and pathways of short duration

4.5.2.1 Pathway 6 – Community outreach to ethnic minorities

A prior targeted study(261) was performed in 2011 in Tayside, was aimed at both raising awareness and increasing testing of HCV amongst people of Pakistani descent. The prevalence of HCV in Pakistan is around 4-5%, compared with 1% in Scotland, making this population a priority for HCV testing locally. Testing and awareness raising sessions were conducted in 3 mosques and one Pakistani women's centre. Following an afternoon HCV awareness meeting with each group, a temporary outreach HCV clinic was set up at each site. Participants who volunteered had blood samples taken and filled out a questionnaire. All results were sent out in the mail. Participants who had a positive result received a phone call and were invited to attend a HCV clinic to discuss the results and start treatment.

This community outreach was a one-off intervention to test a population who have a historical risk, but little on-going risk for future infection (unless they returned to Pakistan and had further exposure). It was therefore feasible to do a one off outreach and testing programme, but would yield little in the way of additional diagnosis if this population was sampled again in the future. This approach also has the effect of raising community awareness and increasing test requesting via conventional pathways.

4.5.2.2 Pathway 7 – GP record search

In 2011 a single General Practice in Dundee in an area of high social deprivation (SIMD category 1) was given health board funding to test 50 patients for HCV. A case record trawl identified patients in the practice who had both a documentation of drug dependence and a current or previous methadone prescription. Identified patients were invited for HCV testing by their GP. 86 people were identified and invited for testing of which 75 people were tested and resulted in 6 new diagnoses of HCV.

4.5.2.3 Pathway 8 – GP health promotion since 2013

A health promotion campaign was rolled out to 19 general practices in Tayside to raise awareness of the risk of HCV and advocate testing for those at risk (e.g. in receipt of an opiate substitution therapy prescription). GPs handed out questionnaires to help patients identify their risk for HCV when they first registered with the practice.

4.5.2.4 Pathway 9 – Targeted GP screening in Glasgow

A general practice in an area of social deprivation in Glasgow with known increased prevalence of HCV. Patients between the age of 30 and 54 were offered an information

leaflet and HCV testing when they attended for non-urgent GP appointments for any reason

A further eight general practices in areas of social deprivation in Glasgow with known increased prevalence of HCV. Patients were offered testing if they had a history of IVDU and fell within the age range of 30-54. If agreeable to HCV testing, they were offered pre-test counselling and venepuncture for HCV antibody and PCR testing. A follow-up appointment was offered to discuss results.

4.5.2.5 Pathway 10 – GP record unification

Twenty four general practices in Dundee cross referenced their practice records regarding HCV testing, results and follow up with the records from the secondary care HCV services. Patients who had been tested but not referred, declined follow up or lost to follow up were identified and re-contacted or referred to HCV services. Representing an exercise in re-linkage to care rather than new diagnostic activity.

4.6 EVALUATION OF THE DIAGNOSTIC PATHWAYS: METHODS

This was a whole population cohort study conducted in a geographically defined region, based on a prospectively collected data set over 27 years with retrospective analyses. Diagnosis data is available over 27 years and testing data for 20 years.

The outcomes and activities of all the diagnostic pathways described above were collated from various data sources including: the NHS Tayside HCV clinical database, the NHS Tayside virology lab database and previously published pilot studies.(261–263) Anonymised data from these sources were exported to create a research password protected spreadsheet on a University of Dundee computer for analysis, which was stored on a regularly backed-up server. From the source databases the number of tests sent via each pathway was established and then the number of those tests positive for HCV. Further analysis was performed to determine the number of positive HCV tests per pathway, which converted to treatment and cure. Cure was defined as sustained virologic response (SVR) at least 12 weeks after completion of DAA treatment.

Using the information regarding the source of testing allowed assessment of the efficacy of the separate pathways, i.e. which pathway yields the highest proportion of HCV-positive results per number of tests taken.

4.6.1 Inclusion criteria

Any individual over 18, ever tested for HCV in NHS Tayside between January 1999 and December 2017.

4.6.2 Exclusion criteria

- Test requesting source originating from outside NHS Tayside
- Age under 18

4.6.3 Data collection

4.6.3.1 Virology laboratory data

A fully anonymised dataset was obtained of all serum samples tested for anti-HCV antibody or HCV RNA in the Virology laboratory of Ninewells Hospital and Medical School in NHS Tayside from January 1999 to December 2017.

The source of the HCV (anti-HCV antibody or HCV PCR) request was identified and each test was assigned to one of seven pathways: primary care, secondary care, drug treatment services, community pharmacies, injecting equipment provision sites (IEPS), prisons and "GP record search" (pathways: 1, 2, 3, 4, 5 and 7). The results of the anti-HCV antibody or HCV PCR were further broken down to show: year of testing, and outcome of the test result i.e. anti-HCV antibody negative or reactive and HCV PCR negative or positive.

The spreadsheet containing all of these data was stored on University of Dundee servers, which are GCP compliant and get backed-up regularly, minimising risk to the data set.

4.6.3.2 Clinical data

The NHS Tayside clinical HCV database was formed during the Interferon and Ribavirin era in order to document patients' progression through testing and treatment. It has evolved over the years to become the single site of information regarding the HCV status for all patients in the region with an anti-HCV antibody reactive result.

Each month the database is updated with details regarding people who have had a reactive anti-HCV antibody or HCV PCR in the preceding month. Relevant clinical data and recent HCV test results are also updated as they become available.

Clinical data held for each individual is input as it becomes available and includes, but is not restricted to: age, HCV risk factor, intravenous drug use (current or remote),

opiate substitution therapy status, fibrosis score, testing year and source, date of last attendance, engagement with services, treatment history, PCR status, SVR status and whether they are in follow up.

The following data were collected and entered anonymously into a Microsoft Excel spreadsheet: demographics; testing source and testing year; results of anti HCV and HCV PCR testing; injecting drug history; opiate substitution therapy status; on engaging with the service and on starting treatment; treatment episodes and outcome. Current PWID were defined as reporting to have injected within the preceding twelve months.

A subsidiary tracker of the NHS Tayside clinical HCV database is the dried blood spot testing database for patients tested in the IEPS. This database details all blood sampling performed (both venous and dried blood spot sampling) in the IEPS along with the relevant clinical data as previously outlined. This was the primary data source for the IEPS pathways (pathway 4).

4.6.4 HCV testing methods

As previously described, antibody testing is used as the initial test to determine whether someone has an active HCV infection. A positive anti-HCV test indicates that the person may be actively infected, may have spontaneously cleared the infection, or the result may be a false positive. Following HCV antibody positivity, active infection is confirmed using RNA testing. Dried blood spot testing offers both antibody and PCR testing on a fingertip capillary sample. This is frequently used in non-clinical settings and for patients with challenging venous access.

4.6.5 Statistical analysis

Descriptive statistics were used to report the baseline patient characteristics and 95% confidence intervals calculated for relevant data sets. IBM SPSS statistics 22 software was used for all descriptive statistics and analysis.

4.6.6 Scottish Index of Multiple Deprivation codes

The Scottish Index of Multiple Deprivation (SIMD) identifies small area concentrations of multiple deprivation across all of Scotland in a consistent way. SIMD codes were allocated to the respective general practices in Pathway 1. SIMD rank small areas (called datazones) from the most deprived to the least deprived people using SIMD. SIMD 1 is equivalent to the most deprived and SIMD five is the least deprived.

The SIMD will be applied to HCV testing data obtained on the GP element of pathway 1 in order to assess for deprivation in the community setting, and then explore the relationship between deprivation and HCV infection.

Details of practice list sizes were obtained from NHS Open Data from NHS Services Scotland.(264)

4.7 RESULTS

Of 109,430 samples tested for anti-HCV antibodies during the nineteen-year period of sample collection, 5176 (4.7%) were found to be reactive. A proportion of these tests were due to repeated testing of individuals who have a persisting risk of contracting HCV e.g. PWID with active injecting drug use but previously had a negative anti-HCV antibody test. Of 16 205 samples tested for HCV RNA during the time period, 7332 (45%) were found to be reactive. This number included retesting for relapse or reinfection in people with a prior HCV infection. HCV PCR testing is repeated throughout treatment to assess treatment response (this practice has reduced in the era of DAA treatment, due to the documented safety and efficacy of DAAs) and at the end of treatment to confirm sustained virologic response (SVR). Therefore, individuals in the study data set may have undergone multiple testing events for both anti-HCV and HCV RNA over the time period in question. As the testing data was not linked to individuals the proportion of people undergoing repeat testing is not known.

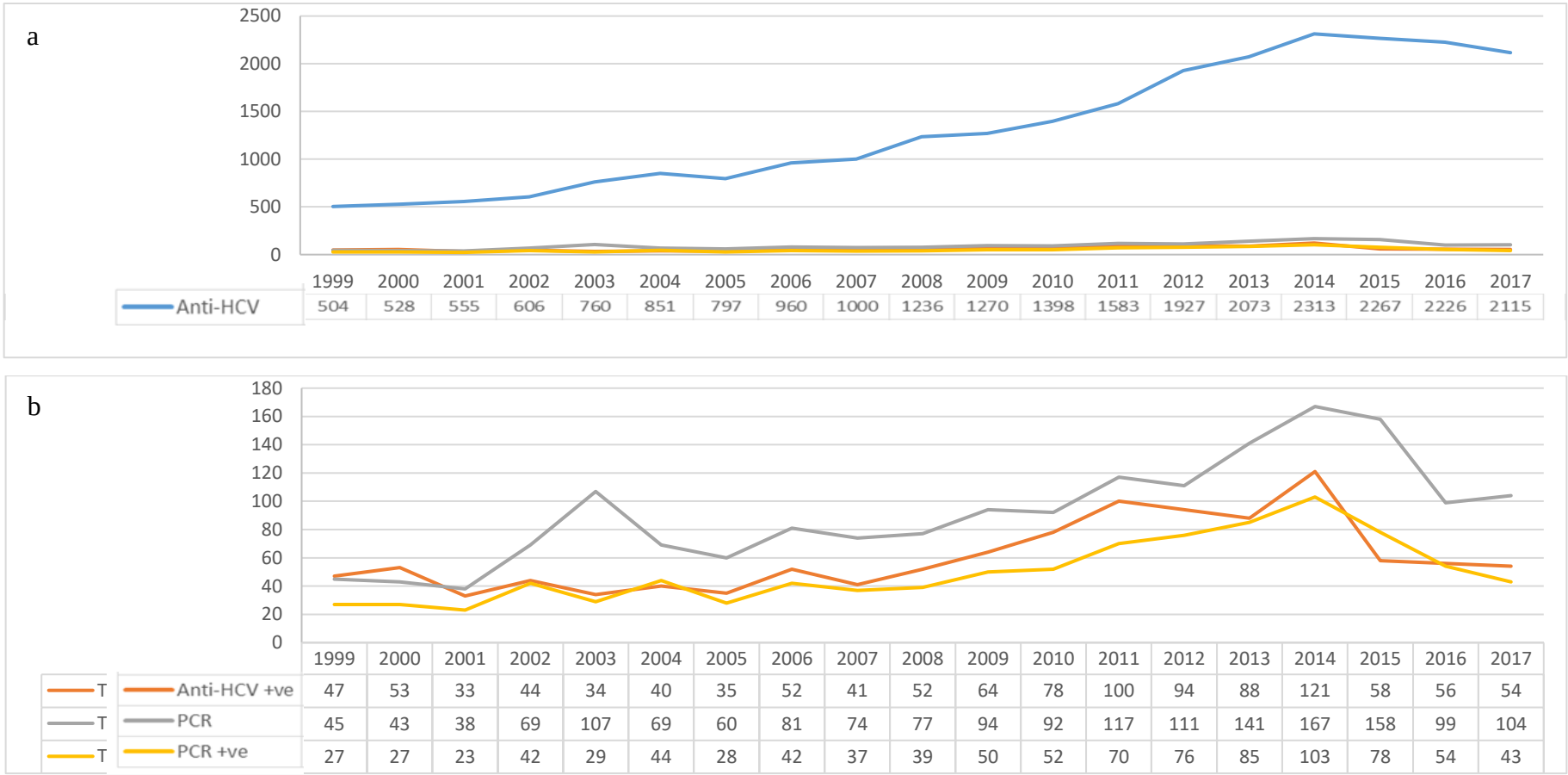
Of the 109,430 anti-HCV samples tested: 24,969 (22.8%) had been tested in over 60 general practices, 77,885 (71.2%) within 432 secondary care sites (a diverse range of wards and specialities including; haematology, renal and respiratory), 2415 (2.2%) within drug treatment services at 3 sites, 193 (0.2%) within 25 community pharmacies, 753 (0.7%) within one central harm reduction injecting equipment provision centre, 2970 (2.7%) within the regions 2 prisons (and a third, now closed prison), 170 (0.2) within 3 of Dundee's mosques and one Pakistani women's centre and 75 (0.07%) through the GP record keeping intervention at one central general practice in Dundee.

The following sections give detailed insights into each pathway's testing activities over the study period.

4.7.1 HCV testing: Entire study period

The figures illustrate the HCV testing activity per pathway over the entire study period. This data gives a detailed insight into the minutiae of each pathway, allowing observations of peaks and troughs of testing activity over time.

4.7.2 Pathway 1: Testing in primary care

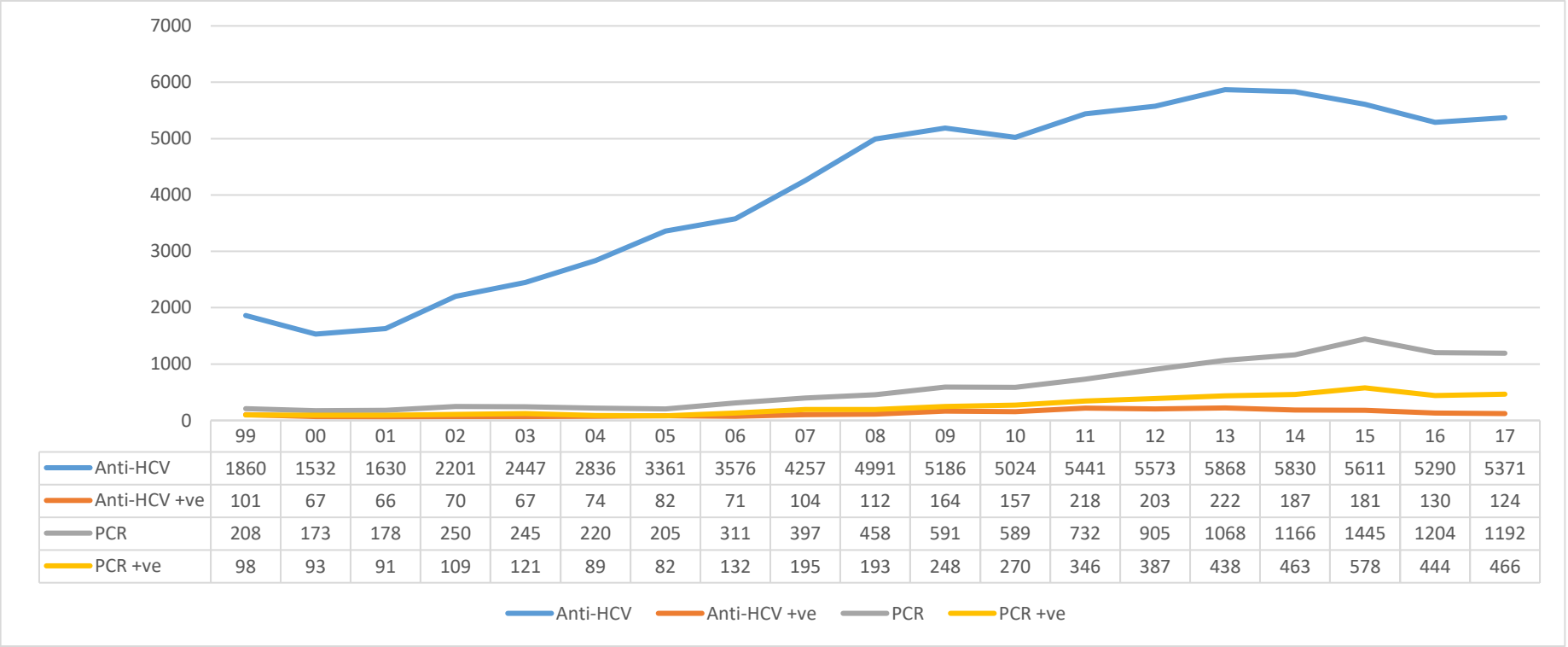


		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
	Anti-HCV	504	528	555	606	760	851	797	960	1000	1236	1270	1398	1583	1927	2073	2313	2267	2226	2115
T	Anti-HCV +ve	47	53	33	44	34	40	35	52	41	52	64	78	100	94	88	121	58	56	54
T	PCR	45	43	38	69	107	69	60	81	74	77	94	92	117	111	141	167	158	99	104
T	PCR +ve	27	27	23	42	29	44	28	42	37	39	50	52	70	76	85	103	78	54	43

Figure 4.3. a&b Testing activity in primary care (pathway 1). Graph a. shows overall testing activity, with Graph b. showing the same data, but with only antibody positive results and PCR testing activity and PCR positivity displayed given the smaller scale.

In primary care, there is a gradual increase in testing evident over a long timeframe, peaking in 2014-2015, before plateauing and mildly attenuating into the 2016 period onwards. The 2014-2015 peak clearly aligns with a concurrent peak in PCR positivity. The graph clearly demonstrates a large volume anti HCV testing, with only a small proportion of those tested having active HCV infection (determined by PCR positivity). This predominantly reflects investigation of patients with symptoms or liver blood test abnormalities rather than risk based screening, hence the low positivity rate. There may be a proportion of risk based screening, but as more specialist pathways were developed from 2009 onwards this did not diminish testing activity, suggesting either little risk based screening activity or minimal overlap between different populations tested by primary care and specialist pathways.

4.7.3 Pathway 1: Testing in secondary care

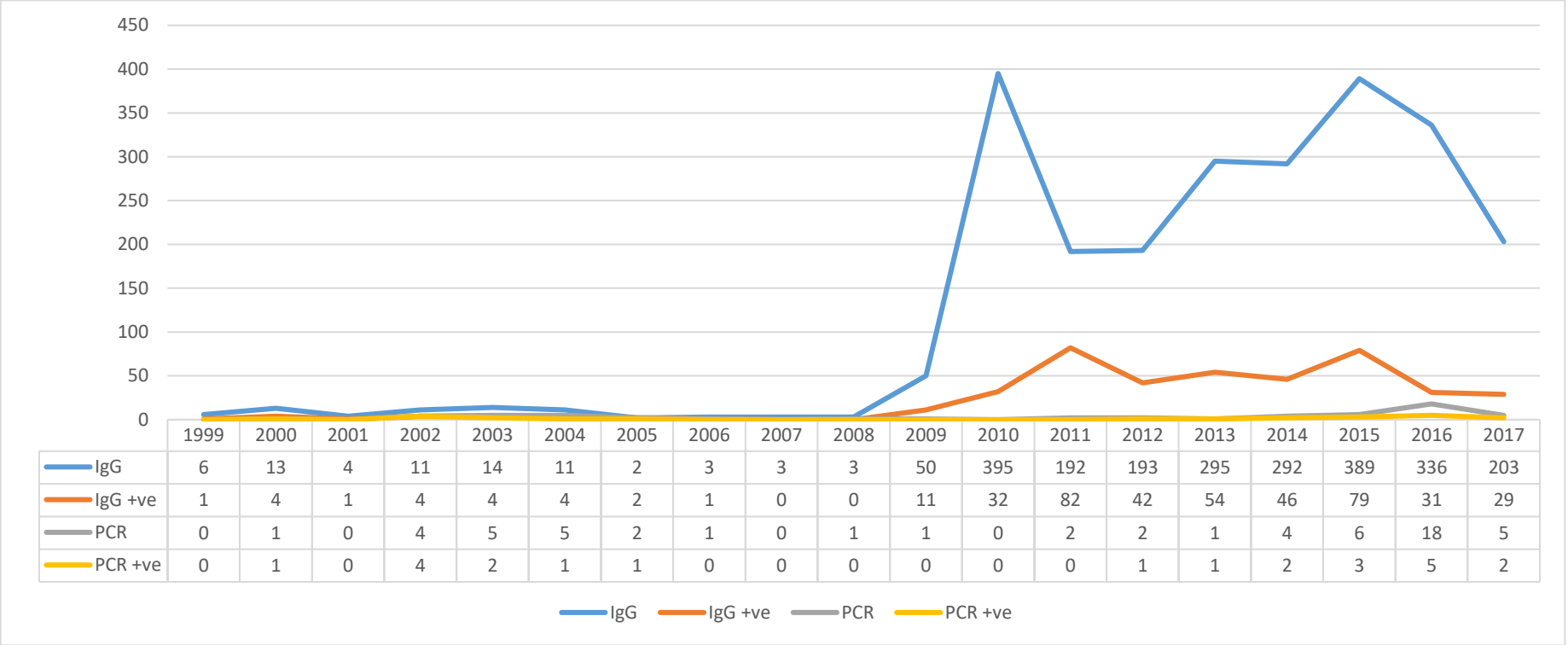


	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Anti-HCV	1860	1532	1630	2201	2447	2836	3361	3576	4257	4991	5186	5024	5441	5573	5868	5830	5611	5290	5371
Anti-HCV +ve	101	67	66	70	67	74	82	71	104	112	164	157	218	203	222	187	181	130	124
PCR	208	173	178	250	245	220	205	311	397	458	591	589	732	905	1068	1166	1445	1204	1192
PCR +ve	98	93	91	109	121	89	82	132	195	193	248	270	346	387	438	463	578	444	466

Figure 4.4. Testing activity in secondary care (pathway 1).

Testing in secondary care follows a slightly different trajectory to that of primary care over the same time period. The volume of testing is far greater, and certainly accounts for the majority of testing in pathway 1. There is a more gradual and sustained level of activity observed over the 2013-2015 period, in contrast to the peak in primary care testing, which then broadly holds pattern into 2016 and beyond. Similar to testing in primary care, it is clear that despite that large volume of anti-HCV testing, only a small proportion of those tested had active HCV infection. So this reflects investigation of patients with symptoms or liver blood test abnormalities to exclude HCV, hence the low positivity rate.

4.7.4 Pathway 2: Testing in drug treatment services

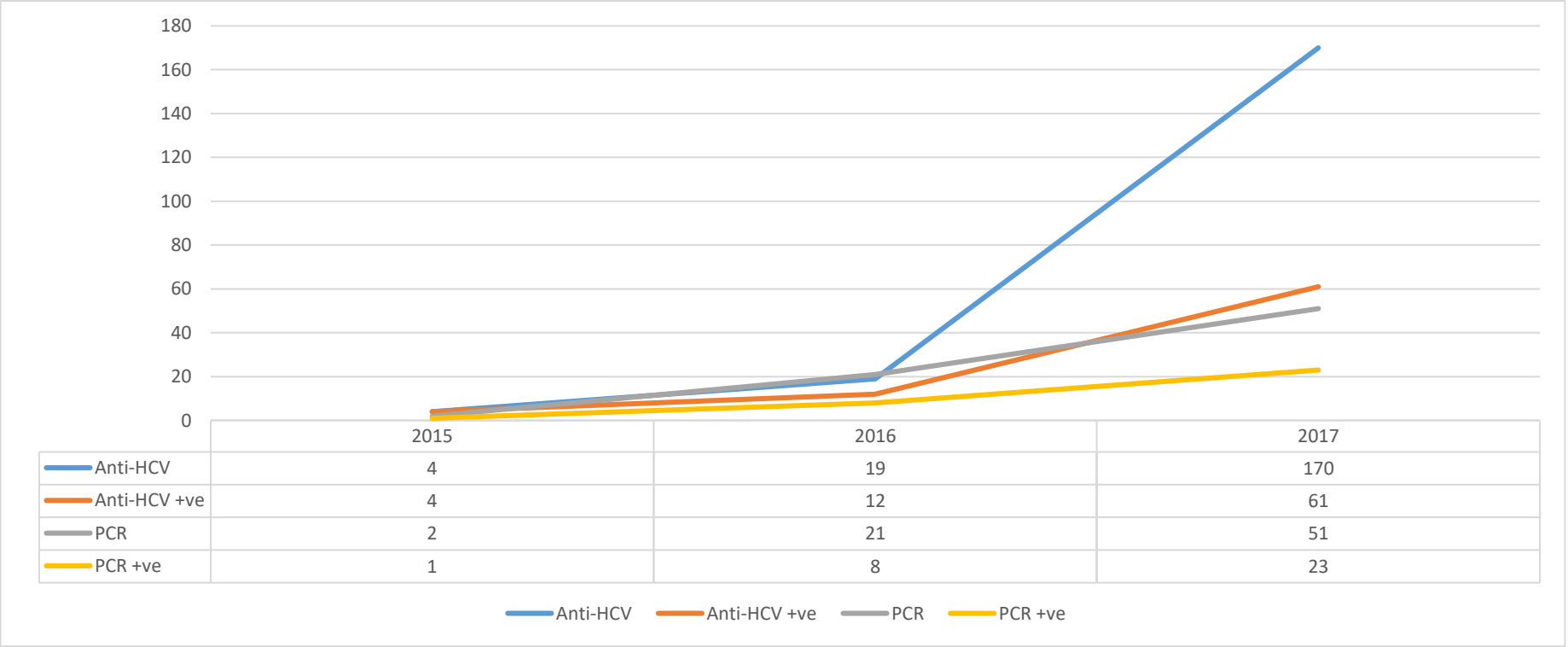


	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
IgG	6	13	4	11	14	11	2	3	3	3	50	395	192	193	295	292	389	336	203
IgG +ve	1	4	1	4	4	4	2	1	0	0	11	32	82	42	54	46	79	31	29
PCR	0	1	0	4	5	5	2	1	0	1	1	0	2	2	1	4	6	18	5
PCR +ve	0	1	0	4	2	1	1	0	0	0	0	0	0	1	1	2	3	5	2

Figure 4.5. Testing activity in drug treatment services (pathway 2).

Figure 4.5 shows testing activity in drug treatment services (pathway 2) over the entire study period. In contrast to pathway 1, there are marked peaks and troughs in testing activity here. However, what is noteworthy in this pathway is the exponential increase in antibody tests conducted from 2010-2011, which aligns with the introduction of DBS testing through these services; also observable in 2015, which aligns with the increased availability of DAAs and corresponding increased focus on targeted testing of PWID. The amount of active infections found through this testing pathway over time has been substantial in proportion to the number of tests conducted, however there is a disparity between number of anti-body positive tests yielding positive results, and number of subsequent PCR tests undertaken, which suggests inadequate follow-up of patients in this pathway. The variation over time shows how dependent this testing activity is on staff, and will be influenced by enthusiasm, outcomes and staff turnover.

4.7.5 Pathway 3: Community pharmacies

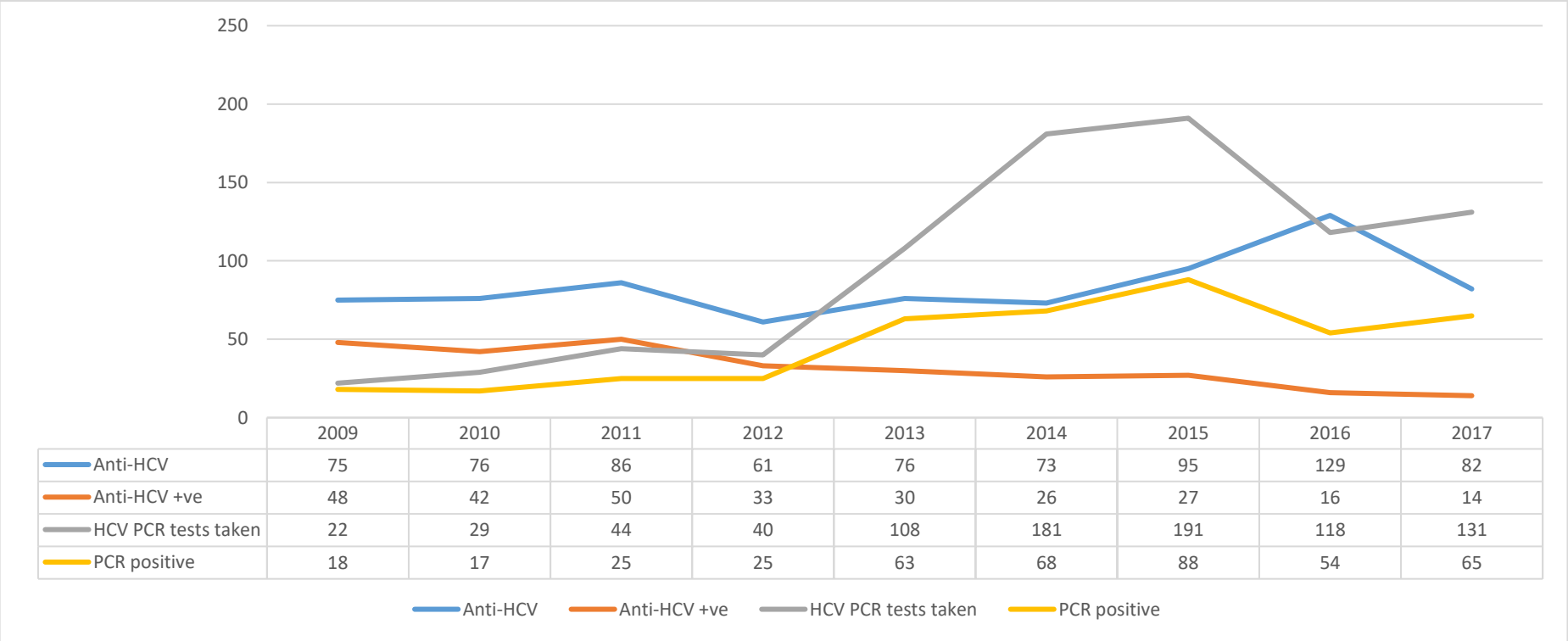


	2015	2016	2017
Anti-HCV	4	19	170
Anti-HCV +ve	4	12	61
PCR	2	21	51
PCR +ve	1	8	23

Figure 4.6. Testing activity in community pharmacies (pathway 3).

HCV testing in community pharmacies was introduced in 2015, and as detailed in Figure 4.6 above. This pathway was instituted initially by providing a research-led pathway, through a trial of testing and then two clinical trials, Dot-C and subsequently SuperDOT-C. Following these trials, the pathway was adopted as standard practice. Testing in 2015 aligns with the pilot study (Dot-C) and the exponential increase over 2016-2017 is activity generated through SuperDOT-C. This pathway specifically targets clients in receipt of OST, who are predominantly previous or current PWID. It focuses on an area where patients are incentivised to attend, they are picking up OST, in an environment they are familiar with and trust. Furthermore due to the fee for service payment structure for pharmacists they are also financially incentivised to treat patients as well as deriving increased professional satisfaction by being directly responsible for clinical care of their patients. It is clear that this testing pathway generated a higher proportion of HCV-positive results than pathways 1 and 2, the actions of these incentivising factors on both participants are highly likely to be relevant to this.

4.7.6 Pathway 4: Testing in injection equipment provision sites



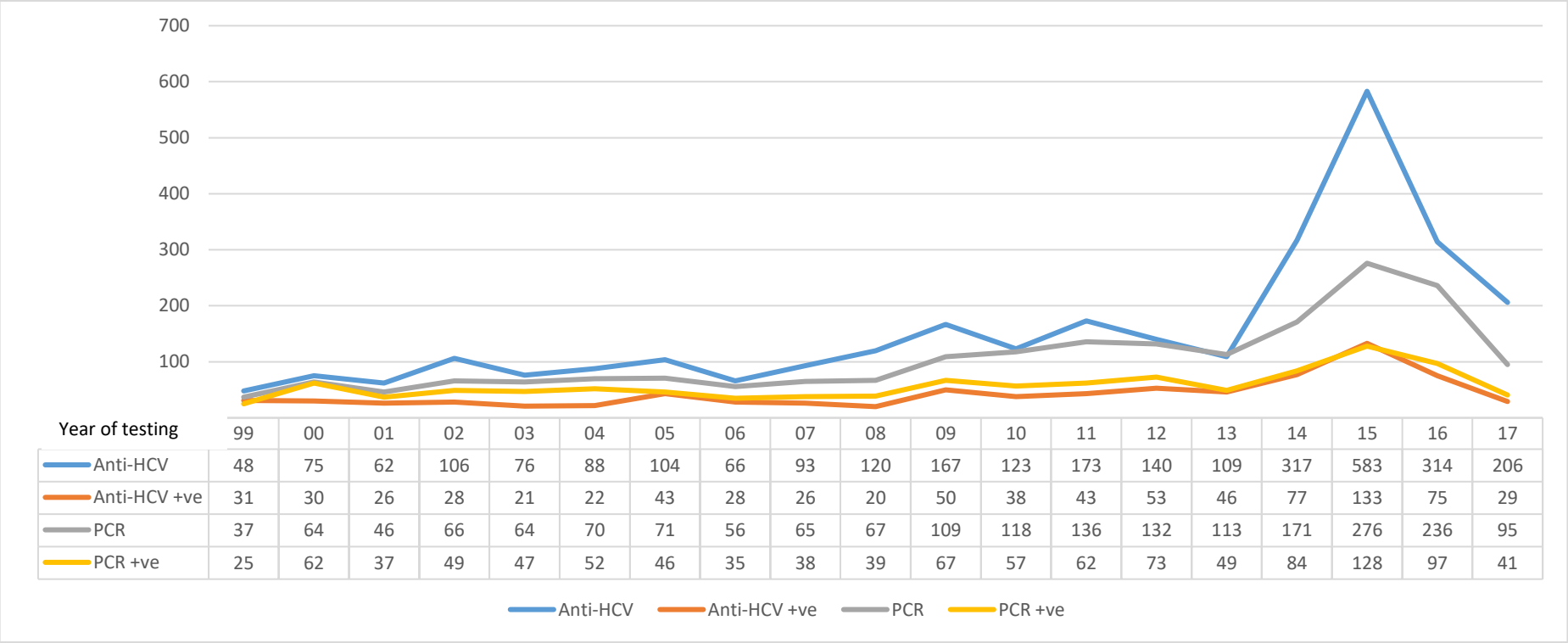
	2009	2010	2011	2012	2013	2014	2015	2016	2017
Anti-HCV	75	76	86	61	76	73	95	129	82
Anti-HCV +ve	48	42	50	33	30	26	27	16	14
HCV PCR tests taken	22	29	44	40	108	181	191	118	131
PCR positive	18	17	25	25	63	68	88	54	65

Figure 4.7. Testing activity in injecting equipment provision sites (pathway 4).

Testing in IEPS commenced in 2009 (Figure 4.7) and held steady in both number of anti-HCV and HCV PCR tests conducted up until mid-2012 when the relationship between them flipped with a dramatic increase in numbers of PCR tests, with antibody tests remaining relatively stable with the exception of 2016. This reflects the advent of HCV treatment pathways within the needle exchange service and the need to monitor for re-infection in the at-risk population that continued to use the needle exchange service after cure. It is interesting to note that the proportion of new antibody tests that are positive falls substantially from 64% in 2009 to 17% in 2017, suggesting a treatment as prevention effect. There was a steep decline in number of PCR tests conducted after 2015, with a concurrent rise in the number of anti-HCV tests, potentially explained by an increase in clients whose HCV status was unknown using IEPS services.

Testing via this pathway yields a higher proportion of patients with active HCV infection than pathways 1-3.

4.7.7 Pathway 5: Testing in prisons



Year of testing	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17
Anti-HCV	48	75	62	106	76	88	104	66	93	120	167	123	173	140	109	317	583	314	206
Anti-HCV +ve	31	30	26	28	21	22	43	28	26	20	50	38	43	53	46	77	133	75	29
PCR	37	64	46	66	64	70	71	56	65	67	109	118	136	132	113	171	276	236	95
PCR +ve	25	62	37	49	47	52	46	35	38	39	67	57	62	73	49	84	128	97	41

Figure 4.8. Testing activity in prisons (pathway 5).

HCV testing across prisons in NHS Tayside modestly increased in quantity from 1999-2012, and held in steady pattern up to that point. In 2012-2013, following introduction of DBS testing and the inception of a dedicated prison blood-borne virus clinic service, anti-HCV testing increased rapidly, with a concurrent rise in follow-up PCR tests. The falloff in number of tests 2016-2017 reflects staff turnover and illustrates the importance of rolling programs of staff training in high turnover areas. The number of positive tests and subsequent PCR-positive tests follow broadly the same trends, indicating a high burden of patients who up until that point had been both untested and untreated for HCV.

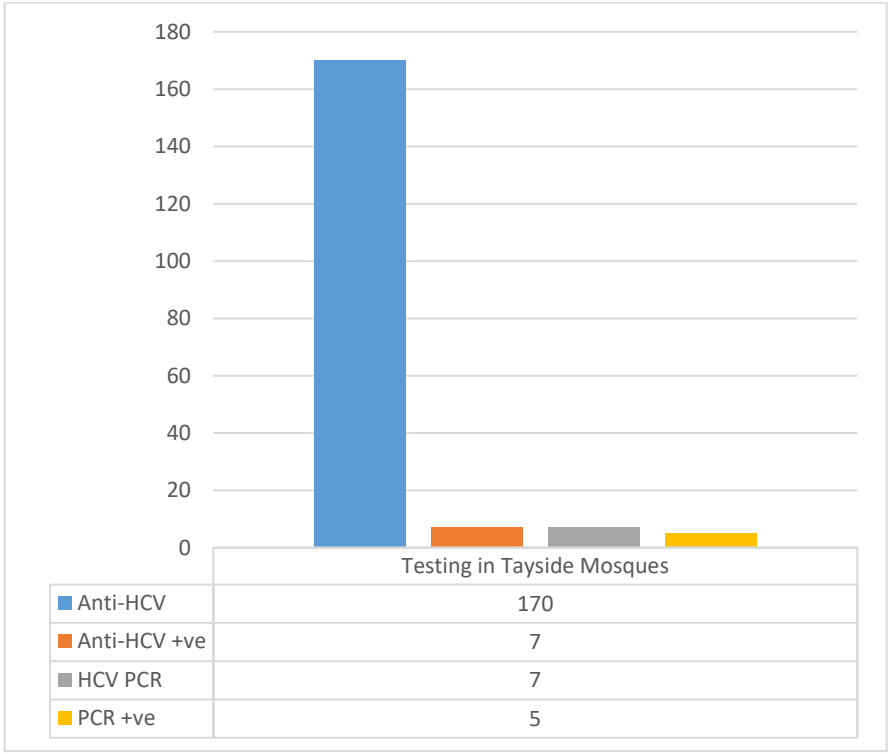


Figure 4.9. Targeted testing in ethnic outreach clinics (pathway 6).

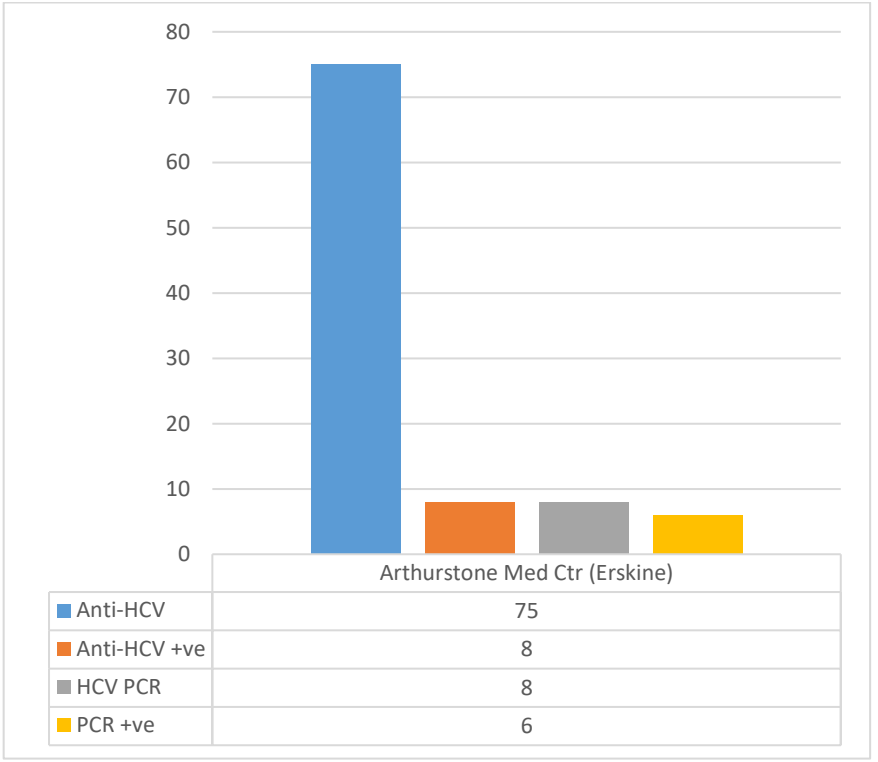


Figure 4.10. Targeted testing in general practice (pathway 7).

4.7.8 Pathway 6: Testing in mosques

Figure 4.9 shows the testing activity for HCV in the ethnic outreach pathway, this was a one-off intervention in a closed population with little risk of re-infection or on-going infection. It is clear that while there was a significant number of anti-HCV tests conducted, this yielded only a small proportion of PCR positive patients (3%), but this reflected the population prevalence in the country of origin for this predominantly Pakistani population. There is another impact in terms of levels of awareness raising which leads to increase testing via conventional pathways.

4.7.9 Pathway 7: Targeted testing in general practice

Figure 4.10 shows the impact of targeted testing in general practice it follows a similar pattern, albeit with a slightly higher proportion of PCR positivity in the tested cohort to Figure 4.9. However the predominant risk factor in this group was previous injection drug use. Therefore one might have expected a much higher prevalence around 40% as opposed to the 8% detected here. This may represent the impact of previous testing via other pathways reaching those at most risk, reducing the prevalence, however if that is the case this still represents an important missed group that might justify one off interventions such as this.

Both of these pathways yielded significantly lower proportions of PCR-positive patients compared to all other pathways, but reached patients others pathways hadn’t.

4.7.10 HCV PCR positivity by testing site

Table 4.1 details the volume of anti-HCV tests performed in Tayside pathways 1-6 and the proportions of HCV PCR positivity per pathway. Pathway 1 (primary and secondary care) showed large volume testing with a relatively low PCR positivity. Pathways 3, 4 and 5 (community pharmacy, injecting equipment needle exchange and prison pathways) resulted in low volume testing but with a higher PCR positivity rate. In pathway 6 there was a notably low proportion of HCV positivity, given the number of tests conducted (but reflects HCV prevalence in Pakistan and a “healthy migrant” effect). It was clear to see that pathway 4 (IEPS pathway) produced the highest proportion of HCV positivity per number of tests conducted.

Table 4.1 Proportion of PCR-positive tests conducted in NHS Tayside in pathways 1-6.

	Anti-HCV tests taken	**Individuals with PCR +ve**	**Percentage of PCR +ve**
General Practice	24969	718	3%
Secondary care	77885	701	1%
Drug treatment services	2415	280	12%
Community pharmacies	193	22	11%
IEPS	753	193	26%
Prisons	2970	428	14%
Mosque	177	6	3%

The stark contrast between pathway 1 and pathway 4 is particularly clear in Figure 4.11 below. This clearly demonstrated that some pathways are much more effective at finding cases than others, but individual pathways may not find all the patients.

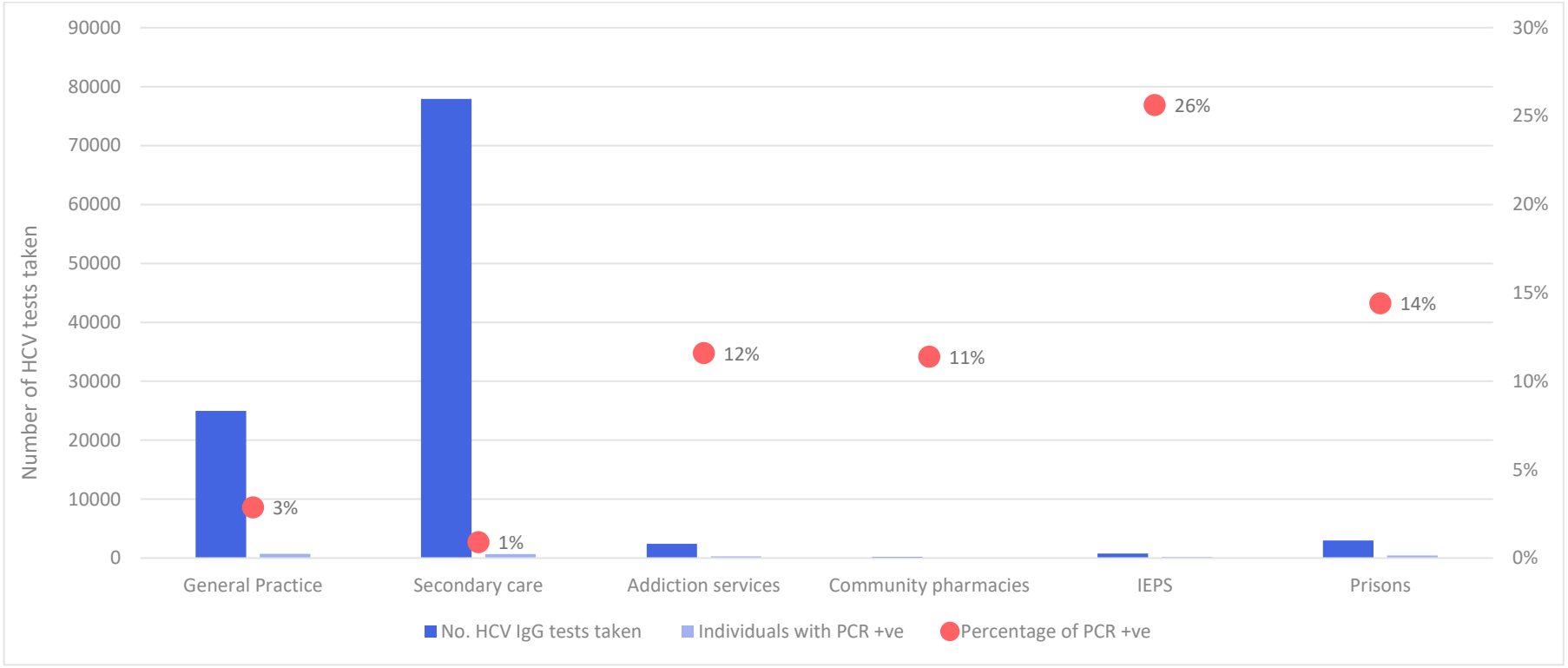
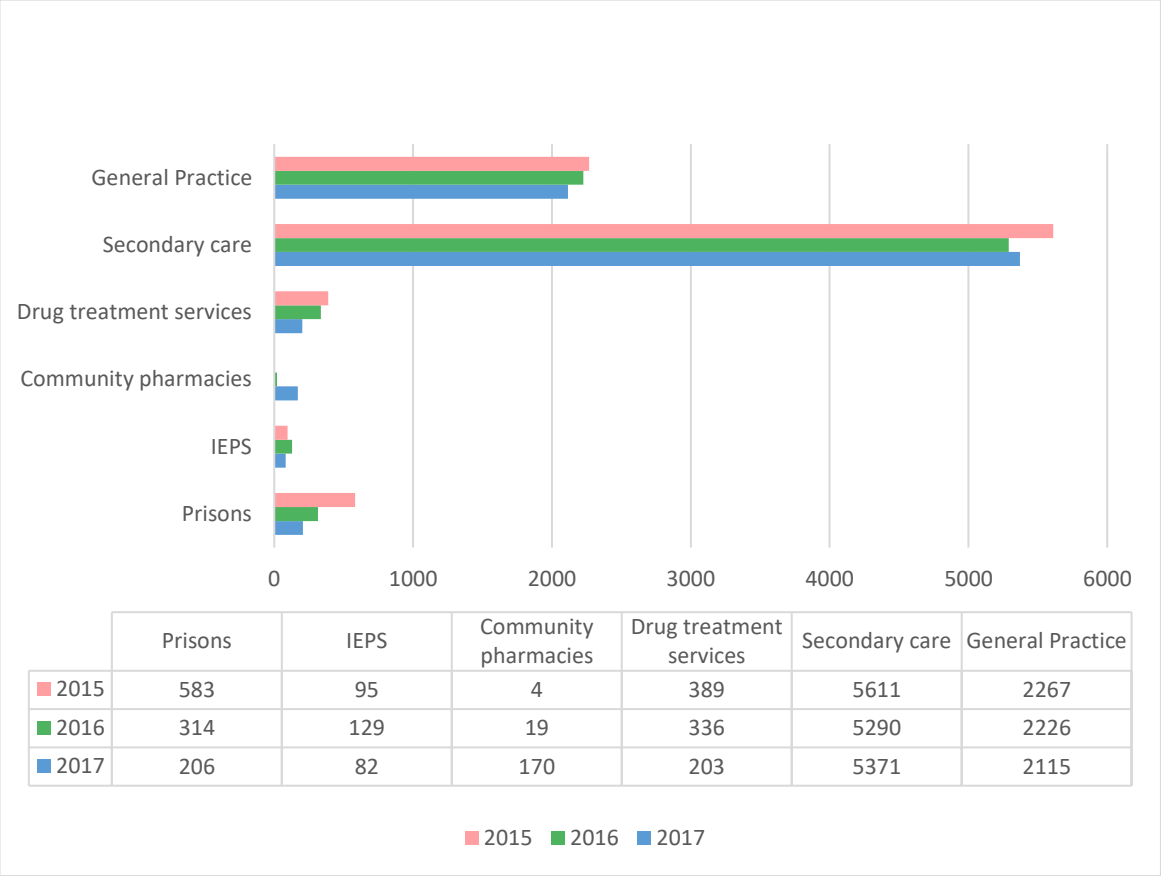


Figure 4.11. The columns demonstrate volume of HCV testing in 6 pathways whilst the red dots demonstrate proportion of active HCV infection (determined by PCR positivity) The GP record search pathway is included in the "general practice" pathway due to small number.

4.7.11 HCV testing NHS Tayside: 2015–2017

In 2015 after the development and evaluation of several new diagnostic and treatment pathways there was a substantial change in the standard of care for HCV. This saw the introduction of multiple interventions for HCV testing and treatment in NHS Tayside with the objective of achieving elimination of HCV as a public health threat. Therefore, it was important to analyse testing data from this period specifically to assess the impact of these changes. Figure 4.12 shows anti-HCV testing across Tayside pathways between 2015 and 2017.



	Prisons	IEPS	Community pharmacies	Drug treatment services	Secondary care	General Practice
2015	583	95	4	389	5611	2267
2016	314	129	19	336	5290	2226
2017	206	82	170	203	5371	2115

Figure 4.12. Anti-HCV testing activity in Tayside pathways between 2015 and 2017.The above graph shows volume of anti-HCV blood tests processed in the NHS Tayside virology laboratory by requesting site for the years 2015 to 2017.

Overall, there were 25 410 tests conducted across testing pathways 1–5. Each year, the majority of tests were conducted in the secondary care setting. General practice conducted the next highest number of tests over this period, followed by drug treatment services, prisons, IEPS and then community pharmacies.

Perhaps surprisingly, year-on-year figures demonstrate a decreasing trend in the number of tests conducted across all pathways except for community pharmacies, which show in excess of a forty-fold increase in number of tests conducted from 2015 to 2017, and

reflected the lag time for this group of healthcare professionals to develop the necessary skills and confidence to roll out new pathways to be standard of care.

Whilst anti-HCV tests are useful for testing individuals with an unknown HCV status, the yield of PCR positivity per number of tests conducted is a superior barometer of appropriate targeted testing. However, HCV testing is not the end point of the process with the conversion of a patient with a positive HCV PCR to an SVR and viral cure considered the ultimate goal of the care pathway. Pathways effective at making a diagnosis may not be as efficient at achieving HCV cure, which is considered next.

4.7.12 HCV treatment activity of each pathway: 2015–2017

Once patients are diagnosed with HCV, the next natural step is to commence appropriate treatment and be managed through the care continuum. The proportionate treatment outcomes for patients diagnosed with HCV in each of the 6 pathways in NHS Tayside from 2015-2017 was reviewed and assessed. This timescale was used as DAAs were available more widely from 2015 and the newer pathways such as the pharmacy pathway were in effect. This allowed a per-pathway comparison and highlighted where diagnosed patients tended to be most likely to have positive outcomes following a diagnosis. Table 4.2 shows the details of the patients found to be anti-HCV positive via the different pathways from 2015-2017, along with their treatment outcomes.

Table 4.2. Progress of persons diagnosed with active HCV infection along care pathway 2015–2017.

Source of initial testing	**No. of patients anti-HCV reactive**		**No. of patients with active HCV infection**		**No. of patients commenced on treatment**		**No of patients with SVR**	
General practice	99	Combined 234	75 (76%)	Combined 171 (73%)	68 (90%)	Combined 124 (73%)	59 (86%)	Combined 101 (81%)
Secondary care	135		96 (71%)		56 (58%)		42 (75%)	
Drug treatment service	91		54 (59%)		42 (77%)		31 (73%)	
Mosque	7		6 (85%)		6 (100%)		6 (100%)	
Pharmacy	72		22 (31%)		21 (95%)		18 (85%)	
IEPS	53		34 (64%)		28 (82%)		21 (75%)	
Prisons	92		45 (49%)		37 (82%)		24 (64%)	

It is important to consider not just the effectiveness of a pathway but also the volume of patients it reaches. General practice and secondary care (pathway 1) detected the most

individuals with anti-HCV positivity, closely followed by prisons (pathway 5) and drug treatment services (pathway 2).

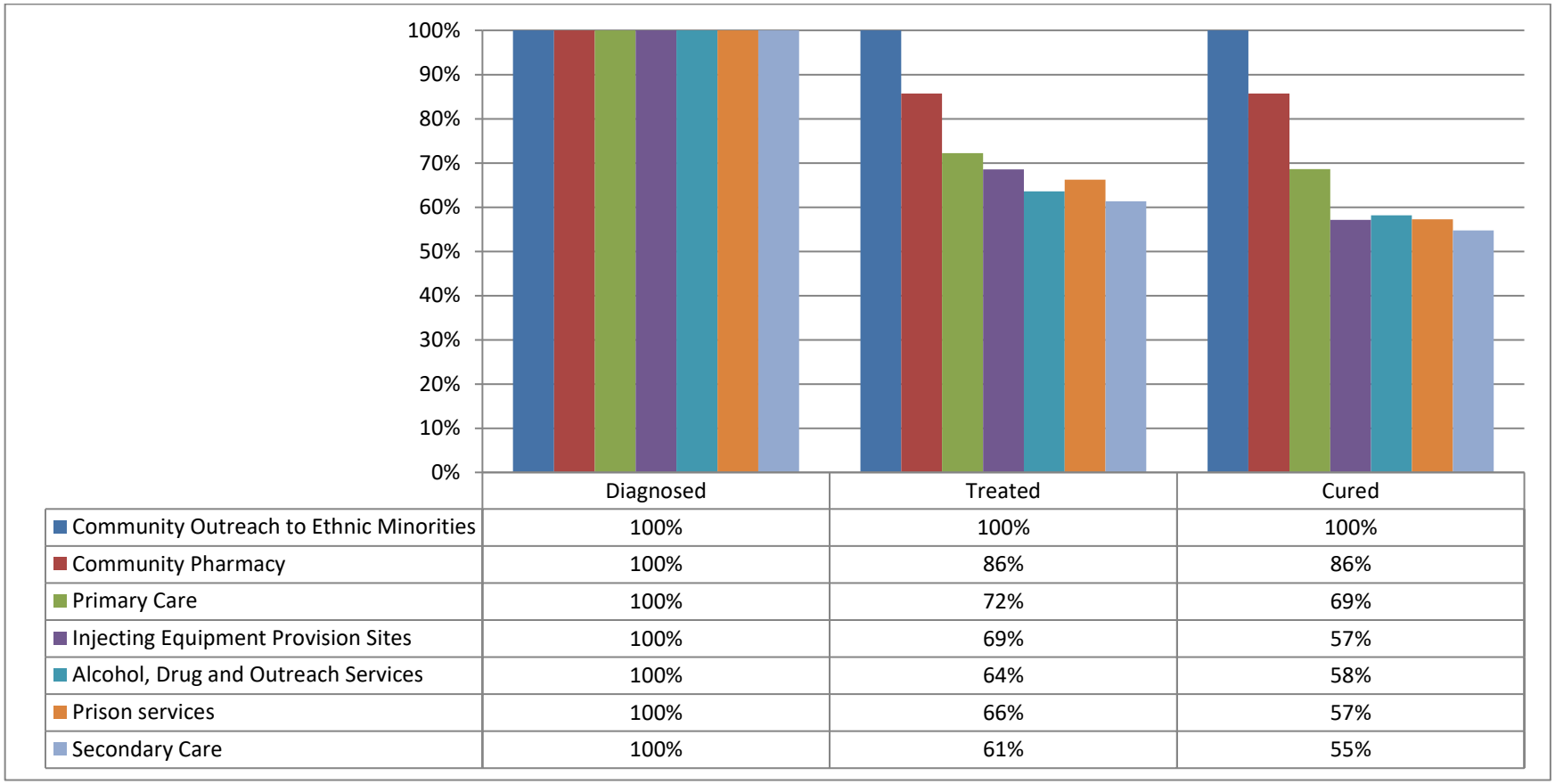
Across all pathways, the proportion of diagnosed individuals who then commenced treatment was over 70% (general practice & secondary care combined as they represent pathway 1). Pathway 1 has the highest accumulation of anti-HCV and PCR reactive patients, as well as the most patients treated and cured, of any of the pathways shown. However, all other pathways have a higher proportion of patients who commenced treatment, with pathways 3 (pharmacy) and 6 (mosque) having the highest proportions (100% and 95% respectively). This would suggest there is an environmental factor at play that affects likelihood to initiate treatment. .

Persons completing treatment via the pathway 5 (prison) reported the lowest proportion of SVR, with levels in pathways 2 (drug treatment) and 4 (IEPS), and secondary care, only moderately superior. There are particular issues in obtaining SVR in prisons due to the short sentences for many of the people in need of treatment. Pathway 3 (pharmacy), general practice, and 6 (mosque) report the highest proportions of SVR attainment. The combined total for pathway 1 is inferior to both pathways 3 and 6, but is still high.

4.7.13 HCV cascades of care

In this section we present our data in the format of a cascade of care, to better illustrate the transition of testing to treatment and cure, in the context of the whole population. The HCV cascade of care (CoC) is recognised as an important monitoring component of the global response to the HCV epidemic. It allows readers, at a glance, to view how many members of a particular patient group has passed through each stage required for effective control of the disease.(265) A CoC can be broadly categorised into: estimated population size; diagnosed population; proportion of that population both treated and cured.

The CoCs in the following sections give first an overview of the proportion of patients passing through the HCV CoC in NHS Tayside, and then a per-pathway breakdown of same for the 2015-2018 period.



	Diagnosed	Treated	Cured
Community Outreach to Ethnic Minorities	100%	100%	100%
Community Pharmacy	100%	86%	86%
Primary Care	100%	72%	69%
Injecting Equipment Provision Sites	100%	69%	57%
Alcohol, Drug and Outreach Services	100%	64%	58%
Prison services	100%	66%	57%
Secondary Care	100%	61%	55%

Figure 4.13. HCV cascade of care overview for pathways 1–6.

Figure 4.13 shows the relative proportion of individuals who were treated and cured of their chronic HCV infection determined by the testing source that detected that infection. It is evident that effectiveness is variable across the pathways once a diagnosis has been reached. A pathway is more effective if persons detected via that pathway are treated and cured, as opposed to being diagnosed and living with chronic HCV infection.

The HCV prevalence in the following figures is the estimated population of Tayside point prevalence in 2015. It is generated from the population of Tayside (416,080) assuming a HCV prevalence of 0.55% and deducting all those patients who have been diagnosed, treated and cured, but including only those also alive and still resident in Tayside. This estimated number of 1436 patients infected with chronic HCV alive and living in NHS Tayside gives the context of a population denominator that each pathway is working toward and the overall HCV prevalence for Tayside.

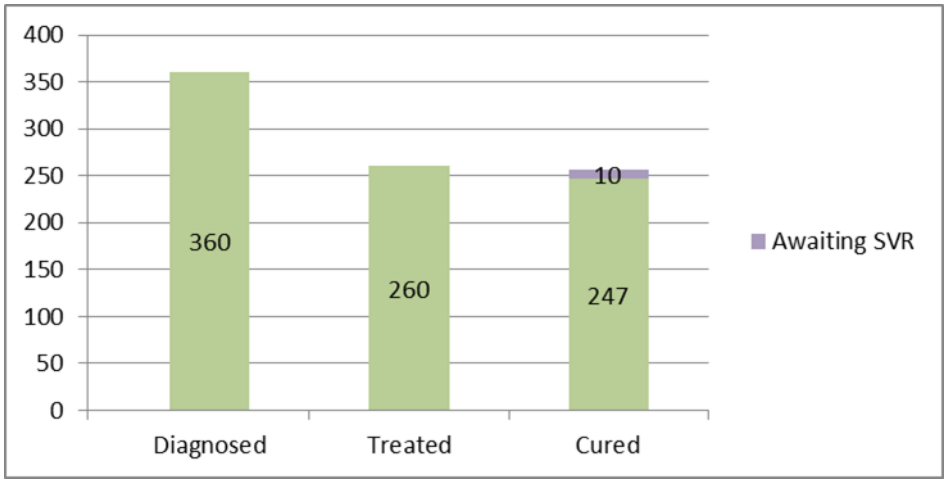


Figure 4.14. Cascade of care in primary care (pathway 1)

Figure 4.14 shows the CoC for the primary care element of pathway 1. 72 % (260/360) of people tested in Primary care started on HCV treatment, with 95% achieving SVR. This total does not include an additional 4% (10/260) who completed treatment and are awaiting SVR.

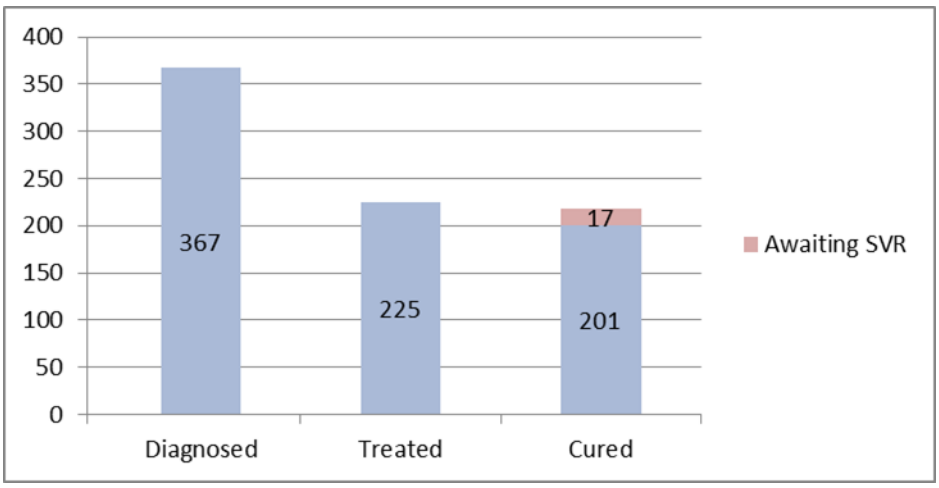


Figure 4.15. Cascade of care in secondary care (pathway 1)

Figure 4.15 shows the CoC for the secondary care element of pathway 1. Of those tested in secondary care, 61% (225/367) started on HCV treatment, with 89% of patients achieving SVR. This total does not include an additional 8% (17/225) who completed treatment and are awaiting SVR.

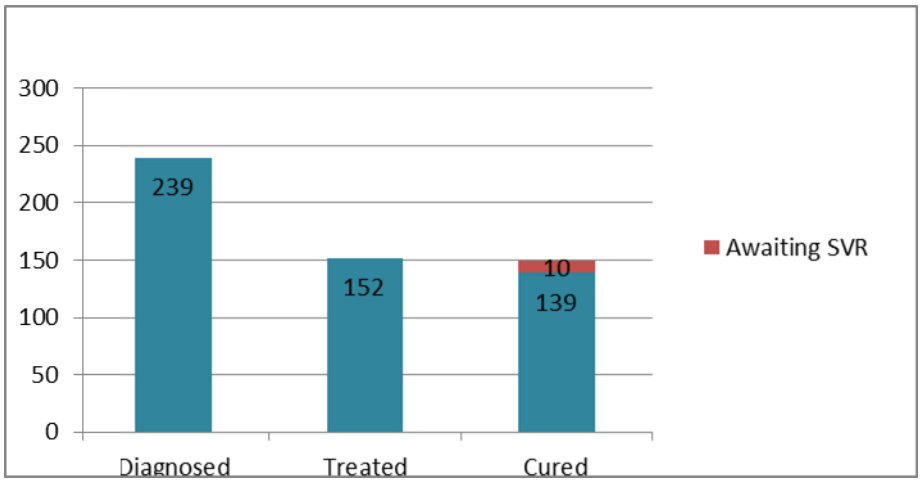


Figure 4.16. Cascade of care in drug treatment services (pathway 2)

Figure 4.16 shows the CoC in drug treatment services (pathway 2). Of those individuals tested in pathway 2, 64 % (152/239) were started on HCV treatment, with 91% achieving SVR. This total does not include an additional 7% (10/152) who completed treatment and were awaiting SVR. Although this pathway commenced slightly fewer on treatment than the primary care element of pathway 1, there was a similar proportion of patients achieving SVR.

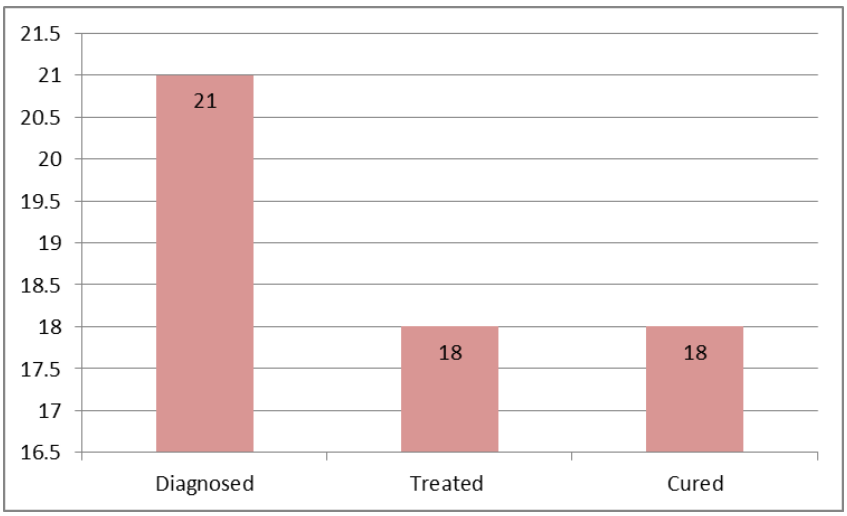


Figure 4.17. Cascade of care in community pharmacies (pathway 3)

Figure 4.17 demonstrates shows the CoC in pathway 3. Of people tested in community pharmacies, 85 % (18/21) were started on HCV treatment with 100% of those treated achieving SVR. The proportions of patients achieving cure was higher than all other pathways except pathway 6, which achieved the same amount. In this pathway, patients regularly attended the pharmacy for another health care needs, so the high level of testing for SVR is not surprising.

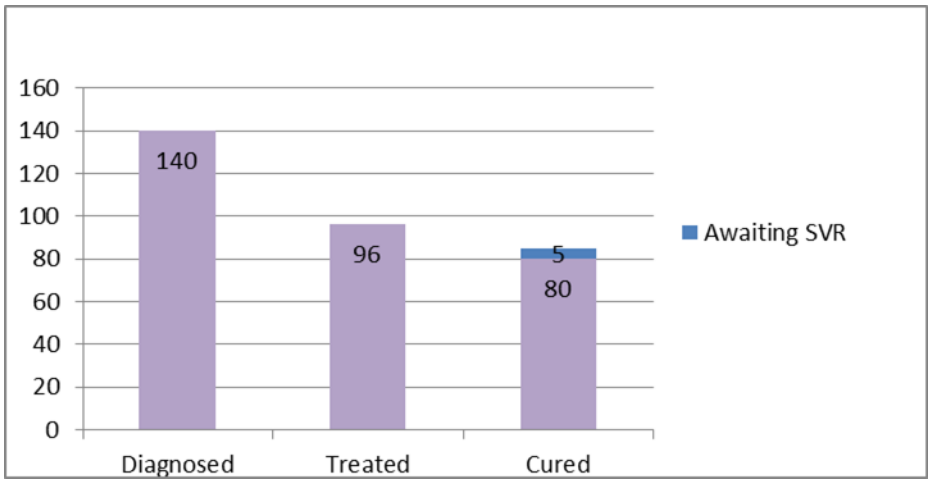


Figure 4.18. Cascade of care in injecting equipment provision sites (pathway 4)

Figure 4.18 shows the shows the CoC in injecting equipment provision sites (pathway 4). Of people tested in injecting equipment provision sites, 69 % (96/140) were started on HCV treatment, with 83% of those achieving a SVR. This does not include an additional 5% (5/96) who completed treatment and were awaiting SVR. The lower rate of SVR may be an indicator of re-infection occurring prior to SVR test, given the patient population treated through this pathway, who tended to be actively injecting drugs.

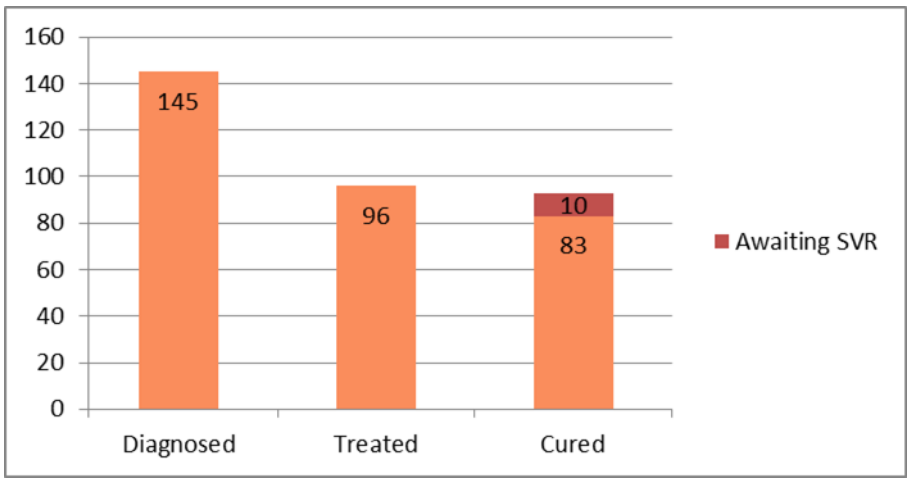


Figure 4.19. Cascade of care in prison services (pathway 5)

Figure 4.19 shows the CoC in prison services. Sixty-six per cent (96/145) of people tested in prison services were started on HCV treatment, with 86% of those achieving SVR. This total does not include an additional 10% (10/96) who completed treatment and were awaiting SVR at the time of data censoring.

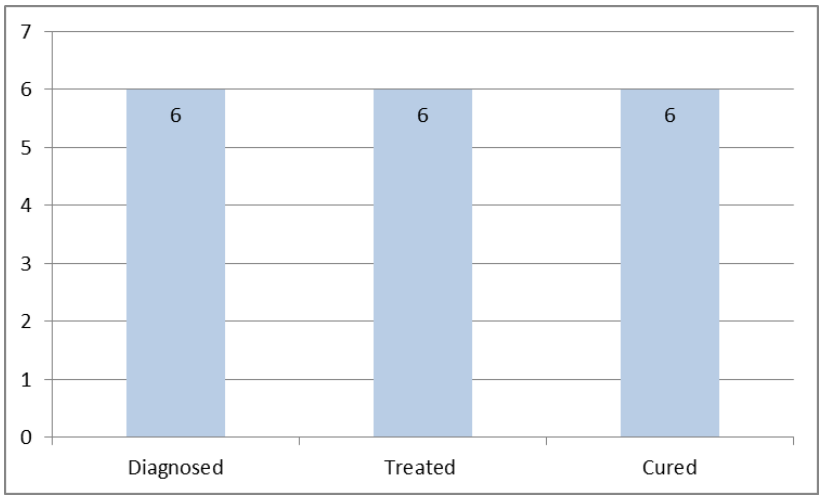


Figure 4.20. Cascade of care in the ethnic outreach pathway (pathway 6)

Figure 4.20 documents the CoC for the ethnic outreach pathway (pathway 6). Patient engagement in this pathway was demonstrably high, with every person who was found to be PCR positive receiving treatment and obtaining SVR.

The variability in the CoC data presented cross the pathways is indicative of the differing levels of engagement one will find in different patient populations and treatment settings. Looking across the CoCs, one might surmise that patients receiving care in stable (pathway 6) and familiar (pathway 3) environments tend to have better treatment outcomes.

4.7.14 Patient characteristics: 2015–2017

Baseline characteristics for patients in all pathways from 2015-2017 are displayed in Table 4.3. Records for individuals tested in these pathways were limited to the years 2015 to 2017 inclusive in order to make equal comparisons across the pathways. The standard care pathways, primary and secondary care, have been in place since 1999, whilst the community pharmacy pathway was introduced as discussed earlier in 2015.

Table 4.3 Patient characteristics for persons in Tayside reported to be hepatitis C anti-HCV positive between 2015–2017.

		General practice	**Secondary care**	**Mosque**	**Drug treatment services**	**Pharmacy**	**IEPS**	**Prison**
		(%; 95% CI)	(%; 95% CI)	(%; 95% CI)	(%; 95% CI)	(%; 95% CI)	(%; 95% CI)	(%; 95% CI)
Gender	Male	64 (65)	85 (63)	7 (100)	65 (71)	42 (58)	32 (60)	91 (99)
	Female	35 (35)	50 (37)	0 (0)	26 (29)	30 (42)	21 (40)	1 (1)*
Age	Mean (±SD)	43.0 (±11.2)	41.3 (±12.2)	36.2 (±10.6)	37.1 (±7.5)	39.1 (±8.1)	37.3 (±7.4)	35.6 (±3.5)
Injecting drug use	Yes	48 (48; CI 38.2-57.8)	96 (71; CI 63.3-78.7)	0 (0; CI 0.0-0.0)	91 (100; 100.0-100.0)	72 (100; 100.0-100.0	53 (100; 100.0-100.0	84 (91; CI 85.5-97.1)
	No	51 (52; CI 42.2-61.8)	39 (29; CI 21.3-36.7)	7 (100; 100.0-100.0)	0 (0; CI 0.0-0.0)	0 (0; CI 0.0-0.0)	0 (0; CI 0.0-0.0)	8 (9; CI 2.9-14.5)
Cirrhosis	Yes	17 (17; CI 9.6-24.4)	8 (6; CI 2.0-10.0)	0 (0; CI 0.0-0.0)	3 (3; CI -0.5-6.5)	1 (1; CI -1.3-4.1)	1 (2; CI -1.8-5.5)	2 (2; CI -0.8-5.2)
	No	82 (83; CI 75.6-90.4)	127 (94; CI 90.0-98.0)	7 (100; 100.0-100.0)	88 (97; CI 93.5-100.5)	71 (99; CI 95.9-101.3)	52 (98; CI 94.5-101.8)	90 (98; CI 94.8-100.8)

* Whilst the all the prisons in Tayside are male only, the female in this cohort was an individual who identified as female and was transitioning to female at the time of her HCV diagnosis.

95% Confidence intervals.

Across the pathways there is a predominance of male patients compared to female patients diagnosed with HCV, with the closest pathway to approaching parity being pathway 4 (IEPS).

The oldest cohorts are within the standard pathways in general practice and secondary care, with the biggest range of ages compared to the prison population, which has the youngest cohort. This may reflect younger patients who are still engaged in high risk behaviour and are more likely to come into contact with drug treatment services and the criminal justice system compared to older individuals who may have historical risk behaviour or other risk factors and are detected in non-targeted pathways.

The proportion of individuals who disclosed injecting drug use behaviour as a possible risk factor to the HCV team is also detailed in Table 4.3 (and displayed graphically in Figures 4.5–4.7). 100% of individuals tested in drug treatment services, injecting equipment provision sites and pharmacies all disclosed a history of injecting drug use. In general practice and secondary care this proportion was much lower and demonstrates greater heterogeneity.

People found to have cirrhosis at the time of testing is greater in the general practice population. The prison population with the youngest aged individuals had the lowest incidence of cirrhosis at diagnosis.

4.7.15 Risk factors per diagnosis pathway

In pathways 2, 3, 4 and 5, the risk factor for HCV infection was almost exclusively injecting drug use (IDU), as shown in Table 4.3. Risk factors for HCV infection in primary care, secondary care (pathway 1) and the community outreach to ethnic pathway (pathway 6) are slightly more heterogeneous, including disclosures such as: migration from a high HCV prevalence country; infection from contaminated blood products; non-injecting drug use; sexual contact; tattoo/piercing; co-infection with HIV combined with IDU; needlestick injury; circumcision; healthcare-associated injections; and household contact. These risk factors are displayed in Figures 4.5, 4.6 (for pathway 1) and 4.7 (for pathway 6).

In Figure 4.21, the disclosed HCV risk factors for individuals found to have a positive anti-HCV antibody in the general practice testing population is shown. A wider mix of patients (i.e. not exclusively PWID) are likely to be seen by healthcare staff through the general practice element of pathway 1, so there naturally will be a wider variety of infection sources, which is represented in the data. Whilst injecting drug use makes up

around half of the population, there is a range of other recognised risk factors including tattoo/piercing, transfusion of infected blood products and being born in a country of high prevalence.

This observation of heterogeneity is repeated in the secondary care element of pathway 1, however there is a clear increase in proportion of IDU-related infections here. Injecting drug use clearly outstrips all other risk factors in this testing pathway, with the next-most common factor being unknown (Figure 4.22). There is a range of other recognised risk factors including healthcare associated needle stick injury, HIV, tattoo/piercing, transfusion of infected blood products and being born in a country of high prevalence, but the quantity of these factors are demonstrably minute in comparison to IDU.

Figure 4.23 shows the disclosed HCV risk factors for the individuals found to have a positive anti-HCV antibody in the Pakistani population tested in the ethnic outreach pathway. The most common risk factor observe across all pathways (injecting drug use) does not appear here. Instead circumcision, healthcare-associated injection therapy and household contacts make up the entirety of the risk factors, which is potentially explained by a difference in cultural factors. It is not clear what household contact refers to. These HCV risk factors are more unique to the first and second generation Pakistani population than the usual Tayside resident, and are an outlier in the NHS Tayside data.

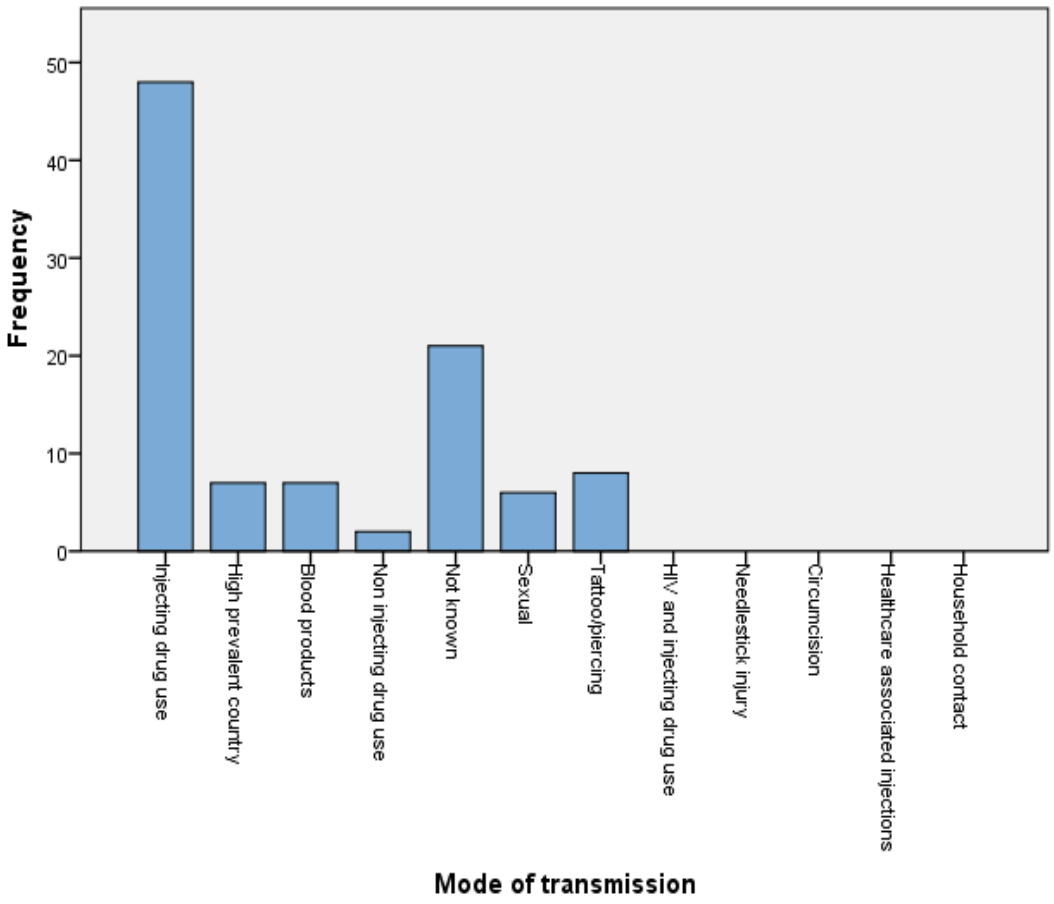


Figure 4.21. Mode of transmission for individuals tested via their general practice (pathway 1).

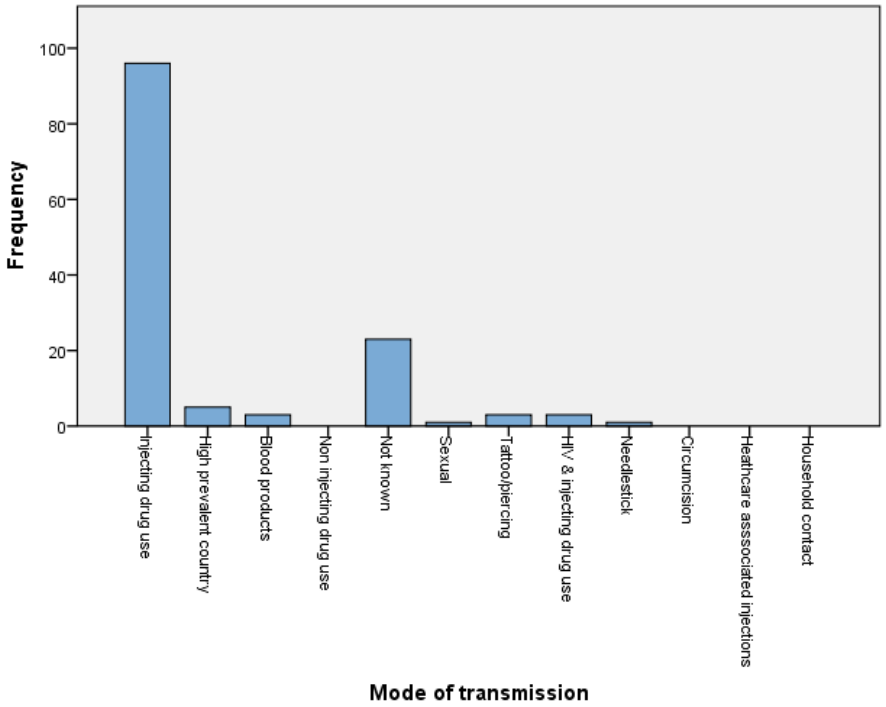


Figure 4.22. Mode of transmission for individuals tested in the secondary care environment.

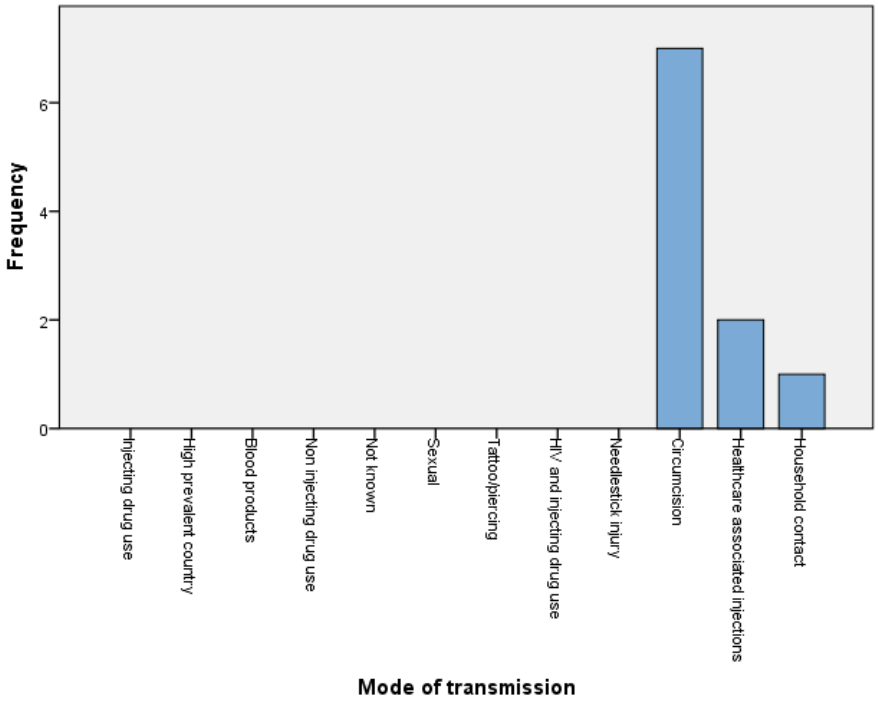


Figure 4.23. Risk factors and possible mode of transmission for individuals with anti-HCV antibodies in the ethnic community outreach pathway (Pathway 6).

4.7.16 Reach and impact

The testing and treatment activity and pathways have to be viewed in the context of the population they are operating within. If all the patients in a geographically area are diagnosed and treated then numbers of new diagnoses and treatment initiations will fall to zero, but equally if the reach of an individual pathway has been exhausted then its outputs will fall to zero, assuming all are parameters of the pathway such as staff are still in place. So the effectiveness of any diagnostic pathway has to be viewed in the context of the activity of other pathways and of the HCV prevalent population

As explained earlier the estimated point prevalence of HCV in 2015 was 1436. It was generated from the population of Tayside (416,080) assuming a HCV prevalence of 0.55% and deducting all those patients who have been diagnosed, treated and cured, but including only those also alive and still resident in Tayside. If the prevalence is reduced by 0.25% then the estimated number falls from 1436 to 1332. This estimated prevalence number of 1436 patients infected with chronic HCV alive and living in NHS Tayside gives the context of a population denominator that each pathway is working toward and the overall HCV prevalence for Tayside. In the period from 2015 to 2018 the proportion of the population infected by chronic HCV diagnosed rose to 1273 out of 1,436 meaning 88.7% had been detected by the pathways described. The proportion of those diagnosed who entered treatment and completed a treatment course was 826 out of 1273, cumulatively across all pathways 64.9%. This later number will rise given longer follow-up as the study was primarily focussed on diagnosis and so the follow up period for entry to treatment was shorter. This suggests that the panel of diagnostic pathways available were highly effective and approaching being close to saturation point but not yet reached it, i.e. the goals set by WHO for HCV viral elimination, so the pathways can be compared and evaluated.

4.7.17 Scottish Index of Multiple Deprivation in General Practice

There is a significant body of evidence, which documents the relationship between HCV infection and social deprivation of those who are at risk of being infected with it. A recent Australian study noted that HCV notifications were seven times more likely to be from people living in the poorest areas, with high rates of unemployment and injecting drug use.(266) Whilst recent Scottish data indicates that 20% of the most deprived of the Scottish population accounts for the same number of HCV cases than

the rest of the population combined, with infections concentrated in areas with high levels of injecting drug use.(18)

Figure 4.24 shows the distribution of the HCV-testing general practices in NHS Tayside mapped against the Scottish Index of Multiple Deprivation categories of their respective catchment areas.

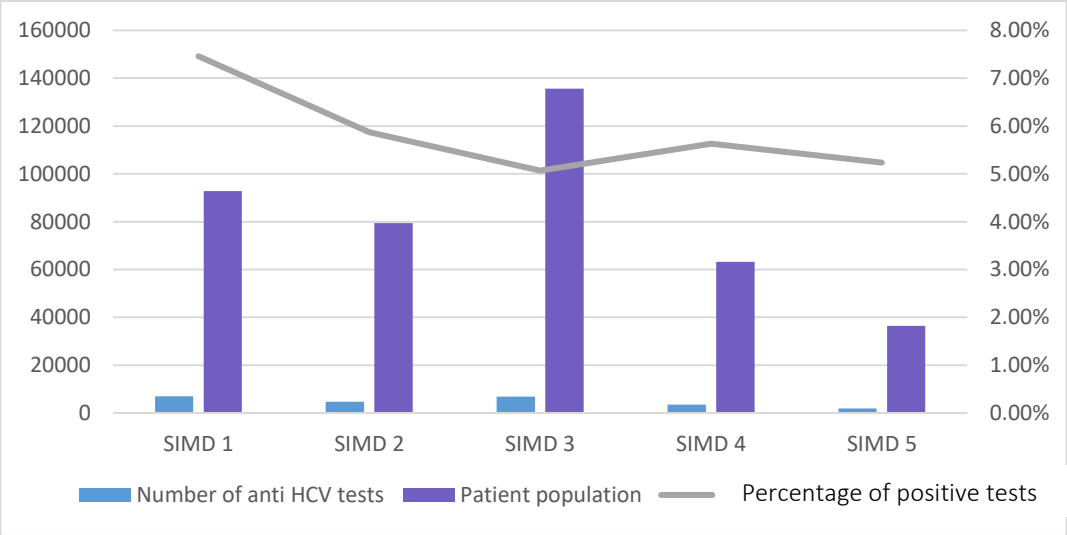


Figure 4.24. Distribution of SIMD deprivation area codes of all the general practices requesting either anti-HCV or HCV RNA testing compared with the deprivation codes for the general practices which generated the highest number of anti-HCV and HCV RNA test.

The skewing to the left (towards SIMD quintile 1) of the number of HCV tests especially in context of the population is indicative that the highest burden of HCV testing originates from general practices serving the most socially and economically deprived clients.

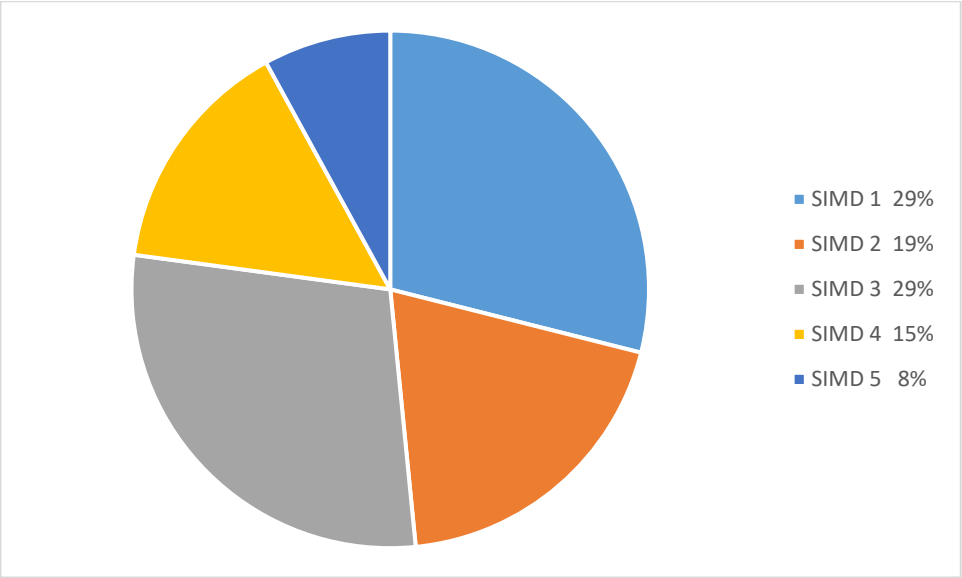


Figure 4.25. Number of anti-HCV tests from general practice according to SIMD deprivation code.

There were, as shown in Figure 4.25, an equal number of HCV tests requested by GP practices serving areas in SIMD quintile 3 – which represents areas of mixed deprivation with some elements of severe deprivation and other areas of relative wealth – as there were from those serving quintile 1 (Figure 4.25), however SMID 3 practices had a higher proportion of the populations. The next highest groups requesting HCV tests were in quintile 2, whilst the fewest tests are requested from GP practices in quintiles 4 and 5, which represented the most affluent areas in NHS Tayside. This trend aligns with the distribution of centrally notified HCV cases across Scotland to end of 2018, so could be considered that the NHS Tayside population is adequately representative of the population of the general UK population.(18)

4.8 Discussion

When assessing the performance of diagnostic pathways, it is vital to do so in the context of the population being tested and acknowledging the goals of the health care provider for HCV treatment and care. Dealing first with the health care provider, there are two broad aims;

- Firstly to minimise the harms and health service costs by focussing on prevention of the expensive complications, which will be confined to older patients with chronic infection.
- Secondly to eliminate HCV from the population by testing and treating everyone.

This study was conducted in a population where the health care provider committed to an elimination strategy and hence the requirement for diagnostic pathways that delivered all HCV infected patients into treatment. This should be the position of most health care providers given the WHO plans for HCV elimination. The population being tested by the health care provider in the case of Tayside is one where infection is mainly driven by recreational injection drug use, as opposed to an iatrogenic health care related outbreak, as such it is very representative of the situation in most developed countries and our findings will be widely applicable.

When assessing the effectiveness of the pathways, it is about scope i.e. how many of the target population have been diagnosed, and efficacy i.e. how many of those diagnosed have initiated treatment and been cured as demonstrated by the presented data. The important outcome of cost effectiveness will be discussed in chapter 5.

The primary observation of this study is that testing and treatment for HCV has increased significantly across all pathways since 1999. These dramatic increases were the result of clinical advances (see Figure 4.1), as well as strategic commitments to HCV elimination in the Tayside region. The step change in diagnostic activity started around 2014 and the period onwards plateauing rapidly as the new treatment environment and testing pathways embedded. The 2014-2015 period was when several developments occurred concurrently leading to the establishment of the modern HCV era of testing and treatment. These were the arrival of DAAs and rapid reduction in restrictions on their use, coupled the availability of dried blood spot testing and several diagnostic pathways coming on line. During the period of the study the diagnostic pathways were operating below a saturation point of cases. So the study represents the pathways operating in an optimal diagnostic environment with patients to be detected and treatment available.

Testing in the standard pathway, both primary and secondary care, show large volume testing increasing over time without any noteworthy increase in new HCV diagnoses, which remained relatively static in number and fell in proportion to total testing. The proportion of positive tests was the lowest of the pathways but the pathway generated the vast majority of HCV tests, even when the other pathways were operational, demonstrating the breadth of this pathway. In contrast, testing in the IEPS and prisons shows a concordant increase in new HCV diagnoses with increased testing, and a corresponding fall in new diagnoses with a fall in testing activity. This would suggest

that there are still prevalent cases within the population tested, whilst we may be reaching the end of cases discoverable in the standard pathways.

There were fluctuations in the level of testing across within the pathways over time. These are attributable to several factors; related to service provision, where embedded staff was used to provide testing, staff turnover and need for retraining was a factor. When staff are under pressure from their main workload, provision of addiction therapy for instance, the added extras such as HCV testing are less likely to be done. In other circumstances the development of new services or tests may lead to slow adoption by staff. The degree of incentivisation of staff will have an impact, this may be novelty, new professional responsibility or financial, the former two will fade over time. In the target patient groups those who are more health conscious may take up new opportunities quickly leading to a surge in uptake which then falls away as the harder to engage group remains as the only ones not tested. Furthermore with multiple options for testing patients may believe themselves already tested or prefer to believe that they remain uninfected as they have been safe in their practices. All of these factors need to be taken into account when planning a sustainable service.

Each pathway provides coverage for different aspects HCV diagnosis. For example the risk factors for HCV in the standard pathways are varied including current or former injection drug use, tattoos, piercings, infected blood products and healthcare associated needle sticks. It is unlikely that individuals with many of these risk factors would be tested in any of the other pathways. Equally the ethnic outreach pathway specifically targets people of Pakistani descent due to the unique risks of being from a country of higher prevalence. There is some cross over between pathways 2-5, in that they all target testing for PWID. In fact, clinically these individuals may move between the pathways and have different aspects of their testing, diagnosis and care provided through different pathways. This flexibility to move between pathways helps to retain people in the CoC. It is important to note that as these alternative diagnostic pathways became fully functional, the demand for testing activity within the standard care pathway did not drop off, suggesting they were reaching a completely different population who were not accessing conventional care.

There was a male preponderance across the pathways to varying degrees. This reflects patient populations from elsewhere where drug use and HCV prevalence is higher in men. However there is a concern that HCV services may not be appropriate for female patients, and as such there may be a proportion of female patients who remain

undiagnosed. The predominance of male patients is easy to account for in the men-only prisons and in the mosques. The proportion of women being tested via IEPS and pharmacies appeared to be higher than in drug treatment services and in primary secondary care. It is not clear whether this difference is significant. Men who inject drugs outnumber women who inject drugs four to one,(267) however it is well recognised that women who inject drugs are more vulnerable than their male counterparts and are more likely to engage in unsafe injecting practices, suffer physical and sexual violence and experience stigma and discrimination.(268,269) The IEPS provide sterile injecting paraphernalia, education about injecting risks, sexual health screening and contraception advice. Whilst these do not directly affect HCV status, by treating women who inject drugs (WWID) holistically we can improve their health, safety and well-being.

The age variation across the pathways gives some insight into clinical aspects of the different patient populations. It would appear from our data that there is a relationship between age at time of diagnosis and incidence of cirrhosis (with older patients presenting more commonly with advanced liver disease), this is further borne out by the literature, it is intuitive that with passing time and therefore ageing, damage to the liver from a chronic virus would be worse. The higher incidence of cirrhosis in pathway 1 (see Table 4.3) is potentially explained by the increased age observed at time of diagnosis and, by inference, a longer time period between infection and detection, allowing HCV to progress undetected for a number of years. This is in contrast to pathway 5, which has both the lowest age profile at time of diagnosis and lowest incidence of cirrhosis. Clearly if a health care provider was focussed on reducing harm as their main aim they would preferentially fund pathway 1 as the most effective pathway for detecting these patients.

Although there was a mix of risk factors in the general practice population, declared PWID still accounted for approximately half of the diagnosed population. HCV also remains a diagnosis strongly associated with social deprivation. This is evidenced by Figure 4.24, showing the spread of SIMD quintiles amongst requesting GP practices. Practices in areas of higher social deprivation requested more HCV tests. Tayside GP practice requesting data matches Scotland-wide data where the majority of HCV antibody diagnoses are among individuals residing in the most deprived quintile.(18) This illustrates that Tayside is a representative microcosm of the general Scottish and

UK population, and that interventions that are beneficial in Tayside are likely to have wider applicability in Scotland and other areas of UK.

The primary care element of pathway 1 documented a large volume of HCV testing, but with a proportionately small detection of PCR positivity. However, a high proportion of those initially tested by primary care then do on to achieve SVR. This trend is worth investigating as it may be due to the patients' more stable lifestyle, relative to PWID. However, if this were the case it would stand in contrast to data from elsewhere which suggests that PWID are just as likely to adhere to DAA treatment as non-PWID, and by extension achieve a cure.(270) As a result, it is worth considering that the increased SVR proportion may be a marker of the patients' quality of long-term engagement with their GP. When considering SVR proportions across the pathways, it is clear that individuals diagnosed with HCV in prison appear least likely to achieve a cure. However, this is likely skewed due to interruption of treatment or follow-up caused by liberation of patients to community, or transfer to another prison, which is common. These factors make it challenging to follow-up patients to obtain SVR blood samples. More generally the likelihood of achieving SVR from a diagnostic test does show a relationship with where the test was taken i.e. if the test occurred somewhere the patient had a long term or recurrent interaction such as primary care or an OST dispensing pharmacy the rate of SVR was high, whereas it was lower in prisons and needle exchanges where the relationship is less robust and a change in a patients circumstances may mean the patient now longer attends those locations e.g. change of address, incarceration or liberation, so is less likely to return for an SVR test. In the era of DAAs with efficacy for cure of over 97% the need for SVR has been questioned. It has been suggested that initiation onto or completion of therapy would be equally good surrogate makers for cure.

With regards to HCV testing from 2015 from 2017, secondary care testing does encompass testing done by the HCV team for hospital-based diagnosis and follow up of at-risk patients. However, it also includes a much larger volume of testing by other secondary care services including renal services (largely driven by their guidelines), and in surgical and medical wards in individuals with abnormal LFTs, so this should be taken into consideration when judging the testing data for this aspect of pathway 1. Further, community pharmacies and injection equipment provision sites do conduct fewer tests annually, but the testing in community pharmacies has increased over the three years due to clinical trials in this setting. Overall, anti-HCV testing activity varies

widely between the testing pathways. In order to determine the most effective pathway(s) it is important to assess the proportion of positive tests compared to the total number of tests taken. Large volume testing of people at low risk of contracting HCV is very likely to be less effective than targeted testing in known at-risk groups, which would naturally yield a greater proportion of positive test results. It is plausible that the PWID-directed pathways would prove better candidates for investing health service resources. However looking across the pathways it is striking that the two parts of pathway 1 which are likely to be testing fewer active PWID actually lead to the diagnosis of the highest total number of HCV infection in NHS Tayside, with a higher number of HCV PCR positivity compared with those pathways designed to test to individuals with a high likelihood of injecting behaviour (2-5). Thus it is important to appreciate the reach of pathways with high volume testing, within standard health care pathways of low prevalence populations may and in this study did diagnose by far the greatest overall number of patients. Such pathways require little investment as the infrastructure already exists and the costs are spread over a large number of other disease and health service activities that utilise these services. In contrast the IEPS pathway 4 provides the highest proportion of PCR positivity per volume of testing, and therefore could be considered the most effective pathway in the health board in linking a highly burdened cohort to treatment. This is perhaps unsurprising as the individuals who are tested via this pathway are likely to be the highest risk group of contracting HCV due to lifestyle factors such as unstable housing, on-going injecting drug use, poverty and possibly of sharing injecting equipment. However it is important to appreciate that each pathway serves a slightly different population and together they offer a fair coverage of those at risk of HCV. Intermediate in this are pathways 2 and 3 based in drug treatment centres and community pharmacies and represent the patients on opiate substitution therapy. They have the lowest HCV PCR positivity, this can be explained by the patient group being amongst the more stable PWID residing in Tayside, who are therefore more likely to have engaged previously with HCV treatment and/or be less likely to expose themselves to an on-going risk of contracting HCV, for example reducing or ceasing injecting due to receipt of OST. Treatment and testing had been available within drug treatment services for some time before the observation period started and a clinical trial of treatment had been conducted in pharmacies, which would have substantially reduced the number patients left to diagnose and treat and these pathways should not be undervalued because of this as our previous work has demonstrated their value (11,21).

It is clear from the data that diagnostic pathways targeting populations most at risk of HCV are more effective at yielding new HCV diagnoses than standard pathways. However while the detection rate in standard pathways is low, the volume of use means they diagnose a large proportion of the target population. However this pathway will not reach high-risk groups, who require community based pathways to overcome access barriers and stigma. These tailored diagnostic pathways appear to resolve some of the health inequalities related to drug use and access to health care, and provide methods of ensuring connection to treatment. The results suggest targeted testing will find the majority of NHS Tayside's undiagnosed population, which would not be possible using only the standard testing pathway.

4.8.1 Study limitations

As this was a retrospective analysis using routine administrative healthcare data, it is open to biases and potential errors, including misallocation at input and linkage problems. Due to volume of testing, we only analysed individual level data for those patients who were PCR positive. As these results represent gross numbers of tests performed it is not possible to link all tests (i.e. anti-HCV and HCV RNA) to individuals, which was possible for those who tested PCR positive. With the clinical data we were able to use individual unique patient identifiers and could therefore manually investigate discrepancies where possible. Given the sample size, certainty regarding potential errors or biases relating to the quality of the data, including possible duplicate entries is not possible. Furthermore, it was not possible to link all tests to individuals, so in the primary analysis the results reported likely include a degree of re-sampling of the same individual(s) (e.g., monitoring for re-infection, on-treatment response monitoring, end of treatment outcome). The likelihood of re-sampling was lower for certain pathways (primary/secondary care, ethnic outreach) relative to others where it was higher (prisons, NSPs, drug treatment centres, pharmacies). This is due to differences in risk, indication for testing and the way treatment delivery changed over time. For example individuals tested in the ethnic outreach pathway had targeted testing and no ongoing risk factors, so would not expect to be re-tested. In comparison those tested via the injecting equipment provision sites could expect annual testing for re-infection, in addition to treatment response checks and end of treatment response as dictated by policies and clinical trials. The proportion of all tests conducted was higher in pathways with lower likelihood of resampling (94.2%) relative to those with higher likelihood (5.8%) suggests the overall proportion of duplicates is likely to be low.

The study has been presented in several sections to reflect and minimise the impact of this on interpretation. The area where this is most obvious is in the proportion of antibody and PCR testing and conversion to individual person tests. One would expect approximately 75% of the positive anti-HCV tests to translate into positive HCV RNA. There is a clear discrepancy between the numbers of tests taken. This could be due to: simultaneous anti-HCV and HCV RNA testing, screening for previous positives and monitoring of therapy (particularly in the interferon era of treatment). These effects are consistent across all pathways, so the effects are systematic.

4.9 CONCLUSION

It is apparent that all of the testing pathways engage different cohorts and risk groups of patients, even reaching sub-sections of PWID populations, such as those on OST or in prison. This widespread engagement has been effective in linking patients to treatment across all pathways, and brining the overall burden of HCV infection in NHS Tayside steadily downwards over time.

The majority risk factor for HCV in NHS Tayside is current or previous injecting drug use and this is reflected in the quantity of pathways targeting PWID (2-5). There is a smaller burden of infection among certain patient groups, such as those who emigrated from a high-prevalence country or those infected due to contaminated blood products, but it would be inefficient only to offer the pathways which serve these patients groups (1 & 6) in isolation, if HCV elimination as a public health threat is the target for the health board.

The downward trend in PCR positive patients across all pathways in recent years indicates that Tayside is nearing the end of the diagnosis of HCV in the region. The numbers of diagnoses equate nearly 89% of the estimated population prevalence of HCV at the start of the pathway analysis of this study; this is very strong evidence that this matrix of diagnostic pathways is the right combination to adopt to achieve HCV elimination. This trend indicates that the pathways in the region ensure appropriate coverage of different patient groups, as well as subgroups (e.g. current –v– previous –v– occasional drug injectors), which represent the highest burden of HCV infection. All patient groups will be represented in different proportions, and no one pathway will serve *all* of those who are at risk of infection. The question now arises as to which combination is most cost effective.

CHAPTER 5 – HEALTH ECONOMIC EVALUATION OF THE TAYSIDE DIAGNOSTIC PATHWAYS

This chapter was published as “Eradicating hepatitis C: Are novel screening strategies for people who inject drugs cost effective” published in International Journal of Drug Policy in 2020.(252) I developed the short term model, along with FM. I collected the data including costings and probabilities for each step along the decision tree either from local data, published data or derived an “expert opinion” through collaboration with JFD. FM and I ran the 1000 monte carlo simulations to derive the results for the cost effectiveness analysis. Data was displayed in cost effective graphs produced by the statistics software. I, along with FM drafted the manuscript. All authors reviewed the full draft of the article.

In keeping with the thesis aims to explore strategies required to find and diagnose all those infected with HCV in the Tayside Health Board a vital part of this work is to determine the cost effectiveness of the pathways in use in order to determine which is the most cost effective strategy or mix of strategies providing testing and treatment for HCV positive individuals.

5.1 SUMMARY

5.1.1 Background

With advances in HCV treatment leading to curative therapy it is crucial to identify people with early stage and asymptomatic infections in order to cure their infection and avoid serious and potentially life-threatening liver damage and escalating healthcare costs. In Tayside, where HCV prevalence is not endemic, we need to understand how to prioritise screening strategies and target different population groups effectively in order to eradicate HCV from the region. This study aims to identify and assess the most cost-effective strategies for diagnosing HCV infection in different patient populations using Tayside, Scotland as case study.

5.1.2 Methods

Four key patient populations were identified: intravenous drug users, prisoners and two subpopulations targeting high risk patients among the general population (high risk individuals in deprived areas and immigrants coming from endemic countries). A cost-

effectiveness analysis was undertaken for each of the above populations. Each strategy, which differed for point of care and targeted subpopulation, was compared against the standard care diagnostic pathways from the Scottish NHS perspective (a symptomatic detection during a GP consultation). A decision tree was developed to explore the incremental cost per additional positive patient detected, over a 1 year time horizon, and a previously published Markov model was adapted and employed to present lifetime outcomes in terms of incremental cost per QALYs gained. Scenario analysis was undertaken to explore impacts of introducing re-infection rate in a static framework, as PWIDs have a higher risk of re-infection.

5.1.3 Results and discussion

Results show that the most cost-effective strategy for PWIDs is testing at Needle Exchange Services, compared to the current practice of self-referral to GP practice, which is the least cost-effective strategy. Access to testing is a significant obstacle for early diagnosis. The most cost-effective strategies are those targeting the highest risk subpopulations at early age of disease, yet there are obstacles to this implementation in practice.

5.2 INTRODUCTION

Whilst we are entering in a new era for HCV treatments, little has been done to address the efficacy of screening at risk individuals in non-endemic areas. Since the UK is not considered an endemic country, the relatively low prevalence does not justify screening the entire population under the WHO criteria.(271) Therefore, in countries like the UK, with a sizeable undiagnosed population, but a low enough prevalence that does not warrant widespread screening it becomes fundamental to understand how to direct and prioritize screening to reach those who are infected yet undiagnosed.

This study aims to evaluate the existing HCV diagnosis and treatment pathways to find the most cost-effective strategy or mix of strategies for diagnosing HCV infection in both high risk and ‘under diagnosed’ populations in NHS Tayside in Scotland. The populations included were the general population, present and past PWIDs, prison inmates and individuals from Pakistan as a country with a higher prevalence than the UK.

In this chapter there is some terminology and concepts specific to health economics evaluation. In order to understand the forthcoming analyses and conclusions I have outlined some of these here;

- Net monetary benefit (NMB) is a statistic calculated as (incremental benefit x threshold) – incremental cost. This represents the value of an intervention in monetary terms when a willingness to pay threshold for a unit of benefit e.g. QALY is known.(272)

- Cost per quality adjusted life year (QALY) is a summary measure of health gain that combines changes in life expectancy and quality of life. It uses health utilities to weight improvements in life expectancy according to the quality of life experienced.(273)

- Willingness to pay (WTP) is based on the premise that an individual (or in this case the health system) has a monetary amount that they would be willing to pay for certain health benefits or a beneficial intervention. In the UK The National Institute for Health and Clinical Excellence (NICE) has been using a cost-effectiveness threshold range between £20,000 and £30, 000. The cost effectiveness threshold is the maximum amount of money a decision maker is willing to pay for a unit of health outcome.(274)

- Incremental cost effectiveness ratio (ICER) is defined as the ratio of the difference in costs between an intervention and a specified comparator to the difference in effectiveness between that intervention and the specified comparator. From the results of a cost-effectiveness analysis, an incremental cost-effectiveness ratio can be calculated that depicts the extra cost per unit of outcome obtained, in comparing one treatment option to another.(274)

- Dominated. This is a concept where one strategy is more cost effective than another. Therefore the most cost effective strategy dominates the less cost effective strategy i.e. the strategy that costs more but does not yield any additional benefit. Strategies which are dominated should be rejected.(274)

5.3 METHODS

This is an anonymised retrospective study using routine health service data from NHS Tayside (Scotland) and data output from published Scottish studies to compare and evaluate a variety of different diagnostic strategies for HCV screening focussing on those sub populations with recognised risk factors. The different treatment pathways as described in Chapter 4 represent the different strategies, with the exception of the secondary care pathway. Costings for the secondary care pathway were similar to the

primary care pathway, but the diagnosis rate was 1% compared with 3% in the primary care pathway. The secondary care pathway was therefore dominated, and no further analyses were performed using this strategy. These strategies grouped according to the four different patient populations they serve and are compared. The cost-effectiveness analyses are undertaken using both a short term and lifetime time horizon. The short term analysis uses a decision tree populated with data directly from observational studies to determine the cost per additional case detected. The long term analysis is a cohort Markov Model which extrapolates the short term results to determine the net monetary benefit and the incremental cost per additional quality adjusted life year (QALY) gained. The comparator for each strategy is the current standard of care in Scotland to detect HCV, which is testing at a GP practice due to symptomatic presentation. The decision analytic model is static; therefore, it is assumed that there is no interaction between populations, e.g. PWID individuals remain PWID for all their time in the Markov Model. In order to get the best mix of strategies, we will identify the most cost-effective strategy between the current practice in NHS Tayside as well as novel strategies trialled elsewhere in Scotland (described in Chapter 4) for each every of the four targeted populations.

5.3.1 Cohorts and strategies

We examined 4 different patient populations based on different HCV prevalence. The four sub groups are: (i) current PWID and PWID who have recently recovered, (ii) general population, (iii)South Asians living in Scotland and (iv) prisoners. Screening strategies varied for each of these populations, as was appropriate to that population.

For the PWID population there are three alternative strategies: a) substance misuse services (SMS), b) injecting equipment provision sites (IEPS) and c) pharmacies, compared against standard GP visit. For the general population two strategies were considered: a) GP offering screening to every patient attending the practice for any reason in deprived areas b) GP offering screening to every patients known to be a former PWID in deprived areas who attended the practice for any reason, compared to a non targeted detection during a standard GP visit. For the South Asians living in Scotland population the strategy was a) outreach testing at religious venues was compared against the standard GP visit, and for the Prisoners population one strategy a) opt out HCV testing on entry to prison was compared against Standard diagnoses at GP for PWID population.

Table 5.1 details the alternative strategies and the different patient population they serve.

Table 5.1. List of the strategies.

Strategy	**Population**	**Description**
1. Standard diagnosis at GP for general population	General population (comparator)	Test requested by a clinician (primary or secondary care) due to a suspicion of HCV infection highlighted by the presence of symptoms, abnormal blood results or signs of liver disease. Average age: 43. Majority of the people detected at severe stage of the disease: F4[1]. Source: observational data from NHS Tayside.
2. Standard diagnosis at GP for PWID population	PWID (comparator)	Counterfactual built as an average of the PWID strategies and the standard diagnosis for the general population, to reflect the higher propensity to screen PWID individuals by GPs. Average age: 39.5. Prevalent disease stage at detection: f0-f1, Source: expert opinions and averages of other strategies.
3. Substance Misuse Services (SMS)	PWID	People on opiate substitution therapy offered a dried blood spot test at first contact with a Substance Misuse Service. Population: current and previous PWID. Average age: 37. Prevalent disease stage at detection: F0-F1. Source: observational data from NHS Tayside. Comparator: strategy 2
4. Needle Exchanges	PWID	People accessing Needle Exchange Services offered a dried blood spot test. Population: current and previous PWID. Average age: 32.5. Prevalent disease stage at detection: F0. Source: observational data from NHS Tayside. Comparator: strategy 2
5. Pharmacies	PWID	Clients receiving Opiate substitution therapies or needles at participating dispensing pharmacies offered a dried blood spot test. Population: current and previous PWID. Average age: 39. Prevalent disease stage at detection: f1. Source: observational data from NHS Tayside. Comparator: strategy 2
6. Prisons	Prisoners	Opt-out testing upon entry for all prisoners in the prison. Population: new prisoners at prison receptions. Average age: 35 Prevalent disease stages at detection: F2. Source: observational data from NHS Tayside. Comparator: strategy 2, with different probabilities to be screened and same disease stage of prisoners.

[1] F0-4 stands for fibrosis stage at diagnosis. F0 is the less severe stage of fibrosis, F4 cirrhosis.

Strategy	Population	Description
7. Community outreach to ethnic minorities	Immigrants from endemic countries	Test offered at mosques for first and second generation individuals coming from Pakistan. Evidence suggests that South-Asian immigrants have higher HCV prevalence,(275) in particular Pakistani immigrants and descendants.(261) Population: ethnic minority (sub-population of general population). Average age: 42. Prevalent disease stages at detection: F4. Comparator: strategy 1.
8. GP Targeted screening: high social deprivation areas	General population	People aged between 30-54 attending GP for any reason in areas with high social deprivation were offered an information leaflet and HCV testing. Population: deprived population (sub-population of general population). Average age: 42. Prevalent disease stages at detection: F4. Source: Anderson et al(276) Comparator: strategy 1.
9. GP Targeted screening: high social deprivation areas with an history of PWID	General population	People aged between 30-54 attending GP with a history of PWID were offered testing. Population: previous and current PWID in deprived areas (sub-population of general population). Average age: 42. Prevalent disease stages at detection: F4. Source: Cullen et al.(262) Comparator: strategy 1

All the strategies were compared with a symptomatic testing at the GP. However, primary data sources for the GP cover the general population as a whole. In order to provide a counterfactual for the subpopulation of PWID being screened at the GP, we used expert opinion and literature sources, since evidence suggests that PWIDs are more likely than the general population to be screened in primary care (Table 5.1).

Every strategy, regardless of the patient population (which identifies the prevalence), differing by 1) attrition across the HCV cascade of care in the short term 2) demographics 3) treatment uptake, forms a different Markov-cohort in our long term model.

Regarding the PWID population, it is reasonable that different venues could identify different subpopulations, which don't overlap between the services. However, in our model, we assumed that the PWID macro-population is homogeneous and that every individual could consider going to any point of care in our strategies and be offered a test. The likelihood of the average PWID individual going to one point of care instead of another was discussed and adjusted based on expert opinions.

5.3.2 Model structure

5.3.2.1 Short term

We developed a short term model of HCV detection for every strategy to assess the cost-effectiveness of HCV detection through a decision tree. The outcome of the decision tree is the incremental cost per positive patient detected and the time horizon for the decision tree was 1 year. Every strategy in the decision tree included the HCV cascade of care: test offer, result delivery, confirmatory test and treatment (Figure 5.1).

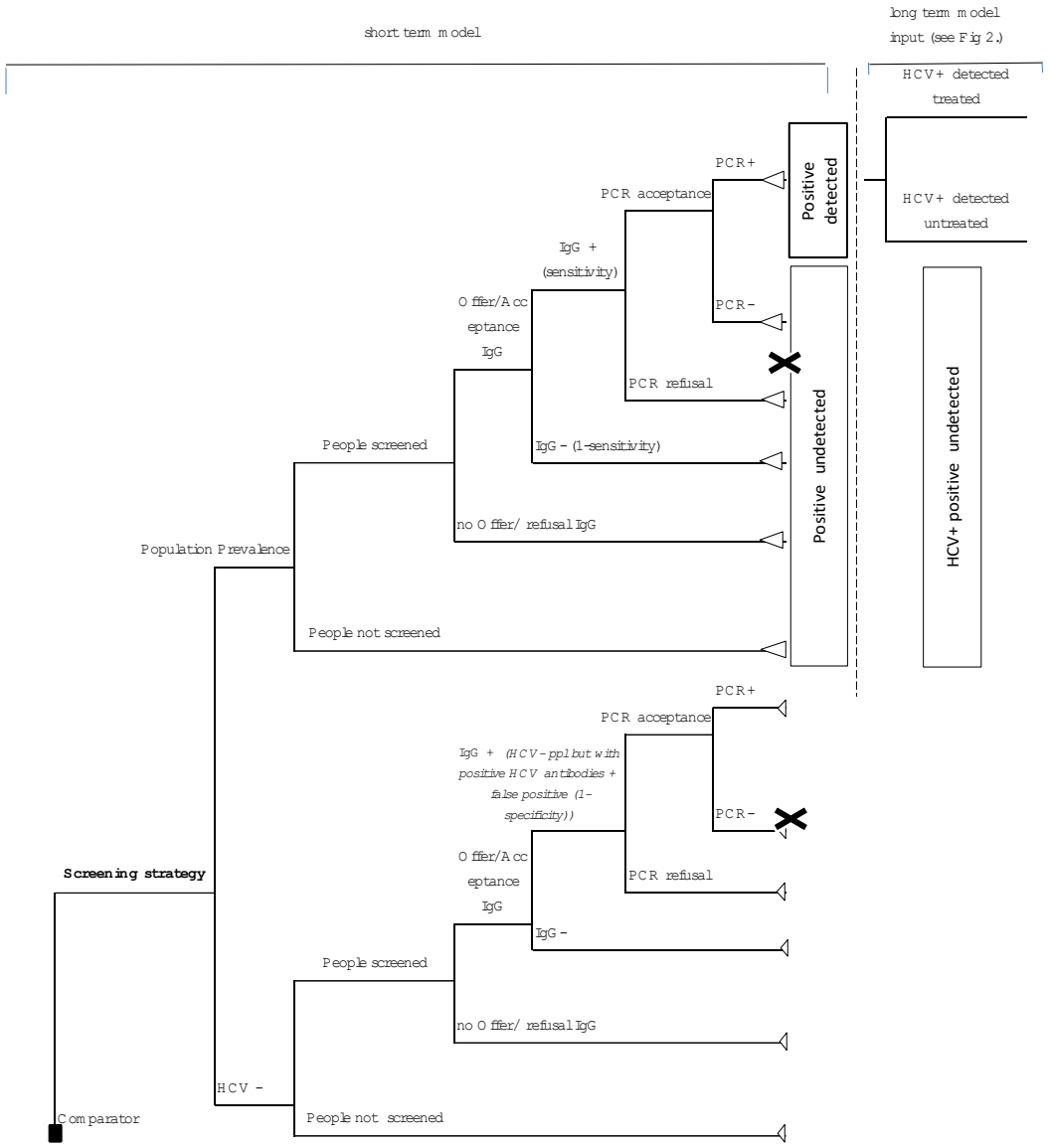


Figure 5.1. Decision tree.

IgG= preliminary test to detect HCV antibodies. Individuals can be IgG positive but they can clear on their own the virus, resulting PCR negative (therefore, not infected). PCR=confirmatory test. PCR is assumed to be 100% accurate so there will not be false positive and/or false negative individuals.

Treatment delivery depends on the stage of liver disease (different drug regimens and treatment lengths depending on liver disease stage) and the individuals willingness to be treated which, according to our data, could vary across strategies. We did not include treatment delivery and related costs in the short term outcome because the time between initial test and treatment completion can exceed the 1 year time horizon. The main differences across strategies over the short term were; costs – personnel involved in the screening and procedure-; type of test (dried blood spot (DBS) or venous sample); and patients' characteristics (demographics and attrition across HCV cascade of care).

Probability of moving through each node of the decision tree from offer and acceptance of the first test (IgG) was driven by observational data concerning pilot strategies in Tayside, Scotland (Strategies 1-3-4-5-6), or previously published Scottish pilot studies (Strategies 7-8-9). As already mentioned, since evidence suggests(263,277) that there is a higher propensity to screen PWID for HCV by GPs, the comparator for PWIDs (Strategy 2) is a counterfactual built on expert opinions and the average of all the PWID strategies and the GP for the general population.

Strategies concerning the general population (Strategies 8-9) target different sub-samples of the general population and consequently have different prevalence. In order to compare these strategies together, and considering them mutually exclusive against strategy 1, they have been considered as complementary strategies of the current practice. In other words, the comparison for the general population will be strategy 8 for its targeted population plus strategy 1 for the remaining general population vs strategy 1 only for all the general population. The same arrangement will occur for strategy 9. Data on prevalence in different populations came from the literature. Probabilities on the likelihood of being screened and offered the test came from the literature and expert opinions. Probabilities in the decision tree subsequent the IgG acceptance came from observational data. Sensitivity and specificity of preliminary antibodies test changes in accordance with the type of test (IgG with a venous sample or DBS). Confirmatory test (PCR) is assumed to be 100% accurate, as a result, there are not false positive and/or false negative individuals at the end of the screening process.

5.3.2.2 Long term

A previously published Markov model(278), modelling the natural history of HCV patients over a lifetime horizon was adapted to estimate the cost-effectiveness of every strategy from the NHS Scotland perspective. Given that the long term model is an extrapolation of the short term results, there are no additional observational data except for aggregate demographics for the people screened in each strategy (see Table 5.2). Initial disease stage was assumed to be the same for positive individuals regardless of their positivity detection.

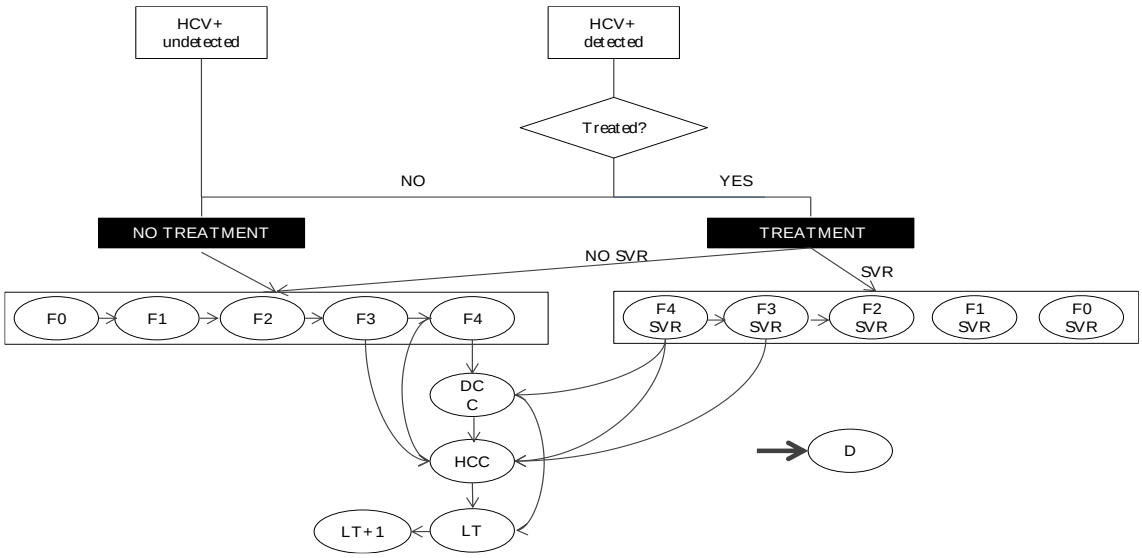


Figure 5.2. Model structure. Source: Younossi 2015(278)

DCC= decompensated cirrhosis, D=death due to HCV, F0-4, metavir score (liver fibrosis stage) in ascending order of severity, HCC, hepatocellular carcinoma, LT, liver transplant, LT+1 after liver transplant, SVR=sustained virologic response

Length of the cycle in the 'Markov model is one year. Screening strategies determined the output of the short term model (the number of people detected and treated out of the total number of infected) and the entry point into the disease model (Figure 5.2). The main health economic outcome was the incremental lifetime cost per QALY gained, expressed both in incremental cost-effectiveness ratio (ICER) and in monetary benefit, with a threshold of £20,000/quality adjusted life years (QALY).

The average age of HCV detection varies by strategy. In order to allow for comparisons, pathways testing the same patient cohort are built to have the same time horizon (and the same number of Markov cycles across strategies). Specifically, all the strategies serving the same population enter in the Markov model at the same average age of the strategy in that cohort which detects patients at the earliest age (see Figure 5.3). The initial stage of liver disease will be the same for all the cohorts addressing the same populations. Cohorts will receive the screening (and subsequent treatments) at different ages dependant on the average age of HCV detection for the strategies. Cohorts tested on average later in life will have more time for disease progression (according to the Markov transition probabilities) with the absence of detection and subsequent treatment. Thus, the treatment effect of strategies which screen earlier consists mainly of lower disease progression prior to detection and treatment, with lower health related costs, and increase in QALY compared to individuals screened later.

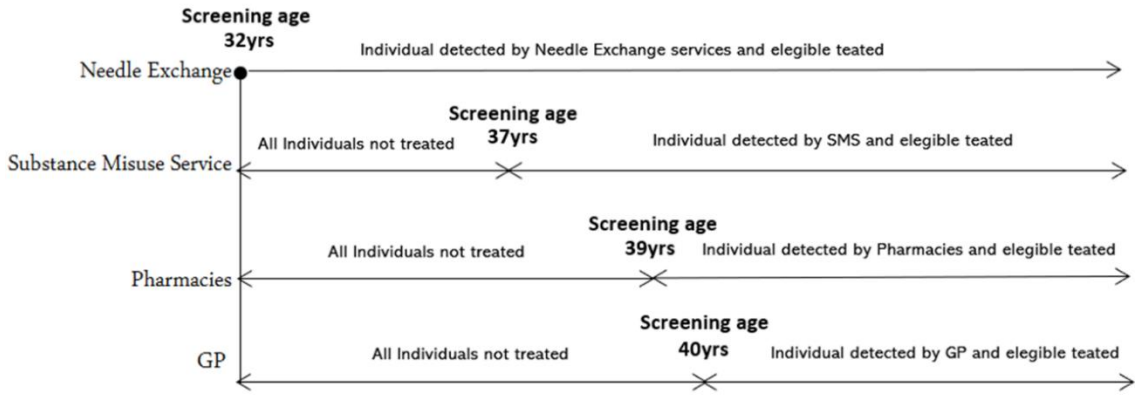


Figure 5.3. Screening timing and disease progression illustration.

Observational data on liver fibrosis stage at the time of detection are available for Strategies 1,3,4,5,6. However, in most strategies, the number of individuals with fibrosis staging at detection is lower than the actual sample size of the strategy (see Table 5.2). This is due in the most part to streamlining HCV services and reducing delay prior to treatment initiation. The proportion of individuals with fibrosis staging varies across the strategies, most notably in Strategy 3 with only 24/54 individuals with initial fibrosis stage reported. Other strategies despite a higher proportion of individuals with a documented fibrosis stage have a reduced sample size (e.g. Strategy 5 has only 22 positive patients detected, as data was obtained from the pilot study where few pharmacies were providing HCV tests in Tayside). To prevent biasing the results in the long term analysis, all the PWID strategies start with an initial fibrosis stage distribution equal to the disease distribution of the earliest strategy in time -Strategy4- (which is also the one with highest sample size). In order to try to take advantage of all the observational data available from NHS Tayside, a sensitivity analysis using observational data for the initial stage of HCV at the time detection was undertaken (see Sensitivity Analysis section). In the prison population, both the strategies enter in the long term model with the disease stage prevalence related to strategy 6.

5.3.3 Data

Model input for the general population and other parameters are summarised in Table 5.2. All data on costs from secondary sources were adjusted to 2017 values. In the long term analysis, future costs and health benefits were discounted at 3.5% annually. Data on prevalence from a combination of different sources were discounted at 2017 prevalence values in accordance with the Health Protection Scotland epidemiology figures of the HCV trend rate over years.(255) We undertook a Probabilistic Sensitivity Analysis (PSA) using 1000 iterations Monte Carlo Simulation. In this PSA we

simultaneously varied all the parameter assumptions including data from multiple sources and expert opinions. Table 5.2 details the distribution form applied to each parameter. All data showing transition probabilities of every stage are taken from the literature, costing and utilities data was based on UK pricing.

Overall, in Scotland the prevalence of HCV genotype 3 among the infected patients is assumed to be 70% and genotype 1 30%.(279) All the strategies are assumed to have the Scottish genotype prevalence, except for strategy 7, which, in accordance with previous evidence and expert opinions, is assumed to be only genotype 3, given the different HCV epidemiology in the migrant population from South Asia.

Background mortality in the Markov model has been adjusted in accordance with the standardised mortality ratio for the specific populations (PWID and prisoners have lower life expectancy), which compared to the general population is 3.38 and 14.68 for prisoners and PWID, respectively.(280,281) Community outreach and the general population (strategies 7,8-9) are assumed to have the same mortality rate which is in accordance with the Scottish life tables for 2017. As a consequence, final results of the long-term analysis are easily comparable within a population but will have to be interpreted with care between populations.

Treatments in the model were obtained from recommendations by the Scottish Medicines Consortium: sofosbuvir-velpatasvir and glecaprevir-pibrentasvir for genotype 1 and 3, respectively. Treatment success is 97% and 95% for f0-3 and f4, respectively.

The sample size of every strategy based on observational data varies depending on the number of people tested and recorded in each pathway between 2015 and 2017.

Table 5.2. Main model parameters.

Observational data	**Individuals with IgG positive**[2]	**N of HCV positive detected**	**N of disease stage reported**
Strategy 1	99	75	60
Strategy 3	91	54	24
Strategy 4	54	48	104[3]
Strategy 5	182	22	21
Strategy 6	92	45	24

Input parameter	Mean Value	Distribution	Parameters Mean (SD)	Source
Short term				
Strategy 1 population prevalence	0.01			Dillon(282)
Strategy 2-3-4-5 population prevalence	0.43			Dillon(282)
Strategy 6 prevalence	0.19	Norm[4]	0.19 (0.012)	Taylor(283)
Strategy 7 prevalence	0.025	Norm	0.025 (0.002)	O'Leary(275)
Strategy 8 prevalence	0.029	Norm	0.029(0.0018)	HPS, ISD(284)
Strategy 9 prevalence	0.17	Norm	0.017(0.011)	HPS, Hutchison(285)
genPop- chance of going to GP once per yr	0.81			ISD Scotland(286)
genPop- Chance of being tested if positive	0.05	Norm	0.05(0.003)	Expert opinion
genPop- Chance of being tested if negative	0.01	Norm	0.010(0.001)	Expert opinion
IgG -Venous sample sensitivity	0.98			Spach(287)
IgG -Venous sample specificity	0.99			Spach(287)
DBS/oral fluid IgG sensitivity	0.92			Judd(288)
DBS/oral fluid IgG sensitivity	0.99			Judd(288)
genPop- IgG+ but PCR-	0.138	Beta	α=12β=75	NHS Tayside
genPop- treatment acceptance	0.907	Beta	α=68β=7	NHS Tayside
genPop- PCR acceptance	0.88	Beta	α=88β=11	NHS Tayside
Cost of tests				NHS Tayside
Cost of clinical and or support personnel				PSSRU 2017(289), NHS Tayside
Long term				
Transition probabilities	Thein,(290) Martin,(291) McEwan,(292) McGarry,(293)Younossi(294)			
Utility values in Markov states	Martin(291)			
Cost of Markov states	Martin(291)			
Cost of treatment	Scottish Medicine Consortium			

[2] IgG positivity is intended as initial of cascade of care, HCV+ detection is the end of the short term model

[3] Higher number of stats on disease stage reported because refers to the 2011-17 period.

[4] Normal distribution concerning prevalence and other parameters is a truncated normal between 0 and 1.

5.3.4 Sensitivity analysis

A Probabilistic Sensitivity Analysis (PSA) was undertaken using 1000 iterations Monte Carlo Simulation in which all key parameter inputs to the model were randomly sampled from a predefined probability distribution. The probability distributions mean values and standard errors used for the PSA for the parameters are reported in Table 5.3. One-way sensitivity analyses were also performed on the following parameters to evaluate further the impact of uncertainty in assumptions and other areas on results:

- 0-100% discount applied to the list price of HCV drug treatments;
- Assumption of 100% treatment uptake after diagnosis;
- 100% increase in offering IgG test by GPs.
- 50% decrease in initial prevalence
- Substitution of the model diseases stage prevalence at detection with the observable data;
- Same age (32 years) and same initial stage of disease across all the strategies
- Treatment regimens assuming all patients were DAA- treatment experienced
- The different likelihood of going to a specific screening site for PWID based on number of positive PCR collected in each screening setting from 2015-2017.

5.3.5 Scenario analyses

Three scenario analyses were performed:

i) Reinfection scenario: The PWID population has a high risk of re-infection due to their high risk lifestyle,(295,296) yet re-infection rates are uncertain and vary based on a variety of risk factors. To account for reinfection in the model, a scenario analysis was undertaken whereby an additional transition probability was introduced from the SVR state to the same non-treated state for all the PWID strategies. In effect, this means that after incurring the cost of treatment, some patients are then immediately re-infected and continue to progress in the model as if they had received no treatment. For the purpose of the model we assumed that once an individual is re-infected after treatment, the individual will not receive further treatment in the future. The reinfection rate adopted for this scenario was based on the most recent data on HCV re-infection for PWID in Tayside.(139) This study mapped reinfection within the same needle exchange centre

included in this analysis. To account for a lower reinfection risk in older individuals(139)(139)(139)(139)(139)(138)(137)(136)(135)(134)(133) (and the consequent reduction in sharing propensity), the transition probability of reinfection used was assumed to decrease over time in accordance with the data.(139) We are aware that our data came from a small sample that reports higher reinfection rates than previous publications,(106,297) and that by using a static model a potential herd immunity factor (see discussion) was not considered, we therefore believe that our final results are conservative estimates. The reinfection rate at 33 years was 0.10 (average age of screening at needle exchange pathway), and at 40 is 0.06 (age for PWID going to GP). The rate of re-infection decreases on an average of 7.5% per year.

ii) Complementary GP strategy. Another scenario was analysed for every strategy not directly involving GPs (Strategies 3-4-5-7), including the prospect of going to the GP in the decision tree for those not going to the strategy-specific point of care (Figure 5.4). For example, in strategy 3, PWIDs not going to SMS could attend their GP instead, which is assumed to always be an option. Therefore, in this scenario, the comparison will be between a combination of a specific screening pathway or the GP alternative, against screening at the GP only (strategy + GP vs GP).

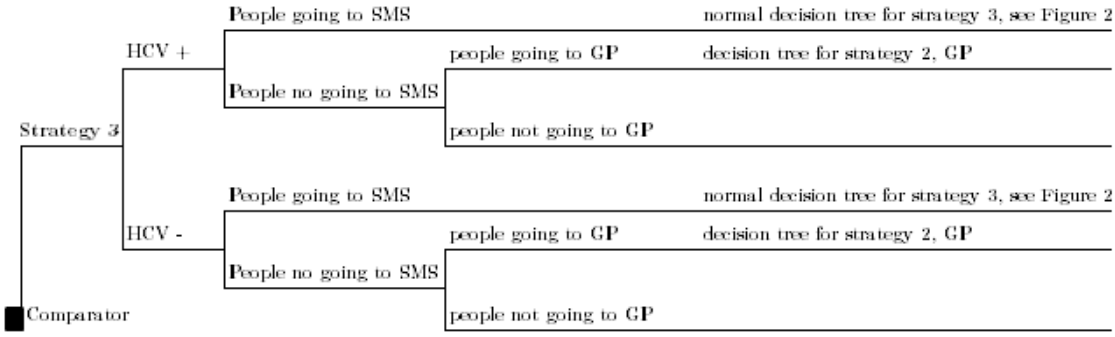


Figure 5.4. Decision tree scenario complementary GP strategy to strategy 3

The decision tree is similar to the baseline, but people not going to the point of care specific of the strategy (substance misuse services for strategy 3), have the chance of going to the GP.

iii) PWID pathways only. As the predominant risk factor for HCV in Scotland is PWID, we carried out additional cost effectiveness analyses on this subpopulation.

5.4 RESULTS

An overview of the results from the short and long term models are shown in Table 5.3.

5.4.1 Short term model

Expected cost of the four strategies varied with the GP strategy being the least expensive and the pharmacy strategy being the most expensive. Once the number of positive cases detected are added to the model the lowest cost per positive case detected is in substance misuse services at £150.00 per positive case detected with the pharmacy strategy remaining the most expensive at £208.00 per positive case detected.

Offering HCV tests at IEPS is the most effective strategy with a 6.7-fold increase in detecting positive patients. However, according to the observational data, SMS has the lowest percentage of treatment adherence after HCV detection (maybe due to a low sample size of positive people). Hence, these short-term benefits were not reflected in long-term outcomes.

Short-term results show that the SMS, IEPS and pharmacies all cost more than the base base strategy (GP), therefore it is necessary to calculate the ICER for each strategies. Both SMS and IEPS provide additional health outcomes in comparison to the GP strategy in terms of additional cases detected. The pharmacy strategy also detects more cases than the GP strategy, but less than both SMS and IEPS at greater cost. The pharmacy strategy is consequently deemed to be dominated as it incurs additional cost without increased health benefit.

The second sub-group compares the base case GP strategy with the two other GP based strategies which involved targeted screening for higher risk individuals. Cost is similar for strategy 9 and the base case, but strategy 8 is more costly at £2.23. Once positive cases detected are entered into the model strategy 9 is cost effective with an ICER of 768, whilst strategy 8 is dominated being both more costly and delivering less positive results. For the purposes of the model it should be discarded. Strategy 9, targeted screening in general practice in areas of high social deprivation and history of PWID, is the most cost effective for the general population.

The third sub-group compares testing of a South Asian population with the GP base case. The strategy is more costly than the base case at £3.68 compared with £0.80. The strategy delivers a positivity rate of 6.9% which is almost twice as effective as screening at GPs, but more than twice as costly.

In the prison sub-group, screening the entire population (strategy 6) increases case detection by more than 9 times with a positive case detection of 82% versus 8.9%. Cost

per positive detected is £346.00 compared with £211.00, but the high yield of positive cases makes this cost effective in the short term.

Table 5.3. Results for the long and short term models for all strategies

Short term				
Strategy	**Expected Cost of the Strategy (£)**	**Number of positive detected (% out of total positive)**	**Cost per positive detected (£)**	**ICER (Incremental cost per case detected £/QALY)**
PWID population				
GP (Strategy2)	5.82	0.0186(4.3%)	313	-
SMS (Strategy3)	15.08	0.1007(23.4%)	150	113
Needle exchange (Strategy4)	19.11	0.1249(29.0%)	153	125
Pharmacies (Strategy5)	19.66	0.0945(21.9%)	208	Dominated
General population				
GP (Strategy 1)	0.62	0.0004(3.5%)	1765	-
Cullen (Strategy 9)	0.77	0.0006(5.6%)	1402	768
Anderson (Strategy 8)	2.23	0.0005(5.2%)	4365	Dominated
South Asian Muslim population				
GP (Strategy 1)	0.80	0.0009(3.5%)	912	-
Mosque (Strategy 7)	3.68	0.0017(6.9%)	2107	3305
Prison population				
GP at prison (Strategy 2)	3.59	0.0170(8.9%)	211	-
Prison (Strategy 6)	53.94	0.1558(82%)	346	363
Long term				
Strategy	**Cost (£)**	**QALY**	**ICER (Incremental Cost per QALY)**	**NMB (WTP at £20,000)**
PWID population				
GP (Strategy2)	11,397	8.28	-	154,331
SMS (Strategy3)	14,064	8.34	48,141	152,772
Needle exchange (Strategy4)	16,561	8.69	12,586	157,373
Pharmacies (Strategy5)	13,981	8.36	25,052	153,994
General population				
GP (Strategy 1)	35,785	9.0314		144,843
Cullen (Strategy 9)	36,370	9.1931	3618	147,492
Anderson (Strategy 8)	36,459	9.1747	Dominated	147,035
South Asian Muslim population				
GP (Strategy 1)	35,762	9.0325	-	144,888
Mosque (Strategy 7)	36,431	9.286	2639	149,289
Prison population				
GP at prison (Strategy 2)	23,022	10.417	-	185,318
Prison (Strategy 6)	34,064	12.144	6394	208,816

ICER = Incremental Cost-Effectiveness Ratio, NMB = Net Monetary Benefit, QALY = Quality Adjusted Life Years. NMB calculated using a willingness to pay of £20,000/QALY. NMB=

[Effectiveness*(Willingness to pay)-Costs]. Due to rounding, figures throughout the table may not add up to the totals. There may be discrepancies between the reported ICER, NMB and those totals

5.4.2 Long term model

Long-term results show how screening at an earlier age (which corresponds to an earlier stage of disease in the model) is more cost effective, especially for the PWID population. Apart from Prisoners with a QALY of 12.14, due to the relative low difference in in the number of people detected and treated across the other sub group populations, there is no high variance in QALY. Across all the sub group populations there is at least one strategy which is cost-effective at £20,000/QALY.

Offering tests at needle exchange centres was associated with a 10% (7.45-fold) increase in cases detected (Table 5.4). Whereas, for SMS and Pharmacies the increase was 8.4% and 7.8%, respectively. Whilst the IEPS strategy cost £13 per test more than GP, the most expensive strategy was screening at Pharmacies at £17.30 and the cheapest was SMS with £9.47. The highest and lowest strategies in terms of cost per HCV positive diagnosis detected are a symptomatic screening at GPs (£335) and screening at SMS (£150), respectively. Screening at SMS costs £112 per any additional person screened compared to GP. Screening at needle exchange services has an ICER of £124 per additional HCV+ detected against GP. Each strategy has a low ICER value and could be considered cost-effective compared to the GP current practice in a pairwise comparison. Using an incremental approach (Table 5.5), screening at SMS is the most effective strategy in the short term.

The results in the long term differ slightly from the short-term, as the proportion of positively detected HCV cases incur costs, quality of life and life expectancy implications over the patient lifetime. In the lifetime analysis all the strategies are considered cost-effective at £30,000/QALY. Screening at needle exchange was the most cost-effective strategy, with an incremental cost-effectiveness ratio value of £12,336/QALY. Indeed, screening at needle exchange generates the greatest QALY gain (0.4 QALYs) in the population due to a higher number of people treated compared to its comparator. Looking at the incremental results, both SMS and Pharmacies are dominated by Needle Exchange and GP.

Table 5.4. Short- and long-term results –pairwise comparison (every strategy vs current practice).

Short term						
Strategy	**Expected Strategy cost £**	**Proportion of detected (% out of total positive)**	**Cost per positive detected**	**Incremental cost £**	**Incremental Effect**	**ICER**
GP PWID	5.61	0.02 (3.9%)	335.07			
SMS	15.08	0.10 (23.4%)	149.82	9.47	8.4%	112
Needle Exchange	19.11	0.12 (28.9%)	152.98	13.49	10.8%	124
Pharmacies	22.91	0.09 (21.9%)	242.16	17.30	7.8%	222
Long term						
Strategy	**Cost £ (95% Cred Inter.)**	**QALY (95% Cred Inter.)**	**Incremental cost**	**Incremental QALY**	**ICER**	**NMB (£)**
GP PWID	5143 (3327,7591)	8.29 (7.93,8.66)	-	-	-	160737
SMS	8032 (5692,10190)	8.42 (8.05,8.78)	2889	0.13	22518	160414
Pharmacies	9321 (7012, 11320)	8.44 (8.09,8.79)	4178	0.15	27402	159609
Needle Exchange	10117 (7532,11787)	8.70 (8.31,9.04)	4974	0.40	12336	161814
Reinfection scenario						
GP PWID	5162 (3333,7608)	8.29 (7.91,8.62)	-	-	-	160589
SMS	8156 (5758,10371)	8.37 (8.00,8.74)	2995	0.08	35813	159267
Pharmacies	9465 (7104,11526)	8.40 (8.04,8.76)	4304	0.11	39969	158439
Needle exchange	10369 (7629,12140)	8.47 (8.07,8.82)	5207	0.19	28000	159102

ICER = Incremental Cost-Effectiveness Ratio, NMB = Net Monetary Benefit, QALY = Quality Adjusted Life Years. NMB calculated using a willingness to pay of £20,000/QALY. NMB= [Effectiveness*(Willingness to pay)-Costs]. Due to rounding, figures throughout the table may not add up to the totals. There may be discrepancies between the reported ICER, NMB and those totals

Table 5.5. Short- and long-term results – incremental comparison.

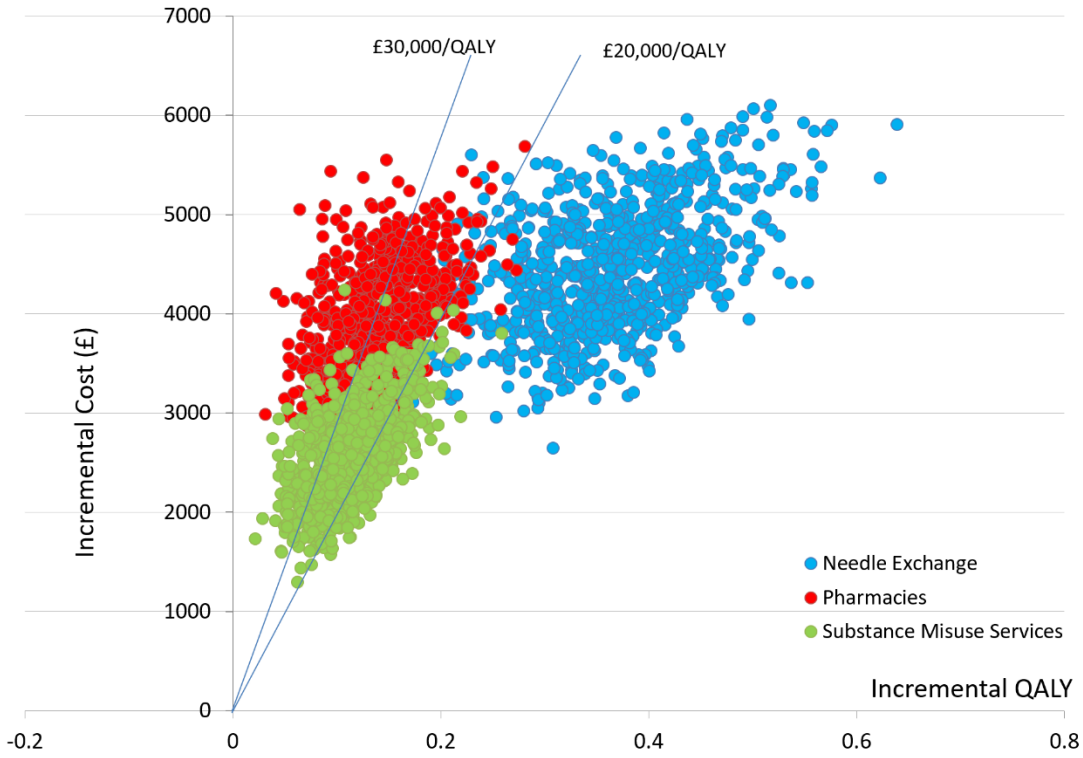
Short term						
Strategy	**Expected Strategy cost £**	**Proportion of detected (% out of total positive)**	**Cost per positive detected**	**Incremental cost £**	**Incremental Effect**	**ICER**
GP PWID	5.61	0.02 (3.9%)	335.07			
Pharmacies	22.91	0.09 (21.9%)	242.16	strictly dominated by SMS		
SMS	15.08	0.10 (23.4%)	149.82	9.47	0.08	118.38
Needle Exchange	19.11	0.12 (28.9%)	242.16	4.03	0.02	201.05
Long term						
Strategy	**Cost £ (95% Cred Inter.)**	**QALY (95% Cred Inter.)**	**Incremental cost**	**Incremental QALY**	**ICER**	**NMB (£)**
GP PWID	5143 (3327,7591)	8.29 (7.93,8.66)	-	-	-	
SMS	8032 (5692,10190)	8.42 (8.05,8.78)	extended dominated by Needle Exchange and GP PWID			
Pharmacies	9321 (7104,11526)	8.44 (8.09,8.79)	strictly dominated by SMS			
Needle Exchange	10117 (7532,11787)	8.70 (8.31,9.04)	4974	0.4	12336	161814
Reinfection scenario						
GP PWID	5162 (3333,7608)	8.29 (7.91,8.62)	-	-	-	
SMS	8156 (5758,10371)	8.37 (8.00,8.74)	extended dominated by Needle Exchange and GP			
Pharmacies	9465 (7104,11526)	8.40 (8.04,8.76)	extended dominated by Needle Exchange and GP			
Needle exchange	10369 (7629,12140)	8.47 (8.07,8.82)	5207	0.19	28000	159102

5.4.3 Sensitivity and scenario analyses

The results of the sensitivity analysis suggest that screening at Needle exchange is highly likely to be a cost-effective strategy. However, there is considerable uncertainty surrounding the cost-effectiveness of both screening at Pharmacies and Substance Misuse Services, respectively, depending on the chosen willingness to pay (WTP) for QALY gains (Figures 5.7, 5.8, 5.9 and 5.10).

Assuming all strategies begin screening at the same age (32 years), with the same disease severity, makes both SMS and Pharmacy strategies cost-effective, bringing them below the £20,000/QALY threshold (Figure 5.5). Alternative assumptions regarding the probability of going to a different point of care based on the number of PCR positive tests, as well as having a 100% treatment uptake, had little impact on the cost-effectiveness results. Using the observed value for disease prevalence at detection makes all the strategies cost-effective at less than £5,000/QALY compared to the screening at GP (Figure 5.5). An increase in treatment price, such as using a worst-case scenario where all the individuals are treatment experienced and require costlier treatments, leads to screening at needle exchange being the only cost-effective strategy (Fig 3a). However, if discounts on the UK list price of treatments were applied, there is the potential for all strategies to be considered cost-effective (24% discount at £30,000 per QALY, and 50% discount at £20,000 per QALY) (Figure 5.6).

When reinfection rates are introduced to the base case model, only screening at needle exchange is likely to be remain cost-effective (ICER: £28,000/QALY).



Pairwise comaprisons	Probability of being cost effective at different willingness to pay tresholds					
	£0	£10,000	£20,000	£30,000	£40,000	£50,000
Needle Exchange	0%	12%	98%	100%	100%	100%
GP	100%	88%	2%	0%	0%	0%
Pharmacies	0%	0%	5%	62%	88%	95%
GP	100%	100%	95%	38%	13%	5%
SMS	0%	0%	29%	83%	95%	99%
GP	100%	100%	71%	17%	5%	1%

Figure 5.5. Incremental cost effectiveness plane with all strategies against the current standard practice – base case scenario. The table represents the probability of being cost effective for every strategy against the current standard of practice (GP) at different willingness to pay thresholds.

In the cost effective plane all three strategies (needle exchange, pharmacies and substance misuse services) yield both a higher cost and increased QALY compared with the comparator general practice base case. In order to determine whether the increased benefit in these three strategies is worth the increased cost the willingness to pay thresholds are then represented in the cost effectiveness plane (Figure 5.5) by the £30,000 and £20,000/QALY lines. The needle exchange strategy remains cost effective at the £20,000 threshold and both the pharmacies and substance misuse strategies are approaching cost effectiveness at the £30,000/QALY threshold.

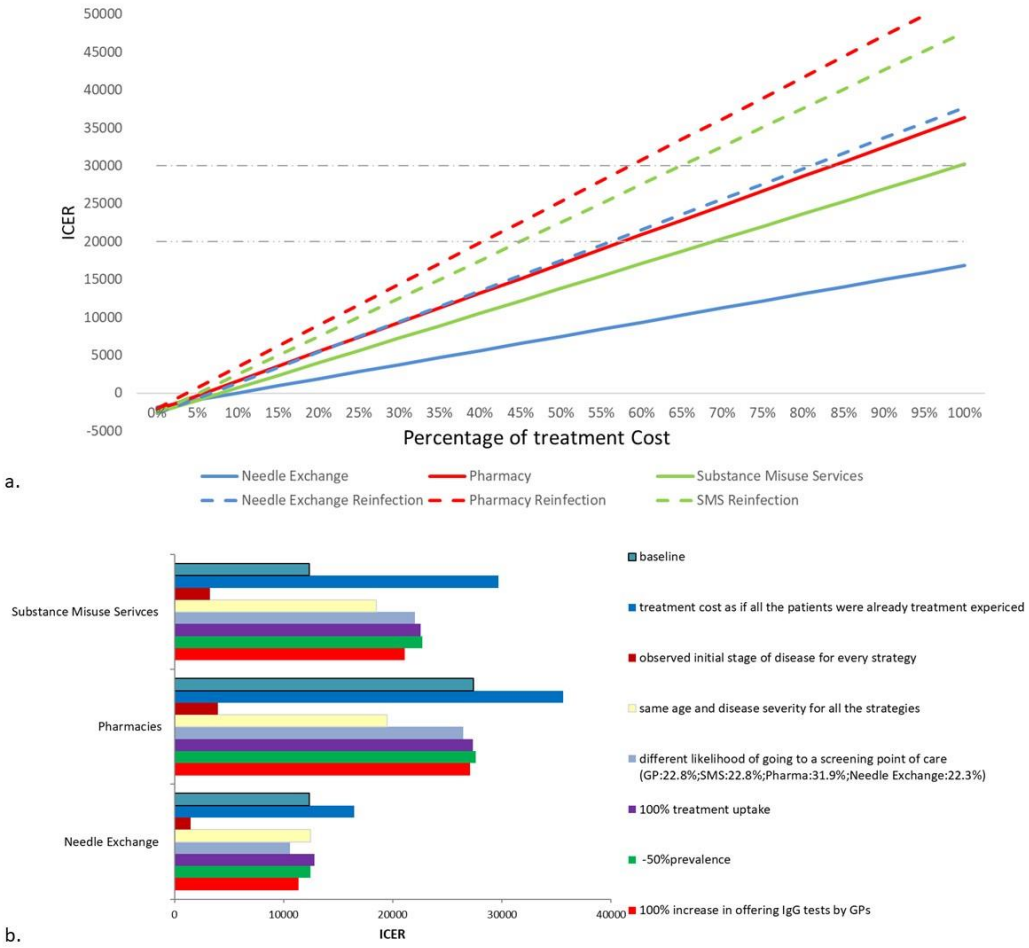


Figure 5.6a. Line chart illustrating the respective ICER for the 3 PWID sub group strategies and their equivalent re-infection scenario ICERs (delineated by the broken lines). Percentage of treatment cost is along the X axis. This graph demonstrates at what percentage of the published list price of the HCV treatment regimens each strategy would be cost effective for the £20,000/QALY and 30,000/QALY WTP thresholds. Needle exchange scenario is cost effective even at the full list price, whereas the pharmacy strategy is only cost effective at the £20,000/QALY WTP threshold at 60% of the list price. Once the reinfection scenarios are included, all would need at reduction between 40-60% of the list price in order to be cost effective at the £20,000/QALY WTP threshold. In Scotland, the Scottish Medicines Consortium was able to negotiate a confidential reduction of the list price of HCV medications, which would render all of the scenarios cost effective.

5.6b. The different sensitivity analyses comparing the baseline scenarios for the 3 PWID sub groups; Increased treatment costs due to the individuals being treatment experienced leading to an increased ICER. The same initial disease stage i.e. degree of fibrosis for each of the pathways leading to a reduction in ICER for SMS and Pharmacy strategies having had a more advanced fibrosis stage initially. The same age on entering the models resulting in an increase in ICER for the SMS and Pharmacy strategies. The likelihood of going to a screening point of care resulting in an increase in ICER for SMS and a minor reduction in ICER for the Pharmacy and Needle exchange strategies.

An increase to 100% treatment uptake results in an increase in ICER for SMS, but little appreciable difference for the Pharmacy and Needle exchange strategies. Reducing the HCV prevalence to 50% results in an increase in ICER for SMS, but little appreciable difference for the Pharmacy and Needle exchange strategies. A 100% increase in GPs offering HCV antibody testing results in an increase in ICER for SMS, but little appreciable difference for the Pharmacy and Needle exchange strategies.

5.4.4 Cost effectiveness acceptability curves

The following cost effectiveness acceptability curves are a graphical representation of the uncertainty associated with the results of the economic evaluation. They summarise the probability of a strategy being cost effective at different willingness to pay thresholds. Each simulated ICER value is compared with a ceiling ratio (willingness to pay threshold), and the proportion of simulated values that are acceptable at that ratio is calculated. This is repeated for each possible value of the willingness to pay threshold. The proportion of simulated ICER values that are acceptable will be different for each willingness to pay.(298) A cost effectiveness acceptability curve plots these together, as shown in the following Figures 5.7-5.10.

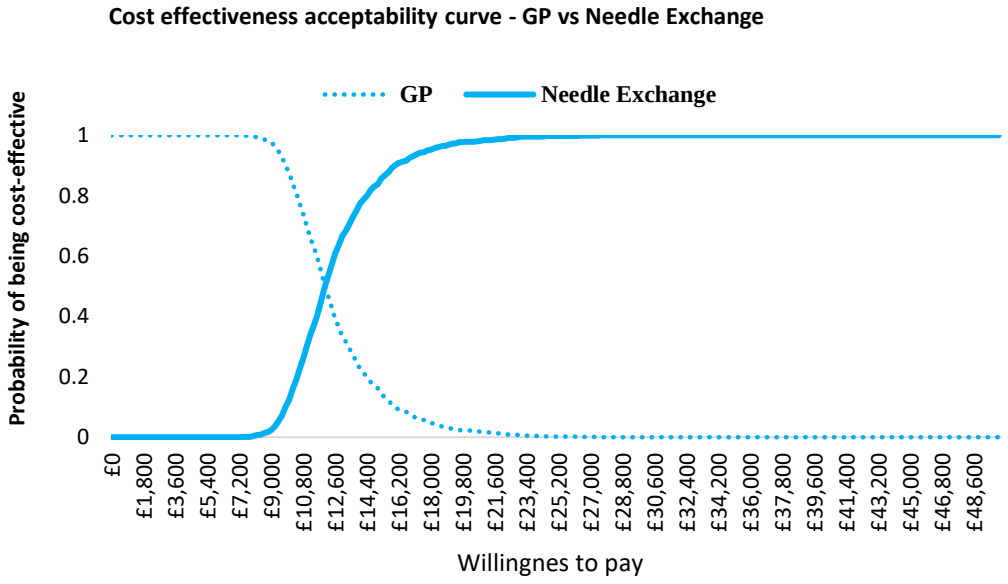


Figure 5.7. Cost effectiveness acceptability curve – GP versus Needle exchange.

Figure 5.7. demonstrates that at a lower willingness to pay threshold the GP strategy high has higher probability of bring cost-effective. As the willingness to pay increases the needle exchange scenario becomes more cost effective than the GP strategy. At a willingness to pay of £20,000 the needle exchange strategy is the most cost effective. As the GP strategy requires little investment, it is cost effective at lower WTP thresholds, however an increase in investment makes the needle exchange strategy cost effective due to the increased HCV detection rate.

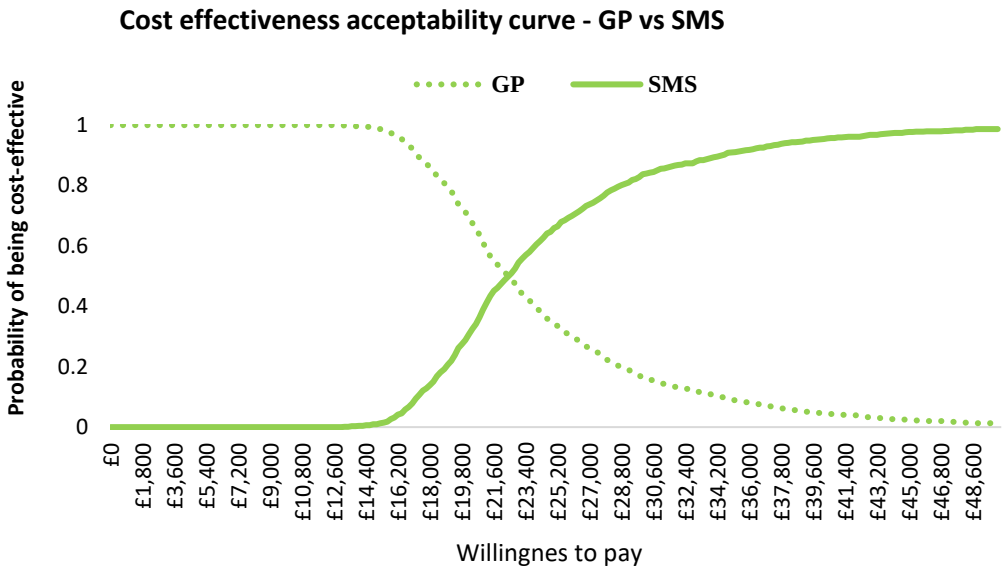


Figure 5.8.Cost effectiveness acceptability curve – GP versus SMS

Figure 5.8. demonstrates that at a lower willingness to pay threshold the GP strategy high has higher probability of bring cost-effective. As the willingness to pay increases the SMS scenario becomes more cost effective than the GP strategy. At a willingness to pay of £20,000 the GP strategy remains the most cost effective. The SMS strategy approaches but never reaches a probability of 1.0 as being cost effective. We have already seen that the SMS scenario is less cost effective in the long term due to the relatively low rate of conversion to treatment compared with the other PWID sub groups.

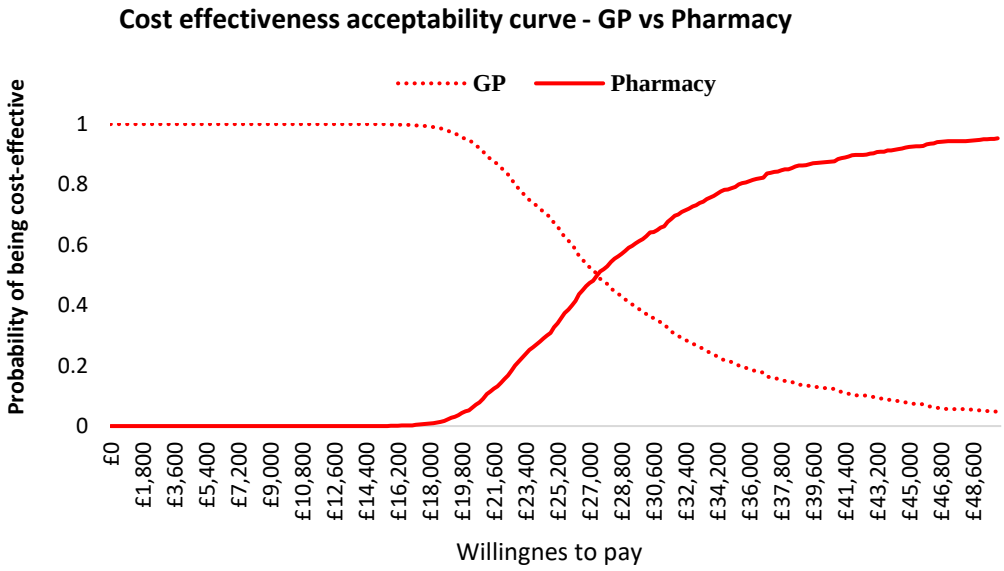


Figure 5.9. Cost effectiveness acceptability curve – GP versus Pharmacy

This diagram demonstrates that at a lower willingness to pay threshold the GP strategy high has higher probability of bring cost-effective. As the willingness to pay increases the pharmacy strategy becomes more cost effective than the GP strategy. At a willingness to pay of £20,000 the GP strategy remains the most cost effective. The pharmacy strategy approaches but never reaches a probability of 1.0 as being cost effective. The pharmacy strategy was the most expensive of the PWID sub groups and therefore is likely to be less cost effective.

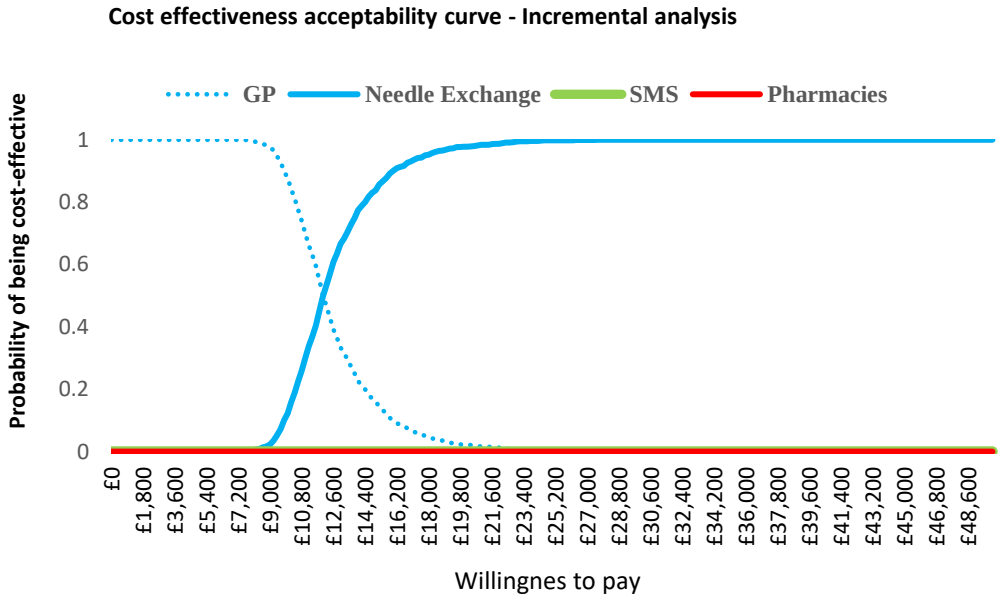


Figure 5.10. Cost effectiveness acceptability curve – incremental analysis. GP versus Needle exchange versus SMS versus Pharmacy.

Figure 5.10. demonstrates the cost effectiveness curves of the three PWID subgroups. As seen in all the individual comparisons the GP strategy is the most cost effective at a lower willingness to pay threshold. The needle exchange strategy becomes more cost effective at approximately £12,500. The SMS and pharmacy strategies are shown to be dominated on this graph, as the cost is equivalent or more than the needle exchange strategy, but will less benefit.

If only one strategy could be used for HCV case detection and treatment amongst the PWID sub-groups, the GP strategy would be most effective at a lower WTP threshold and the needle exchange would be cost effective with a higher WTP threshold.

5.5 DISCUSSION

In this study we compared data from multiple current progressive screening strategies to shed light on how current screening policies are performing in tackling HCV from a health economic perspective. We found that novel strategies for targeting and screening PWID populations are likely to be cost-effective compared to current standard care.

Short-term results show that the most cost-effective approach to detect HCV in current PWID patients is testing at SMS, followed by needle exchange services. Indeed, these strategies, which rely on mostly non-clinician personnel are typically less costly. Although in the long term the higher number of people screened and detected incurs greater costs, screening current PWID at needle exchange remains cost-effective. The difference in cost-effectiveness across strategies between short and lifetime horizon is mainly due to liver fibrosis stage, which is accounted for in the long term. This suggests that testing at an older age, which is more likely in strategies involving SMS and Pharmacies, detects disease at more advanced stages and, therefore, with more advanced liver damage and lower quality of life after treatment. Screening intensification at GPs for current PWID would increase both the number of people detected, but also the overall cost of the strategy in the short-term. Even if more people were screened, the average older age at screening would increase the cost of treatment more than the potential gain in QALY in the long term (see long term sensitivity analysis, Figure 5.6b. Nevertheless, age is not the sole driver of the cost-effectiveness results in the lifetime model: when age is equalised across different strategies, standard screening at the GPs remains the least effective alternative due to the lower detection rate coming from the short-term model (see sensitivity analysis).

In the reinfection scenario, only screening at needle exchange centres was below £30,000/QALY. However, as already mentioned, this is mainly due to our data source which records higher reinfection rates than the rest of the literature.(41) Moreover, the reinfection model was designed to consider only treated individuals who could be re-infected if sharing injecting equipment with those who are infected, reducing the cost-effectiveness in the model. Given the model's static framework, it did not consider that augmenting the number of treated individuals in a population would reduce the pool of potential HCV positive people spreading the infection. A possible change in the propensity of sharing needles after treatment was not taken into account either. In a dynamic scenario, both these two last possibilities could potentially counterbalance the previous. We suggest that the outcome of our reinfection scenario should be interpreted

as an extremely conservative scenario. It is reasonable to expect that with these policies the overall HCV prevalence within the PWID population will decrease. Our results show that changes in prevalence would impact mainly short-term dynamics, but not affect long term conclusions (Figure 5.6b).

With respect to the PWID strategies, they all involve the same macro population and belong to the same model of care piloted and performed in Tayside. However, it is reasonable to expect that different venues could identify different subpopulations, which do not necessary overlap. For instance, the regular client of a pharmacy is likely to have a different profile than the needle exchange frequenter (same reasoning for SMS). Unfortunately, the lack of data, in particular regarding the PWID access to differing points of care, means that we were unable to track the different clients' profile. Thus, we analysed the PWID population as if it was homogeneous across strategies. The result is that screening at Needle Exchange is the most cost-effective option. Nevertheless, there will likely be challenges for the implementation of screening through a single strategy, such as capacity constraints at a single point of care, individuals' preferences or the availability of a specific test setting, and hence complementary strategies should be considered. To allow for more comprehensive policy suggestions based on observational evidence, governments should invest in data collection across local PWID community services (e.g. to map different client profiles to estimate the weight of every strategy within the model of care) to provide stronger evidence of every strategy's characteristics at local levels. We believe that policymakers should run central policies which include a mix of the most cost-effective approaches reflecting the availability of specific points of care and the prevalence of user profile in a specific area.

The sensitivity analysis of the treatment listed price shows that the main driver for the cost-effectiveness analysis is the treatment cost. In Scotland and many other regions and countries there is a nationally published list price for HCV medications, and from these there are confidential negotiations that reduce the costs. Therefore, we believe that our analyses with discounted drug prices on the official listed price by the UK British National Formulary (BNF 2019) are a more realistic representation of the costs in clinical practice. In this regard, a discount of 24% of the treatment listed price makes all the strategies in each scenario cost-effective at a £20,000 WTP threshold. For the re-infection scenario, a discount equal to or greater than 48% makes all strategies cost-effective.

Given the importance of treatment price in our analyses, in countries where the actual HCV treatment price is still high for the health care providers, further negotiation with the industry is crucial to reach sustainable cost-effectiveness strategies. In contexts where this interaction between stakeholders already happens, such as in Scotland, the focus of policymakers should be more on stratagems to detect individuals at early stage of disease, improving engagement within the cascade of care and limiting reinfection.

5.5.1 Strengths and limitations

This study sought to evaluate the cost-effectiveness of the current and potential new approaches to tackle HCV detection. Findings confirm that alternative strategies to detect individuals with HCV can be highly cost-effective. Specifically, approaches that detect at earlier stages of infection (which is likely to mean younger individuals) and higher number of individuals are expected to be the most cost-effective. However, there are also several limitations to our study.

Firstly, the representativeness of this model of care is unclear as it is based on a small sample of potential screening locations and on a sample of the drug-user population in the Tayside area. Moreover, this is a retrospective study using for the first time a multitude of strategies from a relatively small area. Even if these findings can provide insights to policy makers, results may have a local perspective. For national recommendations, prospective cohort studies need to be implemented, which could overcome the potential bias affecting the selection of our counterfactual. In this regard, given the need to reflect regional differences, central policies should be tailored on evidence from a local level.

Secondly, the lack of data on a few key parameters, such as the proportion of people visiting any point of care that are tested, led to the use of secondary data sources. Unfortunately, there is currently limited data available on some community services. Therefore, our HCV test acceptance/offer rate was based on expert and clinical opinions of personnel working within the services described in our study. However, we tried to address this by testing assumptions in one-way sensitivity analyses and using wide uncertainty in the PSA.

Thirdly, the reinfection scenario analysis does not take into account a herd immunity factor. Indeed, in small areas, there should be a decrease in incidence since treating people reduces the number of infected people able to transmit the infection. It should be noted that usually the reinfection rate is not modelled in screening models and, when it

is, it can be very sensitive to authors' assumptions.(297) We decided to include the prospect of reinfection in a scenario analysis in a static setting. As already mentioned, our reinfection model should be interpreted as an extremely conservative scenario.

Lastly, the model is static and, beyond reinfection, it does not allow for a migration from the PWID status. However, the lack of data regarding this potential transition, retrospective cohorts referring to heterogenous samples, and the desire to provide a snapshot of an ongoing policy in its first years of operation led us to build a static model in line with most of the recent literature on cost-effectiveness of HCV treatment(299) and screening.(297) Since the static nature of the analysis does not allow direct assessment of the cost-effectiveness of the strategies over time, a plausible decrease in prevalence due to these policies was considered in the sensitivity analysis.

This study presents a comprehensive analysis of a regional HCV screening strategy in the UK and provides insights that need to be addressed to ensure cost-effective decision-making at a national level. For instance, treatment cost has a crucial role in determining whether screening strategies targeting a PWID population are likely to be cost-effective. Overall, the cost-effectiveness of a strategy increases in the short-term with the engagement in the cascade of care, and in the long term with early diagnosis (associated with a point of care screening at younger ages) and treatment cost. In Tayside, screening at all points of care seems to optimise these requirements. Our results found that screening at Needle exchange was likely to be the most cost-effective strategy. Indeed, with the application of a plausible discount to the treatment price, the study demonstrates how all the screening strategies could be considered highly cost-effective when compared to the current standard care in the UK. Whilst these results are specific to the Tayside region, the study highlights that there is a need for further investigation to understand how these strategies would perform elsewhere. Governments wishing to achieve the 2030 HCV elimination target must shape central policies based on the effectiveness and cost-effectiveness of different screening strategies at a sub-regional level. They should, therefore, invest in further research to enable extensive data collection across regions thus allowing for more comprehensive, tailored and cost-effective decision-making.

CHAPTER 6 – DISCUSSION

The development and availability of DAAs has revolutionised the care for people with hepatitis C.(300) The opportunity this offers to eliminate hepatitis C as a global health threat was recognised and advocated for by the World Health Organisation.(40) However there are still significant barriers to overcome to enable people with HCV to be treated. These include, but are not limited to, access to treatment, stigma and funding.(154,178,246) This thesis has explored the strategies required to find and diagnose all those infected with HCV in the Tayside Health Board. This has involved reviewing the relevant literature by way of a scoping review to identify the aspects of HCV models of care that promote diagnosis, treatment and cure, and also to analyse the efficacy of community and primary care based HCV testing and treatment services using direct acting antivirals. By examining and analysing the different testing and treatment pathways within NHS Tayside with a view to establishing the most effective and cost effective pathways we have also gained insights on how to engage different populations to ensure equity of access.

6.1.1 HCV diagnosis and treatment is feasible for all infected

The scoping review broadly explored models of care that have been developed to effectively deliver HCV care in the DAA era. It is not enough to solely have an effective treatment for HCV. Achieving sustained virologic for a population will require various health system challenges to be addressed.(301) This includes aspects such as access, coverage, quality of services and safety. Different countries have different health systems and challenges to overcome.(13,54) The availability of DAAs has triggered the development of an array of models of care globally which are tailored to meet the needs of different populations. Lessons can be learnt from these differences and implemented elsewhere. Successful models of care needed to be specific, scalable, integrated, patient centred and affordable. In the DAA era, effective MoCs tend to be those with co-located services e.g. opiate substitution services or needle exchanges, or a combination of locally delivered services in various environments which are well co-ordinated and strongly linked. Multidisciplinary team working has been shown to be beneficial especially when care is delivered by frontline workers who are familiar to the clients e.g. addictions workers or OST pharmacists. Long term development and implementation of these strategies requires policymakers and researchers to establish

cost-effective, easily implemented strategies that incorporate interdisciplinary and multi-facility communication with input from healthcare providers, affected populations and other key stakeholders. (301)

The UK health system is split between primary, or community based care and secondary or hospital based care. Historically HCV treatment has always been delivered in the secondary care environment. The ease and safety of DAA treatment lends itself to simplified models of care and possibility of community based treatment. In chapter three, the literature review evaluating community and primary care based pathways using DAAs to treat HCV infection looked more closely at community measures and interventions to increase diagnosis, retention into care and treatment of people with hepatitis C.(219)

Decentralised HCV care is not only possible but can improve access to care and yield SVR rates equivalent to those attained at specialist centres. At the time of the literature review there were relatively few studies exploring the efficacy of community based HCV care, but there has further studies since. An Iranian study with an integrated on-site community-based HCV care model with HCV care including HCV testing and treatment was shown to successfully deliver care outside of hospitals.(302) An American study showed intention to treat SVR rates of 88% for individuals managed in co-located primary care clinics and addiction services with one hospital based primary care clinic and a second primary care clinic providing OST.(303) A cost effectiveness analysis in Australia reported significant cost savings with community based treatment, largely due to increased retention in care.(304)

Whilst many countries and health systems have embraced decentralised care with simplified and outreach models of care, there has not been any randomised controlled trials to compare the efficacy. Systematic reviews and meta-analyses such as in Chapter 3 appear to show non inferiority of community based services to conventional models of care, however outcomes such as treatment uptake and SVR12 in these pooled studies rarely reaches the rates seen in the original drug trials.(230,232,234) There is a concern that publication bias has driven this narrative that decentralised models of care are the most appropriate models of care with the best chance of delivering HCV eradication.

To counter this we should look at the countries that have embraced these novel pathways, such as Iceland, Australia and Scotland.(305–307) All three have made

significant progress towards HCV elimination and in fact Iceland has been able to meet WHO targets ahead of time.(305)

Given how advanced the UK is towards reaching elimination targets, there seems little value to conducting large scale randomised controlled trials comparing models of care. Various studies have shown that there can be successful rigorous clinical trials carried out in populations previously felt to be too unstable and erratic such as PWIDs who are still actively injecting, so patient concordance is not necessarily a limitation.(139,140,308) What has been clear from my research is that the population of people chronically infected with HCV is very heterogeneous even within our health board, let along throughout the rest of the UK and the world. In order to reach elimination targets, I believe that different health systems need assess their individual population needs and plan services accordingly.

6.1.2 Combination of pathways is preferred over prioritising the most effective

Whilst the availability of DAAs has allowed health systems to develop new pathways and services, it is important to reflect on the pre-existing pathways. When working toward the WHO targets for HCV elimination, a thorough understanding of the diagnostic and therapeutic work to date is needed. What is clear is that having a range of different pathways based in both the community and in hospital settings allows different populations to access and engage in treatment. Having pathways targeting those most at risk of HCV, people who inject drugs, allows those most at risk to be treated. It is also treatment as prevention in action.(305,309) By curing people who are at most risk of passing HCV onto others, you prevent possible future transmission and harm.

The declining rate of positive PCR tests seen in Chapter 4 is an early indication that this combination of strategies is yielding results and is enabling Tayside in Scotland to strive towards its elimination target.

The health economics of these pathways demonstrated some interesting conclusions. The two different strategies that were felt to be cost effective were so widely different in terms of costing, patient population and intensity. With the general practice population being relatively resource light, serving a large population and therefore detecting a significant number of infections (albeit at a low positivity rate), whilst the needle exchange pathway was resource heavy, costlier, detected HCV positive patients at an earlier stage in their disease and had a high positive rate of testing. Needle exchange

services provided a 7.45- fold increase in detecting positive individuals and an incremental cost per QALY gained against current practice, with a net monetary benefit of £163,827. However it is clear, especially when aiming to detect and treat a large proportion of the patient population that both strategies as well as others are needed to reach the goal of HCV elimination.

A take home point from the research presented in chapters 4 and 5, is that no single pathway is enough to provide adequate HCV diagnosis and treatment at a population level. No population is homogenous, so the pathways for HCV care need to reflect the different needs of those within the affected group. Both analysing the pathways themselves and the relative costs of the pathways has demonstrated that each pathway contributes to the whole. Pathways that are costlier and resource heavy are often those that serve the subsets of the population who are more difficult to engage and won't be reached using conventional pathways e.g. the needle exchange pathway.

6.1.3 Multiple re-access points within the pathways is needed to minimise lost-to-follow up

There was a degree of overlap in many of the pathways. For example, a patient with a history of injecting drug use could access HCV care via the needle exchange pathway, addictions services or via pharmacies. These multiple access points are vital for retaining or re-engaging people in care. Each of the cascades of care show a drop off between stages from diagnosis to treatment to confirmation of cure. Having multiple re-access points with information sharing between sites allows individuals to be retained in care and reduce those lost to follow up.

6.1.4 Multidisciplinary teams and linked IT systems can help with coordination between pathways

Tayside benefits from a single health board and a single multidisciplinary team overseeing Hepatitis C care for the locality. Strong links with the virology lab, a robust clinical data base and good relationships with key community-based partners such as pharmacists and addictions workers is essential to provide this joined up care between different access points.

Advances in recent years both in testing methods and in the availability of DAAs mean that it has never been easier to test for or treat Hepatitis C infection. Dried blood spot testing, oral fluid testing and point of care testing devices mean that HCV testing is no longer restricted to the hospital setting or general practices with access to the hospital-based laboratory system. This thesis has described the scope of HCV pathways

currently in practice in non-traditional settings such as mobile vans, needle exchange centres and pharmacies. Decentralised and accessible care is possible via outreach into the community and hard to reach populations is both possible and practically achievable.

Analysing the cascade of care for HCV treatment consistently shows drop off in between the key stages in the cascade. Pathways which are simplified and streamlined help to mitigate this attrition. A recent systematic review analysed 148 studies and found that interventions that simplified HCV testing, including dried blood spot testing, point-of-care antibody testing, reflex RNA testing, and opt-out screening, significantly improved testing outcomes compared with a comparator or control.(310)

DAA therapy has revolutionised the whole treatment landscape for people with Hepatitis C infection. The clear benefits of high efficacy, low side effect burden, few interactions, all oral medications and monitoring free regimes has enabled many more people to receive treatment for their HCV, who would previously have been ineligible for PEGylated interferon and ribavirin due to contraindications such as comorbidities or advanced disease.(187)

We therefore have the tools needed to diagnose and treat people, quickly and easily.

A study in March 2021 showed that only 11 of 45 countries studied are on track to achieve elimination by 2030. These countries include Australia, Canada, France, Germany, Iceland, Italy, Japan, Spain, Sweden, Switzerland and the United Kingdom. All these countries are high income and have the resources to make Hepatitis C care a health priority. It is vital that the remaining countries expand screening and treatment in order to meet the elimination targets.(311)

6.1.5 Stigma and poor ability to access healthcare remains a big issue

People living with hepatitis C experience stigma both in their personal lives and when trying to access healthcare. The World Hepatitis Alliance recognised that stigma associated with HCV was a significant factor in patients accessing testing, treatment and HCV care.(312) A US study found 95.5% their participants with a lived experience of HCV encountered some degree of disease associated stigma.(313)

In this thesis we have explored how a defined region in Scotland has approached HCV diagnosis and treatment. Naturally the majority of our efforts were directed towards engaging PWIDs in out pathways as they represent both being the population at highest

risk of contracting and transmitting HCV and of being difficult to engage as previously discussed. However there remain some difficult to reach populations, which may not be easily reached or served by the existing pathways. Whilst we can be relatively confident that the existing pathways are effective at reaching the majority of the population, and indeed in meeting the WHO targets, there is a small but significant group of people who are still to be reached. A known sub group of PWIDs that are difficult to reach are the female population. In chapter 4 there was a marked discrepancy in the proportion of females being tested for HCV, with women making up only 30% of those tested in some pathways. Whilst it is known that male PWIDs outnumber women who inject drugs (WWID) it is recognised that WWID are an especially vulnerable population due to several factors, including mental health problems, physical and sexual violence, sex work, stigma and discrimination.(314,315) In addition, they have an increased risk of acquiring HCV and other blood-borne and sexually transmitted infections due to certain risky practices such as sharing injection equipment or being injected by a peer compared to their male counterparts.(316,317) Factors linked to social network or differences in access to care also lead to higher incidences of HCV infection in WWIDs.

A systematic review showed that females were more likely to be HCV positive in comparison to males at a pooled HCV incidence rate of 20.36 (95% CI: 13.86, 29.90) for females and 15.20 (95% CI: 10.52, 21.97) for males.(313) A study also showed that HCV associated stigma was likely to reduce the probability of WWIDs undergoing liver disease staging or accessing HCV treatment services.(318) A study in Seattle showed that WWID had 64% lower odds of receiving HCV treatment and were more likely to be lost along the cascade of care, with lower rates of HCV testing, confirmatory HCV testing, awareness of positive diagnosis, treatment uptake and SVR.(315)

People with a lived experience of being homeless or in unstable housing are at increased risk of HCV as there is often an overlap with substance use.(319) It is estimated between 9.8-52.5% of homeless individuals are HCV positive.(320) Being homeless is also associated with a risk of unsafe injecting practices.(321) HCV treatment is often not prioritised as there are other more urgent survival concerns. Poor knowledge of HCV, distrust in healthcare, substance use and mental illness are some of the potential barriers to care.(322) Homelessness (AOR 0.39, 0.19−0.80) was associated with a 61 % lower odds of having received treatment with DAAs.(320)

Recent estimates from Public Health England have suggested that of the 81,000 still chronically infected with HCV, 21,600 are current or recent PWID, nearly twice that

number, 50,200, have a history of injecting drug use and 8,700 have no history of injecting. Whilst modelling is imprecise it is assumed that the remaining numbers are people with a history of injecting drug use with no contacts in drug treatment services, prisons or other healthcare settings. Their infection may only come to light when they present with end stage liver failure or hepatocellular carcinoma.(323) Finding this unspecified group with no clear means of identifying their risk remains a big challenge.

6.2 CONCLUSION

Irrespective of WHO elimination targets, every individual with hepatitis C should be given the opportunity to engage in care, receive treatment and attain SVR. It is clear that a "one size fits all" diagnostic/treatment pathway will not come close to achieving that aim.

The pathways examined in this thesis developed organically in response to different health system and patient needs over a 20-year period. A strength of this diversity in pathways is the access to key populations such as PWID, those on OST, in prisons and migrant populations. Each pathway has been shown to be effective in its own right and together they cover the majority of the HCV population in Tayside and enable attainment of the Scottish Government and WHO targets.

These targets do not account for one hundred percent of people chronically infected with hepatitis C and it is important that future work looks to reach the hard to reach and under-served populations including female PWIDs and those with a lived experience of homelessness.

As the prevalence of HCV continues to fall due to increased treatment uptake, the cost effectiveness of the various strategies in their current iteration will reduce. In order to keep the strategies cost effective, there will need to be further negotiation with the drug companies to reduce the list price of their treatments. It is vital that once HCV elimination is reached, that there is ongoing HCV screening and treatment of known cases to prevent any epidemics. Ensuring that testing and treatment remains cost effective is vital to this.

6.3 FURTHER WORK

Integrating newer diagnostic technologies such as point-of-care tests which can provide results in 60 to 90 minutes, into existing pathways may improve the scalability and therefore access to some of the community based pathways. Providing a diagnosis in the course of a single visit has the potential to streamline the cascade of care and reduce drop off of patients between testing positive for HCV and initiating treatment.

The development of targeted interventions and pathways for female PWIDs and the homeless population chronically infected with HCV.

Examining the health economics of different diagnostic tests may determine whether this approach would be feasible. Being able to scale up HCV testing in key populations such as PWID will make attaining WHO elimination targets more feasible.

APPENDICES

APPENDIX 1/CHAPTER 2: WE KNOW DAAS WORK, SO NOW WHAT?

SIMPLIFYING MODELS OF CARE TO ENHANCE THE HEPATITIS C CASCADE

JIM Review

doi: 10.1111/joim.12972

We know DAAs work, so now what? Simplifying models of care to enhance the hepatitis C cascade

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Abstract. Lazarus JV, Pericàs JM, Picchio C, Cernosa J, Hoekstra M, Luhmann N, Maticic M, Read P, Robinson EM, Dillon JF (Barcelona Institute for Global Health (ISGlobal), Barcelona; Biomedical Research Institute Dr Pifarré Foundation, Lleida, Spain; University Medical Centre Ljubljana, Ljubljana, Slovenia; Médecins du Monde France, Paris, France; University of Ljubljana, Ljubljana, Slovenia; Kirketon Road Centre, Sydney, NSW, Australia; University of Dundee, Dundee, UK). We know DAAs work, so now what? Simplifying models of care to enhance the hepatitis C cascade. *J Intern Med* 2019; **286**: 503–525.

Globally, some 71 million people are chronically infected with hepatitis C virus (HCV). Marginalized populations, particularly people who inject drugs (PWID), have low testing, linkage to care and treatment rates for HCV. Several models of care (MoCs) and service delivery interventions have the potential to improve outcomes across the HCV cascade of care, but much of the relevant research was carried out when interferon-based treatment was the standard of care. Often it was not practical to scale-up these earlier models and interventions because the clinical care needs of patients taking interferon-based regimens imposed too much of a financial and human resource burden on health systems. Despite the adoption of highly effective, all-oral direct-acting antiviral (DAA) therapies in recent years, approaches to HCV testing and treatment have evolved slowly and often remain rooted in earlier paradigms. The effectiveness of DAAs allows for simpler approaches and has encouraged countries where the drugs are widely available to set their sights on the ambitious World Health Organization (WHO) HCV elimination targets. Since a large proportion of chronically HCV-infected people are not currently accessing treatment, there is an urgent need to identify and implement existing simplified MoCs that speak to specific populations' needs. This article aims to: (i) review the evidence on MoCs for HCV; and (ii) distil the findings into recommendations for how stakeholders can simplify the path taken by chronically HCV-infected individuals from testing to cure and subsequent care and monitoring.

Keywords: health systems, hepatitis C, models of care, people who inject drugs.

Introduction

Viral hepatitis is a leading cause of mortality globally, with the hepatitis C virus (HCV) responsible for an estimated 350 000 deaths and 9.7 million disability-adjusted life years in 2016 [1]. The World Health Organization (WHO) estimates that 80% of the people living with HCV have not been diagnosed [2]. Although HCV became a highly curable disease with the introduction of all-oral direct-acting antiviral agents (DAAs) in 2013, most countries have been slow to provide unrestricted access to these life-saving drugs [3, 4] and thus decrease the disease's spread [5] and reduce its prevalence.

Given the gravity of the epidemic and the effectiveness of the cure, in 2016 WHO made the elimination of viral hepatitis as a public health threat by 2030 the overriding goal of its first global health sector strategy on viral hepatitis [6]. The strategy stresses equity and leaving no affected populations behind in its ambitious targets of achieving an 80% reduction in HCV incidence and a 65% reduction in HCV mortality by

2030, as exemplified in its prevention target to increase the average number of sterile needles and syringes distributed to people who inject drugs (PWID) from 20 to 300 annually. Today, the unsafe injection of illicit drugs is a main driver of the global HCV epidemic [2, 7]. It is estimated that 15.6 million people injected drugs globally in 2015 [8] and that 6.1 million of them were living with HCV [9]. Globally, if the risk of HCV transmission associated with sharing unsafe injecting equipment amongst people who currently inject drugs was removed, 43% of incident HCV cases would be prevented between 2018 and 2030 [10].

Evidence shows that in many settings, a relatively modest increase in treatment rates can enable a country that already provides good access to DAAs to achieve the WHO strategy's targets. A 2017 study modelling the HCV epidemic in Switzerland concluded that an annual treatment uptake of 10% would eliminate the disease by 2030 in PWID [11]. A second study made comparable projections for other European countries, but also found that some countries would need to scale-up opioid substitution therapy (OST) and needle and syringe exchange programmes (NSP) interventions to reduce chronic HCV prevalence [12]. Yet in most countries of the world, particularly low- and middle-income countries, access to DAAs and harm reduction services remains extremely limited [13–15], and achieving the WHO targets will require major expansion of both forms of access [16]. That is because besides DAA therapy, which enables a sustained virologic response (SVR), the most effective form of HCV prevention for PWID is harm reduction, including OST, NSPs, and supervised injecting centres.

In reality, global elimination of HCV will require major increases in services for all affected populations along the entire cascade of care, including testing, linkage to care, retention in care, treatment, chronic care and prevention of primary infection and reinfection.

The model of care (MoC): a tool for increasing treatment coverage

In 2013, Bruggmann and Litwin found that, whilst HCV treatment had been successfully delivered to many people, through various multidisciplinary models, few treatment settings were adapted to the needs of PWID [17]. PWID who have been treated, for example with OST, are often those who are most motivated to seek out health services, whilst those who are more marginalized find access difficult. What is needed is a *model of care* (MoC) for each setting that specifically targets PWID and other marginalized high-burden populations, such as migrants or the homeless, whilst taking advantage of the characteristics of DAA therapy.

In this review, we use MoC to signify a setting-specific framework that outlines how to provide the relevant services and interventions throughout the HCV cascade of care. An MoC should address four key questions: *where* to provide the services, *what* services to provide, *who* to provide them and *how* to integrate them (Box 1).

The models of HCV care were selected by reviewing the peer-reviewed literature in PubMed/MEDLINE since 2014, references from relevant articles, and abstracts from The Liver Meeting of the American Association for the Study of Liver Diseases (AASLD 2018); European Association for the Study of the Liver International Liver Congress (EASL ILC 2018 and 2019), and the International Network on Hepatitis in Substance Users (2018) by three independent researchers (CP, JC, EMR), who identified 71 studies that reported studies of new models of care to address HCV that had measurable outcomes. Table 1 presents selected case studies by country and population addressed, Table 2 highlights the main populations addressed, Table 3 describes setting, and Table 4 categorizes the provider type. Figure 1 presents the stages of the cascade of care addressed (awareness and prevention, testing and diagnosis, linkage to care, access to medicine, and patient monitoring and evaluation) whilst Table S1 summarizes measurable outcomes, including SVR where available. The search words were as follows:

1 PubMed search string ((HCV[All Fields] OR 'hepatitis c'[MeSH Terms] OR 'hepatitis c'[All Fields]

Box. Selection of new models of hepatitis C care presented in this review

- Nurse-led
- Telemedicine
- Multidisciplinary (including nonmedical personnel in the core team, for example social workers, case managers or psychologists)
- Pharmacist-led
- Mobile van units

Table 1. *Models of care for hepatitis C in people who inject drugs – some representative cases*

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
1. Read *et al.* [77] Kirketon Road Centre (KRC), Sydney, Australia	Primary health care facility targeting PWID, sex workers and 'at-risk' young people	Viral hepatitis testing, DAA therapy, hepatitis A and B vaccination, 'healthy liver clinic' with specialized hepatitis service; sexual health services; drug and alcohol counselling, assessment and referrals; crisis intervention; housing, social service and welfare assistance; methadone access and case management; NSP; street van and bus outreach; HIV testing and counselling; general health services	GPs, nurses, social workers	Integrated primary health care model offering anonymous services to risk populations. DAAs can be provided through a community pharmacy, with a follow-up phone call to confirm treatment initiation, standard of care pathology. Enhanced adherence support includes phone calls or other contact at least weekly, flexible directly observed dispensing of the medications, with or without OST, linkage to partner organizations, DAA delivery to prisons, police cells, psychiatric units and general hospital wards	242 PWID were included, 74% recent or current injectors, 44% enrolled in OST. 79 (32%) of clients chose enhanced daily or weekly dosing support options. Enhanced support was associated with homelessness, daily injecting, Aboriginality, mental health co-morbidity and poly-drug use (all $P < 0.001$). Overall adherence was 86%, and 92% of patients missed one or more doses (median 10, IQR 4-24). The study confirms that PWID can be successfully treated for HCV in a real-world setting using an integrated primary healthcare model and demonstrates the feasibility of scaling DAA therapy up in high-risk PWID populations

Table 1 (*Continued*)

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
2. Mason *et al.* [86] Toronto Community Hep C Program (TCHCP), Toronto, Canada	A partnership between three community health centres to provide underserved populations with low-threshold access to HCV care	Treatment assessment, DAA therapy, weekly pre- and post-treatment questionnaires, follow-up	Nurses, nurse practitioners, family physicians	Integrated multidisciplinary specialist support on site	74 PWID initiated DAA therapy, achieving high adherence and SVR with appropriate support. Participants housing status and income increased significantly during the study
3. Trooskin *et al.* [87] Do One Thing, Philadelphia, United States	Community-based programme in a medically underserved neighbourhood with high rates of HCV and HIV	Social marketing campaign, door-to-door outreach, rapid HIV and HCV screening in a mobile medical unit, immediate phlebotomy for confirmatory testing of reactive antibody tests, facilitation of client enrolment in health insurance, linkage to care and retention in care	Trained HCV test counsellors, phlebotomists, patient navigators, social workers; linkage to primary care physicians and HCV subspecialists	Developed and coordinated a local hospital and local university	Amongst 1301 people screened, 2.8% were chronically infected, half of whom were newly diagnosed. The biggest barrier to retention in care was obtaining referrals for subspecialty providers due to a lack of insurance. Some subjects started treatment, whilst many who were eligible were awaiting approval from insurance companies. This study illustrates how a good model of care can adapt to local circumstances
4. SACC, 2017*; Linnet *et al.* [90] Shared Addiction	12 drug counselling and treatment centres; 1	Hepatitis and HIV counselling and testing; transient	GPs, hospital specialists, social service providers	Decentralised shared care model, in which hospital infectious	More than 700 people were screened for viral hepatitis and HIV. The

Table 1 (*Continued*)

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
Care Copenhagen (SACC) Project, Copenhagen, Denmark	hospital infectious disease department	elastography, DAA therapy, management, follow-up; various drug and alcohol treatment and harm reduction services		disease department was responsible for prescription and monitoring the course of treatment, whilst the drug treatment staff were responsible for testing, assessment, dispensing and adherence support	proportion of clients tested for HCV in the treatment centres increased by 50%, and 208 were diagnosed with chronic HCV infection; 25 of them ended up being treated and cured. The model permitted many more people to be diagnosed and cured than otherwise, despite little tradition of collaboration between the centres and the hospital
5. Cuadrado *et al.* [116] El Dueso Prison, Santoña, Cantabria, Spain	Prison healthcare facility	HBV, HCV and HIV screening and diagnosis; DAA therapy, teleconsultation; phylogenetic analysis of nonresponders, followed by targeted retreatment	Prison health team (physicians, nurses, pharmacist); addiction specialists; social service providers; hospital team (infectious disease specialists, hepatologists, specialized nurses, radiologists, ID specialists, pharmacists,	A video collaboration tool was used for consultations between prison and hospital teams, as well as between treatment recipients and a hospital hepatologist, also after any inmate release. Treatment was prescribed by the hepatologist and administered by the prison healthcare providers. Prisoners	A test-and-treat strategy enabled the prison to screen 99.5% of its inmates for HCV, treated everyone who was infected and would be in prison more than 30 days, established a teleconsultation programme for those who were released. The programme achieved SVR in 97% of the treated prisoners. At the end of the

Table 1 (*Continued*)

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
			psychologists); telemedicine expert	were consulted on study design, and their input contributed to the use of telemedicine and the choice of the quickest treatment regiment (nonribavirin)	programme, no inmate had any detectable HCV RNA
6. Radley *et al.* [36] Directly Observed Therapy for Hepatitis C (DOT-C), Dundee, Scotland, UK	Community pharmacies	Dried blood spot testing, OST, DAA therapy	Pharmacists, physicians	Community pharmacies referring patients who test positive for HCV to clinics for assessment and treatment	HCV testing and treatment is feasible in community pharmacies, especially for patients already receiving OST there. Compared to nurse practitioners, pharmacists were much more likely to get patients to take a rapid HCV test, and for clients with reactive tests, the pharmacist were much more successful in getting them to attend a clinic for assessment and treatment
7. Hashim A et al[b] VALID (vulnerable adults liver disease) Study, Southeast England, UK	Hostels, Community clinics	Point-of-care testing, liver fibrosis assessment (Fibroscan), alcohol and substance misuse	General practitioner, medical specialist	One stop HCV clinic at two major homeless hostels in Southeast England	72 attended the clinic, 71 (99%) were included in the program, 28 (39.4%) were anti-HCV positive, 26/28 consented to further

Table 1 (*Continued*)

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
		counselling/social support (provided by primary care physician) and HCV treatment. A specialist registrar runs the clinics under the supervision of a Hepatologist			testing, 20/26 were HCV RNA positive, 5/20 started DAA treatment. Results in 2019: 131 individuals approached, 127/131 individuals enrolled in the program, 59/127 were HCV Ab positive, 48/59 were HCV RNA positive, 28/48 initiated HCV treatment, 14/17 achieved SVR12, 13 still on treatment/waiting SVR results, 1 discontinued the treatment
8. Shiha G *et al.* [143] HCV elimination in general population, Egypt	Rural setting	Point-of-care testing, liver fibrosis assessment, complete laboratory work, treatment initiation with DAAs	Multidisciplinary	Awareness raising campaign followed by HCV screening by using HCV antibody RDT a week later. Anti-HCV positive got tested for HCV RNA with GeneXpert IV, and on the same day the HCV RNA positive patients had the Fibroscan, abdominal ultrasound and basic laboratory work (liver function,	475 individuals were screened for anti-HCV antibodies by RDT, 56 had PCR HCV RNA, 43 positive for HCV RNA, 40 initiated the treatment, 3 were excluded due to focal hepatic lesion and pregnancy

Table 1 (*Continued*)

Study, project, and location	Where (setting)	What (services)	Who (providers)	How (integration approach)	Findings
				renal function, CBC, AFP) and initiated treatment with DAA	

[a]Shared Addiction Care Copenhagen (SACC). Udvikling og evaluering af et shared care behandlings-system for hepatitis C på misbrugscentre i København Kommune: afsluttende rapport, oktober 2017 [Development and evaluation of a shared-care treatment system for hepatitis C at addiction centres in Copenhagen Municipality: final report, October 2017]. Copenhagen: SACC; 2017.
[b]Hashim A *et al.* Hostel-based models can improve the engagement of homeless individuals with liver services: VALID (vulnerable adults liver disease) study. EASL ILC 2019.

OR 'hepacivirus'[MeSH Terms] OR 'hepacivirus'[All Fields]) AND model[All Fields] AND s[All Fields] AND care[All Fields]

2 Conference abstract search using keywords 'models of care', 'hepatitis C', 'HCV', 'public health'

One of the hallmarks of a good MoC is simplicity. Simplicity is key to the scaling up of interventions and widely considered a predictor of its success [18–21]. Fortunately, because DAAs have few side effects and can be administered orally, MoCs designed to optimize DAA delivery are much simpler than those designed for pegylated interferon treatment, which required more pretreatment diagnostic procedures (e.g. pretreatment liver biopsy, HCV genotyping) to exclude other causes of liver disease, as well as intensive monitoring and dose modification. Other elements that contribute to simplicity include effective linkage to care and the targeting and integration (e.g. co-location) of services [22].

Targeting is also essential. It begins with a concerted effort to test members of hard-to-reach at-risk populations, using outreach to come in contact with them where they are, instead of waiting for them to present at healthcare facilities. Table 2 presents the seven main populations addressed by MoC studies from the DAA era. Of the 71 studies that we reviewed for this paper, 42 targeted PWID.

Amongst PWID and other vulnerable populations, rapid testing has been shown to substantially increase coverage and referral rates [23–25]. To date, many services have not been developed for vulnerable populations such as the homeless, PWID and prisoners, which must both contend with numerous social determinants [26–29] that contribute to poor quality of life and poor social functioning [30, 31] as well as health inequalities [32]. It should be emphasized that HCV treatment should be offered based on clinical rather than social factors or injecting-related behaviours [33, 34], underlining the necessity of overcoming obstacles to HCV treatment delivery to PWID. In particular, several studies demonstrate that HCV treatment achieves acceptable outcomes in active injectors, and outcomes that are just as good in people on OST as in people who do not inject drugs [35–37]. An enabling policy environment is paramount [38], since restrictive drug policies and the

Table 2. *Populations addressed in the models of care selected*

Population (n)	Country	No. of study (from Table S1)
PWUD*/on OST (42/3)	Australia; Belgium; Canada; Denmark; France; Georgia; Greece; Ireland; Norway; Portugal; Spain; Switzerland; UK; USA	Papaluca T *et al.* (1), Alimohammadi A *et al.* (2), Remy AJ *et al.* (3), Bourgeois S *et al.* (4), Chronister KJ *et al.* (6), Valencia JA *et al.* (7), Liberal R *et al.* (8), Inglis SK *et al.* (10), Ford MM *et al.* (11), Borojevic M *et al.* (12), Peters L. (13), Williams B *et al.* (14), Saludes V *et al.* (15), O'Loan J *et al.* (16), Grebely J *et al.* (17), Norton *et al.* (30), Morris *et al.* (31), Schulkind J *et al.* (33), Saludes V *et al.* (34), Radley A *et al.* (35), Alam Z *et al.* (37), Sypsa V *et al.* (40), Kugelmas M *et al.* (42), Howell *et al.* (43), Kraichette N *et al.* (44), Greenan S *et al.* (45), Ryder N *et al.* (46), Doyle J *et al.* (47), Bielen R *et al.* (48), Stvilia K *et al.* (49), Mitchell S *et al.* (50), Thompson H *et al.* (51), Lamond S *et al.* (53), Sinan F *et al.* (54),Midgard H *et al.* (56), Berger SN *et al.* (57), Read P *et al.* (60), Mason K *et al.* (62), Hashim A *et al.* (63), Treloar C *et al.* (64), Chronister KJ *et al.* (65), Linnet *et al.* (65), Barror S *et al.* (66), Simoes D *et al.* (68), Nouch S *et al.* (69), Scherer ML *et al.* (71) Specifically OST: Inglis SK *et al.* (10), Radley A *et al.* (35), Bielen R *et al.* (48)
General population (20)	Australia; Canada, Egypt; India; Mexico; Pakistan; USA	Balcomb A (5), Ford MM *et al.* (11), Trooskin *et al.* (18), Chiong F *et al.* (23), Cooper *et al.* (24), Capileno *et al.* (25), El-Akel *et al.* (26), Kattakuzhy *et al.* (29), Dhiman RK *et al.* (36), Shiha G *et al.* (38), Shiha G *et al.* (39), Greenan S *et al.* (45), Ryder N *et al.* (46), Thompson H *et al.* (51), Perez Hernandez JL *et al.* (52), Lamond S *et al.* (53), Naveed A *et al.* (55), Koren D *et al.* (59), Sokol *et al.* (61), Nouch S *et al.* (69)
Prisoners (11)	Australia; France; Ireland; Portugal; Romania; Spain; Sweden; UK	Papaluca T *et al.* (1), Remy AJ *et al.* (3), Liberal R *et al.* (8), Cuadrado A *et al.* (9), Inglis SK *et al.* (10), Vroling H *et al.* (20), Olsson A *et al.* (21), Bartlett SR *et al.* (22), Overton *et al.* (41), Barror S *et al.* (66), McDonald L *et al.* (70)
Homeless (7)	Australia; Canada, France; Romania; Scotland; Spain; UK	Alimohammadi A *et al.* (2), Remy AJ *et al.* (3), O'Loan J *et al.* (16), Grebely J *et al.* (17), Hashim A *et al.* (28), Macbeth K *et al.* (32), Barror S *et al.* (66)
Sex workers (5)	Australia; Ireland; Italy; Romania; Spain; Portugal; UK	Chronister KJ *et al.* (6), Read P *et al.* (60), Barror S *et al.* (66), Teti E et at. (67), Simoes D *et al.* (68)
Migrants (3)	France, Portugal	Remy AJ *et al.* (3), Saludes V etl al. (34), Simoes D *et al.* (68)
People with mental health issues (2)	Canada, France	Mason K *et al.* (62), Remy AJ *et al.* (2)
Other (reviews) (2)	Multi-country reviews	Pourmarzi *et al.* (19), Wade *et al.* (27)

Table 2 (*Continued*)

Population (n)	Country	No. of study (from Table S1)
Veterans (1)	USA	Fleming BS *et al.* (58)
MSM (1)	Portugal	Simoes D *et al.* (68)

*People who use drugs.

criminalization of drug use not only drive much of the HCV epidemic amongst PWID [39] but also discourage PWID from accessing both HCV services and drug treatment services [40], whilst harm reduction services can offer HCV testing that many PWID would otherwise not access. At the same time, the daily support typically provided to OST clients on HCV treatment might also prove beneficial to other vulnerable individuals receiving treatment.

Perhaps the biggest obstacle to the scale-up of HCV services in many settings is affordability and availability, for both diagnostic tools and treatment. Whilst the right to health suggests that anyone infected with HCV should have access to treatment, irrespective of disease stage and drug use [41], some people must pay for them out of pocket in those countries where high costs and/or discrimination have led to reimbursement restrictions. Most countries that subsidize DAA therapy have restricted access in terms of who can prescribe and disease severity [3], despite evidence that treatment is cost-effective when the long-term costs of morbidity, mortality and onward transmission are included in the calculations, and provided that harm reduction is widely available [35, 42–47]. Strategies that have proven successful in bringing DAA costs down to a fraction of the list price include directly negotiating with pharmaceutical companies, licensing generics and committing to scaling up treatment in order to secure bulk discounts and achieve economies of scale [48].

Other obstacles also need to be overcome to scale-up HCV treatment [49, 50]. They include the heterogeneity of national policies [51–53], a lack of appropriate infrastructure for HCV services in tertiary centres and addiction clinics [17, 54–57], stigma and discrimination [58, 59] (including the reluctance of some physicians to treat PWID [60–62], limited access to point-of-care diagnostics [63], and inadequate knowledge of HCV and HCV treatment and a generally deficient sense of urgency [64–66].

Two other essential characteristics of successful MoCs that Bruggmann and Litwin emphasized in their MoC study [17], a multidisciplinary approach and integration of services, are addressed below in the sections responding to the questions of who and how, respectively.

Where

The delivery of HCV services and interventions varies tremendously in practice. Table 3 identifies the diverse settings where they can be offered. This section and the next draw on the scientific literature for recent experiences in implementing MoCs for HCV, especially amongst PWID, to explore the questions of where, what, who and how.

Because MoCs are setting-dependent, we have devoted particular attention to the question of where. The rest of this section is devoted to the different settings that can provide the primary venue for HCV services. Whilst a 'one-stop-shop' may be ideal, in that it provides continuity, it can be difficult to arrange financing for an integrated clinic offering a variety of health and social services in a system where funding comes from narrowly defined budgets. Moreover, clients often access services according to convenience, and providing services at a variety of sites may offer welcome flexibility. In such cases, it is critical to coordinate service provision so that clients receive consistent, seamless care regardless of location.

Where to provide the services: hospitals

For decades, hepatitis C has been managed as a rule by specialists in hospitals [17, 39]. As evidence became available on the effectiveness of HCV treatment and the need for tailored care pathways, new MoCs were developed. A systematic review of interferon-based treatment for PWID [67] found satisfactory results in the six studies analysing SVR and in the five analysing reinfection [68–70]. Whilst there appeared to be no clear advantage in providing treatment to PWID in hospitals instead of community-based settings [67], most of the studies

Table 3. *Setting in the models of care selected*

Setting (n)	Country	No. of study (from Table S1)
Low-threshold setting (25)	Australia; Belgium; Canada; Denmark; France; Georgia; Greece; Italy; Ireland; Norway; Portugal; Romania; Spain; UK; USA	Alimohammadi A *et al.* (2), Remy AJ *et al.* (3), Bourgeois S *et al.* (4), Valencia JA *et al.* (7), Ford MM *et al.* (11), Williams B *et al.* (14), Saludes V *et al.* (15), O'Loan J *et al.* (16), Grebely J *et al.* (17), Hashim A *et al.* (28), Morris *et al.* (31), Schulkind J *et al.* (33), Saludes V *et al.* (34), Sypsa V *et al.* (40), Howell *et al.* (43), Stvilia K *et al.* (49), Mitchell S *et al.* (50), Sinan F *et al.* (54), Midgard H *et al.* (56), Treloar C *et al.* (64), Chronister KJ *et al.* (65), Linnet *et al.* (65), Barror S *et al.* (66), Teti E *et al.* (67), Simoes D *et al.* (69), Scherer ML *et al.* (72)
Primary care (20)	Australia, Canada, Ireland, Mexico, Pakistan, Romania, Scotland, Spain, UK, USA	Balcomb A (5), Chronister KJ *et al.* (6), Trooskin *et al.* (18) Capileno *et al.*(25), Kattakuzhy *et al.*(29), Norton *et al.* (30), Macbeth K *et al.* (32), Doyle J *et al.* (47), Thompson H *et al.* (51), Perez Hernandez JL *et al.* (52), Lamond S *et al.* (53), Naveed A *et al.* (55), Koren D *et al.* (59), Read P *et al.* (60), Sokol *et al.* (61), Mason K *et al.* (62), Hashim A *et al.* (63), Treloar C *et al.* (64), Chronister KJ *et al.* (65), Barror S *et al.* (66), Nouch S *et al.* (69)
Prison (9)	Australia, Ireland, Romania, Spain, Sweden, Portugal, UK	Papaluca T *et al.* (1), Liberal R *et al.* (8), Cuadrado A *et al.* (9), Vroling H *et al.* (20), Olsson A *et al.* (21), Bartlett SR *et al.* (22), Overton *et al.* (41), Barror S *et al.* (66), McDonald L *et al.* (70)
High-threshold setting (6)	Belgium, Denmark, Switzerland, USA	Borojevic M *et al.* (12), Peters L (13), Alam Z *et al.* (37), Kugelmas M *et al.* (42), Bielen R *et al.* (48), Berger SN *et al.* (57)
Hospital (4)	Australia, Canada, India	Chiong F *et al.* (23), Cooper *et al.* (24), Dhiman RK *et al.* (36), Ryder N *et al.* (46)
Rural (4)	Canada, Egypt, France	Cooper *et al.* (24), Shiha G *et al.* (38), Shiha G *et al.* (39), Kraichette N *et al.* (44)
Regional setting (3)	Canada, Egypt, UK	Inglis SK *et al.* (10), El-Akel *et al.* (26), Greenan S *et al.* (45)
Pharmacy (3)	Scotland, USA	Radley A *et al.* (35), Fleming BS *et al.* (58), Koren D *et al.* (59)
Mobile van (4)	Australia, France, USA	Remy *et al.* (3), Trooskin S *et al.* (18), Kraichette N *et al.* (44), Doyle J *et al.* (47)
Other (2)	Multi-country reviews	Pourmarzi *et al.* (19), Wade *et al.* (27)

comparing HCV treatment in tertiary/specialist settings with community settings in another systematic review showed generally better uptake in the latter [71]. The main challenge is thus simplifying care at integrated centres and limiting the hospital role in HCV treatment. Whilst hospital specialists may continue to play a key role in integrated HCV care for marginalized populations, hospital referrals should ideally be necessary only in cases with severe complications, such as advanced liver disease and certain co-morbidities (which are expected to become much less common as DAA therapy becomes more widespread). First, however, restrictions on DAA treatment in nonhospital settings [72] must be lifted to make such a shift possible.

Primary care facilities

The feasibility of successfully treating PWID receiving OST with interferon-based regimens has been broadly demonstrated in studies where well-trained general practitioners work with nurses, social workers and other professionals in a primary care setting [73–75]. This model can also benefit from telehealth technology [76].

Table 4. *Providers in the models of care selected*

Providers (n)	Country	No. of study (from Table S1)
Multidisciplinary[a] (22)	Australia; Canada; Denmark; Egypt; France; Greece; Ireland; Portugal; Romania; Spain; Switzerland; UK; USA	Alimohammadi A *et al.* (2) Remy *et al.* (3), Balcomb A (5), Chronister KJ *et al.* (6), Valencia JA *et al.* (7), Cuadrado A *et al.* (9), Inglis SK *et al.* (10), Ford MM *et al.* (11), Borojevic M *et al.* (12), Peters L. (13), Trooskin S *et al.* (18), El-Akel *et al.* (26), Morris *et al.* (31), Macbeth K *et al.* (32), Shiha G *et al.* (39), Sypsa V *et al.* (40), Fleming BS *et al.* (58), Mason K *et al.* (62), Chronister KJ *et al.* (64), Linnet *et al.* (66), Barror S *et al.* (66), Simoes D *et al.* (68)
Medical specialists[b] (26)	Australia; Belgium; Canada; France; India; Norway; Pakistan; Portugal; Sweden; UK; USA	Papaluca T *et al.* (1), Alimohammadi A *et al.* (2), Bourgeois S *et al.* (4), Liberal R *et al.* (8), Williams B *et al.* (14), Olsson A *et al.* (21), Bartlett SR *et al.* (22), Chiong F *et al.* (23), Hashim A *et al.* (28), Kattakuzhy *et al.* (29), Norton *et al.* (30), Dhiman RK *et al.* (36), Alam Z *et al.* (37), Overton *et al.* (41), Kraichette N *et al.* (44), Greenan S *et al.* (45), Ryder N *et al.* (46), Mitchell S *et al.* (50), Thompson H *et al.* (51), Lamond S *et al.* (53), Midgard H *et al.* (56), Berger SN *et al.* (57), Sokol *et al.* (61), Hashim A *et al.* (63), McDonald L *et al.* (70), Scherer ML *et al.* (71)
General practitioners (12)	Australia; Belgium; Canada; France; India; Norway; Pakistan; Portugal; Sweden; UK; USA	O'Loan J *et al.* (16), Chiong F *et al.* (23), Hashim A *et al.* (28), Kattakuzhy *et al.* (29), Thompson H *et al.* (51), Perez Hernandez JL *et al.* (52), Lamond S *et al.* (53), Naveed A *et al.* (55)[c], Sokol *et al.* (61), Mason K *et al.* (62), Barror S *et al.* (66), Nouch S *et al.* (69)
Telemedicine (7)	Australia; Spain; Canada; Mexico; USA	Balcomb A (5), Cuadrado A *et al.* (9), Vroling H *et al.* (20), Olsson A *et al.* (21), Cooper *et al.* (24), Perez Hernandez JL *et al.* (52), Komaromy M *et al.* (67)
Nurse-led (14)	Australia; Belgium; Canada; Georgia; Sweden; UK; USA	Papaluca T *et al.* (1), Williams B *et al.* (14), Vroling H *et al.* (20), Olsson A *et al.* (21), Kattakuzhy *et al.* (29), Schulkind J *et al.* (33), Doyle J *et al.* (47), Bielen R *et al.* (48), Stvilia K *et al.* (49), Mitchell S *et al.* (50), Sinan F *et al.* (54), Berger SN *et al.* (57), Hashim A *et al.* (63), McDonald L *et al.* (70)
Specialist nurse (but not nurse-led) (12)	Australia; Belgium; Canada; Norway; UK; USA	Bourgeois S *et al.* (4), O'Loan J *et al.* (16), Bartlett SR *et al.* (22), Chiong F *et al.* (23), Cooper *et al.* (24), Radley A *et al.* (35), Overton *et al.* (41), Greenan S *et al.* (45), Thompson H *et al.* (51), Naveed A *et al.* (55) Midgard H *et al.* (56), Fleming BS *et al.* (58)
Peer support (3)	Australia; Belgium	Bourgeois S *et al.* (4), Chronister KJ *et al.* (6), Treloar C *et al.* (64)
Pharmacists (3)	Pakistan; UK; USA	Radley A *et al.* (35), Fleming BS *et al.* (58), Koren D *et al.* (59)
Nongovernmental organization (1)	Pakistan	Capileno *et al.* (25)
Not reported/Not specified (8)	Australia; Egypt; Spain; USA	Saludes V *et al.* (15), Grebely J *et al.* (17), Saludes V *et al.* 2 (34), Shiha G *et al.* (38), Kugelmas M *et al.* (42), Howell *et al.* (43), Read P *et al.* (60), Teti E *et al.* (67)
Other (reviews) (3)	Multi-country reviews	Pourmarzi *et al.* (19), Vroling H *et al.* (20) Wade *et al.* (27)

[a]A multidisciplinary team was defined as including nonclinical key personnel on the team in addition to clinicians (i.e. social worker, case manager, psychologist, etc.)
[b]A medical specialist was defined as any medical doctor that had speciality training such as; hepatologists, gastroenterologists, infectious disease specialists, sexual health physicians, HCV clinicians).
[c]Defined in manuscript as 'doctors without speciality training'.

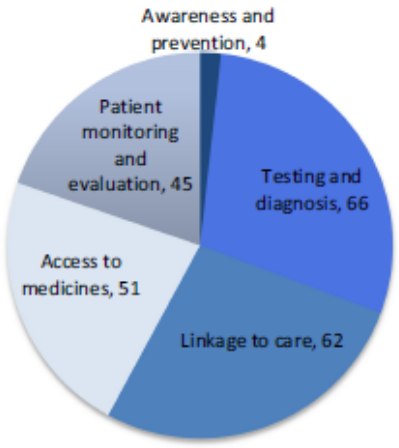

Fig. 1 *Summary of articles included (n = 71) classified by the stages in the cascade of care.*

The experience of Kirketon Road Clinic [77] in Sydney sheds light on the benefits of delivering DAA therapy in primary care (Table 1, Case 1). Amongst 242 marginalized PWID who started DAA therapy, overall 68% achieved SVR by week 12 and only 2 documented virological failures were observed, per protocol SVR12 was therefore 99%, with the remainder not attending for an SVR12 test. Seventy-nine of these people received enhanced support in the form of daily or weekly administration of DAAs. Homelessness was associated with requiring enhanced support, but reassuringly this approach ensured that virological outcomes and adherence were high. Further research is warranted on the impact of housing services on long-term outcomes for PWID [78, 79].

Multidisciplinary primary care facilities in the United States that provide training and support to professional staff have been found to provide high-quality assessment and treatment of PWID with HCV [80–82], but they are not yet common [83]. It is unclear if shifting from an MoC relying on infectious disease doctors working in primary care settings to an integrated-care pathway led by general practitioners or nurse practitioners can be both effective and cost-effective. General practitioners are still prohibited from prescribing DAAs in most countries [3], or are limited to delegated prescribing, but in countries where they may prescribe freely, such as Australia, the proportion of DAAs they prescribe is high [84].

Community health centres

These community-based facilities are not fully integrated into the healthcare system. The term is used here for centres whose primary focus is *not* drug addiction. There are several examples of community health centre MoCs from the interferon era [71]. In 2001–2005, the overall SVR for a Canadian treatment cohort, most of them PWID, was 61%, which was comparable to outcomes from contemporaneous randomized controlled trials [85].

In one systematic review of community-based HCV treatment, most studies were undertaken at OST facilities, but none assessed DAA delivery in the community setting [71]. Studies in Toronto [86] and Philadelphia [87] (Table 1, Cases 2 and 3) provide evidence of the effectiveness of community-based MoCs involving OST and DAAs, and a project in Brighton shows promising preliminary results [88]. A Melbourne trial is comparing a control group treated with DAAs and followed at the tertiary level with an intervention group treated and followed at community health centres [89].

Addiction centres and harm reduction centres

Addiction centres include drug addiction treatment centres, primary addiction care units and facilities providing services to help PWID cope with medical and psychological issues related to addiction. Harm reduction centres include OST facilities, NSPs and supervised injecting centres; many incorporate peer-based services with medical support.

A Danish project has provided important evidence of DAA therapy being used in addiction centres affiliated with hospital infectious disease departments. Preliminary results show that PWID can be tested and treated outside of hospitals, using specialists who prescribe DAAs without ever seeing the patient in person (Table 1, Case 4) [90]. In an East London study, 83 of the PWID attending an outreach clinic, where a consultant hepatologist and a nurse reviewed client cases, expressed interest in receiving antiviral therapy and 58 completed treatment. Compliance was > 80%; homelessness, active drug injection and pretreatment antidepressant therapy were *not* associated with noncompliance [91].

In an Australian multicentre initiative known as ETHOS, 24% of 415 PWID were treated with

interferon-based regimes; of them, 62% were receiving OST. Amongst the treated PWID, adherence was 86% and SVR 74% [92]. Studies of OST cohorts in Norway [93] and Ireland [37] show similarly encouraging results. Such figures are expected to improve even more as the use of DAAs becomes universal.

Scant data are available from recent studies using DAAs in OST settings [94], though an international trial from 2016 concluded that drug use ought not to be a barrier to DAA therapy in patients receiving opioid agonist therapy [95]. Further, acceptability and feasibility of dosing DAAs through an OST infrastructure has been demonstrated [96].

NSPs too have been shown to be effective and cost-effective in preventing both HIV [97] and HCV transmission amongst PWID [98, 99]. They are essential for optimizing linkage to care and testing, especially amongst young PWID [100], and can also serve as a venue for HCV treatment. A large Australian study of PWID attending NSPs in 1999–2011 found that the proportion treated for HCV increased over time, although overall numbers never exceeded 10% [101].

There is also evidence for the effectiveness of supervised injecting centres in preventing HCV and other blood-borne infections and avoiding other serious medical complications [102, 103]. Assessment for liver disease has proven suitable in this setting [104, 105]. However, beyond a survey of hepatitis C services offered at supervised injecting centres globally [106], we found no studies assessing implementation of HCV treatment pathways through such centres. Moreover, models involving these centres, such as the 'service model' used by the European Monitoring Centre for Drugs and Drug Addiction, rarely address HCV [107]. Basic work is thus still needed to conceptualize the role of supervised injecting centres within the HCV cascade.

Prisons

PWID, both former and current, form a large proportion of the prison population [108]. A study involving 3126 HCV-infected individuals incarcerated in the United States showed that rates of linkage to care and treatment for adults were very low, with just 18% being evaluated for initiation of treatment whilst incarcerated, and a mere 10% initiating DAAs [109]. The high burden of HCV infection in prisons, together with the presence of other conditions such as HIV infection, HBV infection or drug use, creates a syndemic cluster that is difficult to address. On the other hand, surveillance and movement restrictions allow for straightforward implementation of diagnostic and therapeutic strategies. For instance, a recent modelling study concluded that incarceration contributes a 28% risk of HCV transmission amongst PWID in Scotland, but scaling up HCV treatment to 80% of chronically infected PWID with sufficiently long sentences (>16 weeks) upon entrance to prison was able to reduce both the incidence and prevalence of HCV by 46% [110]. Offering prisoners HCV services upon intake is quite rare, however. Another recent study using a prevention benefit analysis concluded that increasing HCV testing in United Kingdom prisons is marginally cost-effective compared to current voluntary risk-based testing, but it could be highly cost-effective if DAAs are broadly prescribed and PWID treatment rates increased [111]. A similar U.S. study drew similar conclusions [112]. Other authors have demonstrated that scaling up harm reduction services is a prerequisite to effectively tackling HCV, HIV and drug epidemics in prisons [113]. Another challenge is ensuring prisoners uninterrupted treatment upon release. One study offered prisoners who began DAA therapy whilst in prison but who were released early with their remaining medication to complete treatment in the community [114]. This same study also offered short sentence duration prisoners ineligible for treatment referrals to healthcare services for treatment in the community once released.

A systematic review of the effectiveness of MoCs for HCV in European prisons found that seven studies utilizing second-generation DAAs in France, Italy and Spain achieved SVR rates of 85%–98%, and one study that switched from interferon therapy to DAA therapy increased SVR rates from 62%–68% to 90%–98% [115]. A Spanish study demonstrated that HCV elimination is possible in a prison setting. Using a test-and-treat strategy, the prison tested 99.5% of its inmates, treated all who were infected and would be incarcerated more than 30 days, established a teleconsultation programme for those who were released, and achieved SVR in 97% of the treated prisoners (Table 1, Case 5) [116].

Pharmacies

Available evidence supports including pharmacies as essential service venues in MoCs for treating HCV

in PWID (Table 1, Case 6) [36, 117]. Some pharmacies dispense OST and thus have daily contact with people on OST, and some also offer needle and syringe services. One study demonstrated the feasibility of implementing DAAs through a community pharmacy for PWID receiving OST [36].

In addition, both rapid testing using dried blood spots [118] and syringe distribution [119] have been proven effective in community pharmacies. These findings suggest that any further development of MoC designs and policies to incorporate HCV services for PWID at pharmacies should be based on the use of standard community pharmacies rather than hospital or specialist pharmacies, which can pose barriers to PWID access.

Sexual health clinics

Sexual health clinics provide a good platform for linkage to the HCV cascade. Australian and United Kingdom studies have demonstrated that interferon-based treatment in sexual health clinics, including follow-up and regular assessments, resulted in SVRs comparable to treatment at specialist clinics [120–122]. However, we were unable to identify any studies assessing rapid point-of-care testing followed by DAA therapy in this setting. Other studies from Australia and the United Kingdom linking confirmed HCV infections in sexual health clinics to injecting drug use have shown that HCV and HIV screening is feasible there but probably insufficient [123, 124]. It has not yet been determined whether HCV screening in this setting should be clinician-led, as with these studies (which showed an HCV incidence of around 3%), or whether universal routine HCV testing should be implemented there instead. Guidelines on who to test for hepatitis C in sexual health services are available, and often risk-factor based [125]. In either case, in order to achieve elimination in high-risk populations such as men who have sex with men, primary prevention and the prevention of reinfection will play a major role [126–128].

What, who, and how

What services to provide

It is well worth consulting the latest HCV guidelines from WHO [129, 130], the European Association for the Study of the Liver (EASL) [34], the American Association for the Study of Liver Diseases (AASLD) [131, 132] and the International Network on Hepatitis in Substance Users [133]. These guidelines all include concrete recommendations for providing HCV services to marginalized populations, and the WHO guidelines specifically address the needs of low- and middle-income countries. In addition, several systematic reviews helpfully provide an overview of the evidence for various interventions for PWID in the DAA era [23, 24, 134, 135].

Simplicity, scalability and patient convenience should be the bywords in developing an MoC. They call for a test-and-treat model wherever possible, to eliminate the gaps between testing and treatment [136–143]. Strong referral links in all directions between testing, treatment, harm reduction and social services are of paramount importance. In countries with high diagnosis rates, attention should be paid to reengaging PWID who have been diagnosed in the past and getting them into care. For a high-prevalence population like PWID, rapid antigen or RNA testing is appropriate, the latter providing results within an hour [137, 144, 145], and it may be sensible to omit genotyping if there is no major price differential between pangenotypic DAAs and genotype-specific ones. If transient elastography is not readily available, it may make sense to skip or postpone it too, or use alternative easily available fibrosis assessment tools such as APRI [146]. Table 4 summarizes the findings from the literature search organized by the stages in the cascade of care.

DAA therapy is now the treatment of choice for all patients, and everything should be done to ensure its availability [35, 147]. Access to harm reduction services are critical, as discussed above, to reach key, high-burden populations. Finally, good patient follow-up and contact are essential to help ensure adherence and maximize cure rates. Appropriate peer support, as discussed in the next section, can be crucial in increasing service uptake and retention, particularly in working with marginalized populations.

Who to provide the services

Throughout the HCV cascade of care, multidisciplinary teams of healthcare and social service professionals can help ensure the best possible outcomes, which in turn will improve public health. That is why the International Network on

Hepatitis in Substance Users recommends treating HCV in a multidisciplinary team setting [133]. Multidisciplinary approaches encompassing biomedical, psychoeducational and social interventions have been shown to improve engagement in care [148], treatment uptake [148–150], patient adherence and retention [151–156], management of HCV/HIV coinfection [157] and of HCV in psychiatric patients [158], stigma reduction and patient well-being [28, 87], and reduction in mortality [141]. However, the creation of multidisciplinary teams or structures where existing structures are functioning effectively is not a requirement of a good MoC.

As mentioned above, in moving from MoCs designed around interferon-based treatment to MoCs designed around DAAs, HCV services should be provided in a variety of settings to facilitate scale-up. With DAA therapy, HCV assessment and treatment no longer require specialist training, so it makes sense to expand who may assess HCV infection and prescribe treatment beyond specialists in tertiary care centres. With proper training, anyone can undertake assessment and prescribe DAAs competently, either as a delegated prescriber or a nonmedical prescriber – which again facilitates scale-up. Evidence has shown good results from the prescribing of DAAs by primary care providers, drug and alcohol service providers, nurse practitioners, nurses, including nurse prescribers, and pharmacists [159–162]. Delegated prescribing may be a good option where prescribing is limited by statute. Table 4 presents the diversity of providers featured in the 71 recent MoC studies reviewed for this paper, including 18 studies highlighting the benefits of multidisciplinary teams.

Particularly when using nonspecialist service providers, it is essential to invest in human resources, hiring the best people for the job and providing them with thorough and regular training. One model that has proven useful in helping such providers serve vulnerable and dispersed populations is the model promoted by Project ECHO (Extension for Community Healthcare Outcomes) [163]. By engaging frontline service providers with a continuous learning system and specialist mentors, it can dramatically increase the access of PWID to HCV care and treatment [164, 165].

A peer provider can use shared experience, as someone who has had chronic hepatitis C and/or someone who has been part of a target population, to connect with vulnerable people and help them through the cascade of care. They can also use their experience to help ensure that MoCs reflect client concerns. Limited data from both the interferon era [166] and the DAA era highlight [167, 168] the potential benefit of including peer support workers in MoCs.

Countries with very broad community access to DAAs, such as Australia [169], have been successful in mobilizing the peer workforce and training them to provide services at different points in the cascade of care, where they have been crucial in building momentum towards HCV elimination.

How to integrate services

In the DAA era, as mentioned above, the ideal form for a successful MoC for PWID with HCV is either a one-stop-shop approach, in which all relevant services are integrated in locations where people are already accessing other services, or a flexible approach, in which various sites and services are well coordinated and strongly linked. The challenge in implementing the one-stop approach is to evolve towards comprehensive yet decentralized points of care [170], for instance through single-visit diagnoses [137]. Multidisciplinarity and integration go hand in hand, yet it is important to emphasize two necessary features of the integration process in developing a robust MoC for marginalized populations. First, integration should take place within systems where these populations already access services, particularly OST and NSPs in the case of PWID [171]. The aim should be to bring services closer to the client, rather than expecting the client to seek them out. And secondly, it requires training that is also multidisciplinary and integrated, which will include task-shifting, so that fewer kinds of professionals are providing more services in the same settings, thereby necessitating fewer visits to access them.

In their seminal review on MoCs for HCV, Bruggmann and Litwin contrast various integrated MoCs with conventional secondary and tertiary care models [17]. Where it is feasible and affordable, we advocate integration: delivering integrated care in nonspecialist settings that are better suited to the care of vulnerable individuals. In Scotland, where managed care networks exemplify integrated multiagency MoCs, they have been shown to improve not only HCV outcomes, but also outcomes related to drug use [141, 172, 173].

Although not exhaustive, we have presented many examples demonstrating that integrated MoCs are effective in addressing the entire HCV cascade of care (Fig. 1), plus evidence that an integrated format might be particularly well suited to primary care, community health centres, addiction and harm reduction centres, prisons, sexual health clinics, pharmacies and other settings. Such models of care can target both the typical young drug user and the veteran of addiction treatment [174, 175], for instance, thereby increasing overall eligibility for HCV treatment [176] whilst providing for appropriate counselling, peer support [148] and management of medical, mental health and social issues for both those on opioid substitution therapy and those who are not [75, 88, 177, 178].

Conclusion

Around the world, models of care for HCV need to be redesigned to reflect the recent availability of DAAs if countries are to meet their commitments to eliminating HCV as a public health threat by 2030, as set out by WHO. In some countries, this will require major changes to established care pathways and systems. One immediate challenge for policymakers and researchers is to develop cost-effective, easily implemented mechanisms that incorporate health information and reimbursement systems, and interdisciplinary and multifacility communication. Healthcare providers, affected populations and other key stakeholders should be involved in such development to ensure that the final mechanisms represent relevant perspectives and are mutually beneficial to all. Whilst further research on the feasibility of different MoCs in specific settings is needed, much can be learned from examining the innovative MoCs reviewed here, which suggest that an effective model of care for HCV infection should be simple, targeted, multidisciplinary, scalable, integrated, patient-centred and affordable.

Author contributions

JVL conceived of the article and developed the preliminary outline with input from the other authors. JMP prepared the first draft, which was rewritten by MH and JVL and further revised by all authors. CP, JC and ER carried out the literature search for models of care and prepared the tables. All authors reviewed the full draft of the article, subsequent revisions and approved the final version for submission.

Conflict of interest statement

JVL reports grants and personal fees from AbbVie, Gilead Sciences and MSD, personal fees from Janssen, and personal fees from CEPHEID outside the submitted work. PR has received institutional research funding from Gilead Sciences, and speaker fees and travel for noncommercial educational talks by Gilead Sciences & Merck Sharp & Dohme. JD reports grants and personal fees from Gilead, grants and personal fees from BMS, grants and personal fees from Abbvie, grants and personal fees from Roche, grants and personal fees from MSD, grants and personal fees from Abbott, grants from Genedrive, outside the submitted work. JMP, CP, JC, MH, MM, NL and ER have nothing to disclose.

Acknowledgements

This work was supported by the joint action '677085/HA-REACT', which received funding from the European Union's Health Programme (2014–2020). Additional financial support was provided Gilead Sciences. JVL is supported by a Spanish Ministry of Science, Innovation and Universities Miguel Servet grant. The authors would like to thank Jason Grebely and Kelly Safreed-Harmon for their insights into earlier drafts of this review.

References

1 Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000-2016. Geneva: World Health Organization, 2018.
2 Global hepatitis report, 2017. Geneva: World Health Organization, 2017.
3 Marshall AD, Cunningham EB, Nielsen S *et al.* Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. *Lancet Gastroenterol Hepatol* 2017; **3:** 125–33.
4 Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. Restrictions for medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. *Ann Intern Med* 2015; **163:** 215–23.
5 Progress report on HIV, viral hepatitis and sexually transmitted infections 2019: Accountability for the global health sector strategies, 2016-2021. World Health Organization, 2019. https://www.who.int/hiv/strategy2016-2021/progress-report-2019/en/. Accessed 27 May 2019.
6 WHO global health sector strategy on viral hepatitis 2016–2021: towards ending viral hepatitis. Geneva: World Health Organization, 2016.
7 Nelson PK, Mathers BM, Cowie B *et al.* Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011; **378:** 571–83.

8 Degenhardt L, Peacock A, Colledge S *et al.* Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Health* 2017; **5:** e1192–207.
9 Grebely J, Larney S, Peacock A *et al.* Global, regional, and country-level estimates of hepatitis C virus infection among people who have recently injected drugs. *Addiction* 2018; **114:** 150–66.
10 Trickey A, Fraser H, Lim A *et al.* The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. *Lancet Gastroenterol Hepatol* 2019; **4:** 435–44.
11 Bruggmann P, Blach S, Deltenre P *et al.* Hepatitis C virus dynamics among intravenous drug users suggest that an annual treatment uptake above 10% would eliminate the disease by 2030. *Swiss Med Wkly* 2017; **147:** w14543.
12 Fraser H, Martin NK, Brummer-Korvenkontio H *et al.* Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe. *J Hepatol* 2017; **68:** 402–11.
13 HRI. *Global State of Harm Reduction 2016*. London: Harm Reduction International, 2016.
14 Wiessing L, Ferri M, Běláčková V *et al.* Monitoring quality and coverage of harm reduction services for people who use drugs: a consensus study. *Harm Reduct J* 2017; **14:** 19.
15 Wiessing L, Ferri M, Grady B *et al.* Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a systematic review of data for scaling up treatment and prevention. *PLoS ONE* 2014; **9:** e103345.
16 Lim AG, Qureshi H, Mahmood H *et al.* Curbing the hepatitis C virus epidemic in Pakistan: the impact of scaling up treatment and prevention for achieving elimination. *Int J Epidemiol* 2018; **47:** 550–60.
17 Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. *Clin Infect Dis* 2013; **57:** S56–61.
18 Yamey G. Scaling up global health interventions: a proposed framework for success. *PLoS Med* 2011; **8:** e1001049.
19 Harries AD, Zachariah R, Jahn A, Schouten EJ, Kamoto K. Scaling up antiretroviral therapy in Malawi-implications for managing other chronic diseases in resource-limited countries. *J Acquir Immune Defic Syndr* 2009; **52(Suppl 1):** S14–6.
20 Billings DL, Crane BB, Benson J, Solo J, Fetters T. Scaling-up a public health innovation: a comparative study of post-abortion care in Bolivia and Mexico. *Soc Sci Med* 2007; **64:** 2210–22.
21 World Bank. Scaling up the impact of good practices in rural development: a working paper to support implementation of the World Bank's rural development strategy. Report no. 26031. Washington, DC, USA: World Bank Agriculture and Rural Development Department, 2003.
22 Reimer J, Haasen C. Need-adapted HCV-treatment setting for injection drug users. *Lancet* 2009; **373:** 2090–1.
23 Bajis S, Dore GJ, Hajarizadeh B, Cunningham EB, Maher L, Grebely J. Interventions to enhance testing, linkage to care and treatment uptake for hepatitis C virus infection among people who inject drugs: a systematic review. *Int J Drug Policy* 2017; **47:** 34–46.
24 Zhou K, Fitzpatrick T, Walsh N *et al.* Interventions to optimise the care continuum for chronic viral hepatitis: a systematic review and meta-analyses. *Lancet Infect Dis* 2016; **16:** 1409–22.
25 Girardin F, Hearmon N, Negro F, Eddowes L, Bruggmann P, Castro E. Increasing hepatitis C virus screening in people who inject drugs in Switzerland using rapid antibody saliva and dried blood spot testing: a cost-effectiveness analysis. *J Viral Hepat* 2018; **26:** 236–45.
26 Barror S, Avramovic G, Iglesias M *et al.* Hepcheck- Enhancing HCV identification and linkage to care for vulnerable populations through intensified outreach screening. HepHIV Conference, 2019.
27 Bajis S, Grebely J, Cooper L *et al.* Hepatitis C virus testing, liver disease assessment and direct-acting antiviral treatment uptake and outcomes in a service for people who are homeless in Sydney, Australia: the LiveRLife homelessness study. *J Viral Hepat* 2019; **26:** 969–79.
28 Harris M, Rhodes T. Hepatitis C treatment access and uptake for people who inject drugs: a review mapping the role of social factors. *Harm Reduct J* 2013; **10:** 7.
29 Mah A, Hull MW, DeBeck K *et al.* Knowledge of hepatitis C and treatment willingness amongst people who inject drugs in an era of direct acting antivirals. *Int J Drug Policy* 2017; **47:** 137–43.
30 Fortier E, Alavi M, Micallef M *et al.* The effect of social functioning and living arrangement on treatment intent, specialist assessment and treatment uptake for hepatitis C virus infection among people with a history of injecting drug use: the ETHOS study. *Int J Drug Policy* 2015; **26:** 1094–102.
31 Doyle JS, Grebely J, Spelman T *et al.* Quality of life and social functioning during treatment of recent hepatitis C infection: a multi-centre prospective cohort. *PLoS ONE* 2016; **11:** e0150655.
32 Friedman SR, Tempalski B, Brady JE *et al.* Income inequality, drug-related arrests, and the health of people who inject drugs: reflections on seventeen years of research. *Int J Drug Policy* 2016; **32:** 11–6.
33 Grebely J, Petoumenos K, Matthews GV *et al.* Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: the ATAHC Study. *Drug Alcohol Depend* 2010; **107:** 244–9.
34 European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67:** 370–98.
35 Grebely J, Hajarizadeh B, Dore GJ. Direct-acting antiviral agents for HCV infection affecting people who inject drugs. *Nat Rev Gastroenterol Hepatol* 2017; **14:** 641–51.
36 Radley A, Tait J, Dillon JF. DOT-C: a cluster randomised feasibility trial evaluating directly observed anti-HCV therapy in a population receiving opioid substitute therapy from community pharmacy. *Int J Drug Policy* 2017; **47:** 126–36.
37 Elsherif O, Bannan C, Keating S, McKiernan S, Bergin C, Norris S. Outcomes from a large 10 year hepatitis C treatment programme in people who inject drugs: no effect of recent or former injecting drug use on treatment adherence or therapeutic response. *PLoS ONE* 2017; **12:** e0178398.
38 Birkhead GS, Klein SJ, Candelas AR *et al.* Integrating multiple programme and policy approaches to hepatitis C prevention and care for injection drug users: a comprehensive approach. *Int J Drug Policy* 2007; **18:** 417–25.
39 Bruggmann P, Grebely J. Prevention, treatment and care of hepatitis C virus infection among people who inject drugs. *Int J Drug Policy* 2015; **26(Suppl 1):** S22–6.

40 The Global Commission on Drug Policy. The negative impact of the war on drugs on public health: The hidden hepatitis c epidemic, 2013. http://www.globalcommissionondrugs.org/hepatitis/
41 Grebely J, Haire B, Taylor LE *et al.* Excluding people who use drugs or alcohol from access to hepatitis C treatments - is this fair, given the available data? *J Hepatol* 2015; **63:** 779–82.
42 Cousien A, Tran VC, Deuffic-Burban S *et al.* Effectiveness and cost-effectiveness of interventions targeting harm reduction and chronic hepatitis C cascade of care in people who inject drugs: the case of France. *J Viral Hepat* 2018; **25:** 1197–207.
43 Mabileau G, Scutelniciuc O, Tsereteli M *et al.* Intervention packages to reduce the impact of HIV and HCV infections among people who inject drugs in Eastern Europe and Central Asia: a modeling and cost-effectiveness study. open forum. *Infect Dis* 2018; **5:** ofy040.
44 Bennett H, Gordon J, Jones B *et al.* Hepatitis C disease transmission and treatment uptake: impact on the cost-effectiveness of new direct-acting antiviral therapies. *Eur J Health Econ* 2017; **18:** 1001–11.
45 Iversen J, Grebely J, Catlett B, Cunningham P, Dore GJ, Maher L. Estimating the cascade of hepatitis C testing, care and treatment among people who inject drugs in Australia. *Int J Drug Policy* 2017; **47:** 77–85.
46 Leidner AJ, Chesson HW, Spradling PR, Holmberg SD. Assessing the effect of potential reductions in non-hepatic mortality on the estimated cost-effectiveness of hepatitis c treatment in early stages of liver disease. *Appl Health Econ Health Policy* 2017; **15:** 65–74.
47 Dillon JF, Lazarus JV, Razavi HA. Urgent action to fight hepatitis C in people who inject drugs in Europe. *Hep Med Pol* 2016; **1:** 2. https://doi.org/10.1186/s41124-016-0011-y.
48 Douglass CH, Pedrana A, Lazarus JV *et al.* Pathways to ensure universal and affordable access to hepatitis C treatment. *BMC Med* 2018; **16:** 175.
49 Zeremski M, Zibbell JE, Martinez AD, Kritz S, Smith BD, Talal AH. Hepatitis C virus control among persons who inject drugs requires overcoming barriers to care. *World J Gastroenterol* 2013; **19:** 7846–51.
50 Bruggmann P. Accessing hepatitis C patients who are difficult to reach: it is time to overcome barriers. *J Viral Hepat* 2012; **19:** 829–35.
51 Lazarus JV, Safreed-Harmon K, Stumo SR *et al.* Restrictions on access to direct-acting antivirals for people who inject drugs: the European Hep-CORE study and the role of patient groups in monitoring national HCV responses. *Int J Drug Policy* 2017; **47:** 47–50.
52 Wright N, Reimer J, Somaini L *et al.* Are we ready to treat hepatitis C virus in individuals with opioid use disorder: assessment of readiness in European countries on the basis of an expert-generated model. *Eur J Gastroenterol Hepatol* 2017; **29:** 1206–14.
53 Maticic M, Zorman JV, Gregoricic S, Schatz E, Lazarus JV. Changes to the national strategies, plans and guidelines for the treatment of hepatitis C in people who inject drugs between 2013-2016: a cross-sectional survey of 34 European countries. *Harm Reduct J* 2019; **16:** 37–45.
54 Litwin AH, Kunins HV, Berg KM *et al.* Hepatitis C management by addiction medicine physicians: results from a national survey. *J Subst Abuse Treat* 2007; **33:** 99–105.
55 Grebely J, Tyndall MW. Management of HCV and HIV infections among people who inject drugs. *Curr Opin HIV/AIDS* 2011; **6:** 501–7.
56 Bini EJ, Kritz S, Brown LS Jr, Robinson J, Alderson D, Rotrosen J. Barriers to providing health services for HIV/AIDS, hepatitis C virus infection and sexually transmitted infections in substance abuse treatment programs in the United States. *J Addict Dis* 2011; **30:** 98–109.
57 Grebely J, Bryant J, Hull P *et al.* Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia. *J Viral Hepat* 2011; **18:** e104–16.
58 Paterson BL, Backmund M, Hirsch G, Yim C. The depiction of stigmatization in research about hepatitis C. *Int J Drug Policy* 2007; **18:** 364–73.
59 Moore GA, Hawley DA, Bradley P. Hepatitis C: studying stigma. *Gastroenterol Nurs* 2008; **31:** 346–52.
60 Stoové MA, Gifford SM, Dore GJ. The impact of injecting drug use status on hepatitis C-related referral and treatment. *Drug Alcohol Depend* 2005; **77:** 81–6.
61 Myles A, Mugford GJ, Zhao J, Krahn M, Wang PP. Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada. *Can J Gastroenterol* 2011; **25:** 135–9.
62 Cox J, Graves L, Marks E *et al.* Knowledge, attitudes and behaviours associated with the provision of hepatitis C care by Canadian family physicians. *J Viral Hepat* 2011; **18:** e332–40.
63 Cooke GS, Andrieux-Meyer I, Applegate TL *et al.* Lancet commission: accelerating the elimination of viral hepatitis. *Lancet Gastroenterol Hepatol* 2019; **4:** 135–84.
64 Swan D, Long J, Carr O *et al.* Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: a qualitative exploration. *AIDS Patient Care STDS* 2010; **24:** 753–62.
65 Strathdee SA, Latka M, Campbell J *et al.* Factors associated with interest in initiating treatment for hepatitis C virus (HCV) infection among young HCV-infected injection drug users. *Clin Infect Dis* 2005; **40(suppl 5):** S304–12.
66 Mehta SH, Genberg BL, Astemborski J *et al.* Limited uptake of hepatitis C treatment among injection drug users. *J Community Health* 2008; **33:** 126–33.
67 Aspinall EJ, Corson S, Doyle JS *et al.* Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. *Clin Infect Dis* 2013; **57(Suppl 2):** S80–9.
68 Backmund M, Meyer K, Edlin B. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. *Clin Infect Dis* 2004; **39:** 1540–3.
69 Dalgard O, Bjoro K, Hellum K, Myrvang B, Skaug K, Gutigard B. Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up. *Eur Addict Res* 2002; **8:** 45–9.
70 Currie S, Ryan J, Tracy D *et al.* A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. *Drug Alcohol Depend* 2008; **93:** 148–54.
71 Wade AJ, Veronese V, Hellard ME, Doyle JS. A systematic review of community based hepatitis C treatment. *BMC Infect Dis* 2016; **16:** 202.
72 Lazarus JV, Stumo SR, Maticic M *et al.* HEP-CORE: a cross-sectional study of the viral hepatitis policy environment reported by patient groups in 25 European countries in 2016 and 2017. *J Int AIDS Soc* 2018; **21(S2):** e25052.

73 Jack K, Willott S, Manners J, Varnam MA, Thomson BJ. Clinical trial: a primary-care-based model for the delivery of anti-viral treatment to injecting drug users infected with hepatitis C. *Aliment Pharmacol Ther* 2009; **29:** 38–45.
74 Seidenberg A, Rosemann T, Senn O. Patients receiving opioid maintenance treatment in primary care: successful chronic hepatitis C care in a real world setting. *BMC Infect Dis* 2013; **13:** 9.
75 Brunner N, Senn O, Rosemann T, Falcato L, Bruggmann P. Hepatitis C treatment for multimorbid patients with substance use disorder in a primary care-based integrated treatment centre: a retrospective analysis. *Eur J Gastroenterol Hepatol* 2013; **25:** 1300–7.
76 Arora S, Thornton K, Murata G *et al.* Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med* 2011; **364:** 2199–207.
77 Read P, Gilliver R, Kearley J *et al.* Treatment adherence and support for people who inject drugs taking direct acting antiviral therapy for hepatitis C infection. *J Viral Hepat* 2019. https://doi.org/10.1111/jvh.13175 [Epub ahead of print].
78 Linton SL, Cooper HL, Kelley ME *et al.* Associations of place characteristics with HIV and HCV risk behaviors among racial/ethnic groups of people who inject drugs in the United States. *Ann Epidemiol* 2016; **26:** 619–30. e2.
79 Kim C, Kerr T, Li K *et al.* Unstable housing and hepatitis C incidence among injection drug users in a Canadian setting. *BMC Public Health* 2009; **9:** 270.
80 Sokol R, Early J, Barner A *et al.* Implementation of a multidisciplinary, team-based model to treat chronic hepatitis C in the primary care setting: lessons learned. *Healthc (Amst)* 2018; **6:** 205–9.
81 Ward JW, Valdiserri RO, Koh HK. Hepatitis C virus prevention, care, and treatment: from policy to practice. *Clin Infect Dis* 2012; **55(Suppl 1):** S58–63.
82 Falade-Nwulia O, McAdams-Mahmoud A, Irvin R *et al.* Primary care providers knowledge, attitude and practices related to hepatitis c screening and treatment in the oral direct acting antiviral agents Era. *J Community Med Health Educ* 2016;6.; **pii:** 481.
83 Thomson M, Konerman MA, Choxi H, Lok AS. Primary care physician perspectives on hepatitis C management in the era of direct-acting antiviral therapy. *Dig Dis Sci* 2016; **61:** 3460–8.
84 Hajarizadeh B, Grebely J, Matthews GV, Martinello M, Dore GJ. The path towards hepatitis C elimination in Australia following universal access to interferon-free treatments. *J Hepatol* 2017; **66(S1):** s291–2.
85 Hill WD, Butt G, Alvarez M, Krajden M. Capacity enhancement of hepatitis C virus treatment through integrated, community-based care. *Can J Gastroenterol* 2008; **22:** 27–32.
86 Mason K, Dodd Z, Sockalingam S *et al.* Beyond viral response: a prospective evaluation of a community-based, multi-disciplinary, peer-driven model of HCV treatment and support. *Int J Drug Policy* 2015; **26:** 1007–13.
87 Trooskin SB, Poceta J, Towey CM *et al.* Results from a geographically focused, community-based HCV screening, linkage-to-care and patient navigation program. *J Gen Intern Med* 2015; **30:** 950–7.
88 Hashim A, O'Sullivan M, Williams H, Verma S. Developing a community HCV service: project ITTREAT (integrated community-based test - stage - TREAT) service for people who inject drugs. *Prim Health Care Res Dev* 2017; **19:** 110–20.
89 Wade AJ, Doyle JS, Gane E *et al.* Community-based provision of direct-acting antiviral therapy for hepatitis C: study protocol and challenges of a randomized controlled trial. *Trials* 2018; **19:** 383.
90 Linnet M, Peters L, Raben d, Petersen H, Gerstoft J, Lundgren J. Organizational barriers as an explanation for differences in offer and uptake rates for hepatitis A/B/C and HIV testing in three drug treatment centres in Copenhagen. Poster presented at HepHIV 2017, 2017; Malta. http://www.hiveurope.eu/Portals/0/Conference%202017/Posters/PS1_03.pdf
91 Wilkinson M, Crawford V, Tippet A *et al.* Community-based treatment for chronic hepatitis C in drug users: high rates of compliance with therapy despite ongoing drug use. *Aliment Pharmacol Ther* 2009; **29:** 29–37.
92 Grebely J, Alavi M, Micallef M *et al.* Treatment for hepatitis C virus infection among people who inject drugs attending opioid substitution treatment and community health clinics: the ETHOS Study. *Addiction* 2016; **111:** 311–9.
93 Midgard H, Bramness JG, Skurtveit S, Haukeland JW, Dalgard O. Hepatitis C treatment uptake among patients who have received opioid substitution treatment: a population-based study. *PLoS ONE* 2016; **11:** e0166451.
94 Scherz N, Brunner N, Bruggmann P. Direct-acting antivirals for hepatitis C in patient in opioid substitution treatment and heroin assisted treatment: real-life data. *J Hepatol* 2017; **66:** S726.
95 Dore GJ, Altice F, Litwin AH *et al.* Elbasvir–grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. *Ann Intern Med* 2016; **165:** 625–34.
96 Chronister K, Lothian R, Gilliver R, Kearley J, Read P. Feasibility and acceptability of adherence support for direct acting antiviral therapy for hepatitis C in a low-threshold primary health-care opioid agonist treatment program. *Drug Alcohol Rev* 2019; **38:** 185–9.
97 World Health Organization. *Effectiveness of Sterile Needle and Syringe Programming in Reducing HIV/AIDS among Injecting Drug Users*. Geneva: WHO, 2004. http://www.who.int/hiv/pub/prev_care/effectivenesssterileneedle.pdf
98 Platt L, Sweeney S, Ward Z *et al.* Assessing the impact and cost-effectiveness of needle and syringe provision and opioid substitution therapy on hepatitis C transmission among people who inject drugs in the UK: an analysis of pooled data sets and economic modelling. Southampton, UK: NIHR Journals Library, 2017.
99 Platt L, Minozzi S, Reed J *et al.* Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. *Cochrane Database Syst Rev* 2017; **9:** CD012021.
100 Page K, Morris MD, Hahn JA, Maher L, Prins M. Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. *Clin Infect Dis* 2013; **57(Suppl 2):** S32–8.
101 Iversen J, Grebely J, Topp L, Wand H, Dore G, Maher L. Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999-2011. *J Viral Hepat* 2014; **21:** 198–207.

102 Wright NM, Tompkins CN. Supervised injecting centres. *BMJ* 2004; **328:** 100–2.
103 Schatz E, Nougier M, on behalf of the International Drug Policy Consortium. Drug consumption rooms: evidence and practice, 2012. http://www.drugsandalcohol.ie/17898/1/IDPC-Briefing-Paper_Drug-consumption-rooms.pdf
104 Marshall AD, Micallef M, Ernatt A *et al.* Liver disease knowledge and acceptability of non-invasive liver fibrosis assessment among people who inject drugs in the drug and alcohol setting: the LiveRLife Study. *Int J Drug Policy* 2015; **26:** 984–91.
105 Marshall AD, Grebely J, Dore GJ, Treloar C. 'I didn't want to let it go too far'. The decisions and experiences of people who inject drugs who received a liver disease assessment as part of a liver health promotion campaign: the LiveRLife study. *Int J Drug Policy* 2017; **47:** 153–60.
106 Schatz E, Belackova V. Study on drug consumption rooms on current practice and future capacity to address communicable diseases like HCVE. In: Oral abstracts of the 22nd International AIDS Conference, 23–27 July 2018, Amsterdam, the Netherlands. *J Intern AIDS Soc* 2018; **21:** e25148.
107 European monitoring centre for drugs and drug addiction. Drugs consumption rooms: an overview of provision and evidence, 2017. http://www.emodda.europa.eu/attachements.cfm/att_239692_EN_Drug%20consumption%20rooms_update%202016.pdf
108 Kinner SA. *Drug Use in Prisoners*. New York, NY: Oxford University Press, 2018.
109 Hochstatter KR, Stockman LJ, Holzmacher R *et al.* The continuum of hepatitis C care for criminal justice involved adults in the DAA era: a retrospective cohort study demonstrating limited treatment uptake and inconsistent linkage to community-based care. *Health Justice* 2017; **5:** 10.
110 Stone J, Martin NK, Hickman M *et al.* Modelling the impact of incarceration and prison-based hepatitis C virus (HCV) treatment on HCV transmission among people who inject drugs in Scotland. *Addiction* 2017; **112:** 1302–14.
111 Martin NK, Vickerman P, Brew IF *et al.* Is increased hepatitis C virus case-finding combined with current or 8-week to 12-week direct-acting antiviral therapy cost-effective in UK prisons? A prevention benefit analysis *Hepatology* 2016; **63:** 1796–808.
112 He T, Li K, Roberts MS *et al.* Prevention of hepatitis C by screening and treatment in U.S. prisons. *Ann Intern Med* 2016; **164:** 84–92.
113 Sander G, Murphy F. The furthest left behind: the urgent need to scale up harm reduction in prisons. *Int J Prison Health* 2017; **13:** 185–91.
114 Papaluca T, McDonald L, Craigie A *et al.* Outcomes of treatment for hepatitis C in prisoners using a nurse-led, statewide model of care. *J Hepatol* 2019; **70:** 839–46.
115 Vroling H, Oordt-Speets AM, Madeddu G *et al.* A systematic review on models of care effectiveness and barriers to Hepatitis C treatment in prison settings in the EU/EEA. *J Viral Hepat* 2018; **25:** 1406–22.
116 Cuadrado A, Llerena S, Cobo C *et al.* Microenvironment eradication of hepatitis C: a novel treatment paradigm. *Am J Gastroenterol* 2018; **113:** 1639–48.
117 Radley A, de Bruin M, Inglis S *et al.* Preliminary analysis of Superdot C: a cluster randomised controlled trial of pharmacy led versus conventional treatment for HCV positive patients receiving daily opioid substitution therapy - The Tayside sites. LBP-27. EASL 2019 abstract. *J Hepatol* 2019; **70:** e141–382.
118 Radley A, Melville K, Tait J, Stephens B, Evans JMM, Dillon JF. A quasi-experimental evaluation of dried blood spot testing through community pharmacies in the Tayside region of Scotland. *Front Gastroenterol* 2017; **8:** 221–8.
119 Oramasionwu CU, Johnson TL, Zule WA, Carda-Auten J, Golin CE. Using pharmacies in a structural intervention to distribute low dead space syringes to reduce HIV and HCV transmission in people who inject drugs. *Am J Public Health* 2015; **105:** 1066–71.
120 Ewart A, Harrison L, Joyner B, Safe A. Providing treatment for hepatitis C in an Australian district centre. *Postgrad Med J* 2004; **80:** 180–2.
121 Ward C, Lee V. Experience of acute hepatitis C and HIV co-infection in an inner city clinic in the UK. *J Int AIDS Soc* 2014; **17(4 Suppl 3):** 19639.
122 Tomkins A, Lee V. Intervention to improve management of acute hepatitis C infection in a UK sexual health clinic. *Int J STD AIDS* 2017; **29:** 195–7.
123 Mapagu MC, Martin SJ, Currie MJ, Bowden FJ. Screening for hepatitis C in sexual health clinic attendees. *Sex Health* 2008; **5:** 73–6.
124 Tweed E, Brant L, Hurrelle M, Klapper P, Ramsay M, Hepatitis Sentinel Surveillance Study Group. Hepatitis C testing in sexual health services in England, 2002-7: results from sentinel surveillance. *Sex Transm Infect* 2010; **86:** 126–30.
125 Brook G, Brockmeyer N, van de Laar T, Schellberg S, Winter A. European Guideline for the screening, prevention and initial management of hepatitis B & C infections in sexual health settings. International Union Against STIs, 2017.
126 Ward C, Lee V. Should we offer routine hepatitis C antibody testing in men who have sex with men? *J Int AIDS Soc* 2014; **17(4 Suppl 3):** 19591.
127 Ireland G, Higgins S, Goorney B *et al.* Evaluation of hepatitis C testing in men who have sex with men, and associated risk behaviours, in Manchester, UK. *Sex Transm Infect* 2017; **93:** 404–9.
128 Tomkins A, Vicancos R, Ward C, Kliner M. How can those engaging in chemsex best be supported? An online survey to gain intelligence in Great Manchester. *Int J STD AIDS* 2018; **29:** 128–34.
129 WHO guidelines on hepatitis B and C testing. Geneva: World Health Organization, 2017.
130 Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization, 2018.
131 AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C [Internet], 2017. http://hcvguidelines.org
132 AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis* 2018; **67:** 1477–92.
133 Grebely J, Robaeys G, Bruggmann P *et al.* Recommendations for the management of hepatitis C virus infection among people who inject drugs. *Int J Drug Policy* 2015; **26:** 1028–38.
134 Larney S, Peacock A, Leung J *et al.* Global, regional, and country-level coverage of interventions to prevent and

manage HIV and hepatitis C among people who inject drugs: a systematic review. *Lancet Glob Health* 2017; **5:** e1208–20.
135 Meyer JP, Moghimi Y, Marcus R, Lim JK, Litwin AH, Altice FL. Evidence-based interventions to enhance assessment, treatment, and adherence in the chronic Hepatitis C care continuum. *Int J Drug Policy* 2015; **26:** 922–35.
136 Road to elimination: barriers and best practices in hepatitis C management. Boston Consulting Group, 2017.
137 Grebely J, Applegate TL, Cunningham P, Feld JJ. Hepatitis C point-of-care diagnostics: in search of a single visit diagnosis. *Expert Rev Mol Diagn* 2017; **17:** 1109–15.
138 Chevaliez S, Pawlotsky JM. New virological tools for screening, diagnosis and monitoring of hepatitis B and C in resource-limited settings. *J Hepatol* 2018; **69:** 916–26.
139 Chevaliez S, Feld J, Cheng K *et al.* Clinical utility of HCV core antigen detection and quantification in the diagnosis and management of patients with chronic hepatitis C receiving an all-oral, interferon-free regimen. *Antivir Ther* 2018; **23:** 211–7.
140 Coats JT, Dillon JF. The effect of introducing point-of-care or dried blood spot analysis on the uptake of hepatitis C virus testing in high-risk populations: a systematic review of the literature. *Int J Drug Policy* 2015; **26:** 1050–5.
141 Tait JM, Wang H, Stephens BP *et al.* Multidisciplinary managed care networks-Life-saving interventions for hepatitis C patients. *J Viral Hepat* 2017; **24:** 207–15.
142 Boston Consulting Group: Road to Elimination: Barriers and Best Practices in Hepatitis C Management. Overview of the status of HCV care in Europe and Australia, 2017. http://image-src.bcg.com/Images/BCG-Road-to-Elimination_tcm104-166034.pdf
143 Shiha G, Elsayed R, Mikhail N, Easterbrook P. Towards HCV elimination: feasibility of complete linkage to care by testing and treatment on the same day of screening: a pilot study. *J Hepatol* 2019; **70:** e1–44.
144 Shivkumar S, Peeling R, Jafari Y *et al.* Accuracy of rapid and point-of-care screening tests for hepatitis C: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157:** 558–66.
145 Grebely J, Lamoury FMJ, Hajarizadeh B *et al.* Evaluation of the Xpert HCV Viral Load point-of-care assay from venepuncture-collected and finger-stick capillary whole-blood samples: a cohort study. *Lancet Gastroenterol Hepatol* 2017; **2:** 514–20.
146 Kelly ML, Riordan SM, Bopage R *et al.* Capacity of non-invasive hepatic fibrosis algorithms to replace transient elastography to exclude cirrhosis in people with hepatitis C virus infection: a multi-centre observational study. *PLoS ONE* 2018; **13:** e0192763.
147 Grebely J, Bruneau J, Bruggmann P *et al.* Elimination of hepatitis C virus infection among PWID: the beginning of a new era of interferon-free DAA therapy. *Int J Drug Policy* 2017; **47:** 26–33.
148 Grebely J, Knight E, Genoway KA *et al.* Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. *Eur J Gastroenterol Hepatol* 2010; **22:** 270–7.
149 Grebely J, Genoway K, Khara M *et al.* Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. *Int J Drug Policy* 2007; **18:** 437–43.
150 Mravčík V, Strada L, Stolfa J *et al.* Factors associated with uptake, adherence, and efficacy of hepatitis C treatment in people who inject drugs: a literature review. *Patient Prefer Adherence* 2013; **7:** 1067–75.
151 Curcio F, Di MF, Capraro C *et al.* Together ... to take care: multidisciplinary management of hepatitis C virus treatment in randomly selected drug users with chronic hepatitis. *J Addict Med* 2010; **4:** 223–32.
152 Carrion JA, Gonzalez-Colominas E, Garcia-Retortillo M *et al.* A multidisciplinary support programme increases the efficiency of pegylated interferon alfa-2a and ribavirin in hepatitis C. *J Hepatol* 2013; **59:** 926–33.
153 Ho CJ, Preston C, Fredericks K *et al.* A unique model for treating chronic hepatitis C in patients with psychiatric disorders, substance abuse, and/or housing instability. *J Addict Med* 2013; **7:** 320–4.
154 Hussein M, Benner JS, Lee D, Sesti AM, Battleman DS, Brock-Wood C. Propensity score matching in the evaluation of drug therapy management programs: an illustrative analysis of a program for patients with hepatitis C virus. *Qual Manag Health Care* 2010; **19:** 25–33.
155 Reimer J, Schmidt CS, Schulte B *et al.* Psychoeducation improves hepatitis C virus treatment during opioid substitution therapy: a controlled, prospective multicenter trial. *Clin Infect Dis* 2013; **57(Suppl 2):** S97–104.
156 Rich ZC, Chu C, Mao J *et al.* Facilitators of HCV treatment adherence among people who inject drugs: a systematic qualitative review and implications for scale up of direct acting antivirals. *BMC Public Health* 2016; **16:** 994.
157 Wyles DL, Sulkowski MS, Dieterich D. Management of Hepatitis C/HIV Coinfection in the Era of Highly Effective Hepatitis C Virus Direct-Acting Antiviral Therapy. *Clin Infect Dis* 2016; **63(Suppl 1):** S3–11.
158 Newman AI, Beckstead S, Belcing D *et al.* Treatment of chronic hepatitis C infection among current and former injection drug users within a multidisciplinary treatment model at a community health centre. *Can J Gastroenterol* 2013; **27:** 217–23.
159 Yoo ER, Perumpail RB, Cholankeril G, Jayasekera CR, Ahmed A. Expanding treatment access for chronic hepatitis C with task-shifting in the era of direct-acting antivirals. *J Clin Transl Hepatol* 2017; **5:** 130–3.
160 Yang S, Britt RB, Hashem MG, Brown JN. Outcomes of pharmacy-led hepatitis C direct-acting antiviral utilization management at a veterans affairs medical center. *J Manag Care Spec Pharm* 2017; **23:** 364–9.
161 Lee A, Hanson J, Fox P, Spice G, Russell D, Boyd P. A decentralised, multidisciplinary model of care facilitates treatment of hepatitis C in regional Australia. *J Virus Erad* 2018; **4:** 160–4.
162 Kattakuzhy S, Gross C, Emmanuel B *et al.* Expansion of treatment for hepatitis C virus infection by task shifting to community-based nonspecialist providers: a nonrandomized clinical trial. *Ann Intern Med* 2017; **167:** 311–8.
163 Komaromy M, Duhigg D, Metcalf A *et al.* Project ECHO (Extension for Community Healthcare Outcomes): a new model for educating primary care providers about treatment of substance use disorders. *Subst Abus* 2016; **37:** 20–4.

164 Ní Cheallaigh C, O'Leary A, Keating S *et al.* Telementoring with project ECHO: a pilot study in Europe. *BMJ Innov* 2017; **3:** 144–51.
165 Agley J, Adams ZW, Hulvershorn LA. Extension for Community Healthcare Outcomes (ECHO) as a tool for continuing medical education on opioid use disorder and comorbidities. *Addiction* 2018; **114:** 573–4.
166 Treloar C, Rance J, Bath N *et al.* Evaluation of two community-controlled peer support services for assessment and treatment of hepatitis C virus infection in opioid substitution treatment clinics: the ETHOS study, Australia. *Int J Drug Policy* 2015; **26:** 992–8.
167 Sulkowski M, Ward K, Falade-Nwulia O *et al.* Randomized controlled trial of cash incentives or peer mentors to improve HCV linkage and treatment among HIV/HCV coinfected persons who inject drugs: the CHAMPS Study. *J Hepatol* 2017; **66:** S719.
168 Akiyama MJ, Norton BL, Arnsten JH, Agyemang L, Heo M, Litwin AH. Intensive models of hepatitis C care for people who inject drugs receiving opioid agonist therapy: a randomized controlled trial. *Ann Intern Med* 2019; **170:** 594–603.
169 Henderson C, Madden A, Kelsall J. 'Beyond the willing & the waiting' - The role of peer-based approaches in hepatitis C diagnosis & treatment. *Int J Drug Policy* 2017; **50:** 111–5.
170 Bregenzer A, Conen A, Knuchel J *et al.* Management of hepatitis C in decentralised versus centralised drug substitution programmes and minimally invasive point-of-care tests to close gaps in the HCV cascade. *Swiss Med Wkly* 2017; **147:** w14544.
171 Khan B, Duncan I, Saad M *et al.* Combination interventions for Hepatitis C and Cirrhosis reduction among people who inject drugs: an agent-based, networked population simulation experiment. *PLoS ONE* 2018; **13:** e0206356.
172 Hutchinson SJ, Dillon JF, Fox R *et al.* Expansion of HCV treatment access to people who have injected drugs through effective translation of research into public health policy: Scotland's experience. *IJDP* 2015; **26:** 1041–9.
173 Tait JM, McIntyre PG, McLeod S, Nathwani D, Dillon JF. The impact of a managed care network on attendance, follow-up and treatment at a hepatitis C specialist centre. *J Viral Hepatitis* 2010; **17:** 698–704.
174 Saxon AJ, Malte CA, Sloan KL *et al.* Randomized trial of onsite versus referral primary medical care for veterans in addictions treatment. *Med Care* 2006; **44:** 334–42.
175 Ho SB, Groessl E, Dollarhide A, Robinson S, Kravetz D, Dieperink E. Management of chronic hepatitis C in veterans: the potential of integrated care models. *Am J Gastroenterol* 2008; **103:** 1810–23.
176 Evon DM, Simpson K, Kixmiller S *et al.* A randomized controlled trial of an integrated care intervention to increase eligibility for chronic hepatitis C treatment. *Am J Gastroenterol* 2011; **106:** 1777–86.
177 Knott A, Dieperink E, Willenbring ML *et al.* Integrated psychiatric/medical care in a chronic hepatitis C clinic: effect on antiviral treatment evaluation and outcomes. *Am J Gastroenterol* 2006; **101:** 2254–62.
178 Martinez AD, Dimova R, Marks KM *et al.* Integrated internist—addiction medicine—hepatology model for hepatitis C management for individuals on methadone maintenance. *J Viral Hepat* 2012; **19:** 47–54.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Data extracted from reviewing the literature on hepatitis C models of care (n = 71).■

APPENDIX 2/CHAPTER 3: A SYSTEMATIC REVIEW AND META-ANALYSIS OF COMMUNITY AND PRIMARY-CARE BASED HEPATITIS C TESTING AND TREATMENT SERVICES THAT EMPLOY DIRECT ACTING ANTIVIRAL DRUG TREATMENTS

Radley et al. BMC Health Services Research (2019) 19:765
https://doi.org/10.1186/s12913-019-4635-7

BMC Health Services Research

RESEARCH ARTICLE Open Access

A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments

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Abstract

Background: Direct Acting Antiviral (DAAs) drugs have a much lower burden of treatment and monitoring requirements than regimens containing interferon and ribavirin, and a much higher efficacy in treating hepatitis C (HCV). These characteristics mean that initiating treatment and obtaining a virological cure (Sustained Viral response, SVR) on completion of treatment, in non-specialist environments should be feasible. We investigated the English-language literature evaluating community and primary care-based pathways using DAAs to treat HCV infection.

Methods: Databases (Cinahl; Embase; Medline; PsycINFO; PubMed) were searched for studies of treatment with DAAs in non-specialist settings to achieve SVR. Relevant studies were identified including those containing a comparison between a community and specialist services where available. A narrative synthesis and linked meta-analysis were performed on suitable studies with a strength of evidence assessment (GRADE).

Results: Seventeen studies fulfilled the inclusion criteria: five from Australia; two from Canada; two from UK and eight from USA. Seven studies demonstrated use of DAAs in primary care environments; four studies evaluated integrated systems linking specialists with primary care providers; three studies evaluated services in locations providing care to people who inject drugs; two studies evaluated delivery in pharmacies; and one evaluated delivery through telemedicine. Sixteen studies recorded treatment uptake. Patient numbers varied from around 60 participants with pathway studies to several thousand in two large database studies. Most studies recruited less than 500 patients. Five studies reported reduced SVR rates from an intention-to-treat analysis perspective because of loss to follow-up before the final confirmatory SVR test. GRADE assessments were made for uptake of HCV treatment (medium); completion of HCV treatment (low) and achievement of SVR at 12 weeks (medium).

Conclusion: Services sited in community settings are feasible and can deliver increased uptake of treatment. Such clinics are able to demonstrate similar SVR rates to published studies and real-world clinics in secondary care. Stronger study designs are needed to confirm the precision of effect size seen in current studies. Prospero: CRD42017069873.

Keywords: Hepatitis C, Systematic review, Direct acting antiviral drugs, Primary care

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Background

Of the 71 million persons infected with HCV, 5.6 million (8%) currently inject drugs [1, 2]. The World Health Organization (WHO) has defined global targets for HCV diagnosis and treatment, which represents a major step towards the aim of global elimination by 2030 [3].

However, rates of uptake of HCV testing, linkage to care and treatment remain low across many countries [4]. Barriers to accessing funded Direct Acting Antiviral (DAA) drug treatment may be due to provider concerns regarding co-morbidities, adherence, and side effects management [5]. Social factors affecting treatment access have been categorised as social stigma, housing, criminalisation, health care providers' attitudes and stigmatising practices, and gender [6]. Individuals may prioritise other needs and may be wary of the consequences of a diagnosis on their circumstances; health systems may present complex and rigid arrangements that must be navigated in order to access care [7]. The stigma associated with both injecting drug use and HCV infection is pervasive [8]. The concept of the care cascade has focussed attention on the performance of different pathways and the attrition of patients accessing testing, diagnosis, treatment and care [9].

It is common in many developed and developing countries, for specialist clinicians to provide HCV treatment, often from hospital outpatient facilities [10]. Recently, prescribing of DAAs has become common practice in many countries [10]. Treatment of HCV with these medicines is simple and well-tolerated [11]. The safety profile and high efficacy of DAAs means that HCV treatment can be delivered by a range of non-specialist clinicians including nurses, pharmacists and general practitioners, therefore providing enhanced access to virological cure (SVR) [12]. The ease of transferring care to community and primary care environments is assisted by the use of treatment regimens that do not contain ribavirin or interferon [13]. Progress with implementing treatment pathways provided by non-specialists in community and primary care environments has been identified as one of the key steps in the elimination of HCV [14]. The World Health Organization's Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection promote simplified service delivery models: integration with other services; decentralised services supported by task-sharing; and community engagement, with the intention of reducing stigma and increase uptake of treatment [14].

This review was undertaken to identify rates of treatment uptake, treatment completion and achievement of sustained viral response for adults infected with hepatitis C using DAA-only treatment regimens in community and primary care-based care pathways, evaluated by studies using observational and experimental study designs. Studies that compared community-based treatment care pathways with specialist care were actively sought.

Methods

This systematic review was undertaken and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The methods of analysis and defined inclusion criteria were specified in advance and documented in a study protocol. The study was registered in PROSPERO (CRD42017069873). The PICOS elements defined for this review are set out in Table 1.

The rationale adopted in the design of the PICOS elements was intended to provide some answers to the questions raised by the WHO Guidance and its recommendations for simplified and decentralised treatment delivery models, integrated with other services in community and primary-care environments [14]. Therefore a population over 18 years old was selected, as being less likely to have gained their infection through vertical transmission. Co-infected individuals with other blood borne virus infections were also excluded as their care was likely to be more complex, requiring specialist rather than simplified care. Studies from prison populations were excluded since these individuals lived in contained communities. Studies that utilised interferon and ribavirin-based treatment regimes as the primary intervention were also excluded, since monitoring and patient management requirements, made simplified and decentralised care less likely. Sustained viral response at

Table 1 Elements of the PICOS question defined for this review

	Inclusion	Exclusion
Population	Age 18 years and over Infected with hepatitis C	Age less than 18 years Co-infection with Hepatitis B virus Co-infection with HIV
Intervention	Provision of hepatitis C treatment in any primary care and community environments Treatment using any direct acting antiviral therapy Care provider could be any health care provider	Hepatitis C treatment in prison populations Treatment with ribavirin / interferon regimes as the primary intervention
Comparison	Care in any hospital or secondary care environment or no comparison group	
Outcome	Treatment uptake, treatment completion and SVR outcomes	
Study design	Observational studies, retrospective or prospective cohort studies, randomised trials; conference abstracts; qualitative and mixed methods studies	Case studies; systematic reviews

12 weeks (SVR12) was taken as a marker for virological cure; failure to achieve SVR may be attributed to both treatment failure and loss to follow-up [16]. Studies were restricted to the English language since study resources precluded any translation activities. Published studies were utilised including conference abstracts, in order to capture results from early studies when the first DAAs were introduced into practice.

Search strategy

Published research was identified by formal searches of five electronic databases (Cinahl, Embase, Medline, PsycINFO, PubMed) from January 2013 to December 2017, as well as Google Scholar. The last search was run on 11 December 2017. Search topics included "hepatitis C", "treatment" and "setting". A comprehensive list of search terms related to each of the search topics was used to develop a search strategy for each electronic database. Search strings were formulated by using a combination of keywords and indexed subject headings (MeSH and EMTREE terms). Primary care was defined using the WHO accepted terminology that promotes Primary Care as a key process in the health system: "it is first-contact, accessible, continued, comprehensive and coordinated care" [17] and community environments being the geographical locations where groups of people live.

The full search strategy is set out in Additional file 1. Reference lists of selected articles, citing articles and relevant review articles retrieved during the initial search were handsearched and forward citation checks were undertaken to identify any additional studies. Abstracts from the selected scientific conferences were screened for review eligibility.

Study selection

Data retrieved through the study search strategy were imported into EndNote X8 (Thomson Reuters, New York, NY, USA) and any duplicates removed. Titles obtained from the initial search strategy were screened and irrelevant citations were removed. Abstracts were then assessed using the inclusion and exclusion criteria by two reviewers independently (AR and LT) to establish a relevant pool of evidence for further evaluation. Full-texts from all abstracts identified for further evaluation and were double-screened independently by the two reviewers to assess whether they met the defined inclusion and exclusion criteria. In the event of a disagreement, the senior investigator (JFD) determined final inclusion. The lead author contacted conference abstract authors to attempt to obtain further study results if available. Studies published from identified conference abstracts were screened for review.

Data collection process and data items collected

Data from studies included for analysis were extracted by the lead author (AR) using a standardised data extraction form (Microsoft Excel 2010 Redmond, WA, USA). A second reviewer (ER) also independently assessed the extracted data, and disagreements were resolved by discussion until consensus was reached. The following variables were documented: first author, title, publication year, study design, study location, setting, intervention description, comparator description, sample size outcome description and number of participants achieving SVR12 (and percentage if applicable).

Risk of bias assessment in individual studies

The risk of bias in individual studies was assessed by two reviewers (AR and ER) using the Cochrane Collaboration's risk of bias tool for randomised studies [18] and the "Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses" [19]. For randomised studies, these outcomes were evaluated along the six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The domains deemed as 'high risk' of bias for each study per outcome were determined. Outcomes for the non-randomised studies were evaluated along seven domains: bias due to confounding; bias in selection of participants into study; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in selection of the reported result. The overall risk of bias for these studies was classified into five categories: low risk of bias; moderate risk of bias; serious risk of bias; critical risk of bias or no information.

The NOS scale measures three items: selection of cases and controls including their definition and representativeness; comparability of cases and controls in design and analysis; and exposure ascertainment. The scale has a minimum score of 0 and a maximum score of 9. Risk of bias was rated as high, medium or low according to the scores obtained by reviewing the selection, comparator and exposure categories. Risk of bias was rated low if studies scored 8 or 9; medium risk if studies were scored as 6 or 7. Studies were rated as having a high risk of bias if they were scored as having 5 or less or scored zero for the comparator category [20].

We assessed the strength of evidence using GRADE [21]. The scheme evaluates a required group of domains (study limitations, directness, consistency, precision and reporting bias) and enables grading of the strength of evidence as High; Moderate; Low or Insufficient. Use of this approach enabled us to summarise the outcomes and findings and make clear judgements about the effects of the interventions.

Data analysis

The characteristics and findings of the studies included were summarised and structured using tables. Studies evaluating similar service environments in community

and primary care-settings were grouped together to facilitate comparison.

Study designs, participants, interventions and reported outcomes varied significantly, and a meta-analysis was unable to be performed on all included studies. Studies were excluded from the meta-analysis if the reviewers considered them to be sufficiently flawed so as not to contribute meaningfully to the body of evidence [21].

The characteristics and findings of included studies amenable to meta-analysis were summarised using tables and forest plots. Risk ratio (RR) and corresponding 95% confidence interval (95% CI) was calculated for each study outcome, using the initial number of eligible participants included and the number achieving the outcome of interest in each arm. Analyses were conducted using statistical package Stata v14.0 (College Station, TX, USA).

Data synthesis

Deriving pooled estimates of treatment uptake, treatment completion and SVR

Treatment uptake, treatment completion and SVR and their exact 95% confidence intervals (CIs) were calculated assuming a binomial distribution. Pooled estimates were derived using random- or fixed-effects methods, according to whether significant heterogeneity (defined as $I^2 > 30\%$) was or was not present, respectively. Sensitivity analysis was used to assess the impact of study quality (restricting to studies with an NOS score ≥ 6) on the pooled estimate of SVR.

Further sensitivity analysis was used to assess the impact of conference abstracts on the pooled estimate of SVR. We identified studies using similar environments from which to deliver care and grouped them into categories. Factors identified as linking studies within categories were examined as well as factors that differentiated studies from each other.

Results

Study selection

The searches yielded 9137 publications after removal of duplicates (Fig. 1). This resulted in 121 articles retrieved for full text inspection and 17 included for analysis. Explanations for exclusion of studies at the full text stage are provided in Fig. 1. These included: did not fulfil inclusion criteria; no treatment intervention; review or opinion article; other (e.g. insufficient detail reported in conference abstract).

Study characteristics

Studies evaluated care pathways in primary care [22–28]; in integrated health systems (Extension for Community Healthcare Outcomes, ECHO) [29–32]; in opioid treatment centres [33–35]; in pharmacies/pharmacist clinics [36, 37] and by telemedicine [38]. Characteristics and findings of included studies are set out in Table 2. These studies originated from United States of America (8); Australia (5); United Kingdom (2); and Canada (2). The number of identified studies published as conference abstracts reflected the length of time that DAAs have been widely available outside specialist environments. Six from seventeen studies were only available as conference abstracts. There were two randomised controlled trials, four cohort studies, nine retrospective data analyses and two prospective non-experimental designs. All were conducted on populations at high risk of HCV infection, such as people who inject drugs and people on Opioid Substitution Therapy (OST) programmes. Table 3 describes the outcomes from the meta-analysis of selected studies and Table 4 defines the Strength of Evidence Assessment for identified studies answering the PRISMA objective. Details of assessment of bias and design for studies are located in Additional file 2 (non-randomised) and Additional file 3 (randomised)).

Primary care

Seven studies evaluated interventions to enhance treatment uptake and achievement of SVR in primary care environments [22–28]. One study was a randomised controlled trial (RCT), two were cohort studies and four were non-randomised studies. Four studies utilised nurses in delivery of the care pathway. Three studies included uptake of testing and assessment in their description of care and all the studies discussed uptake of treatment and ascertainment of SVR. The RCT reported a significant difference between those commencing treatment in primary care arm than in the Standard of Care arm (SOC) (75% Vs 34%, $p < 0.001$) and proportion gaining an SVR12 was significantly higher in the primary care arm than in the SOC arm (49% vs 34%, $p = 0.043$).

Two studies reported a reduction in potential SVR rates because of failure of participants to complete the confirmatory blood test at 12 weeks after completion of DAA treatment. All studies reported increased access to treatment in primary care environments and high rates of SVR attainment.

Integrated health systems (ECHO)

Four studies provided evaluations of care through integration of specialist centres with primary care delivery [29–32]. One study was a retrospective cohort study and three were non-randomised studies. Three of the four studies utilised the "ECHO" care pathway in which hepatitis specialists support primary care providers through video-conferencing and collaboration on specific cases, with a defined curriculum and active mentorship [39]. None of the studies discussed uptake of testing amongst their treated cohorts. All studies increased access to treatment and high rates of attainment of SVR.

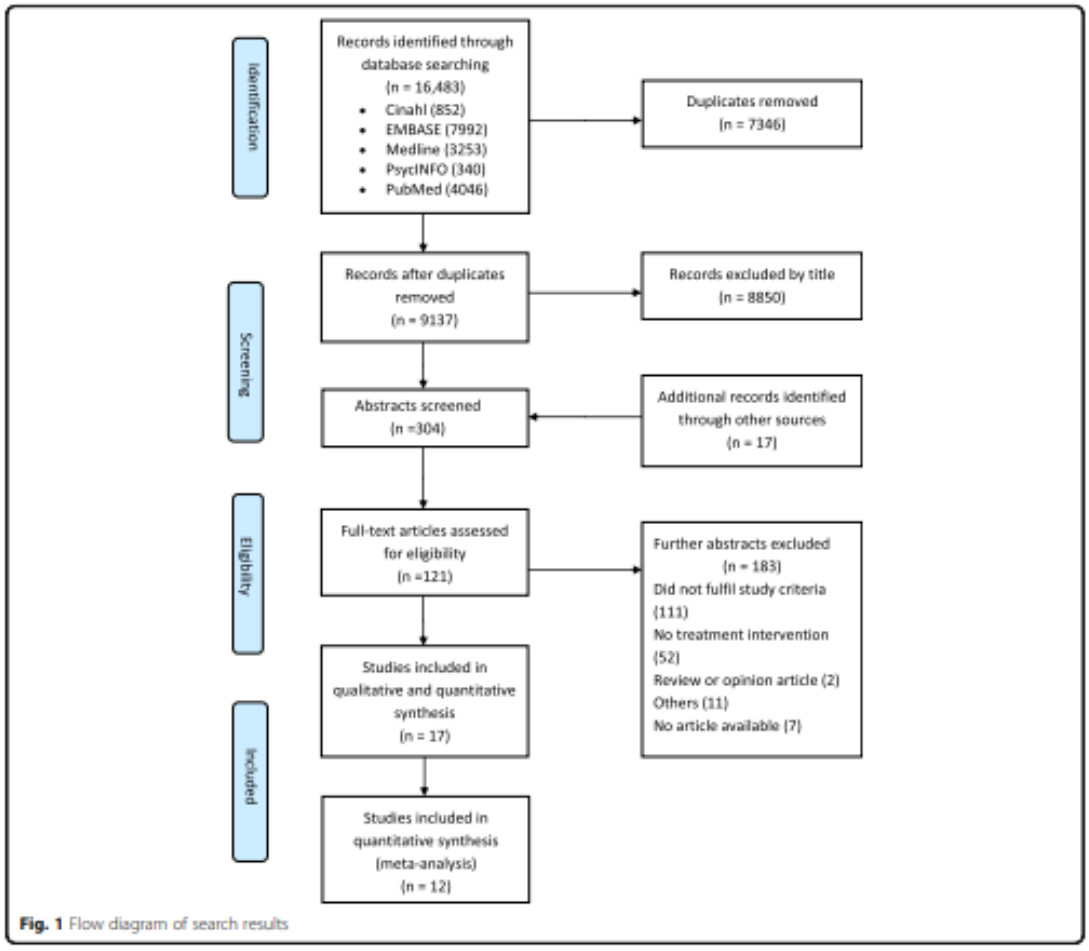

Fig. 1 Flow diagram of search results

Opioid treatment Centres

Three studies evaluated care provision in dedicated setting where people with opioid addiction received harm reduction and treatment services [33–35]. All three studies were non-randomised analyses of treatment data and assessed the uptake and completion of treatment by participants using these services. No assessment of the extent of testing of these populations was discussed. All studies reported high rates of treatment uptake and treatment completion in diagnosed individuals. These studies all described problems with retention of participants in the service post-treatment with consequent reductions in uptake of confirmatory SVR testing.

Pharmacies / pharmacist clinics

Two studies evaluated hepatitis C care provision by pharmacists in community and primary care settings [36, 37]. One study was a feasibility RCT that compared the delivery of a community pharmacy test and treatment pathway with standard hospital-based care. One study was a non-randomised data analysis. The RCT demonstrated an increase in testing uptake, when the participant received all care in a pharmacy environment and showed increased retention in care. Data from this study also demonstrates a marked loss of patients from the care pathway when they were asked to attend the local hospital. The non-randomised study concluded that patients treated in pharmacist clinics achieve high rates of SVR similar to non-pharmacist clinics.

Telemedicine

A single cohort database study [38] compared treatment uptake and SVR rates in participants cared for through a telemedicine pathway ($n = 157$) with participants cared for through a standard care pathway ($n = 1130$). The study

Table 2 Characteristics and findings of included studies

Care Location	Year	Country	Design	Intervention	Comparator	Number of participants	Uptake (%)	SVR (%)
Primary Care								
Bloom	2017	Australia	Prospective cohort study of treatment uptake and SVR	Adherence to DAA treatment protocols	Treatment by tertiary care provider	1044	503 (40.6)	255 (50.2)
Francheville	2017	Canada	Prospective observational study design	Specialist nurse-led care	No comparator group	242	93 (38.4)	82 (88.2)
Kattakuzhy	2017	USA	Non-randomised open label study	Treatment by primary care providers (PCP) and nurse practitioners (NP)	Standard care - Treatment by secondary care clinic	NP 150 PCP 160		NP 134 (89.3) PCP139(86.9)
McClure	2017	Australia	Retrospective data analysis of SVR12	Nurse-led care and GP remote consultation	Specialist care in Tertiary centre	Nurse-led 70	50 (74.3)	46 (65.7)
Miller	2016	USA	Retrospective observational study	Treatment by primary care providers	No comparator group	95		79 (83)
Norton	2017	USA	Retrospective cohort study of SVR	Treatment in urban primary care centre	SVR 12 in PWIDs and non_PWIDs	89		85(95.5)
Wade	2018	Australia	Randomised controlled trial	Testing, assessment and treatment in primary care	Testing, assessment and treatment in tertiary care	59	31 (52.5)	14 (23.7)
Integrated Health Systems (ECHO)								
Abdulmeer	2016	USA	Retrospective data analysis of SVR 12	VA-Echo model supporting primary care providers	No comparator group	588		318 (54)
Beste	2017	USA	Retrospective cohort study of treatment uptake and SVR	VA-Echo model supporting primary care providers	Standard care - Treatment by unexposed primary care providers	6431	1303 (21.4)	(58.2)
Buchanan	2015	United Kingdom	Retrospective data analysis	Community-based outreach clinic	Standard care - Treatment by secondary care clinic	77	24 (31.2)	
Georgie	2016	USA	Retrospective data analysis of SVR12	VA-Echo model supporting primary care providers	Treatment by sub-specialist providers	623		Genotype 1 (GT1) (99) GT2 (98) GT3 (79)
Opioid Treatment Centres								
Bulmer	2017	USA	Retrospective data analysis	Opioid treatment programme	No comparator group	75	750	64 (85.0)
Morris	2017	Australia	Retrospective data analysis of treatment uptake and SVR	Treatment in a community-based harm reduction and treatment facility	No comparator group	127	122 (96)	102 (80.3)
Read	2017	Australia	Retrospective data analysis of	Treatment of PWIDs in primary care	No comparator group	72		59 (81.9)

Table 2 Characteristics and findings of included studies *(Continued)*

Care Location	Year	Country	Design	Intervention	Comparator	Number of participants	Uptake (%)	SVR (%)
			SVR12	setting				
Pharmacies / Pharmacist Clinics								
David	2017	USA	Retrospective data analysis of SVR12	Pharmacy-managed clinics	Treatment by non-pharmacist providers	204		(83.6)
Radley	2017	United Kingdom	Pilot cluster RCT of treatment uptake and SVR	Treatment in community Pharmacy	Treatment by secondary care clinic	26	3 (11.5)	3 (11.5)
Telemedicine								
Cooper	2017	Canada	Retrospective cohort study of treatment uptake and SVR	Use of telemedicine	Treatment by secondary care clinic	157	35.0	18 (11.5)

Table 3 Meta-analysis of studies examining treatment uptake, treatment completion and SVR among people with Hepatitis C treated in a variety of community settings or specialist hospital care

Inclusion Criteria	Treatment Uptake			Treatment Completion			SVR		
	No. Of studies	Heterogeneity (I^2)	Pooled estimate (95% CI)	No. Of studies	Heterogeneity (I^2)	Pooled estimate (95% CI)	No. Of studies	Heterogeneity (I^2)	Pooled estimate (95% CI)
Opioid Treatment Centres				2	77.7%	91.9 (82.2–100)	3	0.0%	82.3 (77.8–86.8)
Integrated Health System (ECHO)	1	Not applicable	75.6 (68.0–83.2)	1	Not applicable	96.8 (93.2–100)	2	84.6%	81.3 (66.9–95.5)
Telemedicine	1	Not applicable	22.3 (15.8–28.8)				1	Not applicable	51.4 (34.8–68.0)
Primary Care	1	Not applicable	67.4 (53.9–80.9)	1	Not applicable	100 (97.95–100)	5	94.9%	74.4 (60.3–88.5)
Pharmacies / Pharmacist Clinics	1	Not applicable	66.67 (58.3–75.1)				2	89.0%	79.0 (79.2–98.9)
Specialist Care	2	0.0%	34.5 (31.79–37.29)				5	96.8%	73.46 (60.9–85.9)

Abbreviations: *CI*, Confidence interval; *SVR*, Sustained virologic response
a. Random-effects method used if $I^2 \geq 30\%$

demonstrated increased access to care form under-served and remote areas and concluded that the telemedicine intervention achieved high rates of treatment initiation and SVR.

Data synthesis

The 12 studies eligible for meta-analysis examined treatment uptake, completion and SVR in a variety of primary care environments; integrated systems (ECHO) that linked specialists with primary care providers; opioid treatment centres; pharmacies / pharmacist clinics; telemedicine and specialist hospital care. The remaining five studies were unsuitable for meta-analysis due to non-reporting of the required outcomes, use of Pegylated interferon or insufficient time to achieve SVR. Across the 12 studies, the pooled estimate is shown in Additional file 4 Table S3. Forest plots for suitable studies are set out in Figs. 2, Fig. 3 and Fig. 4. These plots demonstrate that across the variety of community and primary care environments, a consistent direction of effect to improve treatment uptake, treatment completion and achievement of SVR is seen. Greater uptake was seen for the Primary Care and Pharmacy Locations, compared to the Specialist Care Location and comparable SVR rates were demonstrated (Table 2).

In this analysis, heterogeneity was noted to be high so a sensitivity analysis restricting to higher-quality studies (NOS score ≥ 6) was performed. Despite this the heterogeneity remained high. A further sensitivity analysis was performed restricting the meta-analysis to published studies only. See Additional file 3 in the appendix. This had no impact on heterogeneity.

Discussion

This paper reviews evaluations of care pathways that utilise DAAs in a range of community and primary care settings. The WHO Guidelines on care and treatment of persons diagnosed with chronic HCV infection promote simplified service delivery models; integration with other services; decentralised services supported by task-sharing; and community engagement to address stigma and increase reach [14]. The studies considered in this systematic review

Table 4 Summary of key findings, outcomes and strength of evidence

Outcome	Study designs/ No. Studies	Findings and Direction of Effect	GRADE[21]
1. Uptake of HCV treatment	RCT – 2 Cohort – 3 Observational – 5	Two RCTs assessed as having low risk of bias reported a positive effect on uptake with precision and a consistent positive direction of effect. One cohort study assessed as having medium-grade study limitations also reported a positive effect on uptake.	Medium
2. Completion of Treatment	Cohort - 1 Observational - 2	One cohort study with medium study limitations reported a positive direction of effect on uptake.	Low
3. Sustained Viral Response at 12 weeks (%)(SVR12)	RCT –2 Cohort - 4 Observational - 11	Two RCTs assessed as having low risk of bias reported a positive effect on SVR but were imprecise in the estimate of effect size. Four cohort studies and 11 observational studies with over 10,000 participants all reported a consistent positive direction of effect, but with significant study limitations.	Medium

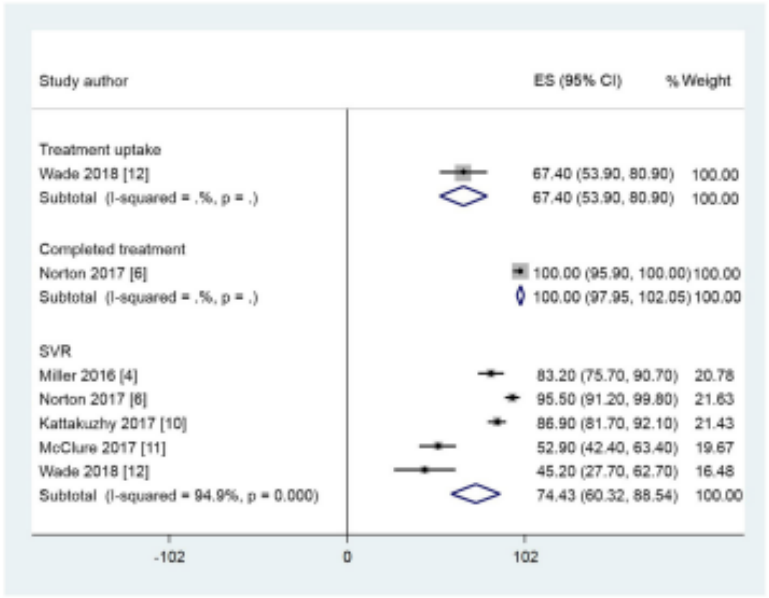

Fig. 2 Forest plots of treatment uptake, completed treatment and SVR rates for selected studies in the Primary Care Location

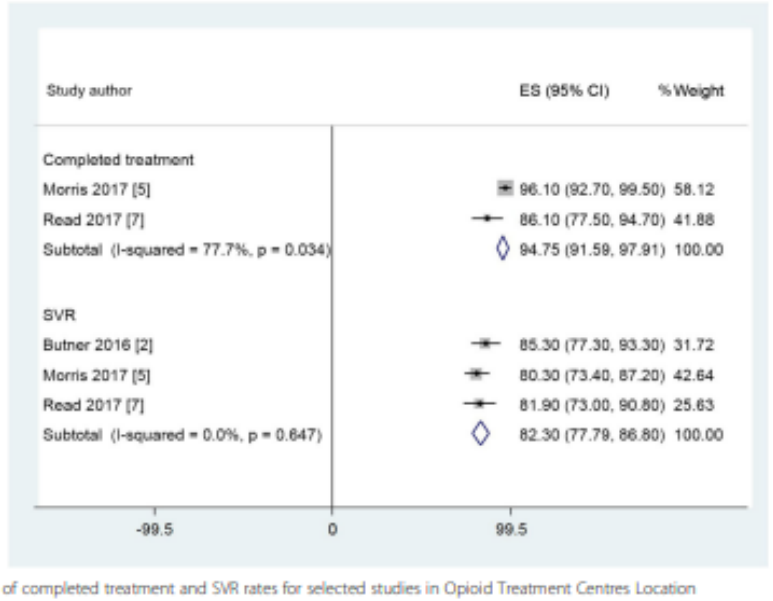

Fig. 3 Forest plots of completed treatment and SVR rates for selected studies in Opioid Treatment Centres Location

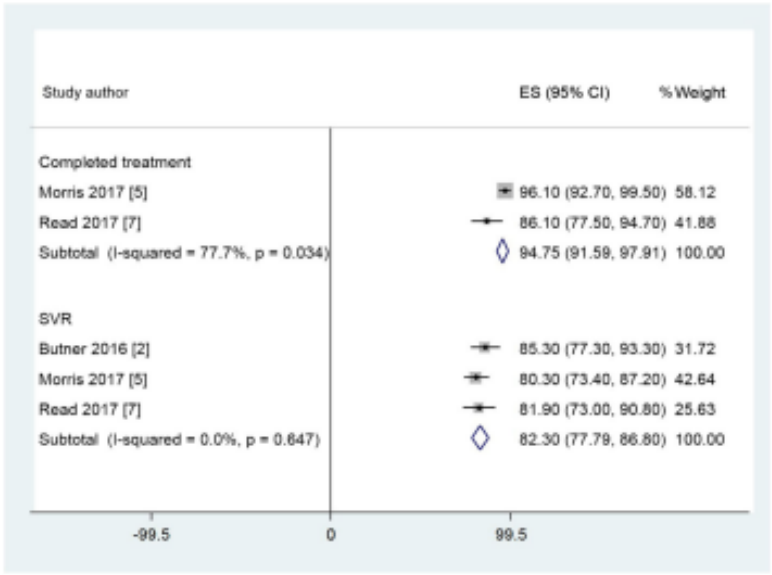

Fig. 4 Forest plots of treatment uptake and SVR rates for studies in the Pharmacy / Pharmacist Clinic Location

and meta-analysis therefore provide some evidence for the extent of implementation of these guidelines.

The studies identified that met our inclusion criteria were grouped according to location: primary care; integrated health care systems (ECHO); opioid treatment centres; in pharmacies / pharmacist clinics; and through telemedicine. These care pathways acknowledged the need to provide local services with reach into the communities where people with hepatitis C live their lives.

In all three areas assessed in our study: uptake of treatment; completion of treatment; and attainment of SVR, a positive outcome was reported by all identified studies. This was seen across each of the distinct environments from which the care was provided. Since the positive outcomes were drawn from distinctly different pathways of care, further confidence might be inferred from this consistency of direction of effect. However, amongst the studies that met our inclusion criteria, there was a lack of studies using comparators from specialist centres. Data contained in these studies nevertheless demonstrated high uptake of treatment and high rates of attainment of SVR: among populations of vulnerable people who normally struggle to access care. Studies that did include comparators showed no significant differences in uptake or SVR. Several of the studies reported an increased uptake of treatment, but most reported equivalence. Some studies reported lower rates of attainment of SVR, because of study participants failing to undergo a confirmatory blood test post-treatment, within the study timelines. With DAAs SVR rates of greater than 97% are delivered if patients adhere to treatment, therefore completion of therapy can be a surrogate for SVR [16].

Previous systematic reviews have considered barriers and facilitators to care, as well as the views and experiences of people who inject drugs [7, 40]. These studies concluded that the target groups for HCV often had poor levels of knowledge about the infection and of the processes involved with testing and treatment. A fear of stigma and discrimination and a reticence to discuss risk behaviours tended to prevent engagement. These barriers could be addressed through educating participants, increasing awareness and redress of institutionalised stigma and integrating HCV treatment pathways into other services where the target group were likely to go.

Increased uptake of testing has been observed when testing is offered at the same time as other routine care [4]; with integrated services for both opioid users and with mental health services. There are advantages to targeting services at populations with predicted high prevalence of HCV [41]. Provision of HCV treatment as part of a directly observed treatment arrangement, increased attainment of SVR [42]. Achievement of these factors within local health systems needs to be commonplace if the WHO target for elimination is to be met [43]. There is some evidence that this is now happening [44].

The results from this systematic review highlight the lack of well-controlled randomised controlled trials and

comparative studies, with just two randomised controlled trials identified and four cohort studies. While the publication of such studies is an important step in building confidence that decentralisation of hepatitis C treatment can be accomplished, the paucity of evidence reflects the difficulty in funding pathways to care studies and the relatively recent removal of the restrictions on the use of DAAs. Two further studies have been commenced identify that further evaluations of interferon-free treatments in primary care environments are underway [45, 46].

As with most systematic reviews, the quality of the studies and the heterogeneity of the study populations included in the analysis present a limitation of this study. The sensitivity analyses performed for our analysis did not have an impact on heterogeneity, meaning that an unexplained source of heterogeneity may be present. These difficulties may reflect the variety of ways in which patients can access HCV treatment. This may be positive and may be explained by the development of more patient centred pathways. These factors prevented a meta-analysis being achieved for many of the studies identified as eligible through the PICOS question defined for this review. Many of the studies that met the inclusion criteria were only available as conference abstracts at the time of review, including one of the randomised controlled trials. Nevertheless, over 10,000 participants were included in the identified studies. All studies had a consistent direction of effect, providing optimism that future evaluations will confirm with precision the effect size that should be delivered by simplifying treatment pathways and decentralising them to primary care. In terms of further limitations, we acknowledge limitations in the chosen methods for the systematic review, including potential publication bias to the findings by excluding non-English language studies; or any other biases introduced by our chosen inclusion and exclusion criteria.

Conclusion

This systematic review and meta-analysis identified studies which demonstrate the feasibility of decentralising care and providing local services with reach into communities of people infected with HCV. Such pathways may increase uptake of treatment and can provide sustained viral responses equivalent to those attained in specialist centres. Further studies are needed to confirm the promising start to the implementation of interferon-free treatment regimens. The successful implementation of such pathways to deliver successful patient outcomes is a key requirement for a "treatment as prevention" strategy as a pathway to elimination of HCV [47].

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12913-019-4635-7.

Additional file 1. Sample search strategy for MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Additional file 2. Table S1 Assessment of risk of bias for included studies – Newcastle/Ottawa Assessment non-randomised studies.

Additional file 3. Table S2 Cochrane Assessment of Randomised Studies.

Additional file 4. Table S3Meta-analysis of published studies examining sustained virologic response among people with Hepatitis C treated in a variety of community settings or specialist hospital care.

Abbreviations

DAA: Direct Acting Antiviral; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HCV: Hepatitis C; HIV: Human Immunodeficiency Virus; NOS: Newcastle Ottawa Scale; OST: Opioid Substitution Therapy; PICOS: Population; Intervention; Comparison; Outcome; Study Design; PRISMA: Preferred Reporting Items for Systematic Reviews and Mata-Analysis; PWID: People Who Inject Drugs; RCT: Randomised Controlled Trial; RR: Risk Ratio; SOC: Standard of Care; SVR: Sustained Viral Response; SVR12: Sustained Viral response at 12 weeks; WHO: World Health Organization

Acknowledgements

Not applicable

Availability of data and material

All data generated or analysed during this are included in this published article (and its supplementary information files).

Authors contributions

Study concept and design – AR, ER, EJA, KA, JFD.
Data acquisition – AR LT, ER, KA.
Interpretation of data – AR, LT, ER.EJA, KA, JFD.
Statistical analysis - ER, EJA.
Drafting of manuscript - AR, ER, EJA, LT, KA, JFD.
Critical review of contributions – AR, ER, EJA, KA, LT, JFD.
Final approval of manuscript – AR, ER, EJA, KA, LT, JFD.
All authors have read and approved the manuscript.

Funding

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

AR: Honorariums from Gilead and Abbvie; Research Grants from Abbvie, Gilead, Bristol Myers Squibb and Roche.
ER: No competing interests to declare.
EJA: no competing interests to declare.
KA: no competing interests to declare.
LT: no competing interests to declare.
JFD: Research Grants, and Honorariums from Abbvie, Bristol Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme and Roche.

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Received: 20 December 2018 Accepted: 14 October 2019
Published online: 28 October 2019

References

1 The Polaris HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017;2:161–76. https://doi.org/10.1016/S2468-1253(16)30181-9.
2 WHO. Global hepatitis report 2017. World Health Organization; Geneva 2017. https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
3 WHO 2016. Combating hepatitis B and C to reach elimination by 2030 – advocacy brief. World Health Organization, Geneva May 2016. http://www.who.int/hepatitis/publications/hep-elimination-by-2030-brief/en/
4 Bajis S, Dore GJ, Hajarizadeh B, Cunningham EB, Maher L, Grebely J. Interventions to enhance testing, linkage to care and treatment uptake for hepatitis C virus infection among people who inject drugs: a systematic review. Int J Drug Policy. 2017;47:34–46. https://doi.org/10.1016/j.drugpo.2017.07.002.
5 World Health Organization Global Health Sector Strategy on Viral Hepatitis 2016-2021. Towards ending viral hepatitis. World Health Organization Geneva 2016 https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/
6 Harris M, Rhodes. Hepatitis C treatment access and uptake for people who inject drugs: a review mapping the role of social factors Harm Reduction Journal 2013 10, 7. doi: https://doi.org/10.1186/1477-7517-10-7.
7 Jones L, Atkinson A, Bates G, McCoy E, Porcellato L, Beynon C. Views and experiences of hepatitis C testing and diagnosis among people who inject drugs: systematic review of qualitative research. Int J Drug Policy. 2014;25:204–11 10.10.1016/j.drugpo.2013.11.004.
8 Dowsett LE, Coward S, Lorenzetti DL, MacKean G, Clement F. Living with hepatitis C virus: a systematic review and narrative synthesis of qualitative literature. Can J Gastroenterol Hepatol. 2017. https://doi.org/10.1155/2017/3268650.
9 Simmons R, Ireland G, Irving W, Hickman M, Sabin C, Ijaz S, Ramsay M, Latimore S, Mandal S. Establishing the cascade of care for hepatitis C in England—benchmarking to monitor impact of direct acting antivirals. J Viral Hepat. 2018;25:482–90. https://doi.org/10.1111/jvh.12844.
10 European Monitoring Centre for Drugs and Drug Addiction. Hepatitis C among drug users in Europe: epidemiology, treatment and prevention, EMCDDA insights 23. Luxembourg: Publications Office of the EU; 2016.
11 Grebely J, Bruneau J, Bruggmann P, Harris M, Hickman M, Rhodes T, Treloar C. Elimination of hepatitis C virus infection among PWID: the beginning of a new era of interferon-free DAA therapy. Int J Drug Policy. 2017;47:26–33. https://doi.org/10.1016/j.drugpo.2017.08.001.
12 Wade AJ, Veronese V, Hellard ME, Doyle JS. A systematic review of community based hepatitis C treatment. BMC Infect Dis. 2016;16:202. https://doi.org/10.1186/s12879-016-1548-5.
13 Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JD, Sulkowski MS. Oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. Ann Intern Med. 2017;166:637–48. https://doi.org/10.7326/M16-2575.
14 Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization; 2018. https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1
15 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux J, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Br Med J. 2009;339:b2700. https://doi.org/10.1136/bmj.b2700.
16 Emmanuel B, Wilson EM, O'Brien TR, Kottilil S, Lau G. Shortening the duration of therapy for chronic hepatitis C infection. Lancet Gastroenterol Hepatol. 2017;2(11):832–6. https://doi.org/10.1016/S2468-1253(17)30053-5.
17 World Health Organisation. Main terminology – primary health care. http://www.euro.who.int/en/health-topics/Health-systems/primary-health-care/main-terminology ().
18 Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org. ().
19 Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp ().
20 Sabbagh HJ, Hassan M, Hassan A, Innes NP, Elkodary HM, Little J, Massey PA. Passive smoking in the etiology of non-Syndromic Orofacial clefts: a systematic review and meta-analysis. PLoS One. 2015. https://doi.org/10.1371/journal.pone.0116963.
21 Berkman ND, Lohr KN, Ansari MT, Balk EM, Kane R, McDonagh M, Morton SC, Viswanathan M, Bass EB, Butler M, Gartlehener G, Hartley L, McPheeters M, Morgan LC, Reston J, Sista P, Whitlock E, Chang S. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015;68:1312e1324.
22 Bloom S, Lubel J, Nicoll A, Gow P, Dev A, Roberts S, Bell S, Kronberg I, Knight V, Sood S, Lewis D, Kemp W, On behalf of the Melbourne Liver Group. Comparison of direct-acting antiviral therapy for hepatitis C between specialist centres and primary care: efficacy and adherence to response assessment. J Gastroenterol Hepatol. 2017;32, 65(suppl 2). https://doi.org/10.1111/jgh.13892.
23 Francheville JW, Rankin R, Beck J, Hoare C, Matemiak S, German G, Barrett L, Bunimov-Wall N, Smyth D. Early success in an open access provincially funded hepatitis C treatment program in Prince Edward Island. Ann Hepatol. 2017;16(5):749–58. https://doi.org/10.5604/01.3001.0010.2757.
24 Kattakuzhy S, Gross C, Emmanuel B, Tefen G, Jenkins V, Silk R, Akoth E, Thomas A, Ahmed C, Espinosa M, Price A, Rosenthal E, Tang L, Wilson E, Bentzen S, Masur H, Kottilil S, the ASCEND Providers. Expansion of treatment for hepatitis C virus infection by task shifting to community-based non-specialist providers: a nonrandomized clinical trial. Ann Inter Med. 2017;167:311–8. https://doi.org/10.7326/M17-0118.
25 McClure T, Olenski M, Ward A, Glasgow S, Stothers L, New K, Papaluca T, Wong D, Burns G, Valaydon Z, Mei SCY, Jeremiah C, Viswanathan K, Croagh C, Howell J, Hong T, Ryan M, Demeduik B, Lust M, Shaw G, Iser D, Nguyen T, Desmond P, Bell S , Thompson AJ. Real-world treatment for hepatitis C in the direct acting antiviral era: Comparing outcomes between the tertiary liver clinic and community J Gastroenterol Hepatol 2017; 32: (suppl 2): 74. DOIhttps://doi.org/10.1111/jgh.13892
26 Miller L, Qualroli K, Lorn J, Fluker SA. Access to and success with new hepatitis c therapy in an urban primary care centre. J. General Internal Medicine 2016: 31 (2) 1: S110. 10.1007%2Fs11606-016-3657-7
27 Norton BL, Fleming J, Bachhuber MA, Steinman M, DeLuca J, Cunningham CO, Johnson N, Laraque F, Litwin AH. High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic. Int J Drug Policy. 2017;47:196–201 https://doi.org/10.1016/j.drugpo.2017.07.021.
28 Wade AJ, Doyle JS, Gane E, Stedman C, Draper B, Iser D, Roberts SK, Kemp W, Petrie D, Scott N, Higgs P, Agius PA, Roney J, Stothers L, Thompson AJ, Hellard ME. Outcomes of Treatment for Hepatitis C in Primary Care, Compared to Hospital-based Care: A Randomized, Controlled Trial in People Who Inject Drugs. Clin Infect Dis. 2019:ciz546. https://doi.org/10.1093/cid/ciz546.
29 Abdulameer A, Leff P, Joshi K, Hepner A, Moore A, Arendt K, Reynolds J, Gish R, Manch R, Kohli A. Effectiveness of sofosbuvir/ledipasvir and sofosbuvir/ simeprevir for the treatment of hepatitis C genotype-1: Real world analysis. Hepatology 2016; 64 (1) S1: 988A-990A.
30 Beste LA, Glorioso TJ, Ho PM, Au DH, Kinsch SR, Todd-Stenberg J, Chang MF, Dominitz JA, Baron AE. Telemedicine speciality support promotes hepatitis C treatment by primary care providers in the department of vetreans affairs. Am J Med. 2017;130(4):432–8. https://doi.org/10.1016/j.ammed.2016.11.019.
31 Buchanan R, Shalabi A, Parkes J, Khakoo S. Hepatology outreach services to overcome inequalities in hepatitis C care in an isolated UK population (PTU 112). Gut. 2015;64(suppl1):A1–A584.
32 Georgie F, Nafisi S, Kohli A, Thornton K, Reynolds J, Moore A, Gish R, Scott J, Deming P, Sedillo M, Qualls C, Box T, Cox P, Mera J, Miller A, Sussman N, Khaderi S, Manch R, Arora S. Primary care physicians utilising the ECHO model equally effective as subspecialists treating HCV using direct-acting antivirals-only regimens: results of the ECHO model (SAT-260). J Hepatol. 2016;64:S631–832. https://doi.org/10.1016/S0168-8278(16)01600-7.
33 Butner JL, Gupta N, Fabian C, Henry S, Shi JM, Tetrault JM. Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program. J Subst Abus Treat. 2017;75:49–53. https://doi.org/10.1016/j.sat.2016.12.014.
34 Morris L, Smirnov A, Kvassay A, Leslie E, Kavanagh R, Alexander N, Davey G, Williams O, Gilks C, Najman J. Initial outcomes of integrated community-based hepatitis c treatment for people who inject drugs: findings from the Queensland injectors' health network. Int J Drug Policy. 2017;47:216–20. https://doi.org/10.1016/j.drugpo.2017.05.056.

35 Read P, Lothian R, Chronister K, Gilliver R, Kearley J, Dore GJ, van Beck I. Delivering direct acting antiviral therapy for hepatitis c to highly marginalised and current drug injecting populations in atargeted primary health care setting. Int J Drug Policy. 2017;47:209–15. https://doi.org/10.1016/j.drugpo.2017.05.032.

36 David C, David D, Essex W, Deming P, Qualls CR, Mera J. Hepatitis c treatment outcomes in a pharmacist-managed clinic in a rural tribal health system. Hepatology 2017; 66 (s1): 331A. Poster 609.

37 Radley A, Tait J, Dillon JF. DOT-C: a cluster randomised feasibility trial evaluating directly observed anti-HCV therapy in a population receiving opioid substitution therapy from a community pharmacy. Int J Drug Policy. 2017;47:126–36. https://doi.org/10.1016/j.drugpo.2017.05.042.

38 Cooper CL, Hatashita H, Corsi DJ, Parmar P, Corin R, Garber G. Direct-acting antiviral therapy outcomes in Canadian chronic hepatitis c telemedicine patients. Ann Hepatol. 2017;16(6):874–80. https://doi.org/10.5604/01.3001.0010.5277.

39 Ní Cheallaigh C, O'Leary A, Keating S, Singleton A, Heffernan S, Keenan E, Robson L, Sears J, Moloney J, Arora S, Bergin C, Norris S On behalf of the Irish Hepatitis C Outcomes Research Network. Telementoring with project ECHO: a pilot study in Europe. BMJ Innovations 2017;3:144–151. doi:https://doi.org/10.1136/bmjinnov-2016-000141.

40 Shehata N, Austin T, Ha S, Timmerman K. Barriers and facilitators of hepatitis C virus screening and testing: a scoping review Canadian Communicable Diseases Reports 2018; 44:7–8. PMID:31011297

41 Aspinall EJ, Doyle JS, Corson S, Hellard ME, Hunt D, Goldberg D, Nguyen T, Ytter YF, Morgan RL, Smith B, Stoove M, Wiktor SZ, Hutchinson S. Targeted hepatitis C antibody testing interventions: a systematic review. Eur J Epidemiol. 2015;30:115–29. https://doi.org/10.1007/s10654-014-9958-4.

42 McDermott CL; Lockhart CM, Devine B. Outpatient directly observed therapy for hepatitis C among people who use drugs: a systematic review and meta-analysis. J Virus Eradication 2018; 4 (2): 118–122. PMC5892673.

43 Grebely J, Dore GJ, Morin S, Rockstroh JK, Klein MB. Elimination of HCV as a public health concern among people who inject drugs by 2030 - what will it take to get there? J Int AIDS Soc. 2017;20(1):22146. https://doi.org/10.7448/IAS.20.1.22146.

44 Wade AJ, McCormack A, Roder C, McDonald K, Davies M, Scott N, Wardrop M, AThan E, Hellard ME. Aiming for elimination: outcomes of a consultation pathway supporting regional general practitioners to prescribe direct-acting antiviral therapy for hepatitis C. J Viral Hepat. 2018:1–10. https://doi.org/10.1111/jvh.12910.

45 Radley de Bruin M, Inglis SK, Donnan PT, Dillon JF. Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: A study protocol for "SuperDOT-C" –a pragmatic cluster randomised trial. BMJ Open 2018 **DOI:** https://doi.org/10.1136/bmjopen-2017-021443

46. Swan D, Cullen W, Macias J, Oprea C, Story A, Surey J, Vickerman P S. Lambert JS. Hepcare Europe - bridging the gap in the treatment of hepatitis C: study protocol, Expert Review of Gastroenterology & Hepatology 2018, 12:3, 303–314, DOI: https://doi.org/10.1080/17474124.2018.1424541

47. Martin NK, Vickerman P, Grebely J, et al. Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. Hepatology. 2013;58:1598–609. https://doi.org/10.1002/hep.26431.

Publisher's Note

APPENDIX 2/CHAPTER 3: FULL SEARCH STRATEGY FOR "A SYSTEMATIC REVIEW AND META-ANALYSIS OF COMMUNITY AND PRIMARY-CARE-BASED HEPATITIS C TESTING"

Sample search strategy for MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Hepatitis C/
2	exp Hepatitis C, Chronic/
3	exp Hepatitis C Antibodies/bl
4	Hepacivirus/
5	Hepatitis C.mp.
6	hepatitic C.mp.
7	Direct Acting Antiviral.mp.
8	Direct-Acting Antiviral.mp.
9	Antiviral Agents/
10	("hepatitis C" or HCV).mp.
11	9 and 10
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11
13	treatment*.mp.
14	family.mp.
15	general.mp.
16	local.mp.
17	regional.mp.
18	walk-in.mp.

19 communit*.mp.

20 primary.mp.

21 outreach.mp.

22 maternal.mp.

23 GP.mp.

24 GPs.mp.

25 dentist$1.mp.

26 healthcentre$1.mp.

27 health centre$1.mp.

28 healthcenter$1.mp.

29 health center$1.mp.

30 healthcare.mp.

31 health care.mp.

32 pharmacy.mp.

33 pharmacies.mp.

34 pharmacist$1.mp.

35 Opiate Substitution Treatment/

36 methadone.mp.

37 buprenorphine.mp.

38 ((opioid or opiate) adj1 (substitution or replacement)).mp.

39 Remote Consultation/

40 Telerehabilitation/

41 telemedicine.mp.

42 telehealth.mp.

43 teleconsultation$1.mp.

44 accessibil*.mp.

45 marginal*.mp.

46 underserved.mp.

47 under-served.mp.

48 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47

49 12 and 13 and 48

50 ..l/ 49 yr=2013-2018

APPENDIX 2/CHAPTER 3: ASSESSMENT OF RISK OF BIAS FOR INCLUDED STUDIES

Table 1: Assessment of risk of bias for included studies – Newcastle/Ottawa Assessment non-randomised studies

Study	**Design**	**Assessment of Bias**			**Comments**
		Selection	**Comparability**	**Outcome**	
Abdulameer	Retrospective data analysis of SVR 12	4	0	1	Conference abstract
Beste	Retrospective cohort study of treatment uptake and SVR12	4	2	3	
Bloom	Prospective cohort study of treatment uptake and SVR 12	4	2	3	Conference abstract
Buchanan	Retrospective data analysis	3	1	1	Conference abstract
Butner	Retrospective data analysis	4	2	3	
Cooper	Retrospective cohort study of treatment uptake and SVR	4	2	3	
David	Retrospective data analysis of SVR12	4	1	2	Conference Abstract
Francheville	Prospective observational study design	2	0	1	
Georgie	Retrospective data analysis of SVR12	4	2	2	Conference Abstract
Kattakuzhy	Non-randomised open label study	3	0	3	
McCLure	Retrospective data analysis of SVR12	4	0	2	Conference abstract
Miller	Retrospective observational study	3	0	3	
Morris	Retrospective data analysis of treatment uptake and SVR 12	3	0	1	
Norton	Retrospective cohort study of SVR 12	3	1	3	
Read	Retrospective data analysis of SVR12	3	0	3	

APPENDIX 2/CHAPTER 3: COCHRANE ASSESSMENT OF RANDOMISED STUDIES

Table 2: Cochrane Assessment of Randomised Studies

Radley	Pilot cluster RCT of treatment uptake and SVR 12	**R**	**A**	**S**	**O**	**B_p**	**B_o**	**I**	
		L	L	L	L	L	L	L	
Wade	Randomised Controlled Trial of treatment uptake and SVR 12	**R**	**A**	**S**	**O**	**B_p**	**B_o**	**I**	Conference abstract
		L	L	L	L	L	L	L	

APPENDIX 2/CHAPTER 3: META-ANALYSIS OF PUBLISHED STUDIES EXAMINING SVR AMONG PEOPLE WITH HCV TREATED IN COMMUNITY SETTINGS OR SPECIALIST HOSPITAL CARE

Table 3: Meta-analysis of published studies examining sustained virologic response among people with Hepatitis C treated in a variety of community settings or specialist hospital care.

Inclusion Criteria	SVR		
	No. Of studies	Heterogeneity[a] (I^2)	Pooled estimate (95% CI)
Places where PWIDs are Treated	3	0.0%	82.3 (77.8-86.8)
Community outreach	1	Not applicable	88.2 (81.6 – 94.8)
Telemedicine	1	Not applicable	51.4 (34.8-68.0)
Primary care	3	81.3%	88.9 (81.6 – 96.3)
Pharmacy	1	Not applicable	93.8 (88.5 – 99.1)
Specialist care	2	97.8%	72.1 (49.9 – 94.2)

APPENDIX 3/CHAPTER 4: R+D APPROVAL FOR THE EVERYONES HCV STUDY

NHS Tayside

12 March 2018

Professor John Dillon
Professor of Hepatology and Gastroenterology
Department of Digestive Diseases
Ninewells Hospital and Medical School
DUNDEE
Scotland
DD1 9SY

Dear Professor Dillon,

R&D MANAGEMENT APPROVAL – TAYSIDE

Title: Evaluation of multiple HCV diagnosis pathways for efficacy, cost effectiveness and cure, in a regionally defined general population. The EVERYONES HCV Study.

Chief Investigator: Professor John Dillon

Principal Investigator/Local Collaborator: Professor John Dillon

Tayside Ref: 2016CO01 **NRS Ref: N/A**

REC Ref: 18/WS/0035

Sponsor: University of Dundee and NHS Tayside

Funder: Gilead

Many thanks for your application to carry out the above project here in NHS Tayside. I am pleased to confirm that the project documentation (as outlined below) has been reviewed, registered and Management Approval has been granted for the study to proceed locally in Tayside.

Approval is granted on the following conditions:-

- ALL Research must be carried out in compliance with the Research Governance Framework for Health & Community Care, Health & Safety Regulations, data protection principles, statutory legislation and in accordance with Good Clinical Practice (GCP).
- All amendments to be notified to TASC R&D Office via the correct amendment pathway. Either direct to the R&D Office or via the Lead Co-ordinating Centre depending on how the study is set up (http://www.hra.nhs.uk/nhshsc-rd-uk-process-management-amendments/).
- All local researchers must hold either a Substantive Contract, Honorary Research Contract, Honorary Clinical Contract or Letter of Access with NHS Tayside where required (http://www.nihr.ac.uk/about-us/CCF/policy-and-standards/research-passports.htm).
- TASC R&D Office to be informed of change in Principal Investigator, Chief Investigator or any additional research personnel locally.

- Notification to TASC R&D Office of any change in funding.
- As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT Security Policies, until destruction of this data.
- All eligible and adopted studies will be added to the Central Portfolio Management System (CPMS). Recruitment figures for eligible and adopted studies must be recorded onto the Portfolio every month. This is the responsibility of the lead UK site. If you are the lead, or only UK site, we can provide help or advice with this. For information, contact Sarah Kennedy (01382 383882 or sarah.kennedy17@nhs.net) or TASCportfolio.tayside@nhs.net.
- Annual reports are required to be submitted to TASC R&D Office with the first report due 12 months from date of issue of this management approval letter and at yearly intervals until completion of the study.
- Notification of early termination within 15 days or End of Trial within 90 days followed by End of Trial Report within 1 year to TASC R&D Office.
- You may be required to assist with and provide information in regard to audit and monitoring of study.

Please note you are required to adhere to the conditions, if not, NHS management approval may be withdrawn for the study.

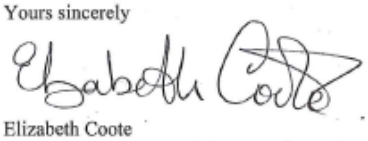
Approved Documents

Document	Version	Date
IRAS Form		
SSI form		
REC Notice of Valid Application Letter		**09/02/18**
REC Favourable Opinion Letter with Conditions		**22/02/18**
REC Favourable Opinion Letter with Conditions Met		**09/03/18**
Sponsorship Letter		**16/01/18**
Insurance Certificate (University of Dundee)		**29/06/17**
Signed Investigator Sponsored Research Agreement		
Caldicott Guardian Approval Letter		**09/03/18**
Funding Award Letter		**20/02/17**
Protocol	**1.0**	**16/01/18**
CV Prof John Dillon		
CV Dr Emma Robinson		**24/10/17**

May I take this opportunity to wish you every success with your project.

Please do not hesitate to contact TASC R&D Office should you require further assistance.

Yours sincerely



Elizabeth Coote
Head of Non-Commercial Research Services

TAyside medical **S**cience **C**entre (TASC)

APPENDIX 3/CHAPTER 4: CALDICOTT APPROVAL = THE EVERYONES HCV STUDY

Information Governance
Maryfield House South
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Dundee
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Dr Emma Robinson
Clinical Research Fellow/
Gastroenterology ST6
Division of Clinical and Molecular Medicine
Level 5 Ninewells Hospital
Dundee
DD1 9SY

Date	9 March 2018
Your Ref	
Our Ref	IGTCAL4762
Enquiries to	Mr J. Donnelly
Extension	70249
Direct Line	N/A
Email	joseph.donnelly@nhs.net

Dear Dr Robinson

CALDICOTT APPROVAL – The EVERYONEs HCV Study

Proposal Sponsor: Professor John Dillon, Professor of Hepatology, NHS Tayside

Data User(s): Dr Emma Robinson, Clinical Research Fellow/Gastroenterology ST6, NHS Tayside

Caldicott approval is given for you to obtain anonymised data on the total number of Hepatitis C antibody and RNA tests sent to the NHS Tayside Virology Laboratory, sorted into positive and negative tests, and referral source. Approval is also given for you to access the Hepatitis C treatment database to determine what percentage of patients per pathway went on to receive treatment for Hepatitis C, and to create an anonymised database for analysis at the University of Dundee, as described in your application and supporting information.

Thank you for your co-operation in providing us with the information requested by us in this process.
Please contact me should any queries arise from the application of this approval.

Yours sincerely

Joseph Donnelly

Joseph Donnelly
Data Protection Officer

disability confident EMPLOYER

APPENDIX 3/CHAPTER 4: FAVOURABLE ETHICAL APPROVAL FOR THE EVERYONES HCV STUDY FROM WEST OF SCOTLAND RESEARCH ETHICS SERVICE

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

Professor John Dillon
Level 5, Division of Clinical & Molecular Medicine
Ninewells Hospital
University of Dundee
Dundee
DD1 9SY

West of Scotland REC 4
Research Ethics
Clinical Research and Development
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SJ
(Formerly Yorkhill Childrens Hospital)

Date 9 March 2018
Direct line 0141 232 1808
E-mail WoSREC4@ggc.scot.nhs.uk

Dear Professor Dillon

Study title: **Evaluation of multiple HCV diagnosis pathways for efficacy, cost effectiveness and cure, in a regionally defined general population. The EVERYONES HCV study.**
REC reference: **18/WS/0035**
IRAS project ID: **242643**

Thank you for your email of 9 March 2018. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 22 February 2018.

Documents received
The documents received were as follows:

Document	*Version*	*Date*
Other [Caldicott Approval Letter]	N/A	09 March 2018

Approved documents
The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor insurance or indemnity]		29 June 2017
IRAS Application Form [IRAS_Form_08022018]		08 February 2018
Letter from funder [Letter from Gilead Re funding]		20 February 2017
Letter from sponsor [Sponsor letter]		16 January 2018

Document	*Version*	*Date*
Other [Caldicott Approval Letter]	N/A	09 March 2018
Research protocol or project proposal [Study protocol]	1.0	16 January 2018
Summary CV for Chief Investigator (CI) [CI CV John Dillon]		
Summary CV for student [Student CV Emma Robinson]		24 October 2017

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

18/WS/0035 **Please quote this number on all correspondence**

Yours sincerely

Rozanne Suarez
REC Manager

Copy to: *Dr Emma Robinson, University of Dundee*
Dr Feruza Nuritova
Liz Coote, Tayside Medical Science Centre

APPENDIX 4/CHAPTER 5: ERADICATING HEPATITIS C: ARE NOVEL SCREENING STRATEGIES FOR PEOPLE WHO INJECT DRUGS COST-EFFECTIVE?

International Journal of Drug Policy 82 (2020) 102811

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research Paper

Eradicating hepatitis C: Are novel screening strategies for people who inject drugs cost-effective?

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ARTICLE INFO

Keywords:
Hepatitis C virus
Economic model
Needle exchange
Economic analysis
Direct acting antiviral

ABSTRACT

Background: In developed countries, people who inject drugs (PWID) have a high prevalence of hepatitis C virus (HCV), yet they are often under-diagnosed. The World Health Organization has set 2030 as a target year for HCV elimination. To meet this target, improving screening in convenient community settings in order to reach infected undiagnosed individuals is a priority. This study assesses the cost-effectiveness of alternative novel strategies for diagnosing HCV infection in PWID. Methods: A cost-effectiveness analysis was undertaken to compare HCV screening at needle exchange centres, substance misuse services and at community pharmacies, with the standard practice of detection during general practitioners' consultations. A decision tree model was developed to assess the incremental cost per positive diagnosis, and a Markov model explored the net monetary benefit (NMB) and the cost per Quality Adjusted Life Years (QALYs) gained over a lifetime horizon. Results: Needle exchange services provided a 7.45-fold increase in detecting positive individuals and an incremental cost of £12,336 per QALY gained against current practice (NMB £163,827), making this the most cost-effective strategy over a lifetime horizon. Screening at substance misuse services and pharmacies was cost-effective only at a £30,000/QALY threshold. With a 24% discount to HCV treatment list prices, all three screening strategies become cost-effective at £20,000/QALY. Conclusions: Targeting PWID populations with screening at needle exchange services is a highly cost-effective strategy for reaching undiagnosed HCV patients. When applying realistic discounts to list prices of drug treatments, all three strategies were highly cost-effective from a UK NHS perspective. All of these strategies have the potential to make a cost-effective contribution to the eradication of HCV by 2030.

Introduction

Hepatitis C virus (HCV) is a blood-borne virus that, if not treated, can cause serious and potentially life-threatening damage to the liver. New HCV treatments can cure over 95% patients (Asselah, Marcellin, & Schinazi, 2018), allowing cured patients to achieve a life expectancy equivalent to the general population. However, most chronic HCV infections are asymptomatic and are therefore only diagnosed in the later, most severe stages of the disease, where cure is less likely. In 2016, the World Health Organization (WHO) set 2030 as a target for HCV elimination (World Health Orrganization, 2016), followed by various countries setting even more ambitious elimination deadlines, such as

Abbreviations: people who inject drugs, (PWID); Hepatitis C virus, (hcv); Net monetary benefit, (NMB); Quality adjusted life years, (QALY); General practitioner, (GP); World health organization, (WHO); Substance misuse services, (SMS); Polymerase chain reaction, (PCR); Dried blood spot, (DBS); Stage liver fibrosis 0, (F0); Stage liver fibrosis 1, (F1); Stage liver fibrosis 2, (F2); Stage Liver Fibrosis 3, (F3); Stage Liver Fibrosis 4, (F4); Decompensated Cirrhosis, (DCC); Hepatocellular carcinoma, (HCC); Liver Transplant, (LT); Post-Liver Transplant, (LT+1); IgG test for HCV antibodies, (IgG); Probabilistic Sensitivity Analysis, (PSA)

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[1] Mr Manca reports grants from Gilead, during the conduct of the study.
[2] Dr. Robinson reports grants from Gilead, during the conduct of the study.
[3] Dr. Dillon reports grants from Gilead, during the conduct of the study; grants and personal fees from Gilead, grants and personal fees from Abbvie, grants and personal fees from Janssen, grants and personal fees from MSD, grants from Cephid, grants from Genedrive, outside the submitted work.
[4] Dr. Boyd reports grants from Gilead Ltd, during the conduct of the study; grants from National Institute for Health Research, grants from Chief Scientist Office for Scotland, grants from Cancer Research UK, outside the submitted work.

https://doi.org/10.1016/j.drugpo.2020.102811

2025 in England (APPG, 2018) and 2024 in Scotland (Health Protection Scotland, 2019). This has encouraged governments to make treatments more widely available, and subsequently, the number of patients receiving HCV treatment has increased worldwide (WHO, 2018). Whilst there have been vast improvements in HCV drug development, the availability of treatment alone is not enough to achieve WHO targets. Enhanced diagnosis and screening strategies are also required (Schröeder et al., 2019).

In the developed world, those most at risk of HCV infection are people who injects drugs (PWID), particularly individuals with unsafe injecting practices, such as sharing injecting equipment. In the UK 143,000 people are living with chronic HCV (Public Health England, 2019) and it is estimated that 90% of them have a history of injecting drug use (NICW, 2012). Yet, this number is considered to be only the "tip of the iceberg" as nearly half of people infected with HCV remain undiagnosed (Dillon, Barclay, Fraser, & Hayes, 2018; Public Health England, 2019). Therefore, to reach the 2030 goal, understanding how to prioritize screening within high-risk populations to reach infected undiagnosed individuals is crucial. In this regard, new models of care based on a complementary involvement of traditional and non-traditional sites of screening have been designed to increase patient engagement in HCV testing and treatment. These non traditional sites of screening include a variety of community settings and points of care. Given the relative newness of these sites of screening there is a need to understand their cost, cost-effectiveness and implications.

The aim of this study was to evaluate the cost-effectiveness of alternative screening strategies for targeting and diagnosing PWID for HCV infections using Tayside (Scotland, UK) as a case study. In recent years, Scotland, and in particular Tayside, has piloted a variety of novel screening strategies. Scotland's Hepatitis C Action Plan (Goldberg David., Innes, & Dillon, 2019; Goldberg et al., 2008), outlined strategies such as moving HCV screening closer to high-risk individuals, including PWIDs, in order to optimise diagnosis and engagement in care. This analysis assessed three alternative screening strategies for HCV detection in PWID that have been piloted in NHS Tayside, Scotland, and compares them to the current UK standard practice of detection during a General Practitioner (GP) consultation.

Methods

Screening strategies & model overview

The strategies we analysed were part of an extensive multipronged model of care for HCV detection developed in Tayside, Scotland. The key difference between the three novel strategies and the standard care was the location/point of care where the screening took place. Novel locations were: a) substance misuse services (SMS), b) needle exchange services, c) community pharmacies providing opiate substitute therapies and injecting equipment. Standard care was screening during GP appointment (see Table 1 for strategies' details). All the strategies were designed to simplify the cascade of care for patients, moving the point of care closer to high-risk individuals and streamlining the screening process, relying on needle exchange workers, nurses or pharmacists rather than doctors. In Tayside, these three novel strategies have all been implemented simultaneously and alongside the standard screening strategy, comprising a pilot of a single complex model of care. The baseline comparator was the current standard care practice in Scotland to detect HCV, which was a screening at a GP practice based on symptoms or high-risk factors. Patients in every strategy differed by (1) attrition across the HCV cascade of care in the short-term (2) demographics, and (3) treatment uptake (see Tables 2 and 3 for details). Testing comprises a HCV antibody test (either dried blood spot test or venous blood test) and a confirmatory PCR test for antibody positive individuals. The PCR is a venous blood test which is more expensive than the antibody test, but provides a confirmed diagnosis of active infection. Different tests require a different amount of time to obtain results, and consequently, this translated into different dynamics and attrition within the cascade. The number of people attending services differed across the strategies, as did the number of tests taken, positive tests results and user-engagement beyond initial testing. Inputs (prevalence, effectiveness, resource use estimates) for the model were derived from observational data from the pilot studies and published literature and were then supported by the knowledge of clinical experts. The model was parameterised to the Scottish and UK context through published life expectancy estimates, utility values, unit cost values and data on PWID-HCV prevalence in Scotland. Model design was based on clinical expert advice and previously published studies analysed in a literature review of economic evaluation of screening strategies for HCV detection (see Supporting Information for details). The needle exchange centre strategy data were obtained from the Cairn Centre Harm Reduction Service in Dundee, which serves approximately 50% of the people who inject drugs in Tayside (NHS Tayside audit data). Pharmacy data were derived from 33 pharmacies dispensing opiate substitute therapies and injecting equipment which provide HCV screening across NHS Tayside. The Dundee Integrated Substance Misuse Service provided the data for SMS service. General Practices across NHS Tayside provided data for the standard practice arm, however, data from this strategy referred to the general population and not to current PWIDs only. Since there is evidence suggesting that there is a higher propensity to screen PWIDs for HCV by GPs (Datta, Horwood, Hickman, & Sharp, 2014; McLeod et al., 2017), and also a likely difference in compliance in the cascade of care, a counterfactual strategy for current PWIDs was built. The counterfactual was based on the average of all the three observed PWID strategies and the available data for screening at GPs for the general population, this estimate was then validated or adjusted based on clinicians' opinions (Table 3). Assumptions regarding the likelihood of a PWID going to a specific testing location were based on advice from clinical experts directly involved in the PWID model of care. The economic analysis initially compares each strategy against the GP strategy (standard care) (pairwise comparison). Strategies are also analysed incrementally to provide the relative cost-effectiveness and

Table 1
HCV Screening strategies.

Screening Strategies:

General practitioner (GP): During a routine GP appointment, there is clinical suspicion that the patient may have HCV and a venous antibody test is requested. The blood sample is sent away for testing and the patient called back in a few days with the results. If positive, a PCR test is also requested. If the result is positive, this is fed back with a further contact to the patient in a few days by the requesting healthcare worker and onward referral is made to HCV specialist services.

Substance Misuse Services: Clients who are being assessed to begin receiving Opiate Substitute Therapies (OST) by the Tayside Substance Misuse Service (SMS), or who are already on an OST, are offered a hepatitis C test. A dried blood spot (DBS) test is taken by an addiction worker at the SMS. Positive antibody tests on DBS are then directly referred to a HCV specialist nurse on site taking routine blood tests and HCV PCR, or working close by in a Needle exchange centre (5 min walking time). If the person is confirmed to have HCV, the patients is contacted in few days to start the treatment, either initiated by the community pharmacists dispensing OST or the HCV specialist nurses in the outreach clinics.

Pharmacies: Clients attending participating community pharmacies to collect their OST are opportunistically offered a HCV test if not previously tested. Clients with positive DBS antibody tests receive a subsequent confirmatory HCV RNA and genotype testing, and their results are delivered in a few days. If HCV infection is confirmed, clients are referred to a HCV service and then they initiate treatment via the community pharmacist or are referred to the HCV specialist nurses for review and treatment in a HCV outreach clinic. Pharmacies running screenings receive fees per patients for using tests, administrative costs and to manage the risk of ordering high cost medications.

Needle exchange centres: People attending the needle exchanges are offered HCV testing via DBS by trained staff at the needle exchange service. If positive, patients are referred to a HCV nurse who take routine bloods tests, including HCV RNA, on site. If the HCV RNA is positive the clients are then contacted in few days and invited to attend an outreach clinic at the needle exchange centre to be started on HCV eradication.

Table 2
Cohorts' figures.

Observational data	Individuals with IgG positive[1]	HCV+ detected	No. individuals with HCV stage assessment	Average age
GP for general population	99	75	60	43[2]
SMS	91	54	24	37
Needle Exchange Centres	61	48	1043	32.5
Pharmacies	77	22	21	39

[1] IgG positivity is intended as initial of the cascade of care, HCV+ detection is the end of the short-term model.
[2] Figure referring to the general population, counterfactual is the result of the average of the other three strategies with the general population.
[3] The higher number of reported disease stage observations is due to repeat assessments during the 2011–17 period.

net monetary benefit of each strategy.

Model structure

We used a deterministic model of HCV treatment and screening to compare the four different screening strategies in the Tayside area. The model comprised a short-term decision tree covering the first year and a Markov model extending it to a lifetime horizon.Theshort-term diagnosis outcomes fed into the long-term analysis (see Fig. 1). The economic analysis took the UK NHS perspective. The decision tree illustrates the HCV cascade of care: the propensity of going to a point of care (screening strategy), type of test offered, result delivery, and if antibody positive a confirmatory PCR test. The main differences across strategies over the short-term were: professional/personnel delivering the screening and type of test (dried blood spot (DBS) or venous sample), timing in delivering the confirmatory test and patients' characteristics (demographics and attrition across the HCV cascade of care). The outcome of the short-term analysis was the incremental cost per additional case detected.

A previously published Markov model (Younossi et al., 2015) was adapted and used to model the treatment and subsequent management pathway which, after screening, followed the natural history of HCV patients over a lifetime horizon. In the model, individuals who had been diagnosed with active HCV infection could be treated or could decline treatment/not respond. If successfully treated, individuals entered into the treatment arm achieving a sustained virologic response (SVR), where they had a much lower probability of progressive liver disease. Patients who were HCV positive but were either untreated, or the treatment failed, moved into the 'no treatment' arm (see Fig. 1). Patients who remained undetected in the short-term model also moved into the 'no treatment' arm in the Markov model, where the natural course of untreated HCV disease progresses (Fig. 1). Patients in both arms could enter the model from mild (stage F0) to severe fibrosis stages (stage F4) and could then potentially progress in the disease moving then further into decompensated cirrhosis (DCC); hepatocellular carcinoma (HCC); liver transplant (LT); post-liver transplant (LT + 1) and death. Outcomes for the lifetime analysis are reported in terms of the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB), based on a willingness to pay threshold of £20,000 per quality-adjusted life year gained (QALY) (NICE 2012).

The different screening strategies determined the outcome of the short-term model (proportion of people detected and treated out of the total number of infected) and their average age at detection. Specifically, the observational data showed a significant difference in mean age of the people accessing the different screening strategies and, therefore, this was applied in the model (Table 1). Thus, all the strategies entered in the model at the same age (32 years, the average age of the population in the strategy with the earliest starting age) but started the screening according to their average age at detection. Disease stage progresses annually with transition probabilities in the model. Hence, strategies with higher average age of screening had a more advanced disease stage at detection (see Supporting Information for more details). A sensitivity analysis using observational data for the initial liver disease severity stage at the time of detection was undertaken (see supporting information and sensitivity analysis section). The length of each cycle in the Markov model was one year. After each cycle patients could remain in their state or change state in line with the model transition probabilities. As the long-term model is an extrapolation of the short-term results, the data coming from strategies' observations were limited to the aggregate demographics of the people screened. The treatment uptake rate, transition probabilities across Markov states, utility values for each state and mortality rates came from published literature relevant to the UK HCV population.

Parameters

Prevalence and transition probabilities

Data on the prevalence of current PWID used in the short-term model came from published literature (Dillon, Barclay, Fraser, & Hayes, 2018; Hutchinson, Bird, & Goldberg, 2005; Surveillance report. hepatitis c antibody positive cases in scotland: results to 31 december 2017, 2017) and experts' advice from clinicians involved in the Tayside model of care (Table 3). The probability of being screened and offered the test was also based on clinicians' opinion. Data on prevalence were derived from a combination of sources and adjusted to year 2017 according to the Health Protection Scotland epidemiology figures of the HCV trend rate over years (Surveillance report. hepatitis c antibody positive cases in scotland: results to 31 december 2017, 2017). This was validated by the clinicians involved in designing the strategies. The probability of every node following the offer or acceptance of the first test (IgG) was driven by observational data from the pilot strategies in Tayside, Scotland. The probability at every node was the proportion of people continuing in the cascade of care. Evidence for the PWID population screened at GPs was based on the average of the figures of the three strategies regarding PWID, with the data coming from the NHS Tayside general population and obtained from GP practices. Sensitivity and specificity of preliminary antibody tests depends on the type of test (a venous sample or DBS). The sample size of every strategy derived from observational data on the number of people tested and recorded in each strategy between 2015 and 2017.

Treatment, mortality and health utilities

HCV treatments applied in the model are the direct-acting antiviral (DAA) regimens recommended by Healthcare Improvement Scotland (Dillon, Barclay, Fraser, & Hayes, 2018). Overall, in Tayside the prevalence of HCV genotype 3 amongst the infected patients is assumed to be 70% and genotype 1 is 30%, in accordance with the local data. Treatment varies based on genotype and on being treatment naïve or experienced (Dillon, Barclay, Fraser, & Hayes, 2018). Treatment regimens were modelled as if all the patients were treatment naïve, a worst-case scenario where all patients were treatment experienced was considered in the sensitivity analysis. Background mortality in the Markov model wasadjusted with the standardised mortality ratio for the PWID population, in accordance with their lower life expectancy (Mathers et al., 2013). Parameters for HCV progression and health utilities for each Markov state were taken from previous published studies (using UK values) (Castelnuovo et al., 2006; McEwan, Kim, & Yuan, 2013; Younossi et al., 2018) (Table 3).

Table 3
Main input parameters.

Parameter	Mean value	Distribution	Source
Population characteristics			
PWID prevalence	0.43	Beta(α = 56.57,β = 74.9)	(Dillon, Barclay, Fraser, & Hayes, 2018; Hutchinson et al., 2005; Surveillance report. hepatitis c antibody positive cases in scotland: results to 31 december 2017, 2017)
Cascade of care			
PWID chance of going to GP	0.25	Norm(μ = 0.25,σ = 0.015)	Assumption
Chance of being screened for all the venues except GP	0.7	Norm(μ = 0.7,σ = 0.043)	Assumption
PWID GP - Chance of being tested if positive	0.20	Norm(μ = 0.2,σ = 0.012)	Assumption
IgG -Venous sample sensitivity	0.98		(Colin et al., 2001)
IgG -Venous sample specificity	0.99		(Colin et al., 2001)
DBS/oral fluid IgG sensitivity	0.92		(Colin et al., 2001; Judd et al., 2003)
DBS/oral fluid IgG specificity	0.99		(Judd et al., 2003)
GP Counterfactual- IgG+ but PCR-	0.138	Beta(α = 12,β = 75)	NHS Tayside
GP Counterfactual- treatment acceptance	0.907	Beta(α = 68,β = 7)	NHS Tayside
GP Counterfactual- PCR acceptance	0.88	Beta(α = 88,β = 11)	NHS Tayside
SMS- IgG+ but PCR-	0.18	Beta(α = 12,β = 54)	NHS Tayside
SMS- treatment acceptance	0.63	Beta(α = 45,β = 26)	NHS Tayside
SMS- PCR acceptance	0.73	Beta(α = 66,β = 25)	NHS Tayside
Needle Exchange- IgG+ but PCR-	0.22	Beta(α = 6,β = 27)	NHS Tayside
Needle Exchange- treatment acceptance	0.76	Beta(α = 103,β = 32)	NHS Tayside
Needle Exchange- PCR acceptance	0.9	Beta(α = 27,β = 3)	NHS Tayside
Pharmacies- IgG+ but PCR-	0.59	Beta(α = 50,β = 72)	NHS Tayside
Pharmacies- treatment acceptance	0.95	Beta(α = 21,β = 1)	NHS Tayside
Pharmacies- PCR acceptance	0.68	Beta(α = 49,β = 21)	NHS Tayside
Transition probabilities			
F0 to F1	0.117	Uniform ± 20%	(Coffin, Scott, Golden, & Sullivan, 2012; Thein, Yi, Dore, & Krahn, 2008)
F1 to F2	0.085	Uniform ± 20%	(Coffin et al., 2012; Thein et al., 2008)
F2 to F3	0.120	Uniform ± 10%	(Coffin et al., 2012; Thein et al., 2008)
F3 to F4	0.116	Uniform ± 20%	(Coffin et al., 2012; Thein et al., 2008)
F3 to HCC	0.002		(Coffin et al., 2012; McEwan et al., 2013; Thein et al., 2008)
F4 to HCC	0.014	Beta(α = 1.93,β = 136.11)	(McEwan et al., 2013; Younossi et al., 2018)
F4 to DC	0.039	Beta(α = 14.62,β = 360.17)	(Martin et al., 2012, 2016)
DC to HCC	0.014	Beta(α = 1.93,β = 136.11)	(Martin et al., 2012, 2016; Younossi et al., 2018)
DC to LT	0.030	Beta(α = 6.53,β = 210.99)	(Martin et al., 2012)
DC to D	0.130	Beta(α = 147.03,β = 983.97)	(Martin et al., 2012)
HCC to LT	0.103		(McGarry et al., 2012; Martin et al., 2012)
HCC to D	0.427	Beta(α = 117.1,β = 155.23)	(McGarry et al., 2012; Martin et al., 2012; Younossi et al., 2018)
LT to D	0.210	Beta(α = 16.28,β = 61.23)	(Martin et al., 2012)
LT1 to D	0.057	Beta(α = 22.9,β = 378.88)	(Martin et al., 2012)
SVR-F3 to SVR F2	0.267		(Younossi et al., 2015)
SVR-F4 to SVR F3	0.076		(Younossi et al., 2015)
SVR relative risk F4 to HCC[a]	0.24		(Morgan et al., 2013; Younossi et al., 2015)
SVR relative risk F3 to HCC[a]	0.24		(Morgan et al., 2013)
SVR relative risk F4 to DC[a]	0.086		(Morgan et al., 2013)
Treatment success, genotype 1 (F0-3)[a]	0.97		(Ahmed et al., 2018)
Treatment success, genotype 1 (F4)[a]	0.95		(Ahmed et al., 2018)
Treatment success, genotype 3 (F0-3)[a]	0.98		(Foster et al., 2015)
Treatment success, genotype 3 (F4)[a]	0.93		(Foster et al., 2015)
Utilities			
F0-F1	0.77	Beta(α = 521.24,β = 155.69)	(Martin et al., 2012)
F2-F3	0.66	Beta(α = 168.25,β = 86.87)	(Martin et al., 2012)
F4	0.55	Beta(α = 521.24,β = 155.69)	(Martin et al., 2012)
HCC	0.45	Beta(α = 123.75,β = 151.25)	(Martin et al., 2012)
DC	0.45	Beta(α = 123.75,β = 151.25)	(Martin et al., 2012)
LT	0.45	Beta(α = 123.75,β = 151.25)	(Martin et al., 2012)
SVR F0-F1	0.82	Beta(α = 65.87,β = 14.46)	(Martin et al., 2012)
SVR F2-F3	0.72	Beta(α = 58.06,β = 22.28)	(Martin et al., 2012)
SVR F4	0.61	Beta(α = 58.05,β = 37.11)	(Martin et al., 2012)
Main Short term unit cost (£ per patient)			
Dried blood spot test	11.55		NHS Tayside(2018)
PCR test	50.25		NHS Tayside(2018)
IgG venous blood sample	12.50		NHS Tayside(2018)
Specialist nurse time	15.25		(Curtis & Burns, 2017)
GP consultation time	28.00		(Curtis & Burns, 2017)
Costs (£ per year)			
DC	12,234	PPInGamma(α = 36.02,β = 253.16)	(Castelnuovo et al., 2006)
HCC	10,904	PPInGamma(α = 18.11,β = 448.8)	(Castelnuovo et al., 2006)
LT	36,664	PPInGamma(α = 89.75,β = 304.5)	(Castelnuovo et al., 2006)
LT +1	1858	PPInGamma(α = 15.22,β = 91.01)	(Castelnuovo et al., 2006)
F4 treated people monitoring expenses	284		NHS reference costs for Ninewells procedures
Treatment costs per cycle			
Genl -cirrhotic	36,500		BNF,2019 prices

(continued on next page)

Table 3 (*continued*)

Parameter	Mean value	Distribution	Source
Gen1-noncirrhotic	36,500		BNF,2019 prices
Gen3-cirrhotic	39,740		BNF,2019 prices
Gen3-noncirrhotic	25,987		BNF,2019 prices
Standardised mortality ratio for PWID	14.68		(Mathers et al., 2013)

[a] Treatment success rate and relative risk parameters do not have distributions, and they were added with no uncertainty into the PSA

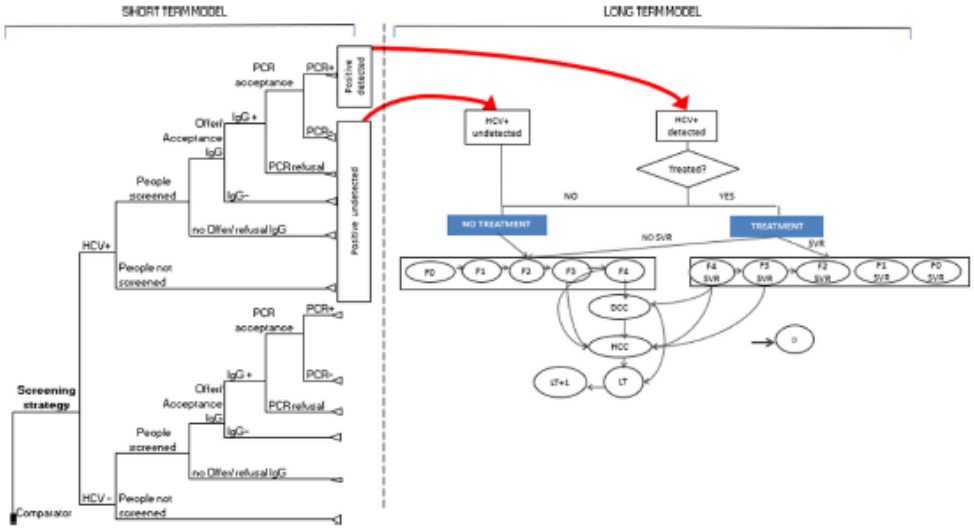


Fig. 1. Short term decision tree & lifetime Markov Model. Markov model structure taken from (Younossi et al., 2018) and adapted to this study. Short term model: IgG= preliminary test to detect HCV antibodies. Individuals can be IgG positive, but they can clear on their own the virus resulting PCR negative (therefore not infected). PCR= confirmatory test. Long term model: DCC= decompensated cirrhosis, D=death, F0-4= metavir score (liver fibrosis stage) in ascending order of severity, HCC= hepatocellular carcinoma, LT= liver transplant, LT+1= after one year of liver transplant, SVR=sustained virologic response.

Costs

Cost data were obtained directly from Ninewells Hospital (Tayside) and NHS Reference costs in accordance with Ninewells procedures. Costs included in the model are those relevant from the UK NHS perspective. This comprised the cost of screening, equipment, testing, treatment and monitoring (Table 3). All costs were adjusted to 2017 prices and discounted annually at 3.5% (NICE 2012). Patients detected and treated at F0, F1, F2 or F3 do not incur further costs. Following treatment patients detected at F4 were assumed to be monitored annually, in accordance with Ninewells Hospital (Tayside) procedures. Scottish national guidelines (Dillon, Barclay, Fraser, & Hayes, 2018) determined the treatment used in the model. Treatment cost was obtained from the British National Formulary. In line with the original model (Martin et al., 2012), individuals with undetected or detected but not treated HCV, were assumed to have no treatment related costs in the model until reaching decompensated cirrhosis. This is the stage when liver disease becomes severe and symptomatic and therefore, patients are assumed to receive care.

Sensitivity analysis

A Probabilistic Sensitivity Analysis (PSA) was undertaken using 1000 iterations Monte Carlo Simulation in which all key parameter inputs to the model were randomly sampled from a predefined probability distribution. The probability distributions mean values and standard errors used for the PSA for the parameters are reported in Table 3. One-way sensitivity analyses were also performed on the following parameters to evaluate further the impact of uncertainty in assumptions and other areas on results:

- 0–100% discount applied to the list price of HCV drug treatments.
- Assumption of 100% treatment uptake after diagnosis.
- 100% increase in offering IgG test by GPs.
- 50% decrease in initial prevalence.
- Substitution of the model diseases stage prevalence at detection with the observable data.
- Same age (32 years) and same initial stage of disease across all the strategies.
- Treatment regimens assuming all patients were treatment experienced.
- The different likelihood of going to a specific screening site for PWIDbased on the number of positive PCR collected in each screening setting from 2015 to 2017.

Scenario analysis

The PWID population has a high risk of re-infection due to their high risk lifestyle (needle and syringe sharing) (Falade-Nwulia, Sulkowski, Merkow, Latkin, & Mehta, 2018; Schulkind et al., 2019), yet re-infection rates are uncertain and vary based on a variety of risk factors. To account for reinfection in the model, a scenario analysis was undertaken whereby an additional transition probability was introduced from the SVR states to the same non-treated state for all the PWID strategies. In effect, this means that after incurring the cost of

Table 4a
Short- and long-term results- pairwise comparison (every strategy vs current practice).

Short term						
Strategy	Expected Strategy cost £	Proportion of detected (% out of total positive)	Cost per positive detected	Incremental cost £	Incremental Effect	ICER
GP PWID	5.61	0.02 (3.9%)	335.07			
SMS	15.08	0.10 (23.4%)	149.82	9.47	8.4%	112
Needle Exchange	19.11	0.12 (28.9%)	152.98	13.49	10.8%	124
Pharmacies	22.91	0.09 (21.9%)	242.16	17.30	7.8%	222
Long term						
Strategy	Cost £ (95% Cred Inter.)	QALY (95% Cred Inter.)	Incremental cost	Incremental QALY	ICER	NMB (£)
GP PWID	5143 (3327,7591)	8.29 (7.93,8.66)	–	–	–	160,737
SMS	8032 (5692,10,190)	8.42 (8.05,8.78)	2889	0.13	22,518	160,414
Pharmacies	9321 (7012, 11,320)	8.44 (8.09,8.79)	4178	0.15	27,402	159,609
Needle Exchange	10,117 (7532,11,787)	8.70 (8.31,9.04)	4974	0.40	12,336	161,814
Reinfection scenario						
GP PWID	5162 (3333,7608)	8.29 (7.91,8.62)	–	–	–	160,589
SMS	8156 (5758,10,371)	8.37 (8.00,8.74)	2995	0.08	35,813	159,267
Pharmacies	9465 (7104,11,526)	8.40 (8.04,8.76)	4304	0.11	39,969	158,439
Needle Exchange	10,369 (7629,12,140)	8.47 (8.07,8.82)	5207	0.19	28,000	159,102

ICER = Incremental Cost-Effectiveness Ratio, NMB = Net Monetary Benefit, QALY = Quality Adjusted Life Years. NMB calculated using a willingness to pay of £20,000/QALY. NMB= [Effectiveness*(Willingness to pay)-Costs]. Due to rounding, Figures throughout the table may not add up to the totals. There may be discrepancies between the reported ICER, NMB and those totals

treatment, some patients were then immediately re-infected and continue to progress in the model as if they had received no treatment. It was assumed that once an individual was re-infected after treatment, the individual did not receive further treatment in the future. The re-infection rate adopted for this scenario was based on the most recent data on HCV re-infection for PWID in Tayside (Rossi et al., 2018). This study mapped reinfection within the same needle exchange centre analysed for the study. To account for a lower reinfection risk in older individuals (Rossi et al., 2018) (and the consequent reduction in sharing propensity), the transition probability of reinfection used was assumed to decrease over time in accordance with the data (Rossi et al., 2018). The reinfection rate at 33 years was 0.10 (average age of screening at needle exchange pathway), and at 40 years was 0.06 (age for PWID going to GP). The rate of re-infection decreased on an average of 7.5% per year.

Results

Offering tests at needle exchange centres was associated with a 10% (7.45-fold) increase in cases detected compared to the standard care (Table 4a). Whereas, for SMS and pharmacies the increase was 8.4% and 7.8%, respectively. Whilst the needle exchange strategy cost £13 per case detected more than screening at GP practices, the most expensive strategy was screening at pharmacies at £17.30 and the cheapest was SMS with £9.47. The highest and lowest strategies in terms of cost per HCV+ detected are a symptomatic screening at GPs (£335) and screening at SMS (£150), respectively. Screening at SMS cost £112 per any additional person screened compared to GP. Screening at needle exchange services had an ICER of £124 per additional HCV+ detected against GP. Each strategy had a low ICER value and could be considered cost-effective compared to the GP current practice in a pairwise comparison. Using an incremental approach (Table 4b), screening at SMS was the most cost-effective strategy in the short term.

The results in the long-term differ from the short-term. Indeed, looking at the cost per QALY in a life time horizon rather than at the cost per case detected, needle exchange was the most cost-effective alternative setting to a screening at GPs. This is because the proportion of positively detected HCV cases incurred costs, quality of life and life expectancy implications over the patient lifetime. In the lifetime analysis only screening at needle exchange was cost-effective with an incremental cost-effectiveness ratio value of £12,336/QALY,generating the greatest QALY gain (0.4 QALYs) in the population due to a higher number of people treated compared to its comparator. Based on the incremental analysis, both SMS and pharmacies were dominated by needle exchange and GP.

Sensitivity & scenario analyses

The results of the PSA suggest that screening at needle exchange was highly likely to be a cost-effective strategy. However, there was considerable uncertainty surrounding the cost-effectiveness of both screening at pharmacies and SMS, respectively, depending on the chosen willingness to pay (WTP) for QALY gains (Fig. 2) (CEAC in Supporting Information).

Assuming all strategies began screening at the same age (32 years) and, with the same disease severity, made both SMS and Pharmacy strategies cost-effective, bringing them below the £20,000/QALY threshold (Fig. 3b). Alternative assumptions regarding the probability of going to a different point of care based on the number of PCR+, as well as having a 100% treatment uptake, had little impact on the cost-effectiveness results. Using the observed value for disease severity at detection made all the strategies cost-effective at less than £5000/QALY compared to the screening at GP (Fig. 3b). An increase in treatment price, such as using a worst-case scenario where allindividuals were treatment experienced and require costlier treatments, led to screening at needle exchange being the only cost-effective strategy (Fig 3b). However, if a 24% discount on the UK list price of treatments was applied, there was the potential for all strategies to be considered cost-effective. (Fig. 3a).

When reinfection rates were introduced to the base case model, all strategies were not cost effective at a threshold of £20,000 per QALY.

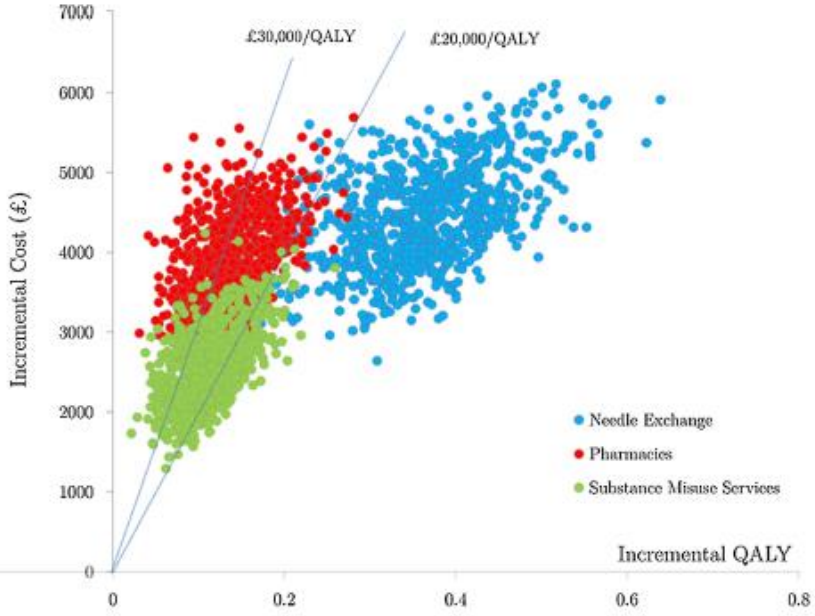
Discussion

In this study we compared each of the three HCV screening strategies both individually and incrementally against the current practice. To the best of our knowledge, this is the first time that data coming from multiple current vanguard screening strategies have been compared to shed light on how current screening policies are performing in tackling HCV from a health economic perspective. We found that novel strategies for targeting and screening PWID populations are likely to be cost-effective compared to current standard care.

While screening at needle exchange resulted in the highest number of cases being detected, the lowest cost per case detected was associated with SMS. Hence, screening at SMS was the most cost effective

Table 4b
Short- and long-term results- incremental comparison.

Short term						
Strategy	Expected Strategy cost £	Proportion of detected (% out of total positive)	Cost per positive detected	Incremental cost £	Incremental Effect	ICER
GP PWID	5.61	0.02 (3.9%)	335.07			
Pharmacies	22.91	0.09 (21.9%)	242.16	Strictly dominated by SMS		
SMS	15.08	0.10 (23.4%)	149.82	9.47	0.08	118.38
Needle Exchange	19.11	0.12 (28.9%)	242.16	4.03	0.02	201.05
Long term						
Strategy	Cost £ (95% Cred Inter.)	QALY (95% Cred Inter.)	Incremental cost	Incremental QALY	ICER	NMB (£)
GP PWID	5143 (3327,7591)	8.29 (7.93,8.66)	–	–	–	
SMS	8032 (5692,10,190)	8.42 (8.05,8.78)	extended dominated by Needle Exchange and GP PWID			
Pharmacies	9321 (7104,11,526)	8.44 (8.09,8.79)	strictly dominated by SMS			
Needle Exchange	10,117 (7532,11,787)	8.70 (8.31,9.04)	4974	0.4	12,336	161,814
Reinfection scenario						
GP PWID	5162 (3333,7608)	8.29 (7.91,8.62)	–	–	–	
SMS	8156 (5758,10,371)	8.37 (8.00,8.74)	extended dominated by Needle Exchange and GP			
Pharmacies	9465 (7104,11,526)	8.40 (8.04,8.76)	extended dominated by Needle Exchange and GP			
Needle Exchange	10,369 (7629,12,140)	8.47 (8.07,8.82)	5207	0.19	28,000	159,102



Pairwise comparison	Probability of being cost effective at different willingness to pay thresholds					
	£0	£10,000	£20,000	£30,000	£40,000	£50,000
Needle exchange	0%	22%	98%	100%	100%	100%
GP	100%	88%	2%	0%	0%	0%
Pharmacies	0%	0%	5%	62%	88%	95%
GP	100%	100%	95%	38%	12%	5%
SMS	0%	0%	29%	83%	95%	99%
GP	100%	100%	61%	17%	5%	1%

Fig. 2. Incremental cost effectiveness plane with all the strategies against the current standard practice - Base case scenario. Table represent the probability of being cost effective for every strategy against the current standard practice (GP) at different willingness to pay.

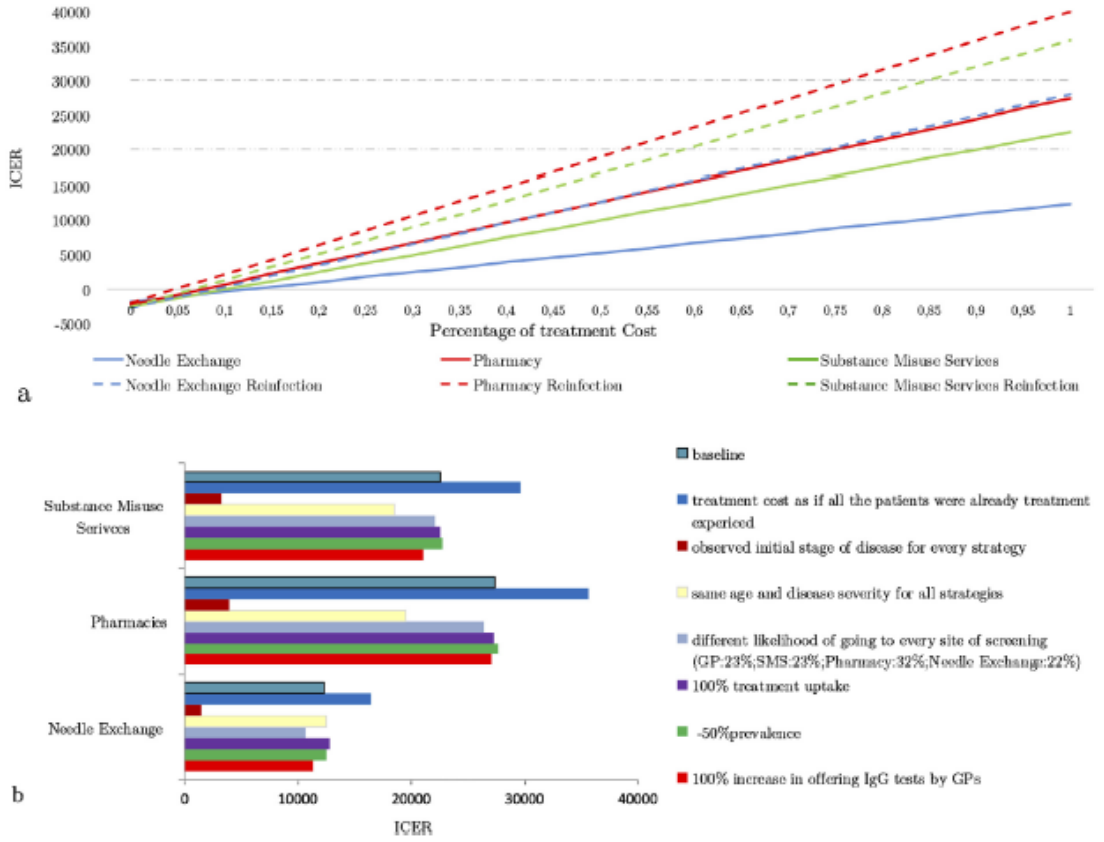


Fig. 3. 3a. Line chart illustrating ICER for screening by the percentage of treatment listed price for baseline and re-infection scenario. 3b. One-way sensitivity analysis.

approach to detect current PWID positive patients, followed by screening at needle exchange services. Indeed, these strategies, which rely on mostly non-clinician personnel are typically less costly. Although in the long term the higher number of people screened and detected incurred greater costs, screening current PWID at needle exchange remained cost-effective. The difference in cost-effectiveness across strategies between short and lifetime horizon was mainly due to disease stage, which was accounted for in the long term. This suggests that screening at an older age, which is more likely in strategies involving SMS and pharmacies, detects disease at more severe stages and, therefore, with more advanced liver damage and lower quality of life after treatment. Screening intensification at GPs for current PWID would increase both the number of people detected, but also the overall cost of the strategy in the short-term. However, even if more people were screened, the average older age of screening would increase the cost of treatment more than the potential gain in QALY in the long term (see long term sensitivity analysis, Fig. 3b). Nevertheless, age was not the sole driver of the cost-effectiveness results in the lifetime model: holding age constant across different strategies, standard screening at the GPs remained the least effective alternative due to the lower detection rate coming from the short-term model (see sensitivity analysis).

In the reinfection scenario, only screening at needle exchange centres was below £30,000/QALY. This may be the result of our data coming from a small sample that reported higher reinfection rates than previous publications (Aspinall et al., 2013; Dimova et al., 2013). Moreover, the reinfection model was designed to consider only treated individuals who could be re-infected if sharing injecting equipment with those who are infected, reducing the cost-effectiveness in the model. However, given the model's static framework, it did not consider that augmenting the number of treated individuals in a population would reduce the pool of potential HCV positive people spreading the infection. A possible change in the propensity of sharing needles after treatment was not taken into account either. In a dynamic scenario, both these last two effects could potentially counterbalance the previous. We suggest that the outcome of our reinfection scenario should be interpreted as an extremely conservative scenario. It is reasonable to expect that with these policies the overall HCV prevalence within the PWID population will decrease. Our results show that changes in prevalence would impact mainly short-term dynamics, but not affect long term conclusions (Fig 3b).

All the strategies involved the same macro population and belonged to the same model of care piloted and performed in Tayside. However, it is reasonable to expect that different screening sites could identify different subpopulations, which do not necessarily overlap. For instance, the regular client of a pharmacy is likely to have a different profile than the needle exchange frequenter (same reasoning for SMS). Unfortunately, the lack of data, in particular regarding the PWID access to differing points of care, means that we were unable to track the

different clients' profile. Thus, we analysed the PWID population as if it was homogeneous across strategies. The result was that screening at needle exchange was the most cost-effective option. Nevertheless, there will likely be challenges for the implementation of screening through a single strategy, such as capacity constraints at a single point of care, individuals' preferences or the availability of a specific test setting, and hence complementary strategies should be considered. To allow for more comprehensive policy suggestions based on observational evidence, governments should invest in data collections across local PWID community services (e.g. to map different client profiles to estimate the weight of every strategy within the model of care) to provide stronger evidence of every strategy's characteristics at local levels. Policymakers should run central policies which include a mix of the most cost-effective approaches reflecting the availability of specific points of care and the prevalence of user profile in a specific area.

The sensitivity analysis of the treatment list price shows that the main driver for the cost-effectiveness analysis is the treatment cost. In Scotland and many other regions and countries there is a nationally published list price for HCV medications, and from these there are confidential negotiations that reduce the costs dependant on volume of sales and other factors. From personal communications reductions in costs are the norm and in the HCV field they are well in excess of 50%. Therefore, analyses with discounted drug prices on the official listed price by the UK British National Formulary (BNF 2019) should be a more realistic representation of the costs in clinical practice. In this regard, a discount of 24% of the treatment listed price made all the strategies in each scenario cost-effective at a £20,000 WTP threshold. For the re-infection scenario, at discount equal to or greater than 48% made all strategies cost-effective. Given the importance of treatment price in our analyses, in countries where the actual HCV treatment price is still high for the health care providers, further negotiation with the industry is crucial to reach sustainable cost-effectiveness strategies. In contexts where this interaction between stakeholders already happens, such as in Scotland where reductions in list costs are the norm, screening strategies are likely to be cost-effective. Hence, the focus of policymakers should be more on stratagems to detect individuals at early stage of disease, improving engagement within the cascade of care and limiting reinfection.

Strengths and limitations

This study sought to evaluate the cost-effectiveness of the current and potential new approaches to tackle HCV detection. Our findings confirm that alternative strategies to detect positive PWID can be highly cost-effective. Specifically, approaches that detect at earlier stages of infection (which is likely to mean younger individuals) and capture a higher number of individuals are expected to be the most cost-effective. However, there were also several limitations to our study.

Firstly, the representativeness of the model of care is unclear as it was based on a small sample of potential screening locations and on a sample of the drug-user population in the Tayside area. Moreover, this was a retrospective study using for the first time a multitude of strategies from a relatively small area. Even if these findings can provide insights to policy makers, results may have a local perspective. For national recommendations, prospective cohort studies need to be implemented, which could overcome the potential bias affecting the selection of our counterfactual. In this regard, given the need to reflect regional differences, central policies should be tailored on evidence from a local level.

Secondly, the lack of data on a few key parameters, such as the proportion of people visiting the different screening sites, led to the use of secondary data sources. Unfortunately, there is currently limited data available on some community services. Therefore, our HCV test acceptance/offer rate was based on expert and clinical opinions of personnel working within the services described in our study. However, this was addressed by testing our assumptions in one-way sensitivity analyses and using wide uncertainty in the PSA.

Thirdly, the reinfection scenario analysis did not take into account a herd immunity factor. Indeed, in small areas, there could be a decrease in incidence since treating people reduces the number of infected people able to transmit the infection. However, it should be noted that usually the reinfection rate is not modelled in screening models and, when it is, it can be very sensitive to authors' assumptions (Geue et al., 2015). We decided to include the prospect of reinfection in a scenario analysis in a static setting. As already mentioned, our reinfection model should be interpreted as an extremely conservative scenario.

Lastly, the model was static and, beyond reinfection, it did not allow for a migration from the PWID status. However, the lack of data regarding this potential transition, the fact that these were retrospective cohorts referring to heterogeneous samples, and the desire to provide a snapshot of an ongoing policy in its first years of operation, led us to build a static model in line with most of the recent literature on cost-effectiveness of HCV treatment (Chhatwal, He, & Lopez-Olivo, 2016) and screening (Geue et al., 2015). Since the static nature of the analysis does not allow direct assessment of the cost-effectiveness of the strategies over time, a plausible decrease in prevalence due to these policies was considered in the sensitivity analysis.

This study presents a comprehensive analysis of a regional HCV screening strategy in the UK and provides insights that need to be addressed to ensure cost-effective decision-making at a national level. For instance, treatment cost has a crucial role in determining whether screening strategies targeting a PWID population are likely to be cost-effective. Overall, the cost-effectiveness of a strategy increases in the short-term with the engagement in the cascade of care, and in the long term with early diagnosis (associated with a point of care screening at younger ages) and treatment cost. In Tayside, screening at all the alternative screening sites seems to respect these requirements. Our results found that screening at needle exchange was likely to be the most cost-effective strategy in the long-term. Indeed, with the application of a plausible discount to the treatment price, the study demonstrates how all the screening strategies could be considered highly cost-effective when compared to the current standard care in the UK. Whilst these results are specific to the Tayside region, the study highlights that there is a need for further investigation to understand how these strategies would perform elsewhere. Governments wishing to achieve the 2030 HCV elimination target must shape central policies based on the effectiveness and cost-effectiveness of different screening strategies at a sub-national level. They should, therefore, invest in further research to enable extensive data collection across regions thus allowing for more comprehensive, tailored and cost-effective decision-making.

Financial support

This work was supported by an Investigator Sponsored Research (ISR) project grant from Gilead Sciences Inc. The design, conduct, analysis and reporting of this study were undertaken by the academic authors and do not reflect the opinions of the funder.

Author contributions

FM and KB designed the economic evaluation. FM analysed data and drafted the manuscript. KB supervised the analysis and reviewed the manuscript. KB, JD designed the study. JD and ER coordinated the study, collected the data and reviewed the final manuscript.

Declaration of Competing Interest

None.

Acknowledgements

We thank Dr Fernando Zanghelini for his contribution in conducting the literature review, during a visiting period at HEHTA. We would also like to thank Robert Heggie for final comments that greatly improved the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2020.102811.

References

Ahmed, H., Abushouk, A. I., Menshawy, A., Attia, A., Mohamed, A., & Negida, A., & Abdel-Daim, M. M. (2018). Meta-analysis of grazoprevir plus elbasvir for treatment of hepatitis C virus genotype 1 infection. *Annals of Hepatology, 17*(1), 18–32.

Aspinall, E. J., Corson, S., Doyle, J. S., Grebely, J., Hutchinson, S. J., & Dore, G. J., & Hellard, M. E. (2013). Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. *Clinical Infectious Diseases, 57*(suppl_2), S80–S89.

Asselah, T., Marcellin, P., & Schinazi, R. F. (2018). Treatment of hepatitis C virus infection with direct-acting antiviral agents: 100% cure? *Liver International, 38*, 7–13.

Castelnuovo, E., Thompson-Coon, J., Pitt, M., Cramp, M., Siebert, U., & Price, A. (2006). *The cost-effectiveness of testing for Hepatitis C in former injecting drug users. NIHR health technology assessment programme: executive summaries.* NIHR Journals Library.

Chhatwal, J., He, T., & Lopez-Olivo, M. A. (2016). Systematic review of modelling approaches for the cost effectiveness of hepatitis C treatment with direct-acting antivirals. *Pharmacoeconomics, 34*(6), 551–567. https://www.ncbi.nlm.nih.gov/books/NBK62307/pdf/Bookshelf_NBK62307.pdf.

Coffin, P. O., Scott, J. D., Golden, M. R., & Sullivan, S. D. (2012). Cost-effectiveness and population outcomes of general population screening for hepatitis C. *Clinical Infectious Diseases, 54*(9), 1259–1271.

Colin, C., Lanoir, D., Touzet, S., Meyaud-Kraemer, I., Bailly, F., & Trepo, C. HEPATIS Group. (2001). Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: An analysis of the literature. *Journal of Viral Hepatitis, 8*(2), 87–95.

Curtis, L. A., & Burns, A. (2017). *Unit costs of health and social care 2017.* University of Kent, Canterbury: Personal Social Services Research Unit.

Datta, S., Horwood, J., Hickman, M., & Sharp, D. (2014). Case-finding for hepatitis C in primary care: A mixed-methods service evaluation. *British Journal of General Practice, 64*(619), e67–e74.

Dimova, R. B., Zeremski, M., Jacobson, I. M., Hagan, H., Des Jarlais, D. C., & Talal, A. H. (2013). Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. *Clinical Infectious Diseases, 56*(6), 806–816.

Falade-Nwulia, O., Sulkowski, M. S., Merkow, A., Latkin, C., & Mehta, S. H. (2018). Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. *Journal of Viral Hepatitis, 25*(3), 220–227.

Foster, G. R., Afdhal, N., Roberts, S. K., Bräu, N., Gane, E. J., & Pianko, S., & Towner, W. J. (2015). Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *New England Journal of Medicine, 373*(27), 2608–2617.

Gesue, C., Wu, O., Xin, Y., Heggie, R., Hutchinson, S., & Martin, N. K. Consortium and BCDC. (2015). Cost-effectiveness of HBV and HCV screening strategies–a systematic review of existing modelling techniques. *PloS One, 10*(12), e0145022.

Goldberg, D., Brown, G., Hutchinson, S., Dillon, J., Taylor, A., & Howie, G. (2008). Hepatitis C action plan for Scotland: Phase II (May 2008-March 2011). *Eurosurveillance, 13*(44-6), 1–2.

Goldberg David., H. S., Innes, H., & Dillon, J. (2019). *Scotland's Hepatitis C Action Plan: Achievements of the first decade and proposals for a Scottish Government Strategy (2019) for the elimination of both infection and disease. Proposal approved by the scottish government july 2019.* Glasgow: Health Protection Scotland. The Scottish Government.

Hutchinson, S. J., Bird, S. M., & Goldberg, D. J. (2005). Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. *Hepatology, 42*(3), 711–723.

Judd, A., Parry, J., Hickman, M., McDonald, T., Jordan, L., & Lewis, K. (2003). Evaluation of a modified commercial assay in detecting antibody to hepatitis C virus in oral fluids and dried blood spots. *Journal of Medical Virology, 71*(1), 49–55.

Martin, N. K., Vickerman, P., Brew, I. F., Williamson, J., Miners, A., & Irving, W. L. (2016). Is increased hepatitis C virus case-finding combined with current or 8-week to 12-week direct-acting antiviral therapy cost-effective in UK prisons? A prevention benefit analysis. *Hepatology, 63*(6), 1796–1808.

Martin, N. K., Vickerman, P., Miners, A., Foster, G. R., Hutchinson, S. J., & Goldberg, D. J. (2012). Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology, 55*(1), 49–57.

Mathers, B. M., Degenhardt, L., Bucello, C., Lemon, J., Wiessing, L., & Hickman, M. (2013). Mortality among people who inject drugs: A systematic review and meta-analysis. *Bulletin of the World Health Organization, 91*, 102–123.

McEwan, P., Kim, R., & Yuan, Y. (2013). Assessing the cost utility of response-guided therapy in patients with chronic hepatitis C genotype 1 in the UK using the MONARCH model. *Applied Health Economics and Health Policy, 11*(1), 53–63.

McGarry, L. J., Pawar, V. S., Panchmatia, H. R., Rubin, J. L., Davis, G. L., & Younossi, Z. M., & Weinstein, M. C. (2012). Economic model of a birth cohort screening program for hepatitis C virus. *Hepatology, 55*(5), 1344–1355.

McLeod, A., Cullen, B. L., Hutchinson, S. J., Roy, K. M., Dillon, J. F., & Stewart, E. A., & Goldberg, D. J. (2017). Limited impact of awareness-raising campaigns on hepatitis C testing practices among general practitioners. *Journal of Viral Hepatitis, 24*(11), 944–954.

Morgan, R. L., Baack, B., Smith, B. D., Yartel, A., Pitasi, M., & Falck-Ytter, Y. (2013). Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: A meta-analysis of observational studies. *Annals of Internal Medicine, 158*(5_Part_1), 329–337.

Health Protection Scotland, (2019). Proposal for Consideration by the Scottish Government. Scotland's Hepatitis C Action Plan: Achievements of the First Decade and Proposals for a Scottish Government Strategy for the Elimination of both Infection and Disease Proposal for Consideration by the Scottish Government; Available from: https://hpspubsrepo.blob.core.windows.net/hps-website/nss/2840/documents/1_HCV-Elimination-Scotland-2019-07-31.pdf.

APPG 2018. Eliminating Hepatitis C in England. 2018 [Retrived 29th September 2019 from: http://www.appghep.org.uk/download/reports/Eliminating%20Hep%20C%20APPG.pdf.

Dillon, J., Barclay, S., Fraser, A., Hayes, P. (2018). National Clinical Guidelines for the Treatment of HCV in Adults. June, 6, 2018. https://hpspubsrepo.blob.core.windows.net/hps-website/nss/1862/documents/1_national-clinical-guidelines-treatment-hepatitis-c-in-adults-june-2018.pdf.

World Health Organization. (2018). *Progress report on access to hepatitis c treatment: focus on overcoming barriers in low-and middle-income countries (No. WHO/CDS/HIV/18.4). Progress report on access to hepatitis c treatment: focus on overcoming barriers in low-and middle-income countries (No. WHO/CDS/HIV/18.4).* Geneva: World Health Organization.

NICE, *The guidelines manual (Process and methods [PMG6]).* (2012). Available at:https://www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness.

Public Health England (2019). *Hepatitis C in the UK 2019. Working to eliminate hepatitis C as a major public health threat.* London: PHE Publications.

Rossi, C., Butt, Z. A., Wong, S., Buxton, J. A., Islam, N., & Yu, A. (2018). Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort. *Journal of Hepatology, 69*(5), 1007–1014.

Schröeder, S. E., Pedrana, A., Scott, N., Wilson, D., Kuschel, C., & Aufegger, L. (2019). Innovative strategies for the elimination of viral hepatitis at a national level: A country case series. *Liver International, 39*(10), 1818–1836.

Schulkind, J., Stephens, B., Ahmad, F., Johnston, L., Hutchinson, S., & Thain, D., & Dillon, J. F. (2019). High response and re-infection rates among people who inject drugs treated for hepatitis C in a community needle and syringe programme. *Journal of Viral Hepatitis, 26*(5), 519–528.

Health Protection Scotland. (2017). *Surveillance report. hepatitis c antibody positive cases in scotland: results to 31 december 2017.* HPS Surveillance Report. Available at: https://www.hps.scot.nhs.uk/web-resources-container/hepatitis-c-antibody-positive-cases-in-scotland-results-to-31-december-2017/.

Thein, H. H., Yi, Q., Dore, G. J., & Krahn, M. D. (2008). Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. *Hepatology, 48*(2), 418–431.

Younossi, Z. M., Park, H., Saab, S., Ahmed, A., Dieterich, D., & Gordon, S. C. (2015). Cost-effectiveness of all-oral Ledipasvir/Sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. *Alimentary Pharmacology & Therapeutics, 41*(6), 544–563.

Younossi, Z., Blissett, D., Blissett, R., Henry, L., Younossi, Y., & Beckerman, R. (2018). In an era of highly effective treatment, hepatitis C screening of the United States general population should be considered. *Liver International, 38*(2), 258–265.

NICE Guidelines (NICE; 2012). Public Health Guidelines.Hepatitis B and C testing: people at risk of infection. Available at: https://www.nice.org.uk/Guidance/PH43.

World Halth Organisation, 2016. Combating Hepatitis B and C to reach elimination by 2030. https://apps.who.int/iris/bitstream/handle/10665/206453/WHO_HIV_2016.04_eng.pdf?sequence=1.

REFERENCES

1. World Health Organisation. Global hepatitis report, 2017 [Internet]. 2017 [cited 2018 Aug 13]. Available from: http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

2. Papatheodoridis G, Hatzakis A. Public health issues of hepatitis C virus infection. Chronic Hepat C Diagn Treat. 2012 Aug 1;26(4):371–80.

3. Martin NK, Vickerman P, Hickman M. Mathematical modelling of hepatitis C treatment for injecting drug users. J Theor Biol. 2011;274.

4. Wedemeyer H, Duberg AS, Buti M, Rosenberg WM, Frankova S, Esmat G, et al. Strategies to manage hepatitis C virus (HCV) disease burden. J Viral Hepat. 2014 May 1;21(s1):60–89.

5. Treloar C, Rance J. How to build trustworthy hepatitis C services in an opioid treatment clinic? A qualitative study of clients and health workers in a co-located setting. Int J Drug Policy. 2014 Sep;25(5):865–70.

6. Goodyear T, Brown H, Browne AJ, Hoong P, Ti L, Knight R. "Stigma is where the harm comes from": Exploring expectations and lived experiences of hepatitis C virus post-treatment trajectories among people who inject drugs. Int J Drug Policy. 2021 Oct;96:103238.

7. Biancarelli DL, Biello KB, Childs E, Drainoni M, Salhaney P, Edeza A, et al. Strategies used by people who inject drugs to avoid stigma in healthcare settings. Drug Alcohol Depend. 2019 May;198:80–6.

8. Blach S, Zeuzem S, Manns M, Altraif I, Duberg AS, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017 Mar 1;2(3):161–76.

9. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013 Apr 1;57(4):1333–42.

10. Omran D, Alboraie M, Zayed RA, Wifi MN, Naguib M, Eltabbakh M, et al. Towards hepatitis C virus elimination: Egyptian experience, achievements and limitations. World J Gastroenterol. 2018 Oct 14;24(38):4330–40.

11. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health. 2017 Dec;5(12):e1192–207.

12. Grebely J, Larney S, Peacock A, Colledge S, Leung J, Hickman M, et al. Global, regional, and country-level estimates of hepatitis C infection among people who have recently injected drugs. Addict Abingdon Engl. 2019 Jan;114(1):150–66.

13. Hellard M, Sacks-Davis R, Doyle J. Hepatitis C elimination by 2030 through treatment and prevention: think global, act in local networks. J Epidemiol Community Health. 2016 Dec 1;70(12):1151.

14. Abutaleb A, Sherman KE. A changing paradigm: management and treatment of the HCV/HIV-co-infected patient. Hepatol Int [Internet]. 2018 Sep 20; Available from: https://doi.org/10.1007/s12072-018-9896-4

15. Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol. 2008;48.

16. Health Protection Scotland. Eliminating hepatitis C [Internet]. Scottish Government; 2019 Jul [cited 2019 Aug 30]. Available from: https://www.gov.scot/news/eliminating-hepatitis-c/

17. Hutchinson SJ, Roy KM, Wadd S, Bird SM, Taylor A, Anderson E, et al. Hepatitis C virus infection in Scotland: epidemiological review and public health challenges. Scott Med J. 2006;51.

18. Health Protection Scotland. Surveillance of hepatitis C testing, diagnosis and treatment in Scotland, 2019 update [Internet]. 2019 [cited 2019 Aug 30]. Available from: https://www.hps.scot.nhs.uk/web-resources-container/surveillance-of-hepatitis-c-testing-diagnosis-and-treatment-in-scotland-2019-update/

19. SHBBV, Health Protection Scotland. Sexual Health and BBV Framework: Indicators for Outcomes 1 - 5 [Internet]. SHBBV Framework Data Portal. 2019 [cited 2019 Aug 30]. Available from: https://hpsmicrosites.scot.nhs.uk/shbbv-framework-data-portal.aspx

20. Wang LS, D'Souza LS, Jacobson IM. Hepatitis C—A clinical review. J Med Virol. 2016 Nov 1;88(11):1844–55.

21. Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: Updated criteria and genotype assignment web resource. Hepatology. 2014 Jan 1;59(1):318–27.

22. Calabrese MJ, Hynicka LM, de Bittner MR, Shaya FT. Future Considerations for the Evaluation of Hepatitis C Virus Treatments in Pan-Genotypic Therapy for Noncirrhotic Treatment-Naive Patients. J Manag Care Spec Pharm. 2018 Jan;24(1):20–2.

23. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014 Nov 1;61(1, Supplement):S58–68.

24. Lingala S, Ghany MG. Natural History of Hepatitis C. Gastroenterol Clin North Am. 2015 Dec;44(4):717–34.

25. Beinhardt S, Payer BA, Datz C, Strasser M, Maieron A, Dorn L, et al. A diagnostic score for the prediction of spontaneous resolution of acute hepatitis C virus infection. J Hepatol. 2013 Nov 1;59(5):972–7.

26. Tada T, Toyoda H, Yasuda S, Miyake N, Kumada T, Kurisu A, et al. Natural history of liver-related disease in patients with chronic hepatitis C virus infection: An analysis using a Markov chain model. J Med Virol. 2019 Oct 1;91(10):1837–44.

27. Gee I, Alexander G. Liver transplantation for hepatitis C virus related liver disease. Postgrad Med J. 2005 Dec 1;81(962):765.

28. Ireland G, Simmons R, Hickman M, Ramsay M, Sabin C, Mandal S. Monitoring liver transplant rates in persons diagnosed with hepatitis C: a data linkage study, England 2008 to 2017. Eurosurveillance [Internet]. 2019 Oct 10 [cited 2022 Jun 2];24(41). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2019.24.41.1900176

29. Younossi ZM, Birerdinc A, Henry L. Hepatitis C infection: A multi-faceted systemic disease with clinical, patient reported and economic consequences. New Perspect HCV Infect. 2016 Oct 1;65(1, Supplement):S109–19.

30. Ishigami M, Honda T, Ishizu Y, Imai N, Ito T, Yamamoto K, et al. Revisiting Prognosis After Liver Transplant in Patients Positive for Hepatitis C Virus: Focus on Hepatitis C Recurrence-Unrelated Complications. Exp Clin Transplant. 2021 Sep;19(9):935–42.

31. Scottish Intercollegiate Guidelines Network. SIGN 133: Managment of hepatitis C. A national clinical guideline [Internet]. SIGN; 2013 [cited 2019 Nov 19]. Available from: https://www.sign.ac.uk/assets/sign133.pdf

32. Holzmayer V, Taylor R, Kuhns MC, Gawel SH, Ndembi N, Mbanya D, et al. Evaluation of hepatitis C virus antibody assay using dried blood spot samples. Sci Rep. 2022 Dec;12(1):3763.

33. NICE. Hepatitis B and C testing: people at risk of infection [Internet]. NICE; 2013. Available from: https://www.nice.org.uk/guidance/ph43

34. Gupta E, Agarwala P, Kumar G, Maiwall R, Sarin SK. Point -of -care testing (POCT) in molecular diagnostics: Performance evaluation of GeneXpert HCV RNA test in diagnosing and monitoring of HCV infection. J Clin Virol. 2017 Mar;88:46–51.

35. Iwamoto M, Calzia A, Dublineau A, Rouet F, Nouhin J, Yann S, et al. Field evaluation of GeneXpert ® (Cepheid) HCV performance for RNA quantification in a genotype 1 and 6 predominant patient population in Cambodia. J Viral Hepat. 2019 Jan;26(1):38–47.

36. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology. 2009 Mar;49(3):1017–44.

37. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology. 2007 Jul;46(1):32–6.

38. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006 Jun;43(6):1317–25.

39. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018 Aug 1;69(2):461–511.

40. World Health Organisation. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. [Internet]. 2018 [cited 2019 May 7]. Available from: https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1

41. Schulkind J, Stephens B, Ahmad F, Johnston L, Hutchinson S, Thain D, et al. High response and re-infection rates among people who inject drugs treated for hepatitis C in a community needle and syringe programme. J Viral Hepat. 2019 May;26(5):519–28.

42. Basyte-Bacevice V, Kupcinskas J. Evolution and Revolution of Hepatitis C Management: From Non-A, Non-B Hepatitis Toward Global Elimination. Dig Dis. 2020;38(Suppl. 2):137–42.

43. Wishart Research Group. Drugbank Online [Internet]. Wishart Research Group; 2022. Available from: https://go.drugbank.com/drugs/DB08934

44. Yee J, Carson JM, Hajarizadeh B, Hanson J, O'Beirne J, Iser D, et al. High Effectiveness of Broad Access Direct-Acting Antiviral Therapy for Hepatitis C in an A ustralian Real-World Cohort: The REACH-C Study. Hepatol Commun. 2022 Mar;6(3):496–512.

45. Bailey JR, Barnes E, Cox AL. Approaches, Progress, and Challenges to Hepatitis C Vaccine Development. Gastroenterology. 2019 Jan;156(2):418–30.

46. Mehta SH, Cox A, Hoover DR, Wang XH, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. The Lancet. 2002 Apr 27;359(9316):1478–83.

47. Grebely J, Conway B, Raffa JD, Lai C, Krajden M, Tyndall MW. Hepatitis C virus reinfection in injection drug users. Hepatology. 2006 Nov 1;44(5):1139–45.

48. Osburn WO, Fisher BE, Dowd KA, Urban G, Liu L, Ray SC, et al. Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. Gastroenterology. 2010 Jan;138(1):315–24.

49. World Health Organisation. Draft global health sector strategies. Viral hepatitis, 2016-2021 [Internet]. 2016 [cited 2019 May 7]. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-en.pdf?ua=1

50. Health and Social care. Sexual Health and Blood Borne Virus Framework 2015-2020 Update [Internet]. Scottish Government; 2015. Available from: https://www.gov.scot/publications/sexual-health-blood-borne-virus-framework-2015-2020-update/

51. Marshall AD, Cunningham EB, Nielsen S, Aghemo A, Alho H, Backmund M, et al. Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. Lancet Gastroenterol Hepatol. 2018 Feb;3(2):125–33.

52. Bajis S, Maher L, Treloar C, Hajarizadeh B, Lamoury FMJ, Mowat Y, et al. Acceptability and preferences of point-of-care finger-stick whole-blood and venepuncture hepatitis C virus testing among people who inject drugs in Australia. Int J Drug Policy. 2018 Nov 1;61:23–30.

53. Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. Restrictions for Medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. Ann Intern Med. 2015 Aug 4;163(3):215–23.

54. World Health Organization. Progress report on HIV, viral hepatitis and sexually transmitted infections 2019: accountability for the global health sector strategies [Internet]. 2019. Available from: https://www.who.int/hiv/strategy2016-2021/progress-report-2019/en

55. Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. Clin Infect Dis Off Publ Infect Dis Soc Am. 2013 Aug;57 Suppl 2(Suppl 2):S56–61.

56. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005 Feb;8(1):19–32.

57. Yamey G. Scaling up global health interventions: a proposed framework for success. PLoS Med. 2011 Jun 28;8(6):e1001049.

58. Harries AD, Zachariah R, Jahn A, Schouten EJ, Kamoto K. Scaling up antiretroviral therapy in Malawi-implications for managing other chronic diseases in resource-limited countries. JAIDS. 2009 Nov;52(Suppl. 1):S14–6.

59. Billings DL, Crane BB, Benson J, Solo J, Fetters T. Scaling-up a public health innovation: a comparative study of post-abortion care in Bolivia and Mexico. Soc Sci Med. 2007 Jun;64(11):2210–22.

60. World Bank. Scaling up the impact of good practices in rural development: a working paper to support implementation of the World Bank's rural development strategy. Washington DC: World Bank Agriculture and Rural Development Department; 2003.

61. Reimer J, Haasen C. Need-adapted HCV-treatment setting for injection drug users. The Lancet. 2009 Jun;373(9681):2090–1.

62. Girardin F, Hearmon N, Negro F, Eddowes L, Bruggmann P, Castro E. Increasing hepatitis C virus screening in people who inject drugs in Switzerland using rapid antibody saliva and dried blood spot testing: a cost-effectiveness analysis. J Viral Hepat. 2019 Feb;26(2):236–45.

63. Bajis S, Dore GJ, Hajarizadeh B, Cunningham EB, Maher L, Grebely J. Interventions to enhance testing, linkage to care and treatment uptake for hepatitis C virus infection among people who inject drugs: A systematic review. Int J Drug Policy. 2017 Sep 1;47(Supplement C):34–46.

64. Zhou K, Fitzpatrick T, Walsh N, Kim JY, Chou R, Lackey M, et al. Interventions to optimise the care continuum for chronic viral hepatitis: a systematic review and meta-analyses. Lancet Infect Dis. 2016 Dec;16(12):1409–22.

65. Barror S, Avramovic G, Iglesias M. Hepcheck - enhancing HCV identification and linkage to care for vulnerable populations through intensified outreach screening [Internet]. HepHIV Conference. 2019. Available from: https://www.eurotest.org/Portals/0/PS1_04.pdf

66. Bajis S, Grebely J, Cooper L, Smith J, Owen G, Chudleigh A, et al. Hepatitis C virus testing, liver disease assessment and direct-acting antiviral treatment uptake and outcomes in a service for people who are homeless in Sydney, Australia: The LiveRLife homelessness study. J Viral Hepat. 2019 May 2;

67. Harris M, Rhodes T. Hepatitis C treatment access and uptake for people who inject drugs: a review mapping the role of social factors. Harm Reduct J. 2013;10(1):7.

68. Mah A, Hull MW, DeBeck K, Milloy MJ, Dobrer S, Nosova E, et al. Knowledge of hepatitis C and treatment willingness amongst people who inject drugs in an era of direct acting antivirals. Int J Drug Policy. 2017 Sep;47:137–43.

69. Fortier E, Alavi M, Micallef M, Dunlop AJ, Balcomb AC, Day CA, et al. The effect of social functioning and living arrangement on treatment intent, specialist

assessment and treatment uptake for hepatitis C virus infection among people with a history of injecting drug use: the ETHOS study. Int J Drug Policy. 2015 Nov;26(11):1094–102.

70. Doyle JS, Grebely J, Spelman T, Alavi M, Matthews GV, Thompson AJ, et al. Quality of life and social functioning during treatment of recent hepatitis C infection: a multi-centre prospective cohort. PLOS ONE. 2016 Jun 29;11(6):e0150655.

71. Friedman SR, Tempalski B, Brady JE, West BS, Pouget ER, Williams LD, et al. Income inequality, drug-related arrests, and the health of people who inject drugs: reflections on seventeen years of research. Int J Drug Policy. 2016 Jun;32:11–6.

72. Grebely J, Petoumenos K, Matthews GV, Haber P, Marks P, Lloyd AR, et al. Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: the ATAHC Study. Drug Alcohol Depend. 2010 Mar 1;107(2–3):244–9.

73. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol. 2012;57:399–420.

74. Grebely J, Hajarizadeh B, Dore GJ. Direct-acting antiviral agents for HCV infection affecting people who inject drugs. Nat Rev Gastroenterol Hepatol. 2017 Nov;14(11):641–51.

75. Radley A, Tait J, Dillon JF. DOT-C: A cluster randomised feasibility trial evaluating d irectly o bserved an t i-H C V therapy in a population receiving opioid substitute therapy from community pharmacy. Int J Drug Policy. 2017 Sep;47:126–36.

76. Elsherif O, Bannan C, Keating S, McKiernan S, Bergin C, Norris S, et al. Outcomes from a large 10 year hepatitis C treatment programme in people who inject drugs: no effect of recent or former injecting drug use on treatment adherence or therapeutic response. PLOS ONE. 2017 Jun 21;12(6):e0178398.

77. Birkhead GS, Klein SJ, Candelas AR, O'Connell DA, Rothman JR, Feldman IS, et al. Integrating multiple programme and policy approaches to hepatitis C prevention and care for injection drug users: a comprehensive approach. Int J Drug Policy. 2007 Oct;18(5):417–25.

78. Bruggmann P, Grebely J. Prevention, treatment and care of hepatitis C virus infection among people who inject drugs. U N Off Drugs Crime UNODC Presents Sci Addressing Drugs HIV State Art Harm Reduct. 2015 Feb 1;26:S22–6.

79. The Global Commission on Drug Policy. The negative impact of the war on drugs on public health: the hidden hepatitis C epidemic [Internet]. 2013. Available from: http://www.globalcommissionondrugs.org/hepatitis/

80. Radley A, de Bruin M, Inglis SK, Donnan PT, Hapca A, Barclay ST, et al. Clinical effectiveness of pharmacist-led versus conventionally delivered antiviral treatment for hepatitis C virus in patients receiving opioid substitution therapy: a pragmatic, cluster-randomised trial. Lancet Gastroenterol Hepatol. 2020 Sep 1;5(9):809–18.

81. Grebely J, Haire B, Taylor LE, Macneill P, Litwin AH, Swan T, et al. Excluding people who use drugs or alcohol from access to hepatitis C treatments – is this fair, given the available data? J Hepatol. 2015 Oct;63(4):779–82.

82. Cousien A, Tran VC, Deuffic-Burban S, Jauffret-Roustide M, Mabileau G, Dhersin JS, et al. Effectiveness and cost-effectiveness of interventions targeting harm reduction and chronic hepatitis C cascade of care in people who inject drugs: the case of France. J Viral Hepat. 2018;25(10):1197–207.

83. Mabileau G, Scutelniciuc O, Tsereteli M, Konorazov I, Yelizaryeva A, Popovici S, et al. Intervention packages to reduce the impact of HIV and HCV infections among people who inject drugs in Eastern Europe and Central Asia: a modeling and cost-effectiveness study. Open Forum Infect Dis. 2018 Mar 1;5(3):ofy040.

84. Bennett H, Gordon J, Jones B, Ward T, Webster S, Kalsekar A, et al. Hepatitis C disease transmission and treatment uptake: impact on the cost-effectiveness of new direct-acting antiviral therapies. Eur J Health Econ. 2017 Nov;18(8):1001–11.

85. Iversen J, Grebely J, Catlett B, Cunningham P, Dore GJ, Maher L. Estimating the cascade of hepatitis C testing, care and treatment among people who inject drugs in Australia. Int J Drug Policy. 2017 Sep 1;47:77–85.

86. Leidner AJ, Chesson HW, Spradling PR, Holmberg SD. Assessing the effect of potential reductions in non-hepatic mortality on the estimated cost-effectiveness of hepatitis C treatment in early stages of liver disease. Appl Health Econ Health Policy. 2017 Feb;15(1):65–74.

87. Dillon JF, Lazarus JV, Razavi HA. Urgent action to fight hepatitis C in people who inject drugs in Europe. Hepatol Med Policy. 2016 Jun 30;1(1):2.

88. Zeremski M. Hepatitis C virus control among persons who inject drugs requires overcoming barriers to care. World J Gastroenterol. 2013;19(44):7846.

89. Bruggmann P. Accessing hepatitis C patients who are difficult to reach: it is time to overcome barriers. J Viral Hepat. 2012 Dec;19(12):829–35.

90. Lazarus JV, Safreed-Harmon K, Stumo SR, Jauffret-Roustide M, Maticic M, Reic T, et al. Restrictions on access to direct-acting antivirals for people who inject drugs: the European Hep-CORE study and the role of patient groups in monitoring national HCV responses. Int J Drug Policy. 2017 Sep;47:47–50.

91. Wright N, Reimer J, Somaini L, Roncero C, Maremmani I, Simon N, et al. Are we ready to treat hepatitis C virus in individuals with opioid use disorder: assessment of readiness in European countries on the basis of an expert-generated model. Eur J Gastroenterol Hepatol. 2017 Nov;29(11):1206–14.

92. Maticic M, Zorman JV, Gregorcic S, Schatz E, Lazarus JV. Changes to the national strategies, plans and guidelines for the treatment of hepatitis C in people who inject drugs between 2013 and 2016: a cross-sectional survey of 34 European countries. Harm Reduct J. 2019 Dec;16(1):32.

93. Litwin AH, Kunins HV, Berg KM, Federman AD, Heavner KK, Gourevitch MN, et al. Hepatitis C management by addiction medicine physicians: results from a national survey. J Subst Abuse Treat. 2007 Jul;33(1):99–105.

94. Grebely J, Tyndall MW. Management of HCV and HIV infections among people who inject drugs. Curr Opin HIV AIDS. 2011 Nov;6(6):501–7.

95. Bini EJ, Kritz S, Brown LS, Robinson J, Alderson D, Rotrosen J. Barriers to providing health services for HIV/AIDS, hepatitis C virus infection and sexually transmitted infections in substance abuse treatment programs in the United States. J Addict Dis. 2011 Mar 31;30(2):98–109.

96. Grebely J, Bryant J, Hull P, Hopwood M, Lavis Y, Dore GJ, et al. Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia: assessment and treatment of HCV infection. J Viral Hepat. 2011 Apr;18(4):e104–16.

97. Paterson BL, Backmund M, Hirsch G, Yim C. The depiction of stigmatization in research about hepatitis C. Int J Drug Policy. 2007 Oct;18(5):364–73.

98. Moore GA, Hawley DA, Bradley P. Hepatitis C: studying stigma. Gastroenterol Nurs. 2008 Sep;31(5):346–52.

99. Stoové MA, Gifford SM, Dore GJ. The impact of injecting drug use status on hepatitis C-related referral and treatment. Drug Alcohol Depend. 2005 Jan;77(1):81–6.

100. Myles A, Mugford GJ, Zhao J, Krahn M, Wang PP. Physicians' attitudes and practice toward treating injection drug users infected with hepatitis C virus: results from a national specialist survey in Canada. Can J Gastroenterol. 2011;25(3):135–9.

101. Cox J, Graves L, Marks E, Tremblay C, Stephenson R, Lambert-Lanning A, et al. Knowledge, attitudes and behaviours associated with the provision of hepatitis C care by Canadian family physicians. J Viral Hepat. 2011 Jul;18(7).

102. Cooke GS, Andrieux-Meyer I, Applegate TL, Atun R, Burry JR, Cheinquer H, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2019 Feb;4(2):135–84.

103. Swan D, Long J, Carr O, Flanagan J, Irish H, Keating S, et al. Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: a qualitative exploration. AIDS Patient Care STDs. 2010 Dec;24(12):753–62.

104. Strathdee SA, Latka M, Campbell J, O'Driscoll PT, Golub ET, Kapadia F, et al. Factors associated with interest in initiating treatment for hepatitis C virus (HCV) infection among young HCV-infected injection drug users. Clin Infect Dis. 2005 Apr 15;40(Suppl. 5):S304–12.

105. Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, Vlahov D, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health. 2008 Jun;33(3):126–33.

106. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013 Aug 15;57(Suppl. 2):S80–9.

107. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. Clin Infect Dis. 2004 Nov 15;39(10):1540–3.

108. Dalgard O, Bjøro K, Hellum K, Myrvang B, Skaug K, Gutigard B, et al. Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up. Eur Addict Res. 2002;8(1):45–9.

109. Currie SL, Ryan JC, Tracy D, Wright TL, George S, McQuaid R, et al. A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. Drug Alcohol Depend. 2008 Jan;93(1–2):148–54.

110. Wade AJ, Veronese V, Hellard ME, Doyle JS. A systematic review of community based hepatitis C treatment. BMC Infect Dis. 2016;16:202.

111. Lazarus JV, Stumo SR, Harris M, Hendrickx G, Hetherington KL, Maticic M, et al. Hep-CORE: a cross-sectional study of the viral hepatitis policy environment reported by patient groups in 25 European countries in 2016 and 2017. J Int AIDS Soc. 2018 Apr;21:e25052.

112. Jack K, Willott S, Manners J, Varnam MA, Thomson BJ. Clinical trial: a primary-care-based model for the delivery of anti-viral treatment to injecting drug users infected with hepatitis C. Aliment Pharmacol Ther. 2009 Jan;29(1):38–45.

113. Seidenberg A, Rosemann T, Senn O. Patients receiving opioid maintenance treatment in primary care: successful chronic hepatitis C care in a real world setting. BMC Infect Dis. 2013 Dec;13(1):9.

114. Brunner N, Senn O, Rosemann T, Falcato L, Bruggmann P. Hepatitis C treatment for multimorbid patients with substance use disorder in a primary care-based integrated treatment centre: a retrospective analysis. Eur J Gastroenterol Hepatol. 2013 Nov;25(11):1300–7.

115. Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med. 2011 Jun 9;364(23):2199–207.

116. Read P, Gilliver R, Kearley J, Lothian R, Cunningham EB, Chronister KJ, et al. Treatment adherence and support for people who inject drugs taking direct-acting antiviral therapy for hepatitis C infection. J Viral Hepat. 2019 Nov;26(11):1301–10.

117. Linton SL, Cooper HLF, Kelley ME, Karnes CC, Ross Z, Wolfe ME, et al. Associations of place characteristics with HIV and HCV risk behaviors among racial/ethnic groups of people who inject drugs in the United States. Ann Epidemiol. 2016 Sep;26(9):619-630.e2.

118. Kim C, Kerr T, Li K, Zhang R, Tyndall MW, Montaner JS, et al. Unstable housing and hepatitis C incidence among injection drug users in a Canadian setting. BMC Public Health. 2009 Dec;9(1):270.

119. Sokol R, Early J, Barner A, Gottfried S, Gumpert R, Libaridian L, et al. Implementation of a multidisciplinary, team-based model to treat chronic hepatitis C in the primary care setting: lessons learned. Healthcare. 2018 Sep;6(3):205–9.

120. Ward JW, Valdiserri RO, Koh HK. Hepatitis C virus prevention, care, and treatment: from policy to practice. Clin Infect Dis. 2012 Jul 15;55(Suppl. 1):S58–63.

121. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. Ann Intern Med. 2017 May 2;166(9):637.

122. Thomson M, Konerman MA, Choxi H, Lok ASF. Primary care physician perspectives on hepatitis C management in the era of direct-acting antiviral therapy. Dig Dis Sci. 2016 Dec;61(12):3460–8.

123. Hajarizadeh B, Grebely J, Matthews GV, Martinello M, Dore GJ. The path towards hepatitis C elimination in Australia following universal access to interferon-free treatments. J Hepatol. 2017;66(1):S291–2.

124. Hill WD, Butt G, Alvarez M, Krajden M. Capacity enhancement of hepatitis C virus treatment through integrated, community-based care. Can J Gastroenterol. 2008;22(1):27–32.

125. Mason K, Dodd Z, Sockalingam S, Altenberg J, Meaney C, Millson P, et al. Beyond viral response: a prospective evaluation of a community-based, multi-disciplinary, peer-driven model of HCV treatment and support. Int J Drug Policy. 2015 Oct;26(10):1007–13.

126. Trooskin SB, Poceta J, Towey CM, Yolken A, Rose JS, Luqman NL, et al. Results from a geographically focused, community-based HCV screening, linkage-to-care and patient navigation program. J Gen Intern Med. 2015 Jul;30(7):950–7.

127. Hashim A, O'Sullivan M, Williams H, Verma S. Developing a community HCV service: project ITTREAT (integrated community-based test – stage – TREAT) service for people who inject drugs. Prim Health Care Res Dev. 2018 Mar;19(02):110–20.

128. Wade AJ, Doyle JS, Gane E, Stedman C, Draper B, Iser D, et al. Community-based provision of direct-acting antiviral therapy for hepatitis C: study protocol and challenges of a randomized controlled trial. Trials [Internet]. 2018 Dec [cited 2019 Jul 9];19(1). Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2768-3

129. Linnet M, Peters L, Rabden D, Peterson H, Gerstoft, Lundgren J. Organizational barriers as an explanation for differences in offer and uptake rates for hepatitis A/B/C and HIV testing in three drug treatment centres in Copenhagen [Internet]. 2017. Available from: http://www.hiveurope.eu/Portals/0/Conference%202017/Posters/PS1_03.pdf

130. Wilkinson M, Crawford V, Tippet A, Jolly F, Turton J, Sims E, et al. Community-based treatment for chronic hepatitis C in drug users: high rates of compliance with therapy despite ongoing drug use. Aliment Pharmacol Ther. 2009 Jan;29(1):29–37.

131. Scherz N, Brunner N, Bruggmann P. Direct-acting antivirals for hepatitis C in patient in opioid substitution treatment and heroin assisted treatment: real-life data. J Hepatol. 2017;66(1):S726.

132. Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, et al. Elbasvir–grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med. 2016 Nov 1;165(9):625.

133. Chronister KJ, Lothian R, Gilliver R, Kearley J, Read P. Feasibility and acceptability of adherence support for direct acting antiviral therapy for hepatitis C in a low-threshold primary health-care opioid agonist treatment program: hepatitis C adherence support for PWID. Drug Alcohol Rev. 2019 Feb;38(2):185–9.

134. Wodak A, Cooney A, World Health Organization. Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users. Geneva: World Health Organization; 2004.

135. Platt L, Sweeney S, Ward Z, Guinness L, Hickman M, Hope V, et al. Assessing the impact and cost-effectiveness of needle and syringe provision and opioid substitution therapy on hepatitis C transmission among people who inject drugs in the UK: an analysis of pooled data sets and economic modelling. Public Health Res. 2017 Sep;5(5):1–118.

136. Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. Cochrane Database Syst Rev. 2017 Sep 18;9(9):CD012021–CD012021.

137. Page K, Morris MD, Hahn JA, Maher L, Prins M. Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. Clin Infect Dis. 2013 Aug 15;57(Suppl. 2):S32–8.

138. Iversen J, Grebely J, Topp L, Wand H, Dore G, Maher L. Uptake of hepatitis C treatment among people who inject drugs attending needle and syringe programs in Australia, 1999-2011. J Viral Hepat. 2014 Mar;21(3):198–207.

139. Schulkind J, Stephens B, Ahmad F, Johnston L, Hutchinson S, Thain D, et al. High response and re-infection rates among people who inject drugs treated for hepatitis C in a community needle and syringe programme. J Viral Hepat [Internet]. 2018 Nov 13 [cited 2019 Feb 20];0(0). Available from: https://doi.org/10.1111/jvh.13035

140. Inglis SK, Beer LJ, Byrne C, Malaguti A, Robinson E, Sharkey C, et al. Randomised controlled trial conducted in injecting equipment provision sites to compare the effectiveness of different hepatitis C treatment regimens in people who inject drugs: A Direct obserVed therApy versus fortNightly CollEction study for HCV treatment—ADVANCE HCV protocol study. BMJ Open. 2019 Aug 1;9(8):e029516.

141. Wright NMJ. Supervised injecting centres. BMJ. 2004 Jan 10;328(7431):100–2.

142. Schatz E, Nougier M. Drug consumption rooms: evidence and practice [Internet]. 2012. Available from: http://www.drugsandalcohol.ie/17898/1/IDPC-Briefing-Paper_Drug-consumption-rooms.pdf

143. Marshall AD, Micallef M, Erratt A, Telenta J, Treloar C, Everingham H, et al. Liver disease knowledge and acceptability of non-invasive liver fibrosis assessment among people who inject drugs in the drug and alcohol setting: The LiveRLife Study. Int J Drug Policy. 2015 Oct;26(10):984–91.

144. Marshall AD, Grebely J, Dore GJ, Treloar C. ‘I didn’t want to let it go too far.’ The decisions and experiences of people who inject drugs who received a liver disease assessment as part of a liver health promotion campaign: The LiveRLife study. Int J Drug Policy. 2017 Sep;47:153–60.

145. Schatz E, Belackova V. Oral abstracts of the 22nd International AIDS Conference, 23-27 July 2018, Amsterdam, the Netherlands. J Int AIDS Soc. 2018 Jul;21:e25148.

146. European Monitoring Centre for Drugs and Drug Addiction. Drug consumption rooms: an overview of provision and evidence [Internet]. 2017. Available from: http://www.emcdda.europa.eu/attachements.cfm/att_239692_EN_Drug%20consumption%20rooms_update%202016.pdf

147. Kinner S. Drug use in prisons. New York, NY: Oxford University Press; 2018.

148. Hochstatter KR, Stockman LJ, Holzmacher R, Greer J, Seal DW, Taylor QA, et al. The continuum of hepatitis C care for criminal justice involved adults in the DAA era: a retrospective cohort study demonstrating limited treatment uptake and inconsistent linkage to community-based care. Health Justice. 2017 Dec;5(1):10.

149. Stone J, Martin NK, Hickman M, Hutchinson SJ, Aspinall E, Taylor A, et al. Modelling the impact of incarceration and prison-based hepatitis C virus (HCV) treatment on HCV transmission among people who inject drugs in Scotland. Addiction. 2017;112(7):1302–1314.

150. Martin NK, Vickerman P, Brew IF, Williamson J, Miners A, Irving WL, et al. Is increased hepatitis C virus case-finding combined with current or 8-week to 12-week direct-acting antiviral therapy cost-effective in UK prisons? A prevention benefit analysis. Hepatology. 2016 Jun;63(6):1796–808.

151. He T, Li K, Roberts MS, Spaulding AC, Ayer T, Grefenstette JJ, et al. Prevention of hepatitis C by screening and treatment in U.S. prisons. Ann Intern Med. 2016 Jan 19;164(2):84.

152. Sander G, Murphy F. The furthest left behind: the urgent need to scale up harm reduction in prisons. Int J Prison Health. 2017 Sep 11;13(3/4):185–91.

153. Papaluca T, McDonald L, Craigie A, Gibson A, Desmond P, Wong D, et al. Outcomes of treatment for hepatitis C in prisoners using a nurse-led, statewide model of care. J Hepatol. 2019 May;70(5):839–46.

154. Vroling H, Oordt-Speets AM, Madeddu G, Babudieri S, Monarca R, O'Moore E, et al. A systematic review on models of care effectiveness and barriers to hepatitis C treatment in prison settings in the EU/EEA. J Viral Hepat. 2018 Dec;25(12):1406–22.

155. Cuadrado A, Llerena S, Cobo C, Pallás JR, Mateo M, Cabezas J, et al. Microenvironment eradication of hepatitis C: a novel treatment paradigm. Am J Gastroenterol. 2018 Nov;113(11):1639–48.

156. Radley A, Melville K, Tait J, Stephens B, Evans JMM, Dillon JF. A quasi-experimental evaluation of dried blood spot testing through community pharmacies in the Tayside region of Scotland. Frontline Gastroenterol. 2017 Jul;8(3):221–8.

157. Radley A, Bruin M de, Inglis S, Donnan P, Beer L, Dillon J. LBP-27-Preliminary analysis of SuperDOT-C: A cluster randomised controlled trial of pharmacy-led versus conventional treatment for HCV positive patients receiving daily opioid substitution therapy-the Tayside sites. J Hepatol. 2019 Apr;70(1):e155.

158. Oramasionwu CU, Johnson TL, Zule WA, Carda-Auten J, Golin CE. Using pharmacies in a structural intervention to distribute low dead space syringes to reduce HIV and HCV transmission in people who inject drugs. Am J Public Health. 2015 Jun;105(6):1066–71.

159. Ewart A. Providing treatment for hepatitis C in an Australian district centre. Postgrad Med J. 2004 Mar 1;80(941):180–2.

160. Ward C, Lee V. Experience of acute hepatitis C and HIV co-infection in an inner city clinic in the UK. J Int AIDS Soc. 2014 Nov;17:19639.

161. Tomkins A, Lee V. Intervention to improve management of acute hepatitis C infection in a UK sexual health clinic. Int J STD AIDS. 2018 Feb;29(2):195–7.

162. Mapagu MC, Martin SJ, Currie MJ, Bowden FJ. Screening for hepatitis C in sexual health clinic attendees. Sex Health. 2008;5(1):73.

163. Tweed E, Brant L, Hurrelle M, Klapper P, Ramsay M, the Hepatitis Sentinel Surveillance Study Group. Hepatitis C testing in sexual health services in England, 2002-7: results from sentinel surveillance. Sex Transm Infect. 2010 Apr 1;86(2):126–30.

164. Brook G, Brockmeyer N, van de Laar T, Schellberg S, Winter AJ. 2017 European guideline for the screening, prevention and initial management of hepatitis B and C infections in sexual health settings. Int J STD AIDS. 2018 Sep;29(10):949–67.

165. Ward C, Lee V. Should we offer routine hepatitis C antibody testing in men who have sex with men? J Int AIDS Soc. 2014 Nov;17:19591.

166. Ireland G, Higgins S, Goorney B, Ward C, Ahmad S, Stewart C, et al. Evaluation of hepatitis C testing in men who have sex with men, and associated risk behaviours, in Manchester, UK. Sex Transm Infect. 2017 Sep;93(6):404–9.

167. Tomkins A, Vivancos R, Ward C, Kliner M. How can those engaging in chemsex best be supported? An online survey to gain intelligence in Greater Manchester. Int J STD AIDS. 2018 Feb;29(2):128–34.

168. Shared Addiction Care Copenhagen. Udvikling og evaluering af et shared care behandlings-system for hepatitis C på misbrugscentre i Københavns Kommune: afsluttende rapport, oktober 2017 [Development and evaluation of a shared-care treatment system for hepatitis C at addiction centres in Copenhagen Municipality: final report]. Shared Addiction Care Copenhagen; 2017.

169. Hashim A. Hostel-based models can improve the engagement of homeless individuals with liver services: VALID (vulnerable adults liver disease) study. EASL ILC; 2019.

170. Shiha G. Towards HCV elimination: Feasibility of complete linkage to care by testing and treatment on the same day of screening: A pilot study. EASL ILC; 2019.

171. World Health Organization. WHO guidelines on hepatitis B and C testing [Internet]. Geneva: World Health Organization; 2017 [cited 2022 May 26]. Available from: https://apps.who.int/iris/handle/10665/254621

172. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug 1;67(2):370–98.

173. AASLD/IDSA HCV guidance: recommendations for testing, managing, and treating hepatitis C. Clin Liver Dis. 2018 Dec;12(5):117–117.

174. AASLD-IDSA HCV Guidance Panel, Chung RT, Ghany MG, Kim AY, Marks KM, Naggie S, et al. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis. 2018 Oct 30;67(10):1477–92.

175. Grebely J, Robaeys G, Bruggmann P, Aghemo A, Backmund M, Bruneau J, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Int J Drug Policy. 2015 Oct;26(10):1028–38.

176. Larney S, Peacock A, Leung J, Colledge S, Hickman M, Vickerman P, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. Lancet Glob Health. 2017 Dec;5(12):e1208–20.

177. Meyer JP, Moghimi Y, Marcus R, Lim JK, Litwin AH, Altice FL. Evidence-based interventions to enhance assessment, treatment, and adherence in the chronic hepatitis C care continuum. Int J Drug Policy. 2015 Oct;26(10):922–35.

178. The Boston Consulting Group. Road to elimination: barriers and best practices in hepatitis C management. Boston, MA: The Boston Consulting Group; 2017.

179. Grebely J, Applegate TL, Cunningham P, Feld JJ. Hepatitis C point-of-care diagnostics: in search of a single visit diagnosis. Expert Rev Mol Diagn. 2017 Dec 2;17(12):1109–15.

180. Chevaliez S, Feld J, Cheng K, Wedemeyer H, Sarrazin C, Maasoumy B, et al. Clinical utility of HCV core antigen detection and quantification in the diagnosis and management of patients with chronic hepatitis C receiving an all-oral, interferon-free regimen. Antivir Ther. 2018 Apr;23(3):211–7.

181. Coats JT, Dillon JF. The effect of introducing point-of-care or dried blood spot analysis on the uptake of hepatitis C virus testing in high-risk populations: A systematic review of the literature. Int J Drug Policy. 2015 Nov 1;26(11):1050–5.

182. Tait JM, Wang H, Stephens BP, Miller M, McIntyre PG, Cleary S, et al. Multidisciplinary managed care networks—Life-saving interventions for hepatitis C patients. J Viral Hepat. 2017 Mar 1;24(3):207–15.

183. Grebely J, Applegate TL, Cunningham P, Feld JJ. Hepatitis C point-of-care diagnostics: in search of a single visit diagnosis. Expert Rev Mol Diagn. 2017 Dec 2;17(12):1109–15.

184. Shivkumar S, Peeling R, Jafari Y, Joseph L, Pant Pai N. Accuracy of rapid and point-of-care screening tests for hepatitis C: a systematic review and meta-analysis. Ann Intern Med. 2012 Oct 16;157(8):558.

185. Grebely J, Lamoury FMJ, Hajarizadeh B, Mowat Y, Marshall AD, Bajis S, et al. Evaluation of the Xpert HCV viral load point-of-care assay from venepuncture-collected and finger-stick capillary whole-blood samples: a cohort study. Lancet Gastroenterol Hepatol. 2017 Jul;2(7):514–20.

186. Kelly ML, Riordan SM, Bopage R, Lloyd AR, Post JJ. Capacity of non-invasive hepatic fibrosis algorithms to replace transient elastography to exclude cirrhosis in people with hepatitis C virus infection: a multi-centre observational study. Lin W, editor. PLOS ONE. 2018 Feb 13;13(2):e0192763.

187. Grebely J, Bruneau J, Bruggmann P, Harris M, Hickman M, Rhodes T, et al. Elimination of hepatitis C virus infection among PWID: The beginning of a new era of interferon-free DAA therapy. Int J Drug Policy. 2017 Sep 1;47:26–33.

188. Grebely J, Knight E, Genoway KA, Viljoen M, Khara M, Elliott D, et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. Eur J Gastroenterol Hepatol. 2010 Mar;22(3):270–7.

189. Mravcik V, Strada L, Štolfa J, Bencko B, Groshkova T, Reimer J, et al. Factors associated with uptake, adherence, and efficacy of hepatitis C treatment in people who inject drugs: a literature review. Patient Prefer Adherence. 2013 Oct;1067.

190. Grebely J, Genoway K, Khara M, Duncan F, Viljoen M, Elliott D, et al. Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. Int J Drug Policy. 2007 Oct;18(5):437–43.

191. Curcio F, Di Martino F, Capraro C, Angelucci F, Bulla F, Caprio N, et al. Together … to take care: multidisciplinary management of hepatitis C virus treatment in randomly selected drug users with chronic hepatitis. J Addict Med. 2010 Dec;4(4):223–32.

192. Carrión JA, Gonzalez-Colominas E, García-Retortillo M, Cañete N, Cirera I, Coll S, et al. A multidisciplinary support programme increases the efficiency of pegylated interferon alfa-2a and ribavirin in hepatitis C. J Hepatol. 2013 Nov;59(5):926–33.

193. Ho CJ, Preston C, Fredericks K, Doorley SL, Kramer RJ, Kwan L, et al. A unique model for treating chronic hepatitis C in patients with psychiatric disorders, substance abuse, and/or housing instability. J Addict Med. 2013 Sep;7(5):320–4.

194. Hussein M, Benner JS, Lee D, Sesti AM, Battleman DS, Brock-Wood C. Propensity score matching in the evaluation of drug therapy management programs: an

illustrative analysis of a program for patients with hepatitis C virus. Qual Manag Health Care. 2010 Jan;19(1):25–33.

195. Reimer J, Schmidt CS, Schulte B, Gansefort D, Gölz J, Gerken G, et al. Psychoeducation improves hepatitis C virus treatment during opioid substitution therapy: a controlled, prospective multicenter trial. Clin Infect Dis. 2013 Aug 15;57(suppl_2):S97–104.

196. Rich ZC, Chu C, Mao J, Zhou K, Cai W, Ma Q, et al. Facilitators of HCV treatment adherence among people who inject drugs: a systematic qualitative review and implications for scale up of direct acting antivirals. BMC Public Health. 2016 Dec;16(1):994.

197. Wyles DL, Sulkowski MS, Dieterich D. Management of hepatitis C/HIV coinfection in the era of highly effective hepatitis C virus direct-acting antiviral therapy: table 1. Clin Infect Dis. 2016 Jul 15;63(Suppl. 1):S3–11.

198. Newman AI, Beckstead S, Beking D, Finch S, Knorr T, Lynch C, et al. Treatment of chronic hepatitis C infection among current and former injection drug users within a multidisciplinary treatment model at a community health centre. Can J Gastroenterol. 2013;27(4):217–23.

199. Yoo ER, Perumpail RB, Cholankeril G, Jayasekera CR, Ahmed A. Expanding treatment access for chronic hepatitis C with task-shifting in the era of direct-acting antivirals. J Clin Transl Hepatol. 2017 Mar 26;5(2):1–4.

200. Yang S, Britt RB, Hashem MG, Brown JN. Outcomes of pharmacy-led hepatitis C direct-acting antiviral utilization management at a veterans affairs medical center. J Manag Care Spec Pharm. 2017 Mar;23(3):364–9.

201. Lee A, Hanson J, Fox P, Spice G, Russell D, Boyd P. A decentralised, multidisciplinary model of care facilitates treatment of hepatitis C in regional Australia. J Virus Erad. 2018 Jul 1;4(3):160–4.

202. Kattakuzhy S, Gross C, Emmanuel B, Teferi G, Jenkins V, Silk R, et al. Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial. Ann Intern Med. 2017 Sep 5;167(5):311.

203. Komaromy M, Duhigg D, Metcalf A, Carlson C, Kalishman S, Hayes L, et al. Project ECHO (Extension for Community Healthcare Outcomes): a new model for

educating primary care providers about treatment of substance use disorders. Subst Abuse. 2016 Jan 2;37(1):20–4.

204. Ní Cheallaigh C, O'Leary A, Keating S, Singleton A, Heffernan S, Keenan E, et al. Telementoring with project ECHO: a pilot study in Europe. BMJ Innov. 2017 Jul;3(3):144–51.

205. Agley J, Adams ZW, Hulvershorn LA. Extension for Community Healthcare Outcomes (ECHO) as a tool for continuing medical education on opioid use disorder and comorbidities. Addiction. 2019 Mar;114(3):573–4.

206. Treloar C, Rance J, Bath N, Everingham H, Micallef M, Day C, et al. Evaluation of two community-controlled peer support services for assessment and treatment of hepatitis C virus infection in opioid substitution treatment clinics: the ETHOS study, Australia. Int J Drug Policy. 2015 Oct;26(10):992–8.

207. Sulkowski M, Ward K, Falade-Nwulia O, Moon J, Sutcliffe C, Brinkley S, et al. Randomized controlled trial of cash incentives or peer mentors to improve HCV linkage and treatment among HIV/HCV coinfected persons who inject drugs: the CHAMPS Study. J Hepatol. 2017;66(1):S719.

208. Akiyama MJ, Norton BL, Arnsten JH, Agyemang L, Heo M, Litwin AH. Intensive Models of Hepatitis C Care for People Who Inject Drugs Receiving Opioid Agonist Therapy: A Randomized Controlled TrialIntensive Models of Hepatitis C Care for People Who Inject Drugs. Ann Intern Med. 2019 May 7;170(9):594–603.

209. Henderson C, Madden A, Kelsall J. 'Beyond the willing & the waiting' — the role of peer-based approaches in hepatitis C diagnosis & treatment. Int J Drug Policy. 2017 Dec;50:111–5.

210. Bregenzer A, Conen A, Knuchel J, Friedl A, Eigenmann F, Näf M, et al. Management of hepatitis C in decentralised versus centralised drug substitution programmes and minimally invasive point-of-care tests to close gaps in the HCV cascade. Swiss Med Wkly. 2017 Nov 20;147(4748).

211. Khan B, Duncan I, Saad M, Schaefer D, Jordan A, Smith D, et al. Combination interventions for hepatitis C and cirrhosis reduction among people who inject drugs: an agent-based, networked population simulation experiment. PLOS ONE. 2018 Nov 29;13(11):e0206356.

212. Hutchinson SJ, Dillon JF, Fox R, McDonald SA, Innes HA, Weir A, et al. Expansion of HCV treatment access to people who have injected drugs through effective translation of research into public health policy: Scotland's experience. Int J Drug Policy. 2015 Nov;26(11):1041–9.

213. Tait JM, McIntyre PG, McLeod S, Nathwani D, Dillon JF. The impact of a managed care network on attendance, follow-up and treatment at a hepatitis C specialist centre: impact of HCV managed care network. J Viral Hepat. 2010 Oct;17(10):698–704.

214. Saxon AJ, Malte CA, Sloan KL, Baer JS, Calsyn DA, Nichol P, et al. Randomized trial of onsite versus referral primary medical care for veterans in addictions treatment. Med Care. 2006 Apr;44(4):334–42.

215. Ho SB, Groessl E, Dollarhide A, Robinson S, Kravetz D, Dieperink E. Management of chronic hepatitis C in veterans: the potential of integrated care models. Am J Gastroenterol. 2008 Jul;103(7):1810–23.

216. Evon DM, Simpson K, Kixmiller S, Galanko J, Dougherty K, Golin C, et al. A randomized controlled trial of an integrated care intervention to increase eligibility for chronic hepatitis C treatment. Am J Gastroenterol. 2011 Oct;106(10):1777–86.

217. Knott A, Dieperink E, Willenbring ML, Heit S, Durfee JM, Wingert M, et al. Integrated psychiatric/medical care in a chronic hepatitis C clinic: effect on antiviral treatment evaluation and outcomes. Am J Gastroenterol. 2006 Oct;101(10):2254–62.

218. Martinez AD, Dimova R, Marks KM, Beeder AB, Zeremski M, Kreek MJ, et al. Integrated internist - addiction medicine - hepatology model for hepatitis C management for individuals on methadone maintenance: multidisciplinary HCV management. J Viral Hepat. 2012 Jan;19(1):47–54.

219. Radley A, Robinson E, Aspinall EJ, Angus K, Tan L, Dillon JF. A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments. BMC Health Serv Res [Internet]. 2019 Dec [cited 2020 Oct 6];19(1). Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-019-4635-7

220. Jones L, Atkinson A, Bates G, McCoy E, Porcellato L, Beynon C, et al. Views and experiences of hepatitis C testing and diagnosis among people who inject drugs: Systematic review of qualitative research. Int J Drug Policy. 2014 Mar;25(2):204–11.

221. Dowsett LE, Coward S, Lorenzetti DL, MacKean G, Clement F. Living with Hepatitis C Virus: A Systematic Review and Narrative Synthesis of Qualitative Literature. Can J Gastroenterol Hepatol. 2017;2017:1–11.

222. Simmons R, Ireland G, Irving W, Hickman M, Sabin C, Ijaz S, et al. Establishing the cascade of care for hepatitis C in England—benchmarking to monitor impact of direct acting antivirals. J Viral Hepat. 2018 May 1;25(5):482–90.

223. EMCDDA. Hepatitis C among drug users in Europe: epidemiology, treatment and prevention [Internet]. European Monitoring Centre for Drugs and Drug Addiction; 2016 [cited 2016 Aug 7]. Available from: http://www.emcdda.europa.eu/publications/insights/hepatitis-c-among-drug-users-in-europe_en

224. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700.

225. World Health Organisation. Main terminology - Primary health care [Internet]. 2004 [cited 2019 Sep 7]. Available from: http://www.euro.who.int/en/health-topics/Health-systems/primary-health-care/main-terminology

226. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. The Ottawa Research Institute; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

227. The Cochrane Collaboration. Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 5.1.0. 2011. Available from: http://handbook-5-1.cochrane.org/

228. Sabbagh HJ, Hassan MHA, Innes NPT, Elkodary HM, Little J, Mossey PA. Passive Smoking in the Etiology of Non-Syndromic Orofacial Clefts: A Systematic Review and Meta-Analysis. Cray J, editor. PLOS ONE. 2015 Mar 11;10(3):e0116963.

229. Berkman ND, Lohr KN, Ansari MT, Balk EM, Kane R, McDonagh M, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015 Nov 1;68(11):1312–24.

230. Bloom S, Lubel J, Nicoll A, Gow P, Dev A, Roberts S, et al. Comparison of direct-acting antiviral therapy forhepatitis C between specialist centers and primarycare: Efficacy and adherence to responseassessment. J Gastroenterol Hepatol. 2017 Aug;32:65–86.

231. Francheville JW, Rankin R, Beck J, Hoare C, Materniak S, German G, et al. Early Successes in an Open Access, Provincially Funded Hepatitis C Treatment Program in Prince Edward Island. Ann Hepatol. 2017 Sep;16(5):749–58.

232. McClure T, Olenski M, Ward A, Glasgow S, Stothers L, New K, et al. Real-world treatment for hepatitis C in the direct-acting antiviral era: Comparing outcomes between the tertiary liver clinic and community. J Gastroenterol Hepatol. 2017 Aug;32:65–86.

233. Miller L, Quairoli K, Lom J, Fluker SA. Access to and success with new hepatitis c therapy in an urban primary care centre. J Gen Intern Med. 2016 May;31(S2):85–922.

234. Norton BL, Fleming J, Bachhuber MA, Steinman M, DeLuca J, Cunningham CO, et al. High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic. Int J Drug Policy. 2017 Sep;47:196–201.

235. Wade AJ, Doyle JS, Thompson A, Hellard M. A randomised trial of community vs hospital direct acting antiviral therapy: preliminary data. J Gastroenterol Hepatol. 2016 Oct;31:65–88.

236. Abdulameer A, Leff P, Joshi K, Hepner A, Moore A, Arendt K, et al. Effectiveness of sofosbuvir/ledipasvir and sofosbuvir/ simeprevir for the treatment of hepatitis C genotype-1: Real world analysis. Hepatology. 2016 Oct;64(S1):811–1050.

237. Beste LA, Glorioso TJ, Ho PM, Au DH, Kirsh SR, Todd-Stenberg J, et al. Telemedicine Specialty Support Promotes Hepatitis C Treatment by Primary Care Providers in the Department of Veterans Affairs. Am J Med. 2017 Apr 1;130(4):432-438.e3.

238. Buchanan R, Shalabi A, Grellier L, Parkes J, Khakoo S. PTU-112 Hepatology outreach services to overcome inequalities in hepatitis c care in an isolated uk population: Abstract PTU-112 Table 1. Gut. 2015 Jun;64(Suppl 1):A111.1-A111.

239. Georgie F, Nafisi S, Kohli A, Thornton K, Reynolds J, Moore A, et al. Primary Care Physicians Utilizing the Echo Model Equally Effective as Subspecialists Treating HCV using Direct-Acting Antivirals-Only Regimens: Results of the Echo Model. J Hepatol. 2016;64(2):S818–9.

240. Butner JL, Gupta N, Fabian C, Henry S, Shi JM, Tetrault JM. Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program. J Subst Abuse Treat. 2017;75:49–53.

241. Morris L, Smirnov A, Kvassay A, Leslie E, Kavanagh R, Alexander N, et al. Initial outcomes of integrated community-based hepatitis C treatment for people who inject drugs: Findings from the Queensland Injectors' Health Network. Int J Drug Policy. 2017 Sep;47:216–20.

242. Read P, Lothian R, Chronister K, Gilliver R, Kearley J, Dore GJ, et al. Delivering direct acting antiviral therapy for hepatitis C to highly marginalised and current drug injecting populations in a targeted primary health care setting. Int J Drug Policy. 2017 Sep;47:209–15.

243. David C, David D, Essex W, Deming P, Qualls C, Mera J. Hepatitis c treatment outcomes in a pharmacist-managed clinic in a rural tribal health system. Hepatology. 2018 Oct;68:184–1353.

244. Cooper CL, Hatashita H, Corsi DJ, Parmar P, Corrin R, Garber G. Direct-Acting Antiviral Therapy Outcomes in Canadian Chronic Hepatitis C Telemedicine Patients. Ann Hepatol. 2017 Nov;16(6):874–80.

245. Emmanuel B, Wilson EM, O'Brien TR, Kottilil S, Lau G. Shortening the duration of therapy for chronic hepatitis C infection. Lancet Gastroenterol Hepatol. 2017 Nov;2(11):832–6.

246. Shehata N, Austin T, Ha S, Timmerman K. Barriers to and facilitators of hepatitis C virus screening and testing: A scoping review. Can Commun Dis Rep Releve Mal Transm Au Can. 2018 Jul 5;44(7–8):166–72.

247. Aspinall EJ, Doyle JS, Corson S, Hellard ME, Hunt D, Goldberg D, et al. Targeted hepatitis C antibody testing interventions: a systematic review and meta-analysis. Eur J Epidemiol. 2015 Feb 1;30(2):115–29.

248. McDermott CL, Lockhart CM, Devine B. Outpatient directly observed therapy for hepatitis C among people who use drugs: a systematic review and meta-analysis. J Virus Erad. 2018 Apr 1;4(2):118–22.

249. Grebely J, Dore GJ, Morin S, Rockstroh JK, Klein MB. Elimination of HCV as a public health concern among people who inject drugs by 2030 - What will it take to get there? J Int AIDS Soc. 2017 Jul 28;20(1):22146–22146.

250. Radley A, de Bruin M, Inglis SK, Donnan PT, Dillon JF. Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for hepatitis C in patients receiving opioid substitution therapy: a study protocol for a pragmatic cluster randomised trial. BMJ Open. 2018 Dec 14;8(12):e021443–e021443.

251. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatol Baltim Md. 2013 Nov;58(5):1598–609.

252. Donnelley RR. Hepatitis C Action Plan for Scotland Phase II: May 2008 – March 2011 [Internet]. Scottish Government; 2008 [cited 2019 May 7]. Available from: https://www.webarchive.org.uk/wayback/archive/20170701194329/http://www.gov.scot/Publications/2008/05/13103055/0

253. Snowdon C. NHS Tayside Director of Public Health 2017/18 report [Internet]. Scottish Government; 2018. Available from: https://www.nhstaysidecdn.scot.nhs.uk/NHSTaysideWeb/idcplg?IdcService=GET_SECURE_FILE&dDocName=PROD_309185&Rendition=web&RevisionSelectionMethod=LatestReleased&noSaveAs=1

254. National Records of Scotland. Mid-Year Population Estimates Scotland, Mid-2018 [Internet]. 2018 [cited 2019 Feb 7]. Available from: https://www.nrscotland.gov.uk/files//statistics/population-estimates/mid-18/mid-year-pop-est-18-pub.pdf

255. The Scottish Public Observatory. Hepatitis C: data on hepatitis C [Internet]. 2018 [cited 2019 Feb 7]. Available from: https://www.scotpho.org.uk/health-wellbeing-and-disease/hepatitis-c/data/scotland-and-uk/

256. McLeod A, Weir A, Aitken C, Gunson R, Templeton K, Molyneaux P, et al. Rise in testing and diagnosis associated with Scotland's Action Plan on Hepatitis C and

introduction of dried blood spot testing. J Epidemiol Community Health. 2014 Dec 1;68(12):1182.

257. Dillon JF, Aspinall EJ. Recommendations on Hepatitis C Virus Case Finding and Access to Care Report of the National Short Life Working Group (SLWG) [Internet]. Scottish Health Protection Network; 2019 [cited 2020 Mar 27]. Available from: https://www.hps.scot.nhs.uk/web-resources-container/recommendations-on-hepatitis-c-virus-case-finding-and-access-to-care/

258. Altice FL, Azbel L, Stone J, Brooks-Pollock E, Smyrnov P, Dvoriak S, et al. The perfect storm: incarceration and the high-risk environment perpetuating transmission of HIV, hepatitis C virus, and tuberculosis in Eastern Europe and Central Asia. The Lancet. 2016 Sep 17;388(10050):1228–48.

259. Kronfli N, Linthwaite B, Kouyoumdjian F, Klein MB, Lebouché B, Sebastiani G, et al. Interventions to increase testing, linkage to care and treatment of hepatitis C virus (HCV) infection among people in prisons: A systematic review. Int J Drug Policy. 2018 Jul 1;57:95–103.

260. Scottish Prison Service NS. Guidance to Support Opt-Out Blood Borne Virus (BBV) Testing in Scottish Prisons [Internet]. Scottish Health Protection Network Executive Leads for Sexual Health & BBV; 2019 [cited 2020 Mar 27]. Available from: https://hpspubsrepo.blob.core.windows.net/hps-website/nss/2819/documents/1_guidance-to-support-opt-out-bbv-testing-in-scottish-prisons.pdf

261. JAFFERBHOY H, MILLER MH, McINTYRE P, DILLON JF. The effectiveness of outreach testing for hepatitis C in an immigrant Pakistani population. Epidemiol Infect. 2012;140(6):1048–53.

262. Cullen BL, Hutchinson SJ, Cameron SO, Anderson E, Ahmed S, Spence E, et al. Identifying former injecting drug users infected with hepatitis C: an evaluation of a general practice-based case-finding intervention. J Public Health. 2012 Mar 1;34(1):14–23.

263. McLeod A, Cullen BL, Hutchinson SJ, Roy KM, Dillon JF, Stewart EA, et al. Limited impact of awareness-raising campaigns on hepatitis C testing practices among general practitioners. J Viral Hepat. 2017 Nov 1;24(11):944–54.

264. NHS National Services Scotland. GP Practices and List sizes July 2018 [Internet]. NHS National Services Scotland; 2018. Available from: https://www.opendata.nhs.scot/dataset/f23655c3-6e23-4103-a511-a80d998adb90/resource/57c17aad-1454-4348-87f8-8a98e990339e/downl

265. Safreed-Harmon K, Blach S, Aleman S, Bollerup S, Cooke G, Dalgard O, et al. The Consensus Hepatitis C Cascade of Care: Standardized Reporting to Monitor Progress Toward Elimination. Clin Infect Dis. 2019 Nov 27;69(12):2218–27.

266. Edmunds BL, Miller ER, Tsourtos G. The distribution and socioeconomic burden of Hepatitis C virus in South Australia: a cross-sectional study 2010–2016. BMC Public Health [Internet]. 2019 Dec [cited 2020 Apr 10];19(1). Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-6847-5

267. Iversen J, Page K, Madden A, Maher L. HIV, HCV, and Health-Related Harms Among Women Who Inject Drugs: Implications for Prevention and Treatment. J Acquir Immune Defic Syndr 1999. 2015 Jun 1;69 Suppl 2(0 1):S176–81.

268. Esmaeili A, Mirzazadeh A, Carter GM, Esmaeili A, Hajarizadeh B, Sacks HS, et al. Higher incidence of HCV in females compared to males who inject drugs: A systematic review and meta-analysis. J Viral Hepat. 2017 Feb;24(2):117–27.

269. Corcorran MA, Tsui JI, Scott JD, Dombrowski JC, Glick SN. Age and gender-specific hepatitis C continuum of care and predictors of direct acting antiviral treatment among persons who inject drugs in Seattle, Washington. Drug Alcohol Depend. 2021 Mar;220:108525.

270. Bielen R, Moreno C, Van Vlierberghe H, Bourgeois S, Mulkay JP, Vanwolleghem T, et al. Belgian experience with direct acting antivirals in people who inject drugs. Drug Alcohol Depend. 2017 Aug 1;177:214–20.

271. World Health Organisation. Screening programmes: a short guide. Increase effectiveness, maximize benefits and minimize harm (2020) [Internet]. 2020. Available from: https://www.euro.who.int/en/publications/abstracts/screening-programmes-a-short-guide.-increase-effectiveness,-maximize-benefits-and-minimize-harm-2020

272. York Health Economics Consortium. Net Health Benefit [online] [Internet]. York Health Economics Consortium; 2016. Available from: https://yhec.co.uk/glossary/net-health-benefit/

273. Shiell A. Health economic evaluation. J Epidemiol Community Health. 2002 Feb 1;56(2):85–8.

274. Glossary of Terms for Health Economics and Systematic Review - Adapted from Chapter 12 of the book Evidence Based Health Economics: From Effectiveness to Efficiency in Systematic Review (Evidence-Based Medicine) (Currie, 2002) and Chapter 16 of ABDELHAMID, A. & SHEMILT, I. 2010. Glossary of terms. Evidence-Based Decisions and Economics Health Care, Social Welfare, Education and Criminal Justice. 2nd ed. Oxford: Wiley-Blackwell, 186-197. [Internet]. Available from: https://methods.cochrane.org/sites/methods.cochrane.org.economics/files/uploads/ccemg_website_glossary.pdf

275. O'Leary MC, Sarwar M, Hutchinson SJ, Weir A, Schofield J, McLeod A, et al. The prevalence of hepatitis C virus among people of South Asian origin in Glasgow – Results from a community based survey and laboratory surveillance. Travel Med Infect Dis. 2013 Sep 1;11(5):301–9.

276. Anderson EM, Mandeville RP, Hutchinson SJ, Cameron SO, Mills PR, Fox R, et al. Evaluation of a general practice based hepatitis C virus screening intervention. Scott Med J. 2009;54.

277. Datta S, Horwood J, Hickman M, Sharp D. Case-finding for hepatitis C in primary care: a mixed-methods service evaluation. Br J Gen Pract. 2014 Feb 1;64(619):e67.

278. Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC. Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. Aliment Pharmacol Ther. 2015 Mar;41(6):544–63.

279. APPG. APPG 2018. Eliminating Hepatitis C in England. [Internet]. 2018. Available from: http://www.appghep.org.uk/download/reports/Eliminating%20Hep%20C%20APPG.pdf .

280. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull World Health Organ. 2013 Feb 1;91(2):102–23.

281. Graham L, Fischbacher CM, Stockton D, Fraser A, Fleming M, Greig K. Understanding extreme mortality among prisoners: a national cohort study in Scotland using data linkage. Eur J Public Health. 2015 Oct;25(5):879–85.

282. Dillon JF, Hayes P, Barclay S, Fox R, Fraser A. National clinical guidelines for the treatment of HCV in adults [Internet]. Health Protection Scotland; 2018. Available from: https://www.hps.scot.nhs.uk/web-resources-container/national-clinical-guidelines-for-the-treatment-of-hcv-in-adults/

283. Taylor A, Munro A, Allen E, Dunleavy K, Cameron S, Miller L. Hepatitis C prevalence and incidence among Scottish prisoners and staff views of its management [Internet]. Available from: http://www.hcvaction.org.uk/resource/hepatitis-c-prevalence-and-incidence-among-scottish-prisoners-and-staff-views-its

284. ISD Scotland. Scottish Drug Misuse Database [Internet]. 2017. Available from: https://www.isdscotland.org/Health-Topics/Drugs-and-Alcohol-Misuse/Publications/2017-04-04/2017-04-04-SDMD-Report.pdf

285. Hutchinson SJ, Bird SM, Goldberg DJ. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. Hepatology. 2005 Sep;42(3):711–23.

286. ISD Scotland. Practice team information (PTI) annual update (2012/13) [Internet]. 2013. Available from: https://www.isdscotland.org/Health-Topics/General-Practice/Publications/2013-10-29/2013-10-29-PTI-Report.pdf

287. Spach D. Hepatitis C diagnostic testing [Internet]. 2020. Available from: https://www.hepatitisc.uw.edu/go/screening-diagnosis/diagnostic-testing/core-concept/all#citations

288. Judd A, Parry J, Hickman M, McDonald T, Jordan L, Lewis K, et al. Evaluation of a modified commercial assay in detecting antibody to hepatitis C virus in oral fluids and dried blood spots. J Med Virol. 2003 Sep;71(1):49–55.

289. Curtis L. Unit Costs of Health and Social Care 2012. Personal Social Services Research Unit: University of Kent; 2012.

290. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008 Aug;48(2):418–31.

291. Martin NK. Assessing the cost-effectiveness of interventions aimed at promoting and offering hepatitis C testing to injecting drug users: an economic modelling report. 2012.

292. McEwan P, Ward T, Yuan Y, Kim R, L'Italien G. The impact of timing and prioritization on the cost-effectiveness of birth cohort testing and treatment for hepatitis C virus in the United States. Hepatology. 2013 Jul;58(1):54–64.

293. McGarry LJ, Pawar VS, Panchmatia HR, Rubin JL, Davis GL, Younossi ZM, et al. Economic model of a birth cohort screening program for hepatitis C virus. Hepatology. 2012;55.

294. Younossi Z, Park H, Saab S, Ahmed A, Dieterich D, Gordon S. Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. Aliment Pharmacol Ther. 2015;41(6):544–63.

295. Falade-Nwulia O, Sulkowski MS, Merkow A, Latkin C, Mehta SH. Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era. J Viral Hepat. 2018 Mar;25(3):220–7.

296. Rossi C, Butt ZA, Wong S, Buxton JA, Islam N, Yu A, et al. Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort. J Hepatol. 2018 Nov;69(5):1007–14.

297. Geue C, Wu O, Xin Y, Heggie R, Hutchinson S, Martin NK, et al. Cost-effectiveness of HBV and HCV screening strategies – a systematic review of existing modelling techniques. PLOS ONE. 2015 Dec 21;10(12):e0145022.

298. Parkin D. Techniques of economic appraisal (including cost-effectiveness analysis and modelling, cost-utility analysis, option appraisal and cost-benefit analysis, the measurement of health benefits in terms of QALYs and related measures e.g. DALYs) [Internet]. 2017. Available from: https://www.healthknowledge.org.uk/public-health-textbook/medical-sociology-policy-economics/4d-health-economics/economic-appraisal

299. Chhatwal J, He T, Lopez-Olivo MA. Systematic review of modelling approaches for the cost effectiveness of hepatitis C treatment with direct-acting antivirals. PharmacoEconomics. 2016 Jun;34(6):551–67.

300. Krassenburg LAP, Maan R, Ramji A, Manns MP, Cornberg M, Wedemeyer H, et al. Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. J Hepatol. 2021 May;74(5):1053–63.

301. Lazarus JV, Pericàs JM, Picchio C, Cernosa J, Hoekstra M, Luhmann N, et al. We know DAAs work, so now what? Simplifying models of care to enhance the hepatitis C cascade. J Intern Med. 2019 Nov 1;286(5):503–25.

302. Mirzazadeh A, Hosseini-Hooshyar S, Shahesmaeili A, Sharafi H, Shafiei M, Zarei J, et al. An on-site community-based model for hepatitis C screening, diagnosis, and treatment among people who inject drugs in Kerman, Iran: The Rostam study. Int J Drug Policy. 2022 Apr;102:103580.

303. Ngo BV, James JR, Blalock KL, Jackson SL, Chew LD, Tsui JI. Hepatitis C treatment outcomes among patients treated in co-located primary care and addiction treatment settings. J Subst Abuse Treat. 2021 Dec;131:108438.

304. Palmer AY, Wade AJ, Draper B, Howell J, Doyle JS, Petrie D, et al. A cost-effectiveness analysis of primary versus hospital-based specialist care for direct acting antiviral hepatitis C treatment. Int J Drug Policy. 2020 Feb;76:102633.

305. Olafsson S, Fridriksdottir RH, Love TJ, Tyrfingsson T, Runarsdottir V, Hansdottir I, et al. Cascade of care during the first 36 months of the treatment as prevention for hepatitis C (TraP HepC) programme in Iceland: a population-based study. Lancet Gastroenterol Hepatol. 2021 Aug;6(8):628–37.

306. J Dore G. Editorial: Elimination of hepatitis C in Australia by 2030: a decade and counting. Aust Prescr. 2021 Apr 1;44(2):36–7.

307. Public Health Scotland. Surveillance of hepatitis C in Scotland Progress on elimination of hepatitis C as a major public health concern: 2022 update A Management Information release for Scotland [Internet]. 2022 [cited 2022 Nov 29]. Available from: https://www.publichealthscotland.scot/media/15549/surveillance-of-hepatitis-c-in-scotland-oct22.pdf

308. Talal AH, Markatou M, Sofikitou EM, Brown LS, Perumalswami P, Dinani A, et al. Patient-centered HCV care via telemedicine for individuals on medication for opioid use disorder: Telemedicine for Evaluation, Adherence and Medication for Hepatitis C (TEAM-C). Contemp Clin Trials. 2022 Jan;112:106632.

309. Hajarizadeh B, Grebely J, Byrne M, Marks P, Amin J, McManus H, et al. Evaluation of hepatitis C treatment-as-prevention within Australian prisons (SToP-C): a prospective cohort study. Lancet Gastroenterol Hepatol. 2021 Jul;6(7):533–46.

310. Cunningham EB, Wheeler A, Hajarizadeh B, French CE, Roche R, Marshall AD, et al. Interventions to enhance testing, linkage to care, and treatment initiation for hepatitis C virus infection: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022 May 1;7(5):426–45.

311. Gamkrelidze I, Pawlotsky J, Lazarus JV, Feld JJ, Zeuzem S, Bao Y, et al. Progress towards hepatitis C virus elimination in high-income countries: an updated analysis. Liver Int. 2021 Mar;41(3):456–63.

312. World Hepatitis Alliance. Overcoming the barriers to diagnosis of viral hepatitis: the role of civil society and the affected community in finding the missing millions white paper [Internet]. 2018. Available from: https://www.worldhepatitisalliance.org/missing-millions/wp-content/uploads/2018/07/Overcoming-the-barriers-to-diagnosis-white-paper-1.pdf

313. Saine ME, Szymczak JE, Moore TM, Bamford LP, Barg FK, Schnittker J, et al. Determinants of stigma among patients with hepatitis C virus infection. J Viral Hepat. 2020 Nov;27(11):1179–89.

314. Karlsson N, Santacatterina M, Käll K, Hägerstrand M, Wallin S, Berglund T, et al. Risk behaviour determinants among people who inject drugs in Stockholm, Sweden over a 10-year period, from 2002 to 2012. Harm Reduct J [Internet]. 2017 Dec [cited 2022 Dec 9];14(1). Available from: http://harmreductionjournal.biomedcentral.com/articles/10.1186/s12954-017-0184-8

315. Khuat OT, Morrow M, Nguyen TN, Armstrong G. Social context, diversity and risk among women who inject drugs in Vietnam: descriptive findings from a cross-sectional survey. Harm Reduct J [Internet]. 2015 Dec [cited 2022 Dec 9];12(1). Available from: http://www.harmreductionjournal.com/content/12/1/35

316. Kåberg M, Karlsson N, Discacciati A, Widgren K, Weiland O, Ekström AM, et al. Significant decrease in injection risk behaviours among participants in a needle exchange programme. Infect Dis. 2020 May 3;52(5):336–46.

317. Simmons J, Rajan S, McMahon JM. Retrospective accounts of injection initiation in intimate partnerships. Int J Drug Policy. 2012 Jul;23(4):303–11.

318. Jones AA, Schneider KE, Falade-Nwulia O, Sterner G, Tobin K, Latkin CA. Social Networks, Stigma, and Hepatitis C Care Among Women Who Inject Drugs: Findings from A Community Recruited Sample. J Psychoactive Drugs. 2022 Dec 1;1–7.

319. Arum C, Fraser H, Artenie AA, Bivegete S, Trickey A, Alary M, et al. Homelessness, unstable housing, and risk of HIV and hepatitis C virus acquisition among people who inject drugs: a systematic review and meta-analysis. Lancet Public Health. 2021 May;6(5):e309–23.

320. Fokuo JK, Masson CL, Anderson A, Powell J, Bush D, Ricco M, et al. Recommendations for Implementing Hepatitis C Virus Care in Homeless Shelters: The Stakeholder Perspective. Hepatol Commun. 2020 May;4(5):646–56.

321. Sutter A, Curtis M, Frost T. Public drug use in eight U.S. cities: Health risks and other factors associated with place of drug use. Int J Drug Policy. 2019 Feb;64:62–9.

322. Celeste-Villalvir A, Wilkerson JM, Markham C, Rodriguez L, Schick V. A qualitative investigation of the barriers and facilitators to Hepatitis C virus (HCV) screening among individuals experiencing homelessness in Houston, Texas. Dialogues Health. 2022 Dec;1:100058.

323. UKHSA. Hepatitis C in England 2022 Working to eliminate hepatitis C as a public health problem Full report [Internet]. 2022. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1057271/HCV-in-England-2022-full-report.pdf

324. Valerio H, Alavi M, Conway A, Silk D, Treloar C, Martinello M, et al. Declining prevalence of current HCV infection and increased treatment uptake among people who inject drugs: The ETHOS Engage study. Int J Drug Policy. 2022 Jul;105:103706.