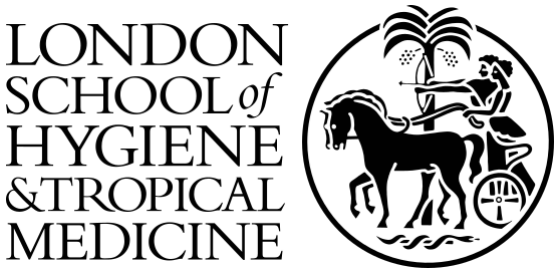


# Assessing the cost-effectiveness of interventions to expand hepatitis C testing to help achieve elimination targets in the United Kingdom

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# Declaration

I, Jack Williams, confirm that the work presented within this thesis is my own. Where information is derived from other sources, this is clearly indicated within the thesis.

# Abstract

**Introduction:** In 2016, the UK adopted World Health Organization goals to eliminate the hepatitis C virus (HCV) as a public health burden by 2030. Testing is currently recommended for those most at risk. However, in order to diagnose and treat the estimated 118,000 cases of HCV in the UK, testing needs to be expanded to people who are currently unlikely to receive testing.

**Research aims and objectives:** To identify and evaluate the cost-effectiveness of three novel HCV testing strategies which seek to test those who are unlikely to be offered HCV testing under the current testing guidance, in the UK. This research also sought to explore issues of heterogeneity, and the impact of this upon cost-effectiveness estimates.

**Findings:** Three economic evaluations were performed. Two HCV testing interventions in primary care (general practice) were considered. An algorithm to identify those at elevated risk of HCV was highly likely to be cost-effective. In contrast, the cost-effectiveness of HCV screening for birth cohorts, when offered to everyone attending the NHS health check for those aged 40-74 years old in primary care, was highly uncertain, with additional empirical evidence required. HCV testing in Emergency Departments (ED) was also evaluated, since the prevalence tends to be higher than in the general population, and this may be the only healthcare setting that some people engage with. Testing was cost-effective, and highly likely to be cost-effective when the chronic HCV prevalence was 0.5%. Finally, a methodological analysis found that assuming homogeneity amongst the testing population can lead to considerable inaccuracies in on economic model estimates.

**Conclusions:** HCV testing in primary care and the ED can be cost-effective, and testing guidelines and policies should be updated to reflect this. Future economic evaluations should consider the heterogeneity amongst the testing population to accurately capture the impact of new testing interventions.

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# Abbreviations

| | |
|---|---|
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| BBV | Blood-borne virus |
| DAA | Direct acting antiviral |
| EASL | European Association for the Study of the Liver |
| ECDC | European Centre for Disease Prevention and Control |
| ED | Emergency department |
| GP | General practitioner |
| GUM | Genitourinary medicine |
| HAI | Histology Activity Index |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HepCAPP | Hepatitis C Virus Case Finding in Primary Care Pilot |
| HepCATT | Hepatitis C Assessment Through to Treatment Trial |
| HES | Hospital Episode Statistics |
| HIV | Human Immunodeficiency Virus |
| HPRU | Health Protection Research Unit |
| HRQoL | Health related quality of life |
| HSA | Health Security Agency |
| HTA | Health Technology Assessment |
| ICER | Incremental cost-effectiveness ratio |
| LT | Liver transplant |
| MSM | Men who have sex with men |
| NAAT | Nucleic Acid Amplification Test |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health Research |
| ONS | Office of National Statistics |
| OST | Opioid substitution therapy |
| PCR | Polymerase chain reaction |
| PHE | Public Health England |
| PrEP | Pre-exposure prophylaxis |

| | |
|---|---|
| PWID | People who inject drugs |
| QALY | Quality adjusted life year |
| RCT | Randomised controlled trial |
| RCT | Randomised controlled trial |
| RNA | Ribonucleic acid |
| RR | Rate ratio |
| SIGN | Scottish Intercollegiate Guidelines Network |
| STI | Sexually Transmitted Infection |
| SVR | Sustained virological response |
| WHO | World Health Organisation |

# 1 Introduction

## 1.1 Epidemiology and natural history of hepatitis C

The Hepatitis C virus (HCV) is a blood-borne ribonucleic acid (RNA) virus that causes inflammation and damage of the liver.[1] There are six genotypes, with numerous subtypes identified.[2] These genotypes vary regionally, with genotype 1 being the most common globally, and also in Europe.[3] The virus is transmitted via several routes including contact with infected blood. This can occur from the re-use of unsterilised medical equipment, particularly injecting equipment, or transfusion of unscreened blood products. HCV can also be transmitted through sexual contact as well as vertically transmitted from mother to child during pregnancy.[1,4] In Europe, transmission of the virus is predominantly from sharing of intravenous drug equipment, such as needles and syringes.[4]

HCV causes progressive liver fibrosis, which can lead to liver cirrhosis after two to three decades of infection. This can subsequently lead to liver cancer, known as hepatocellular carcinoma (HCC), and decompensated cirrhosis, in which the liver deteriorates and is unable to fully function, resulting in a wide variety of symptoms.[5,6] The onset of HCC or decompensated cirrhosis are associated with reduced health related quality of life (HRQoL), and a poor prognosis in terms of survival.[7-9]

Following the initial infection with HCV, there is an acute phase of the infection (the first six months), which is asymptomatic for most people.[4,10] Approximately 20-25% of people will clear the virus naturally.[10] For those who do not clear the virus, a chronic phase of infection occurs, which is often referred to as chronic HCV.[4] The majority of people with chronic HCV do not exhibit symptoms following infection.[1] Furthermore, for those who are symptomatic, the symptoms tend to be general, and similar to other viral infections, such as fatigue, nausea, tiredness, abdominal pain and muscle ache.[4,10] These symptoms can occur for short periods of time before disappearing, and may or may not return. Due to the asymptomatic nature of the infection, there may not be many opportunities to diagnose the infection. Even for those who do display symptoms, many do not seek healthcare, and even if they do, the general nature of the symptoms means that an HCV test may not be performed.

This period of asymptomatic infection with chronic HCV can persist for many decades, leaving people unaware of their infection status, while liver fibrosis and cirrhosis develop slowly.

Severe symptoms usually begin to appear after the onset of advanced liver disease (decompensated cirrhosis) or HCC, upon which the prognosis is poor.[5,7,8]

HCV is a major public health threat globally with a particularly high prevalence in central and western regions of sub-Saharan Africa, eastern Europe, and central Asia.[3] In 2019, 58 million people were estimated to be living with chronic HCV worldwide with 290,000 recorded HCV-related deaths due to liver cirrhosis and liver cancer.[11]

Whilst the focus of this thesis is to identify cost-effective interventions to expand HCV testing in the UK, in one analysis, testing for HCV and hepatitis B virus (HBV) are both considered in Emergency Departments (ED). This is because recommendations for HIV testing in the ED already exist, but expanding this to a full blood borne virus (BBV) test is of interest, which would include testing for HIV, HCV and HBV (additional information on this is discussed in Chapter 7). The natural history of HBV is similar to that of HCV in that it causes chronic liver disease, which can subsequently lead to the development of HCC and decompensated liver cirrhosis.[12]

## 1.2 Diagnostic tests

Given the asymptomatic nature of HCV, diagnostic testing is key in identifying those who may be infected. Whilst there are several types of tests for HCV, the most common are HCV antibody tests, and HCV RNA tests.

An antibody test identifies the presence of HCV antibodies in the blood.[13-15] A positive test indicates that an individual has, at some point in their life, been infected with HCV, and therefore developed antibodies to the virus. However, it can take several months before an individual develops HCV antibodies after being exposed, with an average time of approximately 60 days.[16] This means that if a person is tested shortly after becoming infected, then they may test negative whilst they are infected. Once the antibodies have developed, they persist for life following infection.[16]

Following a positive antibody test, a confirmatory test for HCV RNA is required. This is performed using a Nucleic Acid Amplification Test (NAAT), which usually involves a polymerase chain reaction (PCR) technique.[14] For this reason, tests for HCV RNA are also sometimes referred to as PCR tests. This test searches for the presence of HCV RNA in the blood, with a positive test confirming a current infection. The HCV RNA test is the gold standard test with a

sensitivity of around 98% and specificity of more than 99%.[17,18] Tests for HCV RNA can also remain highly accurate when performed on dry blood spot (DBS) samples, compared to the more traditional use of whole blood samples.[19] In this thesis, the HCV RNA test is assumed to 100% accurate.

HCV RNA can be detected around 2-21 days after infection, although approximately 25% of people will spontaneously clear the virus, and therefore will not progress to chronic HCV.[16] If the infection persists for at least six months then this indicates chronic HCV, after which point the probability of spontaneous clearance decreases.[16,20] For those with no recent transmission risk, a positive HCV RNA test strongly suggests a chronic HCV infection, as the infection is unlikely to have occurred recently. For people who inject drugs (PWID) or those with a recent exposure to HCV, a repeat HCV RNA test prior to the onset of treatment may be performed to ensure the individual has not spontaneously cleared the virus in the meantime. HCV RNA testing is the gold standard test for active HCV infection.[21]

Another type of test used is for the presence of HCV core antigen, with a positive antigen test indicating a current HCV infection, similar to an HCV RNA test. However this test is marginally less sensitive than RNA tests, with a sensitivity of approximately 96-97%, and a specificity of 100%.[14,21]

## 1.3 The evolution of hepatitis C treatment and a viral hepatitis elimination strategy

Unlike hepatitis A and B infections, there is no vaccine for HCV. Treatment for HCV previously involved interferon based regimens, in combination with ribavirin.[22,23] These interferon based treatments were long in duration, with regimens of 16 to 48 weeks. They also resulted in a high incidence of adverse events, which lead to treatment discontinuation for many patients.[13,24-26] Furthermore, a sustained virological response (SVR), equivalent to cure, varied depending on the HCV genotype of each patient, with SVR probability of around 75-85% for those with HCV genotype 2 and 3, but as low as 40-50% for those with HCV genotype 1.[23] When interferon based treatments were used to treat HCV, the proportion of those diagnosed with HCV that subsequently received treatment was low, approximately 12% in England, based on routine statistics.[27] There are many reasons for the low treatment uptake, but the long treatment duration and the adverse events associated with interferon based treatments were two important factors.[26,28,29] More recently, oral based direct acting antiviral (DAA) treatments

have been developed to treat HCV, and are able to achieve SVR in more than 90% of patients.[30] Furthermore, pan-genotypic treatments are available and effective across all six HCV genotypes.[25] As well as having a much higher probability of SVR, these treatments are shorter in duration (usually 8 to 12 weeks), associated with fewer side effects, and are easier to administer than previous HCV treatments because they are taken orally, rather than by injection.[30] As such, these DAA treatments are now the first line treatment for HCV in the UK, and many other countries around the world.[10,13] Although these treatments are highly effective, there is a possibility that individuals can be reinfected with HCV after they have previously achieved SVR. This transmission can occur in the same way as an initial infection, through contact with infected blood.

Treatment of chronic HCV has two distinct benefits. First, since HCV is a progressive disease, early diagnosis and treatment can stop (or considerably slow) liver fibrosis and cirrhosis, which can lead to more advanced disease stages that are associated with increased mortality.[31] Treatment is associated with an increase the quality of life, but it also avoids any further decline in quality of life associated with disease progression.[9,32] It also avoids the costs associated with advanced liver disease stages, such as additional monitoring and hospital stays, additional treatments for liver cancer, and also the need for a liver transplantation.[24] The other benefit of HCV treatment is that by achieving an SVR, those previously infected with HCV can no longer transmit the virus, thereby reducing new infections. This has been described as 'treatment as prevention', and has been considered important for groups who are likely to transmit the virus, such as PWID.[33-36]

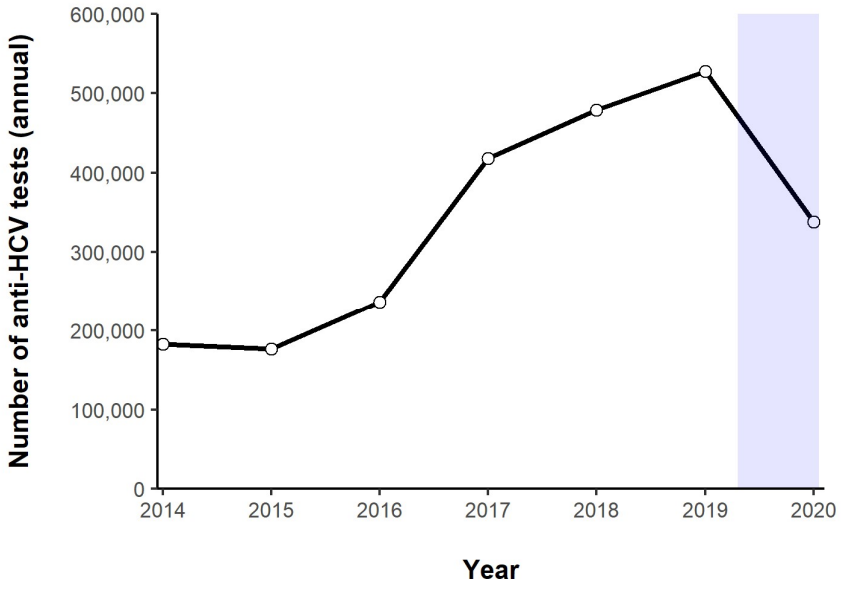
The availability of these highly effective DAA treatments led to the World Health Organisation (WHO) to develop a Global Health Strategy in 2016, with targets to eliminate viral hepatitis as a public health threat by 2030.[37] The targets include a 65% reduction in HCV mortality, 90% reduction in incidence, and also include service targets such as 90% diagnosis coverage and 80% treatment uptake. The same targets apply for HBV. In the UK, the NHS previously set its own target of 2025 to achieve the WHO goals, and have recently agreed to an ambitious procurement deal with the pharmaceutical industry to supply drugs for HCV elimination.[38-40] This deal also involves pharmaceutical industry investment to increase testing and linkage to care for those currently living with HCV in England, many of whom remain undiagnosed.[41]

## 1.4 Hepatitis C in the UK

In the UK, there are approximately 118,000 people living with HCV as of 2019, with an estimated 89,000 in England.[41,42] The majority of these patients are either undiagnosed, or have been diagnosed but do not wish to engage with treatment, since such highly effective DAA treatments are widely available. The majority of new infections in the UK are attributable to PWID, accounting for around 90% of laboratory diagnoses in which risk factors were reported.[41] However, HCV infection is associated with other factors, such as transfusions of contaminated blood prior to 1991, when screening for HCV infection began to be routinely performed, or amongst people born in countries with a high prevalence of HCV.[15] Since the vast majority of new infections in the UK are attributed to PWID, those currently injecting still remain at risk of HCV, even if they have previously cleared the infection. The probability of HCV reinfection amongst those who are not injecting drugs is believed to be very low, since the likelihood of exposure to HCV infected blood is very low, albeit not impossible.

Testing for HCV is the main public health strategy to reduce the burden of infection in the UK.[15] Testing and subsequent treatment is crucial to identify and halt (or dramatically reduce) disease progression. Given the recent availability of highly effective and well tolerated treatments, and HCV elimination targets, there is now a strong emphasis on diagnosing and treating those living with HCV in the UK.[41] The rates of both HCV testing and provision of HCV treatment have been increasing over the last decade, and as a consequence, the prevalence of HCV has been steadily decreasing in the UK.[41,43,44] The annual numbers of tests performed in England is reported in Public Health England's (PHE) annual sentinel surveillance report, with recent testing numbers shown in Figure 1-1. The coverage of sentinel surveillance is approximately 40%, so the number of tests shown are not reflective of total numbers being performed across England, but the trends are likely to be consistent.[43]

Figure 1-1: Number of HCV antibody (anti-HCV) tests performed in England per year, as reported by Public Health England sentinel surveillance of blood borne virus reports.[43] The blue shaded area represents the impact of the COVID-19 pandemic on HCV antibody testing.




Yet, HCV is unequally distributed amongst the UK population, and is over-represented in specific groups. Since the HCV prevalence amongst the UK general population is low (approximately 0.18% as of 2019), population based testing is not currently recommended due to the high costs and relatively low number of positive cases that would be identified.[41] Instead, testing is focused towards those who are deemed to be at an increased risk of HCV.[15] This risk-based approach to testing is also known as case-finding, whereby resources are targeted towards those perceived to be at risk.

In the UK, the National Institute for Health and Care Excellence (NICE) recommends testing for HCV for those meeting specific risk criteria. Testing is recommended for current or previous injecting drug users, those receiving a historical blood transfusion or blood product (pre-1991 in UK), those born in a country with high HCV prevalence, human immunodeficiency virus (HIV) positive men who have sex with men (MSM), those in prison, have grown up in care, or are homeless.[15] Close contacts of HCV positive individuals, including children of mothers with HCV, are also recommended for testing. To identify those at risk of HCV, testing is recommended in settings in which these populations attend, such as drug treatment services, harm reduction services, prisons, and genitourinary medicine (GUM) clinics. Testing is also recommended in primary and secondary care, but only for those identified as being at risk (i.e. meeting one of

the risk criteria), those with an abnormal liver function test, or those with symptoms that suggest liver damage.[15]

Whilst those identified as high risk are more likely to test positive for HCV, risk-based testing will likely miss those without obvious risk factors. This includes those who are either unaware of their past exposure or do not link their historical exposures or behaviours with their current risk of HCV.[45] This is particularly true for those people who feel well.[45] Those receiving blood transfusions or blood products prior to 1991 may not be aware of their exposure, and are likely to remain hidden from risk-based screening. This may also be true for those who may have contracted iatrogenic HCV, in countries with poorly funded healthcare systems or settings with inadequate infection control.

Whilst injecting drug use is estimated to account for approximately 90% of infections in the UK in which risk factors are reported, it is unclear what proportion of these can be attributed to current (or recent) injecting drug use, compared to those who may have used drugs many years ago.[41] Furthermore, it is unlikely that those who injected drugs in the past would disclose their previous behaviours unless prompted by a healthcare worker, especially if they are unaware of how this is connected to their current health.[45] Even then, both healthcare workers and patients may be reluctant to question, discuss or disclose this information, potentially due to the stigma associated with injecting drug use.[45-47] Many of those who have ceased using drugs may not attend services targeted towards current or recent drug users, such as needle and syringe services, opioid substitution therapy (OST) in pharmacies, or substance misuse and addiction services. As such, primary or secondary care may be the only settings these individuals are currently likely to attend and receive an HCV test.

Furthermore, knowledge of HCV amongst general practitioners (GPs) has been historically poor, although it is likely to have improved more recently due to increasing hepatitis awareness alongside new HCV elimination targets.[48,49] Since GPs do not routinely ask about historical risk factors or behaviours during primary care appointments, it is also difficult to identify those who may be at risk.[47] Therefore those who are not currently at risk of HCV are unlikely to be tested for HCV in primary care, unless they display symptoms. This will include people who have previously injected drugs, or were potentially exposed to contaminated blood products. In order to increase diagnoses and meet WHO elimination targets, more needs to be done to increase HCV testing in these groups, and to evaluate how novel testing interventions can expand testing coverage to those who are currently unlikely to receive it. This will ensure that the remaining undiagnosed cases of HCV in the UK can be identified and treated.

## 1.5 Economic evaluation for HCV testing interventions

### 1.5.1 Overview

Since resources for healthcare are scarce, economic evaluation can help to inform how these resources can be allocated efficiently, in order to maximise overall population health.[50] Economic evaluation seeks to estimate the costs and outcomes associated with alternative courses of actions, and considers whether a particular intervention represents an efficient use of resources.[51]

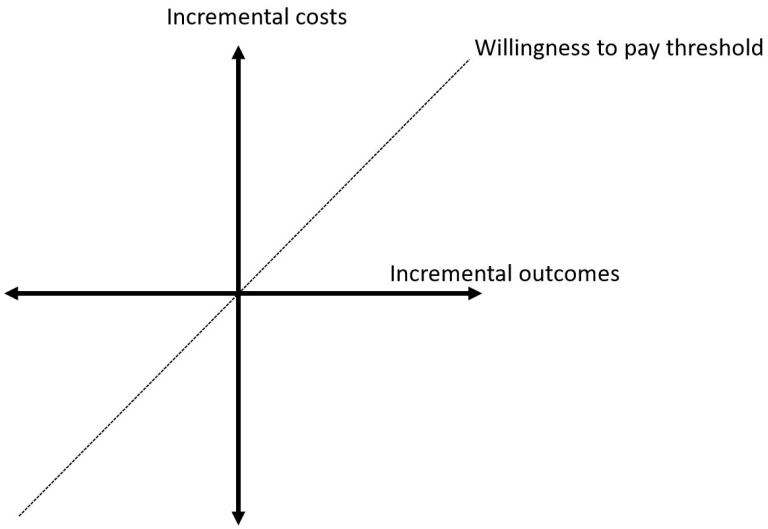
The incremental costs and the incremental outcomes associated with an intervention can be estimated compared to the comparator(s) and plotted on a cost-effectiveness plane. An example is shown in Figure 1-2. The intervention may result in positive incremental health outcomes at a negative incremental cost, in which case it would fall in the south-east quadrant of the cost-effectiveness plane. The intervention is clearly beneficial and is therefore said to be dominant. Conversely, the intervention may result in negative incremental health outcomes, and positive incremental costs, and will therefore fall in the north-west quadrant of cost-effectiveness plane. In this case, the intervention is dominated (and the comparator is dominant), and the intervention should not be adopted.

More commonly however, the intervention will have positive incremental costs and incremental outcomes (i.e. more effective and more costly) and fall within the north-east quadrant, or will have negative incremental costs and outcomes (i.e. less effective and less costly) and fall in the south-west quadrant, compared to the comparator. In these instances, there is a clear trade-off between the incremental costs and incremental outcomes. We can invest more resources for more health outcomes, or reduce our resource expenditure and achieve lower health outcomes.

In order to make a decision, we need to place a value upon these health outcomes, which can be represented using a willingness to pay threshold, or cost-effectiveness threshold. The threshold should reflect the value of what is being given up in order to fund this particular intervention. For example, the health outcomes that could have been gained had the resources (or money) been invested in the next best alternative.[52] This is known as the opportunity cost. Once the threshold has been identified, this allows for a relatively simple decision rule; if the cost of obtaining outcomes is lower or equal to the cost that we are willing to pay for them, then we do so. Alternatively, if the cost per outcome is above the threshold

value, this suggests that the technology should not be provided. This is a simple decision rule in the absence of uncertainty, however when uncertainty exists in the outcomes of the cost-effectiveness model, other approaches for decisions which account for such uncertainty can be used.[53-55]

Figure 1-2:Cost-effectiveness plane




In order to compare the cost per outcome of any given intervention to the willingness to pay threshold, we must calculate an incremental cost-effectiveness ratio (ICER). This is calculated using the formula below:

$$ICER = (Cost_{Intervention} - Cost_{Comparator}) \div (Outcomes_{Intervention} - Outcomes_{Comparator})$$

### 1.5.2 NICE guidelines for economic evaluations

NICE has specific guidelines for performing economic evaluations of new technologies in England and Wales, with guidelines published in 2013, and more recently in 2022.[56,57] This includes expressing health outcomes as quality adjusted life years (QALYs), a multi-dimensional outcome measure which combines a person's length of life, with their health-related quality of life. Expressing health outcomes as QALYs allows for comparisons between different healthcare interventions across different disease areas. For technology appraisals NICE has set its own willingness to pay threshold (or cost-effectiveness threshold) at which it considers new

interventions to be cost-effective. The threshold is between £20,000 and £30,000 per QALY gained for health technology appraisals.[56] This range means that interventions that result in an ICER of less than £20,000 per QALY are likely to be cost-effective, whilst those that are more than £30,000 per QALY are unlikely to be cost-effective, except in other specific circumstances. In NICE 2013 guidelines, the additional factors which NICE considered to be of additional value included innovative medicines, and other criteria such as technologies which extend life for those with a low life expectancy, or interventions which help to meet other NHS objectives.[56] These criteria differ in recent updates, with a severity modifier considering the QALY shortfall between the condition of interest, and the general population without the condition.[57] The QALY weights are inflated based on this QALY shortfall, giving a higher inflation factor when the severity of disease (and QALY shortfall) is higher.

The NICE guidelines for health technology appraisals state that costs included in the evaluation should be from the perspective of the NHS and personal and social services.[56] This means the inclusion of direct costs incurred by the NHS only, whilst direct costs incurred by the patient, and indirect costs (e.g. productivity losses) are not included. The economic evaluation should also only include the direct health effects as a result of the intervention.

### 1.5.3 Important aspects of economic evaluation, and how these relate to economic evaluations of HCV testing intervention

The NICE guidelines for technology appraisals contain an appropriate guide to follow when performing an economic evaluation in the UK. However, for any particular decision problem, the scope of an economic evaluation, and the details in how to appropriately perform the analysis, must still be defined. This will include the identification of the appropriate comparators for the intervention, whether a model is required, and if so, the choice of modelling approach required to appropriately estimate the costs and effects, and the time horizon over which the costs and effects should be considered. These will depend on both the intervention being considered and the disease area which is being analysed. The following sections discuss some of the key aspects, with a focus on how these relate to HCV testing interventions.

#### 1.5.3.1 Cost-effectiveness of HCV treatments as a pre-requisite for an economic evaluation of testing interventions

A testing intervention should only be performed if there is an effective treatment or course of action that can be taken to improve health outcomes following a diagnosis. If not, then there may be no benefit of performing the test, unless there is a benefit to the individual from receiving a diagnosis alone. Furthermore, an intervention such as test can only be cost-effective if providing subsequent treatment is also cost-effective. This is because at an individual level, the benefit achieved is the benefit received by treatment (unless a diagnosis without treatment is believed to have a benefit). In addition, the costs of testing and treatment can only be higher than the cost of treatment alone, since testing requires resources. As such, the cost-effectiveness of a 'test and treat' intervention will be less cost-effective than the treatment itself. However a notable exception is when the model includes transmission, as the benefit of treatment is received by the individual treated and by those who subsequently avoid being infected. Another exception may be if testing results in subsequent behavioural changes, which may reduce an individual's risk of infection thereafter.

Based on NICE submissions for the treatment of chronic HCV, DAA's are cost-effective in the UK, even at list prices of up to £44,827 for patients that receive 12 weeks of treatment.[58-60] Since the negotiations around the procurement of DAA treatments, the prices have reduced to around £5,000 to £10,000 per course.[61] Treatment is now considered highly cost-effective, as the cost of the treatment itself was the main incremental cost. This means there is significant scope to invest in HCV testing in order to identify those with undiagnosed HCV to be cost-effective too.[15]

#### 1.5.3.2 Choosing an appropriate time horizon and extrapolating testing study results

When estimating the costs and outcomes within an economic evaluation, another important choice to make is the time horizon over which these are considered. In most instances, a lifetime time horizon is preferable to ensure that all costs and outcomes across a person's lifetime are included, and this is particularly necessary when the intervention impacts upon survival or results in benefits that remain for a person's lifetime.[56] For an HCV testing intervention, the benefit of a diagnosis is the opportunity to treat the individual, and for them to clear the virus and avoid the liver damage and deteriorating quality of life associated with this.[5,6] Since an HCV infection causes chronic disease if left untreated, there is a potentially

lifelong benefit to those who achieve SVR. A lifetime time horizon is therefore most appropriate.

#### 1.5.3.3 Modelling analysis, and extrapolating testing study results

Empirical studies of HCV testing interventions often only involve short-term follow up of those who are tested, usually up until the point that individuals are referred to treatment, receive treatment, or the outcomes of treatment are reported (approximately 6 months after treatment initiation).[62-66] This can raise difficulties because studies tend not to collect data on the resulting health outcomes, or if they do, these outcomes are related to the clinical status of the patient (e.g. SVR) rather than the improvement in their long-term health outcomes, based on changes in quality of life and long-term overall survival estimates. In order to capture the effects over a person's lifetime, a mechanism by which the benefits of HCV testing can be extrapolated over a lifetime time horizon is needed.

A model-based analysis can extrapolate the results of a short-term testing study, by combining the study data with additional data sources from the literature on the natural history of HCV, and the long-term costs and health related quality of life for those at different stages of chronic HCV. This allows for the impact of testing to be extrapolated beyond the study period, to predict the lifetime impact of testing upon the costs and health outcomes.

Since HCV is a chronic infection which can remain undiagnosed over many years, a Markov modelling approach is a reasonable option to model the impact of an HCV testing intervention. A Markov model explicitly accounts for the amount of time spent in mutually exclusive health states, which is beneficial for chronic diseases such as HCV. This is particularly the case when accounting for the differences in chronic disease progression, which can differ for those diagnosed and receiving treatment, compared to those who remain undiagnosed and continue to experience liver fibrosis and disease progression. A cohort-based approach is frequently associated with Markov modelling, with a homogenous cohort moving through the model health states over time.

Cohort models can account for heterogeneity in the model population by performing separate model analyses for different subgroups of patients, with some or all of the parameters differing for each subgroup (e.g. using different transition and mortality probabilities for males and females). Alternatively, the model can also account for heterogeneity by stratifying the cohort into different health states within the model structure, allowing each subgroup to follow different pathways within the model. However, these differences in the subgroups must

be known in advance of the decision, so that a decision can be made for each subgroup accordingly, and so that the analysis can appropriately account for them.[67]

If heterogeneity is likely to exist between patients, and these have a non-linear relationship with the model outcome, then using an individual patient level model and aggregating the results for all of these patients can provide a more accurate estimation of the average costs and effects compared to using the average characteristics in a cohort-based analysis.[67] Furthermore, if multiple events that occur within the model can alter the model parameters following these events, then a more complex modelling approach may be beneficial to overcome the memoryless nature of the Markov model. For example, if each repeated clinical event results in a change in the future disease progression, but this change also depends on the characteristics of the individual, then the memoryless nature of the Markov model would limit the possibility to account for this in a Markov model, and an individual patient level simulation would likely be appropriate. Although individual patient level simulation models overcome some of the limitations of a Markov model, the models are more complex to develop, and there tends to be a high computational burden when running the model because each individual must be analysed In the model sequentially (rather than analysing the whole cohort).[68]

Heterogeneity does exist amongst those living with HCV. Those who are currently injecting drugs are at increased risk of mortality compared to those who do not. However, when testing is likely to include both of these groups, these characteristics can be easily accounted for within a Markov model by running separate analyses for PWID and non-PWID, and aggregating the results. Therefore, a cohort-based Markov model can be deemed appropriate, and the model does not need to simulate individual patients to accurately assess the costs and effects of different testing strategies.

#### 1.5.3.4 Identifying an appropriate testing intervention and the comparators

In the UK, NICE guidelines already recommend routine HCV testing in drug and alcohol services, prisons, and in primary care for those deemed at increased risk.[15] These guidelines are applicable to Scotland and Northern Ireland too.[69,70] There is also evidence to support the cost-effectiveness of testing in these settings.[71-75] Since testing is already offered to those who are deemed at risk of HCV, there are many additional HCV testing strategies that could be considered. These could be offering an HCV test to everyone, offering testing to those with other risk factors (which are not currently recommended by NICE), or it could involve a new

intervention or pathway to improve the testing amongst those who are recommended to receive testing, but may not do so at present.

Since it compares alternative courses of action, an economic evaluation must identify the appropriate comparators to include within the analysis, which can be challenging for testing interventions. Numerous settings in the UK already offer HCV testing to those who are deemed to be at risk. If HCV testing is introduced to a new setting, for example to everyone attending a pharmacy, then the study comparator (i.e. the control) may be no testing in the pharmacy. However, it is important to quantify the benefits of the alternative courses of action to the individuals who receive testing, and some of those who are tested in the pharmacy might receive a test in another settings at a later point in time. This is particularly relevant to HCV, which can remain undiagnosed for decades, giving a significant period of time in which a diagnosis can be made.

An appropriate comparison for an economic evaluation may be a new HCV testing intervention in addition to current HCV testing practice, versus current HCV testing practice only. This is the approach taken by previous modelling studies used to inform NICE hepatitis testing guidelines.[72] Outside of the new testing setting, a 'background' probability of testing is assumed to occur for those at risk of HCV, accounting for the probability of testing in other settings.[71,72] The probability of testing in another setting will depend on the likelihood that people attend these settings, and how likely they are to be offered and accept an HCV test once they attend.

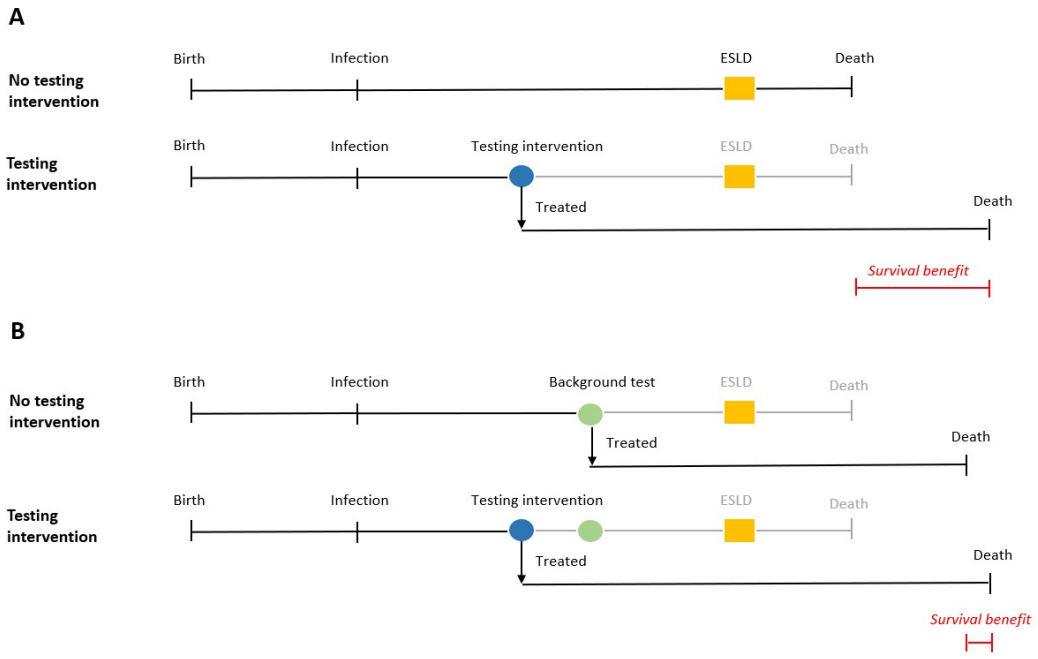
#### 1.5.3.5 Evaluating the benefit of HCV testing interventions in modelling analyses

To evaluate the long-term effects of an HCV testing intervention, an economic model needs to capture both testing and linkage to treatment. The benefit of testing therefore depends on both the number of persons identified (i.e. the prevalence amongst those receiving testing), and the proportion of those positive cases that are subsequently linked to care (i.e. engaging with health services) and receive treatment. Since the benefit depends on the interaction between these two aspects, testing may be more cost-effective in populations with a lower prevalence of infection, if the subsequent linkage to care is higher compared to other testing interventions in populations with higher prevalence, but with a lower proportion of patients linked to care.

In modelling analyses, the parameterisation of the background rate of testing can have a large impact upon the benefit associated with a new testing intervention. If those tested as part of a

new intervention are likely to receive testing in another setting, then the benefit of the new intervention may be limited, since those undiagnosed are likely to receive testing elsewhere, shortly after. In contrast, if those tested as part of the new intervention would not have received testing in any other setting, then those with chronic HCV would likely remain undiagnosed until the onset of symptoms indicating advanced liver disease (e.g. decompensated cirrhosis or HCC). In this scenario, the benefit of testing would be much higher. A simplistic, diagrammatic representation of this concept is presented in Figure 1-3.

Figure 1-3: Impact and benefit associated with a testing intervention for A) individual who would not otherwise be tested for hepatitis C and B) an individual who would be tested for hepatitis C shortly after the testing intervention




ELSD: End-stage liver disease

Unfortunately studies of new HCV testing strategies rarely collect data on the frequency of HCV testing amongst those attending the new testing service, and there are limitations of existing datasets. For example, the UK Health Security Agency (HSA) has a sentinel surveillance dataset of HCV testing, with approximately 40% coverage in testing from the general population.[43] Coverage of DBS testing is separate, with these tests often performed in drug services, outreach services or prisons but sent to separate laboratories. Whilst the coverage of

DBS testing is higher, the exact coverage is uncertain because it is difficult to estimate a denominator for services that offer DBS testing. Unlike general practices or hospitals performing testing, there is no fixed list of drug services, and the providers frequently change too. Furthermore, given that limited identifiers are provided to those working with the sentinel surveillance dataset, it can be difficult to de-duplicate testing occurring across different settings. These complexities increase the uncertainty in the testing data available nationally. Asking attendees to recall their previous HCV test is another possibility, but such data would be subject to recall bias. For these reasons, estimating what would have happened in the absence of the testing intervention for the comparator group of an HCV testing intervention can be challenging.

### 1.5.4 The rationale for evaluating new HCV testing interventions in the UK

With the WHO and NHS target dates for the HCV elimination approaching, and with additional funding for testing as part of the recent NHS deal with the pharmaceutical industry, there is increased interest in novel testing strategies that can expand screening to 'new' populations. The PHE annual hepatitis report in 2017 stated that increasing testing, improving prevention and raising awareness were critical in order to meet the 2030 elimination goals.[76] This represents an opportunity to evaluate the cost-effectiveness of new HCV testing interventions, and to assess the methodology being used in economic evaluations of such interventions.

## 1.6 Overview of the thesis

### 1.6.1 Background and context of the work

The work included in this thesis was partially funded by research grants from the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Blood Borne and Sexually Transmitted Infections. The unit involves a partnership between academia (University College London and The London School of Hygiene and Tropical Medicine) and PHE, which is now UK HSA. The aim of the unit is to conduct research to improve population health, and to develop policy guidelines for those working in heath protection.[77]

The aims and objectives of this thesis were aligned to also achieve the aims of the NIHR HPRU, specifically to inform health policy and guidelines. This involved working directly with

government agencies to generate evidence to support decision making by the NHS and policy makers. This thesis focused specifically on expanding HCV testing to those who are unlikely to currently receive it.

### 1.6.2 Structure of the thesis

This thesis contains 10 Chapters and is presented in research paper style.

This Chapter has provided an introduction to HCV, with a focus on the public health challenge of identifying and treating those living with undiagnosed infection. It has also discussed the importance of economic evaluation as a tool for resource allocation for new HCV testing interventions.

Chapter 2 outlines the aims and objectives of the thesis.

UK and European hepatitis C testing guidelines are reviewed in Chapter 3. The review of testing guidelines is then supplemented by a literature review to identify economic evidence of HCV testing interventions in the UK, which is presented in Chapter 4. This review aimed to identify any recent economic evidence not included in the NICE guidance for HCV testing in the UK, ensuring all the relevant literature is identified, in order to identify knowledge gaps in the UK.

The thesis then focuses on three economic evaluations of HCV testing strategies, with each evaluating the cost-effectiveness of a novel HCV testing strategy.

Chapter 5 considers the cost-effectiveness of a hypothetical birth cohort screening intervention for HCV. It is based on an elevated test positivity rate amongst tests performed in UK sentinel surveillance for those born between 1950 and 1979. The analysis considered the possibility of adding a HCV test onto the NHS health check, a general health check performed in primary care, in which those aged 40-74 years of age are invited once every 5 years. This analysis is presented as a manuscript, published in *Value in Health*.[78]

An alternative testing intervention in primary care was also evaluated in Chapter 6, based on the results of the Hepatitis C Assessment Through to Treatment Trial (HepCATT) cluster-randomised controlled trial. The trial involved the use of an algorithm to identify patients with evidence of HCV risk factors in their primary care medical records, with those identified offered to return to primary care to receive an HCV test. Unlike the universal screening strategy for birth cohorts, this testing intervention was targeted towards those with evidence

of HCV risk factors. NICE testing guidelines already recommend testing for those with HCV risk factors, but most patients do not receive it currently, meaning there is scope for an intervention to address this issue.[15,47] This analysis has been re-written to focus on the economic evaluation only, since the original manuscript, published in the *BMJ*, reported the economic evaluation alongside the results of the randomised controlled trial.[62] The published manuscript is provided in Appendix Section 10.4.

Chapter 7 then considers the cost-effectiveness of offering universal testing for HCV and HBV, for people attending a hospital emergency department (ED) who are already receiving a blood test as part of their routine care. Since testing is already recommended for HIV in EDs which have an elevated prevalence of the infection, numerous studies have considered the possibility of expanding testing to those with HCV and HBV, to perform a full BBV screen. It is for this reason that HCV and HBV testing was considered in the ED, but not in the other two economic evaluations of primary care testing. The HCV and HBV prevalence amongst ED attendees is routinely higher compared to the general population, which suggests that those attending are at higher risk of infection. It is also likely that for some individuals, the ED is the only healthcare setting which they attend, and therefore may be unlikely to receive testing elsewhere. This analysis is also presented as a manuscript published in *Value in Health*.[79]

In Chapter 8, a methodological analysis explores the ways in which economic models of HCV testing strategies handle heterogeneity, with a particular focus on the counterfactual or control arm for future testing. This Chapter explores potential issues when parameterising the background rate of testing for heterogenous populations, in particular when the risk of background testing is correlated with the prevalence of HCV amongst sub-groups within the model population. This Chapter is presented in manuscript format, albeit in a longer version, with a shorter version of the manuscript being prepared for submission.

Finally, Chapter 9 provides an overview and discussion of the key findings of this thesis, and discusses some of the limitations and areas for future research. It also gives recommendations for policy changes in HCV testing, as well as providing reflection on the thesis as a whole. A brief conclusion to the thesis is also provided.

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# 2 Aims and objectives

## 2.1 Aims

The aim of this thesis is to assess the cost-effectiveness of novel HCV testing interventions and subsequent linkage to care in the UK, with a focus on testing strategies that seek to expand testing to groups who are unlikely to receive HCV testing otherwise, in order to inform HCV testing policies.

## 2.2 Objectives

The aim of the thesis will be achieved by the following objectives:

- Identify evidence gaps in the economic literature of HCV testing strategies in the UK, with a focus on the evidence gaps highlighted as areas of interest by testing guideline committees or policy makers.
- Evaluate the cost-effectiveness of three HCV testing strategies that seek to expand testing to those currently unlikely to receive it, to help inform UK testing guidelines and policy decisions.
- Consider different modelling methods for parameterising the counterfactual HCV testing rate in economic evaluations, and how these methods can account for heterogeneity in the HCV risk and current HCV testing rates amongst those included in the testing population.

# 3 Summary of hepatitis testing guidelines

Since the overall aim of the thesis is to guide policy decisions of UK hepatitis testing, I conducted a review of HCV testing guidelines to consider the current settings or populations in which HCV testing is recommended. An understanding of the current recommendations is needed in order to identify gaps in the literature. Guidelines from both the UK and Europe were considered, in order to compare any differences in recommendations between them. These differences could be either recommendations in whom or where current testing is offered, or in recommendations for future research.

The review included guidelines that were deemed relevant to the UK. It therefore focused primarily on guidelines from within the UK (England and Wales, Scotland, Northern Ireland). European guidelines were also considered relevant because these may be more likely to be used for decision making around testing, particularly if these guidelines are more recent than those from within the UK.

Guidelines from other high-income countries were not considered, as the epidemiology, and the costs associated with HCV testing and treatment, were deemed to potentially have an impact on guideline recommendations. Furthermore, since the rationale for reviewing the guidelines was to identify where UK testing policies already exist and identify knowledge gaps that could be addressed by this thesis, it was not necessary to consider guidelines specific to other countries in order to identify the testing strategies which would be evaluated in this thesis. However, once the three testing strategies were identified, both guidelines and existing economic evaluations around these testing interventions were reviewed. The comparisons of UK economic evaluations and policy recommendations were subsequently compared and to those in other countries, and these are provided in the Introduction and Discussion sections of the relevant economic evaluation Chapters (Chapters 5, 6 and 7).

Four different guidelines providing recommendations for HCV testing were identified. They report current HCV testing recommendations and the evidence gaps, and are briefly summarised below.

The main guidelines for HCV testing in the UK are public health guidelines reported by NICE, which provide recommendations for England and Wales. The guidelines report testing recommendations, but also discuss considerations and recommendations for future research, with the intention of providing guidance around testing in these settings once more evidence is available. These ‘areas of interest’ reported by NICE are of particular importance for this

thesis, given that it aims to provide perform research that will guide HCV testing policy in the UK. The most recent guideline was published in 2012.[1] A consultation was performed in 2017 to decide whether any updates were required, but concluded there was insufficient evidence to introduce any new recommendations, as no evidence was identified that would invalidate previous guideline recommendations.[2]

The Scottish Intercollegiate Guidelines Network (SIGN) 2013 guidelines for the management of HCV were also reviewed, as they contain a section of HCV testing recommendations.[3] Despite having their own recommendations for populations to offer a HCV test (with minor differences compared to NICE guidelines), the SIGN guidelines also state that the recommendations in the NICE hepatitis testing guidelines are directly applicable to Scotland. No guidelines covering HCV testing in Northern Ireland were identified. A recent HCV elimination plan for Northern Ireland refers to NICE guidelines for testing those at risk of HCV annually, suggesting they are likely to be applicable to Northern Ireland too.[4]

European guidelines on hepatitis testing are also available from two sources. These were reviewed since they may highlight differences in the recommendations between European and NICE guidelines, and may also note different areas of interest for future research.

The European Centre for Disease Prevention and Control (ECDC) published public health guidance on HIV, hepatitis B and C testing in Europe in 2018.[5] Although there are no recommendations made to specific countries, the guidelines are highly detailed, and capture more recent studies across Europe.

The European Association for the Study of the Liver (EASL) have published clinical guidelines in 2018 that focus on the treatment of HCV, but also provide a short commentary on hepatitis testing.[6] The guidelines only state that testing depends on the local epidemiology, and that regional and national guidelines for testing should be determined, and therefore were not considered due to a lack of specific recommendations.

## 3.1 NICE guidelines

The NICE guidelines, published in 2012, include recommendations for HCV testing that are considered cost-effective.[1] These recommendations include both for *whom* and *where* hepatitis testing should be performed. The guidelines also report a 'Considerations' section, which includes an economic modelling subsection, and a 'Recommendations for future

research section', to show the evidence gaps within the guidelines. These are summarised below. During their review of the guidelines in 2017, NICE released a surveillance report which included their consultation findings. A summary of this report is provided in Section 3.1.3.

### 3.1.1 NICE recommendations for HCV testing: Populations and settings for testing

The NICE guidelines identify those who are considered at high risk of HCV. This is based on those most likely to have been exposed (e.g. people who inject drugs, received blood transfusion prior to 1991), but also include 'high-risk' and under-served populations that are deemed more likely to have potentially been exposed to HCV (e.g. prisoners, homeless, looked after children).

The following groups in the UK are considered at increased risk of HCV:

- People who have ever injected drugs
- People who have received a blood transfusion prior to 1991 or any blood product prior to 1986
- People born or brought up in a country with an intermediate or high prevalence of chronic HCV (≥2%)
- Babies born to mothers infected with HCV
- Prisoners and younger offenders
- Looked-after children and young people, including those living in care homes
- People living in hostels or homeless or sleeping on the streets
- HIV positive MSM
- Close contacts of someone known to have chronic HCV (includes family members, close friends, household contacts and sexual partners)

The NICE guidelines also make recommendations for the settings in which testing can take place, to increase testing for the above mentioned groups:

- Testing for HCV in primary care
    - Offer testing to those at increased risk of infection, particularly migrants and PWID
    - Offer testing to newly registered individuals at increased risk of infection
    - GPs and nurses should ask newly registered individuals if they have ever injected drugs, which would indicate the need for a hepatitis test
    - Those with abnormal liver function tests should be explored, including offering a hepatitis test

- Testing for HCV in prisons and immigration removal centres
- Testing for HCV in drug services
- Testing for HCV in sexual health and GUM clinics
    - Offer and promote HCV testing for all users at increased risk of infection, including those <18 years old
- Contact tracing (testing close contacts)
    - Primary care practitioners should promote HCV testing for children exposed to HCV at birth or during childhood

### 3.1.2 NICE considerations and recommendations for future research

The NICE guidelines contain sections on their considerations for economic modelling, and recommendations for future research for novel testing approaches. Briefly, these areas include birth cohort (or age-based) screening, testing for those with historical HCV risk factors in primary care (based on a review of patients medical notes), testing in community pharmacies, testing in primary care for MSM, testing in primary care for migrants, testing in 'other' drug populations (those using snorting equipment, and those injecting performance enhancing drugs). These areas, and other areas highlighted as being of interest in the NICE 2017 surveillance report, are described in more detail in Table 3-1.

Considerations were also described for interventions aimed at increasing case-finding and treatment within prisons, as well as ensuring the continuity of treatment from the prison to the community. Testing within prisons is already recommended, so these are not areas for novel testing strategies. Instead, the considerations are focused on the delivery of testing and ensuring linkage to treatment following prison release.

In Chapter 4, the considerations and recommendations for future research shown in Table 3-1 are compared to the recent literature, in order to identify which of these areas may still represent evidence gaps that could be addressed by this thesis.

### 3.1.3 NICE 2017 Consultation and Surveillance report

In 2017, NICE published a surveillance report which considered the evidence and stakeholder views of their hepatitis testing guidelines.[2]

It identified 13 studies, but none were considered to impact the guideline recommendations. Four studies showed the benefits of testing PWID in non-clinical settings such as needle exchange services, drug treatment services, and outreach services. Other studies evaluating the effectiveness of HCV testing included testing in GUM clinics for MSM, in mosques or women's centres for Pakistani migrants, and one study compared testing practices in prisons. Other studies identified did not consider the effectiveness of HCV testing.

One area highlighted in the report was HCV testing in hospital EDs. Evidence in the literature suggests a relatively high HCV prevalence amongst ED attendees, which varies geographically, with a HCV prevalence of up to 2.7% in some areas.[7,8] ED based testing was acknowledged as an area of interest by NICE. However, there was no recommendation for testing in this setting due to a lack of published evidence to demonstrate the effectiveness or cost-effectiveness of testing.

Table 3-1: NICE hepatitis testing guidelines: Areas for consideration or areas recommended for future research

| **Testing strategy / setting** | **NICE Description** |
|---|---|
| Birth cohort or age-based screening as part of the NHS health check | The guidelines state the possibility to test all those aged between 40 and 65 or 70, based on US studies of a similar intervention. However, since prevalence is lower in England versus the US, an independent, comprehensive testing programme was thought unlikely to be cost-effective. The guidelines suggested that adding HCV testing to the NHS health check could overcome this, however there was uncertainty surrounding the overall cost-effectiveness, stating more evidence was required before a recommendation could be made. |
| Primary care testing for those with historical HCV risk factors | The guidelines state there was a lack of evidence to suggest whether general practices reviewing patient notes to identify those considered high risk, and inviting them to return to testing, would be cost-effective. |
| Community pharmacy testing | The guidelines state encouraging evidence from community pharmacists providing HCV testing, but there is a lack of evidence to recommend uniform testing by community pharmacists. Recommendations are made to extend the pilot studies, including testing by pharmacists providing needle exchange and those involved in the NHS health checks. |
| Primary care testing for MSM | The guidelines state a lack of evidence for HCV testing amongst MSM in primary care, however they also state that with a reasonably high prevalence it is likely to be cost-effective. |
| Testing migrants in primary care with invitation | Recommendations for HCV testing of migrants were based on economic modelling, due to a lack of empirical evidence from interventions to provide evidence. The modelling estimates that prevalence of 2% is required for finding, testing and treating to be cost-effective. |
| Other drug populations non-traditional injecting drug populations | The guidelines note that those injecting performance enhancing drugs and those sharing snorting equipment could be groups targeted for testing, however there was a lack of evidence of the prevalence of HCV in these groups, and there were questions of the biological plausibility over transmission from shared snorting equipment. |
| Testing all receiving blood samples in EDs | Evidence suggests relatively high prevalence rates of HCV in ED attendees compared to the general population. No published evidence was identified however to show the effectiveness of HCV testing in this setting. The guidelines noted this was an area of interest, and ongoing studies will be considered at the time of the next surveillance. |

## 3.2 SIGN guidelines

The SIGN 2013 guidelines provide recommendations for the management of HCV in Scotland.[3] These guidelines include a subsection on the recommendations for HCV testing. They state that the following groups should be offered testing:

- Patients unexplained persistently elevated alanine aminotransferase
- People with a history of injecting drug use
- People who are HIV positive
- Recipients of blood clotting factor concentrates prior to 1987, or blood and blood components before September 1991 and organ/tissue transplants in the UK before 1992
- Children whose mother is known to be infected with HCV
- Healthcare professionals following percutaneous or mucous membrane exposure to blood which is, or is suspected to be, infected with HCV
- People who have received medical or dental treatment in countries where HCV is common and infection control may be poor
- People who have had tattoos or body piercing in circumstances where infection control procedure is, or is suspected to be, suboptimal
- People who have had a sexual partner or household contact who is HCV infected

There are several differences between the SIGN guidelines and the NICE guidelines around who should receive HCV testing. Firstly, the SIGN guidelines recommend testing for those who have had medical or dental treatment in countries where HCV is common and infection control is poor, those who have been exposed to tattoos or piercings where infection control is suboptimal, and those with elevated alanine aminotransferase (i.e. an abnormal liver function test result). These three groups do not appear in the recommendations for HCV testing in the NICE guidelines. However, under the 'Considerations' section in the NICE guidelines, these three groups are described as 'smaller groups at increased risk of HCV infection'.[1] Another difference is that NICE recommends testing for HIV positive MSM, whereas in Scotland the SIGN guidelines recommend testing for anyone who is HIV positive.

There are also some groups recommended for testing in NICE guidelines which do not appear in the SIGN guidelines. This includes people born in countries with an intermediate or high prevalence of HCV (≥2%), prisoners and young-offenders, looked-after children or young people, and those who are homeless or living on the streets. Despite these groups not being

explicitly included in the SIGN guidelines, it seems likely that they are recommended to receive testing since the NICE guidelines for hepatitis testing are directly applicable to Scotland.

## 3.3 ECDC guidelines

### 3.3.1 ECDC recommendations for who to test and healthcare settings for testing

The ECDC guidelines state the following groups as high risk and should be targeted for HCV testing. These groups are broadly similar to those stated by NICE guidelines, except for the inclusion of trans people (used as an overarching term and defined in the document as those with an internal perception different to gender at birth).

The ECDC guidelines consider the following groups for targeted testing:

- MSM, when indicated by individual risk behaviours (e.g. sexual behaviours, HIV infection, history of sexually transmitted infections [STI])
- Trans people
- Sex workers
- PWID
- People in prison
- Migrants from intermediate/high endemicity or migrant communities with high prevalence
- Homeless people
- Haemodialysis recipients
- People who have received blood products, organs or surgical interventions prior to 1992 or in countries with suboptimal infection control settings
- Sexual partners or injecting partners of people with HCV
- Heterosexuals with multiple serial or concurrent sexual partners, or a history of STIs

### 3.3.2 ECDC recommendations for testing across various healthcare settings

The guidelines state that testing strategies to date have primarily been risk-based, and have not been very effective at impacting epidemics. They also state that increasing testing in healthcare settings will help to normalise testing, whilst noting that opportunistic testing will have a small incremental cost.

#### 3.3.2.1 Geographical based testing for all, across health care settings

The guidelines state that testing could be performed in geographical locations where the prevalence of infection is high. This follows similar recommendations for HIV in the UK, in which testing for HIV is performed in various settings with prevalence above 0.2%.[9] Whilst ECDC guidelines state that there is no evidence to support geographical based population testing for HCV, they do state that it should be considered when the prevalence is more than or equal to 2%.

#### 3.3.2.2 Birth cohort testing for HCV

The guidelines refer to the possibility of birth cohort testing, but discuss previous research recommending that data on the HCV seroprevalence by year of birth is required prior to developing any screening recommendations.

#### 3.3.2.3 Testing in primary healthcare

The guidelines state that all those who are identified as high risk should be tested regardless of geographical location. For areas of prevalence of ≥2%, HCV testing should be offered and recommended to people that have never been tested and are having a blood test for another reason. However, the guidelines state that primary care testing is often suboptimal due to factors that discourage healthcare professionals from testing.

#### 3.3.2.4 Testing in hospital settings

Routine testing in hospital EDs is acceptable to patients and staff, but supported by limited evidence. The guidelines state that in areas of HCV prevalence ≥2%, testing should be offered to those attending the ED and already having a blood test as part of their care. The guidelines also state that anyone diagnosed with HBV or HIV should be tested for HCV. Otherwise, testing should only be offered to those identified as 'high risk'.

#### 3.3.2.5 Testing in other healthcare settings and community-based settings

Other healthcare settings in the guidelines are defined as anything other than hospital or primary care settings, and include STI clinics, GUM clinics, dermato-venereology clinics, antenatal services, pharmacies, prison health services, drug and harm-reduction services and others.

The majority of recommendations in the ECDC guidelines mirror those in the NICE guidelines, such as offering tests for migrants from countries with ≥2% HCV prevalence, testing everyone attending drug and harm reduction services, testing all people in prison, and testing in STI and GUM clinics, based on an assessment of risk.

The guidelines also state that despite limited evidence, testing could be made available in community-based pharmacies. This was mentioned in the NICE 2017 consultation, although it did not lead to a recommendation.

#### 3.3.2.6 Self-sampling and self-testing

The ECDC guidelines state that evidence for self-sampling is very limited for HCV. Self-sampling kits have been shown to be effectively distributed through various channels but should be based on local target populations. The guidelines concluded that there was insufficient evidence surrounding self-testing of HCV. This topic was not considered within NICE guidelines.

## 3.4 Discussion of guidelines and potential evidence gaps for research

The NICE, SIGN and ECDC guidelines provide similar recommendations for people who should be offered HCV testing, and the populations or settings in which HCV testing should be offered. They recommend testing for groups based on the presentation of various risk factors, such as current or historical injecting drug use, being born in a country with high HCV prevalence, being HIV positive, or being a close contact of a person with HCV. This has formed the basis for testing recommendations in settings which these populations are likely to attend, such as drug treatment centres, harm reduction services, prisons, and sexual health services, in addition to risk-based testing for those at risk in primary care or in hospitals.

Whilst there were some minor differences between the NICE guidelines for England and Wales, and the SIGN guidelines for Scotland, this is likely to be of limited impact, since the SIGN guidelines also stated that NICE guidelines are directly relevant to Scotland.

The ECDC guidelines provide recommendations for testing everyone in a geographical location, or providing testing to all ED attendees receiving a blood test, when prevalence is intermediate or high (≥2%). The guidelines do not cite any specific evidence to support this, and therefore it seems likely that this prevalence threshold is justified from a clinical or public health perspective, rather than being based on any economic evidence. Neither NICE nor SIGN

guidelines make recommendations for widespread testing based on high prevalence in geographical areas.

Whilst risk-based testing is likely to be most effective, with the highest test positivity rates, a change to the current testing recommendations is required in order to meet the WHO 2030 elimination targets in the UK. Many individuals living within the UK are unaware that their previous behaviours or exposures mean that they are at risk of HCV, particularly for those who report feeling well.[10] There is also a perceived stigma around historical injecting drug use, meaning that many individuals choose not to discuss or confirm their previous injecting activity, due to concerns around stigmatisation and confidentiality.[10] Ultimately, the current testing guidelines are likely to miss many individuals who have historically been at risk of HCV transmission, but are unaware of their risk and who are currently unlikely to be offered a test.

## 3.5 References


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# 4 Review of published economic literature

This Chapter presents a literature review of economic evaluations of HCV testing interventions in the UK. The review was performed to identify studies published since the development of the NICE HCV testing guidelines in 2012, as recent studies may have addressed some of the evidence gaps or recommendations for research that were recommended by NICE. This would allow for an update of the evidence gaps remaining in the UK, which could potentially be addressed by this thesis. These evidence gaps may be a lack of cost-effectiveness evidence for specific HCV testing interventions, or that the existing cost-effectiveness evidence is insufficient to make appropriate recommendations on HCV testing policies, meaning that additional research is required. This literature review, alongside a review of the testing guidelines presented in Chapter 3, addresses the first objective of this thesis.

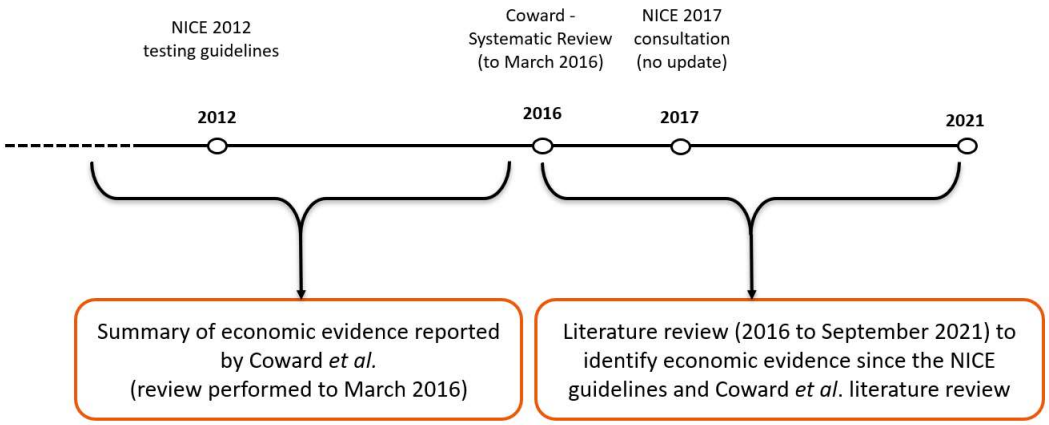
## 4.1 Overview of the literature review

A previous systematic literature review of HCV testing and linkage to care has been published by Coward *et al.*, which reviewed published literature up to March 2016.[1] Firstly, the economic evidence as part this published systematic review is summarised.

Following this, I performed a literature review to identify any new economic literature published since the systematic review published by Coward *et al.* The aim of this review was to consider what research has been performed in the UK outside of the settings and populations already identified for testing in the NICE hepatitis testing guidelines, and published since the searches performed by Coward et al.

Figure 4-1 shows a timeline during which evidence was captured by the systematic review published by Coward et al., and the timeframe captured by the literature review for this thesis.

Figure 4-1: Timeline showing literature reviews performed by Coward et al. (published systematic literature review), and literature review performed as part of this thesis




As already mentioned in Section 3, since the aim of the guideline review and literature review were to identify the relevant knowledge gaps in the cost-effectiveness evidence for the UK, only UK evidence was deemed of interest. However, for each of the three relevant testing strategies identified and evaluated within this thesis, additional literature reviews were performed to identify economic evaluations of these testing strategies. These were performed in order to understand how the testing strategy was implemented, and also the methods used to undertake the economic evaluation. As such, comparisons with the existing published literature (in any country) appear in the Chapters for each economic evaluation individually (Chapters 5, 6 and 7).

## 4.2 Results from previously identified systematic review (Coward *et al., to March 2016*)

A previous systematic review of the cost-effectiveness of all HCV case-finding interventions has been published by Coward et al. 2017, which searched publications from database inception until March 2016.[1] The review included evidence from any country reporting the cost-effectiveness of a HCV testing intervention. A total of ten UK studies were included, with one study considering two settings. These studies considered the cost-effectiveness of testing in the following populations or settings: PWID, prisoners, migrants from high prevalence countries, pregnant women, hospital EDs and GUM clinics.

There were eight UK based studies which reported cost-effectiveness results in settings or populations already recommended for testing by NICE guidelines. This included four studies in PWID (across various settings) and two studies in prisons. These studies were published between 1999 and 2008, and were included in the NICE 2012 guidelines which recommended testing in the groups.

An earlier paper, published in the 1990's, assumed all tests were performed in high risk individuals in the UK, and calculated that opportunistic HCV screening in these individuals was not cost-effective.[2] However, these results were based on only 15% of those testing positive receiving treatment, and an SVR rate of 33% with pegylated interferon and ribavirin, limiting their relevance to current practice.

There was also one study of HCV testing of migrants from areas with an elevated prevalence of HCV. The model used a base case prevalence of 2%, which relates to the NICE definition of countries with intermediate of high HCV prevalence (defined as prevalence of ≥2%). The study assessed the impact of prevalence on the cost-effectiveness outcomes, because there is considerable heterogeneity amongst migrant or community groups. This study was commissioned to inform NICE 2012 testing guidelines, and a report of the same modelling study is available in NICE documents.[3,4] The study reports an ICER of £23,200 per QALY, with cost-effectiveness ranging from 34-71% likely at £20,000 and £30,000 per QALY thresholds. The authors conclude that additional research is required, and that this should focus on the cost of the intervention and the background rate of testing. In the absence of a control group, the analysis assumed that those who did not receive testing had an annual background probability of testing of 4.1% based on the Health Protection Agency data. An analysis of covariance (ANCOVA) showed that the background probability of testing had the greatest impact on the model outcomes.

Three papers were identified in populations that could be considered outside of those recommended by NICE guidelines. One study found that antenatal screening and testing was likely to be cost-effective in the UK, with an estimated ICER of £2,400/QALY based on interferon and ribavirin treatment, and £3,100 to £9,100 per QALY with DAA treatments (with and without interferon and ribavarin retreatment, respectively).[5] Interestingly, unlike the analysis of testing for migrants from Miners et al., the analysis seems to assume that those who are not tested remain undiagnosed and untreated (albeit that this is not stated explicitly). The study was published in 2015, and therefore was not included in the 2012 NICE guidelines. Testing in antenatal services was not mentioned in the NICE 2017 consultation report.[6]

Another study published in 2016 estimated the cost per HCV case detected for those being tested in an ED setting (£988 per case).[7] The analysis assumed a cost of £7 per test for HCV, HBV and HIV. It did not consider any other costs, and did not estimate cost-utility, and therefore would not be of sufficient quality for making policy recommendations.

Lastly, one study from 2003 evaluated the cost-effectiveness of universal HCV screening for those who attend GUM clinics in the UK.[8] The intervention compared screening to no screening, which assumed that those unscreened would be identified 11 years later, which was the difference in age between those identified from screening, and those receiving treatment in another RCT study. The intervention was deemed unlikely to be cost-effective for all of those attending GUMs services, but was borderline cost-effective (£27,000/QALY) when restricted to previous injecting drug users only.

There were no UK studies reporting on the cost-effectiveness of birth cohort screening, or general population testing for HCV, although evidence of the cost-effectiveness of these interventions was available from other countries. There were a total of 8 studies of the cost-effectiveness of birth cohort screening for HCV. There were 5 studies from the US, and studies from Canada, Italy and Japan. The ICER's ranged from £3,700 to £45,100 per QALY gained, when converted into British pounds, with all studies reporting that birth cohort screening is likely to be cost-effective.[1]

Whilst all of these studies compared to 'no birth cohort screening', there were differences in exactly what this comparator included. In some analyses, there was no other opportunity for testing outside of the birth cohort screening intervention, at least until the development of advanced disease stages (cirrhosis and HCC), when it was assumed that all patients would be diagnosed due to the severity of their disease.[9,10] Other models included opportunistic testing to account for current HCV testing practices. This included testing based on the development of symptoms (at any stage), or performed as part of current risk-based testing strategy.[11-14] There was variation in how opportunistic testing was included in the analyses however. In some studies, the probability of opportunistic testing was higher for those infected compared to those uninfected, whilst in others it was higher for those at earlier fibrosis stages compared to later fibrosis or cirrhosis stages.[11,13] Moreover, sometimes it was only considered in those with undiagnosed infection, and ignored for those uninfected.[12,14]

Other models took an alternative approach, and rather than considering a model population of those with HCV (who may be diagnosed or undiagnosed), the model instead considered the testing option as an immediate decision (e.g. to test or not test the individual). These models

tended to evaluate some or all of the following comparators; no testing, testing for people with risk factors, birth cohort testing, and general population testing. These models did not consider a specific setting for testing, or the competing opportunities for individuals to receive testing in other settings.[15,16]

## 4.3 Review of recently published literature (2016 to September 2021)

### 4.3.1 Aim of the literature review

A literature review was performed to update the cost-effectiveness evidence previously reported by Coward et al. The purpose of the review was to identify cost-effectiveness evidence for HCV testing in a UK setting, as this is the focus of this thesis. The review identified what cost-effectiveness evidence for HCV testing interventions currently exists in the UK, and whether it is sufficient to inform HCV testing recommendations. For this reason, cost-effectiveness studies from other countries were not included.

This review did not seek to identify studies assessing the effectiveness of novel testing strategies without an economic evaluation. The identification of appropriate data to parameterise the economic evaluations performed in this thesis were done separately.

### 4.3.2 Search strategy and study selection

The literature review utilised search terms reported by Coward et al., with additional terms included to limit the search to studies performed in the UK (or those that referred to the NHS or NICE). In order to identify publications since the Coward et al. review, the search was limited to 2016 onwards (or 20 November 2015 where this was possible, 6 months prior to when previous searches were ran, where possible). These limits were included to provide a conservative crossover period to ensure all publications of interest were identified.

The following databases were searched: EMBASE, MEDLINE, Econlit and NHS HTA EED. These were the same four databases that were searched by Coward et al.[1] Searches were performed up until the 22nd September 2021. Full search terms for each database are provided in Appendix Section 10.2. The search was not limited to full papers, as it was deemed that abstracts could provide information on current areas of interest for HCV testing and may also

indicate upcoming publications of economic evaluations. There were no language restrictions applied.

The keywords included in the search strategy were defined according to PICOS (population, intervention, comparator, outcome, study design) criteria (Table 4-1). These criteria also formed the main inclusion criteria for the review.

Table 4-1: PICOS criteria informing search strategy and inclusion criteria

| | |
|---|---|
| **Population** | Those being tested for HCV in the UK |
| **Intervention** | Interventions to diagnose hepatitis C amongst those living with the virus |
| **Comparator** | Any (or uncontrolled) |
| **Outcomes** | Cost-effectiveness of testing, expressed as costs and benefits of testing (cost per case identified, QALYs gained, Life years gained) |
| **Study design** | Any study reporting an economic evaluation |

The following exclusion criteria were also applied:

- Cost-effectiveness estimates from non-UK settings
- Studies reporting clinical evidence or costing analyses only, without any cost-effectiveness component

The literature review was performed by myself only and did not include a second reviewer to independently select studies to include. This approach differs from the systematic review performed by Coward et al., in which abstract review and full-text review were performed by two independent reviewers, as is recommended for systematic literature reviews.[17,18] This was due to the limited availability of other researchers to be involved in the literature review, and does represent a limitation of this research. Although this is a limitation, the use of a single researcher was deemed appropriate because the main aim of the review was to identify recent economic evaluations of HCV testing in the UK which may have already filled an evidence gap reported by NICE. Once the remaining evidence gaps were identified and the testing strategies to be evaluated within this thesis were selected, additional literature reviews were performed

for each topic area. This meant that other relevant literature from both the UK and other countries could also have been identified from these subsequent reviews. The individual reviews to identify previous literature on the testing strategies selected also gave a second opportunity to identify any UK studies which may have been originally missed in this review.

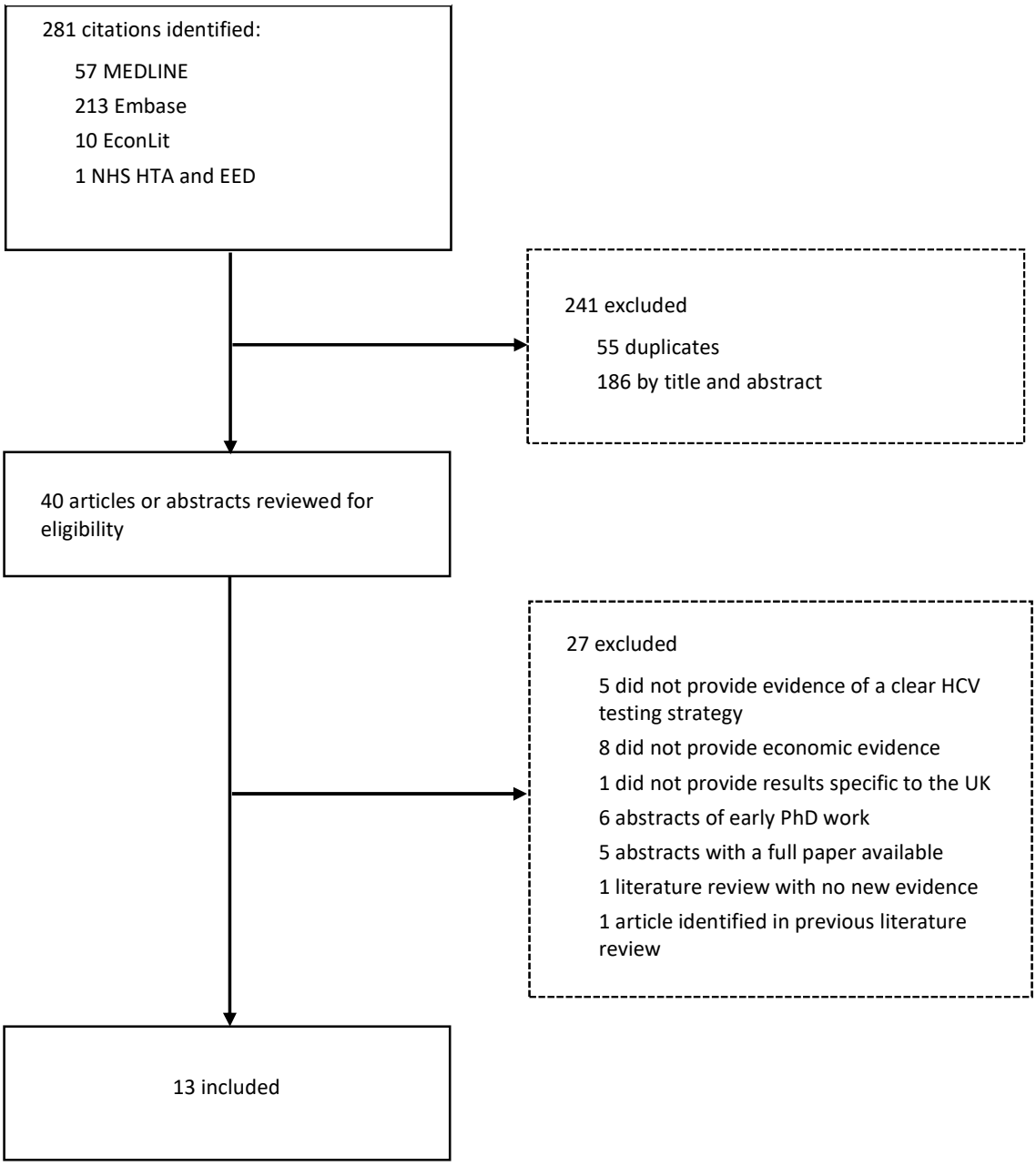
### 4.3.3 Literature review results

A total of 281 citations were identified, of which 55 were duplicates, leaving 226 citations. Of these, 186 were excluded by title and abstract, with 40 citations retrieved for full text review (Figure 4-2).

Of the 40 citations reviewed, a total of 27 were excluded. Of those excluded, 5 did not involve a clear testing strategy for HCV, 8 did not provide any economic evidence, 1 was not based on UK data, 5 were conference abstracts with the same data used in a journal article and 1 was a literature review of HCV testing strategies, but did not contain any evidence beyond that already reported by Coward et al. or this review. There was also 1 paper that was eligible for inclusion but was identified previously by the review from Coward et al., which was likely due to the overlap in literature review dates. Finally, 3 journal articles and 3 conference abstracts contained economic evidence forming part of this thesis, and were subsequently excluded for the purposes of this review.

A total of 13 studies provided economic evidence of HCV testing strategies in the UK.

Figure 4-2: Flow diagram of literature search



Amongst the 13 citations that were included, there were 10 journal articles and 3 conference abstracts. In total, these analyses evaluated 17 testing strategies, since some analyses evaluated testing in multiple settings. A breakdown of the settings and/or populations targeted for testing are provided in Table 4-2. The majority of analyses focused on testing for people in prison or testing PWID in settings that they may be expected to attend, such as drug treatment or substance misuse services, needle and syringe services, or community pharmacies offering OST. There were also analyses targeting people who are homeless, migrants from countries with high HCV prevalence, MSM and birth cohorts. As demonstrated in Table 4-2, testing can be provided in multiple settings for any given sub-population of people, and vice-versa, with testing in some settings capturing a range of different sub-populations.

Table 4-2: Populations and settings in which an economic evaluation of HCV testing strategies was reported

| Population | Setting | Number of analyses | Source |
|---|---|---|---|
| People in prison | Prison | 4 | Mohamed[19], Manca[20], Martin[21], Darke[22] |
| PWID | Substance misuse service / Drug treatment centre | 4 | Ward[23], O'Sullivan[24], Selvapatt[25], Manca[26] |
| | Pharmacy‡ | 2 | Buchanan[27], Manca[26] |
| | Needle exchange services | 1 | Manca[26] |
| People who are homeless | Outreach | 1 | Ward[28] |
| Migrants (from high HCV prevalence countries)† | Outreach | 1 | Manca[20] |
| | Primary care | 1 | Flanagan[29] |
| MSM | Sexual Health / HIV clinic | 1 | Macgregor[30] |
| Any HCV risk factor | Pharmacy | 1 | Buchanan[27] |
| Birth cohort | Primary care | 1 | Selvapatt[31] |

†The definition of migrants from Flanagan et al. is an individual or their parents born in a country with a prevalence of viral hepatitis of more than 2% (according to WHO estimates)[29], whilst the definition from Manca et al. is individuals from countries of increased prevalence.[20]

‡Pharmacy testing for PWID was based on offering testing to those receiving opioid substitution therapy.

## 4.4 Discussion of literature review results

Since the previous literature review by Coward et al., there have been numerous economic evaluations of HCV testing interventions. These have mainly focused on testing in populations that are already recommended by NICE, but also include some novel testing strategies.

There were a total of 10 analyses of testing for PWID or people in prison or for PWID. For PWID, testing strategies were predominantly in drug treatment or substance misuse services. There was also an analysis of testing at a needle exchange service, and two analyses of testing in community pharmacies.[26,27] One of the analyses of HCV testing in community pharmacies considered the impact of testing for patients with any HCV risk factor, or whether testing should be restricted to injecting drug users only.[27] Testing those with any HCV risk factor was deemed the most cost-effective strategy.

One study evaluated an outreach testing service provided for the homeless (and other marginalised communities), which was also deemed highly cost-effective.[28]

Two studies evaluated HCV testing for migrants. The two studies defined this group differently; one included individuals from countries with a high HCV prevalence, whilst the other included the same definition but also included those whose parents were born in a country of high HCV prevalence. One of the studies was a large randomised controlled trial (RCT) of testing for migrants in primary care, called the HepFREE study. The trial reported that testing was highly cost-effective, even when incentives were provided to primary care facilities, with an ICER of £8,540 per QALY gained.[29] The other study reported results in a conference abstract, which therefore lacked the full details around how testing for migrants was provided as part of community outreach service, but reported that testing was highly cost-effective, with an ICER of £4,275 per QALY gained.[20]

One study reported testing amongst MSM, which evaluated the frequency of HCV testing for HIV negative men who are, and are not, using pre-exposure prophylaxis (PrEP), and increased frequency of testing amongst HIV positive men.[30] The study found that testing should be performed every 12 months for HIV negative men, whether they are using PrEP or not. It was deemed that for HIV positive men, increasing screening frequency from every 12 months to every 6 months would not be cost-effective.

There was little cost-effectiveness evidence for a population-based testing intervention for HCV. A conference abstract suggested that birth cohort testing was unlikely to be cost-effective, albeit that this conclusion seemed highly uncertain.[31] A threshold analysis was

performed to estimate the costs at which testing would remain cost-effective, given the uncertainty around the costs of implementing such an intervention. The study estimated that with interferon-based treatments, £24.52 could be spent per person screened to remain cost-effective, whilst using DAA treatments, this would increase to £41.31 per screened patient. The abstract does not report the costs used for DAA treatments, or the assumptions around their effectiveness. The authors noted that the prevalence estimates used within the model were not specific to birth cohorts, and that further research should address this, and provide an estimate of the cost associated with screening.

As mentioned in Section 4.3.2, one limitation was that the review was not performed according to systematic literature review standards, which involves the use of more rigorous methodology, most notably the use of two independent researchers to perform the abstract review and full-text review.[17] Having only a single reviewer raises the possibility that other studies published since the review by Coward et al., have been missed during the review process.

## 4.5 Evidence gaps remaining, for future research

Overall, a number of studies provide cost-effectiveness evidence for HCV testing studies in the UK. However, there are numerous evidence gaps that remain, either because there are no economic evaluations which consider testing in these settings, or because existing economic evaluations have limitations that limit the clarity of their conclusions in terms of decision making, and therefore further research is warranted.

Table 4-3 provides a summary of the evidence gaps of interest reported by NICE, with a brief summary of the evidence identified to fill these gaps, and whether additional evidence may be required.

Several of the evidence gaps have been addressed, or at least partially addressed. Most notably this includes a large RCT and economic evaluation considering testing for migrants in primary care (which provide more robust parameter estimates than the previous analysis of testing in migrants by Miners et al.[3]), and a modelling study assessing the preferred frequency of testing amongst MSM, based on their HIV status, and PrEP status for those HIV-negative.[29,30] There were also two studies in pharmacies, although both studies noted that the local data used to populate the model may not be generalisable to the UK. This suggests there may be

scope for an additional, high-quality cost-effectiveness analysis in this setting when more robust testing data across multiple regions of the UK are available.[26,27]

There was limited economic evidence from a conference abstract to suggest that birth cohort screening was unlikely to be cost-effective in the UK.[31] A threshold analysis was performed, which estimated a maximum cost at which the testing intervention could be to remain cost-effective. However, the authors noted that the prevalence estimates were not specific to birth cohorts, and that this should be addressed in future research. They also stated that there were no cost estimates for birth cohort screening, which is likely to be the rationale for the threshold analysis approach. In addition to the limitations of the data used which were discussed within the abstract, the reporting of the cost-effectiveness results in an abstract, rather than a full publication, means there is no possibility to evaluate the methods or data sources used with the economic evaluation, or what other assumptions and limitations may exist.

Apart from an ED based study reporting a simple cost per case identified (based only on the cost of the diagnostic test), which would not be sufficient to consider the cost-effectiveness of the intervention when developing testing guidelines, there was no economic evaluation of HCV amongst ED attendees receiving blood tests as part of their routine care.[7] There was also no economic evaluation to provide evidence of the cost-effectiveness of a primary care based intervention to review patients notes and invite those at risk of HCV for testing, or for a testing intervention for other drug using populations (e.g. those injecting performance enhancing drugs, or snorting drugs).

Overall, this leaves several evidence gaps, which could be addressed with high quality cost-effectiveness analyses of HCV testing interventions in the UK. This thesis includes three economic evaluations, with each providing cost-effectiveness evidence for an existing evidence gap. These economic evaluations considered the cost-effectiveness of adding birth cohort screening for HCV onto the NHS health check, the cost-effectiveness of a HCV testing intervention in primary care for those with risk factors for HCV in their medical records, and the cost-effectiveness of viral hepatitis testing in the ED. The testing strategies included in this thesis were chosen because I was able to provide evidence around the cost-effectiveness of testing when their was previously no evidence available, or the cost-effectiveness evidence was insufficient to make a decision. However, it was only possible to perform an economic evaluation if sufficient data around the effectiveness, or the potential for a testing intervention to be effective, were available. For this reason, I did not perform an economic evaluation of

HCV testing in pharmacies, or on HCV testing in other (non-traditional) injecting drug users, because of a lack of data available to me on the effectiveness of these testing strategies.

It should also be noted that the considerations and recommendations for future research reported in the NICE guidelines are unlikely to be a comprehensive analysis of all the possible HCV testing interventions that could be implemented. This is most notable in the publication of an economic evaluation for universal HCV testing in antenatal services, which concluded testing was cost-effective in London, and stated that antenatal testing should be considered as a national screening programme.[5] This was not previously noted as a consideration or recommendation for future research in NICE guidelines.[32] Moreover, general population testing is not included as an area recommended for research either, despite evidence from other high income countries reporting mixed results with regard to it's cost-effectiveness.[11,33-35]

Finally, this literature review did not focus on identifying data on the effectiveness of HCV testing strategies. Instead, the review sought to identify evidence gaps where UK based cost-effectiveness analyses of HCV testing interventions may be of value. After identifying HCV testing strategies that were of interest to UK policy makers and the relevant UK testing guidelines, evidence of the effectiveness of these testing interventions were subsequently identified. This involved collaborations with the UK HSA, and with collaborators at other universities working on HCV testing and treatment. This was further supported by reviewing the literature for other relevant studies.

Table 4-3: Update of cost-effectiveness evidence from the UK published since the evidence gaps reported by NICE 2012 hepatitis testing guidelines (this evidence includes publications identfied from Coward et al., and the literature review presented in Section 4.3)

| **Testing strategy / setting** | **Cost-effectiveness evidence published since NICE 2012 hepatitis testing guidelines†** | **Evidence gap addressed since NICE guidelines†** | **Evidence gap addressed by this thesis** |
|---|---|---|---|
| Testing migrants in primary care with invitation | A large cluster RCT with 58 primary care practices involved. A cost-effectiveness analysis found testing was highly cost-effective.[29] | Yes | No |
| Primary care testing for MSM | A modelling study evaluated testing frequency amongst MSM who do and do not take PrEP, and HIV positive men.[30] The study concluded testing should be offered every 12 months for HIV negative men (independent of PrEP use), and HIV positive men. | Yes | No |
| Community pharmacy testing | Yes. Two economic evaluations have been identified.[26,27] One reported that pharmacy testing was highly cost-effective, with testing for anyone with a risk factor for HCV most cost-effective. Another study noted that pharmacy testing was cost-effective when assuming a 24% discount of the list price of DAA treatments. | Yes, although if higher quality data becomes available, an updated economic evaluation may be warranted. | No |
| Birth cohort or age-based screening as part of the NHS health check | An abstract was identified, but stated that economic evaluations should use HCV prevalence data specific to each birth cohort.[31] The abstract suggested birth cohort testing was unlikely to be cost-effective, based on cost thresholds for testing. This analysis did not consider testing as part of the NHS health check however. | No. An updated analysis is warranted using evidence of HCV prevalence by birth cohorts, and modelling HCV testing incorporated into existing health services. | Yes |
| Testing all receiving blood samples in EDs | One study reported the cost per HCV case identified through testing.[7] The costs or health outcomes associated with treatment were not considered, and there was no modelling or extrapolation in the analysis. | No. An economic evaluation extrapolating beyond the cost per case identified is warranted | Yes |
| Primary care testing for those with historical HCV risk factors | No economic evidence identified. | No | Yes |
| Other drug populations‡ | No economic evidence identified. | No | No |

†Excludes publications within this thesis

‡Non-traditional injecting drug populations

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# 5 Cost-Effectiveness of One-Time Birth Cohort Screening for Hepatitis C as Part of the National Health Service Health Check Program in England

## 5.1 Overview of Research Paper 1

In this Chapter, the cost-effectiveness of a hypothetical birth cohort screening intervention is evaluated.

In the United States, several economic evaluations have reported that birth cohort screening for HCV is likely to be cost-effective, based on the high prevalence of undiagnosed HCV in those born between 1945 and 1965.[1-5] This subsequently led to screening being recommended by the United States Centre for Disease Control and Prevention.[6]

There are no empirical studies of the effectiveness of a birth cohort screening intervention for HCV in the UK, but NICE have highlighted the potential for a HCV birth cohort screening intervention to be added onto the NHS health check, an existing health check in primary care for those aged between 40 and 74 years of age in England.[7,8] A previous UK modelling analysis evaluated a hypothetical birth cohort screening intervention for HCV, albeit that this was an exploratory analysis with results reported in a conference abstract only.[9] The analysis did not use prevalence estimates specific to birth cohorts, and only estimated the maximum cost per person screened at which the intervention would be cost-effective, likely because of the hypothetical intervention modelled. The authors concluded birth cohort screening is unlikely to be cost-effective in the UK, but that further analyses using age-based prevalence estimates and costs specific to the screening intervention are required. Since the publication of this abstract, the prevalence of undiagnosed HCV has been estimated across age groups in England using a Bayesian modelling approach to synthesise routine HCV data.[10] This provides scope for an updated analysis, addressing one of the limitations of the previous cost-effectiveness study.

This paper presents an economic evaluation of a hypothetical birth cohort screening intervention for HCV in England, assumed to occur as part of the NHS health check in primary care. The model uses the age-based prevalence estimates for birth cohorts and estimates whether birth cohort screening is likely to be cost-effective, based on current evidence. This back-calculation model was adapted to report the model results stratified into 5-year birth cohorts (e.g. 1950-1954, 1955-1959 etc.), which were the subgroups used within the economic

model, compared to the original back-calculation model outputs which were reported into age bands (e.g. those aged 30-39, 40-49 etc.). The back-calculation model methodology and input parameters all remained the same, meaning the same burden of disease was estimated. The only difference was the stratification used when reporting results.

Since the intervention is hypothetical, the study also performed value of information analyses to evaluate whether additional research is likely to be justified from an economic perspective, and if so, which parameters should be prioritised for data collection.

My role included the identification of the input data sources, processing of parameter data from external sources (i.e. processing the outputs from the back-calculation model), developing the economic model structure and performing the analyses. I wrote the draft version of the manuscript, and incorporated comments from co-authors into the manuscript. I submitted the manuscript and addressed peer review comments. The prevalence estimates for each birth cohort were derived from a modelling exercise performed by Public Health England (now UK Health Security Agency); I was not involved in the development of the back-calculation model, or running any analyses for that project.[10] The study did not involve any primary data collection, or any individual patient level data (also described as human data in LSHTM ethics documentation). As such, it was deemed that that the research did not require LSHTM ethical approval.

This study was published in Value in Health as an open-access article, on the 1st of November 2019. It was published under a CC BY-NC-ND license, which allows the article to be shared or re-distributed in any format, as long as the work is properly cited.[11] The full reference for the article is:

*Williams J, Miners A, Harris R, Mandal S, Simmons R, Ireland G, et al. Cost-Effectiveness of One-Time Birth Cohort Screening for Hepatitis C as Part of the National Health Service Health Check Program in England. Value in Health. 2019;22(11):1248-56.*

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# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

## SECTION A – Student Details

| | | | |
|---|---|---|---|
| **Student ID Number** | 1405199 | **Title** | Mr |
| **First Name(s)** | Jack | | |
| **Surname/Family Name** | Williams | | |
| **Thesis Title** | Assessing the cost-effectiveness of interventions to expand hepatitis C testing to help achieve elimination targets in the United Kingdom | | |
| **Primary Supervisor** | Alec Miners | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

## SECTION B – Paper already published

| | | | |
|---|---|---|---|
| Where was the work published? | Value in Health | | |
| When was the work published? | 1 November 2019 | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | N/A | | |
| Have you retained the copyright for the work?* | **No** | Was the work subject to academic peer review? | **Yes** |

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| Where is the work intended to be published? | |
| Please list the paper's authors in the intended authorship order: | |

| | |
|---|---|
| Stage of publication | Choose an item. |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role included identification of the input data sources, processing of input from external sources (i.e. processing data from the back-calculation model), developing the economic model, performing the analyses.<br>I wrote the draft version of the manuscript, and incorporated comments from co-authors into the manuscript. I submitted the manuscript, and addressed peer review comments. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | Jack Williams |
| **Date** | 18/02/2022 |

| | |
|---|---|
| **Supervisor Signature** | Alec Miners |
| **Date** | 25/02/2022 |

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Economic Evaluation

# Cost-Effectiveness of One-Time Birth Cohort Screening for Hepatitis C as Part of the National Health Service Health Check Program in England

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## ABSTRACT

*Background and Objectives:* Birth cohort screening for the hepatitis C virus (HCV) has been implemented in the US, but there is little evidence of its cost-effectiveness in England. We aim to evaluate the cost-effectiveness of one-time HCV screening for individuals born between 1950 and 1979 as part of the National Health Service health check in England, a health check for adults aged 40 to 74 years in primary care.

*Methods:* A Markov model was developed to analyze add-on HCV testing to the National Health Service health check for individuals in birth cohorts between 1950 and 1979, versus current background HCV testing only, over a lifetime horizon. The model used data from a back-calculation model of the burden of HCV in England, sentinel surveillance of HCV testing, and published literature. Results are presented from a health service perspective in pounds in 2017, as incremental cost-effectiveness ratios per quality-adjusted life years gained.

*Results:* The base-case incremental cost-effectiveness ratios ranged from £7648 to £24 434, and £18 681 to £46 024, across birth cohorts when considering 2 sources of HCV transition probabilities. The intervention is most likely to be cost-effective for those born in the 1970s, and potentially cost-effective for those born from 1955 to 1969. The model results were most sensitive to the source of HCV transition probabilities, the probability of referral and receiving treatment, and the HCV prevalence among testers. The maximum value of future research across all birth cohorts was £11.3 million at £20 000 per quality-adjusted life years gained.

*Conclusion:* Birth cohort screening is likely to be cost-effective for younger birth cohorts, although considerable uncertainty exists for other birth cohorts. Further studies are warranted to reduce uncertainty in cost-effectiveness and consider the acceptability of the intervention.

*Keywords:* cost-benefit analysis, hepatitis C, mass screening, national health programs, health services.

VALUE HEALTH. 2019; 22(11):1248–1256

## Introduction

Hepatitis C virus (HCV) is major global public health problem.[1] An estimated 143 000 people were living with HCV in England in 2015, and mortality related to HCV doubled between 2005 and 2014 as individuals acquiring their infections decades earlier progressed to advanced liver disease.[2,3] More recently, HCV-related deaths have fallen due to the rollout of new direct-acting antiviral (DAA) treatments.[3] DAAs can cure (achieve a sustained virological response [SVR]) more than 90% of patients, are simpler to administer, and have fewer side effects than previously used interferon and/or ribavirin-based treatments.[4]

The World Health Organization's (WHO's) Global Health Strategy targets to eliminate viral hepatitis as a major public health threat include 90% diagnosis coverage and 80% treatment uptake.[5] Interventions to increase diagnoses and improve linkage to care are required if countries are to achieve WHO targets, and the efficiency, cost-effectiveness, and overall impact of these interventions needs to be evaluated.

Analysis of HCV antibody tests in England by birth cohorts shows a high proportion of positive tests among those born

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between the 1950s and mid-1980s, based on unpublished Public Health England (PHE) sentinel surveillance of bloodborne viruses (BBV) laboratory diagnoses from 2012-2016 (3.7%-6.5% for first recorded tests). Due to the asymptomatic nature of HCV, many infected individuals remain undiagnosed and do not associate their previous exposures to their current risk of infection.[6]

Cost-effectiveness analyses of birth cohort screening interventions have been performed in several countries, including the United States, Canada, Italy, Japan, and Korea.[7–12] Only the United States has implemented birth cohort screening, while Japan has recommended one-time testing for the general population.[5,13] Evidence on the cost-effectiveness of birth cohort screening in an English context is limited. A single abstract has reported that birth cohort screening in the United Kingdom was unlikely to be cost-effective.[14] Yet, the authors concluded that further studies should incorporate more accurate information on HCV prevalence by age and include cost implications associated with screening. One possible means of limiting the additional cost of screening could be to add HCV testing to the existing NHS health check program. The NHS health check is a free health check delivered in primary care in England that is offered to adults aged 40 to 74 years, once every 5 years, to assess and reduce a person's risk of heart disease, diabetes, kidney disease, and stroke.[15] This possibility was highlighted in the National Institute for Health and Care Excellence (NICE) hepatitis testing guidelines, but it also states that more information is required before a recommendation can be made due to the uncertainty around its cost-effectiveness.[16]

In this study, we evaluate the cost-effectiveness of a one-time HCV screening intervention for individuals born between 1950 and 1979 included as part of the NHS health check, who have not previously been diagnosed with HCV.

## Methods

### Model Analysis

A state-transition Markov model was used to analyze the impact of a one-time HCV antibody test, given to those in each eligible birth cohort attending the NHS health check program.[15] The model analyzed birth cohorts, in 5-year age bands, for those born between 1950 and 1979, and not previously diagnosed with HCV. Current practice includes those tested for hepatitis based either on their symptoms or risk status. No birth cohort screening, with current background testing only, was the only comparator in the model, with a background probability of HCV testing in England. Patients moved between discrete health states using a 6-month cycle length. The analysis was performed from the perspective of NHS England with results displayed in pounds in 2017, with the intervention modeled to begin in 2018. Outcomes were measured in quality-adjusted life years (QALYs). A lifetime time horizon was used, and all costs and outcomes were discounted at 3.5%, as per NICE guidelines.[17] The model calculated the incremental cost-effectiveness ratio (ICER), representing the incremental costs associated with the intervention divided by the incremental QALYs, to give a cost per QALY gained. The model was developed in TreeAge Pro 2017.

### Model Population and HCV Prevalence

The prevalence and disease severity of undiagnosed HCV infection in England was estimated using an adapted version of a previously published back-calculation model.[2,18] Its details have been published elsewhere, but essentially it uses UK hospital episode statistics and Office for National Statistics data on decompensated cirrhosis, hepatocellular carcinoma, and HCV-related mortality to estimate the burden of HCV.[6] The most recent model also incorporates the estimated people who inject drugs population size.[2]

The back-calculation model provides estimates for HCV birth cohort populations by diagnosis status, injecting drug user (IDU) status (current-, ex- and never-IDU), and disease severity, which informed the economic model parameters. It also provides statistical uncertainty in the form of credible intervals, which were used when estimating parameter uncertainty.

Our model assumed that birth cohort screening would not be used to identify current IDUs, providing a conservative estimate of the prevalence among health check attendees (since prevalence is higher amongst current IDUs), but assumed ex-IDUs were as likely to attend as non-IDUs. Details on the total estimated population in each birth cohort is provided in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006. A scenario was performed in which ex-IDUs were assumed to be 50% less likely to attend compared to non-IDUs (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006). A scenario performed in the back-calculation model analysis was also considered, in which the current IDU population size was estimated using longer hospital episode statistics data and not constrained by an informed prior, resulting in higher estimated prevalence, particularly in younger groups.[2]

### Model Structure

The Markov model captured the natural history of HCV, and is similar to those used in previous economic evaluations, and also aligns with the data used to parameterize disease severity in the model.[19,20] It consists of 8 main health states (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006). Individuals enter the model as either uninfected or classified in a disease state according to the modified Histology Activity Index (Ishak) score in the following health states: mild HCV (F0-F2), moderate HCV (F3-F5), and compensated cirrhosis (CC) (F6), from which they experience further disease progression. From these states individuals progress to later disease states, decompensated cirrhosis, hepatocellular carcinoma, and liver transplant, in which the HCV status was assumed to be known due to the severity of the disease, an assumption that has been made in previous models.[2,19] Those testing positive but not receiving treatment were assumed to accrue health state costs after diagnosis.

The model does not capture disease transmission, and thus assumes that those uninfected will remain uninfected, and that those who achieve SVR cannot be reinfected. In addition to HCV-related mortality, age-adjusted background rates of mortality were applied to all health states in the model, to capture the risk of non-HCV related mortality.[21]

### Background Probability of Testing and Linkage to Care

The background probability of testing of HCV for each birth cohort was estimated from PHE sentinel surveillance of BBV testing statistics and Office for National Statistics population statistics for England.[22] Testing from all reported care settings, excluding drug services and prison services, were included. All tests up to an individual's first positive test were included. The annual probability of testing ranged from 1.9% to 3.6% (Table 1), with the same rate across mild moderate and CC health states.

While the prevalence of HCV is higher among those tested compared to the general population, by excluding current IDUs and those previously testing positive for HCV in this analysis, it is unknown whether the background rate of HCV testing would

**Table 1.** Key economic model parameters.

| Parameter | Mean value | Distribution | Source |
|---|---|---|---|
| Probabilities | | | |
| Intervention effect (uptake) | 48.3% | Beta (α = 5 767 770, β = 6 176 881) | 28 |
| Proportion of reflex RNA tests | 65% | Beta (α = 26 537, β = 14 319) | 23 |
| Proportion RNA positive | 67.7% | Beta (α = 24 094, β = 11 475) | |
| Probability of referral and attendance | 63.4% | Beta (α = 35.966, β = 20.7627) | 24,25 |
| Probability of treatment (postreferral) | 50% | Uniform (0.35, 0.65) | Assumption |
| Costs | | | |
| HCV antibody test | £3.64 | Uniform (£1.82, £5.46) | 38 |
| Nurse cost for test (10 min) | £38/hr | Uniform (£30.40, £45.60) | 39 |
| RNA test | £68.38 | Uniform (£34.19, £102.57) | 38 |
| Cost additional consultation (RNA testing) | £32 | Uniform (£25.60, £38.40) | 39 |
| Outpatient evaluation | £238 | Uniform (£190.40, £285.60) | 49 |
| Further outpatient evaluation | £262 | Uniform (£209.60, £314.40) | 49 |
| DAA treatment | £10 000 | N/A | Assumption[40] |
| DAA treatment (re-treatment) | £15 000[‡] | N/A | Assumption[40] |
| DAA treatment monitoring | £1310 | Uniform (£1048, 1572) | 49 |
| Prevalence of undiagnosed chronic HCV (RNA+ among health check attendees*) | | | |
| 1950-1954 | 0.10% | Beta (α = 38.1, β = 37 215) | 2 |
| 1955-1959 | 0.16% | Beta (α = 53.4, β = 32 359) | |
| 1960-1964 | 0.23% | Beta (α = 58.1, β = 25 614) | |
| 1965-1969 | 0.27% | Beta (α = 68.1, β = 25 168) | |
| 1970-1974 | 0.25% | Beta (α = 65.7, β = 26 137) | |
| 1975-1979 | 0.19% | Beta (α = 68.2, β = 36 490) | |
| Annual probability of background testing[†] | | | |
| 1950-1954 | 1.89% | Beta (α = 98.1, β = 5084) | 22 |
| 1955-1959 | 2.09% | Beta (α = 97.9, β = 4580) | |
| 1960-1964 | 2.19% | Beta (α = 97.8, β = 4358) | |
| 1965-1969 | 2.26% | Beta (α = 97.7, β = 4218) | |
| 1970-1974 | 2.67% | Beta (α = 97.3, β = 3550) | |
| 1975-1979 | 3.57% | Beta (α = 96.4, β = 2601) | |

DAA indicates direct-acting antivirals; HCV, hepatitis C virus.
*Prevalence excludes current-IDUs.
[†]Background rate of testing excluding drug services and prison settings.
[‡]Cost of retreatment assumed to be £5000 higher than first DAA treatment in scenario analyses.

differ between those infected and uninfected; however, in the model we assumed it would be equal. We considered those infected having double the probability of testing in a sensitivity analysis. Because testing may be more likely with cirrhosis, a scenario with background testing 50% lower for mild and moderate HCV health states was performed.

All individuals without a previous HCV diagnosis and not current IDUs were included in the screening population. The PHE sentinel surveillance of BBVs suggests reflex RNA tests (performed on the same antibody positive sample to avoid repeat attendance) were performed on 65% of HCV antibody positive tests.[23] The remainder were assumed to be RNA tested at a subsequent appointment. Based on PHE statistics, 67.7% of antibody positive tests would be RNA positive. The proportion of patients successfully referred and attending their referral was based on the midpoint of the proportions referred from general practitioners in 2 retrospective studies of hepatitis care pathways in England (63.4%).[24,25] The uptake of DAA treatment for those attending their referral is unknown, but expected to be higher than published values for non-DAA treatments (21%).[23] We assumed 50% would receive treatment (35%-65% in sensitivity analyses).

Treatment outcomes for first-line DAA treatment were derived from real-world evidence with SVR rates of 92.8% and 90.8% for non-cirrhotics and cirrhotics, respectively.[26] Individuals not achieving SVR were assumed to be retreated once, with SVR rates for retreatment of 93.9% and 85.5% for people without and with cirrhosis, respectively.[27] Lower retreatment SVR rates (70%) were also considered. The analysis was pan-genotypic and did not stratify outcomes by HCV genotype.

### Intervention Effect

We assumed that testing would take place alongside the NHS health check, of which 48.3% of those invited attended (as of January 2018), and we assumed all attendees were tested for HCV.[28] Lower uptake was considered in a sensitivity analysis. The intervention effect was assumed as additional to the background rate of HCV testing, which would continue in other settings. There is an opportunity for those not originally attending the health check to be tested at their next health check appointment 5 years later; however, this was not modeled.

### Transition Probabilities

For mild, moderate, and CC health states, 2 sources of transition probabilities were identified and considered in the model (see Appendix Tables 2 and 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006).

First, transition probabilities were derived from a health technology assessment in the United Kingdom by Shepherd et al,[29] based on clinical cohorts, which have been used in other

HCV models,[19,20,30] and have informed NICE HCV testing guidelines,[16] with additional transition probabilities for progression of cirrhotic individuals achieving SVR.[31,32]

We also considered transition probabilities from mild, moderate, and cirrhotic health states generated by the back-calculation model by Harris et al, which used prior values from Sweeting et al, and estimated age-based transition probabilities in the model fitting process.[2,33]

While the probabilities from Shepherd et al[29] are comparable to other economic evaluations, those generated from the back-calculation model align with HCV prevalence and severity parameters derived from the same source, and are thus consistent with other model inputs.

A previously published analysis explored the differences between 2 models estimating costs and QALYs for HCV in the United Kingdom, based upon the 2 sources of transition probabilities described above.[34] The authors concluded that in addition to transition probabilities from Shepherd et al,[29] the age-dependent transition probabilities estimated by Harris et al should also be considered in future modeling work, due to considerable differences in estimated costs and QALYs. Because of the uncertainty around the most appropriate choice of transition probabilities, we present the base-case results using both sources.

For value of information analyses in which transition probabilities were available from both Shepherd et al[29] and the back-calculation model, a uniform distribution was created to capture the uncertainty in the estimates from the 2 sources. Addition details are provided in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006.

### Utilities

Utility values were derived from a UK randomized controlled trial of mild HCV infection, and a UK study of patients with later-stage disease.[35,36] They were converted into a utility decrement and subtracted from UK general population utility estimates to provide age-adjusted values (see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006).[37]

### Costs

It was assumed that individuals would receive a HCV antibody test (£3.64).[38] The cost of administering this test was assumed to take 10 minutes by a practice nurse (band 5, £38/hour).[39] No other intervention costs were included. Costs associated with the NHS health check (eg, invitations) were not included as these are already established. Costs for RNA tests (£68.38) and subsequent appointments (£32, for those not receiving reflex testing) and outpatient visits prior to treatment were applied (Table 1).[23,38,39] The DAA acquisition costs for the NHS are confidential; however, an approximate £5000 price has been reported (reduced from list prices of >£30 000).[40] To remain conservative, we assumed DAA treatment costs of £10 000 for first treatment, and £15 000 for retreatment. We also considered DAA treatment costs of £5000, and show results across a range of DAA costs in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006. Treatment costs were conditional on achievement of SVR, as per NHS policy.[41]

Health state costs were derived from a previous health technology assessment, while costs associated with SVR were derived from Grishchenko et al (see Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006).[29,42] All costs were inflated to 2017 costs.[39] Individuals that were infected but undiagnosed were assumed not to accrue health state costs.

### Sensitivity Analyses

One-way deterministic sensitivity analyses (DSAs) were performed for individual parameters and shown in a tornado plot to capture the impact upon the ICER. The key DSA results for 1 birth cohort are shown (full DSA results for 2 cohorts, by source of transition probabilities, are available in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006). Probabilistic sensitivity analysis was performed, with all probabilistic parameters sampled simultaneously over 10 000 model simulations.

Value of information analyses show the maximum amount that should be paid to eliminate the uncertainty in all model parameters (the expected value of perfect information [EVPI]). This considers the loss of health benefits and resources by making the wrong decision, due to uncertainty. The EVPI can also consider the maximum value of research for individual or groups of model parameters, known as the expected value of partial perfect information (EVPPI).[43]

The EVPI analysis was performed using 10 000 simulations, for each birth cohort. For each of the EVPPI analyses, we ran 1000 inner loops (relating to the probabilistic sensitivity analysis) and 1000 outer loops (relating to the parameter[s] of interest assessed as part of the EVPPI analysis). These inner and outer loop simulation numbers were chosen to provide a sufficient number of probabilistic simulations while considering the computational time required to perform all analyses. For probabilistic sensitivity analysis, EVPI and EVPPI analyses, we use a willingness-to-pay threshold of £20 000, representing the lower bound of NICE's threshold range.[17] The eligible population for EVPI and EVPPI calculations is provided in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006.

## Results

The deterministic base-case results for each birth cohort are shown in Table 2. The ICERs for each birth cohort using the Shepherd et al[29] transition probabilities ranged from £18 681 to £46 024 with the most favorable ICERs for younger birth cohorts. When considering the back-calculation transition probabilities, the ICERs ranged from £7648 to £24 434, with ICERs below £20 000 for those born from 1955 to 1979.

### Probabilistic Sensitivity Analysis

When using the transition probabilities from Shepherd et al[29] at the willingness-to-pay threshold of £20 000 per QALY gained, the intervention is unlikely to be cost-effective for those born between 1950 and 1964 (probability of 1%-27%), but is borderline cost-effective for those born between 1965 and 1979 (probability of 41%-53%, Fig. 1). Yet, when using transition probabilities from the back-calculation model, the intervention is likely to be cost-effective for those born from 1955 to 1959 (69% probability), and is highly likely to be cost-effective for those born from 1960 to 1979 (94%-99.5% probability).

### Deterministic Sensitivity Analyses

One-way DSA was performed on the 1970-1974 birth cohort using Shepherd et al[29] transition probabilities (Fig. 2). The source of transition probabilities had the largest impact upon the ICER, followed by the probability of attending referral and receiving treatment. The ICER was also sensitive to the assumed prevalence among testers (0.25% to 0.14%) and a higher antibody test cost (£10). Reducing the uptake of the intervention did not affect the

**Table 2.** Cost-effectiveness results per individual eligible to attend the NHS health check for each birth cohort, by source of transition probabilities.

| Birth cohort | Testing option | Total costs (£) | Total QALYs | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|
| Shepherd et al[29] | | | | | | |
| 1950-1954 | Background testing | 15.21 | 10.1396 | | | |
| | Birth cohort screening | 23.68 | 10.1398 | 8.47 | 0.00018 | £46 024 |
| 1955-1959 | Background testing | 27.33 | 11.7818 | | | |
| | Birth cohort screening | 38.47 | 11.7822 | 11.14 | 0.00036 | £31 051 |
| 1960-1964 | Background testing | 38.28 | 13.2980 | | | |
| | Birth cohort screening | 52.04 | 13.2986 | 13.76 | 0.00056 | £24 364 |
| 1965-1969 | Background testing | 40.92 | 14.8456 | | | |
| | Birth cohort screening | 55.99 | 14.8463 | 15.07 | 0.00071 | £21 100 |
| 1970-1974 | Background testing | 36.97 | 16.2488 | | | |
| | Birth cohort screening | 49.87 | 16.2495 | 12.90 | 0.00067 | £19 236 |
| 1975-1979 | Background testing | 29.96 | 17.6997 | | | |
| | Birth cohort screening | 38.84 | 17.7002 | 8.89 | 0.00048 | £18 681 |
| Back-calculation model | | | | | | |
| 1950-1954 | Background testing | 24.60 | 10.1387 | | | |
| | Birth cohort screening | 31.42 | 10.1390 | 6.82 | 0.00028 | £24 434 |
| 1955-1959 | Background testing | 42.90 | 11.7801 | | | |
| | Birth cohort screening | 51.33 | 11.7806 | 8.43 | 0.00054 | £15 535 |
| 1960-1964 | Background testing | 64.11 | 13.2948 | | | |
| | Birth cohort screening | 73.87 | 13.2957 | 9.76 | 0.00093 | £10 542 |
| 1965-1969 | Background testing | 76.44 | 14.8404 | | | |
| | Birth cohort screening | 87.12 | 14.8418 | 10.68 | 0.00133 | £8037 |
| 1970-1974 | Background testing | 68.63 | 16.2441 | | | |
| | Birth cohort screening | 78.17 | 16.2453 | 9.54 | 0.00125 | £7648 |
| 1975-1979 | Background testing | 51.54 | 17.6963 | | | |
| | Birth cohort screening | 58.47 | 17.6972 | 6.93 | 0.00085 | £8196 |

NHS indicates National Health Service; ICER, incremental cost-effectiveness ratios; QALY, quality-adjusted life year.

ICER, since there was no fixed cost of the intervention; however, the overall health benefit would be reduced.

### EVPI and EVPPI

Assuming the intervention remains viable for all individuals in each birth cohort to be invited to the NHS health check (5 years), the EVPI across all birth cohorts (representing the maximum value for future research) was £11 289 902 at £20 000/QALY, with the highest value in birth cohorts born between 1955 and 1969 (Table 3).

The aggregated EVPPI results across all birth cohorts showed the highest value in reducing uncertainty was in the linkage to care parameters (£3 587 609); the utility of those achieving SVR (£2 487 084); and the transition probabilities from mild, moderate, and compensated cirrhosis health states (£1 617 959, Table 3). Additional EVPI results and EVPPI results by birth cohort are available in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006.

## Discussion

While previous studies show diagnosis and treatment should be prioritized among high-risk populations actively transmitting infection, we demonstrate that birth cohort screening as part of the NHS health check can also be cost-effective in England.[20,30,44]

Our findings indicate that the intervention is likely to be cost-effective for those born in the 1970s under the base-case modeling assumptions, but there is uncertainty as to whether the intervention would be cost-effective for those born between 1955 and 1969.

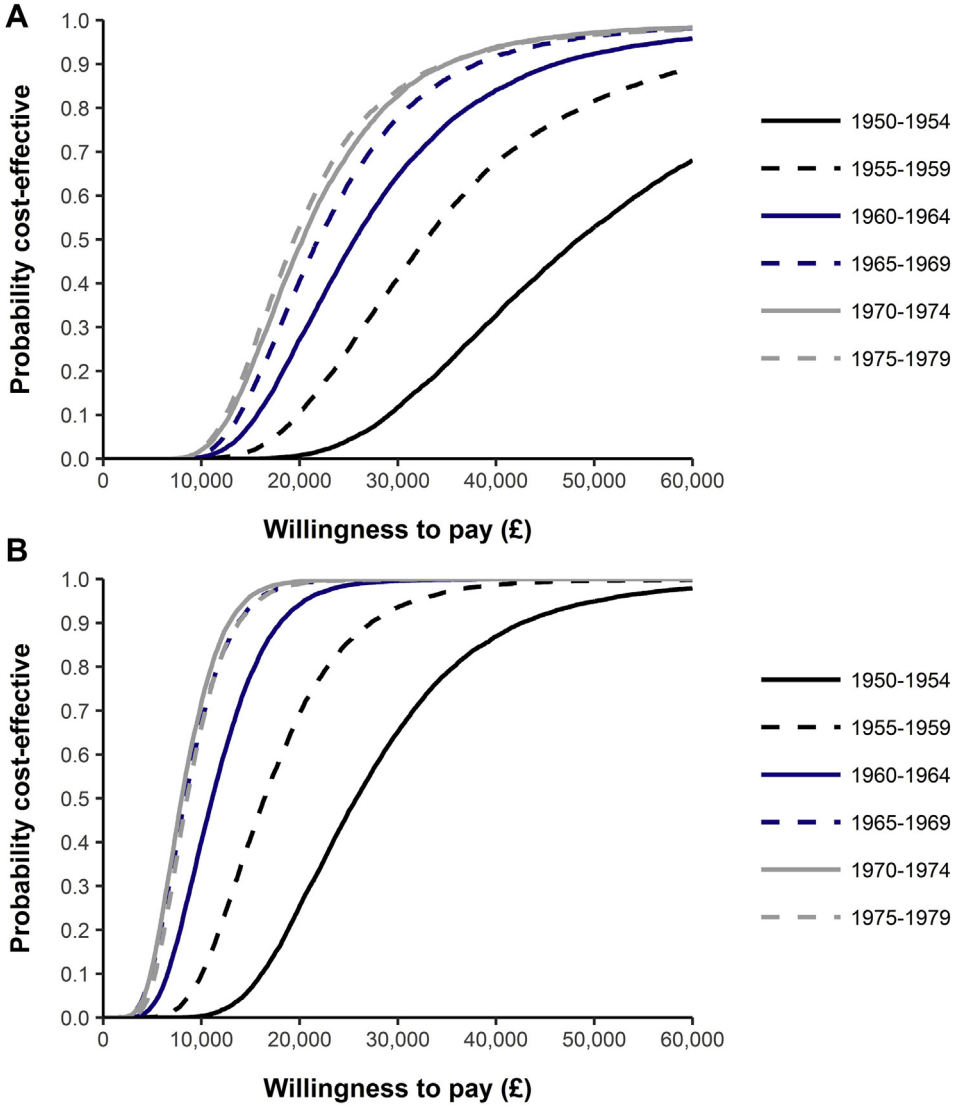
While the prevalence was slightly higher for younger birth cohorts, the lower ICERs also result from a longer duration of benefit associated with treatment at younger ages (due to higher utility associated with SVR). Our analysis also shows that further research for birth cohort screening as part of the NHS health check is justified to reduce the uncertainty and assess the acceptability of adding HCV testing to the NHS health check, with a high maximum value of future research of £11.3 million across birth cohorts. The EVPPI has shown future research is most valued in reducing the uncertainty in the linkage to care, the utility associated with SVR and HCV transition probabilities, as the uncertainty in these parameters caused the most uncertainty in the underlying decision upon cost-effectiveness. Deterministic analyses also demonstrated the impact of assumptions made surrounding the prevalence among testers. The sensitivity of the cost-effectiveness results to linkage to care also suggests case-finding interventions are more likely to be cost-effective following improvements in the proportion linked to care among those testing positive, and these improvements should precede or complement future investment in case finding interventions.

Our results also build upon previous work demonstrating the differences in model predictions using 2 sources of HCV transition probabilities.[34] In our analysis, the decision on cost-effectiveness for 3 of the 6 birth cohorts changed based only upon the source of transition probabilities. This supports previous conclusions that further research of progression rates is required to reduce the uncertainty for decision makers in the United Kingdom and elsewhere.[34]

### Comparison With Other Research

There is no other published evidence in the United Kingdom of the cost-effectiveness of birth cohort screening for HCV. Although our results differ considerably by transition probabilities, our

**Figure 1.** Cost-effectiveness acceptability curves for each birth cohort, for 2 sources of transition probabilities, derived from (A) Shepherd et al[29] and (B) the back-calculation model.

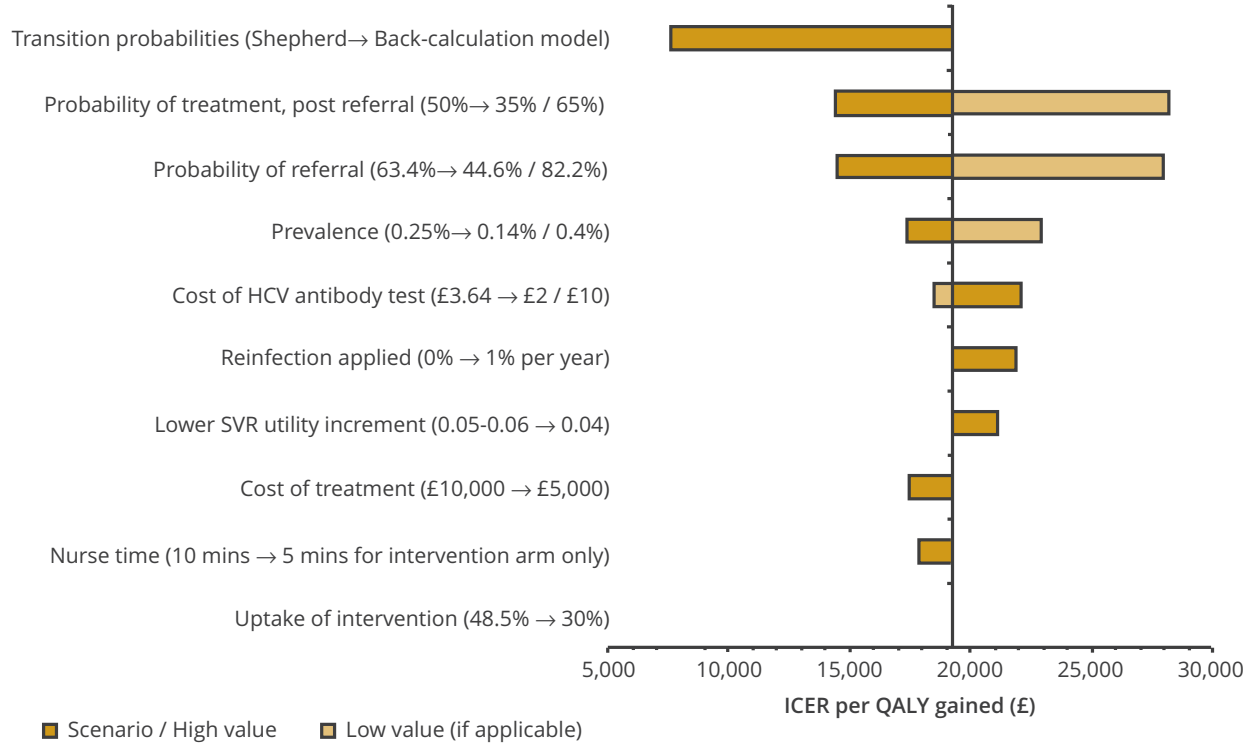



results are similar to those derived from the US ($35 700-$37 720/QALY), Canada (Can$36 471/QALY), and France (cost-effective from €26 000-€60 000/QALY).[7–9,45,46] These analyses used higher DAA costs, but tended to use higher health state utilities and higher prevalence estimates. Further details on these comparisons are available (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006.) Many European countries are developing national HCV elimination plans to meet WHO elimination targets.[47] Similar to the results from France, our results suggest that birth cohort screening can be cost-effective in areas of relatively low prevalence of HCV, if testing is added onto existing health services, such as the NHS's health check program.

### *Limitations*

In the absence of a study of the intervention itself, there is uncertainty about the extent to which current and ex-IDUs are likely to attend the health check, influencing the estimated prevalence among attendees. We assumed current IDUs and those previously testing positive could be tested through other targeted screening interventions; and ex-IDUs would attend at the same rate as never IDUs, an assumption that has a considerable impact upon cost-effectiveness. Furthermore, any inaccuracies in the estimated prevalence from the back-calculation model, which has its own methodological limitations, would significantly influence our results, and thus a study that estimates the seroprevalence among attendees would reduce the uncertainty of our results.[2] Moreover, while we have demonstrated the uncertainty in the estimated cost-effectiveness using 2 sources of transition probabilities, it is unclear which is most appropriate for economic evaluations in the United Kingdom. The use of transition probabilities from Shepherd et al[29] creates an inconsistency between our economic analysis and other model inputs estimated by the back-calculation model (the distribution of prevalence and disease stage across age groups). Nevertheless, this can be considered conservative, since a lower disease progression in the back-calculation model would have resulted in a higher estimated

**Figure 2.** One-way deterministic sensitivity analysis for 1970 to 1974 birth cohort, using transition probabilities from Shepherd et al.[29]




HCV indicates hepatitis C virus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; SVR, sustained virological response.

prevalence and therefore would have decreased the estimated ICERs.

There is also uncertainty surrounding the background HCV testing rate of infected and uninfected individuals. We assumed that infected individuals in this population would be tested at the overall population rate of testing, with no differences between those infected and uninfected. Methods to adequately capture the efficacy of expanding risk-based testing should be considered, as testing is likely to become less efficacious with upscaling, a trend observed in PHE sentinel surveillance data.[3,23] This will be important for future evaluations of case finding interventions in different population groups that may have differing rates of background testing. There could also be additional benefits to testing, such as testing among close contacts of those testing positive. Furthermore, we assume no disease transmission due to the assumptions around the population modeled.

**Table 3.** EVPI and EVPPI for all birth cohorts.

| Birth cohort/parameter | EVP(P)I at £20 000 WTP |
|---|---|
| EVPI | |
| 1950-54 | £175 023 |
| 1955-59 | £2 264 784 |
| 1960-64 | £3 577 217 |
| 1965-69 | £2 270 456 |
| 1970-74 | £1 644 936 |
| 1975-79 | £1 357 486 |
| Total | £11 289 902 |
| EVPPI (Total for all birth cohorts) | |
| Linkage to care parameters* | £3 587 609 |
| Utility of SVR health states | £2 487 084 |
| Transition probabilities from mild, moderate and CC health states† | £1 617 959 |
| Utility of non-SVR health states | £337 008 |
| Health state costs | £98 650 |
| Prevalence and initial values‡ | £0 |
| Background rate of testing | £0 |

CC indicates compensated cirrhosis; EVPI, expected value of perfect information; EVPPI, expected value of partial perfect information; SVR, sustained virological response; WTP, willingness to pay.
*Includes probability of referral and the probability of accepting treatment.
†Using uniform distributions estimated using values from both Shepherd et al[29] and back-calculation model.
‡Includes prevalence, probability of RNA+, and initial starting distribution (proportion mild/moderate/cirrhotic).

Despite considerable uncertainty and the limitations of our analysis, value of information analyses have sought to address the impact of parameter uncertainty by evaluating where future research would be most valued to reduce uncertainty. Nevertheless, due to assumptions made in the model that were not parameterized, additional uncertainty exists that is not reflected in these results. This includes the absence of startup costs for the intervention, assumptions surrounding health check attendees (thus influencing the estimated prevalence), and assumed equal testing among those infected and uninfected in other testing settings. For this reason, the value of information estimates can be considered conservative. Furthermore, patients with existing pre-conditions, such as heart disease, kidney disease, diabetes, or previous stroke, may not receive a health check invitation, thus uncertainty exists about how testing could be provided to these patients, or whether the prevalence of HCV in this group might differ.

## Conclusions

Our analysis suggests any future research for birth cohort testing should prioritize younger birth cohorts, as these are the

most likely to be cost-effective. We have also shown the importance of the care pathway on the cost-effectiveness of case-finding interventions, and the benefit of integrating HCV testing with existing health services. A feasibility study would allow a full costing analysis to be undertaken, and could capture the proportion of patients successfully linked to care and receiving treatment. Additional to the parameter uncertainty, this study could assess the acceptability of the intervention as part of the NHS health check to primary care providers, and to health check attendees to avoid unintended negative consequences, such as decreased attendance.

Finally, with many case-finding interventions in HCV currently being evaluated in the United Kingdom,[19,48] future modeling work should consider all potential testing interventions in combination to identify and prioritize the most cost-effective combination of interventions. For example, a more sophisticated risk-based testing algorithm may provide a more targeted approach to case-finding in primary care, although the sensitivity of these algorithms is unknown.[48] The use of more complex economic models comparing multiple case-finding interventions can help to inform the allocation of HCV resources in England to reduce disease burden and meet WHO targets.

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## Supplemental Material

Supplementary data associated with this article can be found in the online version at https: https://doi.org/10.1016/j.jval.2019.06.006.

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# 6 An economic evaluation of the HepCATT (Hepatitis C Assessment Through to Treatment Trial) intervention: a cluster RCT in Primary Care to increase uptake of HCV testing and treatment

## 6.1 Overview of Research Paper 2

In this Chapter, I focus on an economic evaluation of the 'Hepatitis C Awareness Through to Treatment' (HepCATT) trial, which aimed to increase HCV testing and linkage to care in a primary care setting.

The HepCATT intervention involved an algorithm-based identification system to highlight patients who were at an elevated risk of HCV, based on the risk factors within their medical records. It also involved training and education to increase awareness of HCV amongst general practice staff and patients. The study was a large cluster randomised controlled trial, which included 43 general practices. These practices had almost 470,000 patients registered, of which 24,473 (approximately 5%) were identified as being at an elevated risk of HCV and invited back to primary care to receive testing. There were also computer-based alerts to remind staff to offer an HCV test to these individuals when they returned to the practice.

NICE guidelines have previously referred to the possibility of staff in primary care reviewing patients medical records and offering testing to those at risk.[1] The HepCATT intervention seeks to automate this process, to ensure that all of those who should be offered a test are automatically identified. Such a testing intervention could easily be scaled up across primary care practices, and would ensure that those patients with risk factors for HCV are offered testing. Previous studies have found that the majority of these patients with HCV risk factors are not currently tested within primary care, and unlikely to be tested elsewhere, demonstrating the need for an intervention to improve this.[2]

This Chapter, along with Chapters 5 and 7, fulfil the second objective of this thesis. It has been re-written from the original publication. The original publication is open-access, and published under the Creative Commons Attribution-Non Commercial 4.0 International License (CC BY-NC 4.0), which allows for the work to be reproduced in this thesis, as long as it is appropriately cited.[3] The original article is available in Appendix 10.4. The reference for the full publication is:

*Roberts K, Macleod J, Metcalfe C, Hollingworth W, Williams J, Muir P, et al. Cost effectiveness of an intervention to increase uptake of hepatitis C virus testing and treatment (HepCATT): cluster randomised controlled trial in primary care. BMJ. 2020;368:m322.*

The original publication reported the overall results of the clinical trial, including the trial intervention, recruitment, testing results, statistical analyses, and an economic analysis. This Chapter has therefore been rewritten to focus on the details of the economic evaluation of the HepCATT trial only, which was the section that I developed. My primary PhD supervisor (Alec Miners), and the PI for the HepCATT study (Matthew Hickman) were both involved in the supervision of this economic evaluation.

This economic evaluation uses data from analyses performed by other researchers involved in the HepCATT trial, such as regression models from a statistical analysis of the testing data. This was used to estimate the rate of testing amongst the control and intervention arm. The model also uses the mean costs (per patient) from a costing analysis of the trial data, performed by another researcher at the University of Bristol. The economic analysis performed as part of this thesis did not involve any dataset, and I did not have access to the trial data. I only received aggregate data such as total numbers of patients at each stage of the trial (numbers tested, positive, linked to care), regression outputs for the testing rate ratio, and mean costs associated with the intervention.

The cost-effectiveness model extrapolates the results of the one-year trial period to estimate the longer-term economic impact of the HepCATT testing intervention. This Chapter also includes additional sensitivity analysis results that did not appear in the original paper or supplementary materials, which is allowed by the license agreement.[4]

The HepCATT trial received all of the appropriate ethical approvals. This included approval from the South West Frenchay Research Ethics Committee, part of the NHS Health Research Authority.[5] For the economic analysis, LSHTM did not receive the HepCATT dataset. Since the economic analysis did not involve any primary data collection, or any individual patient level data (also described as human data in LSHTM ethics documentation), it was deemed that the economic model did not require ethical approval from LSHTM.

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# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

## SECTION A – Student Details

| | | | |
|---|---|---|---|
| **Student ID Number** | 1405199 | **Title** | Mr |
| **First Name(s)** | Jack | | |
| **Surname/Family Name** | Williams | | |
| **Thesis Title** | Assessing the cost-effectiveness of interventions to expand hepatitis C testing to help achieve elimination targets in the United Kingdom | | |
| **Primary Supervisor** | Alec Miners | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

## SECTION B – Paper already published

| | | | |
|---|---|---|---|
| Where was the work published? | BMJ | | |
| When was the work published? | 26 February 2020 | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | N/A | | |
| Have you retained the copyright for the work?* | **Yes** | Was the work subject to academic peer review? | **Yes** |

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

## SECTION C – Prepared for publication, but not yet published

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| Where is the work intended to be published? | |
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| | |
|---|---|
| Stage of publication | Choose an item. |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role included indentification of the input data for the economic model, developing the economic model, and performing the cost-effectiveness analyses.<br>I wrote the economic model section of the draft version of the manuscript. I addressed peer review comments only on the economic model section. |

**SECTION E**

| | |
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| | |
|---|---|
| **Supervisor Signature** | Alec Miners |
| **Date** | 25/02/2022 |

## 6.2 Introduction

As has been discussed in the thesis introduction, testing for HCV in the UK is mainly targeted towards PWID and marginalised communities, whether this is current or previous injectors. As such, testing is typically focussed on settings where these individuals are likely to engage with care, such as drug and alcohol (or substance misuse) services, drug treatment centres or pharmacies providing OST, pharmacies providing needle and syringe services, in hostels or shelters for the homeless, and in the justice system (prisons and probation services). There are also outreach services targeted towards engaging those involved in injecting or those who are homeless. However, whilst these groups are the most likely to test positive for HCV, and therefore testing coverage is highest in these settings, there remain many people with HCV in the UK who either do not attend services where routine HCV testing occurs, or they are not easily identifiable by the risk factors associated with HCV. As such, it is harder to identify these groups as being at risk of HCV.

Despite testing being more frequent in those attending the aforementioned settings, many HCV tests are performed in primary care each year (approximately 30% of tests recorded in sentinel surveillance).[6] However, unlike routine testing performed in other settings, HCV testing in primary care is only offered to those deemed to be at risk of HCV, which requires GPs to have a reasonable knowledge of HCV risk factors, and to be able to identify those to offer a HCV test.

A study from 2014 in primary care showed that only around 19% of those at risk of HCV in primary care were screened, and even tests for PWID were relatively low, ranging from 29% to 62% across practices.[2] There are many barriers to testing, but poor knowledge of HCV risk factors, and GPs not asking about patients risk factors are prominent, as well as difficulties in accessing patients previous HCV test results. Indeed, there is evidence that the likelihood of being offering an HCV test depends on individual practitioners.[7]

There is also thought to be a lack of awareness from people about their own risk of HCV infection, who may be infected but remain asymptomatic and living in good health for many years or decades.[8] As such, people may not feel the need to disclose their previous behaviours, as they are unaware of their risk, or may have concerns about disclosing their current or previous behaviours (such as injecting drug use) to healthcare professionals due to a fear of being stigmatised.[8] Finally, some people may have been previously diagnosed with HCV, but were not engaged in care at the time of their previous diagnosis. This may have been due to previous attitudes towards treating individuals who continued to use drugs, or concerns

around the duration of previous interferon based treatments, and the well documented side effects associated with them.[9]

One mechanism of identifying people at increased risk of infection is to search their primary care medical records for evidence of risk factors for HCV. This was considered in NICE testing guidelines, but there was insufficient evidence around the effectiveness or cost-effectiveness to make a recommendation.[1] Furthermore, the additional burden of performing this task manually is likely to be considerable.

The HepCATT trial was a general practice level cluster randomised controlled trial of HCV testing in primary care. The trial randomised 45 general practices across South West England, with outcomes reported for 43 of them. The intervention arm of the trial involved the development of a computer algorithm to identify people deemed at risk of HCV infection, based on the presence of high-risk codes stored in their medical records.[10] This software based algorithm offers the opportunity to scan the medical records of all patients to identify those at an elevated risk of HCV. Once identified by the algorithm, patients were offered an HCV test, unless the primary care staff had a reason to exclude them from testing, such as those with a short life expectancy. The offer of a test was first sent to the patient by letter, inviting them to make an appointment. There were also computer-based alerts for practice staff to opportunistically offer testing when the patient next returned to the practice. The intervention arm of the study also involved training and education for primary care staff, and raising awareness of HCV amongst patients. The practices in the control arm did not have the intervention, but still provided HCV testing opportunistically, as per usual practice. Control practices were informed of their randomisation and were contacted at the end of the study.

There were approximately 470,000 patients registered across intervention and control practices, with 24,473 patients (around 5%) being identified as being at risk of HCV by the HepCATT algorithm. During the study, 15.8% of patients identified by the algorithm in the intervention arm were tested, whilst in the control arm 10.2% of people at an elevated risk of HCV were tested. This resulted in an adjusted rate ratio (RR) of testing of 1.59 (95% confidence interval [CI] of 1.21 to 2.08). There was also some evidence to suggest the proportion of those tested that were HCV positive was higher in the intervention arm (adjusted RR of 1.4, 95% CI: 0.99 to 1.95). Furthermore, the referral rates to specialist hepatology care following a positive PCR test were also higher in the intervention arm (45.6% vs. 23.1%), with an adjusted rate ratio of 5.78, (95% CI: 1.6 to 21.6).

The aim of this analysis is to evaluate the cost-effectiveness of using this risk-based algorithm to identify and offer HCV testing and treatment to those at an elevated risk of HCV.

## 6.3 Methods

### 6.3.1 Model analysis

A Markov model was developed to compare the costs and outcomes associated with the HepCATT primary care testing intervention. The intervention included an audit tool, including an algorithm which identified patients deemed to be at elevated risk of HCV. The intervention also involved training of staff for the audit tool, which was costed in the analysis. The intervention was compared to the trial control group over the same time period, who did not receive the intervention, and therefore represents the current practice for hepatitis testing in primary care (i.e. opportunistic HCV testing for those at risk, as per NICE testing guidelines).[1] These were the only comparators in the model.

Across the intervention and control practices, 24,473 people met at least one of the risk criteria used in the algorithm, which represents approximately 5% of people in each practice. A breakdown of the number of individuals meeting each of these risk criteria are provided in Table 6-1. A full list of risk markers and medical read codes used to identify those at an elevated risk of HCV are available in the supplementary materials of the full publication.[5]

Table 6-1: Number and proportion of individuals in the intervention and control arms which meet each of the risk criteria for inclusion in the testing population of the HepCATT trial

| | **Proportion meeting each risk criteria†** | |
|---|---|---|
| **HCV risk criteria** | **Intervention (n=13,097)** | **Control (n=11,376)** |
| History of HCV exposure or testing | 8295 (63.3%) | 6476 (56.9%) |
| History of opioid/injecting drug use | 2930 (22.4%) | 3315 (29.1%) |
| History of HIV or HBV infection | 971 (7.4%) | 829 (7.3%) |
| History of blood transfusion or transplant | 423 (3.2%) | 378 (3.3%) |
| History of childhood in care or imprisonment | 899 (6.9%) | 1024 (9.0%) |
| Altered alanine aminotransferase (ALT) concentration | 5120 (39.1%) | 3895 (34.2%) |

†The sum of the proportions of individuals across the risk criteria exceeds 1, since an individual can meet more than one risk criteria.

The model captures the increased rate of testing and the higher linkage to care observed in the intervention arm, versus no intervention. The analysis was performed from an NHS perspective, and results are presented in 2017 pounds (£, GBP). Outcomes are reported as QALYs. Both costs and QALYs were discounted at 3.5%, as per NICE guidelines.[11] In the model, individuals moved between health states during each six month cycle length, over a lifetime time horizon. The model results are presented as ICERs, which were calculated as the incremental costs divided by the incremental QALYs, to give a cost per QALY gained. A willingness to pay threshold of £20,000 per QALY gained was used, since this is the lower bound of the NICE cost-effectiveness threshold in its Technology Appraisals programe.[11]

Since the Markov model considers a static population, the intervention was assumed to occur for one year only in the base case analysis, upon which individuals in both groups had the same probability of HCV testing in the future. This future probability of testing was assumed equal to the probability of testing in the control group. To consider the impact of the intervention upon new individuals joining a particular primary care centre, an analysis excluding training costs was performed.

The mean age of those receiving an HCV test in the HepCATT trial was not collected. Those entering the model were assumed to be 45 years of age, on average. This was based on previous research showing that the majority of chronic infections of HCV are amongst those aged 40 to 49 years of age in England, as of 2015.[12] This was also the age band with the highest

number of chronic HCV infections amongst those who have previously injected drugs, which is one of the HepCATT algorithm risk factors.

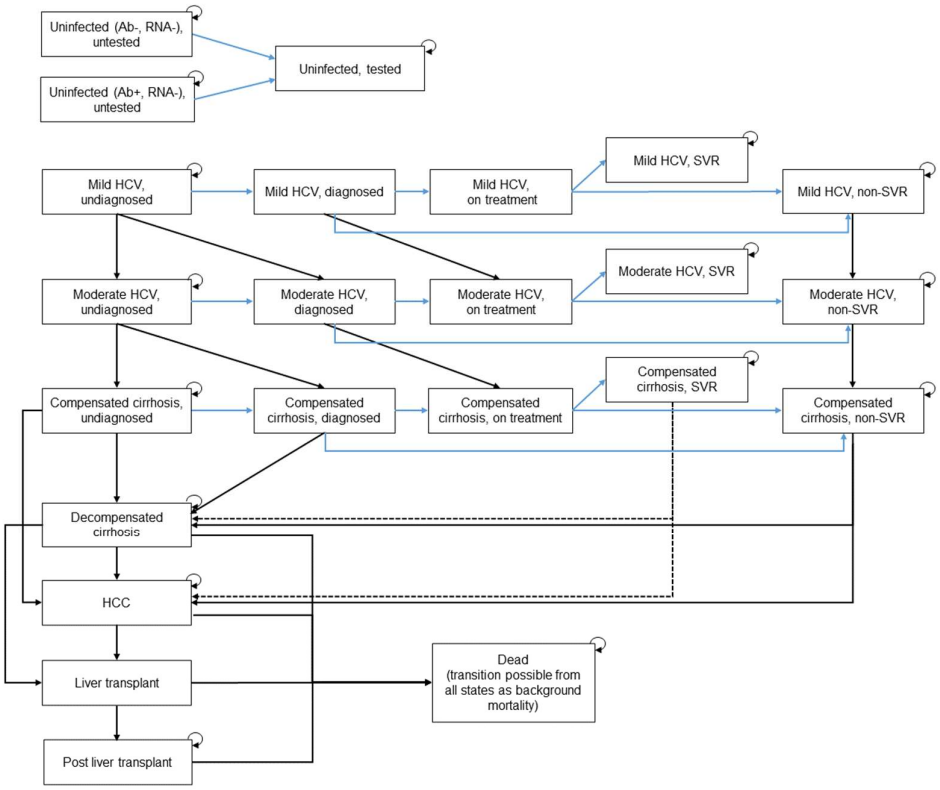
The model was developed in TreeAge Pro 2017.

### 6.3.2 Model structure

The Markov model captures the natural history of HCV using eight main clinical health states, and is similar to the model previously used to evaluate the cost-effectiveness of birth cohort testing in the UK (Figure 6-1).[13] For early health states, disease status is classified according to the modified Histological Activity Index (HAI) score, also known as the Ishak score, for mild HCV (F0-F2), moderate HCV (F3-F5) and compensated cirrhosis (F6).[12,14] For individuals with mild HCV, moderate HCV or compensated cirrhosis, health states are mirrored to also capture the following diagnosis statuses; 'undiagnosed', 'diagnosed', 'on-treatment', 'SVR', or 'non-SVR'. Individuals progressing beyond compensated cirrhosis were assumed to be aware of their diagnosis due to the severity of their disease. In addition to HCV related mortality associated with decompensated cirrhosis, HCC and liver transplant health states, the model also captures the risk of non-HCV related mortality, for all individuals in the model (i.e. regardless of their current health state). This mortality risk was derived from UK life tables.[15]

Although a history of intravenous drug use or a history of engagement in OST was a risk factor that resulted in an invitation to test, there was no other information from the HepCATT trial about the proportion of those invited to test who may be currently injecting drugs. As such, we did not include people currently injecting drugs in the model, and therefore did not account for any onward disease transmission. This is likely to result in a conservative estimate for the ICER, as it does not consider the prevention benefit associated with reduced onward transmission as a result of testing and treatment. However, a scenario considering the impact of lower utility values associated with PWIDs was performed, in which all individuals in the model were given these lower utility values. A threshold analysis also considered the maximum probability of reinfection at which the intervention would be cost-effective, since the reinfection risk was assumed to be zero amongst non-PWID in the base case analysis.

Figure 6-1: Economic model structure




Black lines represent disease progression. Black dotted lines represent disease progression at reduced rate, compared to those who do not achieve SVR. Blue lines represent change in diagnosis or treatment status (without disease progression)

### 6.3.3 Intervention effects (testing uptake and linkage to care)

The probability of HCV antibody testing in both the intervention and control groups was estimated using a random-effects Poisson regression model. This model adjusted for general practice location (Bristol versus elsewhere) and the historical rate of HCV testing (high versus low), as indicated by Public Health England testing records. Using the regression equation and the average baseline characteristics, the estimated probability of testing was 9.7% in the control group. Using an adjusted rate ratio of 1.59 (95% CI: 1.21 to 2.08), the annual probability of testing in the intervention group was 14.9%. After the first year (i.e. the intervention period), both the intervention and the control group were assumed to have the same annual probability of testing (9.7%) throughout the remainder of the model.

Given that the annual probability of testing prior to the trial period was estimated at approximately 6.6% (since 3.3% of individuals received testing in the six-month baseline prior to the trial period), a sensitivity analysis was performed in which the probability of testing in the control arm was 6.6%. This gave a probability of testing of 10.3% during the intervention, based on the testing rate ratio of 1.59 applied for the intervention arm.

Amongst those receiving testing, there was some suggestive evidence that the prevalence of HCV antibodies was higher amongst the intervention group compared to the control group (6.2% versus 4.4%), suggesting that testing in the intervention arm had a higher yield of positive cases. However, to be conservative, this difference was not included in the base case analysis, and was instead only considered in a sensitivity analysis by adjusting the probability of testing for infected and uninfected individuals within the intervention arm to achieve a higher antibody yield as suggested by the intervention (risk ratio of 1.42). A threshold analysis was also performed to consider the minimum prevalence of HCV amongst those receiving testing at which the intervention would remain cost-effective.

Of those who tested HCV antibody positive in either arm of the trial, it was assumed that reflex PCR testing (a PCR test on the same blood sample used for the HCV antibody test) was performed. Of all PCR tests performed, 56 were positive and 83 were negative, with 41 either having missing results or insufficient sample to confirm. The proportion of RNA positive PCR tests was derived from all conclusive test results available, with an estimated 40.3% (56/139) testing positive. It was unclear why such a high proportion of PCR tests were inconclusive (18% of all PCR tests). However, to consider the impact of this low proportion of PCR positive tests, a

sensitivity analysis considered a higher RNA positive proportion, derived from PHE sentinel surveillance statistics (72.3%).[6]

Evidence of a viral load test in secondary care for those testing RNA positive in primary care was considered as successful referral (and engagement) with secondary care. The adjusted rate ratio for viral load tests between the arms was 5.78 (95% CI: 1.55, 21.61). However, for the parameterisation of the economic model, the proportion receiving a viral load test subsequent to a positive RNA test was used. Of all those testing RNA positive, 47% in the intervention arm (20/43) and 23% in the control arm (3/13) were successfully referred and engaging in secondary care (based on a viral load test in secondary care). In the base case analysis, the unadjusted proportions for the intervention and control arms were used for this parameter. To assess the impact of this outcome (the proportion of patients successfully linked to care) on the cost-effectiveness results, a sensitivity analysis was performed in which the linkage to care following a positive PCR test was equal for both control and intervention groups, based on the overall linkage to care in the study (Table 6-2). There was no data available on the proportion of individuals engaged in secondary care that went on to receive DAA treatment, however it was assumed that this would be the majority of patients. An assumption was made that 90% of those engaged in secondary care would receive treatment, although a deterministic sensitivity analysis considered a lower proportion of 60%.

The probability of achieving SVR was derived from a real world study performed in the UK.[16] For individuals that did not achieve SVR with their first treatment, it was assumed that they would be retreated once, and the SVR rates associated with retreatment were derived from a clinical study amongst individuals that had not responded to prior DAA containing therapy.[17] The economic model analysis was pan-genotypic and did not consider outcomes by genotype.

Table 6-2: Base case parameters for testing intervention and linkage to care

| Base case probabilities | Mean | Distribution | Source |
|---|---|---|---|
| ***Testing rate and intervention effect*** | | | |
| Annual probability of testing (control) | 9.7% | Multivariate normal distribution[‡] | HepCATT |
| Antibody testing rate ratio (intervention) | 1.59[†] | Multivariate normal distribution[‡] (95% CI 1.21, 2.08) | HepCATT |
| ***Antibody prevalence*** | | | |
| Antibody prevalence (combined) | 5.57% | Beta (α=180, β=3,054) | HepCATT |
| Antibody yield treatment effect rate ratio – Scenario[§] | 1.42 | N/A | HepCATT |
| ***Linkage to care*** | | | |
| Proportion of reflex PCR tests | 100% | N/A | Assumption |
| Proportion of RNA+ (of Ab+) | 40.3% | Beta (α=56, β=83) | HepCATT |
| Proportion of RNA+ (of Ab+) – Scenario | 72.3% | N/A | Simmons 2018[6] |
| Probability of referral and attendance (control) | 23.1% | Beta (α=3, β=10) | HepCATT |
| Probability of referral and attendance (intervention) | 46.5% | Beta (α=20, β=23) | HepCATT |
| Probability of referral and attendance (combined) – Scenario | 41.1% | Beta (α=23, β=33) | HepCATT |
| Probability of treatment (post referral) | 90% | Uniform (0.8, 1) | Assumption |
| Initial proportion mild | 55.9% | Dirichlet (55.9,33.9,10.2)[*] | Ward 2016[18] |
| Initial proportion moderate | 33.9% | Dirichlet (55.9,33.9,10.2)[*] | Ward 2016 |
| Initial proportion cirrhotic | 10.2% | Dirichlet (55.9,33.9,10.2)[*] | Ward 2016 |
| **Treatment outcomes** | | | |
| Mild / moderate | 92.8% | Beta (α=376, β=29) | Irving 2017[16] |
| CC | 90.8% | Beta (α=736, β=75) | Irving 2017 |
| Mild / moderate (retreatment) | 93.9% | Beta (α=77, β=5) | Bourlière 2017[17] |
| CC (retreatment) | 85.5% | Beta (α=59, β=10) | Bourlière 2017 |

[†]The deterministic annual probability of testing in intervention group is 14.9%, calculated from the annual rate of testing in the control group and the antibody testing rate ratio.

[‡]Multivariate normal distribution of Cholesky decomposition, derived from the random effects Poisson regression model. Antibody testing rate ratio covariate included for intervention arm.

[§]Treatment effect in base case analysis equal to 1 due to model structure

[*]Assumed sample size of 100 for probabilistic distribution

### 6.3.4 Costs

The intervention, care pathway, and health state costs used in the economic model are shown in Table 6-3. The cost of training for the HepCATT intervention was estimated as part of a separate costing analysis of the trial (by other researchers involved in the trial) and was used as an input for the economic model presented in this analysis. This cost was based on an assumed 30 minutes of training time for staff members, and a total of two hours for staff providing training (plus travel costs). The total training costs were divided by the total number of individuals eligible for screening as part of the intervention, to give a cost per person included in the study. The training cost per individual included on the HCV screening list was estimated to be £1.22 per individual. Across the intervention general practice sites, this cost ranged from £0.39 to £3.89, and this was used to inform the gamma distribution used in the probabilistic sensitivity analysis (Table 6-3). This is likely to be an overestimation of the variance around the mean estimate for each patient in the HepCATT trial, as this instead represents the uncertainty at the practice level, rather than the individual level, and was therefore considered a conservative approach for the probabilistic sensitivity analysis.

A mean cost for screening-based activities was also calculated as part of a separate costing analysis. This mean cost included the cost of the Audit+ software, which is now available to general practices and is paid for centrally by government. The costing analysis assumed a license fee and support cost of £500 per year, per practice, and although the system is not exclusive to HCV case finding, this was assumed to be its only purpose in the costing analysis. Practice staff time was estimated based on installing and running the software, and extracting the patient lists to screen for eligibility, and sending invitations to patients deemed eligible. The overall cost of these screening activities was estimated to be £2.06 per individual included in the study. The practice level uncertainty ranged from £0.56 to £9.13, and similar to the training costs described above, this was used to inform the gamma distribution used in the probabilistic sensitivity analysis for this parameter.

For the remainder of the testing pathway, the cost of an antibody test was £8.12 per test, derived from Public Health England, and an HCV phlebotomy appointment was assumed to cost £14.10, derived from private healthcare costs. The cost of a PCR test, assumed to be performed as a reflex test, was £90.64. The cost of DAA treatments per course in the UK is confidential, although it is believed to be significantly lower than UK list prices (approximately £35,000), with suggestions that these costs are below £10,000.[19] In this analysis, we assumed

first line DAA costs were £10,000, and that for re-treatment, the cost would be £15,000. Under the current NHS policy, treatment costs were only incurred upon achievement of SVR.[20]

Health state costs were derived from a previous health technology assessment (HTA) performed in the UK.[21] The health state costs associated with SVR (for mild, moderate and compensated cirrhosis health states) were derived from Grishchenko 2009 (Table 6-3).[22] Health state costs were inflated to 2017 costs using the Hospital and Community Health Services Pay and Prices inflation index.[23]

There were no financial incentives for general practices in the HepCATT trial, although other trials of primary care testing have included these.[24] We performed a sensitivity analysis in which a £500 incentive was costed for each practice in the intervention group, which equated to £0.84 per individual eligible included in the model. A larger incentive of £1000 (£1.68 per individual) was also considered. The sensitivity analyses of incentives assumed there was no additional increase in testing above that observed in the trial.

Another sensitivity analysis was performed which considered a lower DAA treatment cost of £5,000 per course, with the cost of re-treatment assumed to be £10,000 per course. We also show a sensitivity analysis in which the DAA costs are varied up to £35,000.

Table 6-3: Base case costs

| Description | Cost | Distribution | Source |
|---|---|---|---|
| ***Intervention and care pathway costs*** | | | |
| Cost of training per individual (intervention) | £1.22 | Gamma (k=1.7746, θ=1.4546) | HepCATT trial |
| Cost of screening per individual (intervention) | £2.06 | Gamma (k=0.8879, θ=0.431) | HepCATT trial |
| Cost HCV appointment | £14.10 | Varied by staff cost variation[†] | Private practice[*] |
| HCV antibody test | £8.12 | Varied by test cost variation[‡] | Public Health England |
| Cost of PCR test | £90.64 | Varied by test cost variation[‡] | Public Health England |
| Outpatient evaluation | £238 | Uniform (£190.40, £285.60) | NHS reference costs 2016/17[25] |
| Further outpatient evaluation | £262 | Uniform (£209.60, £314.40) | NHS reference costs 2016/17 |
| DAA treatment (first treatment) | £10,000 | N/A | Hurley 2018[19] |
| DAA treatment (re-treatment) | £15,000 | N/A | Assumption |
| DAA treatment monitoring | £1,310 | Uniform (£1048, 1572) | NHS reference costs 2016/17 |
| ***Health state costs (per year, except where noted)*** | | | |
| Mild HCV | £195 | Gamma (k=25.6995, θ=5.3698) × PPI[§] | Shepherd 2007[21] |
| Moderate HCV | £1,014 | Gamma (k=88.8502, θ=8.0698) × PPI[§] | Shepherd 2007 |
| Cirrhosis HCV | £1,610 | Gamma (k=24.2342, θ=46.9584) × PPI[§] | Shepherd 2007 |
| Decompensated cirrhosis | £12,901 | Gamma (k=36.0249, θ=253.1582) × PPI[§] | Shepherd 2007 |
| Hepatocellular carcinoma | £11,496 | Gamma (k=18.1081, θ=448.8045) × PPI[§] | Shepherd 2007 |
| Liver transplant (per transplant) | £38,661 | Gamma (k=89.7536, θ=304.5004) × PPI[§] | Shepherd 2007 |

| | | | |
|---|---|---|---|
| Cost of care in year of liver transplant | £13,379 | Gamma (k=13.7788, θ=686.4168) × PPI[§] | Shepherd 2007 |
| Cost of care post liver transplant | £1,959 | Gamma (k=15.2189, θ=91.0053) × PPI[§] | Shepherd 2007 |
| Mild SVR | £286 | Gamma (k=25, θ=8.08) × PPI[§] | Grishchenko 2009[22] |
| Moderate SVR | £349 | Gamma (k=25, θ=9.88) × PPI[§] | Grishchenko 2009 |
| Cirrhosis SVR | £618 | Gamma (k=25, θ=17.48) × PPI[§] | Grishchenko 2009 |

[†]Cost of staff calculated by using a multiplier for staff costs, following a uniform distribution from 0.8 to 1.2.

[‡]Cost of test calculated by using a multiplier for tests costs, following a uniform distribution from 0.8 to 1.2.

[§]Costs inflated to 2016/17 costs using Hospital and Community Health Services Pay and Prices Inflation Index to 2016/17 (2002/03 = 1.41, 2006/07 = 1.21)

[*]Based on a phlebotomy appointment at a private practice, derived from HepCATT trial collaborators correspondence with a private medical practice[5]

### 6.3.5 Utilities

Utilities for mild, moderate and cirrhotic health states were derived from the UK HCV trial, which reported EQ-5D values for each health state (Table 6-4).[26] Utilities associated with SVR health states were derived from the same source, but were only available for mild and moderate patients who achieve SVR. An assumption was made that the utility increment associated with SVR for those with cirrhosis was the same as the utility increment for those with moderate HCV achieving SVR, which was a utility increment of 0.06. Similar assumptions have been made in other economic evaluations.[27,28] For later disease stages, utilities were derived from a UK study in individuals receiving liver transplants.[29] These utilities have been used in previous UK HTAs.[21,27] Utilities were also adjusted to decline with age, in line with UK utility values amongst the general population.[30]

A sensitivity analysis was performed in which the utility values for all individuals in the model were decreased by 18% (i.e. using a 0.82 multiplier) to reflect the lower utility associated amongst PWID without chronic HCV (utility of 0.76), compared to equivalent, age matched, general population value (utility of 0.93). This was performed to consider a scenario in which the utility values in the model were equal to those of PWID.[31] Similar analyses of lower utilities amongst PWID have been performed in other economic evaluations.[32]

Table 6-4: Base case health state utility values

| Health state | Value | Distribution | Source |
|---|---|---|---|
| Mild | 0.77 | Beta (α=521.2375, β=155.6943) | Wright 2006[26] |
| Moderate | 0.66 | Beta (α=168.2461, β=86.6723) | Wright 2006 |
| Cirrhosis | 0.55 | Beta (α=47.1021, β=38.5381) | Wright 2006 |
| Decompensated cirrhosis | 0.45 | Beta (α=123.75, β=151.25) | Ratcliffe 2002[29] |
| HCC | 0.45 | Beta (α=123.75, β=151.25) | Ratcliffe 2002 |
| Liver transplant (first year) | 0.45 | Beta (α=123.75, β=151.25) | Ratcliffe 2002 |
| Liver transplant (after first year) | 0.67 | Beta (α=32, β=16) | Ratcliffe 2002 / Wright 2006[27] |
| Mild SVR | 0.82 | Beta (α=65.8678, β=14.4588) | Wright 2006 |
| Moderate SVR | 0.72 | Beta (α=58.0608, β=22.5792) | Wright 2006 |
| Cirrhosis SVR | 0.61 | Beta (α=58.0476, β=37.1124) | Wright 2006 / Hartwell 2011 |

### 6.3.6 Transition probabilities

The transition probabilities used in the base case are presented in Table 6-5. These transition probabilities were similar to those used in a previous HTA in HCV,[21] but also incorporate additional transitions for those with compensated cirrhosis achieving SVR. More recent evidence suggests that this group remain at risk of developing decompensated cirrhosis and HCC, albeit at a much lower probability compared to those who do not achieve SVR.[33,34] Adding these transition probabilities also ensures that the benefit of treatment is not overestimated. They have also been used in many recent economic evaluations.[28,32,35]

A deterministic sensitivity analysis was performed which considered an alternative set of transition probabilities. It considered transition probabilities estimated from a back-calculation model performed in England, for progression from mild HCV, moderate HCV and compensated cirrhosis health states (Table 6-6).[12] The methodological details of the back-calculation model are described in more detail in Chapter 5, but the model uses hospital episode statistics (HES) and office of national statistics data (ONS) to estimate historical HCV burden in England, and to then project these estimates forward.[36] The transition probabilities from this method are generated through a Bayesian model fitting process, and differ by age. In this sensitivity analysis, all other transition probabilities remained the same, except for those reported in Table 6-6. Only the deterministic values for these transition probabilities are presented, since they were considered in deterministic sensitivity analyses.

Table 6-5: Base case transition probabilities

| Transition probability | Value | Distribution | Source |
|---|---|---|---|
| Mild HCV to moderate HCV | 0.025 | Beta (α=38.086, β=1485.4) | Shepherd 2007[21] |
| Moderate HCV to CC | 0.037 | Beta (α=26.905, β=700.3) | Shepherd 2007 |
| CC to DC | 0.039 | Beta (α=14.617, β=360.2) | Shepherd 2007 |
| CC to HCC | 0.014 | Beta (α=1.9326, β=136.1) | Shepherd 2007 |
| CC SVR to DC (relative risk vs. non-SVR) | 0.07 | Lognormal (95% CI 0.03, 0.2) | Van der Meer 2012[33] |
| CC SVR to HCC (relative risk vs. non-SVR) | 0.23 | Lognormal (95% CI 0.16, 0.35) | Morgan 2013[34] |
| DC to HCC | 0.014 | Beta (α=1.9326, β=136.1074) | Shepherd 2007 |
| DC to liver transplant (LT) | 0.03 | Beta (α=6.5256, β=210.9945) | Shepherd 2007 |
| DC to death | 0.13 | Beta (α=147.03, β=983.97) | Shepherd 2007 |
| HCC to LT | 0.03 | Beta (α=6.5256, β=210.9945) | Shepherd 2007 |
| HCC to death | 0.43 | Beta (α=117.1033, β=155.23) | Shepherd 2007 |
| Post LT (0-12 months) to death | 0.21 | Beta (α=16.2762, β=61.2294) | Shepherd 2007 |
| Post LT (>12 months) to death | 0.057 | Beta (α=22.9017, β=378.8825) | Shepherd 2007 |

Table 6-6: Sensitivity analysis transition probabilities, derived from Harris et al.[12]

| Health state | Age | Value |
|---|---|---|
| Mild HCV to moderate HCV | 30-39 | 0.025 |
| | 40-49 | 0.042 |
| | 50-59 | 0.129 |
| | 60-69 | 0.110 |
| | 70+ | 0.130 |
| Moderate HCV to compensated cirrhosis | 30-39 | 0.062 |
| | 40-49 | 0.068 |
| | 50-59 | 0.089 |
| | 60-69 | 0.062 |
| | 70+ | 0.081 |
| Compensated cirrhosis to DC | 30-39 | 0.133 |
| | 40-49 | 0.106 |
| | 50-59 | 0.088 |
| | 60-69 | 0.082 |
| | 70+ | 0.082 |
| Compensated cirrhosis to HCC | 30-39 | 0.004 |
| | 40-49 | 0.007 |
| | 50-59 | 0.017 |
| | 60-69 | 0.039 |
| | 70+ | 0.044 |

### 6.3.7 Sensitivity analyses

Various deterministic one-way sensitivity analyses were undertaken by varying one parameter and observing the influence upon the ICER. These parameters considered in these analyses have been described in their relevant methods sections.

Probabilistic sensitivity analyses were performed to consider all parameter uncertainty within the model concurrently using 10,000 Monte Carlo simulations. A cost-effectiveness acceptability curve demonstrates the proportion of simulations in which the intervention was cost-effective, across a range of willingness to pay thresholds.

An ANCOVA analysis was also performed using the results of the probabilistic sensitivity analysis to consider the percentage of change in incremental costs and incremental QALYs explained by the uncertainty in each parameter (or group of parameters).

Threshold analyses were performed to consider the parameter values at which the cost-effectiveness decision changes, at a £20,000 willingness to pay threshold. This identified the minimum increase in antibody testing required, the minimum prevalence of HCV, and the maximum reinfection rate at which the intervention would remain cost-effective.

## 6.4 Results

### 6.4.1 Base case results

The costs and outcomes associated with the testing intervention are shown in Table 6-7. The testing intervention was highly cost-effective in the base case analysis, with an ICER of £6,916 per QALY gained.

Table 6-7: Base case cost-effectiveness results, per individual in the model

| Testing option | Total costs | Total QALYs | Incr. costs | Incr. QALYs | ICER |
|---|---|---|---|---|---|
| Control arm | £417 | 16.2207 | | | |
| Intervention arm | £424 | 16.2218 | £7.45 | 0.00108 | £6,916 |

### 6.4.2 Deterministic sensitivity analysis

The results of the one-way deterministic sensitivity analyses are presented in Table 6-8.

The analyses which had the greatest impact on the results were those which reduced the linkage to care and the proportion receiving treatment following a positive HCV RNA test. The intervention remained cost-effective, but very close to the cost-effectiveness threshold, when assuming that the intervention had no effect on the linkage to care, with an ICER of £19,289 per QALY gained. An analysis which considered a lower proportion of patients receiving treatment after being referred to hepatology care (60% rather than 90% in the base case analysis), the ICER increased to £11,350 per QALY gained. When considering a lower annual probability of testing in the control arm, equal to the probability of testing in the pre-trial baseline period (6.6%), the ICER increased to £8,970 per QALY gained. This analysis resulted in an annual testing probability of 10.3% in the intervention group, as the relative effect of the intervention on testing rates remained the same, albeit that the absolute effect reduced. Assuming a lower utility, similar to the expected utility amongst PWID, also increased the ICER to £8,463 per QALY gained.

Table 6-8: Deterministic sensitivity analyses

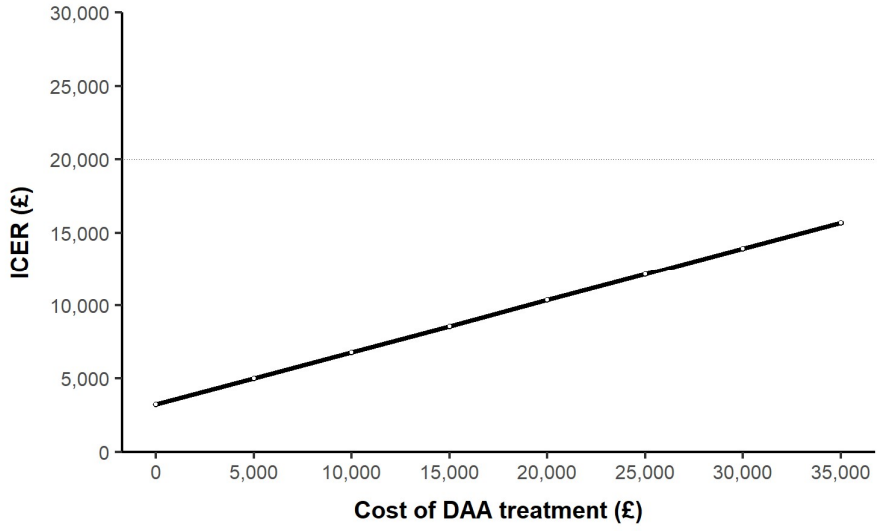
| Sensitivity analysis | Total costs | Total QALYs | Incr. costs | Incr. QALYs | ICER |
|---|---|---|---|---|---|
| **Training costs excluded** | | | | | |
| Control arm | £417 | 16.2207 | | | |
| Intervention arm | £423 | 16.2218 | £6.23 | 0.00108 | £5,783 |
| **No treatment effect for linkage to care (referral and attendance)** | | | | | |
| Control arm | £416 | 16.2212 | | | |
| Intervention arm | £424 | 16.2216 | £8.56 | 0.00044 | £19,289 |
| **Proportion referred to care receiving treatment (60%)** | | | | | |
| Control arm | £423 | 16.2170 | | | |
| Intervention arm | £431 | 16.2177 | £8.15 | 0.00072 | £11,350 |
| **£500 incentive for general practice (£0.84 per patient included)** | | | | | |
| Control arm | £417 | 16.2207 | | | |
| Intervention arm | £425 | 16.2218 | £8.29 | 0.00108 | £7,697 |
| **Annual probability of testing in control group (6.6%)†** | | | | | |
| Control arm | £386 | 16.2187 | | | |
| Intervention arm | £393 | 16.2195 | £7.28 | 0.00081 | £8,970 |
| **£5000 per DAA** | | | | | |
| Control arm | £389 | 16.2207 | | | |
| Intervention arm | £395 | 16.2218 | £5.52 | 0.00108 | £5,126 |
| **Utility adjusted to PWID utilities (all multiplied by 0.82)** | | | | | |
| Control arm | £417 | 13.2557 | | | |
| Intervention arm | £424 | 13.2565 | £7.45 | 0.00088 | £8,463 |
| **Treatment effect for higher yield of antibody positives in intervention arm** | | | | | |
| Control arm | £417 | 16.2207 | | | |
| Intervention arm | £429 | 16.2223 | £12.14 | 0.00159 | £7,635 |
| **PCR results from PHE RNA positive statistics (rather than with trial)** | | | | | |
| Control arm | £732 | 16.1298 | | | |
| Intervention arm | £742 | 16.1318 | £10.43 | 0.00193 | £5,396 |
| **Transition probabilities derived from back-calculation model** | | | | | |
| Control arm | £655 | 16.1843 | | | |
| Intervention arm | £658 | 16.1862 | £2.13 | 0.00196 | £1,089 |

†This results in an annual probability of 10.3% in the intervention arm

The intervention was more cost-effective when excluding training costs (ICER £5,783 per QALY gained), assuming lower HCV drug costs (£5,126 per QALY), assuming the proportion of tests that were PCR positive being the same as national testing statistics (£5,396 per QALY), or when considering alternative HCV progression rates (£1,089 per QALY). Increasing the HCV test yield increased the ICER to £7,635 per QALY, due to the higher costs and higher benefits associated with testing, although this resulted in a higher incremental net monetary benefit for the intervention. Although there were no incentives provided for general practices participating in the HepCATT intervention, it would have remained cost-effective if a £500 incentive per practice was included (£7,697 per QALY) or if an incentive of £1000 was used (£8,477 per QALY).

When considering the impact of the discount on DAA costs, the HepCATT intervention would have remained cost-effective even if the cost was increased to £35,000 per course (Figure 6-2).

Figure 6-2: Incremental cost-effectiveness ratio across DAA treatment costs




### 6.4.3 Threshold analyses

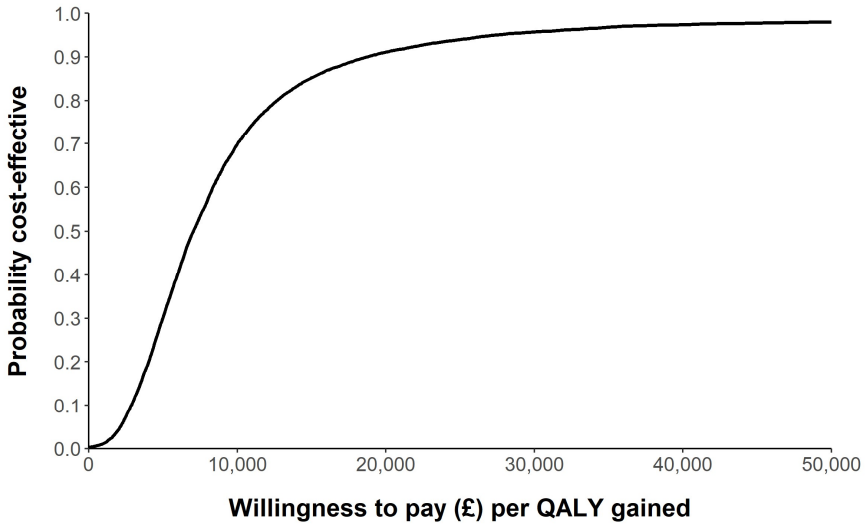
Since the HepCATT intervention resulted in two intervention effects (increased probability of testing and increased probability of linkage to care following a positive HCV RNA test), we considered threshold analyses of each intervention effect individually. The intervention

remained cost-effective when the intervention led to higher linkage to care, even if the HCV antibody testing rate was equal for both arms, with an ICER of £4,105. When assuming that the linkage to care was equal for both groups, the intervention would be cost-effectiveness with an antibody testing was a risk ratio of 1.53 or higher (i.e. a 53% increase in HCV testing). When considering the HCV prevalence amongst those tested, the intervention would remain cost-effective at an HCV antibody prevalence of 1.2% or higher. This equates to 0.46% HCV RNA prevalence, using the proportion of HCV RNA positives amongst HCV antibody positives derived from the trial. Finally, when considering the potential for reinfection, the intervention remained cost-effective whilst the annual probability of reinfection was equal to or less than 9.1%.

### 6.4.4 Probabilistic analyses

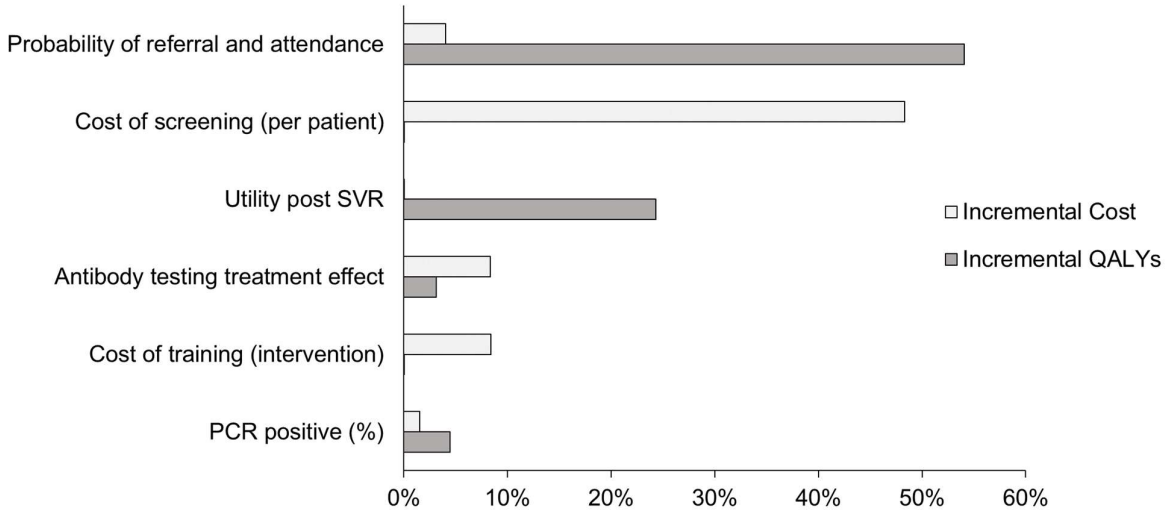
In the base case probabilistic sensitivity analysis, the intervention was 90.8% likely to be cost-effective at the £20,000 per QALY threshold (Figure 6-3). In a sensitivity analysis excluding the initial staff training costs, the intervention was 93.3% likely to be cost-effective.

Figure 6-3: Cost-effectiveness acceptability curve, using the base case probabilistic sensitivity analysis results



An ANCOVA analysis showed the parameters that caused the most variation in the probabilistic model results were the costs of screening per patient, which accounted for 48% of the uncertainty in the incremental costs, and the probability of referral and attendance, which caused around 54% of the variation in the incremental QALYs (Figure 6-4). The utility values following SVR also had a considerable impact on the incremental QALYs estimated, accounting for approximately 24% of the uncertainty in incremental QALYs.

Figure 6-4: Analysis of covariance (ANCOVA) for probabilistic sensitivity analysis



## 6.5 Discussion

### 6.5.1 Main results

The HepCATT intervention resulted in a modest increase in testing and improved the proportion of patients referred to and attending their appointments following a positive HCV diagnosis. The results of the economic analysis demonstrate that the intervention was estimated to be highly cost-effective. Moreover, there was little uncertainty in this conclusion, as demonstrated in the probabilistic sensitivity analysis, and by the fact that the intervention remained cost-effective across a range of sensitivity analyses. Although two intervention effects were included in the analysis (probability of testing, and probability of referral and attendance), the intervention would have remained cost-effective with either of these intervention effects alone. As such, there is clear evidence that an algorithm-based identification of those at higher risk of HCV can used to help identify those who should receive testing in primary care. In addition to this economic analysis, qualitative evidence has also shown that the intervention is acceptable and that practices were willing to engage with the intervention.[37]

Whilst the HepCATT intervention did not include incentives, when incentives of £500 or £1,000 per general practice were included in the economic analysis, this only resulted in a small impact upon the ICER, and the intervention remained highly cost-effective. When considering the implementation of the algorithm in a real-world setting, such incentives could be used to ensure that the effectiveness of the intervention is maintained or even improved.

### 6.5.2 Strengths and limitations

This economic analysis has a number of strengths, particularly when compared alongside other economic evaluations of HCV testing strategies. The main strength of the analysis is the availability of practice level, randomised controlled study data to estimate the impact of the testing intervention. As such, the results of this analysis can be considered more robust compared to economics analyses of HCV testing strategies using studies without a control arm (or studies lacking any empirical data at all).

Despite the strength of the study design upon which this economic evaluation is based, there are several limitations of the data derived from the trial. Firstly, there was a large uplift in testing amongst the control group during the intervention period, compared to a baseline

period prior of the trial. In the control group, 3.3% of those identified at high risk were tested in the six months leading up to the trial. Over the one-year trial period (i.e. twice the length of time as the baseline period), 10.2% of those at high risk received testing, representing a considerable increase for the control group. This suggests that there may have been some contamination between the two treatment arms, particularly given many of the practices were in the Bristol region. There have previously been national initiatives to re-engage patients who have previously been diagnosed with HCV but are not engaged with treatment services, which occurred primarily through general practices, although PHE documents suggest that re-engagement exercise may have formally begun after the period in which the HepCATT trial was conducted.[38] Alternatively, it may have been as a result of other local case-finding or re-engagement initiatives. Despite this limitation of the study, it is likely to have only diluted the effect of the intervention (rather than having overestimated it), in which case the intervention would be even more cost-effective than this analysis suggests.

Another limitation of this analysis is that it evaluated the impact of the overall intervention and did not consider the cost-effectiveness of the intervention stratified by each of the high-risk codes used within the algorithm. The prevalence of HCV infection differed across these groups, showing there was some variation in the likelihood of testing positive following identification depending on risk factors, albeit that for some groups the prevalence was somewhat uncertain given the low number of tests performed. It is also possible that the linkage to care would differ, although a much larger study would be required to evaluate such differences.

There was also no consideration as to the effectiveness of the algorithm with regards to identifying patients with HCV. There was no testing performed in those who were not identified as being at higher risk of HCV, so it was not possible to compare the prevalence of those with and without HCV risk factors. However, the prevalence in those not identified by the algorithm is likely to be far lower than the 5.5% testing HCV antibody positive amongst those identified as being at high risk. Given the lack of testing in those without the pre-defined risk factor codes used in this study, there could yet be other codes, or combinations of codes, which could have been used to identify others who are also have at a higher risk of HCV. Considering the intervention was highly cost-effective, and remained cost-effective at lower prevalence's of HCV infection (≥1.2% HCV antibody positive), it is likely that testing would remain cost-effective if the invitation list was expanded, even if the resulting group invited to receive testing was a lower overall risk than that of identified during the HepCATT intervention (and hence likely to have a lower test positivity rate). Whilst expanding the list to groups for

those remaining above the prevalence threshold at the margin (i.e. each medical code introduced is above or equal to the prevalence threshold) would increase the overall ICER, most importantly, it would result in a higher net benefit. This would also help spread the fixed costs associated with the intervention (i.e. the cost of the software) over a larger number of people included and tested. When considering other potential groups that could be included in the algorithm, economic evidence from testing of migrants in primary care and screening everyone in particular birth cohorts (as presented in Chapter 5) could be considered.[13,24]

### 6.5.3 Other Evidence

The original cost-effectiveness model underpinning NICE guidance for HCV testing in primary care was based on a non-randomised pilot study in 8 practices with high levels of deprivation.[39] The study used financial incentives for participation, and involved searching practice lists for a smaller sub-group of patients with opioid dependence history. Testing was deemed cost-effective, with an ICER of £13,900, higher than that estimated from the base case ICER of this study.

Another recent trial in primary care (HepFREE) found that HCV testing in migrants in a primary care setting was also cost-effective, with an ICER of £8,540 per QALY gained, similar to this analysis.[24] The trial was performed in areas with high levels of migrants, and also involved an algorithm to identify those eligible for testing. The trial provided additional clinical support and also provided a modest incentive for general practices to run the algorithm (£500), neither of which were provided as part of the HepCATT intervention. If the same incentive had been used for the HepCATT intervention, it would have remained cost-effective, with an ICER of £7,697, and would have remained cost-effective with larger incentives too. Furthermore, such incentives may have potentially increased the effectiveness of the intervention in terms of reaching more patients, which in turn would reduce the ICER, and thus this could be considered a conservative estimate.

A previous study in Ireland found an increase in HCV testing in general practices that were encouraged to follow clinical guidelines recommending HCV testing for patients on methadone, although there was no economic evidence available from the study.[40] However, in the UK it has been established that case-finding and early treatment for opioid dependent patients is highly cost-effective and there are multiple alternative case-finding and care pathways being tested and developed in the community for this population groups – including through prisons, pharmacies, needle exchange services, and homeless services.[28,41,42] Yet these

care-pathways will not capture many of those individuals identified by the HepCATT intervention. This includes people in primary care who may no longer be opioid dependent or on opioid agonist treatment, or those with other historical risk factors, which means they may not attend any services were routine HCV testing is performed. Furthermore, these historical factors are unlikely to be discussed or considered in a regular GP consultation, meaning a HCV test is unlikely to be offered, at least until symptoms of HCV develop, usually at more advanced stages of the infection.[8]

In the US, birth cohort screening is offered in a primary care setting.[43,44] An economic analysis of a hypothetical birth cohort screening intervention in primary care in the UK has also been considered as part of this thesis. However, there is a high degree of uncertainty around whether this testing strategy would be cost-effective, particularly given the lack of empirical data, and the far low prevalence expected amongst those who would receive testing compared to those identified by the algorithm in the HepCATT intervention.

Whilst there are other viable alternatives or complementary testing strategies that could be pursued for HCV testing in primary care, these strategies should not be considered as exclusive options. In principle, all of these primary care testing strategies identify specific groups attending primary care services, and offer HCV testing. The main difference between these strategies is how those at risk are identified and offered testing. Future research should focus on how primary care testing can combine the various risk groups across these interventions (i.e. history of HCV risk factors, ethnicity, and date of birth), and potentially others risk factors (or combinations of them), into a comprehensive primary care testing strategy. If an algorithm-based identification approach is preferable, then aspects of these other testing strategies could be incorporated (i.e. by expanding testing to migrants or birth cohorts). This would also help spread the fixed costs of the software used to identify those at risk, improving the efficiency of this approach.

## 6.6 Conclusion

The HepCATT intervention was highly cost-effective, and the economic findings were robust across a range of sensitivity analyses. This economic evidence complements the qualitative evidence showing that practices were willing to engage with the intervention.[37] Although the

increase in testing was relatively modest, the economic and qualitative evidence supports the implementation of an algorithm based testing intervention in primary care.

Further research should consider how the algorithm could be expanded to include other groups at elevated risk of HCV, whilst ensuring the intervention remains cost-effective. For example, the algorithm could be expanded to include migrants, to whom testing in primary care is highly likely to be cost-effective, and to include other groups that may have an elevated risk of HCV. Consideration should also be given to incentives for general practices to ensure that the effectiveness of the intervention is maintained (or increased) when implemented at full scale, as such incentives would not jeopardise the cost-effectiveness of the intervention.

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# 7 An Economic Evaluation of the Cost-Effectiveness of Opt-Out Hepatitis B and Hepatitis C Testing in an Emergency Department Setting in the United Kingdom

## 7.1 Overview of Research Paper 3

In this Chapter, the cost-effectiveness of universal, opt-out HCV and HBV testing in the ED is evaluated. Previous studies have demonstrated that the prevalence of HCV and HBV is elevated amongst hospital ED attendees compared to the general population. Although there is geographical variation, the prevalence of these infections can be as high as 2.7% in some areas.[1-3] For some people the ED may be the only healthcare setting which they attend, especially if they are not registered with a GP or only seek healthcare when they have an immediate health issue, or in an emergency. Underserved groups with more complex healthcare needs, such as those who are homeless or PWID, are also more likely to attend the ED than other groups, which may also explain the elevated prevalence of HCV and HBV amongst attendees. Despite this, the ED is a healthcare setting which the general population will attend, even if some groups attend more frequently than others.

Similar to the Chapters 5 and 6, this economic evaluation addresses an area of interest outlined in the NICE hepatitis testing guidelines.[4] In their 2017 surveillance report, NICE stated that although the prevalence of HCV and HBV is higher in the ED, there was no evidence of the effectiveness of offering hepatitis testing in this setting.[5] Since this report, several small studies evaluating the effectiveness of HCV and HBV testing in the ED have been published.[3,6-8] Many EDs already perform routine opt-out testing for HIV, and therefore there is interest in whether this routine testing should be expanded to include HCV and HBV testing too.

I performed an economic evaluation which used data from these studies to consider whether HCV and HBV testing in the ED is likely to be cost-effective. The analysis considered both infections because the studies evaluated testing for both hepatitis infections in addition to HIV testing, and because there is a willingness to perform testing in the ED as a BBV screen. This BBV screen would include tests for HIV, HCV, and HBV, all performed on existing blood samples taken as part of routine care in the ED. Three different studies of ED-based hepatitis testing were identified in the UK, and all of them reported the results of both HBV and HCV tests from

the same blood sample, providing further justification that the economic analysis should consider both infections.

This can help to align hepatitis testing guidelines with the current testing guidelines for HIV, whereby universal opt-out testing is recommended by NICE at a prevalence of 0.2% or higher.[9] There is currently no equivalent threshold prevalence at which HCV or HBV testing is recommended by NICE. As such, there remains a clear gap in the testing policy recommendations for both HCV and HBV testing in the ED. Moreover, the introduction of a potential BBV screen would require cost-effectiveness analyses for both HCV and HBV to consider whether one, or both, could be recommended alongside HIV testing in the ED, and if so, what the prevalence threshold should be for these tests to be cost-effective, and therefore recommended.

Despite the potential to add both HBV and HCV testing onto the existing recommendations for HIV testing, the cost-effectiveness model developed in this analysis considered testing for both HCV and HBV as separate decisions, since there were no shared costs between them. This is because testing for one infection could be cost-effective whilst testing for the other is not. This is particularly important given the geographical differences in prevalence of HCV and HBV, which are not necessarily correlated. Therefore I assessed the threshold prevalence at which testing is likely to be cost-effective for both HCV and HBV individually.

This Chapter, along with the two previous Chapters, fulfils the second objective of this thesis. My role included identifying the input data sources, developing the economic model, and performing the analyses. I wrote the draft version of the manuscript, and incorporated comments from co-authors into the manuscript. I submitted the manuscript and addressed peer review comments. The analysis received ethical approval from the LSHTM Ethics Committee (Project ID: 14668).

This study was published in Value in Health as an open-access article, in August 2020. It was published under a CC BY-NC-ND license, which allows the article to be shared or re-distributed in any format, as long as the work is properly cited.[10] The full reference for the article is:

*Williams J, Vickerman P, Douthwaite S, Nebbia G, Hunter L, Wong T, et al. An Economic Evaluation of the Cost-Effectiveness of Opt-Out Hepatitis B and Hepatitis C Testing in an Emergency Department Setting in the United Kingdom. Value in Health. 2020;23(8):1003-11*

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# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

## SECTION A – Student Details

| | | | |
|---|---|---|---|
| **Student ID Number** | 1405199 | **Title** | Mr |
| **First Name(s)** | Jack | | |
| **Surname/Family Name** | Williams | | |
| **Thesis Title** | Assessing the cost-effectiveness of interventions to expand hepatitis C testing to help achieve elimination targets in the United Kingdom | | |
| **Primary Supervisor** | Alec Miners | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

## SECTION B – Paper already published

| | | | |
|---|---|---|---|
| Where was the work published? | Value in Health | | |
| When was the work published? | August 2020 | | |
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| | |
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**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role included identification of the input data sources, developing the economic model, and performing the analyses. I wrote the draft version of the manuscript, and incorporated comments from co-authors into the manuscript. I submitted the manuscript, and addressed peer review comments. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | Jack Williams |
| **Date** | 18/02/2022 |

| | |
|---|---|
| **Supervisor Signature** | Alec Miners |
| **Date** | 25/02/2022 |

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Economic Evaluation

# An Economic Evaluation of the Cost-Effectiveness of Opt-Out Hepatitis B and Hepatitis C Testing in an Emergency Department Setting in the United Kingdom

Jack Williams, MSc,* Peter Vickerman, DPhil, Sam Douthwaite, MBChB, MRCP, Gaia Nebbia, MRCP, FRCPath, PhD, Laura Hunter, MBChB, FRCEM, Terry Wong, MD FRCP, Murad Ruf, MD MPH FFPH, Alec Miners, PhD

## ABSTRACT

*Objectives:* The prevalence of hepatitis is high in emergency department (ED) attendees in the United Kingdom, with a prevalence of up to 2% for hepatitis B (HBV) HBsAg, and 2.9% for hepatitis C (HCV) RNA. The aim of this paper is to perform an economic evaluation of opt-out ED-based HCV and HBV testing.

*Methods:* A Markov model was developed to analyze the cost-effectiveness of opt-out HCV and HBV testing in EDs in the UK. The model used data from UK studies of ED testing to parameterize the HCV and HBV prevalence (1.4% HCV RNA, 0.84% HBsAg), test costs, and intervention effects (contact rates and linkage to care). For HCV, we used an antibody test cost of £3.64 and RNA test cost of £68.38, and assumed direct-acting antiviral treatment costs of £10 000. For HBV, we used a combined HBsAg and confirmatory test cost of £5.79. We also modeled the minimum prevalence of HCV (RNA-positive) and HBV (HBsAg) required to make ED testing cost-effective at a £20 000 willingness to pay per quality-adjusted life-year threshold.

*Results:* In the base case, ED testing was highly cost-effective, with HCV and HBV testing costing £8019 and £9858 per quality-adjusted life-year gained, respectively. HCV and HBV ED testing remained cost-effective at 0.25% HCV RNA or HBsAg prevalence or higher.

*Conclusions:* Emergency department testing for HCV and HBV is highly likely to be cost-effective in many areas across the UK depending on their prevalence. Ongoing studies will help evaluate ED testing across different regions to inform testing guidelines.

*Keywords:* hepatitis B, hepatitis C, cost-benefit analysis, emergency service hospital, diagnostic tests, routine, mass screening.

VALUE HEALTH. 2020; 23(8):1003–1011

## Introduction

Across Europe there are approximately 29 million people living with the hepatitis C virus (HCV) or hepatitis B virus (HBV).[1] These individuals are often asymptomatic in the early stages of infection, with disease progression leading to liver complications including cirrhosis, hepatocellular carcinoma, and liver failure, and eventually causing death.[2,3] Despite the United Kingdom having a lower estimated prevalence of HCV and HBV compared with the European average, there are approximately 210 000 individuals living with HCV (0.3% among the general population) despite curative direct-acting antiviral (DAA) treatments available, and an estimated 440 000 individuals living with HBV (0.7% among the general population), with only 19% diagnosed.[4–6]

The United Kingdom has adopted the World Health Organization targets to eliminate viral hepatitis as a major public health threat by 2030, which includes diagnosing 90% of cases and providing treatment to 80% of diagnosed individuals (where eligible).[7] Moreover, with DAA treatments for HCV achieving high cure rates (sustained virological response [SVR]) at decreasing prices, and generic HBV treatments now available, there is considerable scope for case-finding activities to be cost-effective.[7–9]

In Europe, current recommendations for HCV and HBV case-finding activities are largely risk-based, with routine testing limited to settings attended by high-risk populations, such as drug treatment services, prisons, and sexual health centres.[10,11] HBV testing is also routinely performed in antenatal services to prevent mother-to-child transmission.[11] Emerging UK evidence suggests an additional setting for HCV and HBV case-finding is emergency departments (EDs), as the prevalence of viral hepatitis tends to be higher among ED attendees (up to 2.9% HCV RNA, and 2% HBV HBsAg) compared with the general population, as a result of higher attendance rates among marginalized communities.[5,12–17] In 2019, 25.6 million people attended EDs in England, with

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approximately 40% receiving blood tests as part of their routine care, providing a valuable opportunity for bloodborne virus (BBV) testing.[14,15,18] The National Institute for Health and Care Excellence (NICE) currently recommends HIV testing in EDs for areas with prevalence of ≥0.2%.[19] Nevertheless, there is currently no equivalent UK guidance for HCV or HBV testing in EDs owing to a lack of cost-effectiveness evidence, although NICE did recently highlight ED testing as an area of interest for its next surveillance point.[20]

The aim of this article is to perform a cost-effectiveness analysis of opt-out ED-based HCV and HBV testing and linkage to care for all individuals over age 16, and to consider the prevalence thresholds above which this intervention may be cost-effective in the United Kingdom.

## Methods

### Model Analysis and Decision Problem

We developed a decision model to analyze opt-out HCV and HBV testing, performed for all individuals attending the ED and receiving a blood test (as part of routine care) who did not opt out of hepatitis testing. Emergency department testing for HCV and HBV was compared with no ED testing, which consisted of a background rate of hepatitis testing, occurring in other settings, only. Opting out of testing involved the patient declining testing when informed by the clinician that a viral hepatitis test would be performed. As there are no shared costs between the 2 tests, the model considered opt-out testing of HCV and HBV separately, both compared with no immediate testing. The decision model consists of a decision tree, with HBV and HCV testing options, which feed into 3 distinct state transition Markov models representing chronic HBV, chronic HCV, and no infection. We assumed all individuals started at an age of 45 years based on data of BBV testing in EDs from the UK.[14,15] For each Markov model, patients move between discrete health states using an annual cycle length. The analysis was performed from the perspective of the UK National Health Service (NHS), and all results are presented in pounds (£, GBP) for 2017. Outcomes were measured in quality-adjusted life-years (QALYs). A lifetime time horizon was used, and all costs and outcomes were discounted at 3.5%, as per NICE guidelines.[21] Results are presented as incremental cost effectiveness ratios (ICERs) per QALY gained.

### Model Structure and Parameterization

To capture the impact of the intervention, we identified 3 UK studies of ED-based HCV and HBV testing and linkage to care. We included 2 studies that performed testing and reflex (ie, same sample) confirmatory testing, with ED-based linkage to care.[14,15] We did not include a study that performed ED testing without reflex confirmatory testing, because individuals from this study were required to return to a local sexual health service for confirmatory testing, before being linked to care.[22]

#### Model Structure

A decision tree was developed to determine the impact of the intervention on testing and subsequent linkage to care. It captured the following: outcome of test (HBsAg+, HCV RNA+, negative), diagnosis status (new diagnosis vs previously known diagnosis), proportion of patients contacted after a positive diagnosis, and the probability of attendance to referral. The proportion of patients receiving treatment was captured in the HCV model. For the HBV model, the model captures the proportion of individuals that engage in care, as not all individuals identified will require immediate treatment. The model structures are shown and described in Appendix Figures 1-4 in the Supplementary Materials found at https://doi.org/10.1016/j.jval.2020.03.014.

For individuals with HCV, an estimated 54.5% of new ED diagnoses that were successfully contacted were current- or ex-people who inject drugs (PWID).[14] Risk factor information was not available for patients who were not contacted. A lower proportion representing only current-PWIDs (27.3%) was also considered.[14] For HCV-infected PWIDs, the disease progression, reinfection rate, and background risk of mortality differed compared with non-PWIDs. We did not consider PWID status in the HBV model because this was not reported as a risk factor in the same ED study.[14] The model did not capture the benefit associated with reduced onward transmission after treatment. Nor did the model consider the potential for HCV/HBV coinfection to occur in patients, as this was rare across patients in both ED testing studies (<1% of those testing positive).[14,15]

#### Prevalence

The combined prevalence from the included studies was 1.4% HCV RNA prevalence (132/9423) and 0.84% HBsAg prevalence (80/9476).[14,15] One ED study reported HCV antigen prevalence; however, we assumed these would be RNA positive. These were varied in threshold sensitivity analyses to estimate the minimum prevalence thresholds at which the intervention remains cost-effective, since BBV prevalence varies geographically (ranging from 0.6%-2.9% for HCV and 0%-2% for HBV across UK studies).[14–17]

We also performed a sensitivity analysis of testing by age group (16-29, 30-49, 50-69, 70+) using stratified prevalence estimates.[14,15] Other model parameters were assumed to remain unchanged due to a lack of age-specific data (see Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.014).

#### Linkage to care

For individuals testing positive in the ED, from the 2 included studies we derived the proportion that were successfully contacted (*contact rate*), the proportion requiring linkage to care (defined as those not previously diagnosed, or those previously diagnosed but not currently linked to care), the proportion attending their referral after being contacted, and the proportion engaging in care.[14,15] Different linkage to care parameters were explored in sensitivity analyses.

For those testing HCV RNA positive, it was estimated that 49.5% would require linkage to care (new diagnoses, or known diagnoses disengaged with care), of which 64.7% would be successfully contacted. Of those contacted, 90.3% would attend at least 1 clinic appointment, of which 85.7% would engage in care. We assumed that all HCV patients engaged in care would receive DAA treatment.

Of those testing HBsAg positive, it was estimated that 52.4% would require linkage to care, of which 64.7% would be successfully contacted. Of those contacted, 90.3% would attend at least 1 clinic appointment, of which 85.7% would engage in care. Patients engaged in care were assumed to receive treatment if indicated, (ie, in active disease or cirrhotic health states).

#### Treatment and outcomes

For HCV, individuals received DAA treatment, with SVR rates (91%-93%) derived from a UK national cohort.[23] There were no treatment restrictions for PWID, as per current NHS policy. We assumed those not achieving SVR with their first treatment would be re-treated once.

For HBV, treatment was assumed to be provided to those presenting with active disease, and all patients with cirrhosis,

based on NICE guidelines.[24] Various clinical studies informed the treatment outcomes for HBV, and NICE guidelines informed treatment stopping rules (based on HBeAg status and cirrhosis), with full details provided in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.014.[24–29] In summary, individuals were assumed to be treated with peginterferon alfa-2a (PegIFNα) and tenofovir disoproxil fumarate (TDF), and 13% of HBeAg-positive and 1% of HBeAg-negative individuals received emtricitabine alongside TDF, based on 1 clinical study used in our analysis.[26] Treatment aims to achieve HBsAg seroconversion, or HBeAg seroconversion (for HBeAg-positive individuals) or inactive disease (for HBeAg-negative individuals). We also performed a sensitivity analysis in which TDF was the first and only treatment used, without PegIFNα. We modeled the likelihood that some HBV patients will disengage from treatment over time as has been observed in long-term studies of patients on HBV treatment (Table 1). This is to remain conservative regarding the benefit associated with identifying new HBV patients, as was assessed in a sensitivity analysis.

### Transition probabilities

Transition probabilities capturing disease progression from early disease health states up to the compensated cirrhosis health state were derived from a meta-regression of HCV progression rates.[30] Equivalent transitions for those identified as PWIDs with HCV were derived from a study estimating PWID disease progression.[31] For compensated cirrhosis and more advanced states, a previous health technology assessment (HTA) was used for transitions between health states.[32]

For HBV, HBeAg status-specific transition probabilities were derived from a previous HTA performed in the United Kingdom, and have been used for previous economic models.[33,34] For all individuals in the model receiving treatment, there was no risk of HBV-related mortality (until they progressed beyond compensated cirrhosis), as mortality is comparable to the general population.[35] Details on HBV transition probabilities are available in the Appendix Tables 2 and 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.014.

For both models, a background rate of mortality derived from UK life tables was applied to all health states, in addition to mortality associated with disease progression.[36] For PWIDs, a standardized mortality ratio of 7.8 was applied to background mortality, with injecting drug use assumed to cease after 11 years (Table 1).[37,38]

### Background rate of testing

The annual background probability of testing was derived from Public Health England sentinel surveillance of BBV laboratory diagnoses, with 40% estimated coverage in the population, estimated from UK national population data.[36,39] The annual HCV testing probability (considering testing from all settings) was calculated as 1.9%, whereas the annual HBV testing probability, derived from non-antenatal screening tests, was 2%.

The probability of testing is likely to be higher for those currently infected, since the yield of positive tests across the UK observed in national statistics (1.4% for HCV and 1% for HBV) differs from prevalence among testers in the ED setting.[39] We adjusted the prevalence yield among background testing to account for the higher likelihood of testing in infected versus uninfected individuals to match the prevalence observed in national statistics.

For patients receiving background testing, it was assumed that the probability of referral and engaging in care was the same as for those individuals successfully contacted as part of the intervention.

### Utilities

For HCV, utility values for fibrosis and cirrhosis were derived from a UK RCT.[40] Pre-cirrhotic HBV utility values were derived from a previous economic evaluation, and subsequently used in a UK HTA.[34,41] Hepatitis B virus cirrhosis utility was assumed to be the same as HCV cirrhosis.[40] Utility values for advanced liver disease, for both HBV and HCV, were derived from a UK study of transplant patients.[42] A sensitivity analysis was performed considering a lower utility for PWIDs, using an alternative data source (maximum utility of 0.57, and therefore no utility benefit associated with achieving SVR).[43,44]

### Costs

Hepatitis C virus test costs were derived from another ED testing study from London.[22] Both included studies performed an initial antibody test (£3.64), but confirmatory testing differed; one used a reflex RNA test[14], wheras the other performed a reflex HCV antigen test.[15] The model assumed confirmatory RNA testing (£68.38) was performed for those testing antibody positive.[22] For HBV, we assumed a HBsAg test was initially performed, followed by a confirmatory reflex HBsAg neutralization assay, with a combined cost of £5.79, derived from a London hospital (Guy's and St Thomas' NHS Trust, personal email communication, November 2017). We assumed the same test costs for individuals receiving background testing. Because tests were performed on routinely collected blood samples, costs for retrieving blood were not included. The model assumes all diagnostic and confirmatory tests were 100% accurate.

The time required to contact patients was reported by one ED study to be 15.7 minutes for HCV and 6.7 minutes for HBV, and we assumed an additional 10 minutes for administration activities.[14] We assumed this was performed by a hospital nurse.[45] The contact costs were applied to all individuals testing positive. Background testing could occur in various settings but was assumed to be the cost of a general practitioner appointment (£31).[45] A lower hypothetical cost (£10) was also considered, since testing could occur in other healthcare settings, with lower costs compared with a general practitioner appointment.

National Health Service DAA treatment costs are confidential, but may be as low as £5000 per course of treatment.[8] Due to uncertainty, we assumed costs of £10 ,000 for DAA treatment, and £15 000 for re-treatment, incurred only upon SVR, as per NHS policy.[46] Hospital outpatient visits prior to treatment and outpatient treatment monitoring costs were applied (Table 2).[47] We show results across DAA costs of £0 to £35,000 in a sensitivity analysis (see Appendix Figure 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.014).

Hepatitis B virus treatment costs were derived from the British National Formulary. The cost of 48 weeks of PegIFNα was £3672, assumed for 1 annual cycle.[48] The NHS is using generic TDF, with an estimated annual cost of £578.[9,48,49] For those receiving TDF with emtricitabine, the annual cost was £1299.[26,48] Treatment monitoring costs for HBV were assumed to be captured in health state costs.

Health state costs were derived from previous HTAs for HBV and HCV.[32,33,45] Individuals who were undiagnosed or diagnosed but not engaged in care were assumed to not accrue health state costs until they are diagnosed or reach decompensated cirrhosis or hepatocellular carcinoma health states.

**Table 1.** Base case decision parameters for intervention effects.

| Base case probabilities | Mean value | Distribution | Source |
|---|---|---|---|
| HCV parameters | | | |
| Prevalence (RNA+) | 1.4% | Beta (α = 132, β = 9291) | 14,15 |
| Proportion of Ab+ testing RNA+ on reflex test | 62.9% | Beta (α = 132, β = 78) | 14,15 |
| Proportion of diagnoses requiring linkage to care* | 49.5% | Beta (α = 55, β = 56) | 14,15 |
| Proportion contacted | 61.8% | Beta (α = 47, β = 29) | 14,15 |
| Proportion attending referral | 85.1% | Beta (α = 40, β = 7) | 14,15 |
| Proportion receiving treatment, post-referral | 62.5% | Beta (α = 25, β = 15) | 14,15 |
| Background testing probability (annual) | 1.9% | Beta (α = 347 440, β = 17 645 144) | 36,39 |
| Background testing yield (RNA+ prevalence among testers) | 1.4% | Beta (α = 4982, β = 342 458) | 39 |
| Proportion F0 | 22.7% | Dirichlet (F0,F1,F2,F3,cirrhotic)‡ | 14 |
| Proportion F1 | 22.7% | Dirichlet (F0,F1,F2,F3,cirrhotic)‡ | 14 |
| Proportion F2 | 22.7% | Dirichlet (F0,F1,F2,F3,cirrhotic)‡ | 14 |
| Proportion F3 | 15.9% | Dirichlet (F0,F1,F2,F3,cirrhotic)† | 14 |
| Proportion cirrhotic (F4) | 15.9% | Dirichlet (F0,F1,F2,F3,cirrhotic)† | 14 |
| Proportion current PWID | 54.5% | Beta (α = 6, β = 11) | 14 |
| Standard mortality ratio for IDU (while currently injecting) | 7.8 | Normal (95% CI = 5.4-10.8) | 37 |
| Duration of injecting (years) | 11 | Uniform (6, 16) | 38 |
| Annual probability of reinfection among PWIDs | 19.3% | Beta (α = 15, β = 62)‡ | 51 |
| HBV parameters | | | |
| Prevalence (HBsAg) | 0.84% | Beta (α = 80, β = 9396) | 14,15 |
| Proportion of diagnoses requiring linkage to care† | 52.4% | Beta (α = 33, β = 30) | 14,15 |
| Proportion contacted | 64.7% | Beta (α = 33, β = 18) | 14,15 |
| Proportion attending referral | 90.3% | Beta (α = 28, β = 3) | 14,15 |
| Proportion accepting treatment, post-referral (if indicated) | 85.7% | Beta (α = 24, β = 4) | 14,15 |
| Background testing probability (annual) | 2% | Beta (α = 355 585, β = 17 636 999) | 36,39 |
| Background testing yield (HBsAg prevalence among testers) | 1% | Beta (α = 3543, β = 352 042) | 39 |
| Proportion with inactive disease (HBeAg+ seroconverted or HBeAg- inactive disease) | 80% | Beta (α = 80, β = 20) | 52 |
| Proportion HBeAg+ | 14.5% | Beta (α = 71, β = 419) | 52 |
| Proportion cirrhotic (of those with active disease) | 12% | Beta (α = 3, β = 22) | 14 |
| Annual loss to follow-up from treatment | 3.3% | Uniform (1.7%, 5.0%) | 28 |

CI indicates confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug user; PWID, people who inject drugs.
*New diagnosis or known diagnosis not currently engaged in care.
†Sample size of 44, Dirichlet(10,10,10,7,7).
‡Annual probability calculated from 0.906 years mean follow-up (per person).

### Sensitivity Analyses

We performed probabilistic sensitivity analysis with values for each parameter sampled simultaneously from their distributions, and 10 000 individual simulations being performed (distributions available in Tables 1-2, and Appendix Tables 1-5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.014). Lastly, threshold analyses were undertaken to determine the minimum prevalence at which the intervention is cost-effective at a willingness-to-pay (WTP) threshold of £20 000 per QALY. We also performed threshold analyses for the prevalence required for cost-effectiveness across a range of patient contact rates and test costs (see Appendix Figure 8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.014).

## Results

### Base-Case Analysis

Under the base-case settings, testing for HCV and HBV were both highly cost-effective. The ICER for HCV testing was £8019 per QALY, and for HBV testing was £9858 per QALY (Table 3). At a WTP of £20 000 per QALY, the threshold analysis suggested testing for both HCV and HBV would be cost-effective at 0.25% or higher (Fig. 1). For both HCV and HBV, the ICER reduced and then plateaued at higher prevalence estimates, although was never cost saving.

### Deterministic Sensitivity Analyses

Hepatitis C virus and HBV testing remained cost-effective under all deterministic analyses, with the maximum ICER less than £12 000 per QALY (Fig. 2). For HCV, the ICER was sensitive to the cost of DAA treatment, the proportion of individuals tested that are current PWIDs, and the utility values for PWIDs. For both HCV and HBV testing, the results were also sensitive to the cost of the diagnostic test used, and the proportion of individuals requiring linkage to care. The results were somewhat sensitive to the proportion accepting treatment once referred and the proportion of diagnosed patients successfully contacted. The cost of contacting patients and the cost of background appointments had very little impact on the ICER for either HCV or HBV.

When considering ED testing by age, testing was highly cost-effective for those aged 16 to 69, but most cost-effective in those aged 30 to 69, with ICERs below £10 000 for both testing strategies. For those aged over 70 years (assuming a mean age of 80), the ICERs increased to £21 569 per QALY for HCV testing and £18 766 per QALY for HBV testing.

**Table 2.** Intervention and linkage to care costs.

| Costs | Mean cost | Distribution | Reference |
|---|---|---|---|
| HCV | | | |
| HCV antibody test | £3.64 | Uniform (£2.91, £4.37) | [22] |
| HCV RNA test | £68.38 | Uniform (£54.70, £82.06) | [22] |
| DAA treatment | £10 000 | N/A | [8] |
| DAA retreatment | £15 000 | N/A | [8]/assumption |
| Outpatient evaluation | £238 | Uniform (£190.40, £285.60) | [47] |
| Further outpatient evaluation | £262 | Uniform (£209.60, £314.40) | [47] |
| DAA treatment monitoring | £1310 | Uniform (£1048, £1572) | [47] |
| HBV | | | |
| HBsAg test (and confirmatory neutralization assay for HBsAg+) | £5.79 | Varied by test cost multiplier | Guy's and St Thomas' NHS Trust, personal email communication, November 2017. |
| PegIFNα (annual) | £3672 | N/A | [48] |
| TDF (annual) | £578 | N/A | [48] |
| TDF + emtricitabine (annual) | £1299 | N/A | [48] |
| Outpatient evaluation | £238 | Uniform (£190.40, £285.60) | [47] |
| Further outpatient evaluation | £262 | Uniform (£209.60, £314.40) | [47] |
| Contact costs (HBV and HCV) | | | |
| Cost per HCV contact* | £15.85 | Uniform (£7.92, £23.77) | [14,45] |
| Cost per HBV contact* | £10.30 | Uniform (£5.15, £15.45) | [14,45] |
| Cost of appointment (background testing) | £31.30 | Uniform (£15.65, £46.95) | [45] |

DAA indicates direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; N/A, not applicable; PegIFNα, peginterferon alfa-2a; TDF, tenofovir disoproxil fumarate.
*Cost of both successful and unsuccessful contacts.

### *Probabilistic Sensitivity Analyses*

In the base-case analysis, HCV testing was 99.1% likely to be cost-effective, and HBV testing 98.4% likely to be cost-effective, at a WTP of £20 000 per QALY.

We also evaluated the probability that the intervention is cost-effective at different HCV and HBV prevalence. At HCV RNA and HBsAg prevalence of 0.5%, testing remained highly likely to be cost-effective for both, with HCV testing 94% likely, and HBV testing 95% likely to be cost-effective. At a prevalence of 0.3%, testing remained likely to be cost-effective for both strategies, but with less certainty (70% and 71% likely cost-effective for HCV and HBV testing, respectively). At a lower 0.2% prevalence, testing was unlikely to be cost-effective for either strategy, with a HCV testing 23% likely to be cost-effective, and HCV testing 24% likely to be cost-effective. Cost-effectiveness acceptability curves showing the probability of cost-effectiveness across a range of WTP thresholds, with base case and lower prevalence scenarios for HCV and HBV available in Appendix Figure 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.014.

## Discussion

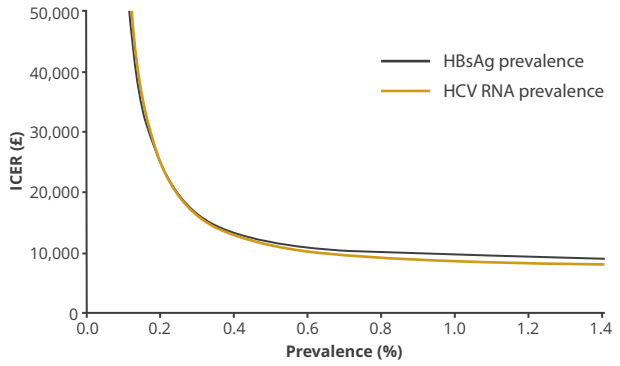
To our knowledge, this is the first economic evaluation of ED testing for HCV and HBV in the United Kingdom and adds to previous work demonstrating EDs are a viable setting for HCV and HBV testing in many areas of the United Kingdom.[14,15,22] At our base-case prevalence of 1.4% and 0.8% for HCV (RNA) and HBV (HBsAg), both testing strategies were highly cost-effective with ICERs below £10 000 per QALY, and the ICER did not increase above £12 000 for either testing strategy in any of the deterministic sensitivity analyses examined. While our analysis is an early economic evaluation in the absence of long-term testing data, the results of our probabilistic analysis suggest that testing remains highly likely to be cost-effective at 0.5% prevalence for both HCV and HBV. This compares favorably to the prevalence observed in recent ED testing studies across the United Kingdom. A recent study across 4 UK sites reported a pooled prevalence of 1.69% HCV RNA (range: 0.6%-2.9%), and 0.95% HBsAg (range: 0%-2%),[16] whereas other studies in London EDs have reported HCV RNA or antigen prevalence of 0.9% to 1.6% and HBsAg prevalence of 0.8% to

**Table 3.** Cost-effectiveness results for HCV and HBV screening per individual tested.

| Testing | Testing option | Total costs | Total QALYs | Incr. costs | Incr. QALYs | ICER |
|---|---|---|---|---|---|---|
| HCV | No screening | £160.68 | 16.4879 | | | |
| | ED screening | £184.47 | 16.4908 | £23.79 | 0.0030 | £8019 |
| HBV | No screening | £90.66 | 16.5497 | | | |
| | ED screening | £114.66 | 16.5522 | £24.00 | 0.0024 | £9858 |

ED indicates emergency department; HBV, hepatitis B virus; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

**Figure 1.** Incremental cost-effectiveness ratio (ICER) by HCV RNA and HBsAg prevalence achieved during testing in an ED setting.

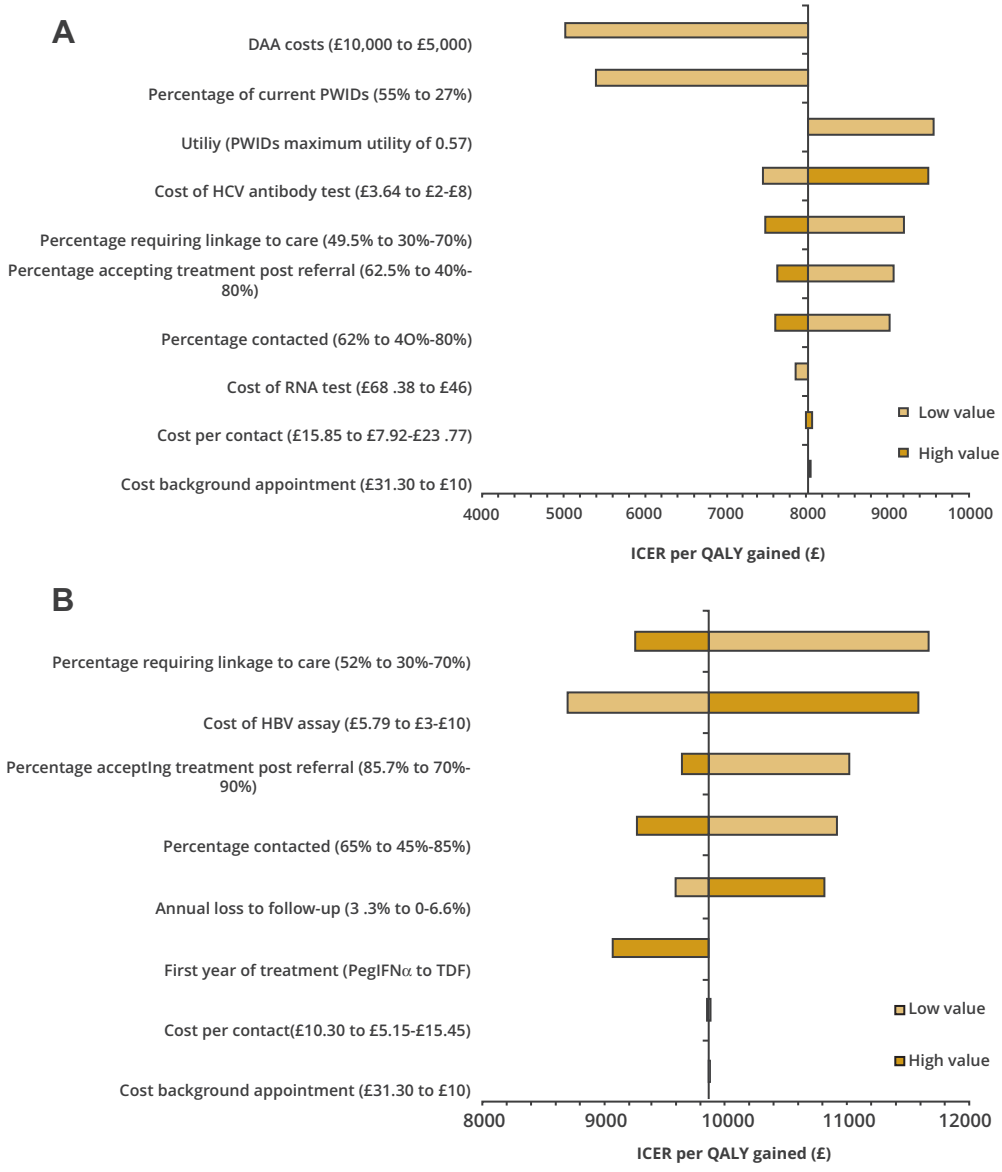



HCV indicates hepatitis C virus.

1.1%.[14,15,17] Thus, our study suggests ED testing is likely to be cost-effective in most UK settings. Furthermore, since the general population prevalence of HCV and HBV across Europe (1.1% and 0.9%, respectively) is similar to the base-case ED prevalence used in our analysis, ED testing could be cost-effective in other European settings, and also in other high-income countries with a HCV and HBV prevalence similar to or higher than the United Kingdom.[6]

Our prevalence threshold analysis suggests that ED testing would remain cost-effective even at low HCV RNA and HBsAg prevalence among ED attendees (0.25% or higher for both). These thresholds are similar to NICE recommendations for HIV testing in EDs in the United Kingdom (≥0.2%).[19] Nevertheless, there is no current NICE recommendation for ED testing for HCV and HBV, citing the absence of effectiveness or cost-effectiveness evidence for hepatitis testing in this setting in their 2017 review.[11] While the European Centre for Disease Prevention and Control

**Figure 2.** One-way deterministic sensitivity analysis (DSA) for A) HCV and B) HBV testing.




HBV indicates hepatitis B virus; HCV, hepatitis C virus.

guidelines recommend HCV and HBV testing in EDs with intermediate or high prevalence (≥2%), they do not cite any evidence for these much higher prevalence thresholds compared to our estimates.[10] While our prevalence threshold estimates provide guidance for the cost-effectiveness of ED-based HBV and HCV testing and linkage to care, further studies of ED testing would be of value to reduce the uncertainty at these thresholds, particularly as they will be sensitive to other model parameters that may differ from those used in our base-case analysis.

Our results also suggested that the cost-effectiveness of testing those aged 70 and above is uncertain, due to lower prevalence and lower life expectancy from the point of treatment. Nevertheless, further analyses are required to assess this in more detail owing to the limitations of the data available for this analysis.

### *Limitations*

Our analysis is based on 2 non-controlled, observational studies from the United Kingdom, which have considerable limitations. The studies were either short in duration, or with a low uptake of hepatitis testing among eligible blood samples. Evans et al undertook 6 weeks of testing, with 56% testing uptake, whereas Parry et al undertook 9 months of testing, but with only 25% testing uptake. For this reason, our analysis does not evaluate how long testing should be implemented. The prevalence threshold results estimate the minimum prevalence required for the intervention to remain cost-effective, although this assumes that other parameters remain constant.

In addition to prevalence, early evidence suggests other parameters included in our model differ across ED departments, such as the type and sequence of tests performed and their costs, the proportion of individuals in the population that require linkage to care, and the effectiveness of contacting those testing positive.[50] These parameters influenced the estimated ICERs, and while they did not change the base case cost-effectiveness, they are likely to influence the prevalence thresholds for cost-effectiveness. Another limitation was the lack of detailed cost data relating to the intervention. Although the results of the sensitivity analyses showed this had little impact upon our results, we did not include staff training costs or incentives to increase testing rates that have been previously reported.[22] The intervention consists of a number of individual parts, including the initial test, informing the patient of the result, and linking individuals to care following a positive diagnosis. Although the model incorporates all of these components, we acknowledge that they are separate factors and that there are many ways in which they could be individually optimized.

Lastly, our model did not capture the potential prevention benefit associated with a reduction in onward transmission among PWIDs with HCV who achieve SVR, and thus likely underestimates the impact of HCV testing.

## Conclusion

Although there is uncertainty regarding many of the parameters, our results suggest that ED-based HCV and HBV testing and linkage to care is highly cost-effective at our base-case prevalence. Moreover, the sensitivity analyses strongly suggest that this conclusion is robust. At a lower 0.5% prevalence, HCV and HBV testing remained highly likely to be cost-effective. This suggests the introduction of ED testing is likely to be cost-effective for many areas of the United Kingdom, since most ED-based HCV and HBV prevalence estimates from the United Kingdom exceed this.[14–16] Nevertheless, there is uncertainty around the prevalence thresholds at which HCV and HBV testing becomes cost-effective, although our analysis shows it is likely to be low.

Although our results suggest implementation of ED testing should be performed even in areas with a relatively low prevalence, interventions should be evaluated at a local level, using local data to inform key parameters and identify which of these context-specific parameters influence cost-effectiveness. Lastly, budget impact analyses using local data will be helpful for planning in areas introducing ED testing. These analyses will help reduce the uncertainty in our results and provide data to inform local healthcare decision-making bodies.

## Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.03.014.

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# 8 The background probability of testing in the counterfactual arm of HCV economic models: An evaluation of heterogeneity in the testing probability and the impact on the cost-effectiveness of HCV testing interventions

## 8.1 Overview of Research Paper 4

In this Chapter, I present an analysis of one of the methodological issues associated with economic evaluations of HCV testing interventions, which I encountered whilst performing this research.

In Chapters 5, 6, and 7 I have examined the cost-effectiveness of three HCV testing interventions, which aimed to increase testing amongst people who were unlikely to currently receive it. However, when evaluating HCV testing among those without obvious risk factors (e.g. PWID), those included in the testing population are likely to be heterogenous with regards to their risk of HCV, and their probability of being offered an HCV test elsewhere in the future. PWID are known to have a higher rate of testing for HCV, but there is uncertainty around the rates of testing in other groups, such as people who have historically injected drugs but ceased injected many years ago, or those born in countries with a high prevalence of HCV. This led to complexities in parameterising the background probability of testing, which is further complicated by the limitations of national surveillance datasets. As previously mentioned, these datasets have a relatively low coverage, and data is not missing at random.[1] Moreover, whilst they provide testing metrics across specific location types (e.g. primary care, drug and alcohol services, prisons), they do not record the risk factors associated with those testing.

This issue of parameterising the background probability of testing, and the extent to which heterogeneity may exist amongst different groups, has led to a particular methodological issue throughout this thesis. This Chapter seeks to perform an exploratory analysis to consider this issue in more detail, with the aim of demonstrating how heterogeneity in the testing population can influence the cost-effectiveness results.

This Chapter addresses the third objective of this thesis. It is unpublished and has not yet been submitted for publication. I intend to submit a modified version of this Chapter for publication

in the future. I anticipate that the co-authors for the manuscript will include my two supervisors, Alec Miners and John Cairns. Given that this analysis uses data from the HepCATT randomised controlled study, it is also likely that Professor Matt Hickman will also be a co-author.

For this study, I accessed anonymised data from the HepCATT randomised controlled study. Ethical approval was received from the LSHTM Ethics committee (Project ID: 21267).

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# RESEARCH PAPER COVER SHEET

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| **Thesis Title** | Assessing the cost-effectiveness of interventions to expand hepatitis C testing to help achieve elimination targets in the United Kingdom | | |
| **Primary Supervisor** | Alec Miners | | |

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| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role included desinging and performing all analyses, and manipulating the input data for the economic analyses. I wrote the manuscript, and incorporated feedback from my supervisors. |

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| **Supervisor Signature** | Alec Miners |
| **Date** | 25/02/2022 |

## 8.2 Introduction

### 8.2.1 Screening in infectious diseases

Screening is a broadly used term, but is defined by the WHO as the identification of unrecognised disease in an otherwise healthy or asymptomatic population, by means of testing or examination.[2] Screening programmes can be performed at a population level, or they can be targeted to certain groups. Risk-based testing involves testing those who meet a given risk threshold. This is sometimes also described as case-finding.[3-5] Risk-based testing interventions are often used to detect communicable diseases associated with either a long incubation period or mild, non-specific symptoms. This allows for diagnosis and treatment of infections that would otherwise remain undiagnosed, at least until the infection causes severe disease and symptoms.

Screening or testing interventions for infectious diseases can differ in their effectiveness to identify infections in the population, depending on the prevalence, the target population, and the accuracy of the test. Whilst a population screening approach may identify the majority of infections, this will likely incur a relatively high financial cost per case identified when prevalence is low. Alternatively, risk-based testing can identify a higher proportion of positive cases, but the absolute number will be smaller, as those infected but below the risk-threshold are missed.

### 8.2.2 Hepatitis C testing in the UK

As discussed earlier in this thesis, risk-based testing for HCV is currently recommended by NICE, with similar policies being adopted across the UK.[6] With an estimated 118,000 HCV infections in the UK, this equates to a prevalence of approximately 0.18% in the general population (based on Office of National Statistics estimates for the UK population).[7,8] However, HCV is over-represented in certain groups (or populations) in the UK.

The majority of new infections are associated with injecting drug use (>90%), with around a quarter of current or recent injecting drug users infected.[7] Although PWID have the highest risk of new or recent infections, there are other populations also at increased risk of chronic HCV. These include people who have been imprisoned, are homeless, are recipients of blood product or a blood transfusion prior to 1991, were born in countries with high HCV prevalence, are HIV positive, or were a close contact of someone with chronic HCV.[6]

Currently, testing is targeted towards those who meet these risk factors, or in settings frequently attended by those with risk factors, such as drug treatment services and prisons.[6] The burden of HCV in these groups is shown by the higher test positivity rates amongst HCV tests performed from 2005-2014 in England, with around 20% of HCV antibody tests being positive in drug services, and 14% in prisons.[9] In contrast, only 0.4% of HCV tests in occupational health were positive over the same period, the lowest of any setting, presumably due to the fact that testing is not based on the individuals risk, or a consequence of a patient with poor liver function and the resulting symptoms.[9] More recently, data from new blood donors in England in 2018 found that just 0.012% (12.4 per 100,000) were HCV antibody positive. This clearly demonstrates how HCV is over-represented in specific risk groups, and shows the rationale for risk-based testing.[10]

### 8.2.3 The benefit associated with testing, and the relationship between risk, testing, and test positivity

Whilst the benefit of risk-based testing is the identification of a higher proportion of cases amongst tests performed, a complex relationship exists between risk, the testing (or screening) rate, and test positivity rate for the testing intervention. For example, analysis of chlamydia screening from the Natsal-3 study data showed that the risk of infection (defined as the force of infection, representing the risk of infection per unit time) and the background screening rate both impact upon test positivity. A higher risk of infection and a lower screening rate are both associated with higher test positivity.[11] For any given risk group, the test positivity will reduce as the screening rate increases, since many of those testing positive will be treated and will clear the infection. In contrast, for any given risk group, the test positivity will be higher when screening rates are lower.

These trends are true for any group at any given risk. Of course, there will be differences in the positivity rate between risk groups, since those at higher risk of infection will be more likely to be infected (if testing rates are equal). In the example of chlamydia, those with multiple sexual partners over a specified period of time would be at higher risk than those with one sexual partner.

These relationships describe the likelihood of diagnosis amongst those at different risk of infection. However, using an example in HCV, from a health outcome perspective the benefit associated with the identification of an HCV case is also linked to their testing rate, or ‘background probability of testing’. For any individual identified, the benefit of testing at any

given point is greater when their future probability of testing is lower. The identification and treatment of an HCV case can reduce disease progression, subsequently improving quality of life and overall survival compared to those untreated. For the counterfactual of a testing intervention, under the assumption that no other testing would occur, those infected with HCV would continue to progress until symptomatic disease, which would likely occur after progression to a more advanced disease stage. In contrast, if those identified by the testing intervention would have likely been tested and treated elsewhere shortly after, then the benefit of that intervention would be lower. A simplistic example is shown diagrammatically in the Introduction section, in Figure 1-3 (Section 1.5.3.5).

To accurately quantify the incremental health benefit and incremental costs associated with a testing intervention, economic analyses need to accurately capture testing in the counterfactual group. Specifically, what would happen in the absence of the intervention. However, given the complex relationship between the risk of infection and HCV testing rates, modelling the counterfactual can be difficult.

### 8.2.4 Summary of economic modelling approaches to parameterise the background probability of HCV testing

There are various modelling approaches which have been used to capture the background rate of testing for counterfactual or control arms of HCV testing interventions. This section provides a brief descriptive summary of modelling approaches that have been used to date, which I have encountered throughout this thesis. I used previously identified studies involving cost-effectiveness models and categorised them according to the modelling approach taken when parameterising the background probability of testing. The studies categorised included those assessing the cost-effectiveness of general population or birth cohort HCV testing interventions in the Coward et al. review.[12] In addition, I also categorised modelling studies identified in the review of UK based economic evaluations since 2016 (see Section 4.3). A summary of these recent UK cost-effectiveness analyses is shown in Table 4-2. Finally, a few other key studies identified during the thesis were also categorised. A table containing the studies included in each of the categories in provided in Appendix Section 10.6, but the approaches taken are described below, with studies cited.

Firstly, the most simplistic approach assumes that testing will not occur in any other settings outside of the testing intervention, with those infected never being tested, and remaining undiagnosed until the onset of advanced disease states (i.e. end-stage liver disease).[13-16] This

approach may be appropriate for countries without any HCV testing strategies, or for populations with no possibility of receiving a test elsewhere, but will almost certainly overestimate the health benefits associated with a HCV testing intervention in countries with existing risk-based HCV testing strategies.

Second, a number of models have considered a fixed background rate of testing for the counterfactual group. The rate of testing is applied to the cohort, and therefore assumed equal for all individuals in the model. This approach implicitly assumes the testing population is homogenous with regard to their risk factors, and that the probability of testing is equal for those infected and uninfected.[17-21] This is likely to be a reasonable assumption for testing in target populations with a specific risk factor, or those with a similar probability of testing in other settings. However, if the risk factors, and consequently the background probability of HCV testing, differ amongst groups in the testing population then this assumption of homogeneity may be inaccurate. This can also cause issues if the test positivity in the background rate of testing is higher than the prevalence in the model population, as this suggests that a more than proportional amount of background tests are being performed on those infected.

Third, other models have assumed a differential rate of testing amongst those who are infected and uninfected.[22-26] This may involve a rate ratio of testing in infected versus uninfected individuals in the model, or alternatively the model may not capture any tests performed amongst those uninfected, only considering a probability of diagnosis amongst those infected. This method can address the issue of an increased test positivity in background tests (i.e. under risk-based testing recommendations) compared to the overall prevalence in the testing population. However, this approach is likely to simplify the relationship between the probability of infection and the probability of testing, particularly as those who are easiest to identify are likely to be tested first. Moreover, previous research has shown that these differential rates of testing can change over time.[27]

Lastly, other models have accounted for the heterogeneity in the model population by stratifying the population into risk groups.[28-33] Amongst these, most models either stratify the testing rate for 'high' and 'low' risk groups, or for PWID and non-PWIDs, with or without separating non-PWIDs into never-PWID and ex-PWID.[29,31] Some of these studies have performed multiple stratifications, for those who are current- or ex-PWID, receiving drug treatment (OST) or not, and whether they are homeless or not.[32,33] One study considered the ideal frequency of testing amongst different heterogenous groups, and therefore did not parameterise the testing rate but instead varied this parameter.[30] It should also be noted that

some studies used a model fitting approach (using nonlinear methods) to approximate the testing rate parameter in the model.[31-33] These testing rates can therefore change over time to fit the model, and thus tend not to be reported.

A number of economic evaluations were not categorised. Some studies did not consider a specific testing intervention, and instead assessed the cost-effectiveness of offering a test to specific populations, with the decision based on whether or not a test should be offered to each group.[34-37] There was no consideration of future testing in these analyses, as the decision was simply whether the individual should be offered testing or not. Other studies were also not categorised if they did not extrapolate beyond a cost per diagnosis[38,39] or if there was insufficient detail on how the background rate of testing was modelled.[40-42]

Overall, there are a number of ways in which the background probability of testing can be included in an economic evaluation of a new HCV testing intervention. The most appropriate approach to use will depend on the extent to which risk-based HCV testing already occurs in a given country and within a specific population, and whether there is likely to be heterogeneity amongst the testing population. For example, a simple approach assuming no possibility of HCV testing outside of the intervention may be a reasonable assumption in areas or populations that are highly unlikely to receive testing until the onset of symptoms. Furthermore, for models which include a relatively homogenous cohort of patients, then using an average estimate for the background rate of testing may be reasonable.

However, when heterogeneity does exist in the population being considered, then a more complex approach which accounts for this may be more reasonable. Of the approaches described above, only analyses that have differential testing rates for infected versus uninfected, or allow differential testing rates across stratified subgroups within the overall model population, account for the heterogeneity that might exist in the background probability of testing. This is a particular issue for mass screening interventions in which the estimated prevalence of the target testing population is lower than the test positivity amongst those receiving tests from this group. This occurs when those at higher risk of infection in the target population are more likely to be infected and more likely to be tested. An example of this is seen when considering the prevalence of HCV amongst birth cohorts, whereby the estimated prevalence is far lower than the test positivity rates observed in national HCV sentinel surveillance testing databases (HCV antibody prevalence of 3.7%-6.5%).[43]

### 8.2.5 Aim

The aim of this analysis was to evaluate how heterogeneity in the background rate of testing amongst different groups attending HCV testing interventions can impact upon the cost-effectiveness of these testing interventions.

## 8.3 Literature review

### 8.3.1 Review of studies analysing the background rate of testing or differential testing rates

Prior to performing any model-based analyses considering heterogeneity, a narrative literature review was performed to identify studies which might have already researched this issue. The review considered testing studies with a particular focus on the background rate of testing, or statistical or model-based analyses considering differential rates of testing amongst different risk groups, which may help gain a better understanding of how the background rate of testing should be parameterised in economic models of HCV testing interventions.

The literature review included search terms for hepatitis B, hepatitis C, HIV, TB and common STIs (gonorrhoea, chlamydia, syphilis). These are all infectious diseases with public health guidelines recommending various risk-based testing interventions.[6,44-46] Therefore a similar relationship between infection risk and the background rate of testing is likely to exist for these infections too. These infections were also a strategic priority for Public Health England's infectious disease strategy, with plans to reduce or eliminate infection levels in the population.[47] As testing is expanded to new populations who are at a lower overall risk of infection, these issues of differences between test positivity in risk-based testing and expanded testing interventions may have also become more apparent in other modelling analyses, especially those seeking to parameterise the counterfactual or background rate of testing.

The literature was searched from database inception to the 11th of October 2021, in the following databases: Embase, Medline, Econlit and Web of Science. Details of the search strategy are available in Appendix 10.7. The inclusion criteria for the review were studies that could be described by any of the following:

- Any studies that performed a statistical analysis and evaluated different approaches to estimating or parameterising the background rate of testing for infections which are identified through risk-based testing
- Any studies that evaluated differential testing rates, either for different risk groups, or differential rates between those infected and uninfected, in a statistical or model-based analysis.

Economic evaluations which referred to a background rate of testing, or a testing rate in control or counterfactual group, were not included unless they explicitly reported analysing the impact of different assumptions or approaches to parameterising the background testing rates.

### 8.3.2 Literature review results

A total of 10 papers were identified for full text review, of which 4 were included.[11,27,48,49] The papers which were excluded did not perform any analyses on the background rate of testing or analyse the relationship or impact of differential rates of testing.

The four papers included are discussed in detail below.

A study by Paltiel and Kaplan 1997 performed a hypothetical economic evaluation, which considered the cost per HIV diagnosis when considering differential rates of testing amongst those infected and uninfected. The study noted that despite the general population prevalence of HIV in the United States being approximately 0.5% in 1990, around 5% of tests performed were positive, suggesting that those infected were far more likely to seek testing than those uninfected. The study then showed that this differential participation amongst infected and uninfected individuals in HIV testing interventions has a significant impact upon the estimated cost-effectiveness of a testing intervention.[48] The analysis notes that increasing uptake of a testing intervention may lead to a higher proportion of uninfected individuals seeking testing rather than infected individuals, resulting in additional costs per case identified, when calculating cost-effectiveness. It shows that failure to capture these differential rates of testing can result in inaccurate cost-effectiveness estimates. However, there was no extrapolation of the testing results beyond the cost per diagnosis.

Two papers considered the relationship between the rate of testing, the proportion of positive tests, and the underlying prevalence, using data from the Natsal-2 and Natsal-3 surveys on sexually transmitted infections.[11,27] A paper by Smid et al. 2019 showed that previous models of chlamydia testing had overestimated the impact of screening interventions, as chlamydia prevalence had remained stable despite increased rates of testing, and suggested this must have resulted from an increasing proportion of tests in those at lower risk of infection.[27] Furthermore, the model based analysis found that the ratio of tests amongst infected versus uninfected individuals decreased over time, suggesting a more than proportional increase in testing of those uninfected as testing rates increased.

A paper by Lewis and White 2020 displayed similar finding to those observed by Smid. This paper also showed a differential rate of screening amongst participants, with a positive correlation between the higher number of sexual partners in the previous year (indicating higher risk of infection) and the probability of being screened (asymptomatically) for chlamydia.[11] Furthermore, the paper showed that the force of infection (i.e. the risk of infection over time) and the rate of screening both influenced the proportion of positive tests amongst those tested.

Finally, Vermeiren et al. 2012 found that, an increasing rate of HCV testing over time was associated with a drop in positive cases amongst those tested.[49] The authors suggest the additional proportion of screening tests performed has disproportionally more often included people who are at a lower risk of HCV. In other words, the expansion of testing has resulted in testing amongst people who are, on average, at a lower risk of HCV. The authors used a capture-recapture analysis, an epidemiological analysis which considers the completeness of surveillance data used to refine incidence or prevalence estimates, by considering repeat samples over time.[50] The capture-recapture analysis was used to estimate the characteristics of individuals with the highest likelihood of being infected and undiagnosed in the Netherlands, to predict where targeted testing should be focused, based on where the disease burden is highest.

All of the papers identified show the complex relationship between the rate of testing, and its correlation with the risk of infection amongst participants. Three papers discussed the impact of rate of screening on the proportion of tests that are positive, with consensus that these are not scalable (i.e. an increase in the rate of screening will likely lead to a reduction in the test positivity, because increasing testing tends to lead to more than proportional increase in testing amongst those at lower risk).[11,27,49]

For HCV testing interventions in the UK, the prevalence of infection amongst those attending a novel testing strategy will be captured from the intervention. However there remains uncertainty around the rate at which this group would have tested otherwise, and the extent to which those at higher risk of HCV would have been more likely to have otherwise tested elsewhere, whilst those at a lower risk would be less likely to be tested elsewhere.

## 8.4 Modelling methods

An exploratory analysis was performed to evaluate how heterogeneity amongst different groups attending HCV testing could change the economic model predictions, and subsequent cost-effectiveness results.

The analysis adapted two existing economic models of HCV testing interventions to evaluate assumptions of homogeneity in the testing population. The economic models evaluated the impact of HCV birth cohort screening as part of the NHS health check in primary care (Chapter 5), and the HepCATT HCV testing algorithm in primary care (Chapter 6).[43,51]

The details of the two economic models are described in their relevant Chapters, but both models assume homogeneity amongst the HCV testing population included in the model. This Chapter evaluates the impact of this assumption. Adapted versions of both models are developed, in which heterogeneity in the model population is considered by stratifying the population into risk groups. In the birth cohort model, this includes stratification based on injecting drug use status (ex-PWID and never-PWID). In the HepCATT model, the differences in the prevalence and background rate of testing are quantified for people meeting each of the risk criteria, based on the medical codes used to identify those included in the HepCATT trial. In both analyses, the impact on the overall cost-effectiveness was then evaluated, comparing the analyses with and without consideration of heterogeneity. The analyses focus on differences in the prevalence of HCV, and the future probability of HCV testing amongst these groups. The influence of this stratification on the estimated cost-effectiveness of testing interventions is considered.

The linearity of both models was assessed by comparing the deterministic base case ICER to the mean ICER of 10,000 probabilistic simulations (using the mean incremental costs and incremental outcomes to estimate the ICER). Both of the models were relatively linear, with the deterministic ICER comparable to the mean probabilistic ICER derived from the average of all probabilistic simulations. For the birth cohort model the ICERs were £18,681 per QALY gained and £18,934 per QALY gained, for deterministic and probabilistic analyses respectively. The difference for the HepCATT model was also small, with deterministic and probabilistic ICERs of £6,916 and £7,014 per QALY gained, respectively. Since the models were relatively linear, only deterministic analyses evaluating the impact of heterogeneity in the model population were considered.

### 8.4.1 HCV Birth cohort screening analysis

#### 8.4.1.1 Original model description and key parameters

This analysis explored the influence of heterogeneity amongst those included in the 1975-1979 birth cohort only, although the principle remains the same across birth cohorts.

The prevalence estimates used to inform the original economic model (as presented in Chapter 5) were derived from a back-calculation modelling study, which estimated HCV prevalence amongst different risk groups (current-PWID, ex-PWID, South Asian never-PWID, and all other never-PWID) in England.[52]

The original model made a conservative assumption that birth cohort screening would not identify current-PWID as they would not attend, with these individuals being more likely to receive testing elsewhere. The model also assumed that ex-PWID and never-PWID (of all ethnicities) are equally likely to attend the NHS health check and receive HCV screening. The overall HCV RNA prevalence was 0.19% amongst those attending, in this birth cohort. However, ex-PWID constitute a relatively small proportion of the overall testing population (1.7%) but have an elevated RNA prevalence compared to those with no previous injecting history (10.11% vs. 0.02%).

Despite this, the model assumed homogeneity since ex-PWID and never-PWID were assumed equally likely to attend, and equally likely to receive testing in other settings. This 'background probability of testing', representing the probability that an individual would receive testing in any other setting outside of the intervention, was estimated to be 3.57% per year.

Despite the HCV prevalence estimates from the back-calculation model for this birth cohort being low, the proportion of HCV antibody positive tests in UK HSA sentinel surveillance data was 5%, based on peoples first recorded HCV test between 2012-2016. Of these, 66% tested RNA positive, giving an estimated RNA prevalence of 3.3%. When excluding tests performed in prisons and drug services (most likely capturing current- or recent- PWID), the estimated RNA prevalence was 2.4% (amongst those receiving testing). This strongly suggests that existing HCV testing is already targeted towards populations that are more likely to be infected with HCV. However, there are other uncertainties. Firstly, these estimates are likely to still include current-PWID who receive testing at other settings, such as primary care, sexual health services, and emergency departments (where a combined 84% of all tests were performed from 2012-2016). Therefore, the background test positivity amongst those who would have been included in a birth cohort testing intervention is unknown, as there is no way of

identifying this target population within UK HSA sentinel surveillance dataset. In addition, it is not known if any of those tested in these datasets might have received testing after experiencing symptoms or following an abnormal liver function test result. If so, this would suggest that those diagnosed were not offered HCV testing based on their risk, but instead because of disease progression, and thus are more likely to be at a more advanced disease stage and therefore have a poorer prognosis.

#### 8.4.1.2 Model Analyses

First, a one-way sensitivity analysis was initially performed on the background probability of testing for the overall testing population, with the assumption of this being equal for ex-PWID and never-PWID (i.e. a homogenous group). The background probability of testing was varied from 1% to 5% to assess the uncertainty in this parameter, which was deemed a wide, but plausible range given the uncertainty in the background rate of testing amongst this group.

Second, an alternative analysis assumed that the annual background probability of testing remained constant for the overall model population (at 3.57%, in the first cycle), but with different probabilities of testing amongst ex-PWID and never-PWID. The probability of testing for ex-PWID was elevated, whilst the probability of testing for never-PWID was reduced proportionately, to maintain the same overall probability of tests performed in the first model cycle (i.e. 3.57%). The function used to estimate the probability of testing in never-PWID when the probability of ex-PWID was altered across sensitivity analysis is provided below.

$$Never\text{-}PWID\ probability\ of\ testing = \frac{Total\ annual\ tests - (Ex\text{-}PWID\ annual\ testing\ probability\ \times\ ex\text{-}PWID\ population)}{Never\text{-}PWID\ population}$$

This sensitivity analysis assessed probabilities of background testing of ex-PWID up to 25%, similar to that reported by current- and ex-PWID in PHE UAM statistics (47% tested in the current or previous year, equivalent to 27% per year).[53] The proportion of tests that were RNA positive for these sensitivity analyses was also recorded for the control group to see the impact of differential testing rates on the overall test positivity.

The third analysis involved a combination of the first and second analyses. It considered a differential probability of background testing between ex-PWID and non-PWID (up to 25%

probability for ex-PWID), at overall background probabilities of testing for the whole cohort between 1% and 5%.

#### 8.4.1.3 Minor differences in prevalence calculation compared to the original economic evaluation of HCV birth cohort screening (Chapter 5)

It should be noted that the mean deterministic ICER generated in the base case of this analysis differs marginally from that reported in the original economic evaluation (Chapter 5). In the original publication, the prevalence estimates were not supplied as a single parameter, instead the model stratified individuals into the following:

- Birth cohort (in 5-year cohorts, e.g. 1940-1944, 1945-1949 etc.)
- PWID and ethnicity status (current-PWID, ex-PWID, South Asian never-PWID, all other never PWID),
- Disease stage (uninfected, mild, moderate, compensated cirrhosis)
- Diagnostic status (undiagnosed, diagnosed, and SVR)

Each of the values provided was stratified by all of the above, and provided with upper and lower credible intervals, to account for their uncertainty. The prevalence of undiagnosed HCV for each birth cohort was then calculated as the proportion of undiagnosed chronic HCV infections amongst the population, after excluding current-PWID and those with diagnosed HCV (whether or not they had achieved SVR).

Since the calculation of the prevalence was based on many values (each with their own variance) generated from the back-calculation model, in order to estimate the mean and variance of the prevalence parameter, for each birth cohort I ran 5,000 Monte Carlo simulations that assessed the uncertainty in all of the back-calculation estimates jointly. Each value was assumed to be normally distributed. This was performed to estimate the mean and variance for each prevalence value used in the economic model, so that a distribution around this prevalence could be assigned. A beta distribution was used, based on the mean and standard error of these 5,000 simulations, and the alpha and beta parameters of the distribution are reported in Chapter 5, Table 1.

In the original economic model, the mean deterministic value for the model was derived directly from this beta distribution, resulting in a very small difference compared with the deterministic value calculated from the back calculation model, due to random error in the sampling when using the Monte Carlo simulations to estimate the beta distribution. The

resulting difference is very small (<0.001% in the estimated prevalence), but did result in a very marginal difference in the mean ICER. The original ICER being £18,681 (Table 2, Chapter 5), based on the average of these Monte Carlo simulations with a mean prevalence of 0.1865%. The deterministic approach taken to estimate the prevalence in this analysis resulted in an estimated prevalence of 0.1873%, and an ICER of £18,664, which is £17 lower.

### 8.4.2 Analysis of HepCATT HCV testing algorithm

#### 8.4.2.1 Original model description and key parameters

The HepCATT study, presented in Chapter 6, involved the identification of those at elevated risk of HCV, based on an algorithm which screened patients primary care records.

In the trial, the intervention increased the proportion of people tested in intervention practices (15.8%) compared to control practices (10.2%), with an adjusted rate ratio of 1.59 (95% CI 1.21: 2.08). There was also a higher likelihood of those in the intervention arm to be linked to care (i.e. referred to a hepatologist) following a positive RNA test (46.5% vs. 23.1%). The model included those who met at least one of the risk criteria included in the study. Briefly, these risk criteria included: exposure to HCV or a previous positive HCV test; a history of injecting drug use or OST; a history of HIV or HBV infection; a history of a transplant (pre-1992), receipt of blood products (pre-1986) or blood transfusions (pre-1991); a history of childhood care or imprisonment; an altered ALT test. Each individual could be included in more than one risk factor group.

The economic model included all those identified by the testing algorithm, with the intervention performed for one year in a static cohort. After the first year, both groups are assumed to have the testing probability of the control group. The model population was assumed to be homogenous in terms of the probability of testing antibody positive (5.6%), and their background probability of testing after the intervention (9.7% per year). This analysis sought to evaluate this assumption by stratifying those 'high-risk' groups included in the model based on the risk criteria which they met.

#### 8.4.2.2 Model Analyses

First, the rate of testing in the control arm was estimated amongst patients with the presence of each risk criterion. This annual rate of testing was estimated using a mixed-effects Poisson

regression model, as per the original analysis.[51] The proportion of antibody tests that were positive amongst all those who received testing (in either the control or intervention arm of the trial) was estimated. The differences in the probability of receiving testing and the antibody prevalence across each of these groups is then presented.

Second, based on the variation in the probability of testing and the HCV antibody prevalence observed across the risk criteria groups, a two-way sensitivity analysis was performed, which varied the background rate of testing from 1% to 15%, and the antibody prevalence from 5% to 40%. These ranges are similar to the higher and lower values observed across the risk criteria groups, in the first analysis described (these results are shown in Table 8-3). An estimated 40.3% of antibody positive tests were RNA positive in the base case analysis, which equates to an estimated HCV RNA prevalence of 2% to 16.1%.

This analysis was performed under the assumption that all other base case parameters remained the same, since the trial was not powered to detect differences in the intervention effects for each of the six subgroups considered in this analysis. Based on this, the testing rate ratio and linkage to care intervention effects included in the model remained equal across these sensitivity analyses. The model does not attempt to evaluate the trial results specifically for each risk criteria group, but instead considers an exploratory two-way sensitivity analysis of the future rate of testing and the HCV prevalence, for subgroups within the base case population. Instead, this analysis assesses the extent that these parameters may influence the cost-effectiveness results. This is because the cost-effectiveness results would have assumed that the overall relative intervention effects applied to each risk group, which may not be the case, but also because each risk group had people that had other risk factors and were included in another risk group. Therefore the cost-effectiveness of testing for any given risk group will depend on the combination of other criteria that are already being considered. Whilst analyses which consider the combination of risk factors that would be most cost-effective may be of interest, this was considered outside of the scope of this exploratory paper.

## 8.5 Results

### 8.5.1 HCV Birth cohort screening analysis

#### 8.5.1.1 Homogenous sensitivity analysis of background rate of testing

Under the assumption of a homogenous cohort, the background probability of testing is applied to all those in the model who are not tested as part of the intervention, and assumes that never- and ex-PWID have the same annual probability of being tested (3.57%). In the base case analysis, the ICER was £18,664 per QALY gained. Under the assumption of homogeneity, deterministic sensitivity analyses considering alternative values for the background rate of testing have a modest impact upon the ICER. When considering a background probability of 1% the ICER increases to £20,624 per QALY gained, whilst at 5%, the ICER falls to £17,945 (Table 8-1).

As described in section 8.2.3, the incremental health outcomes associated with the testing intervention are highest when the background rate of testing after the intervention is low. This is because those who do not receive the intervention would likely remain undiagnosed until the onset of advanced liver disease (e.g. decompensated cirrhosis or hepatocellular carcinoma), due to the low likelihood of receiving testing elsewhere. The incremental outcomes are therefore large, because those not receiving the testing intervention have a greater likelihood of remaining undiagnosed until the onset of advanced stage liver disease.

When the background probability of testing increases, there is an increasing likelihood that those in the control arm (who do not receive testing as part of the intervention) will receive a test elsewhere before the onset of advanced liver disease, therefore avoiding the poor health outcomes associated with this. As such, the incremental outcomes associated with the testing intervention decrease as the probability of testing elsewhere increases.

A similar pattern is observed with the incremental costs, as these also decrease as the background rate of testing increases. Since the costs of testing and providing treatment represent a large cost in the model, when the background testing rate is low, the control group are unlikely to be tested elsewhere and therefore unlikely to incur the treatment costs and the additional costs associated with being diagnosed in the model. As the background rate of testing increases however, those in the counterfactual arm become increasing likely to incur the same costs of testing and treatment as those in the intervention arm, only in a slightly later

period of time. This then reduces the incremental difference between the intervention and counterfactual arm.

The ICER was lower when the background probability of testing was high, showing more favourable cost-effectiveness of the testing intervention.

Table 8-1: Deterministic sensitivity analysis on background rate of testing parameter, under the assumption of homogeneity in the testing population

| **Background probability of testing** | **Incremental costs** | **Incremental outcomes** | **ICER** |
|---|---|---|---|
| 1% | £13.14 | 0.00064 | £20,624 |
| 2% | £11.17 | 0.00057 | £19,739 |
| 3% | £9.64 | 0.00051 | £19,017 |
| 3.57% (base case) | £8.43 | 0.00046 | £18,664 |
| 4% | £7.46 | 0.00042 | £18,427 |
| 5% | £6.67 | 0.00038 | £17,945 |

#### 8.5.1.2 Differential background rates of testing between subgroups

When disaggregating the model population into ex-PWID (1.6% of model population) and never-PWID (98.4%), sensitivity analyses of different background probabilities of testing in these groups result in a larger variation in the ICER observed (Table 8-2), despite the overall probability of testing in the model remaining the same as the base case (3.57%). When the ex-PWID annual testing probability was increased to 25% probability of testing, the ICER increased to £27,233 (Table 8-2).

Table 8-2: Incremental cost-effectiveness ratio, based on the differential background probabilities of testing for ex- and never-injecting drug users

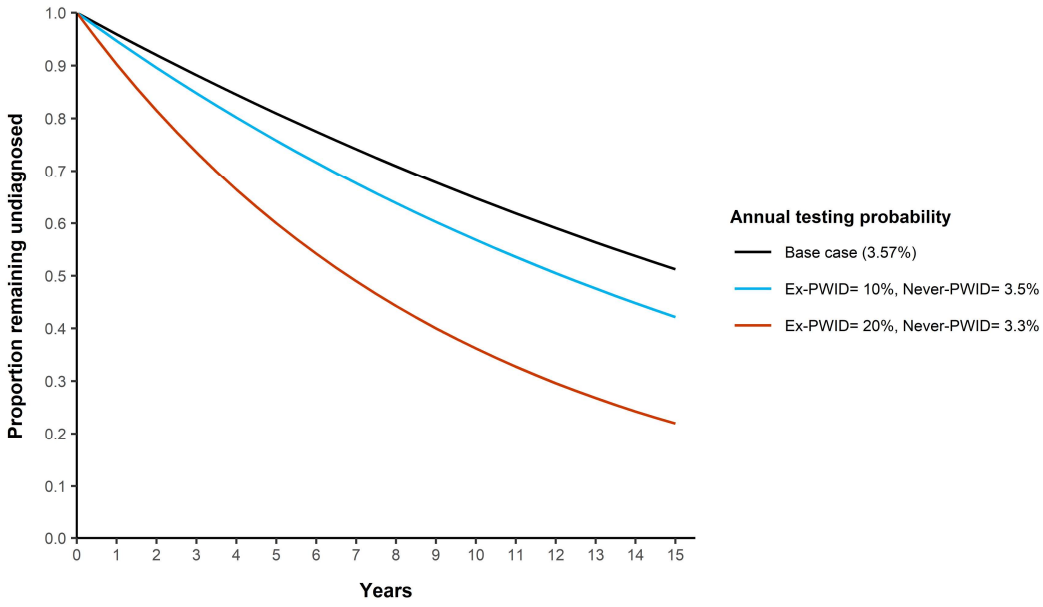
| Ex-PWID annual test probability | Never-PWID annual test probability | Proportion of tests RNA positive[†] | ICER |
|---|---|---|---|
| **Assumed homogeneity between two groups** | | | |
| 3.57%[‡] | 3.57%[‡] | 0.19% | £18,664[*] |
| **Allowing for heterogeneity between groups** | | | |
| 5% | 3.55% | 0.25% | £18,986 |
| 10% | 3.47% | 0.49% | £20,751 |
| 15% | 3.38% | 0.74% | £22,899 |
| 20% | 3.30% | 0.99% | £25,094 |
| 25% | 3.22% | 1.25% | £27,233 |

[†]The proportion of RNA positive tests from background testing in the first model cycle (i.e. outside of the birth cohort screening intervention).

[‡]Results of homogenous assumption (3.57% probability of testing for ex-PWID and never-PWID).

The proportion of tests that were RNA positive (test positivity rate) also increased with the probability of testing amongst ex-PWIDs, due to the higher probability of infection in this group compared to the never-PWID. This also reduced the proportion of undiagnosed HCV cases remaining over time (Figure 8-1). This suggests that inaccuracies in this modelling approach would also impact upon epidemic modelling studies, as well as economic analyses.

Figure 8-1: The proportion of undiagnosed cases over the model time horizon, depending on the probability of testing in ex-PWID (at an overall probability of testing of 3.57% for the overall testing population)

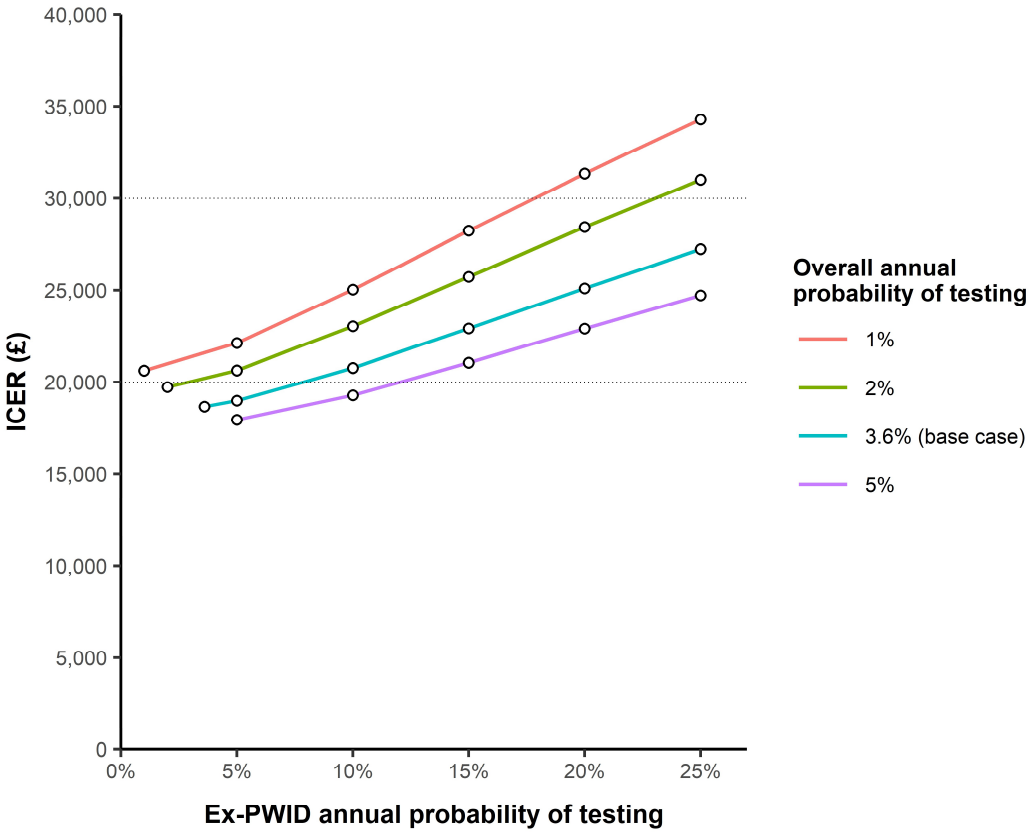



8.5.1.3 Evaluation of the differential background rates of testing between subgroups and parameter uncertainty in a two-way sensitivity analysis

The results presented in Table 8-2 and Figure 8-1 assume a fixed probability of testing of 3.57% in the first year of the model across the two groups. In contrast, Figure 8-2 shows the uncertainty in the ICER produced when also capturing the parameter uncertainty (varied from 1-5%), as well as considering the uncertainty in the relative likelihood of testing across the two groups (ex-PWID and never-PWID).

Overall, the results suggest that the differential probability of testing between ex-PWID and never-PWID has a larger impact on the ICER compared to the uncertainty in the parameter value for the probability of testing itself.

Figure 8-2: Incremental cost-effectiveness of screening, at differential rates of testing for ex-injecting drug users (y-axis), to achieve an overall probability of testing for all individuals in the analysis (coloured lines)




## 8.5.2 Analysis of HepCATT HCV testing algorithm

### 8.5.2.1 Evidence of heterogeneity amongst risk criteria groups

In the HepCATT economic evaluation, the estimated annual probability of testing for all patients in the control group was 9.7% per year. Table 8-3 presents the background probability of testing for the control group and the antibody prevalence stratified for each of the risk criterion included in the HepCATT analysis. This was adjusted for the high testing practice and Bristol location, based on all practices in the study. Individuals included could meet more than one of the risk criteria, and therefore be included in more than one group.

There is a large difference between the background probability of testing for each risk criterion. The annual background probability of testing in the control arm ranged from 0.5% – 16.8% across each risk factor subgroup, with the lowest rate of testing for those with historical

blood transfusion or transplant. The probability of being antibody positive in each subgroup also differed amongst risk criteria. The proportion of antibody positive tests varied from 4.9% (in those with elevated ALT levels) to 39.8% (in those with a history of injecting drug use) amongst groups that reported positive tests.

Table 8-3: The estimated annual probability of testing and the proportion of positive tests amongst participants in control practices in each HCV risk criterion. Each individual meets one or more risk criteria.

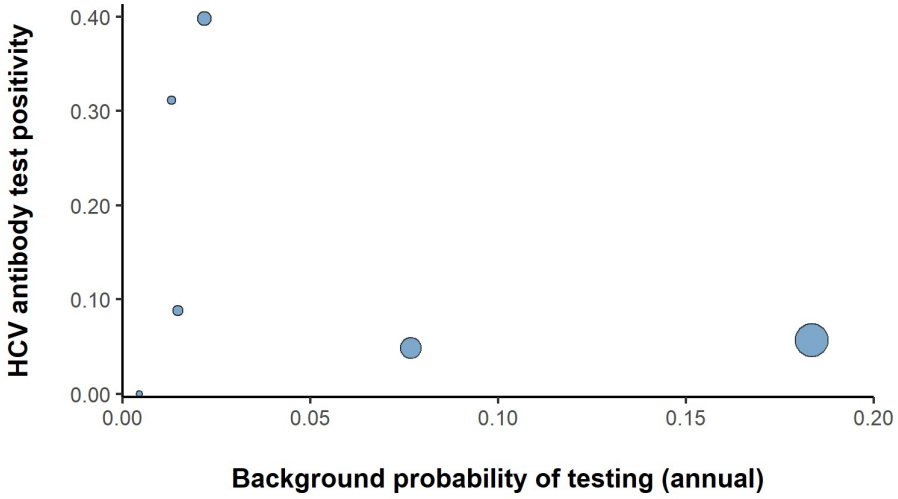
| **Risk criteria** | **Estimated adjusted rate (per year)**[†] | **Estimated probability (annual)** [‡] | **Antibody test positivity (%)** |
|---|---|---|---|
| History of HCV exposure or testing | 0.1835 | 16.76% | 179/3154 (5.7) |
| History of injecting drug use | 0.0217 | 2.15% | 107/269 (39.8) |
| History of HIV or HBV infection | 0.0147 | 1.46% | 9/102 (8.8) |
| History of blood transfusion or transplant | 0.0045 | 0.45% | 0/43 (0) |
| History of childhood in care, or imprisonment | 0.0130 | 1.29% | 19/61 (31.1) |
| Altered ALT level | 0.0767 | 7.38% | 46/945 (4.9) |
| **All patients** | **0.1020** | 9.70% | **180/3234 (5.6)** |

[†]Estimated annual rate of testing, estimated using a mixed-effects Poisson regression model, adjusted for high testing practice and Bristol location.

[‡]Formula for converting annual rates to annual probabilities: *probability = 1 – exp { 1 – rate }*

The results of Table 8-3 are also shown diagrammatically in Figure 8-3, by plotting the HCV antibody test positivity again the annual background probability of testing for each risk group included. Although no formal assessment was performed, there is little evidence of correlation between the two variables across risk groups.

Figure 8-3: Scatterplot showing the relationship between HCV antibody test positivity and the background probability of testing amongst different groups within the HepCATT trial. Each point relates to the number of the patients in each of the groups (numbers presented in Table 8-3).




8.5.2.2 Two-way sensitivity analysis of background rate of testing

A two-way sensitivity analysis evaluated the impact of the background probability of testing and HCV prevalence upon the estimated cost-effectiveness of the HepCATT intervention.

Assuming all other base case parameters remained constant, the results show that the ICER differed considerably across the two-way sensitivity analysis, ranging from £2,714 to £30,277 per QALY gained (Table 8-4). The lowest ICERs were associated with higher background testing rates and higher prevalence (test positivity).

In this analysis an increase in the background rate of testing was associated with a lower ICER, for several reasons. Firstly, the intervention effect is a relative effect, and is included in the model as a testing rate ratio (1.59, 95% CI 1.21: 2.08) compared to the control group (the control group consisting of the background rate of testing only). Therefore, the testing intervention does not have an absolute effect, but rather a relative effect, which means that the background rate of testing (for the control group) and the rate of testing in the intervention are not independent. As such, a higher background rate of testing also meant a higher absolute effect of the intervention, although the validity of this assumption was not considered across each risk group.

Furthermore, a higher proportion of patients were linked to care (46.5%) when receiving testing as part of the intervention compared to the control group (23.1%). Therefore, when the background probability of testing was higher, more patients were identified, and an even larger proportion were linked to care increased. This meant that amongst the overall intervention arm, a higher proportion of the overall cohort would be linked to care, because a higher proportion received testing and linkage to care as part of the intervention. As a result, the ICER associated with the intervention reduced.

In addition to the larger absolute effect of the intervention when the background rate of testing increased, the ICER also decreased because there are fixed costs associated with the intervention. This included costs for the software and training primary care staff to use it, as well as the time to review the patient lists for each practice. As the background rate of testing increased, and therefore the number of people testing in the intervention also increased, these fixed costs represented a smaller proportion of incremental costs associated with the intervention (i.e. these fixed costs were spread over a higher number of people receiving testing).

The combination of these factors all contribute to the an increasing background rate of testing leading to a lower ICER of the intervention.

Table 8-4: A two-way sensitivity analysis showing the ICER, based on the background probability of testing and the HCV antibody prevalence of individuals entering the economic model

| **HCV Antibody Prevalence (RNA prevalence[†])** | **Background probability of testing (annual)** | | | |
|---|---|---|---|---|
| | **1%** | **5%** | **10%** | **15%** |
| 5% (2%) | £30,277 | £11,227 | £7,136 | £5,104 |
| 10% (4%) | £18,852 | £8,207 | £5,306 | £3,738 |
| 15% (6%) | £15,044 | £7,200 | £4,696 | £3,283 |
| 20% (8.1%) | £13,140 | £6,696 | £4,391 | £3,055 |
| 25% (10.1%) | £11,997 | £6,394 | £4,208 | £2,919 |
| 30% (12.1%) | £11,236 | £6,193 | £4,086 | £2,828 |
| 35% (14.1%) | £10,692 | £6,049 | £3,999 | £2,762 |
| 40% (16.1%) | £10,284 | £5,941 | £3,933 | £2,714 |

[†]An estimated 40.3% of antibody positive tests were estimated to be RNA positive.

## 8.6 Discussion

### 8.6.1 Overview

In order to evaluate the impact of introducing a new testing intervention, it is necessary to consider the appropriate alternative; what would have happened in the absence of such an intervention (the counterfactual). Ideally this would be estimated from a control group, either in a randomised study or a matched analysis, or a baseline period in which the same individuals are followed to capture their probability of testing prior to the intervention. Unfortunately, this level of information is often unavailable when evaluating testing interventions, and is also difficult to estimate from national surveillance data.

The current guidance for risk-based HCV testing in the UK means those who are identified as being at higher risk of HCV are more likely to receive a test. Therefore, if the risk of HCV in the cohort is heterogenous, with some groups within the model population also more likely to receive testing, then it is likely that the probability of testing will also be heterogenous. Despite the difficulties in estimating the counterfactual, the heterogeneity in the testing rates across the model population should be accounted for, in order to more accurately quantify the incremental costs and benefits associated with a new testing intervention.

If the model incorrectly assumes homogeneity, this can result in inaccurate model predictions. When considering a high degree of heterogeneity in the birth cohort analysis (with a 25% probability of testing for ex-PWID and a 3.2% probability for never-PWID), the ICER was £27,233, compared to the base case ICER of £18,664. As would be expected, the level of this inaccuracy depends on the extent of heterogeneity between the different subgroups within the population. When the differences between the subgroups are large, there is the potential for considerable inaccuracy (or bias) in the estimated ICERs, and this could lead to the wrong recommendations in terms of implementing testing policies (Table 8-2).

In studies that assume a homogenous cohort in the base case analysis, but uncertainty around the extent to which heterogeneity exists within the background rate of testing, then sensitivity analyses considering this heterogeneity should be performed. These analyses should consider stratifying the model population and assessing differential probabilities of testing across different groups within the model population. This is particularly important because where uncertainty exists in the background rate of testing, deterministic sensitivity analyses altering this parameter under the assumption of a homogenous model population (i.e. without

consideration for differential testing rates within the model population) can underestimate the uncertainty in the cost-effectiveness decision.

### 8.6.2 The relationship between risk, testing rates, and test positivity

Whilst it a reasonable assumption that those at higher risk of HCV are more likely to be tested, the evidence from the HepCATT study showed that a higher test positivity amongst a particular subgroup may not correlate with a higher HCV testing rate (Figure 8-3). This may be a result of increased testing in specific risk groups resulting in a decrease in the prevalence of HCV in this group, following diagnosis and treatment. As such there is an interaction between risk of infection, testing rate, and the test positivity, a relationship that has been previously found by Lewis and White in national chlamydia screening data.[11]

Considering this relationship, modelling analyses which simply use a higher rate of testing amongst infected versus uninfected individuals are likely to over-simplify this relationship and may be inaccurate. The ratio of testing in infected versus uninfected individuals will likely change over time, especially if testing is scaled up, because this increase in testing will likely expand testing to groups that are, on average, at a lower risk of HCV.[27,48] Furthermore, those individuals who are hardest to identify, and without risk factors, will become a greater proportion of the infected population as the overall prevalence of HCV decreases.[27]

### 8.6.3 Implications for modelling studies

Future modelling studies of HCV testing interventions should carefully consider the target population included in the testing study and consider whether heterogeneity exists in the model population. If the probability of testing and the risk of HCV infection differ for subgroups within the model population, then this should be addressed in the economic analysis, where possible. This can be addressed by stratification of the cohort within the model structure, or by running the model separately for subgroups. This is likely to be particularly important for mass HCV testing interventions, or population-based testing strategies, as those included in the testing population will likely differ in both their risk of HCV, and their probability of HCV testing. If this heterogeneity is not accounted for in the model, i.e. by accounting for the structural uncertainty across different groups, it is important to note that traditional deterministic sensitivity analyses that change the background rate of testing may

not capture the full extent to which these parameters influence cost-effectiveness, as demonstrated in Table 8-1 and Table 8-2.

For modellers, the ability to identify different subgroups amongst the testing population, and appropriately stratify them in the economic model will depend on the availability of data from specific testing studies. If such data are available and allow for the model structure to account for this, the next issue is parameterising the testing rates for these groups (along with other parameters that may differ between these groups).

Studies of testing interventions rarely collect data on the individuals most recent test, and where this occurred, as this is not a priority for study. As such, estimating the likelihood that these individuals would receive HCV testing in the absence of the intervention is often difficult to parameterise, and data from the literature is often scarce. It is possible to estimate an average probability of testing in the general population, dividing the total tests by the eligible population. However these tests are not performed at random in the population, which is often demonstrated by the higher test positivity amongst current risk-based testing, an example of which is seen in the birth cohort analysis. Even where data on testing in specific settings exist, the extent to which individuals attend multiple settings which provide HCV testing in uncertain. Unfortunately, it is not possible to get a robust estimate of testing rates for those with different risk factors based on UK HSA sentinel surveillance data, since the data links to testing location, not to individuals and their characteristics.

In the absence of such data, economic evaluations tend to link HCV prevalence and the rate of HCV testing to injecting drug use status, such as current-, ex-, or never-PWID. Whilst a cross-sectional survey of people who inject drugs (currently or recently) is performed annually as part of the UK UAM survey data, estimating testing rates for ex- or never-PWID is more challenging.[54] The extent to which ex-injecting drug users attend services which offer routine HCV testing is likely to be highly variable depending on their needs, and the services they attend are likely to change over time, which would mean changes in testing rates may occur depending on the time since cessation of injecting.

It is also difficult to parameterise testing rates for those without obvious HCV risk factors. Whilst this group may receive testing in primary or secondary care, testing in these settings is not exclusive to these groups. Furthermore, there may be clinical indications associated with later disease states that may prompt testing in those without risk factors, rather than testing being offered for those asymptomatic, indicating that testing would be more likely at more advanced disease stages. Finally, whilst many modelling studies do stratify by injecting drug

use, there are likely to be other factors that may influence the probability of receiving HCV testing, such as the presence of other risk factors (e.g. country of birth), and possibly age, sex, ethnicity and geographical location.

### 8.6.4 Limitations

Firstly, whilst this analysis demonstrates that incorrectly assuming homogeneity in amongst the testing population can result in inaccurate model results, this has only been shown in theory. The analysis of the birth cohort testing intervention used a stratification based on history of injecting drug use status, whilst a simplistic analysis was performed to consider the HCV testing rates amongst different subgroups from the HepCATT study. Given that there remains uncertainty in the background rate of testing amongst different groups, for example ex-PWID and never-PWID, it is difficult to quantify the extent to which these assumptions are likely to bias cost-effectiveness results in practice, although the background rate of testing amongst HepCATT subgroups suggests it could be considerable.

The uncertainty in the underlying data and limitations of this analysis also means that it is not possible to recommend a conclusive method with which to tackle the issue of heterogeneity in HCV testing interventions. For example, this analysis did not assess the potential impact of assuming a ratio of testing amongst infected and uninfected individuals. This differential rate of testing between those infected and uninfected has been shown to change considerably over time in Chlamydia screening analyses, suggesting this approach may be simplistic.[27]

Furthermore, defining subgroups of patients into PWID or non-PWID, or into further categories such as current-, ex- or never-drug users remains a simplification. PWID can cease and re-initiate injecting practices, and injecting status alone does not predict an individual's attendance to services providing HCV testing. For example, people may or may not also engage in drug and alcohol services, receive OST, or may be more likely to receive testing if there are outreach testing for the homeless. In contrast, others who currently or have previously injected drugs may not attend any of these services, may live a stable lifestyle, and may not be recognised to be at risk unless they disclose their current or previous behaviours to a healthcare worker. The HepCATT analysis also demonstrates that other groups, such as those with a history of being in care, are likely to differ too, although this analysis did not explore the extent of crossover between these groups.

The two economic models used in this example differ in how the treatment effect is applied (an absolute rate of testing is applied in the birth cohort model, whereas the testing increase in the HepCATT intervention is relative). This ultimately leads to differences in the impact that changes to the background rate of testing may have on the results of the economic analyses. This is also true if there are differences between the linkage to care amongst the intervention and testing in other settings. Consideration should be given to this when evaluating the uncertainty around the background probability of testing in model analyses.

Overall, when considering economic evaluations of new testing studies, it is unclear whether an absolute or relative effect of a testing intervention is likely to be most appropriate. The choice is likely to differ depending on whether the intervention, is seen as a one-time testing strategy or whether it is likely to influence the testing rate over time. For a one-time only testing intervention (e.g. a mass screening event), an absolute intervention effect may be most appropriate as the coverage of the one-time testing can be estimated. In contrast, if the intervention involves changing the way testing is delivered, for example ensuring those who should receive testing are offered it because of a notification system, then a relative effect may be more appropriate because this is likely to be linked to the underlying testing rate already occurring.

Another limitation is that the background rate of testing is estimated from recently available testing data available from the UK, but this probability is extrapolated into the future under the assumption that it remains constant, despite evidence suggesting that testing for HCV is increasing. Other limitations of the modelling approach taken in this example are that it did not consider stratification by age, despite evidence that the highest number of chronic infections are amongst those aged 40 to 49 years old.[52] It is also likely that the background rate of testing differs considerably by age, based on national testing data.[9] The model also does not consider disease transmission, which will likely underestimate the benefit of a HCV diagnosis and treatment for those currently injecting drugs, as an earlier diagnosis and treatment can halt onward transmission of the virus. The model also does not consider the value of repeated testing amongst those who may be at risk of reinfection in the future, following diagnosis and successful treatment.

Finally, the scope of the narrative literature review is another limitation. The review sought to identify studies evaluating the background rate of testing, but it would have only identified studies where this was the main aim of the research. Studies analysing the background rate of testing or differential testing rates within a larger body of research are likely to have been missed. For example, economic evaluations which may have considered heterogeneity in

testing rates in their model analyses would have been missed unless details were provided in the abstract of the article.

### 8.6.5 Future research to help parameterise economic models

Studies of HCV testing strategies should collect data on patient characteristics and the risk factors amongst those tested, and whether the individual has received one or more HCV tests recently (for example in the previous year), and if so, in which setting(s). This would provide information on the proportion of individuals who are testing elsewhere and help to gain an understanding about the other services that those individuals are engaged with. This is particularly true for studies of mass screening interventions, which are likely to capture a heterogenous population.

Alternatively, if population testing data are available, then statistical analyses to estimate the testing rates would be helpful to parameterise the background testing rates in economic models of HCV testing interventions. Improving both the coverage of the sentinel surveillance datasets and gaining more insight into the risk factors of individuals who receive testing in a national dataset may help to ensure such data is available, although such a comprehensive dataset is unlikely to be available for HCV soon.

## 8.7 Conclusion

Economic analyses of HCV testing interventions should consider whether heterogeneity exists amongst the testing population. If testing captures those at differing risk of HCV, then it is likely that differences in the background rate of testing and the test positivity will exist between groups. Where possible, these differences should be accounted for in the model analysis, in order to avoid inaccurate model results, and the possibility of making the wrong policy recommendation. Where there is uncertainty in the heterogeneity, sensitivity analyses considering differential probabilities of testing amongst heterogenous groups within the model population should be performed, otherwise the uncertainty in the decision may be underestimated. Ideally, the design of HCV testing studies could help to address the uncertainty around this in the future, to help ensure the accuracy and validity of subsequent economic analyses.

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# 9 Discussion

## 9.1 Research objectives (Overview)

The aim of this thesis was to assess the cost-effectiveness of novel HCV testing interventions, with a focus on testing identifying people with HCV in the UK who are currently unlikely to be tested.

The first objective was to identify areas of interest for new HCV testing strategies for health policy makers and guideline groups which lacked economic evidence. This was successfully achieved with a review of NICE and ECDC HCV testing guidance, and supplemented by literature reviews to identify the knowledge gaps in the cost-effectiveness literature.

The second objective was to evaluate the cost-effectiveness of three novel HCV testing interventions that seek to expand testing to include people who are currently unlikely to receive it. They included the addition of HCV screening to the NHS's Health Check programme as a mechanism to test specific birth cohorts, introducing testing to all attendees receiving blood tests at hospital EDs, and using a risk-based algorithm in primary care to identify people at elevated risk of HCV. All three have been considered, or recommended for future research, by NICE hepatitis testing guidelines, as outlined in Section 4.5 (Table 4-3), and all lacked high quality economic evidence of their cost-effectiveness prior to this research.[1] They are clearly areas which policy makers and guideline committees have considered as potential testing strategies, perhaps anticipating that HCV testing in the UK would need to be scaled up in order to achieve the WHO elimination targets.[2] Prior to this thesis, the only cost-effectiveness evidence of these testing strategies was a conference abstract reporting the maximum cost available to deliver birth cohort screening and remain cost-effective, and a cost per case diagnosed for ED based HCV testing.[3,4] The economic evaluations within this thesis will help to inform HCV testing policies, and to also inform the need and design of future feasibility or pilot studies.

The final objective of this thesis was to consider the impact of heterogeneity amongst the HCV testing population which can exist when testing is expanded to groups that are at lower risk of HCV, and who may also be less likely to be tested elsewhere. Heterogeneity in economic evaluations tends to be addressed by subgroup analysis. Whilst this approach could be possible for some testing studies whereby specific groups may or may not be offered testing (e.g. the HepCATT risk algorithm), this wasn't possible when offering universal HCV testing

strategies for all those attending a specific setting (e.g. the NHS health check or the ED). Instead, this heterogeneity existed in the model parameter values, and caused uncertainty around how the model should handle this.

This thesis has demonstrated that cost-effectiveness estimates can be inaccurate when heterogeneity exists in the testing population but is not accounted for in an economic analysis. Of particular importance for HCV is accounting for the probability that people receive a HCV test elsewhere, or the 'background probability of testing'. This parameter is influential since the benefit of a diagnosis is closely linked to the probability that the person would receive testing and be diagnosed elsewhere. Whilst this thesis does not provide a definitive solution to overcome this issue for HCV models, it is hoped that highlighting it will help other health economists and decision modellers to consider heterogeneity when conceptualising their economic evaluations and/or model-based analyses. Moreover, it is also hoped this analysis will encourage those designing HCV testing studies to consider collecting data to help address this issue, such as the frequency of HCV testing amongst those attending the new testing service, to help provide more accurate cost-effectiveness estimates.

The thesis makes two key contributions to the existing literature. Firstly, the analysis of the methodology used to parameterise the background probability of testing in economic models provides a novel contribution to the existing health economic literature. It adds to existing literature showing the complex relationship between risk, probability of testing, and test positivity, and demonstrates the importance of accounting for heterogeneity that may exist in the economic model populations, showing the potential inaccuracies in model outcomes that can occur when this heterogeneity is ignored. It is hoped this analysis will help researchers when developing economic models for new testing strategies, particularly when existing risk-based testing strategies are recommended and thus likely to be included as a model comparator.

The three economic evaluations of HCV testing policies also contribute to the existing literature, with recommendations of interest to policy makers and local decision makers. These strategies were selected because they are of interest to UK policy makers and because they provide cost-effectiveness estimates where none previously existed, or because they significantly improved upon previously available analyses. However, these economic evaluations will also help provide additional resources for other health economists modelling HCV testing, with the strengths and limitations of the modelling approach and the parameterisation of the model discussed in detail within these papers. The areas for future research to address some of the limitations in the modelling approaches are also discussed.

## 9.2 Key findings

### 9.2.1 Testing strategies

This thesis has demonstrated that there are cost-effective interventions that will expand current HCV testing to people who are less likely to receive testing based on current recommendations. Moreover, testing strategies can remain cost-effective even when the prevalence of HCV is relatively low, meaning that they can help the UK meet the WHO targets for diagnosing 90% of chronic HCV infections by 2030 without compromising overall population health.[2] The cost-effectiveness of each of these testing strategies has been presented in their relevant Chapters, and the key findings from these economic evaluations in primary care and the ED are provided in the following subsections.

However, the recommendations for these testing strategies should be seen as complimentary to, rather than instead of, other HCV testing services that are currently recommended, particularly those aimed at people most at risk of HCV (i.e. PWID).

#### 9.2.1.1 Testing in primary care

Of the three interventions, arguably the strongest cost-effectiveness evidence was for the novel HCV testing strategy evaluated in the HepCATT study. The intervention was highly cost-effective and based on a randomised trial. It included a full costing analysis of the trial data, and sensitivity analyses demonstrated that the intervention would remain highly cost-effective even if incentives for primary care practices were used. Previous qualitative analyses have also demonstrated that the intervention is acceptable to healthcare workers too.[5]

A similar tool to the HepCATT testing algorithm is the 'Patient Search Identifier' tool, developed by Merck Sharp & Dohme (MSD).[6] The details of the intervention and how it differs from the HepCATT intervention are sparse, since the Patient Search Identifier tool medical codes have not been published. However, it is believed that the two interventions are very similar with only minor differences between the medical codes utilised (based on personal correspondence).[7] Both interventions scan patient medical records and highlight those patients at an elevated risk of HCV based on specific medical codes, and therefore the general approach is the same. The Patient Search Identifier is currently being piloted by NHS England

and NHS Improvements, although no data on the uptake of testing, or number of tests performed are publicly available yet.[6,8]

Whichever tool is preferred, further research to expand the criteria used to select patients to invite for an HCV test is highly recommended. A marginal analysis of the test positivity and cost-effectiveness for each additional risk criteria (or other characteristics, such as age or country of birth) would help to provide an evidence-based approach to selecting the criteria used to highlight patients at risk by the tool. The process of identifying and inviting patients to receive testing in the HepCATT trial was very similar to that used in the HepFREE study, although testing was for HBV and HCV, and was targeted at migrants who were born in countries with a high HBV or HCV prevalence, or whose parents were born in these countries.[9] Both the HepCATT and HepFREE interventions were highly cost-effective, with both using an algorithm to identify patients, send invitation letters, and provide electronic prompts to staff to offer testing to patients opportunistically. A review and meta-analysis, including mostly US-based studies, has also shown that electronic medical record alerts can be effective in increasing both HBV and HCV screening rates.[10] There may be opportunities for the risk-based identification of patients to include tests for HBV and HIV too, since some risk factors are common across all three.[1,11] NICE also recommends a simplified delivery of testing for both HBV and HCV at the same time, for those at risk of both.[1]

In contrast to the robust evidence to support the introduction of an algorithm or 'patient identifier' for HCV testing in primary care, the effectiveness of introducing an HCV birth cohort screening intervention attached to the NHS health check remains uncertain. Since the hypothetical intervention involved offering all attendees to the NHS health check a test, the average risk of HCV is likely to be far lower. This is demonstrated by the average test positivity in the HepCATT intervention (1.7% HCV RNA positive) versus the birth cohort intervention (0.1%-0.27% HCV RNA prevalence, estimated from back-calculation modelling outputs[12]).

The results of the model suggested considerable uncertainty in the decision, albeit that testing younger birth cohorts (1970-1979) was likely to be cost-effective. However, the model only captures some of the uncertainty around the decision. Firstly, the model included a hypothetical intervention, and only included the costs of the test and nurse time to perform the test, and not the costs associated with patient information or staff training. Furthermore, it assumed that a blood sample is already being performed as part of the health check, and that an HCV test can be added to this sample, but there is uncertainty about whether this would be the case across all settings providing this health check. Secondly, the prevalence amongst those attending testing was based on a modelling study rather than empirical evidence, which

also introduced uncertainty in the disease progression parameters as a result. Finally, the acceptability of the intervention to primary care staff, and those attending the NHS health check is unknown.

However, the main aim of the study was not to provide a policy recommendation around whether birth cohort screening should be implemented on the NHS health check. Instead, it was to consider whether such an intervention had the potential to be cost-effective, and if so, to identify the key parameters around the decision which should be collected in further research. The value of information analyses demonstrated that the linkage to care parameters had the highest priority for future research, followed by the utility increment for those achieving SVR.

Since the publication of the birth cohort cost-effectiveness analysis, a study to assess the impact of HCV birth cohort testing has been funded by NHS England, which has been named as the HepCAPP study (Hepatitis C Virus Case Finding in Primary Care Pilot).[13,14] The proposal draws on evidence from the birth cohort testing evaluation, showing that such an intervention could be cost-effective. The study will enrol 100,000 people aged between 40 and 64 years of age, inviting them to perform an oral HCV test delivered by a postal kit. It is anticipated that this will provide a robust estimate of the HCV prevalence and the subsequent linkage to care in this group, both of which were uncertain in the birth cohort model. The results of this pilot study will provide data for an updated cost-effectiveness analysis, which will help to make recommendations for a future HCV birth cohort testing policy.

Alternatively, depending on the success and cost-effectiveness of the birth cohort screening via postal test kits, another possibility that could be explored is whether the HepCATT (or Patient Search Identifier) tool could be adapted to combine some or all of these various groups that are deemed to be of sufficiently elevated risk of HCV to justify testing. For example, if a testing algorithm is pursued in primary care, then this could easily incorporate country or birth (as per the HepFREE study), and could also consider testing specific birth cohorts, if further empirical evidence supports testing in this group. It could also be that birth cohort testing is combined with other patient characteristics, or local prevalence estimates of undiagnosed HCV, to provide a more nuanced approach to identifying those at risk of HCV. This algorithm could also be adjusted over time, accounting for changes to the HCV epidemic, to ensure that both clinical and economic perspectives are accounted for in the sensitivity and specificity of the testing algorithm to identify those at risk of HCV. However, one issue with expanding the testing algorithm to identify more patients is that in some areas it has already returned an excessive number of primary care patients for testing, which has raised issues about the

workload for general practices.[5,8] This is, in part, one of the benefits of adding testing onto an existing service which already involves a blood sample being taken, since there is no incremental staff resources at the point of testing as it avoids the need for a separate, additional appointment. This cost will also be avoided with self-testing postal kits, although if the uptake of testing is lower then this would reduce the overall impact of the intervention. Furthermore, if a large proportion of postal tests are sent but not returned, this would still incur a cost, but without any benefit.[13]

#### 9.2.1.2 Emergency department testing

In EDs, opt-out HCV testing is likely to be cost-effective in many areas across the UK. The analysis showed testing is highly likely to be cost-effective where the HCV RNA prevalence is 0.5% or higher. Moreover, the minimum prevalence at which testing can remain cost-effective was even lower (around 0.25%), although there is greater uncertainty around this, particularly given the limitations of the studies used to parameterise the model. The analysis used data from two small ED-based testing studies, and the extent to which the outcomes of these studies are reflective of ED-based HCV testing in practice are uncertain.[15,16]

Despite these uncertainties, providing a conservative threshold prevalence at which HCV testing is recommended would allow for additional data to be collected in EDs. Following this data collection, a more robust estimate of the prevalence threshold at which HCV testing is cost-effective in the ED could be calculated. In fact, an updated economic evaluation of HCV testing in the ED is currently ongoing. Further details are stated in the 'Future research' section below (Section 9.6), but briefly, this includes long-term HCV testing from two EDs, in London and Leeds.[17,18] Following the demonstration of additional evidence of the prevalence thresholds at which ED testing for HCV is cost-effective, it is hoped that testing in this setting will be included in any update of the NICE hepatitis testing guidelines, since this has been highlighted as an area of interest.[19] With cost-effectiveness findings available, this should help to support the introduction of guidance for testing in the ED. This would also align NICE hepatitis testing guidelines with their prevalence based recommendations for HIV testing.[11] It would also create more coherent guidance for hospital EDs to decide for which of the three BBVs (HBV, HCV and HIV) to test for in ED attendees. In addition to NICE guidelines, the ECDC testing guidelines recommend testing in the ED where the prevalence is ≥2%, but the results of this analysis suggest testing can be cost-effective at a far lower prevalence, potentially having implications for testing in European EDs too.[20]

At the time of thesis submission, there were no other UK economic evaluations of ED based HCV testing, and only one other study has been identified outside of the UK. This study evaluated ED testing in Canada and the US, and was published at a similar time as the ED testing analysis presented in this thesis.[21] It found that testing for all ED attendees was cost-effective, when compared to no HCV testing, and ED testing only for those born between 1945 and 1975 (i.e. in birth cohorts), with an ICER of just under $20,000 Canadian Dollars (CA$). The ICERs are slightly higher than those reported in our analysis, likely due to differences in several key parameters (to which the ICER was sensitive to in the UK based ED testing model). This includes the cost of DAA treatment (CA$60,000 per course in Canada, and US$89,700 in the US), and the cost of HCV antibody tests (CA$24). This contrasts to parameters used for the UK, with DAA treatment costs of £10,000 per course, and an HCV antibody cost of £3.64. Other costs also tended to be higher than those used in our analysis. In Canada, universal ED testing also remained cost-effective at the lowest prevalence evaluated (1%). Although these findings are in a Northern America context, they further indicate that the 2% threshold recommendation for ED testing in European testing guidelines may be too high.[20] Interestingly, this analysis also considered testing ED attendees based on their age, similar to a birth cohort screening intervention, but this strategy was not cost-effective (by extended dominance). This is likely because previous economic evaluations in the USA and Canada have concluded birth cohort screening for HCV is cost-effective.[22-24]

Finally, as part of this thesis a scenario analysis considered the cost-effectiveness of ED testing across different age bands. The ICERs were similar across groups aged 16 to 69 (from £4,262 to £7,778 per QALY gained), but higher for those aged 70 and above (£21,600 per QALY gained), suggesting that testing in this age group may not be cost-effective. However, a number of assumptions were made in this analysis, since other data were not stratified by age, resulting in a higher degree of uncertainty in the ICERs compared to the base case analysis. The cost-effectiveness amongst different age groups should be considered in future research, as some ED testing studies in the UK have limited testing to adults aged 65 years of age and under, whilst others have not added any upper age limit.[15,16,18,25] Whether policy makers wish to provide guidance about an upper age limit for testing is unknown, but differences across ED studies already exist.

### 9.2.2 Economic analyses informing testing service design: Ensuring effective linkage to care following diagnosis

Another key finding of this thesis is the importance of linking those testing positive for HCV to treatment, and the impact that this has upon the cost-effectiveness. Ultimately, the benefit of testing is only realised when those testing positive receive treatment, as a diagnosis alone is unlikely to improve a persons quality of life without treatment.[26] Across all three evaluated testing strategies, the proportion of patients linked to care has a large impact upon the ICER. Testing strategies should therefore ensure that adequate resources are allocated to contacting and linking those testing positive onto treatment, to minimise the loss to follow-up along the care pathway. This is particularly import when testing those at a lower risk of HCV, as the number needed to test to identify one positive case is high.

There are various ways in which those testing positive can be contacted and subsequently supported to engage in care and receive treatment. For example, this could involve contacting patients by phone (call or text), letters to patients and/or GPs, or re-engaging patients opportunistically at their next visit. Having integrated links or collaborating with other community and healthcare services is also likely to be beneficial. This is particularly true for testing in the ED, which may be one of the only health services that some people attend, and some may not have up to date contact details. The value of ensuring links with other services has been demonstrated in two recent ED testing studies in Leeds and London, with ED nurses collaborating with other services (drug and alcohol services, outreach services, and services for the homeless) to increase linkage to care rates.[18,27-29] Education and support for those with HCV is also important.[30] For example, the Hepatitis C Trust is a patient-led and patient-run organisation that provides education programmes and peer support, which has been shown to increase the linkage to care and treatment rates.[31-34]

### 9.2.3 Economic evaluation methodology

This thesis has demonstrated the challenges in modelling the comparator for HCV testing strategies, based on the complex relationship between risk, current testing rates, and test positivity. Each of the testing strategies evaluated have been assumed to be in addition to current testing rates, but modelling the current testing rates is complex, particularly when the model population is likely to be heterogenous.

In the HepCATT evaluation, the trial had a control arm which provided the probability of testing in the absence of the intervention. However, this probability was significantly higher than the baseline period (prior to the start of the trial), posing questions about the reason for the increase in testing in the control arm, and whether this increase was likely to be sustained thereafter. The analysis also assumed that those at elevated risk were not receiving testing in other settings, and only in primary care, which is a simplification. Since the HepCATT testing population identifies those who *should* receive testing under current guidelines, but are unlikely to do so, the rate of testing in the control group (or baseline period) is not reflective of the testing rate for those without risk factors. As such, this study was not used to inform the testing rates for the two universal opt-out testing studies, as part of the NHS health check or in the ED. In these two economic evaluations, the background probability of testing was derived by taking the estimated total number of HCV tests performed in England annually (adjusting for the testing coverage of testing numbers reported by UK HSA sentinel surveillance) and divided by the total adult population of England. This is a very simplistic approach to derive a mean probability of testing, and assumes testing is performed at random in the population. It ignores the possibility that testing may differ amongst those within the model population. The methodological analysis presented in Chapter 8 showed how this could lead to inaccurate model predictions if these probabilities differ considerably between groups and are not accounted for.

Economic evaluations of HCV testing interventions which include a heterogenous testing population should therefore seek to account for this within the economic analysis, if sufficient data is available to do so. Stratifying the populations into risk groups, where possible, is one way in which this could be done to help to improve the accuracy of the cost-effectiveness results. Where there is uncertainty around the extent to which heterogeneity exists, structural sensitivity analyses should consider the possibility that heterogeneity exists. This is important because sensitivity analyses of the background rate of testing under the assumption of a homogenous cohort can underestimate the uncertainty around the cost-effectiveness estimates.

Improving the design of studies into HCV testing strategies could provide modellers with more data to understand the population characteristics (i.e. risk factors) of those attending a particular testing strategy, and the extent to which they attend other settings where they may be offered an HCV test. By collecting such data, the incremental costs and benefits of a new testing intervention can be estimated more precisely. This will be increasingly important as HCV testing is scaled up further, since the probability of an individual being offered testing

across multiple settings will increase. This is particularly important for those who are not currently at risk of acquiring HCV infection, as repeat tests are unlikely to be a good use of resources in this group.

## 9.3 Policy Implications

In primary care, an algorithm or patient identification tool similar to the HepCATT intervention should be implemented in order to identify and provide testing for those at an elevated risk of HCV, and who have not recently been tested. This is supported by high quality evidence that such an intervention would be cost-effective. Testing in those with risk factors for HCV is already recommended by NICE, but since the extent of testing for those with historical risk factors is sub-optimal, the algorithm-based identification of those at an elevated risk can help to ensure that those who should be tested are offered it.[35] The Patient Search Identifier developed by MSD is now available across all GP practices, albeit that the proportion of primary care practices that have run the algorithm has been relatively limited so far (based on personal correspondence).[6,8,36] MSD are funding the intervention as part of their case-finding initiatives linked to the DAA treatment procurement deals.[36,37] Since the intervention does not expand the population to be tested, it is likely to remain appropriate and cost-effective even if the general population HCV prevalence continues to decline with ongoing HCV elimination efforts.

Unlike the Patient Search Identifier intervention in primary care, the cost-effectiveness of birth cohort testing is uncertain. However, with funding for additional research secured, an updated cost-effectiveness analysis using the results of this study will help to inform more robust policy recommendations for a birth cohort screening intervention in the future.[13]

In EDs, universal opt-out HCV testing for those already receiving blood tests should be recommended when the prevalence is 0.5% or higher, since testing is highly likely to be cost-effective at this prevalence. NICE guidelines for HCV testing should be updated to reflect the cost-effectiveness of ED testing at these prevalence thresholds, which would help to align them more closely to the prevalence based recommendations by NICE for HIV testing in EDs.[11] Testing may remain cost-effective at even lower prevalence, but there is greater uncertainty around this. Further empirical evidence on the effectiveness of ED testing will help to refine these prevalence thresholds, using data from long-term testing studies. In England, ED testing initiatives have started in 12 EDs, in 7 HCV ODNs (as of January 2022, based on personal

correspondence with NHS England and NHS Improvements).[36] However, the design of ED testing interventions differs across areas. There are differences in who receives testing (opt-out vs. opt-in testing), and how patients are contacted following a positive test (e.g. some EDs have a peer worker for contacting those testing positive, whilst others do not). There would be value in comparing the designs of these testing interventions, and assessing their cost-effectiveness, to provide evidence-based recommendations for areas who want to start ED testing. However, since there are differences across regions, it remains to be seen whether a single specific approach to ED testing can, or should, be recommended without consideration for some of these local factors. For example, it may be difficult to make recommendations for the most appropriate way for ED staff to work with existing outreach or inclusion health teams to link patients into care, since these services are likely to vary considerably across different areas.

The prevalence-based recommendations for ED testing will help identify areas where testing is cost-effective. However it will also help to inform when testing may no longer become cost-effective in some areas, since ongoing elimination efforts in the UK will likely reduce the HCV prevalence over time. Graham Foster, the National Clinical Lead for HCV ODNs for NHS England and NHS Improvements, has stated that the goal for NHS England is to offer testing to everyone at risk and ensure those who test positive are offered treatment, but that in the future this elimination drive will need to move to a 'Maintenance' phase, in which resources are moved elsewhere.[38,39] It may be ED testing can support the elimination drive by identifying many of those living with undiagnosed HCV, but is phased out when prevalence falls, and fewer resources are allocated to the HCV elimination agenda.

If only one HCV intervention could be implemented, then the HepCATT intervention should be prioritised. The intervention resulted in the lowest ICER of all the analyses, suggesting that testing is the most cost-effective option of all interventions included in this thesis. Furthermore, the data used to parameterise the cost-effectiveness analysis is the most robust of all three analyses, since it was derived from a large trial with thousands of patients included. It also included a full costing analysis of the intervention, whereas the costs associated with the other two studies were more uncertain.

## 9.4 Knowledge exchange and personal development

As mentioned in the introduction to this thesis, the work undertaken during my PhD was funded by the NIHR HPRU on Blood Borne and Sexually Transmitted Infections, with the aim of directly impacting health policy. The Unit is closely linked to the UK HSA (formerly PHE) and involves many collaborations which have helped to support this research. For the economic modelling aspects of the thesis, I have worked independently on developing the economic models. However, the selection of testing strategies to evaluate, and the identification of data to parameterise the models involved considerable support from the research Unit, staff at the UKHSA, and other academics working on HCV testing (particularly those at the University of Bristol). I feel that it is important to recognise this as an area of knowledge exchange and collaboration across institutions that has influenced the direction of the research presented in this thesis.

There have been other activities that have helped to shape the research performed, allowed me to receive constructive criticism and provided me with opportunities to present my results. I have presented early findings of some of these studies at various conferences, including the International Liver Congress, HepHIV conference, and the International Conference on Hepatitis Care in Substance Users.[40-42] These allowed me to incorporate feedback from experts involved in various areas of hepatitis and public health research, including those working directly in the delivery of hepatitis testing strategies, those working with patients, those performing academic research, and those involved in policy and decision making. With regard to dissemination activities, I have also been fortunate that the NIHR has taken an interest in my research, and helped to promote the implications of the findings.[43,44] I have also received support from LSHTM with a short communication piece to help disseminate the research.[45]

More recently, I have had the opportunity to be involved in several other new projects. For example, my research into the cost-effectiveness of HCV testing in the ED has resulted in me receiving a grant to perform an updated economic analysis using long-term testing data from two EDs. This work is currently ongoing and has given me the opportunity to manage my own research project. In addition to this, it has also led to my involvement in various other HCV testing projects. As part of an ongoing HRPU grant held at UCL, I have been asked to work alongside an NHS England and NHS Improvement Task and Finish group, to address the cost-effectiveness of various HCV testing strategies in antenatal services. This model will be used to inform testing recommendations by the UK National Screening Committee. Finally, I am

involved in an ongoing NIHR HTA of testing and treatment policies in people who inject drugs, in collaboration with the University of Bristol.[46]

## 9.5 Limitations

The limitations of each individual study have already been discussed in their relevant Chapters. Although some of the limitations are similar across studies, given the similar methodology and issues encountered in performing economic evaluations of HCV testing in the UK, this section will focus on the limitations of the overall thesis.

### 9.5.1 Comparison of HCV testing strategies within an economic model framework

A limitation of this thesis is that it does not compare the three novel testing strategies to one another within the same economic model. Having all of the testing options as comparators within one 'comprehensive' model could inform which combination of testing strategies is the most cost-effective, which is something that is not addressed in this research. Since two of the testing interventions were highly cost-effective (risk-based primary care testing and ED testing), such a model could evaluate whether one intervention remained cost-effective if the other was implemented (e.g. would ED testing remain cost-effective if an algorithm-based testing strategy is implemented in primary care?).

However, parameterising such a model would be a complex undertaking. Firstly, the model would likely need to consider the UK general population, since each testing strategy includes a different testing population, which differed by age, HCV risk, and PWID status. Second, it would need to consider the extent to which individuals who receive testing in each of the three testing strategies evaluated would likely receive testing in other settings, either as part of current testing, or as part of the other testing strategies being evaluated. It is already challenging to estimate the extent to which individuals in the model receive testing in existing settings, so estimating the extent to which individuals in the general population may engage in each of three testing strategies evaluated in this thesis would be even more difficult, particularly since they have not yet been introduced across the UK.

Ultimately, designing such a model, which accounts for this was considered too challenging for this thesis. A grant has recently been awarded by the NIHR to undertake such an analysis for all HCV testing strategies in England.[46] However, the model being developed will only consider

PWID, rather than the general population, and is therefore conceptually simpler than a general population approach, which would be needed to evaluate testing in both primary care and EDs. To the best of my knowledge, an analysis considering all population-based testing strategies alongside current risk-based screening, across multiple healthcare settings, has yet to be performed for HCV testing in any other country. If such a model were developed however, it could also consider other testing strategies not considered in this thesis, such as testing in antenatal services, which has been shown to be cost-effective in the UK and is currently being evaluated by the National Screening Committee and NHS England.[38,39,47]

### 9.5.2 Parameterising the model comparator: current testing practice

There are also limitations in how the comparator for all three of the testing interventions (current testing practice) was parameterised in each of the three economic evaluations. Specifically, there were issues around the extent to which the probability of testing elsewhere may differ amongst the model population due to heterogeneity, whether the linkage to care may differ in other settings compared to the intervention, and how the probability of testing is extrapolated in the economic model. These three aspects are discussed below.

The current testing practice comparator was deemed to include HCV testing in all other settings or services. However, the extent to which the current testing practice differed amongst individuals in the model population was not considered in the economic evaluations. This was explored in a separate methodological analysis, which demonstrated the inaccuracies in the model predictions that can result from this. Although I was unable to provide a definitive solution to this issue, there are recommendations for potential ways to overcome it. One way is to stratify the population according to differences in their HCV risk and probability of receiving an HCV test currently. However, the extent to which this heterogeneity exists is still uncertain, because of the uncertainty in the background rate of testing amongst various subgroups within the population. This makes it difficult to confirm the extent to which this may have influenced the results of these analyses.

Statistical analyses could be undertaken to estimate the extent to which individuals included in each of the three economic evaluations may attend existing services offering HCV testing, using UK HSA datasets on sentinel surveillance. However, this would be particularly difficult to estimate given the relatively low coverage of the sentinel surveillance datasets (~40%), and because of other uncertainties around datasets, including the effectiveness of de-duplications given the limited patient identifiers available on laboratory results reported to the UK HSA.

Whilst there would certainly be value in undertaking such a statistical analysis, it would likely be a very time-consuming undertaking, and it is unclear whether access to the dataset would be possible outside of the UK HSA. For these reasons, and in order to keep the research focused on the evaluation of new testing strategies, this research was not undertaken.

Another limitation is that the current testing practice comparator did not account for differences in the proportion of patients linked to care following a positive test, across different settings. For the two universal opt-out testing strategies (birth cohort screening and ED testing), the model assumed that the linkage to care following a positive test was the same for the new testing strategy (the intervention) and for current testing practices (testing in settings other than the intervention). This is particularly important as the linkage to care parameters had a large influence upon the cost-effectiveness results. This is demonstrated within the HepCATT intervention, in which the intervention would have been cost-effective even if it did not increase testing, because it resulted in a higher proportion of patients linked to care.

The rationale for this approach was that the individuals who test positive would be equally likely to be contacted and accept treatment in any setting in which they received testing. However, it is very difficult to distinguish the extent to which linkage to care rates are a result of the population being tested, or the setting in which they receive testing. Those in marginalised groups can be difficult to engage in care, as they may also have other acute healthcare or social needs which are a higher priority compared to their HCV diagnosis, or may be more difficult to contact, especially if they are not registered to a GP.[48] In contrast, those accepting an invitation to an existing health check may be more likely to prioritise their health, simply based on their decision to attend such a service. However, this assumption overlooks the potential for some settings to be more effective in linking patients to care. For example, patients do not attend the ED regularly, unlike primary care or other community services where HCV testing may occur. As such, contacting patients from the ED may be more challenging. In addition, the effectiveness of each setting at following up with individuals who test positive will also be important, as settings that invest more resources for nurses or other healthcare staff to link patients to care are likely to be more successful. Education, support and raising awareness also tend to increase linkage to care, as shown in the HepCATT trial, and other interventions which involve specialist peer support workers in outreach teams.[32,49]

Lastly, in each economic evaluation, the model estimates the current HCV testing rates to give a mean annual probability of testing, and then this value is used to estimate the probability that individuals with HCV will be tested in the future. However, HCV testing in the UK has been

increasing over recent years (at least until the Covid-19 pandemic), particularly since the introduction of elimination goals.[50-52] This is likely due to several factors, such as HCV testing being introduced in new settings (e.g. testing in pharmacies, probation services, or additional outreach services[32,53,54]) or additional resources being provided to increase testing strategies within existing settings (e.g. large-scale test and treat events in prisons[55]). It is also likely that current testing strategies have received more resources, allowing testing to be increased in the same service. Increased awareness of HCV is also likely to have led to increasing offers of testing for those at risk (e.g. in primary care), and potentially more requests for testing from individuals who learn that they are at risk.[56] Whatever the reason for the increase in testing over time, this trend is not accounted for in the extrapolation of future HCV testing rates, despite it being likely that testing will continue to increase to meet these elimination goals. It is also possible that testing rates may decrease when the elimination goals are achieved (or are close to being achieved), as resources are likely to be moved away from HCV testing. This change is difficult to predict or account for in economic models, but it must be acknowledged that it is an uncertainty that is not considered within the models used.

### 9.5.3 Uncertainty around the model structure and disease progression parameters

Two different model structures were used to represent the early stages of HCV, without any formal assessment of which is to be preferred. There is also uncertainty surrounding the sources of transition probabilities used to parameterise the model, with the original publications using different methodologies to estimate these.

The economic model in the analysis of birth cohort screening and the analysis of the HepCATT intervention for HCV testing in primary care used the Histology Activity Index (HAI), also known as Ishak score, to represent early HCV health states (up to the onset of compensated cirrhosis). This included 'Mild HCV' and 'Moderate HCV' health states, before progression to 'Compensated cirrhosis'. This was based on Ishak scores of F0-F2 (Mild HCV), F3-F5 (Moderate HCV), and F6 (Compensated cirrhosis). In the birth cohort analysis, this aligned directly with the outcomes from the back-calculation analysis, which reported the prevalence of chronic HCV across birth cohorts in England, stratified by severity according to the Ishak scores.[12] These values were therefore used as initial distributions to inform the fibrosis stage for those with undiagnosed HCV in the birth cohort analysis. Many other UK based economic modelling studies have adopted this model structure, based on Ishak scores, including those informing NICE guidelines.[57-59] UK based economic evaluations using this structure tend to use transition

probabilities estimated from an RCT in mild HCV patients in the UK, reported by Wright et al.[60] These transition probabilities are also widely cited as being derived from a UK HTA by Shepherd et al., since this HTA also reported the uncertainty around the transition probabilities (in the form of alpha and beta parameters for the beta distribution).[61]

In the HCV birth cohort screening analysis, the Ishak based model structure had other advantages. Using the same structure as the back-calculation model allowed for transition probabilities estimated through the Bayesian model fitting process to be analysed in sensitivity analyses in the economic analysis, to assess the impact of these transition probabilities on the cost-effectiveness results. The use of the age-based transition probabilities reported by Harris et al. in this Bayesian analysis had a significant impact upon the cost-effectiveness estimates and the cost-effectiveness decision.[12] This presents an obvious methodological issue. The UK based transition probabilities reported by Wright et al. are based on clinical evidence of HCV progression, and ensure comparability with other UK based economics evaluations.[60] In contrast, the transition probabilities estimated from the Bayesian model fitting approach are based on data which have considerable limitations, which are reported in the original publication.[12] However, these Bayesian transition probabilities were used to estimate the prevalence of HCV in the UK, and if these are considered inaccurate, or inferior to the empirical estimates from clinical research, then this inherently suggests that the prevalence estimates used in the birth cohort model must also be inaccurate.

A separate study from Gubay et al. 2018 explored the influence of the two sources of transition probabilities, as a standalone study.[62] This analysis included a study by Martin et al. 2012, which used fixed transition probabilities reported by the Shepherd et al. 2007 HTA, and compared these to transition probabilities estimated from a previous version of the back-calculation model used to estimate the prevalence of HCV in the UK.[57,61,63] The two approaches resulted in vastly different estimates of the number of deaths and liver transplants, with up to a 300% difference between predictions for certain cohorts, which had a large impact on cost-effectiveness estimates. These results were similar to those reported in the HCV birth cohort screening analysis, in which the model estimates differed considerably, providing further evidence of the uncertainty in the economic model predictions. The study by Gubay et al. also recommended further research to address this uncertainty.

A different approach was taken for the analysis of HCV testing in the ED. Instead, the progression of HCV was captured using METAVIR scoring system. The definitions for METAVIR scores F0 to F4 are as follows: no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with rare septa (F2), numerous septa without cirrhosis (F3), and compensated cirrhosis (F4).[64]

Using the METAVIR scoring system, the model structure included four health states from F0 to F3, instead of two health states, Mild HCV and Moderate HCV, using the Ishak staging. The reason for using a different model structure in the analysis was because the progression rates between METAVIR scores are available from a large meta-analysis and evidence synthesis, which reported transition probabilities specific to PWID and non-PWID populations.[65] None of the economic evaluations considered the impact of using the METAVIR score instead of the Ishak score, so the impact that this has upon the cost-effectiveness estimates is unknown.

The differences in the model structures, based on progression using the Ishak score or the METAVIR score, have been discussed in other research, although the majority do not provide strong recommendations for either, except one study which suggests that the METAVIR based probabilities reported by Thein et al. provide the highest quality data.[66-68] From the studies identified in the literature review in Chapter 4, most, but not all, of the recent model based economic evaluations from the UK use a model structure based on METAVIR scores.[69-73] Interestingly, these analyses still use the same costs and utility values based on Ishak scores, with the costs and utilities for METAVIR F0 and F1 equal and equivalent to mild HCV, whilst the costs and utilities for F2 and F3 health states are often equal and equivalent to moderate HCV.[69-73] Therefore it is primarily the disease progression parameters that are responsible for the change in the different model structure choices, and the main factor in differences between the model predictions. There remains some uncertainty around which sources are the most appropriate, which ultimately depends on an evaluation of the quality of the evidence from these studies, and whether UK-based estimates are preferred to estimates from a large meta-analysis. Given the meta-analysis from Thein et al has been recently updated, it seems likely that more future UK-based economic evaluations will adopt this model structure, which will also help comparability across screening interventions.[74]

The lack of a coherent model structure across the three economic evaluations could be deemed as a limitation of this research. However, given the uncertainty around which of these structures is most appropriate, perhaps a more valid limitation is that the differences in the cost-effectiveness estimates resulting from these two approaches have not been assessed. Whilst it may be worthwhile demonstrating the differences in the model outputs based on the two approaches, additional research of progression in UK cases is likely to be required in order to address which most accurately represents disease progression. However, with most people diagnosed with HCV receiving treatment, and the slow rate of HCV progression, this is likely to be a very difficult study to undertake. With the elimination targets to achieve, this area of research is also unlikely to be a priority.

### 9.5.4 DAA treatment costs – driver of cost-effectiveness

A limitation of this thesis, and of recent economic evaluations of HCV testing strategies in the UK, is the uncertainty around the DAA treatment costs. The negotiated prices paid by the NHS, upon achievement of SVR, are commercially sensitive and therefore confidential.[37,75,76] Whilst this is standard practice in pricing of medicines, it presents difficulties in interpreting the results of economic evaluations. This is particularly true since the DAA costs have a relatively large influence upon the cost-effectiveness results, and given the extent of the discounted prices, which are believed to now be less than £10,000 per course compared to list prices of approximately £30,000 to £45,000.[75,77,78] The uncertainty around the treatment costs contributes to uncertainty in the cost-effectiveness results, increasing the chance for incorrect recommendations regarding testing. In each of the economic evaluations, sensitivity analyses have been presented to evaluate the cost-effectiveness of testing at different DAA prices, although these are only deterministic analyses, and therefore do not consider joint parameter uncertainty. This thesis takes a pragmatic viewpoint, using an estimated £10,000 per course of DAA treatment, although the treatment costs may be even lower. Another consideration is whether these negotiated prices are linked to the HCV elimination goals and therefore time limited. If so, the results of the economic evaluations may no longer be relevant once this discount ends. Under this scenario however, the prevalence and epidemiology of HCV will likely also have changed, and therefore the economic evaluation results are likely to require updating.

### 9.5.5 Other limitations

There are also other limitations of the research that should be considered.

This research involved the development of static, cohort-based models, which do not consider disease transmission. This modelling approach was taken because the testing strategies evaluated were not primarily aimed at identifying PWID, and instead were believed to mostly identify those who may have historical risk factors for HCV but are unaware of their current risk. However, some of those attending the three testing strategies will be PWID. This was the case in the ED testing study, with approximately 27% estimated to be people who currently use drugs. No onward disease transmission was included in the models, meaning that the benefit of treatment as prevention is not considered. The model for ED testing did include

reinfection for PWIDs, so as not to overestimate the benefit of achieving an SVR in this group. Sensitivity analyses were performed in the economic evaluations of primary care testing too but had little impact upon cost-effectiveness unless the reinfection rates were high, which is very unlikely in this group. All three models assumed that the risk of reinfection amongst non-PWIDs would be zero, since the risk of new infections in the UK is highly associated with injecting drug use, as stated in Section 1.4.

The cost-effectiveness analyses did not formally consider the accuracy of the diagnostic tests. Some people recently infected may not have developed antibodies when they test and could therefore be missed when receiving an HCV antibody test. However, two of the three economic evaluations were based on empirical testing data, so the proportion of people identified is not over-estimated. In the hypothetical screening intervention for birth cohorts, very few of those ex-PWID and never-PWID would likely have been infected recently. As such, whilst this is a simplification of the modelling approach, it is unlikely to have much impact on the cost-effectiveness of the testing interventions evaluated.

Finally, although the aim of this thesis was to evaluate the cost-effectiveness of novel HCV testing strategies in the UK, most of the data used in the economic models were derived from England, which may limit their generalisability to other UK nations. The HepCATT trial and the ED testing studies were performed in England, but the generalisability of these interventions across the UK is likely to be high. For the HepCATT intervention, the same medical codes are likely to be appropriate since testing recommendations across the UK are similar, and the issue of suboptimal testing amongst these groups in primary care is likely comparable across the UK. The intervention was also highly cost-effective, suggesting it is also likely to be cost-effective in other UK settings. For ED testing, the prevalence-based threshold estimates mean that the intervention is likely to be cost-effective across these areas if the prevalence of chronic HCV meets or exceeds these levels.

In contrast, the birth cohort screening analysis was assumed to be added to the NHS health check, which is offered to those aged 40 to 74 years old in England.[79] A similar health check was previously offered in Scotland to those aged 40 to 64 years old in areas of high deprivation, but this seems to have been stopped.[80] To my knowledge, there are no equivalent schemes in Wales or Northern Ireland. This limits the generalisability of the results of the cost-effectiveness analysis to other UK nations, since the economic analysis assumed testing for people already attending an existing service. However, NHS England has funded a study to assess an age-based HCV screening intervention which involves a self-testing kit which, if cost-effective, would be easier to replicate across all UK nations.[13]

## 9.6 Future research

### 9.6.1 Additional research into the testing strategies evaluated in this thesis

As discussed in the key findings section (Section 9.2.1.1), additional research into the Patient Search Identifier tool in primary care is needed. The tool is currently being piloted in the NHS, and further research should be conducted to consider how this could be expanded to include a higher proportion of people who may be at an elevated risk of HCV, to improve the effectiveness and cost-effectiveness of the intervention. Since the results of the HepCATT study showed that the intervention is highly cost-effective, there is likely to be scope to expand the criteria and identify more individuals who may be at risk of HCV.

Such a study could take a random sample of those not identified by the tool, and consider whether other characteristics, or combinations of characteristics, are associated with elevated HCV risk. Alternatively, an assessment of the existing literature or testing statistics could be undertaken to consider additional risk factors or characteristics associated with undiagnosed HCV infection. The incremental cost-effectiveness could be estimated at the margin, for each additional group added to the existing patient identification tool. This would help to maximise the number of individuals tested for HCV, whilst only offering testing to those to whom it is cost-effective.

Further research is also required before any recommendation around the feasibility and cost-effectiveness of HCV birth cohort screening can be made. Updated estimates of the HCV prevalence are needed, and this will be addressed by the HepCAPP study, which will invite 100,000 people to self-test across three different regions of England.[13] It is uncertain whether the NHS health check or postal kits would be the best option for delivering testing. Since the NHS has funded the study for opt-in postal kits for HCV testing, this suggests that there is a preference for testing to be delivered in this way, potentially to avoid additional burden to existing healthcare services following the COVID-19 pandemic. If postal testing kits are effective and acceptable, then an updated cost-effectiveness analysis will help to provide policy makers with appropriate recommendations. Alternatively, if policy makers did wish to pursue a birth cohort screening intervention as part of the NHS health check, a feasibility study would be required to consider the acceptability of testing to attendees, the potential barriers to adding HCV screening to the service, the most appropriate type of diagnostic test to be used, and the additional resources that may be needed to undertake testing. Whichever

approach for HCV birth cohort screening is preferred, it is important to understand how likely it is that those being tested would be offered testing elsewhere, and whether this likelihood of testing differs amongst the population invited.

For ED testing, additional research is already underway to address some of the limitations of the analysis presented in Chapter 7. The model will be parameterised by two long-term ED testing studies performed in Leeds and London.[17,18] The analysis is expected to provide a more robust estimate of the HCV RNA prevalence at which testing remains cost-effective, and will also include a budget impact analysis, to help inform decision makers of the cost associated with an ED testing intervention. However, further research is required. This updated analysis will still only include two UK locations, and early results indicate that there are considerable differences across the two locations, particularly in the linkage to care rates. Further research should focus on the pathway used to link patients into care and the staff resources required to do this effectively, to ensure that as many patients as possible are linked to treatment. Another question to consider is whether there should be an upper age limit for HCV testing in the ED. Some studies have not included any upper age limit, but others have restricted opt-out testing to those aged 65 and under.[15,16,18,25] The model results suggest testing for those aged 70 and above may not be cost-effective, but these results were highly uncertain due to the simplistic analysis performed. Larger testing studies are needed to allow for cost-effectiveness analyses that stratify testing by age, with sufficient samples to inform the proportions of patients requiring linkage to care and being successfully linked to treatment in each age group. This will help to inform policy makers of an appropriate cut-off for HCV testing, from an economic perspective.

### 9.6.2 Population based economic model considering all possible HCV testing strategies

In the future, a 'comprehensive' model could be developed to consider all possible HCV testing options for the UK general population, with each testing strategy included in the model. This would allow all testing interventions to be evaluated and compared to each other, including those included in this thesis. The model could identify which combinations of testing strategies are the most cost-effective. It could also evaluate other testing strategies, such as HCV testing in antenatal services, which has previously been shown to be cost-effective in England, and is currently being evaluated by the National Screening Committee and NHS England.[38,39,47] Such a model could also consider whether additional resources should be invested into additional testing services, or whether possible strategies to improve linkage to care might be a more

efficient use of resources. However, as already discussed in Section 9.5.1, developing such a model would be complex, difficult to parameterise, and very time-consuming.

### 9.6.3 Understanding the current probability of testing amongst those attending HCV testing services, including the heterogeneity that exists

One of the main limitations of the thesis is uncertainty about the probability that those included in the economic models will receive a HCV test under current practice, and in particular, the extent to which this may differ amongst different subgroups within the testing population.

A study addressing this evidence gap would help to reduce the uncertainty regarding this 'background probability of testing' parameter and could also highlight the extent to which heterogeneity may exist between groups of individuals, depending on their risk factors. Whilst PWID are known to have a higher probability of testing, there is little data around what happens to those who cease injecting drugs, and how their attendance at services which offer HCV testing may change over time. Understanding the rate of testing amongst those with no known HCV risk factors, would also be helpful to parameterise models evaluating testing which the general population attends, such as birth cohort screening and the ED. This study may also be helpful for other BBV research, which are likely to share the same issues when modelling testing interventions. Such a study could even consider testing data for other viruses such as HBV and HIV too.

Whilst there are various ways in which research studies could be designed, collecting data on the risk factors for a subset of patients included in existing testing studies, and identifying their HCV testing history to date, either through recall methods or surveillance datasets (if possible), would help to provide data on testing frequency. However there are likely many other ways in which a study could be designed. Statistical and data linkage methods of sentinel surveillance datasets might also be possible, albeit that the limitations of these datasets have been discussed already. Whilst such a study may not seem initially attractive to funders, it would be very helpful for paramaterising models of HCV testing, and potentially other BBV testing strategies too.

### 9.6.4 Research considerations as HCV elimination nears

In the future, consideration will need to be given to the role of economic evaluation for HCV testing strategies, as we near the elimination of HCV as a public health threat in the UK. As the prevalence decreases, the cost-effectiveness of many testing strategies will reduce, since the same resources are required but the test positivity is lower. The characteristics of those living with HCV are also likely to change, and this will depend on which testing strategies are implemented, and the groups that receive testing as a result. Future analyses should try to quantify these changes, particularly if those infected many years ago and remaining undiagnosed become a decreasing small proportion of the prevalent HCV cases. In this scenario, testing strategies that include those without any HCV risk factors may no longer be cost-effective and should no longer be implemented unless the UK intends to eradicate HCV in the future, which is highly unlikely in the near future.

## 9.7 Conclusion

HCV testing strategies which help to identify those living with HCV who may not receive testing elsewhere can be cost-effective in primary care and in EDs in the UK. These testing interventions can remain cost-effective despite a low prevalence of HCV. Testing those at an elevated risk of HCV in primary care based on an algorithm looking through medical records (HepCATT intervention) and testing all individuals in the ED are highly likely to be cost-effective, and these interventions are now being performed in some areas of the UK. Testing guidelines for HCV should be updated to consider including these interventions in their recommendations. The cost-effectiveness of a birth cohort screening strategy as part of the NHS health check, is highly uncertain, and further research, including empirical data collection, is required before any recommendation can be made. Future economic evaluations of HCV testing interventions should carefully consider the heterogeneity amongst the testing population, particularly for testing strategies that include many different groups of people, who may be at different risks of HCV. This recommendation is therefore particularly relevant to economic analyses of mass testing interventions, since these attract a heterogeneous testing population. This will improve the accuracy of cost-effectiveness estimates produced from model-based analyses.

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# 10 Appendix

## 10.1 Ethics approvals

**London School of Hygiene & Tropical Medicine**
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**www.lshtm.ac.uk**

**Observational / Interventions Research Ethics Committee**

Mr Jack Williams
Research Fellow
Department of Health Services Research and Policy (HSRP)
LSHTM

23 January 2018

Dear Mr Jack Williams ,

**Study Title:** Cost-effectiveness of Hepatitis C testing in A&E Emergency Departments

**LSHTM ethics ref:** 14668

Thank you for your application for the above research, which has now been considered by the Observational Committee.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

**Conditions of the favourable opinion**

Approval is dependent on local ethical approval having been received, where relevant.

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| Document Type | File Name | Date | Version |
|---|---|---|---|
| Protocol / Proposal | Viraemic GSTT HRA submission | 03/07/2017 | 1 |
| Investigator CV | CV - Jack Williams | 11/12/2017 | 1 |
| Local Approval | HRA Decision Tool | 13/12/2017 | 1 |
| Local Approval | FW RE guys' and St Thomas evaluation of hepatitis testing in AE (1) | 13/12/2017 | 1 |
| Local Approval | Honorary Contract - Jack Williams (Signed) v2 | 13/12/2017 | 1 |
| Investigator CV | CURRICULM VITAE Alec Miners short | 13/12/2017 | 1 |

**After ethical review**

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

**Professor John DH Porter**
**Chair**

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**Observational / Interventions Research Ethics Committee**

Mr Jack Williams
LSHTM

9 October 2020

Dear Jack

**Study Title:** Economic modelling methods for capturing the background risk of testing, and the probability of testing positive amongst the control (or counterfactual) group

**LSHTM Ethics Ref:** 21267

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

**Conditions of the favourable opinion**

Approval is dependent on local ethical approval having been received, where relevant.

**Approved documents**

The final list of documents reviewed and approved is as follows:

| Document Type | File Name | Date | Version |
|---|---|---|---|
| Local Approval | Original IRAS - HepCATT in Primary Care FullDatasetTrialForm FINAL 12032015 | 12/03/2015 | 1 |
| Local Approval | Original - 15 Sw 0094 FOWC ltr (17 April) | 17/04/2015 | 1 |
| Local Approval | Original approval letter 15.SW.0094 FOWC valid letter (21 May) | 21/05/2015 | 1 |
| Protocol / Proposal | HepCATT Protocol v2.0 22052015 FINAL VERSION | 22/05/2015 | 1 |
| Local Approval | Amendment IRAS - AM01 22052015 AmendmentForm | 22/05/2015 | 1 |
| Consent form | HepCATT Invitation Letter template V1.0 27052015 FINAL VERSION | 27/05/2015 | 1 |
| Local Approval | Amendmet - 15 SW 0094 SA1 fav op ltr AM01 (17June) | 17/06/2015 | 1 |
| Investigator CV | CV - Jack Williams | 05/10/2020 | 1 |
| Protocol / Proposal | Protocol - Counterfactual andbackground risk of testing (PhD) | 05/10/2020 | 1 |

**After ethical review**

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

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**Chair**

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**Improving health worldwide**

## 10.2 Literature review of UK economic evaluations (as outlined in Section 4.3.2)

### 10.2.1 EMBASE

1. exp hepatitis C/di [Diagnosis]
2. exp Hepatitis C virus/di [Diagnosis]
3. 1 or 2
4. exp hepatitis C/ or exp Hepatitis C virus/
5. exp hepatitis C antibody/
6. exp hepatitis C antigen/
7. (hepatitis c or hcv or hepacivirus*).tw.
8. 4 or 5 or 6 or 7
9. exp screening/
10. (screen* or test* or case finding).tw.
11. 9 or 10
12. 8 and 11
13. 3 or 12
14. exp economic evaluation/
15. exp economic aspect/
16. hidden markov model/
17. (economic evaluation* or cost benefit* or cost effective* or cost utilit* or cost minimization or cost or costs or costing or (economic adj5 model*) or economics).tw.
18. 14 or 15 or 16 or 17
19. 13 and 18
20. limit 19 to english language
21. limit 20 to animal studies
22. limit 20 to (human and animal studies)
23. 21 not 22
24. 20 not 23
25. limit 24 to (editorial or letter)
26. 24 not 25
27. (United Kingdom or UK or Britain or British or GB or Engl* or Wales or Welsh or Ireland or irish or scotland or scottish or NHS or national health service or NICE or national institute for health).tw.
28. 26 and 27
29. limit 28 to dc=20151120-20210922

### 10.2.2 MEDLINE

1. exp Hepatitis C/di [Diagnosis]
2. Hepacivirus/
3. (hepatitis c or hcv or hepacivirus*).tw.
4. exp Hepatitis C Antigens/ or exp Hepatitis C Antibodies/ or exp Hepatitis C/
5. 2 or 3 or 4
6. Mass Screening/
7. (screen* or test* or case finding).tw.
8. 6 or 7
9. 5 and 8
10. 1 or 9
11. exp Hepatitis C/ec [Economics]
12. exp "Costs and Cost Analysis"/
13. exp models, economic/
14. markov chains/
15. Quality-Adjusted Life Years/ or choice behavior/
16. Mass Screening/ec [Economics]
17. (economic evaluation* or cost benefit* or cost effective* or cost utilit* or cost minimization or cost or costs or costing or (economic adj5 model*) or economics).tw.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 10 and 18
20. limit 19 to english language
21. limit 20 to animals
22. limit 20 to (animals and humans)
23. 21 not 22
24. 20 not 23
25. limit 24 to (editorial or letter)
26. 24 not 25
27. (United Kingdom or UK or Britain or British or GB or Engl* or Wales or Welsh or Ireland or irish or scotland or scottish or NHS or national health service or NICE or national institute for health).tw.
28. 26 and 27
29. limit 28 to dt=20151120-20210922

### 10.2.3 Econlit

1. (hepatitis c or hcv or hepacivirus).mp.
2. (screen* or test* or case finding).mp.
3. 1 and 2
4. limit 3 to yr="2016 -Current"

### 10.2.4 NHS HTA and EED

1. (hepatitis C) AND (testing) OR (screening)
2. 1 IN HTA FROM 2016 TO 2021

## 10.3 Birth cohort screening economic evaluation – Supplementary materials (Research Paper 1)

# The cost-effectiveness of one-time birth cohort screening for hepatitis C as part of the NHS health check programme in England

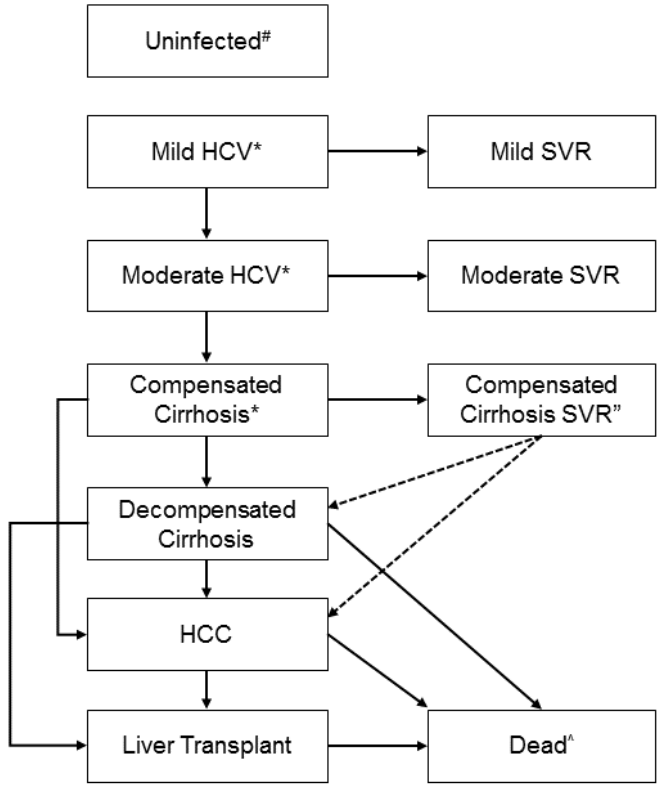
**Model structure**

We present two model structure schematics. Figure 1 shows the clinical health states that individuals progress through during the model. Figure 2 shows the clinical health states, including all the stages of the care pathway that individuals can be included in, such as ‘undiagnosed’, ‘diagnosed’, ‘on-treatment’, ‘SVR’ and ‘non-SVR’. For individuals reaching later health states (DC, HCC, liver transplant), it is assumed that all individuals are aware of their HCV diagnosis.

The number of DC, HCC and liver transplant events in the model, as well as the overall survival of the cohorts, were assessed during model development to ensure the validity of the model estimates.

Transitions to the dead state, due to all-cause mortality, is possible from all health states in the model.

*Figure 1: Model structure including main clinical health states*



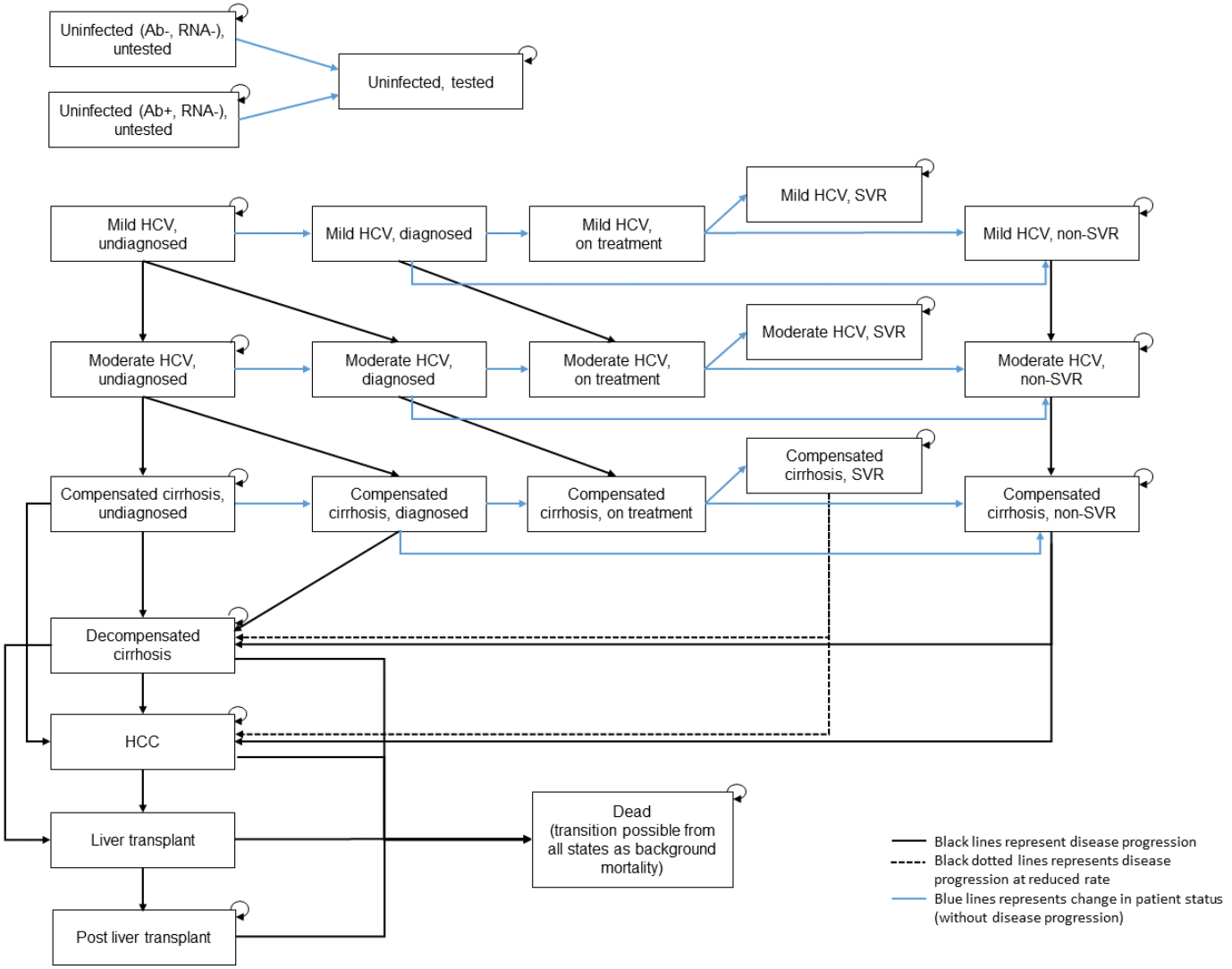

#Uninfected state contains the following health states: 'Untested (HCV antibody negative, RNA negative)', 'Untested (HCV antibody positive, RNA negative)' and 'Tested'.

*Mild, moderate and compensated cirrhosis health states contain the following states: 'Undiagnosed', 'Diagnosed', 'On treatment', 'SVR' (shown in figure) and 'Non-SVR'.

^Transitions occur from all health states to dead at the general population mortality rate. Arrows from decompensated cirrhosis, HCC and liver transplant health states depicted hepatitis C related mortality (additional to general population mortality).

"Dotted transition lines represent disease progression from compensated cirrhosis SVR health state to decompensated cirrhosis and HCC health states, which occurs at reduced rate compared to non-SVR compensated cirrhosis health states.

*Figure 2: Model structure including all clinical health states, with care pathway status (undiagnosed, diagnosed, on treatment, SVR and non-SVR)*



## Burden of HCV and background rate of HCV testing in England

*Table 1: Burden of hepatitis C in England, by birth cohort, estimated from back-calculation model[1] (unless otherwise stated)*

| | Birth cohort | | | | | |
|---|---|---|---|---|---|---|
| | **1950-1955** | **1955-1959** | **1960-1964** | **1965-1969** | **1970-1974** | **1975-1979** |
| ***Number of infections (all)*** | | | | | | |
| Number not infected | 3,057,395 | 3,280,227 | 3,530,052 | 3,712,458 | 3,791,171 | 3,815,285 |
| Number infected, diagnosed | 1,688 | 3,145 | 6,354 | 10,339 | 13,059 | 14,077 |
| Number infected, undiagnosed | 3,412 | 6,139 | 9,518 | 12,593 | 12,975 | 10,976 |
| ***Number of infections (excl. current-IDUs)*** | | | | | | |
| Number not infected | 3,057,145 | 3,279,581 | 3,528,611 | 3,709,695 | 3,786,508 | 3,808,407 |
| Number diagnosed | 1,424 | 2,491 | 4,898 | 7,881 | 9,476 | 9,476 |
| Number undiagnosed | 3,128 | 5,406 | 8,018 | 10,004 | 9,508 | 7,159 |
| ***Distribution of severity in undiagnosed (excl. current-IDU)*** | | | | | | |
| Number mild HCV (%) | 446 (14.3%) | 942 (17.4%) | 2036 (25.4%) | 4385 (43.8%) | 5713 (60.1%) | 5017 (70.1%) |
| Number moderate HCV (%) | 1737 (55.5%) | 2833 (52.4%) | 3954 (49.3%) | 4018 (40.2%) | 2742 (28.8%) | 1624 (22.7%) |
| Number cirrhotic HCV (%) | 945 (30.2%) | 1631 (30.2%) | 2028 (25.3%) | 1601 (16.0%) | 1053 (11.1%) | 519 (7.2%) |
| Dirichlet distribution (mild, moderate, severe) | (446, 1737, 945) | (942, 2833, 1631) | (2036, 3954, 2028) | (4385, 4018, 1601) | (5713, 2742, 1053) | (5017, 1624 519) |
| ***Estimated prevalence^ of undiagnosed cases*** | | | | | | |
| Prevalence (current-IDU, ex-IDU and never-IDU) | 0.11% | 0.19% | 0.27% | 0.34% | 0.34% | 0.29% |
| Prevalence excl. current-IDUs (Beta distribution) | 0.10% (α=38.1, β=37215) | 0.16% (α=53.4, β=32359) | 0.23% (α=58.1, β=25614) | 0.27% (α=68.1, β=25168) | 0.25% (α=65.7, β=26137) | 0.19% (α=68.2, β=36490) |
| Scenario: Prevalence excl. current IDUs, ex-IDUs 50% less likely to attend NHS health check | 0.06% | 0.10% | 0.13% | 0.15% | 0.14% | 0.10% |
| Scenario: Prevalence (excl. current-IDUs) derived from back-calculation scenario with higher PWID population estimate* | 0.08% | 0.16% | 0.28% | 0.40% | 0.44% | 0.41% |
| ***Background (current) rate of testing [2,3]*** | | | | | | |
| Annual probability of testing | 1.91% | 2.12% | 2.25% | 2.36% | 2.81% | 3.78% |
| Annual probability of testing, excluding drug service and prison testing (Beta distribution) | 1.89% (α=98.1, β=5084) | 2.09% (α=97.9, β=4580) | 2.19% (α=97.8, β=4358) | 2.26% (α=97.7, β=4218) | 2.67% (α=97.3, β=3550) | 3.57% (α=96.4, β=2601) |

*Scenario analysis from back-calculation provides outputs based on longer HES data (2004-2016) and no constraint on estimated PWID population in England from national treatment agency data.[1]

^Prevalence of chronic hepatitis C infection (i.e. RNA positive)

**Key model assumptions**

- In the absence of data on the IDU status of NHS health check attendees, the attendance amongst ex-IDU's was assumed to be equal to non-IDU's, and it was assumed that current IDU's would not attend.
- The model assumes all health check attendees would receive HCV testing.
- The model assumes 10 minutes of administration time for the test to be explained and performed, and assumes this is performed by a band 5 nurse.
- We have assumed a 100% sensitivity and specificity amongst the HCV antibody and HCV RNA tests used in this analysis, meaning that the model does not capture the impact of false negative or false positive tests.
- Our analysis does not consider the distribution or potential differences in treatment success and subsequent outcomes, by genotype. The SVR rates used in the analysis were derived from a real-world study, and we did not adjust these by genotype or DAA regimen.
- We did not model specific DAA regimens, and the cost of DAA treatment (£10,000 first treatment, £15,000 if retreatment, payed with achievement of SVR) in the base case analysis is based on an assumption around the cost negotiated by NHS England in the UK.[4] If restrictions upon treatment resulted in a lower proportion of those diagnosed receiving treatment, this would reduce the estimated cost-effectiveness of the intervention.
- The analysis assumes that there are sufficient DAA treatments available for all those attending their referral and receiving treatment. This assumption is based on the NHS England elimination deal with treatment manufacturers.[5]
- We assume that for those not achieving SVR with DAA treatment, they will be retreated only once with DAA's. If they do not achieve SVR upon re-treatment, they are assumed to remain in the non-SVR health states.
- We assume that treatment monitoring involves five hospital based, consultant led attendance visits, based on personal correspondence with a consultant hepatologist.

- The background rate of testing did not differ for those with mild HCV, moderate HCV, or CC health states in the base case analysis, and was assumed to be equal for those infected and uninfected with HCV.
- The model assumes that those undiagnosed do not accrue health state costs, with those diagnosed do accrue health state costs (even if they do not receive treatment).
- It was assumed that once individuals progressed beyond the CC health state, to DC or HCC health states, their HCV diagnosis was known.
- The model does not capture disease transmission, and therefore does not capture the potential for onward transmission by those infected, or the potential for reinfection for individuals achieving SVR.

**Transition probabilities**

The estimated transition probabilities for four model transitions (mild HCV to moderate HCV, moderate HCV to CC, CC to DC, DC to HCC) are shown in Table 2, with their respective distributions capturing uncertainty. The resulting beta distributions for the transition probabilities used by Shepherd *et al.* and the back-calculation posterior distributions are shown in Figure 3. Transition probabilities differ by current age in the back-calculation model estimates, but do not differ by age in the estimates used in the Shepherd *et al.* model.

The uniform distribution was estimated for each transition probability, by age, by simulating 1000 values from each of the two beta distributions. The upper and lower bounds of the uniform distribution represent the 2.5% and 97.5% percentiles of the combined 2000 simulations for each transition probability.

*Table 2: Transition probabilities for four transitions by age, from Shepherd et al., the back calculation model and the estimated uniform transition probabilities*

| | Annual transition probability | | |
|---|---|---|---|
| **Age (by transition)** | **Shepherd *et al.* (Beta distribution)** | **Back-calculation model, posterior estimates (Beta distribution)** | **Uniform distribution range** |
| ***Mild HCV to moderate HCV*** | | | |
| 40-49 | | 0.042 (α=39.937, β=900.3) | 0.019-0.054 |
| 50-59 | 0.025 (α=38.086, | 0.129 (α=52.297, β=351.9) | 0.019-0.159 |
| 60-69 | β=1485.4) | 0.110 (α=21.999, β=178.2) | 0.019-0.147 |
| 70-89 | | 0.130 (α=15.894, β=106.5) | 0.019-0.180 |
| ***Moderate HCV to CC*** | | | |
| 40-49 | | 0.068 (α=21.192, β=290.1) | 0.026-0.093 |
| 50-59 | 0.037 (α=26.905, | 0.089 (α=31.404, β=322.1) | 0.026-0.115 |
| 60-69 | β=700.3) | 0.062 (α=12.276, β=187.1) | 0.026-0.093 |
| 70-89 | | 0.081 (α=9.917, β=112.2) | 0.027-0.124 |
| ***CC to DC*** | | | |
| 40-49 | | 0.106 (α=103.724, β=876.8) | 0.023-0.121 |
| 50-59 | 0.039 (α=14.617, | 0.088 (α=127.874, β=1321.1) | 0.023-0.102 |
| 60-69 | β=360.2) | 0.082 (α=129.57, β=1447.4) | 0.024-0.094 |
| 70-89 | | 0.082 (α=58.703, β=657) | 0.024-0.099 |
| ***CC to HCC*** | | | |
| 40-49 | | 0.007 (α=580.186, β=88322.2) | 0.002-0.034 |
| 50-59 | 0.014 (α=1.9326, | 0.017 (α=137.312, β=7897.3) | 0.002-0.033 |
| 60-69 | β=136.1) | 0.039 (α=125.552, β=3105.1) | 0.003-0.045 |
| 70-89 | | 0.044 (α=77.031, β=1692.3) | 0.003-0.052 |

*Figure 3: Comparison of beta distributions estimated from the back-calculation model and Shepherd et al., by transition probability and current age*

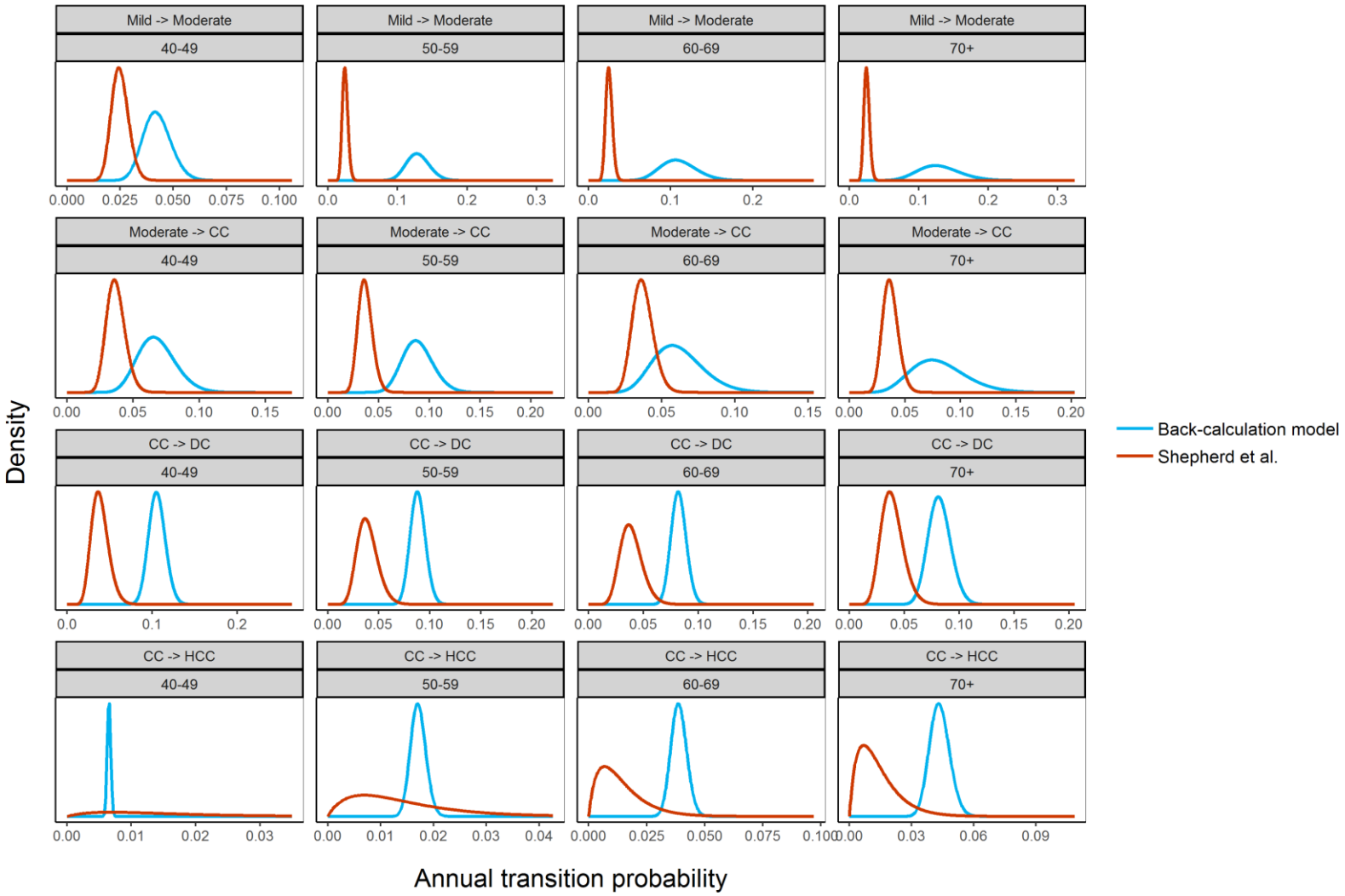


*Table 3: Transition probabilities from CC SVR, DC, HCC, and LT health states, and DAA treatment outcomes for mild, moderate and CC health states*

| Base case probabilities | Annual transition probability | Distribution | Source |
|---|---|---|---|
| ***Annual transition probability*** | | | |
| CC SVR to DC (relative risk vs. non-SVR) | 0.07 | Lognormal (95% CI 0.03, 0.2) | 6 |
| CC SVR to HCC (relative risk vs. non-SVR) | 0.23 | Lognormal (95% CI 0.16, 0.35) | 7 |
| DC to HCC | 0.014 | Beta (α=1.9326, β=136.1074) | 8 |
| DC to liver transplant (LT) | 0.03 | Beta (α=6.5256, β=210.9945) | 8 |
| DC to death | 0.13 | Beta (α=147.03, β=983.97) | 8 |
| HCC to LT | 0.03 | Beta (α=6.5256, β=210.9945) | 8 |
| HCC to death | 0.43 | Beta (α=117.1033, β=155.23) | 8 |
| Post LT (0-6 months) to death | 0.21 | Beta (α=16.2762, β=61.2294) | 8 |
| Post LT (>6 months) to death | 0.057 | Beta(α=2.902, β=378.8825) | 8 |
| ***SVR related probabilities (post-DAA)*** | | | |
| Mild / moderate | 92.8% | Beta (α=376, β=29) | 9 |
| CC | 90.8% | Beta (α=736, β=75) | 9 |
| Mild / moderate (retreatment) | 93.9% | Beta (α=77, β=5) | 10 |
| CC (retreatment) | 85.5% | Beta (α=59, β=10) | 10 |

## Utilities

*Table 4: Base case model utilities*

| Utility estimates | Mean | Distribution | Source |
|---|---|---|---|
| ***Health state utility*** | | | |
| Mild | 0.77 | Beta (α=521.2375, β=155.6943) | [11] |
| Moderate | 0.66 | Beta (α=168.2461, β=86.6723) | [11] |
| Cirrhosis | 0.55 | Beta (α=47.1021, β=38.5381) | [11] |
| Decompensated cirrhosis | 0.45 | Beta (α=123.75, β=151.25) | [12] |
| HCC | 0.45 | Beta (α=123.75, β=151.25) | [12] |
| Liver transplant (first year) | 0.45 | Beta (α=123.75, β=151.25) | [12] |
| Liver transplant (after first year) | 0.67 | Beta (α=32, β=16) | [12] |
| Mild SVR | 0.82 | Beta (α=65.8678, β=14.4588) | [11] |
| Moderate SVR | 0.72 | Beta (α=58.0608, β=22.5792) | [11] |
| Cirrhosis SVR | 0.61 | Beta (α=58.0476, β=37.1124) | [13,14] |
| ***Uninfected / general population utility*** | | | |
| 25-34 | 0.93 | | [15] |
| 35-44 | 0.91 | | [15] |
| 45-54 | 0.85 | | [15] |
| 55-64 | 0.8 | | [15] |
| 65-74 | 0.78 | | [15] |
| >75 | 0.73 | | [15] |

Utility values for mild HCV, moderate HCV, and CC, as well as mild SVR and moderate SVR health states, were derived from a UK study of hepatitis C treatment, in which utility values were estimated using the EQ-5D and OLS regression analysis.[11]

The utility of those achieving SVR in the cirrhosis health state was assumed to be equal to the utility increment associated with achieving SVR in the moderate health state (i.e. 0.06 higher than non-SVR health states). This is an assumption made in previous a previous HTA in chronic HCV, and has been used in other economic evaluations.[13,14] We performed a sensitivity analysis in which the utility increment associated with SVR was derived from a US study assessing the health related quality of life amongst treatment naïve individuals receiving HCV treatment. This study used the EQ-5D questionnaire and reported a mean utility increment of 0.04 for those achieving SVR.[16]

Utility values for DC, HCC, liver transplant and post-liver transplant health states were derived from a UK study reporting costs and outcomes post liver transplant, measuring health related quality of life using the EQ-5D.[12] Utility values for DC and HCC were assumed to be equal to the baseline utility of those receiving a liver transplant, since these were inclusion criteria for liver transplantation. This is an assumption made by other analyses and economic models.[11,14,17]

Health state utilities were calculated by taking the health state utility and subtracting an age-based decrement based on the general population age-adjusted utility estimates, assuming that health state utilities were reflective of those aged 35-44, since this reflected the mean age amongst all participants in the UK mild hepatitis C trial.[11] For example, an individual with mild HCV aged 50 would have a utility of 0.71 (0.77 – (0.91-0.85)). We also performed a sensitivity analysis in which the health state utilities did not decline with age, as has been performed in some economic evaluations.[18]

## Health state costs

*Table 5: Base case health state costs*

| Costs (per year, except where noted) | Inflated cost | Cost year | Distribution | Source |
|---|---|---|---|---|
| ***Health state costs (per year, except where noted)*** | | | | |
| Mild diagnosed | £192 | 2002/03 | Gamma (k=25.6995, θ=5.3698) × PPI± | 8,11 |
| Moderate diagnosed | £996 | 2002/03 | Gamma (k=88.8502, θ=8.0698) × PPI± | 8,11 |
| Cirrhosis diagnosed | £1,582 | 2002/03 | Gamma (k=24.2342, θ=46.9584) × PPI± | 8,11 |
| Decompensated cirrhosis | £12,675 | 2002/03 | Gamma (k=36.0249, θ=253.1582) × PPI± | 8,11 |
| Hepatocellular carcinoma | £11,295 | 2002/03 | Gamma (k=18.1081, θ=448.8045) × PPI± | 8 |
| Liver transplant (per transplant) | £37,983 | 2002/03 | Gamma (k=89.7536, θ=304.5004) × PPI± | 8 |
| Cost of care in year of liver transplant | £13,145 | 2002/03 | Gamma (k=13.7788, θ=686.4168) × PPI± | 8 |
| Cost of care post liver transplant | £1,925 | 2002/03 | Gamma (k=15.2189, θ=91.0053) × PPI± | 8 |
| Mild SVR | £240 | 2006/07 | Gamma (k=25, θ=8.08) × PPI± | 19 |
| Moderate SVR | £294 | 2006/07 | Gamma (k=25, θ=9.88) × PPI± | 19 |
| Cirrhosis SVR | £520 | 2006/07 | Gamma (k=25, θ=17.48) × PPI± | 19 |

±PPI = Hospital and Community Health Services Pay and Prices Index inflation to 2016/17 costs (2002/03 = 1.41, 2006/07 = 1.21)

**Additional details for costs associated with the intervention**

Test costs for antibody tests (£3.64) and RNA test costs (£68.38) were derived from a study of hepatitis testing in an emergency department in England, performed from 2015 to 2016.[20] There are no standardised national test costs in the UK, and therefore these costs vary by setting, and tend to be confidential.

The cost of a band 5 nurse (£38/hour) for testing was derived from health and social costs for the UK[21], and an assumption of the additional resource use for testing was made, and this was assumed to be 10 minutes (with a scenario for 5 minutes also considered).

For those not receiving reflex RNA testing, it was assumed that these individuals would attend a general practitioner (GP) appointment, which was also derived from health and social care costs for the UK.[21]

Two outpatient visits prior to treatment were applied, which were assumed to be equal to two consultant led hepatology visits (first £238, follow-up £262), based on UK National Reference Costs.[22] For DAA monitoring costs (£1310), we assumed that this would incur five follow-up hepatology visits (5 x £232) for monitoring throughout treatment and after ceasing treatment, based on correspondence with a hepatologist.

**Population estimates (for EVPI/EVPPI)**

The estimated population size for each birth cohort in England was calculated from mid-2016 ONS population statistics for England (Table 6).[3]

The proportion of individuals eligible for the NHS health check was derived from the NHS health check statistics for the 2018-2019 eligible population. This calculates the population for each local area, and estimates the number of individuals on existing disease registers that make them ineligible for the NHS health check. Overall, 76.67% of individuals were offered the NHS health check. Whilst it is likely that the proportion of individuals eligible for the NHS health decreases with age (due to the higher incidence of existing disease), this data was not available and we thus we have assumed the same eligibility across birth cohorts.

The proportion of individuals eligible for a HCV test was estimated by the back-calculation, by excluding those with the following characteristics:

- Current PWIDs
- Previously diagnosed with HCV
- Those previously infected with HCV who have achieved SVR

*Table 6: Estimated eligible population for each birth cohort*

| Birth cohort | Estimated population | NHS health check eligibility (%) | HCV test eligibility (%) | Eligible population |
|---|---|---|---|---|
| 1950-1954 | 2,878,925 | 76.67% | 99.93% | 2,205,670 |
| 1955-1959 | 3,079,080 | 76.67% | 99.86% | 2,357,513 |
| 1960-1964 | 3,597,471 | 76.67% | 99.74% | 2,751,006 |
| 1965-1969 | 3,925,553 | 76.67% | 99.58% | 2,997,147 |
| 1970-1974 | 3,800,169 | 76.67% | 99.45% | 2,897,467 |
| 1975-1979 | 3,386,878 | 76.67% | 99.36% | 2,579,990 |

## Additional results

*Figure 4: Incremental cost-effectiveness ratio, by source of transition probabilities*

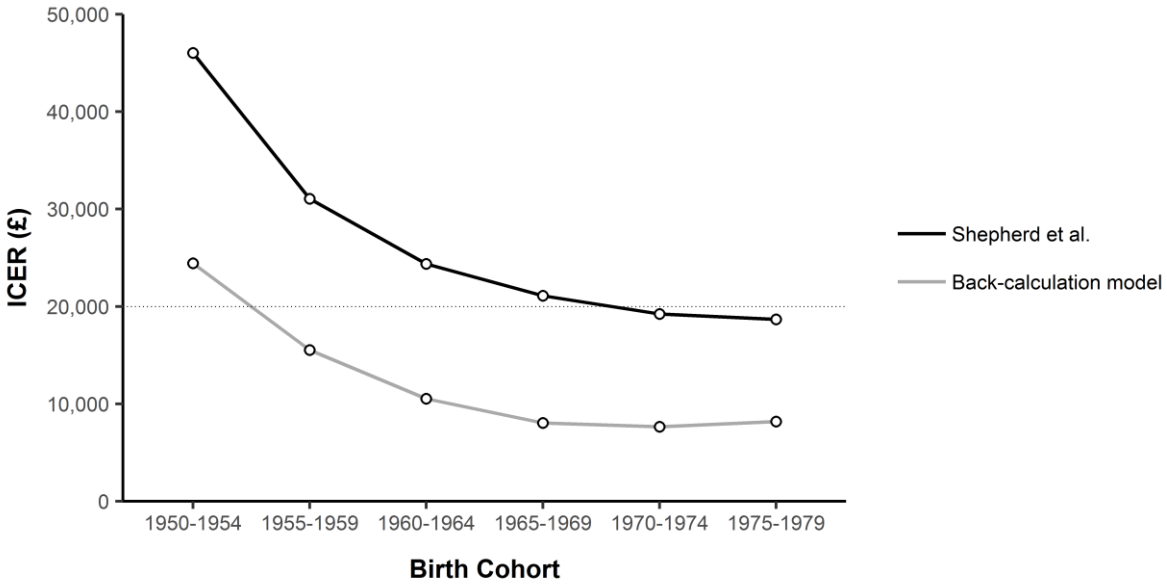


*Figure 5: One-way deterministic sensitivity analysis for 1970-1974 birth cohort, using transition probabilities from Shepherd et al.*

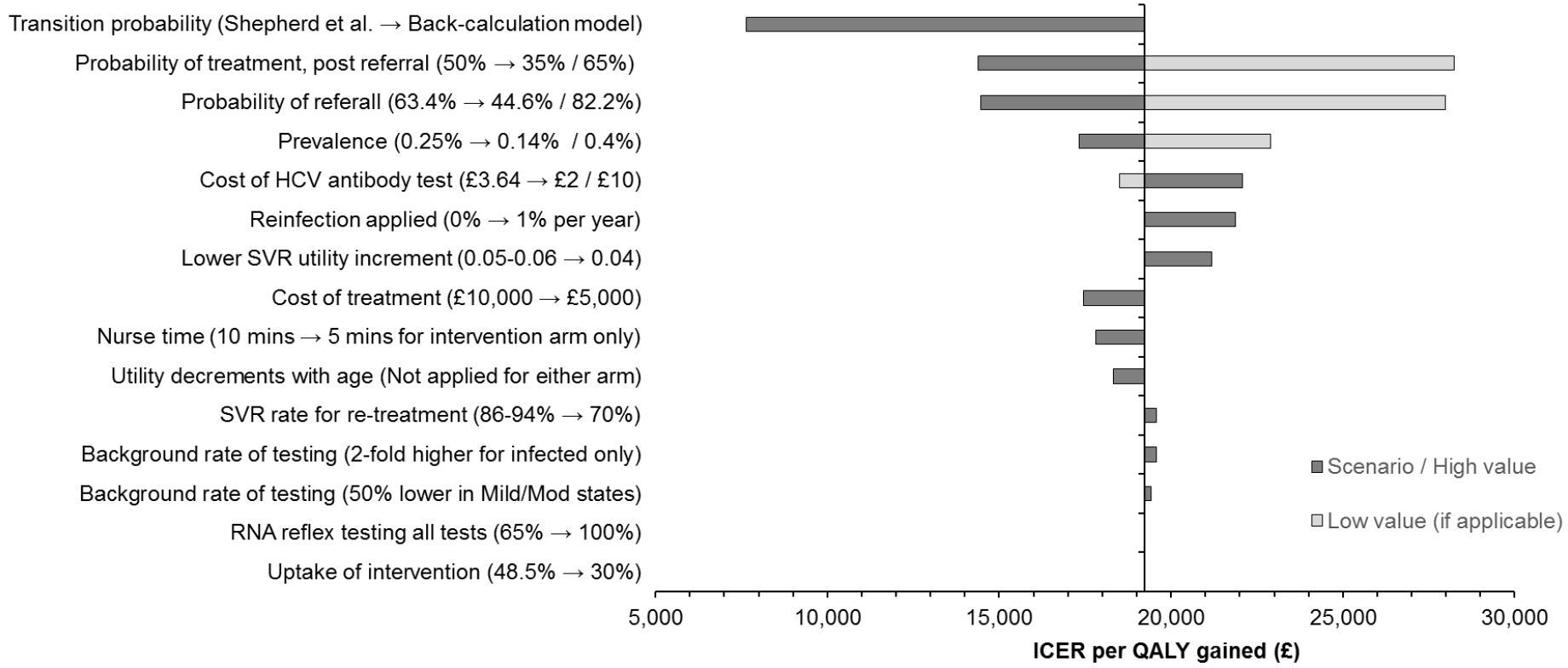


*Figure 6: One-way deterministic sensitivity analysis for 1970-1974 birth cohort, using transition probabilities from the back-calculation model*

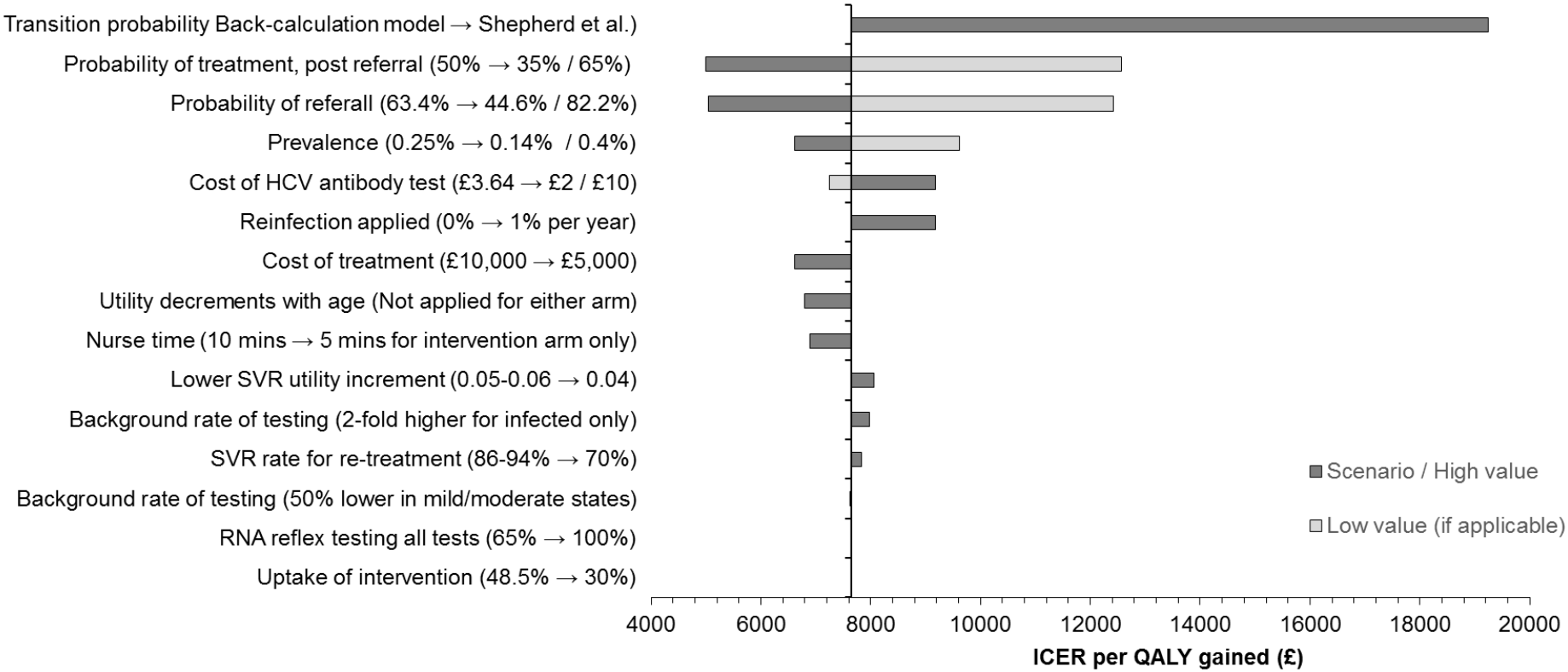


*Figure 7: One-way deterministic sensitivity analysis for 1955-1959 birth cohort, using transition probabilities from Shepherd et al.*

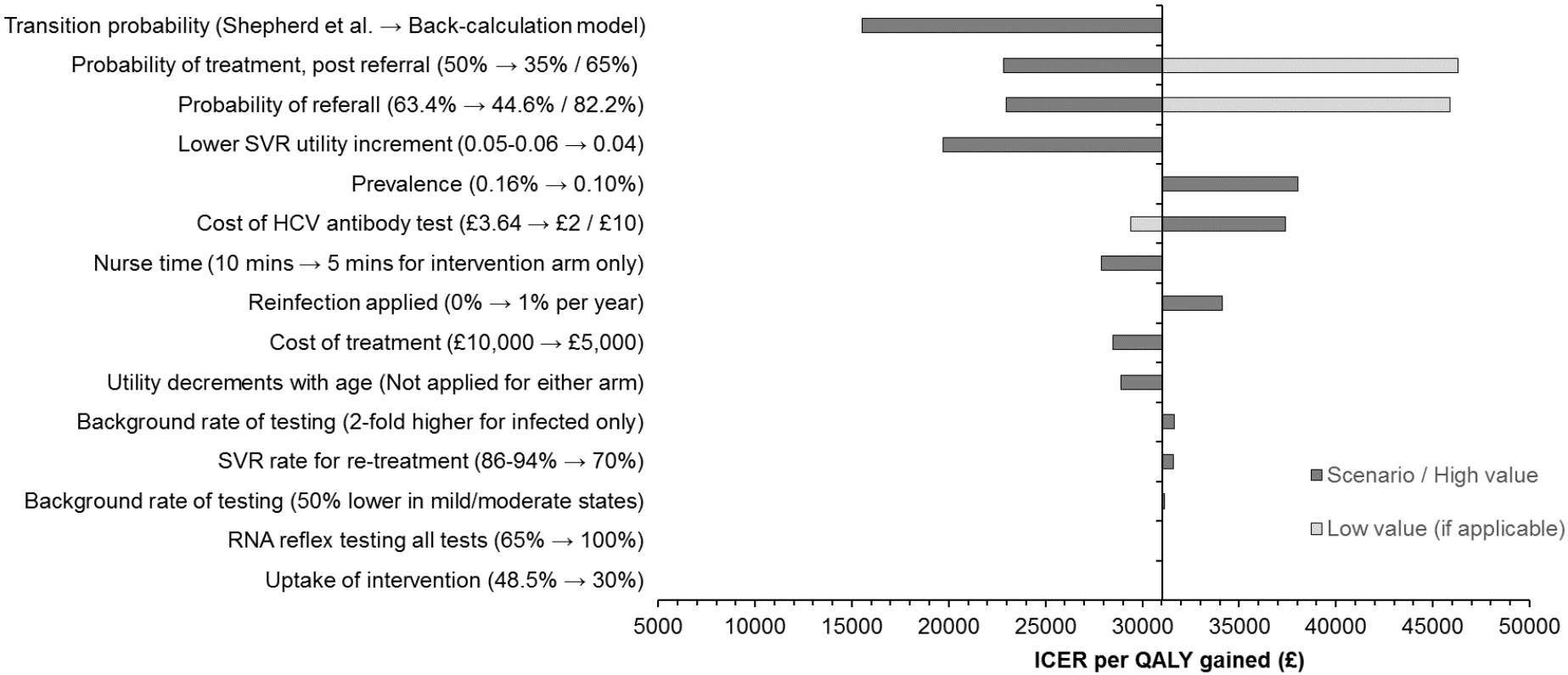


*Figure 8: One-way deterministic sensitivity analysis for 1955-1959 birth cohort, using transition probabilities from the back-calculation model*

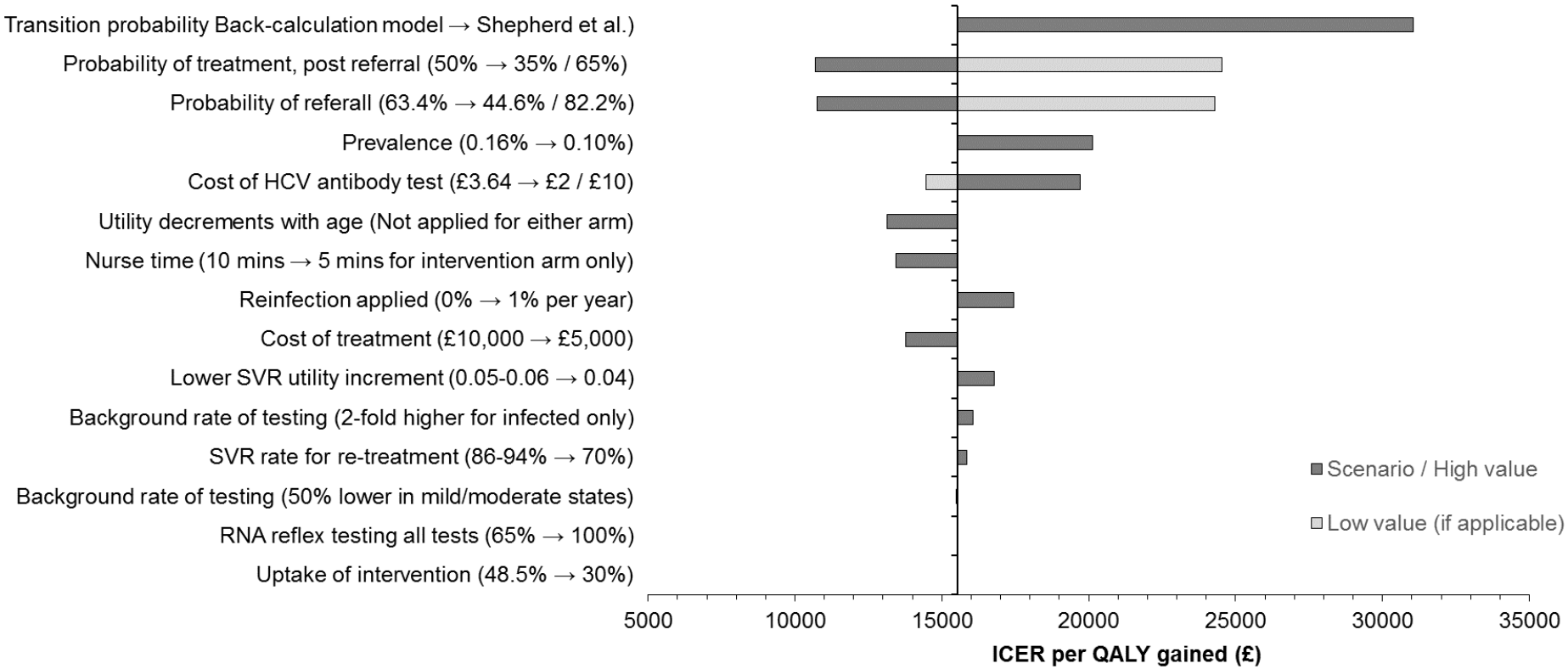


*Figure 9: Incremental cost-effectiveness ratio (ICER) by DAA treatment costs for all birth cohorts, using transition probabilities from A) Shepherd et al. and B) the back-calculation model*

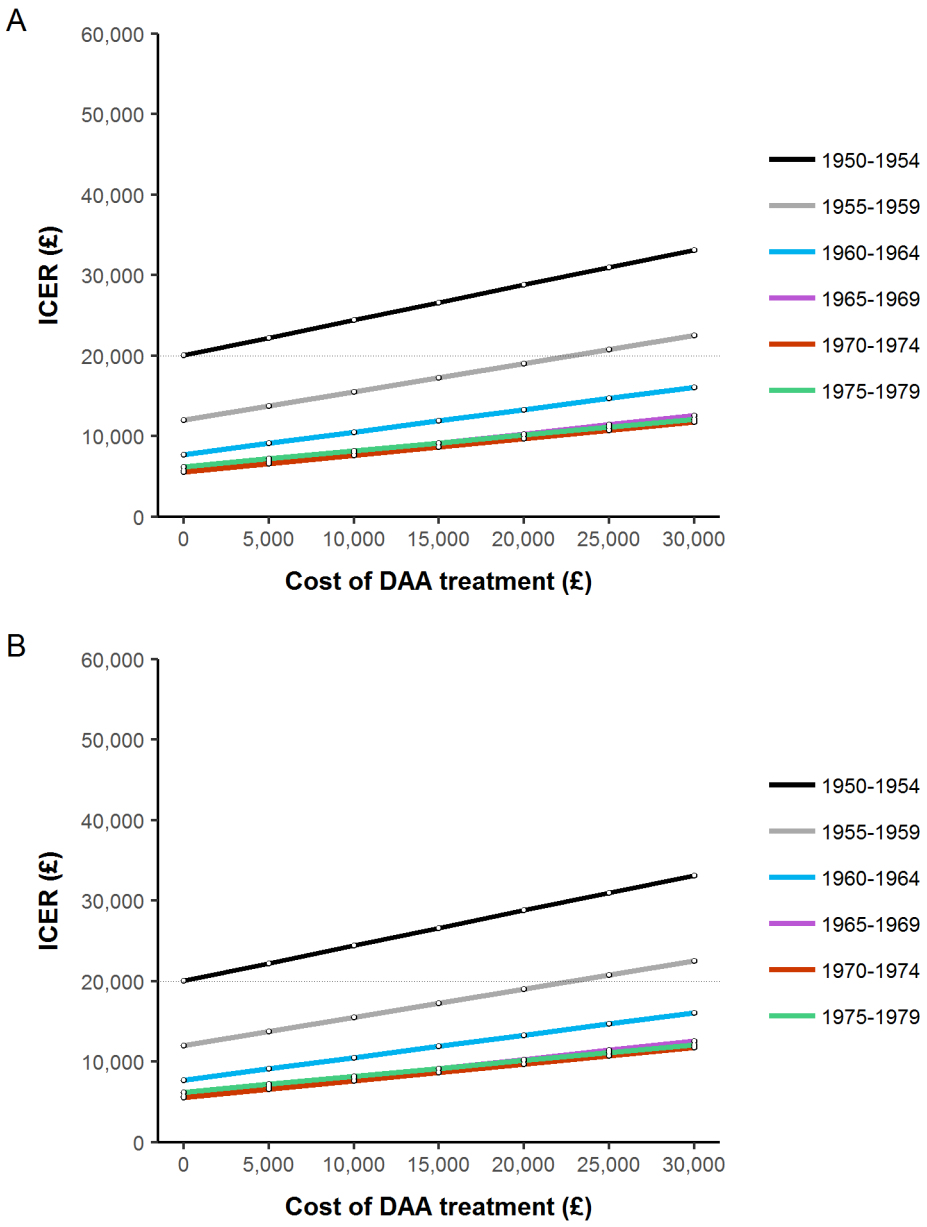


*Figure 10: Expected value of perfect information (EVPI), by birth cohort*

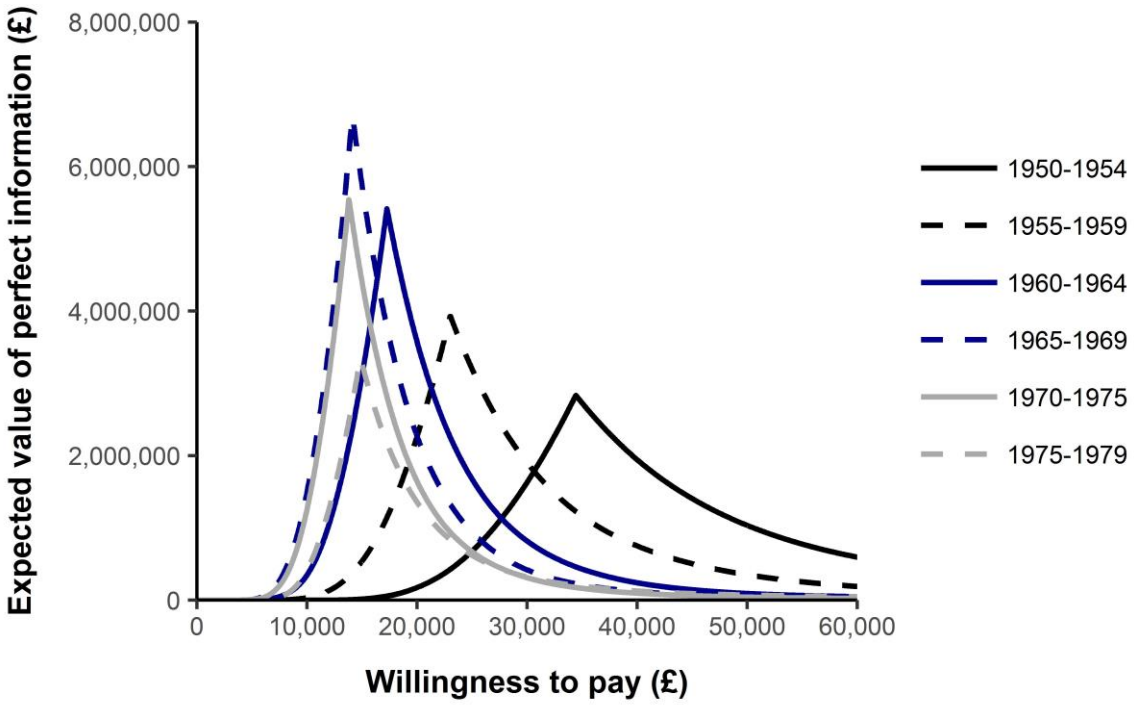


*Table 7: Expected value of partial perfect information (EVPPI), for selected groups of parameters, by birth cohort*

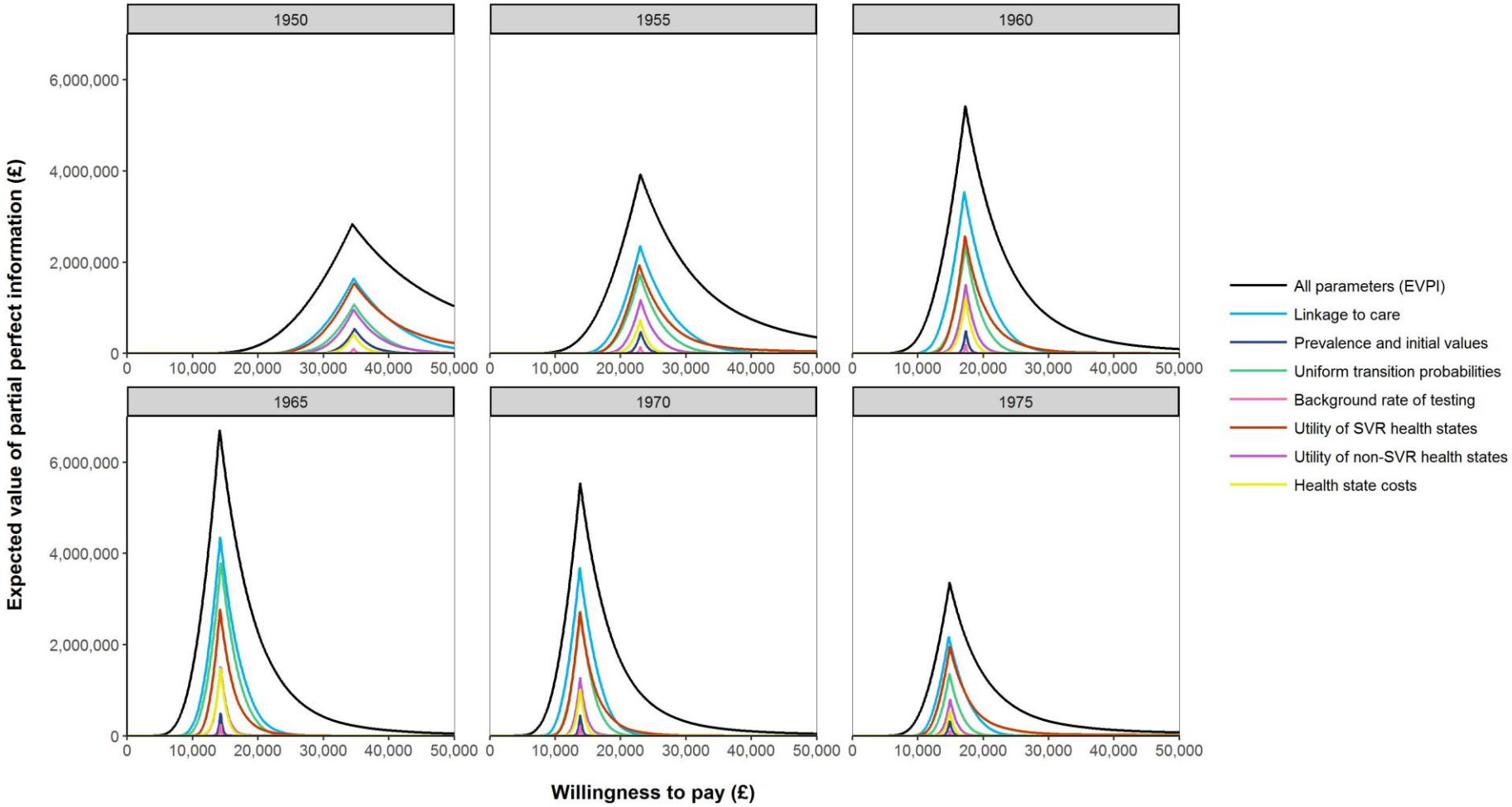
| | EVP(P)I at £20,000 WTP | | | | | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **1950-54** | **1955-59** | **1960-64** | **1965-69** | **1970-74** | **1975-79** | **Total** |
| Linkage to care parameters^ | £0 | £894,135 | £1,688,937 | £506,431 | £212,672 | £285,434 | **£3,587,609** |
| Utility of SVR health states | £0 | £590,572 | £1,080,800 | £183,281 | £233,341 | £399,090 | **£2,487,084** |
| Transition probabilities from mild, moderate and CC health states (Uniform transition probabilities)* | £0 | £497,574 | £747,798 | £293,031 | £50,065 | £29,491 | **£1,617,959** |
| Utility of non-SVR health states | £0 | £124,331 | £203,750 | £6,836 | £583 | £1,508 | **£337,008** |
| Health state costs | £0 | £36,579 | £62,071 | £0 | £0 | £0 | **£98,650** |
| Prevalence and initial values± | £0 | £0 | £0 | £0 | £0 | £0 | **£0** |
| Background rate of testing | £0 | £0 | £0 | £0 | £0 | £0 | **£0** |

^Includes the probability of referral and the probability of accepting treatment

*Transition probabilities from mild, moderate and cirrhotic health states (uniform distributions based on values derived from both Shepherd *et al.* and back-calculation model)

±Includes prevalence, probability of RNA+, and initial starting distribution (proportion mild/moderate/cirrhotic)

*Figure 11: Expected value of partial perfect information (EVPPI), for selected groups of parameters, by each birth cohort*



## Comparisons with other research

Whilst analyses suggest birth cohort screening in the US was cost-effective (ICERs of $35,700 and $37,720/QALY), there is a higher estimated prevalence of undiagnosed chronic HCV in US birth cohorts (1.5% to 1.9%) compared to our analysis (0.11%-0.34%).[23,24] Despite not being subsequently recommended, a study from Canada suggested birth cohort screening may be cost-effective ($36,471/QALY) for 45-64 year olds, although there was a higher proportion of patients estimated to receive treatment upon testing positive compared to our analysis (58.3% vs. 31.7%), and a higher prevalence (0.8% vs. 0.11-0.34%).[25,26]

One cost-effectiveness analysis from France compared various testing strategies with current risk based testing, with a similar HCV prevalence to our analysis (ranging from 0.03% to 0.9% across age bands).[27] Whilst risk based testing only was most likely to be cost-effective at lower WTP thresholds, testing for those aged 40 to 80 was most likely to be cost-effective at WTP thresholds between €26,000 and €60,000 per QALY gained, whilst universal screening (testing everyone aged 18 to 80) was cost-effective at thresholds above €60,000. Another influential factor in these results is the considerably higher DAA treatment costs used compared to our analysis. Furthermore, across all of these analyses utility values tended to be higher for health states, particularly SVR states (ranging to 0.80 to 0.95, in contrast to utility values of 0.61 to 0.82 in our analysis).

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## 10.4 HepCATT trial and economic evaluation – Published article (Research Paper 2)

# Cost effectiveness of an intervention to increase uptake of hepatitis C virus testing and treatment (HepCATT): cluster randomised controlled trial in primary care

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## ABSTRACT

### OBJECTIVE

To evaluate the effectiveness and cost effectiveness of a complex intervention in primary care that aims to increase uptake of hepatitis C virus (HCV) case finding and treatment.

### DESIGN

Pragmatic, two armed, practice level, cluster randomised controlled trial and economic evaluation.

### SETTING AND PARTICIPANTS

45 general practices in South West England (22 randomised to intervention and 23 to control arm). Outcome data were collected from all intervention practices and 21/23 control practices. Total number of flagged patients was 24 473 (about 5% of practice list).

### INTERVENTION

Electronic algorithm and flag on practice systems identifying patients with HCV risk markers (such as history of opioid dependence or HCV tests with no evidence of referral to hepatology), staff educational training in HCV, and practice posters/leaflets to increase patients' awareness. Flagged patients were invited by letter for an HCV test (with one follow-up) and had on-screen pop-ups to encourage opportunistic testing. The intervention lasted one year, with practices recruited April to December 2016.

### MAIN OUTCOME MEASURES

Primary outcome: uptake of HCV testing. Secondary outcomes: number of positive HCV tests and yield (proportion HCV positive); HCV treatment assessment at hepatology; cost effectiveness.

### RESULTS

Baseline HCV testing of flagged patients (six months before study start) was 608/13 097 (4.6%) in intervention practices and 380/11 376 (3.3%) in control practices. During the study 2071 (16%) of flagged patients in the intervention practices and 1163 (10%) in control practices were tested for HCV: overall intervention effect as an adjusted rate ratio of 1.59 (95% confidence interval 1.21 to 2.08; P<0.001). HCV antibodies were detected in 129 patients from intervention practices and 51 patients from control practices (adjusted rate ratio 2.24, 1.47 to 3.42) with weak evidence of an increase in yield (6.2% *v* 4.4%; adjusted risk ratio 1.40, 0.99 to 1.95). Referral and assessment increased in intervention practices compared with control practices (adjusted rate ratio 5.78, 1.6 to 21.6) with a risk difference of 1.3 per 1000 and a "number needed to help" of one extra HCV diagnosis, referral, and assessment per 792 (95% confidence interval 558 to 1883) patients flagged. The average cost of HCV case finding was £4.03 (95% confidence interval £2.27 to £5.80) per at risk patient and £3165 per additional patient assessed at hepatology. The incremental cost effectiveness ratio was £5783 per quality adjusted life year (QALY), with 93.3% probability of being below £20 000 per QALY.

### CONCLUSION

HepCATT had a modest impact but is a low cost intervention that merits optimisation and implementation as part of an NHS strategy to increase HCV testing and treatment.

### TRIAL REGISTRATION

ISRCTN61788850.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Chronic hepatitis C virus (HCV) infection can now be cured in more than 95% of patients

HCV case finding is critical for NHS England to increase HCV treatment and eliminate HCV as a public threat by 2025, five years before the WHO target

Economic models and guidance recommending increasing HCV testing for at risk patients in primary care are not based on robust evidence

## WHAT THIS STUDY ADDS

HepCATT is complex intervention based around an electronic algorithm integrated with primary care practice systems that identifies and flags patients with risk markers of HCV infection

HepCATT can increase HCV case finding by a modest amount and be highly cost effective

The intervention would benefit from being optimised before implementation across UK primary care

## Introduction

Hepatitis C virus (HCV) infection, predominantly transmitted by exposure to blood, is a major cause of chronic liver disease and cirrhosis.[1 2] More than 100 000 people in England are estimated to have chronic HCV infection, and more than 85% of these infections were acquired through injecting drug use.[3]

Chronic HCV infection can now be cured in more than 95% of patients with a range of highly tolerable, single pill a day, short regimen (8-12 weeks) direct acting antiviral agents.[4-6] Consequently, the World Health Organization developed a strategy to eliminate HCV as a public health threat,[7] setting targets for

decreasing the incidence of HCV by 80% and HCV related mortality by 65% by 2030.[8] NHS England aims to achieve the WHO goals by 2025.

Since 2016 more than 10 000 people a year have been treated for HCV and an estimated 50 000 people have been diagnosed as having it, although many of these may not have been assessed or be under management by HCV services.[3 9] Primary care is the largest source of HCV testing, comprising nearly 30% of all HCV antibody positive tests in laboratory surveillance.[10]

The UK's National Institute for Health and Care Excellence (NICE) suggests that interventions to increase case finding in drug treatment centres and primary care are likely to be cost effective.[11] However, robust evidence from randomised controlled trials on such interventions is lacking, and rates of case finding and drug treatment at many sites are low.[12 13] For instance, NICE's recommendations and economic models were based on a small uncontrolled study in eight practices (selected from areas of high deprivation and high prevalence of injecting drug use).[14]

We sought to update the evidence on HCV case finding in primary care and conduct a cluster randomised controlled trial, at general practice level, to establish whether a complex intervention to identify and invite patients at high risk of HCV was effective and cost effective at increasing HCV case finding and referral of people with HCV disease for assessment at specialist services.

## Methods

HepCATT (Hepatitis C Assessment Through to Treatment Trial) was a pragmatic, two armed, practice level, cluster randomised controlled trial carried out in general practices in the South West of England with both qualitative and economic evaluation components.[15] The nested qualitative study is reported separately.[16]

### Randomisation

General practices were the unit of allocation and were randomised by an independent statistician in a 1:1 ratio to either receive the intervention or continue care as usual (control group). Randomisation was stratified by area (Bristol and non-Bristol, in case differences existed at baseline between city and semi-rural practices) and minimised by current rate of HCV testing as measured by Public Health England laboratory surveillance (high (≥1% of practice list) versus low (<1%)) and practice size.[10] Minimisation retained a random element such that each practice being allocated was more likely to be, but was not inevitably, allocated to the group that achieved the best balance in HCV testing and practice size between intervention and control groups. Of 93 practices in our target area, 15 (16%) had high HCV testing rates.

### Intervention

The intervention (registered: http://www.isrctn.com/ISRCTN61788850) follows NICE recommendations.[17] It is described in more detail in our protocol[15] (and in the supplementary material). In brief, the intervention had multiple components. (1) HCV audit tool and patient flag: we designed a new algorithm for the Audit+ software (Informatica Systems Ltd), which is fully integrated with primary care systems once installed in practices and would identify and flag patients with high risk HCV markers (see supplementary material for a full list of risk markers and associated Read codes). The audit tool automatically aims to exclude any patients tested less than one year previously who were negative for HCV antibodies, referred to hepatology, receiving low doses of buprenorphine and methadone for pain management, or at end of life. (2) Training was provided in use of the HCV audit tool. We recommended that practices should first screen their list of patients and exclude on the system any patient for whom they thought that an invitation for HCV testing or discussion of treatment was not appropriate. Then eligible patients should be offered HCV testing either opportunistically (responding to on-screen pop-ups) or through encouragement to book an HCV test by letter generated automatically by the software (see supplementary material). We also recommended that patients should be followed up to arrange appointments. (3) Educational training: practice staff were encouraged to make use of free online HCV educational resources (eg, Royal College of General Practitioners e-learning module: https://elearning.rcgp.org.uk/). (4) Raising patients' awareness: information posters and leaflets, produced by the HCV Trust, were provided to practices. (5) Clinical history: practices were encouraged to add a question about injecting drug use to their new patient registration.

Practices delivered this intervention over a 12 month study period. Patients with a positive antibody test were managed according to local practice, which would be referral to specialist services unless contraindications were present. Practice start date varied from April to December 2016.

Control practices continued to do opportunistic HCV case finding as usual. We contacted control practices only at the time of randomisation and at the end of the intervention period when we asked them to install and run the same HCV audit to generate outcome data. The control practices also were given a one year licence for the Audit+ software.

### Outcomes

The main outcome was uptake of HCV testing. The secondary outcomes were yield (number of HCV positive tests and proportion of HCV tests that were positive), and referral and assessment for treatment of patients with chronic HCV at hepatology.

We collected outcomes and data on patients' risk profile from general practices by using the Audit+ software in the intervention practices and control practices and linked them, using patient identifiers, with Public Heath England laboratory data on HCV test results (HCV antibody and polymerase chain reaction). We identified patients assessed in hepatology by linking HCV tests—that is, a viral load test in secondary care





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following both positive HCV antibody and polymerase chain reaction tests in primary care (validated previously as a measure of HCV treatment referral and assessment[18])—for our final report to funders. This was a change from our protocol in relation to secondary care to save time because of delays in obtaining data from controls owing to changes in research governance. We subsequently confirmed assessment through linkage between the laboratory and specialist services. In a sensitivity test, we linked HCV antibody tests in primary care to polymerase chain reaction tests in secondary care, as some polymerase chain reaction tests in primary care were missing.

### Sample size calculation

In our original calculation, we assumed that an average practice would have a list of 4225 adult patients aged 15-65 years, of whom approximately 1% (n=42) would have an injecting drug history, and that 40% (n=17) of these would be HCV positive. We consequently assumed that at least 10 patients would be identified as at high risk in each practice. We assumed an intra-cluster correlation coefficient of 0.05 and hence a design effect of 1.45 to accommodate variation in antibody testing rates across practices. We needed, therefore, a sample size of 46 practices (23 intervention and 23 control; 230 patients at high risk identified in each arm) to detect a true absolute difference in HCV antibody testing uptake of 12% (from 5% to 17% of patients at high risk identified), with 90% power at the 5% significance level.[14 19]

### Statistical analysis

The trial cohort comprised those patients identified as at high risk by the HCV audit tool. Analyses followed the intention to treat principle, with practices being analysed in the groups to which they were randomly allocated. We used Stata statistical software version 15.1 for all analyses. The primary analysis was pre-specified before collection of the outcome data.[15] We estimated the proportion of patients with high risk markers tested for HCV antibodies, compared between intervention and control arms as a rate ratio, in a random effects Poisson regression model (random effects assumed to be normally distributed), adjusted for potentially prognostic variables used to stratify the random allocation (site of practice, HCV testing rate at baseline). This regression model accommodated any additional variation in the outcome measure between practices by incorporating an extra parameter and also allowed for the shorter follow-up period at two practices by including practice follow-up time as an offset term. The use of a mixed effects Poisson model is a variation to the analysis pre-specified in the protocol,[15] in which we stated that we would be using negative binomial regression. Mixed effects Poisson regression models, by allowing a multi-level model, more easily accommodate covariates at both the practice and individual levels. Both approaches are elaborations of Poisson regression, the key difference being that the negative binomial model assumes a $\gamma$ distribution of testing rates across practices. In fact, the observed distribution of antibody testing rates was closer to a $\gamma$ distribution than to a normal distribution, but repeating the analyses with practice level covariates using each of the two methods in turn gave practically identical results. We adapted this approach to the secondary outcome measures. The model was extended with the addition of an interaction term to compare the effect of the intervention on the primary outcome between subgroups specified in terms of being at high risk owing to opioid dependence/ injecting drug use or being at high risk owing to one of the other factors (exploratory analysis). We present a crude estimate of the risk difference for the primary outcome with 95% confidence interval (calculated by making the normal approximation), with, at the suggestion of a reviewer, an adjusted risk difference estimated using Stata's adjrr.[20]

### Economic analysis

Our economic evaluation first estimated the cost per HCV test and referral from the trial and practice perspective and then estimated the cost per quality adjusted life year (QALY) gained associated with the intervention by using an existing Markov model.[21 22] Both analyses were performed from the NHS perspective, with results presented in pounds sterling in 2017. Full details of the economic evaluation methods are given in our protocol[15] and supplementary material.

Briefly, for the within trial analysis, we compared costs between intervention and control practices by using mixed effects linear regression, clustered by practice, adjusting for sampling stratification and length of follow-up. We estimated the cost of HCV case finding per patient at high risk identified through the HCV algorithm and calculated the incremental cost per patient assessed at secondary care in intervention versus control practices. We used a cost effectiveness acceptability curve to explore uncertainty.[23] In a second analysis, we removed the costs and the Audit+ installation, training, and maintenance costs, as Audit+ is now routinely available to general practices with much wider functionality than just HCV case finding.

In the economic model, we compared the HepCATT intervention versus current practice, using a Markov model over a lifetime time horizon. We assumed that the intervention was implemented for one year in a static cohort. The model produces incremental cost effectiveness ratios (ICERs) per QALY gained, with both costs and QALYs discounted at 3.5%,[24] and estimates the probability of cost effectiveness at a willingness to pay threshold of £20 000 per QALY for the NHS. We did multiple scenario and sensitivity tests (excluding training costs; assuming lower health utility values associated with opioid dependent people; assuming linkage to care for each arm was equal; halving estimated HCV direct acting antiviral treatment cost to £5000 per course). We also did a "threshold analysis" to estimate the minimum increase in HCV antibody

testing needed for the intervention to remain cost effective. Table 1 shows the economic inputs.

### Patient and public involvement

During the set-up of the trial, we consulted with Bristol Drugs Project (BDP) and its volunteer group, which included current and previous drug injectors and people with HCV infection. Members of the BDP volunteer group reviewed the invitation letter sent by practices to invite patients for an HCV test and the patient information sheet. The information resources were developed in conjunction with the Hepatitis C Trust patient group and National Hepatitis C Patient Council. The Hepatitis C Trust and BDP will also help us to co-produce a summary of the study and support dissemination of findings with patients and practitioners

## Results

### Practice recruitment

The NIHR South West of England Clinical Research Network invited 90 practices across Bristol, North Somerset, and Gloucestershire; 45 practices agreed, and 22 were randomised to the intervention and 23 to the control arm. Figure 1 shows the CONSORT flow diagram. The intervention and control practices were comparable in mean list size, area deprivation score, and proportion of the local community of non-white ethnicity. None of the intervention practices opted to ask new patients about injecting drug use history at registration; 15/22 practices carried out all of the other elements of the intervention (fig 1). Outcome and risk algorithm data were collected from all of the 22 intervention practices and 21/23 control practices. Two intervention practices merged during the study period, which we treat as one in our analyses.

### HCV audit risk algorithm

The total number of patients identified in both control and intervention practices was 24 473—approximately 5% of the patient list, varying from 0.2% to more than 13% by practice (supplementary table S1A and S1B). Table 2 shows the frequency with which each of the risk criteria was met by the patients identified, with 8838 (36%) meeting two or more criteria. The proportion of patients identified with an opioid/injecting drug use history was approximately 1%, ranging from less than 0.1% to more than 6%. More than half of the cohort had evidence of a previous HCV test (63% in intervention and 57% in control practices). Other common criteria were a history of injecting or opioid drug use (2930 (22%) in intervention and 3315 (29%) in control practices) and unexplained elevated alanine aminotransferase concentrations.

### HCV testing

*Pre-intervention*

At baseline, in the six month period immediately before the study period, 608/13 097 (4.6%) of the patients in the intervention practices and 380/11 376 (3.3%) of those in the control practices who were identified by the algorithm were tested for HCV. HCV testing for patients identified with opioid/injecting drug use history was 69/2930 (2.4%) and 48/3315 (1.4%) in the six months before the intervention in intervention and control practices respectively.

*Post-intervention*

During the study period, 2071 (16%) of patients identified in the intervention practices and 1163 (10%) of those in control practices were tested for HCV (table 3). We found strong evidence of a higher rate of antibody testing in the intervention practices (adjusted rate ratio 1.59, 95% confidence interval 1.21 to 2.08; P<0.001) compared with the control practices. The magnitude of this intervention effect was unaffected by adjustment for practice location and historical HCV testing rate. We estimated the crude risk difference to be 5.6% (95% confidence interval 4.8% to 6.4%), and the adjusted estimate with variation between general practices accommodated was 5.3% (2.2% to 8.51%).

**Table 1 | Unit costs (2016/17) used in economic analysis and Markov model**

| Item | Unit cost | Source |
|---|---|---|
| Cost of Audit+ (per practice) | £500 (£0 in sensitivity analysis) | Assumption |
| Trainer time (per hour) | £53 | Estimate |
| Trainer travel expenses (per mile) | £0.45 | University of Bristol policy |
| GP time (per hour) | £137 | Unit costs of health and social care |
| Administrative staff (band 2) time (per hour) | £23 | Unit costs of health and social care |
| Healthcare assistant (band 2) | £23 | Unit costs of health and social care |
| Nursing staff (band 6) | £44 | Unit costs of health and social care |
| Practice manager (band 7) | £53 | Unit costs of health and social care |
| Phlebotomy appointment | £14.10 | Based on private practice (SE Bridge Street Medical Centre) |
| HCV antibody blood test | £8.12 | Public Health England |
| HCV PCR blood test | £ 90.64 | Public Health England |
| HCV related GP consultation | £37 | Unit costs of health and social care |
| Hepatology consultation | £219 | NHS reference costs |
| Hepatology evaluation (outpatient, initial) | £238 | NHS reference costs |
| Hepatology evaluation (outpatient, follow-up) | £262 | NHS reference costs |
| DAA treatment (first treatment) | £10 000 | Hurley 2018 |
| DAA treatment (retreatment) | £15 000 | Assumption |
| DAA treatment monitoring | £1,310 | NHS reference costs |

DAA=direct acting antiviral; GP=general practitioner; HCV=hepatitis C virus; PCR=polymerase chain reaction.







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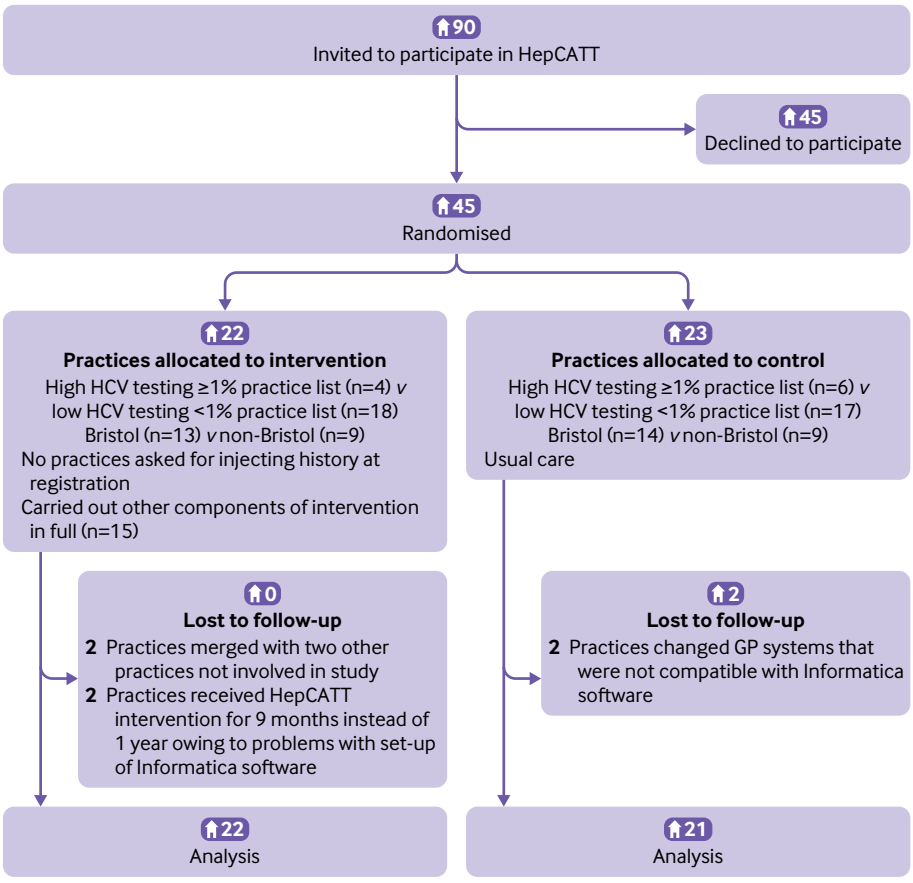


**Fig 1 | Consort diagram. No practices added "have you ever injected recreational drugs?" to their patient registration proforma. Mean patients registered: intervention 11 225 (SD 4245), control 10 937 (3916); mean area deprivation score: intervention 6 (3.26), control 6 (3.23); mean % non-white ethnic population: intervention 12 (14.25), control 11 (11.49). GP=general practice; HCV=hepatitis C virus**

In an exploratory analysis, also shown in table 3, we found that the intervention had a slightly greater effect on patients with an opioid/injecting drug use history (adjusted rate ratio 2.73) than other patient risk groups (adjusted rate ratio 1.45), with evidence against the null hypothesis of equal intervention rate ratios between the two subgroups (interaction test P<0.001). The crude risk differences, however, were similar in the two subgroups at 4-5%.

We estimate that the intra-cluster correlation coefficient was 0.067 (95% confidence interval 0.042 to 0.105) on the basis of a random effects logistic regression model (with the same covariates as the adjusted model in table 3) to allow comparison with the estimate used in the sample size calculation.

### Other outcomes: HCV test yield, chronic infection, referral and assessment

The rate of positive antibody tests was also greater in the intervention practices compared with the control practices (table 3) (1.0% *v* 0.5%; adjusted rate ratio 2.24, 1.47 to 3.42). A greater proportion of the antibody tests were positive in the intervention group (6.4%; 129/2017) than in the control group (4.4%; 51/1163), although the evidence was weaker and consistent with chance (adjusted risk ratio 1.40, 0.99 to 1.95; P=0.053).

Of those people with a positive antibody test, no polymerase chain reaction tests were recorded for 9/129 patients in intervention practices and 1/51 patients in the control practices, and insufficient

**Table 2 | Number of participants in intervention and control practices meeting each hepatitis C virus (HCV) audit criterion. All cohort members met one or more criteria**

| HCV audit criteria | Intervention (n=13 097): positive risk criteria (%) | Control (n=11 376): positive risk criteria (%) |
|---|---|---|
| History of HCV exposure or testing | 8295 (63.3) | 6476 (56.9) |
| History of opioid/injecting drug use | 2930 (22.4) | 3315 (29.1) |
| History of HIV or HBV infection | 971 (7.4) | 829 (7.3) |
| History of blood transfusion or transplant | 423 (3.2) | 378 (3.3) |
| History of childhood in care or imprisonment | 899 (6.9) | 1024 (9.0) |
| Altered ALT concentration | 5120 (39.1) | 3895 (34.2) |

ALT=alanine aminotransferase; HBV=hepatitis B virus.

**Table 3 | Hepatitis C virus (HCV) antibody testing, HCV positive test yield, polymerase chain reaction (PCR) tests for chronic infection, and referral to secondary care in intervention and control practices, with intervention effect estimated as rate ratio from random effects Poisson regression model that accommodates any variations in testing between practices**

| | Number (%) | | | |
|---|---|---|---|---|
| | Intervention (n=13 097) | Control (n=11 376) | Rate ratio (95% CI) | P value |
| **Tested** | | | | |
| Crude | 2071 (15.8) | 1163 (10.2) | 1.57 (1.18 to 2.09) | 0.002 |
| Adjusted* | | | 1.59 (1.21 to 2.08) | <0.001 |
| Subgroup analysis†: | | | | |
| Opioid/injecting drug use | 189/2930 (6.5) | 80/3315 (2.4) | 2.73 (1.95 to 3.82) | - |
| No opioid/injecting drug use | 1882/10 167 (18.5) | 1083/8061 (13.4) | 1.45 (1.08 to 1.95) | - |
| Ratio of rate ratios‡ | - | - | 1.91 (1.45 to 2.52) | <0.001 |
| **Antibody test positive** | | | | |
| Crude | 129 (1.0) | 51 (0.4) | 2.30 (1.41 to 3.75) | 0.001 |
| Adjusted* | | | 2.24 (1.47 to 3.42) | <0.001 |
| **PCR test positive** | | | | |
| Crude | 43 (0.3) | 13 (0.1) | 3.17 (1.38 to 7.31) | 0.007 |
| Adjusted* | | | 2.96 (1.34 to 6.58) | 0.008 |
| **Referred/positive antibody and PCR tests** | | | | |
| Crude | 20 (0.2) | 3 (<0.1) | 6.25 (1.67 to 23.38) | 0.007 |
| Adjusted* | | | 5.78 (1.55 to 21.61) | 0.009 |
| **Referred/positive antibody test (sensitivity analysis)** | | | | |
| Crude | 27 (0.2) | 7 (<0.1) | 3.43 (1.36 to 8.65) | 0.009 |
| Adjusted* | | | 3.40 (1.35 to 8.52) | 0.009 |

*Adjusted for practice location (Bristol versus elsewhere) and historical HCV testing rate (low versus high, as indicated by Public Health England).
†Subgroups defined by history of opioid/injecting drug use.
‡Estimated ratio of rate ratios in two subgroups (opioid/injecting drug use and no opioid/injecting drug use, and control practices as reference within each), with interaction test P value estimated from model with covariates as in above*.

sample (no result) was recorded for an additional 17 intervention and 14 control patients. Evidence of chronic disease from polymerase chain reaction tests in primary care, in people with a positive antibody test, was detected in 43 (0.3%) in intervention practices and 13 (0.1%) in control practices (table 3) (adjusted rate ratio 2.96, 1.34 to 6.58).

We found strong evidence that referral and assessment were increased in intervention practices compared with control practices (adjusted rate ratio 5.78, 1.55 to 21.6). The absolute difference between intervention and control practices, however, was modest: 20/43 patients with HCV RNA detected or 15 in 10 000 patients at high risk in intervention practices, compared with 3/13 or 3 in 10 000 patients at high risk from control practises. This equates to a number needed to help of one extra HCV diagnosis, referral, and assessment per 792 (95% confidence interval 558-1883) patients flagged. In a sensitivity analysis relaxing the requirement for a positive polymerase chain reaction test from primary care, the intervention effect was slightly attenuated but still strong (adjusted rate ratio 3.40, 1.35 to 8.52).

### Change in baseline HCV testing: potential contamination/dilution of effect

Supplementary table S1A shows evidence that HCV testing increased in general in the community. Overall and in 18/21 of the control practices, the number and proportion of HCV tests among patients at high risk in the six months before the intervention (380; 3.3%) more than doubled during the intervention period (1163; 10.2%). We found no evidence that testing increased over time in control practices among patients with an opioid/injecting drug use history (HCV testing in this patient group was 1.4% in the six months before the intervention and 2.4% in the 12 months during the intervention).

### Economic evaluation

A small number of patients (287/24 473 (1.2%) appeared in the records of more than one practice. We retained these in the analysis of the intervention effect reported above to avoid excluding a more mobile section of the study sample but excluded them from the economic analysis, which is based on the remaining 23 896 patients (12 922 in the intervention arm and 10 974 in the control arm).

High variability existed between practices in the time estimated to complete each stage of the case finding process (supplementary table S2). The most time consuming stage was screening the list of patients to identify appropriate candidates for the screening invitation; this varied from an estimated one hour to 30 hours. This stage was also the most expensive, as the task was most often carried out by a general practitioner. Other elements of the case finding were more often carried out by the practice manager or administrative staff. The mean total cost of the case finding process was £1272 per practice, or £624 per practice if software and installation costs are excluded.

The intervention led to a very small increase in the number and the cost of HCV related general practice consultations during the study period, but this had little effect on total costs (table 4). The additional cost of case finding per patient at risk in the intervention practices was £7.10 (95% confidence interval £4.75 to £9.45). The average cost per additional patient





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**Table 4 | Cost effectiveness of hepatitis C virus (HCV) case finding**

| Task | Intervention (n=12 922) | Control (n=10 974) | Difference (95% CI) |
|---|---|---|---|
| Training cost | £1.22 | £0 | - |
| Screening cost | £2.06 | £0 | - |
| Mean HCV antibody test cost per patient | £3.54 | £2.33 | £1.21 (£1.02 to £1.40) |
| Mean HCV PCR test cost per patient | £0.89 | £0.41 | £0.48 (£0.28 to £0.68) |
| No (%) HCV related consultations: no; yes | 12 187 (94); 735 (6) | 10 467 (95); 507 (5) | |
| Mean HCV related consultation cost per patient | £2.27 | £2.10 | £0.17 (−£0.09 to £0.44) |
| Mean hepatology referral cost per patient | £0.44 | £0.12 | £0.32 (£0.12 to £0.52) |
| Total mean case finding cost per patient | £10.42 | £4.96 | £7.10 (£4.75 to £9.45)* |
| No (%) patients referred to hepatology for treatment | 20 (0.15) | 3 (0.03) | - |
| Cost per additional patient referred to hepatology for treatment | - | - | £5569 |

PCR=polymerase chain reaction.
*Adjusted mean difference from mixed effects linear regression, clustered by practice, adjusted for previous HCV testing, Bristol practice, and length of follow-up.

referred to hepatology for assessment was £5569. Figure 2 shows the cost effectiveness acceptability curve based on the cost per additional case identified. Alternatively, after exclusion of the training, software, and installation costs, the cost of case finding was £4.03 (£2.27 to £5.80) and the average cost per additional patient referred to hepatology for treatment was £3165.

### Economic model

Table 5 shows the estimated ICERs per QALY gained from the economic model. The base case analysis generated an ICER of £6916 per QALY with a probability of 90.8% of being below £20 000 per QALY (fig 3). After exclusion of training and installation costs, the ICER was £5783 per QALY (with 93.3% probability of being below £20 000 per QALY). Table 5 also shows our sensitivity analyses. The intervention was still cost effective when we assumed no effect of the intervention on the linkage to care (ICER £19 289 per QALY) and a reduced utility in patients who may continue to be opioid dependent and/or inject drugs (ICER £8463 per QALY) and was more cost effective when we assumed lower HCV drug costs (ICER £5126 per QALY).

### Threshold analyses

In our threshold analysis of the effect of the intervention on the rate ratio of antibody testing, the base case analysis will always be cost effective at an ICER less than £20 000 per QALY because the intervention led to higher linkage to care. If we assume that linkage to care was equal for control and intervention practices, then the cost effectiveness threshold for the intervention effect of increasing HCV antibody testing was a rate ratio of 1.53 (or a 53% increase in HCV testing).

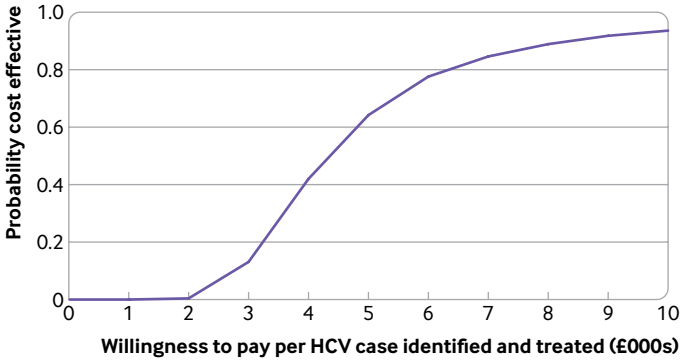


**Fig 2 | Probability that hepatitis C virus (HCV) case finding is cost effective per additional case identified: cost effectiveness acceptability curve**

## Discussion

The size of the effect of the HepCATT primary care intervention was comparatively modest but at low cost to the NHS. The risk difference was 1.3 per 1000 or a "number needed to help" of one extra HCV diagnosis, referral, and assessment per 792 patients flagged on primary care systems. A threefold to sixfold increase in linkage to specialist care occurred. The intervention cost was £624 per practice (with software and installation costs removed as the HCV audit tool is now incorporated in many clinical software systems) equating to approximately £4.03 per patient flagged, an average cost per additional patient referred to HCV specialist services of £3165 and an ICER of £6212 per QALY (well below NICE's guidance of £20 000 per QALY or even the average cost of NHS treatments of approximately £13 000 per QALY[25]).

### Limitations of study

Overall, the trial was completed as planned, but some potential limitations to the study exist. Firstly, we detected some evidence of contamination between control and intervention sites. A clear increase in HCV testing during the intervention period occurred among people with a previous HCV test in the control practices, but we found no evidence of any increase in testing in those with an opioid/injecting drug use history. This was probably due to increased steps nationally and regionally to increase HCV testing as part of HCV treatment targets for operational delivery networks. Nevertheless, the HepCATT intervention managed to increase uptake of HCV testing and increased linkage to care.

Secondly, our sample size calculations had assumed that around 10 people at high risk would be identified per practice and that we would have sufficient power to detect a difference in HCV testing between 5% in the control group to 17% in the intervention group. In our trial, the average number of patients flagged (across control and intervention practices) was more than

Table 5 | Base case and scenario analysis results per patient identified as at high risk by HepCATT intervention

| Testing option | Total costs | Total QALYs | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| Base case results: | | | | | |
| Control arm | £417 | 16.2207 | - | - | - |
| Intervention arm | £424 | 16.2218 | £7.45 | 0.00108 | £6916 |
| Training costs excluded: | | | | | |
| Control arm | £417 | 16.2207 | - | - | - |
| Intervention arm | £423 | 16.2218 | £6.23 | 0.00108 | £5783 |
| Scenario—no treatment effect for linkage to care (referral and attendance): | | | | | |
| Control arm | £416 | 16.2212 | - | - | - |
| Intervention arm | £424 | 16.2216 | £8.56 | 0.00044 | £19 289 |
| Scenario: £5000 per DAA: | | | | | |
| Control arm | £389 | 16.2207 | - | - | - |
| Intervention arm | £395 | 16.2218 | £5.52 | 0.00108 | £5126 |
| Scenario—utility adjusted to PWID utilities (all multiplied by 0.82): | | | | | |
| Control arm | £417 | 13.2557 | | | |
| Intervention arm | £424 | 13.2565 | £7.45 | 0.00088 | £8463 |

DAA=direct acting antiviral; ICER=incremental cost effectiveness ratio; PWID=people who inject drugs; QALY=quality adjusted life year.

500 and the average number of people with an opioid/injecting drug use history was 148. The observed difference was smaller than anticipated, partly because of improvements in HCV testing in the community, and the intra-cluster correlation coefficient at 0.067 was marginally greater than our assumed 0.05, but both of these factors will have been more than offset by the greater than anticipated number of people at high risk found at the vast majority of practices.

Thirdly, as this was a cluster randomised controlled trial, we did not seek consent from individual patients for participation in the full study (which was justified as the intervention was following NICE recommendations). A consequence of this was that we did not seek patients' consent to examine their records—for example, to explore reasons for the insufficient samples for polymerase chain reaction testing in so many cases.

Fourthly, general population samples tend to find a lower proportion of people with chronic disease (detectable HCV RNA/ polymerase chain reaction positive) than do clinical samples.[26 27] In our sample—excluding those with no polymerase chain reaction tests or tests with insufficient sample—we found that 40% had chronic HCV infection. It was not clear whether this was because people had been previously treated (but not recorded in clinical information that could be searched by the HCV algorithm) or had cleared the virus and previously been found to be HCV negative. This reduces the yield and potentially the cost effectiveness of the intervention (although the intervention was shown to be highly cost effective).

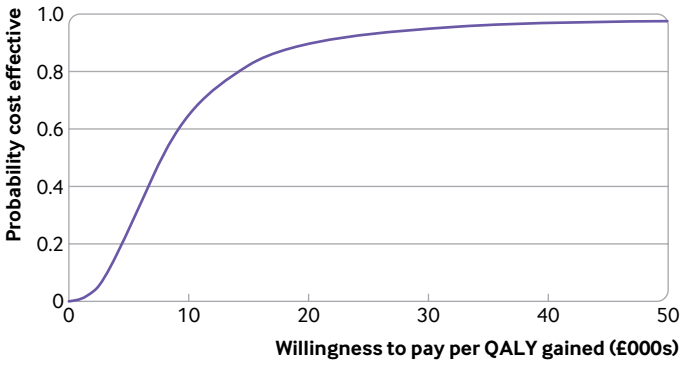


Fig 3 | Probabilistic sensitivity analysis that hepatitis C virus case finding is cost effective at different thresholds of willingness to pay per quality adjusted life year (QALY)

### Other evidence

Large scale trials on HCV case finding in primary care are rare.[13] We also did a pilot trial of NICE recommendations to appoint HCV case facilitators in community drug clinics.[28] The original cost effectiveness model underpinning NICE guidance in primary care was based on a non-randomised pilot study in eight practices with high levels of deprivation.[14] The earlier study used financial incentives for participation, searched practice lists for a smaller sub-group of patients with a history of opioid dependence, and the intervention was estimated to be less cost effective than ours (at an estimated ICER of £13 900 per QALY), although the original pilot generated a higher yield of patients with chronic HCV infection.

A recent complementary trial (HepFREE), also motivated by the lack of robust evidence in support of NICE guidance on hepatitis case finding,[17 19] showed that combining case finding for HCV and hepatitis B virus in migrant populations in primary care could be effective and broadly cost effective.[29] The HepFREE trial was conducted in general practices with a high density of migrants and involved a modest incentive (£500) for general practitioners to run an algorithm that would identify patients for contacting by letter and add an electronic prompt to the patient's record. Additional clinical support was available to help practices run the case finding exercise. HepFREE also found a comparatively low proportion of viraemic patients (at approximately a third of people with HCV antibody tests), which as for HepCATT reduces the yield of the study and has implications for the re-engagement exercise recently launched by Public Health England and NHS England (https://www.gov.





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uk/government/publications/hepatitis-c-patient-re-engagement-exercise).

A previous study in Ireland found an increase in HCV testing in general practices that were encouraged to follow clinical guidelines recommending HCV testing for patients taking methadone.[30] In the UK, case finding and early treatment for opioid dependent patients has been established to be highly cost effective, and multiple alternative case finding and care pathways are being tested and developed in the community for this population group, including through prisons, pharmacies, needle exchange services, and homeless services.[12 28 31 32] However, these care pathways do not cover our study patients—people in primary care who may no longer be opioid dependent or taking opioid agonist treatment.

An alternative, and possibly complementary, approach is to conduct birth cohort screening, whereby all patients born between specific years (such as 1945 to 1965 as recommended by the Centers for Disease Control and Prevention in the US) are invited to be screened for HCV.[33 34] An economic model suggests that adding HCV screening to the NHS health check for people aged 45 to 70 could be cost effective, although no empirical evidence yet supports such a change.[35]

### Implications

The nested qualitative study suggests that practices are willing to engage with our intervention.[16] Our intervention was highly cost effective but increased HCV testing by only a modest amount—lower than expected from our original sample size calculation. The overall findings are strong enough for us to recommend optimisation as part of implementation across primary care in the UK. However, HepCATT cannot be seen as the only solution to increasing HCV case finding in primary care and to identifying patients at risk who may not be aware of their HCV infection. Other interventions, such as evaluating birth cohort screening as part of NHS health checks, and additional components to the HepCATT intervention, such as incentives for the practices for running the algorithm and additional clinical support for achieving higher uptake, are needed to enhance the impact.


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**Contributors:** All authors contributed to editing of the manuscript. MH and KR drafted the manuscript for authors to contribute and comment on. MH, JH, and WI led the NIHR grant and study. All authors were members of the project team and contributed to interpretation of the study findings. MH, JH, WI, CM, WH, and PV, with support from BRTC, designed the study. KR, PM, CW, CC, FG, PN, PM, and RS contributed to and supported data collection and conducted the trial with support from BRTC and the CRN. CM, WH, KR, MH, JW, AM, PV, CC, and JH analysed the data collected during the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MH is the guarantor.

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**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support for the submitted work as described above;MH has received unrestricted honorariums for presenting at meetings from Abbvie, Gilead, and MSD; PV has received unrestricted honorariums for presenting at meetings from Abbvie and Gilead; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** This trial was approved by the South West Frenchay Research Ethics Committee and carried out in accordance to the declaration of Helsinki and all UK regulatory requirements.

**Data sharing:** The algorithm is defined in the supplementary materials, and the software is now available for practices and the NHS. Relevant anonymised data will be made available on reasonable request.

**Transparency declaration:** The lead author and guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

**Dissemination to participants and related patient and public communities:** The authors plan to send a summary of the results to participating practices and undertake extensive knowledge exchange work with the NHS (primary care, Public Health England, HCV operational delivery networks, NHS England, and public health departments in local government). They will co-produce summary information on the study with Bristol Drug Project and Hepatitis C Trust.





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## Supplementary materials

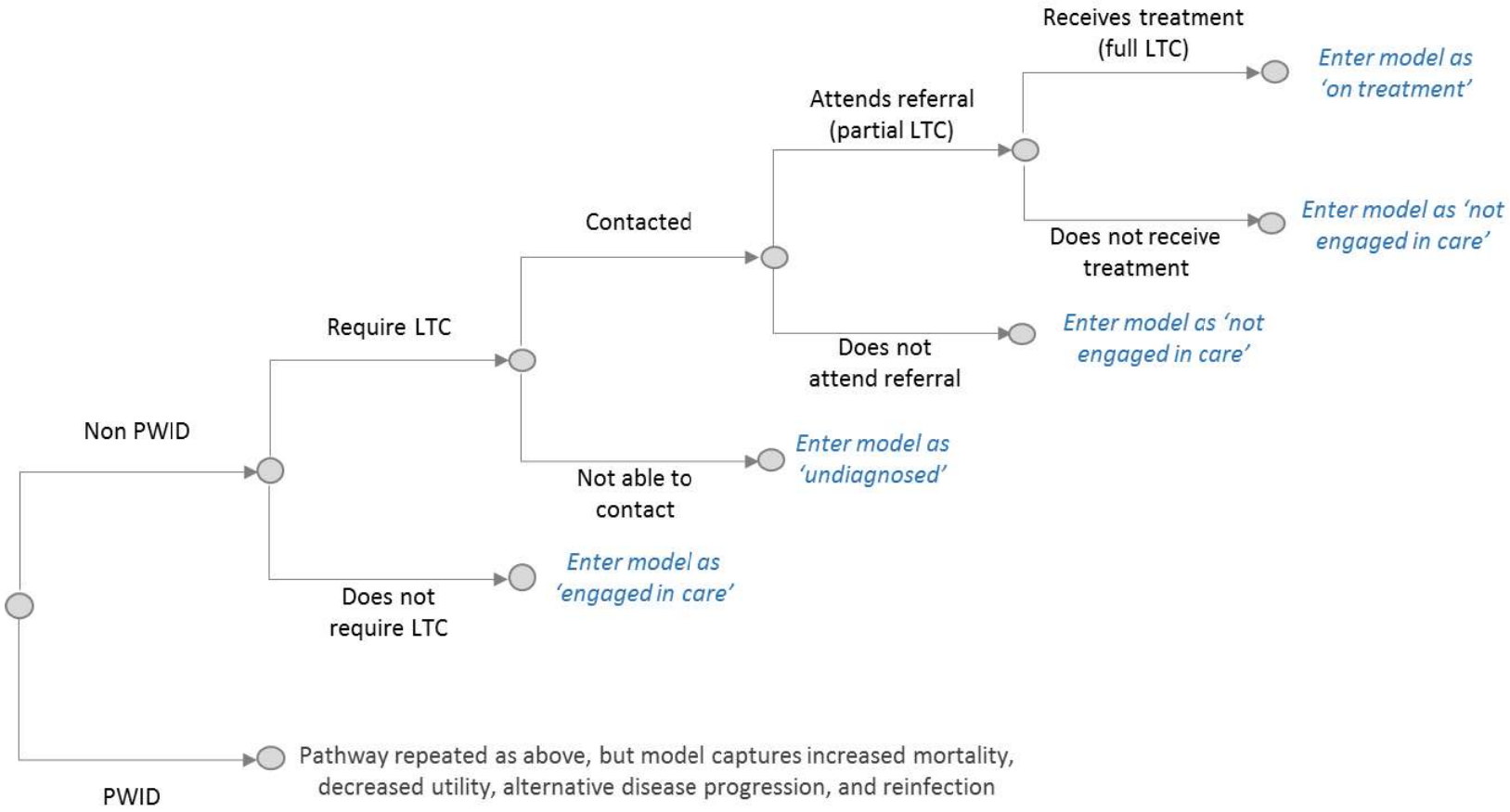
## 10.5 Emergency department testing economic evaluation - Supplementary materials (Research Paper 3)

**Model structure**

The movement through the decision tree informed the distribution of the patients entering into the Markov models. Patients entered the Markov models as either 'undiagnosed', 'diagnosed and engaged in care', 'already engaged in care', or 'diagnosed and not engaged in care'. Individuals who were not contacted were assumed to remain undiagnosed (and thus could be tested and diagnosed in the future). Individuals who were contacted but did not attend their referral or did not accept treatment when indicated were assumed to enter the model 'not engaged in care'. For both HCV and HBV, the infection status of those with decompensated cirrhosis (DC) and HCC was assumed to be known due to the severity of the disease, and these individuals were assumed to engage in care, an assumption that has been made in previous models.[1]

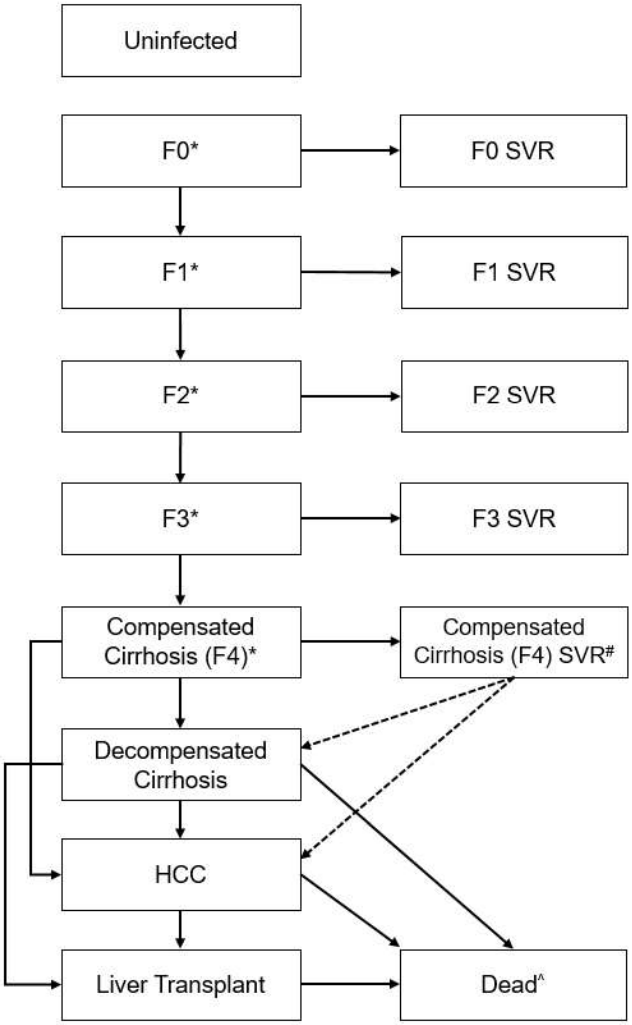
The estimated overall survival, and rate of progression to advanced disease health states (DC, HCC and LT) were assessed during the model development to ensure the accuracy and validity of the model estimates.

*Figure 1: Hepatitis C Decision Tree Structure*



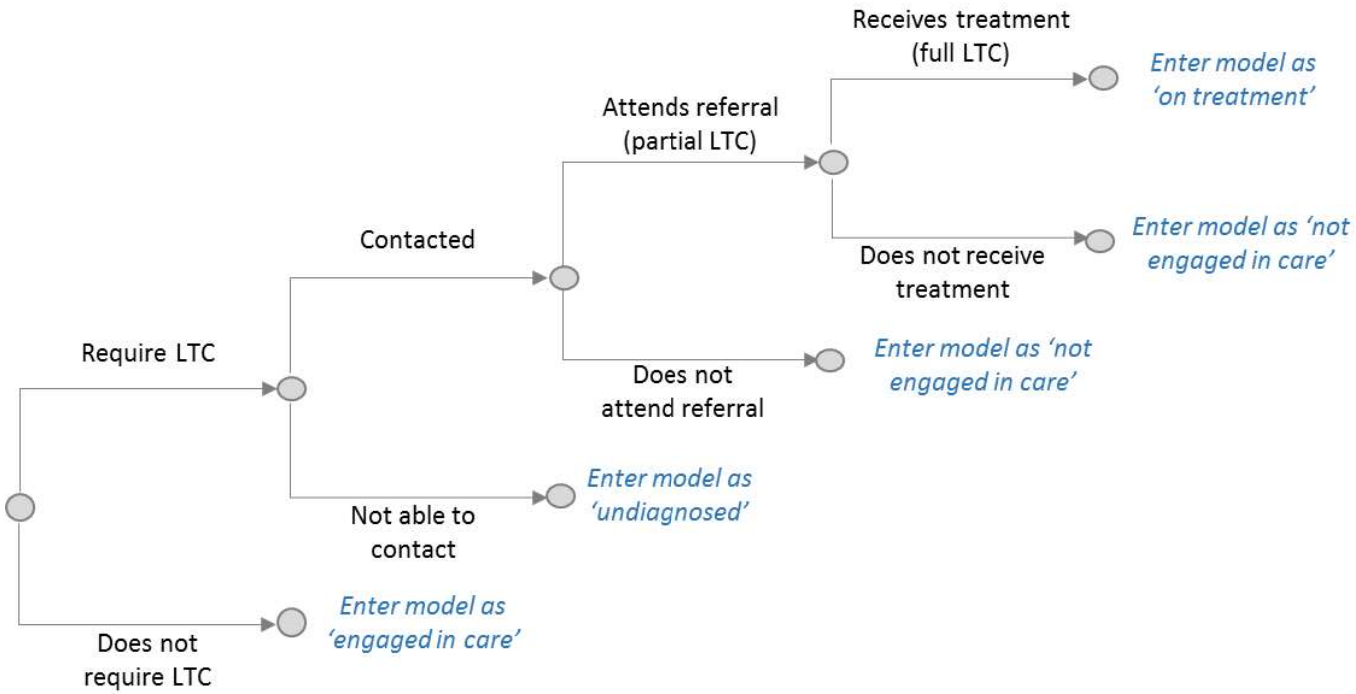

LTC: Linkage to care, PWID: People who inject drugs

*Figure 2: Hepatitis C Markov model structure*



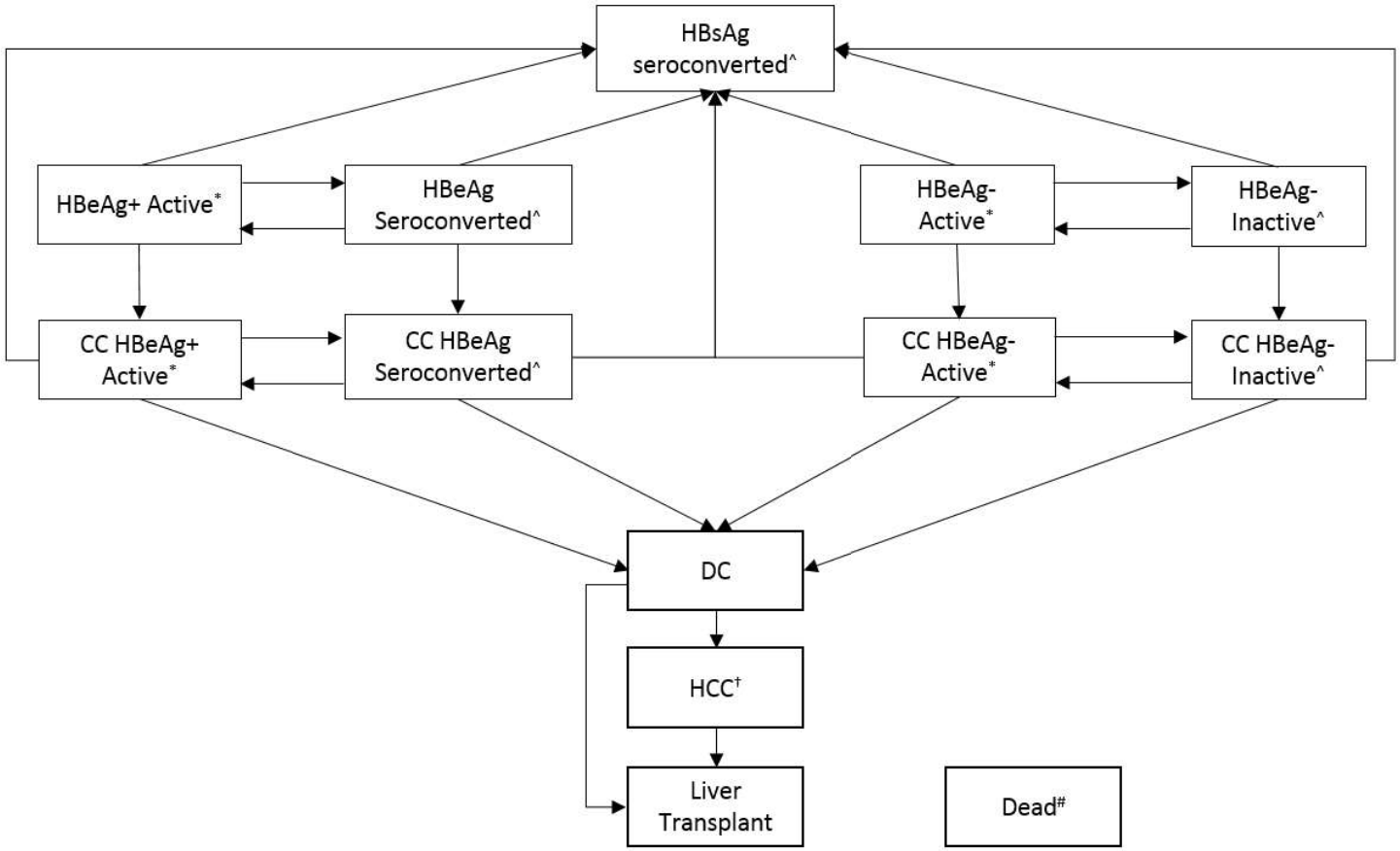

*F0-F4 health states contain the following states: 'undiagnosed', 'on treatment', 'SVR' (as shown above), 'engaged in care, non-SVR' and 'not engaged in care'
#Dotted transition lines represent disease progression at lower probability vs. non-SVR health states.
^Transitions possible from all health states to dead, arrows depicted show disease related mortality only.

*Figure 3: Hepatitis B decision tree structure*




LTC: Linkage to care

*Figure 4: Hepatitis B Markov model structure*




*Active health states include the following states: 'undiagnosed', 'on treatment (year 1)', 'on treatment (>1 year)', 'diagnosed, not engaged in care'
^Seroconverted/inactive/HBsAg seroconverted health states include the following states: 'undiagnosed', 'diagnosed, engaged in care' 'diagnosed, not engaged in care'
#Transition to death possible from all other health states as background (general population) mortality. Disease progression to death also occurs from active disease health states (without treatment), DC, HCC and Liver transplant health states.
†Transitions to HCC possible from all health states, except from liver transplant and dead states.

## HCV transition probabilities

*Table 1: Base case health state transition probabilities and treatment outcomes for HCV*

| Base case probabilities | Mean | Distribution | Source |
|---|---|---|---|
| ***Transition probabilities*** | | | |
| F0 to F1 – non PWID | 0.089 | Beta(α=22.68, β=232.02) | [2] |
| F1 to F2 – non PWID | 0.088 | Beta(α=22.72, β=236.52) | [2] |
| F2 to F3 – non PWID | 0.124 | Beta(α=21.77, β=153.19) | [2] |
| F3 to CC (F4) – non PWID | 0.090 | Beta(α=22.66, β=228.94) | [2] |
| F0 to F1 – PWID | 0.128 | Beta(α=23.69, β=161.41) | [3] |
| F1 to F2 – PWID | 0.059 | Beta(α=22.73, β=362.48) | [3] |
| F2 to F3 – PWID | 0.078 | Beta(α=44.45, β=525.37) | [3] |
| F3 to CC (F4) – PWID | 0.116 | Beta(α=21.96, β=167.33) | [3] |
| CC to DC | 0.039 | Beta(α=14.617, β=360.1732) | [4] |
| CC to HCC | 0.014 | Beta(α=1.9326, β=136.1074) | [4] |
| CC SVR to DC (relative risk vs. non-SVR) | 0.07 | Lognormal(95% CI 0.03, 0.2) | [5] |
| CC SVR to HCC (relative risk vs. non-SVR) | 0.23 | Lognormal(95% CI 0.16, 0.35) | [6] |
| DC to HCC | 0.014 | Beta(α=1.9326, β=136.1074) | [4] |
| DC to liver transplant (LT) | 0.03 | Beta(α=6.5256, β=210.9945) | [4] |
| DC to death | 0.13 | Beta(α=147.03, β=983.97) | [4] |
| HCC to LT | 0.03 | Beta(α=6.5256, β=210.9945) | [4] |
| HCC to death | 0.43 | Beta(α=117.1033, β=155.23) | [4] |
| Post LT (0-6 months) to death | 0.21 | Beta(α=16.2762, β=61.2294) | [4] |
| Post LT (>6 months) to death | 0.057 | Beta(α=2.902, β=378.8825) | [4] |
| ***SVR related probabilities (post-DAA)*** | | | |
| Mild / moderate | 0.928 | Beta(α=376, β=29) | [7] |
| CC | 0.908 | Beta(α=736, β=75) | [7] |
| Mild / moderate (retreatment) | 0.939 | Beta(α=77, β=5) | [8] |
| CC (retreatment) | 0.855 | Beta(α=59, β=10) | [8] |

PWID: People who inject drugs, CC: Compensated cirrhosis, DC: Decompensated cirrhosis, HCC: Hepatocellular carcinoma, LT: Liver transplant, DAA: Direct acting antiviral

**HBV treatment outcomes and transition probabilities**

The transition probabilities for the natural history of HBV were largely based upon a HTA performed by Shepherd et al., which synthesised clinical data from a number of studies.[9] For transition probabilities associated with treatment (i.e. treatment outcomes), we sourced data from various clinical trials, specific to HBeAg status (details below). Since treatment of HBeAg negative individuals and those with cirrhosis is continuous, we captured the potential loss to follow up over time of those diagnosed with HBV. It was assumed that 3.33% of individuals per year would disengage with care, thus moving from 'engaged in care' or 'on treatment' health states to 'not engaged in care' health states. This was based an open-label extension from Marcellin, capturing all individuals lost or excluded from the final analysis for any reason other than a clinical justification (e.g. treatment switch due to tolerability or off treatment subsequent to seroconversion).[10]

*HBeAg positive CHB*

Based on NICE treatment guidelines for CHB, it was assumed that HBeAg positive patients identified with active disease were treated with Peginterferon Alfa-2a (PegIFNα) for 48 weeks (assumed one model cycle).[11] For those that do not achieve e-antigen seroconversion after 48 weeks (i.e. moving to health state 'HBeAg seroconverted'), patients were treated with tenofovir disoproxil fumarate (TDF) until e-antigen seroconversion was achieved.[12] For HBeAg positive patients, 13% received Emtricitabine alongside TDF.[13]

Of those receiving PegIFNα, 32% of individuals e-antigen seroconverted after one year of treatment, whilst 3% would achieve HBsAg seroconversion.[9,14] For those not achieving HBsAg or HBeAg seroconversion, the annual probability of those e-antigen seroconverting whilst treated with TDF was estimated to be 5.6%. This was derived from a long term study of TDF, in which the annual probability of e-antigen seroconversion was calculated from the rate of seroconversion between week 48 and week 240.[13] The data from 0 to 48 weeks were not included since the e-antigen seroconversion probability declined considerably after the first year of treatment, and individuals in the HBV model were assumed to be treated with PegIFNα for the first year. The annual probability of HBsAg

seroconversion was estimated to be 1.8% on TDF.[13] The transition probabilities associated with the risk of disease progression for individuals receiving treatment, with either PegIFNα or TDF, were assumed to be the same as for individuals achieving e-antigen seroconversion, due to the relatively high virological control and decrease in HBV DNA whilst on treatment.[13,14] This is supported by long term data in which 98% of individuals treated with TDF achieved a virological response at 8 years.[10] This cost was applied to in the economic model to align with the clinical data used. HBeAg positive individuals with no cirrhosis were assumed to cease treatment upon e-antigen seroconversion. However, for those not achieving e-antigen seroconversion, it was assumed that treatment with TDF would continue. For cirrhotic individuals, treatment with TDF was assumed to continue for those experiencing e-antigen seroconversion.

*HBeAg negative CHB*

Similarly to those with HBeAg positive disease, individuals with HBeAg negative disease were treated with PegIFNα for one year, and then treated with TDF thereafter (independent of disease activity), in line with NICE guidelines.[11] Whilst the aim of treatment for HBeAg positive individuals in long-term viral suppression and inducing HBeAg seroconversion, for HBeAg negative individuals, treatment aims for long-term viral suppression of HBV DNA.

It was assumed that in the first year of treatment with PegIFNα, 63% would achieve a virological response after one year, defined as HBV DNA <400 copies per ml, or 69 IU/ml.[15,16] Furthermore, 2.8% of individuals with HBeAg negative disease achieved HBsAg seroconversion during one year of treatment with PegIFNα.[16]

All patients received TDF after one year of treatment with PegIFNα (independent of virological response). For HBeAg negative patients, 1% received Emtricitabine alongside TDF.[13] Data from Marcellin et al. show long term virological control for HBeAg negative patients receiving TDF was 99% over five years, with 96% achieving virological response after 48 weeks.[13] We assumed an annual probability of 96% that individuals receiving TDF would achieve virological response (i.e.

transitioning from 'CHB HBeAg active disease' to 'HBeAg inactive disease'). Individuals with HBeAg negative inactive disease, with or without cirrhosis, were assumed to remain on TDF after achieving virological control, as per treatment guidelines.[11]

During five years of follow-up from Marcellin et al, one individual had HBsAg loss, but it was not confirmed whether this individual achieved HBsAg seroconversion.[13] A conservative approach was taken and patients receiving TDF were unable to transition to the HBsAg seroconversion state, nor were those not receiving treatment.[13,15] Similarly to HBeAg positive individuals, it was assumed that for HBeAg negative individuals on treatment, the risk of disease progression was identical to those with inactive disease, due to the high levels of virological control. Data suggests that both HBeAg positive and negative patients receiving long-term TDF experience regression of fibrosis scores, with 42% of patients improving their fibrosis score and only 5% having a worse fibrosis score at 5 years follow up. Furthermore, 74% of cirrhotic individuals at baseline experienced regression to a non-cirrhotic status in this study.[13] Whilst this supports the assumption that individuals on treatment had a reduction in disease progression compared to those not receiving treatment, a conservative approach was taken for cirrhotic individuals, as the model did not allow for regression of cirrhosis to non-cirrhotic status in the model. For both HBeAg positive and negative patients, the model assumes that the seroconversion probabilities applied were identical for those with and without compensated cirrhosis.

*TDF treatment sensitivity analysis*

A sensitivity analysis was performed in which TDF treatment was initiated as the first treatment, instead of PegIFNα, which is common practice in the UK.[17] For HBeAg positive individuals, this meant 1.8% of individuals would achieve HBsAg seroconversion, whilst 21% would achieve HBeAg seroconversion in the first year of treatment. For those with HBeAg negative disease, the probability of achieving inactive disease with TDF was assumed to be 96% in the first year, although there was no possibility of achieving HBsAg seroconversion. The probability of disease progression was assumed to remain the same.

*Table 2: Base case HBV transition probabilities for individuals entering the model with CHB and HBeAg positive disease*

| To:<br>From: | HBsAg seroconverted | HBeAg+ active disease | HBeAg seroconverted | HBeAg+ CC active | HBeAg+ CC seroconverted | DC | HCC | LT (first year) | LT (≥1 year) | Dead |
|---|---|---|---|---|---|---|---|---|---|---|
| HBsAg seroconverted | # | - | - | - | - | - | 0.0001 | - | - | - |
| HBeAg seroconverted | 0.02 | 0.03 | # | 0.01 | - | - | 0.001 | - | - | - |
| HBeAg+ active disease no treatment | 0.0175 | # | 0.05 | 0.05 | - | - | 0.005 | - | - | 0.0035 |
| HBeAg+ active disease, treatment with PegIFNα | 0.0295 | # | 0.32 | 0.01 | - | - | 0.0028 | - | - | - |
| HBeAg+ active disease, treatment with tenofovir | 0.018 | # | 0.0557 | 0.01 | - | - | 0.0028 | - | - | - |
| HBeAg+ compensated cirrhosis (CC) HBeAg seroconverted | 0.02 | - | - | 0.03 | # | 0.01 | 0.001 | - | - | - |
| HBeAg+ CC active - No treatment | - | - | - | # | 0.05 | 0.05 | 0.025 | - | - | 0.051 |
| HBeAg+ CC active - Treatment response with PegIFNα | 0.0295 | - | - | # | 0.32 | 0.01 | 0.0065 | - | - | - |
| HBeAg+ CC active - Treatment response with tenofovir | 0.018 | - | - | # | 0.0557 | 0.01 | 0.0065 | - | - | - |
| Decompensated cirrhosis (DC) | - | - | - | - | - | # | 0.025 | 0.03 | - | 0.39 |
| Hepatocellular carcinoma (HCC) | - | - | - | - | - | - | # | - | - | 0.56 |
| Liver Transplant (LT, first year) | - | - | - | - | - | - | - | # | - | 0.21 |
| LT (≥1 year post transplant) | - | - | - | - | - | - | - | - | # | 0.057 |

#represents the remainder of all transition probabilities (i.e. 1-all other transitions)
Transition probabilities are modelled probabilistically using a Dirichlet distribution, assuming a sample of size of 200, as performed in previous economic evaluations.[18]
Sources: Shepherd 2006,[9] Lau 2005,[14] Marcellin 2013,[13] Kim 2015[19]

*Table 3: Base case HBV transition probabilities for individuals entering the model with CHB and HBeAg negative disease*

| To:<br>From: | HBsAg seroconverted | HBeAg- active disease | HBeAg- inactive disease | CC active disease | CC inactive disease | DC | HCC | LT (first year) | LT (≥1 year) | Dead |
|---|---|---|---|---|---|---|---|---|---|---|
| HBsAg seroconverted | # | - | - | - | - | - | 0.0001 | - | - | - |
| HBeAg- inactive disease | - | 0.029 | # | 0.01 | - | - | 0.005 | - | - | - |
| HBeAg- active disease no treatment | - | # | 0.015 | 0.09 | - | - | 0.005 | - | - | 0.0035 |
| HBeAg- active disease, treatment with PegIFNα | 0.0282 | # | 0.63 | 0.01 | - | - | 0.0028 | - | - | - |
| HBeAg- active disease, treatment with tenofovir | - | # | 0.96 | 0.01 | - | - | 0.0028 | - | - | - |
| HBeAg- compensated cirrhosis (CC) seroconverted | - | - | - | 0.029 | # | 0.01 | 0.005 | - | - | - |
| HBeAg- CC active - No treatment | - | - | - | # | - | 0.05 | 0.025 | - | - | 0.051 |
| HBeAg- CC active - Treatment response with PegIFNα | 0.0282 | - | - | # | 0.63 | 0.01 | 0.0065 | - | - | - |
| HBeAg- CC active - Treatment response with tenofovir | - | - | - | # | 0.96 | 0.01 | 0.0065 | - | - | - |
| Decompensated cirrhosis (DC) | - | - | - | - | - | # | 0.025 | 0.03 | - | 0.39 |
| Hepatocellular carcinoma (HCC) | - | - | - | - | - | - | # | - | - | 0.56 |
| Liver Transplant (LT, first year) | - | - | - | - | - | - | - | # | - | 0.21 |
| LT (≥1 year post transplant) | - | - | - | - | - | - | - | - | # | 0.057 |

[#]represents the remainder of all transition probabilities (i.e. 1-all other transitions)
Transition probabilities are modelled probabilistically using a Dirichlet distribution, assuming a sample of size of 200, as performed in previous economic evaluations.[18]
Source: Shepherd 2006,[9] Marcellin 2004,[14] Marcellin 2013,[13] Kim 2015,[19] Takeda 2007[20]

## Utility

*Table 4: Base case utilities*

| Utility estimates | Mean value | Distribution | Source |
|---|---|---|---|
| ***HCV mean utility*** | **Mean utility** | | |
| Mild (F0/F1) | 0.77 | Beta(α=521.2375, β=155.6943) | 21 |
| Moderate (F2/F3) | 0.66 | Beta(α=168.2461, β=86.6723) | 21 |
| Mild SVR | 0.82 | Beta(α=65.8678, β=14.4588) | 21 |
| Moderate SVR | 0.72 | Beta(α=58.0608, β=22.5792) | 21 |
| Cirrhosis SVR | 0.61 | Beta(α=58.0476, β=37.1124) | 22,23 |
| ***HBV**** | **Mean utility decrement^** | | |
| HBsAg / HBeAg seroconverted | 0 | N/A | 9,24 |
| Chronic HBV (Active or inactive disease) | 0.04 | Beta(α=14.7512, β=354.0288) | 9,24 |
| ***HBV and HCV*** | **Mean utility** | | |
| Cirrhosis | 0.55 | Beta(α=47.1021, β=38.5381) | 21 |
| Decompensated cirrhosis | 0.45 | Beta(α=123.75, β=151.25) | 25 |
| HCC | 0.45 | Beta(α=123.75, β=151.25) | 25 |
| Liver transplant (first year) | 0.45 | Beta(α=123.75, β=151.25) | 25 |
| Liver transplant (after first year) | 0.66 | Beta(α=32, β=16) | 25 |
| ***Uninfected / general population utility*** | **Mean utility** | | |
| 25-34 | 0.93 | N/A | 26 |
| 35-44 | 0.91 | | |
| 45-54 | 0.85 | | |
| 55-64 | 0.8 | | |
| 65-74 | 0.78 | | |
| >75 | 0.73 | | |

*Age based utility decrements were also applied in line with the general population estimates, with no decrement for the 35-44 age group, then 0.06 decrement for 45-54 etc. For example, mild HCV utility at 50 years of age, utility of 0.77 – 0.06 = 0.71.

## Health state costs

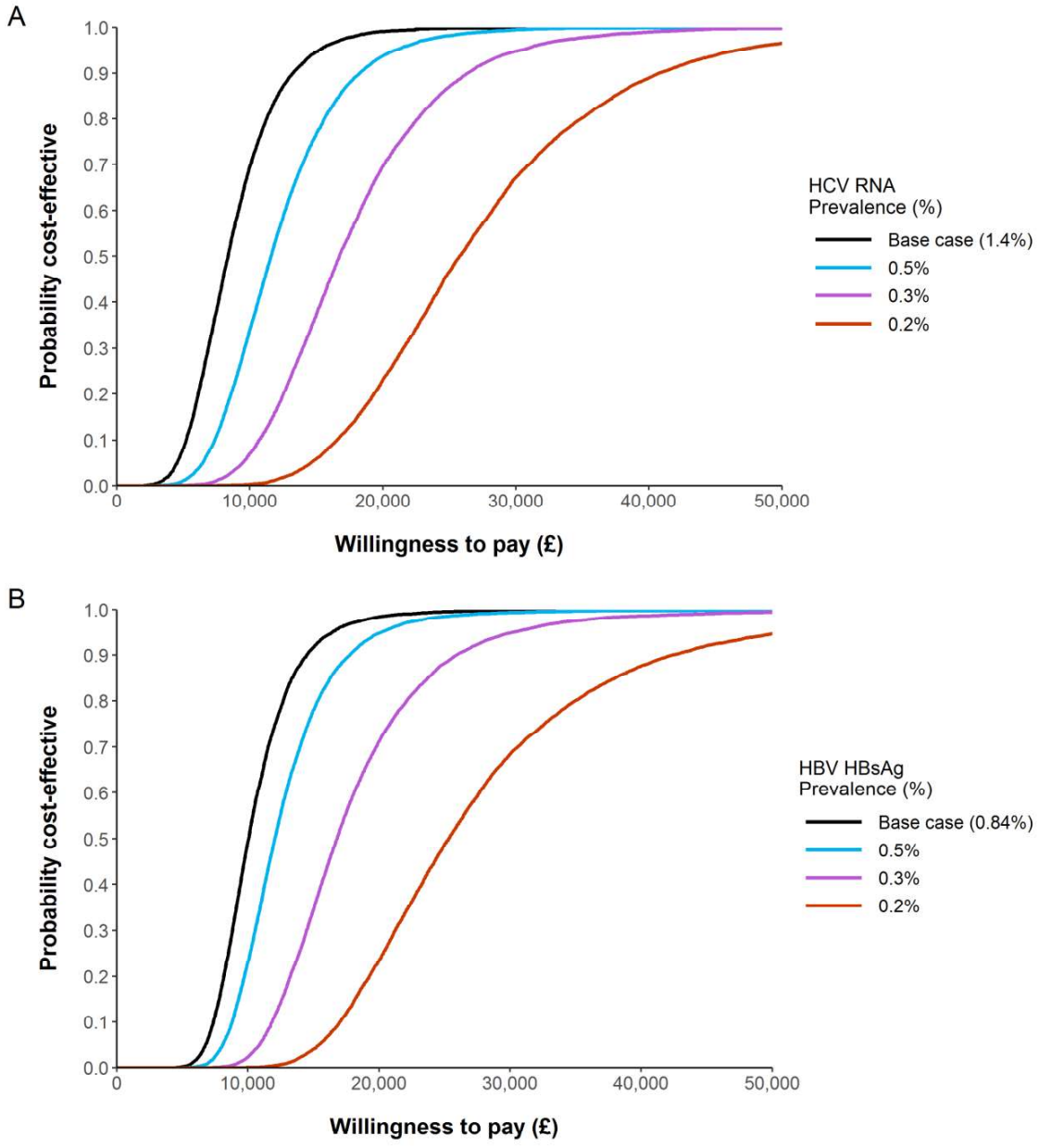
*Table 5: Health state costs*

| Costs (per year, except where noted) | Mean cost | Cost year | Distribution | Reference |
|---|---|---|---|---|
| ***HCV health state costs*** | | | | |
| Mild HCV | £196 | 2002/03 | Gamma (k=25.6995, θ=5.3698) × PPI[±] | [4] |
| Moderate HCV | £1,019 | 2002/03 | Gamma (k=88.8502, θ=8.0698) × PPI[±] | [4] |
| Mild SVR | £245 | 2006/2007 | Gamma (k=25, θ=8.08) × PPI[±] | [27] |
| Moderate SVR | £300 | 2006/2007 | Gamma (k=25, θ=9.88) × PPI[±] | [27] |
| Cirrhosis SVR | £531 | 2006/2007 | Gamma (k=25, θ=17.48) × PPI[±] | [27] |
| ***HBV health state costs*** | | | | |
| HBsAg seroconverted | £0 | 2002/03 | N/A | [9] |
| HBeAg seroconverted / inactive disease | £379 | 2002/03 | Gamma (k=25, θ= 10.6708) × PPI[±] | [9] |
| CHB HBeAg+ or HBeAg- active disease | £764 | 2002/03 | Gamma (k=25, θ=21.4992) × PPI[±] | [9] |
| ***HCV and HBV shared disease states*** | | | | |
| Cirrhosis | £1,617 | 2002/03 | Gamma (k=24.2342, θ=46.9584) × PPI[±] | [4] |
| Decompensated cirrhosis | £12,955 | 2002/03 | Gamma (k=36.0249, θ=253.1582) × PPI[±] | [4] |
| Hepatocellular carcinoma | £11,545 | 2002/03 | Gamma (k=18.1081, θ=448.8045) × PPI[±] | [4] |
| Liver transplant (per transplant) | £38,823 | 2002/03 | Gamma (k=89.7536, θ=304.5004) × PPI[±] | [4] |
| Cost of care in year of liver transplant | £13,435 | 2002/03 | Gamma (k=13.7788, θ=686.4168) × PPI[±] | [4] |
| Cost of care post liver transplant (>12 months) | £1,967 | 2002/03 | Gamma (k=15.2189, θ=91.0053) × PPI[±] | [4] |

[±]PPI = Hospital and Community Health Services Pay and Prices Index inflation to 2017/18 costs (2002/03 = 1.42, 2006/07 = 1.22)

## Cost-effectiveness acceptability curves

*Figure 5: Cost-effectiveness acceptability curve (CEAC) across different estimates of A) HCV RNA prevalence and B) HBsAg prevalence*



**Cost-effectiveness of HCV and HBV testing, stratified by age group**

An analysis of the cost-effectiveness of HCV and HBV ED testing, stratified by age, was performed. The HCV RNA and HBsAg prevalence amongst age groups is presented in (Table 6).

The analysis was performed by altering the mean starting age in the model, and the estimated prevalence. Due to a lack of data, all other parameters remained the same as the base case analysis, including the proportion of patients that required linkage to care, the proportion testing positive that were contactable, the linkage to care and proportion receiving treatment, treatment outcomes, and the distribution of patients across initial health states (e.g. fibrosis level for HCV, and proportion cirrhotic, proportion HBeAg positive, and proportion with inactive or HBeAg seroconverted disease for HBV).

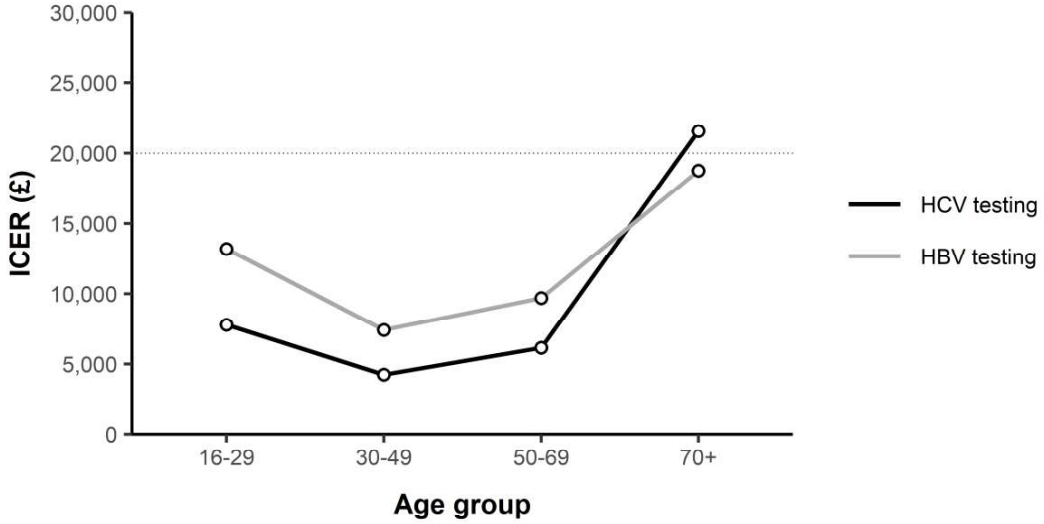
Since many of these parameters are likely to differ by age, the following results should be interpreted with consideration to these limitations.

*Table 6: Prevalence and incremental cost-effectiveness ratios for HCV and HBV testing, stratified by age group*

| Age group | Mean age (estimated) | Prevalence± | ICER |
|---|---|---|---|
| ***HCV testing*** | | | |
| 16-29 | 23 | 0.39% | £7,778 |
| 30-49 | 40 | 2.12% | £4,262 |
| 50-69 | 60 | 1.91% | £6,151 |
| 70+* | 80 | 0.82% | £21,569 |
| ***HBV testing*** | | | |
| 16-29 | 23 | 0.31% | £13,187 |
| 30-49 | 40 | 1.23% | £7,412 |
| 50-69 | 60 | 0.82% | £9,695 |
| 70+* | 80 | 0.64% | £18,766 |

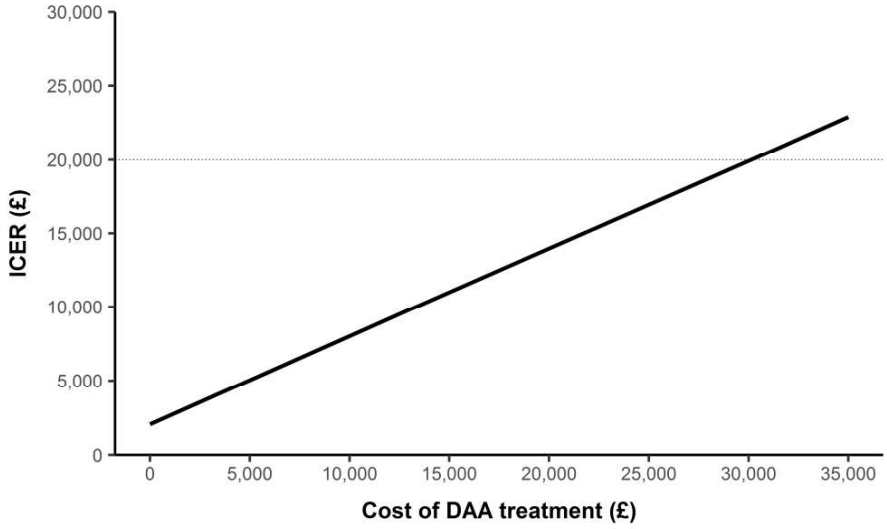
±HCV RNA and HBsAg prevalence. *The mean was estimated as the midpoint between age categories. For 70+ age group, the midpoint between 70 and 89 years of age.

*Figure 6: Incremental cost-effectiveness ratios for HCV and HBV testing, stratified by age groups*



**DAA treatment cost scenario**

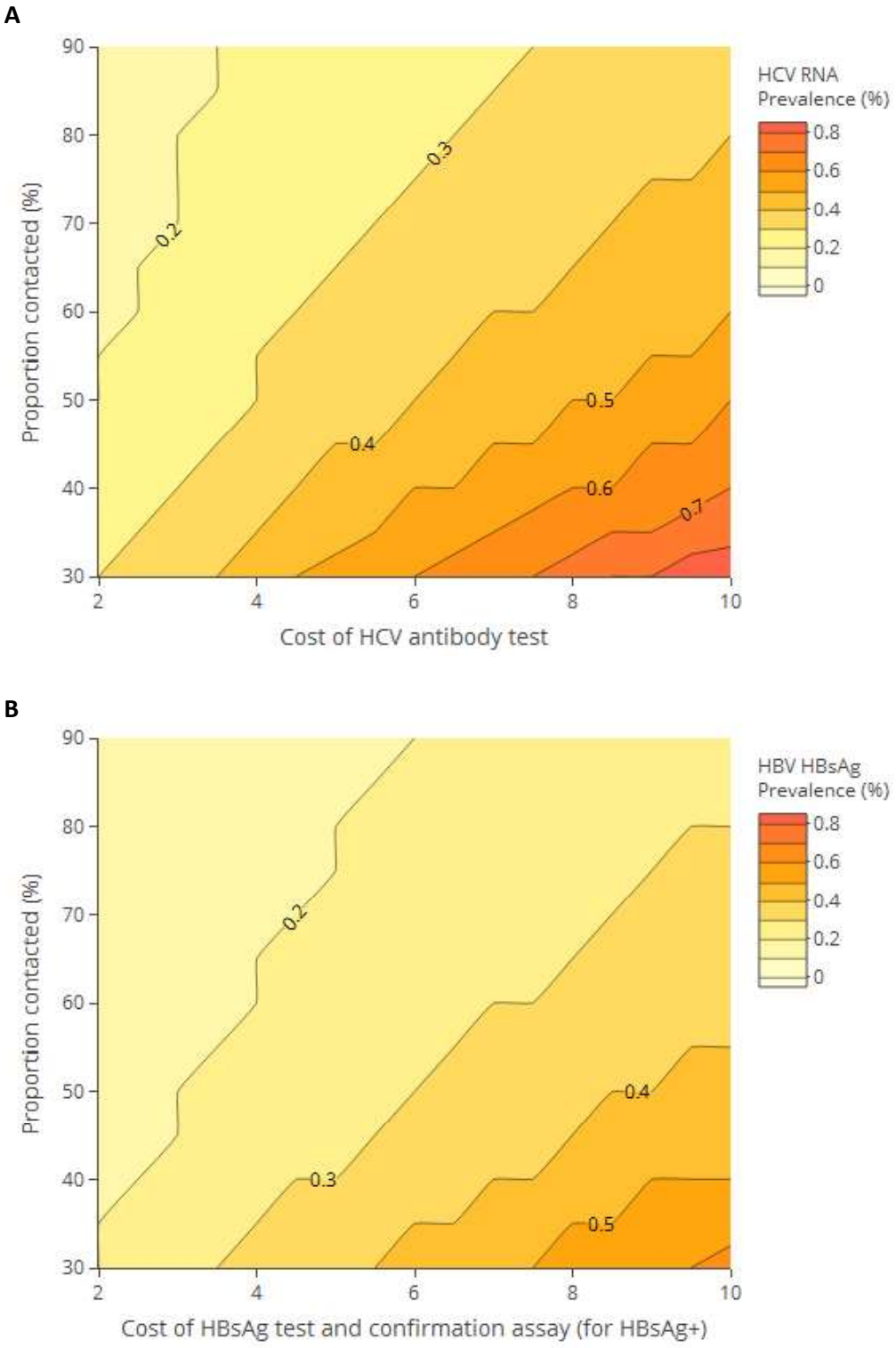
*Figure 7: Incremental cost-effectiveness ratio (ICER) for HCV testing, by DAA treatment cost*



**Three-way threshold scenarios**

A sensitivity analysis was performed to show the minimum prevalence required for cost-effectiveness at a £20,000 WTP threshold across a range of screening test costs and contact rates (Figure 8). For example, at £4 HCV antibody test cost, with 70% of patients successfully contacted, the intervention would be cost-effective at 0.3% HCV RNA prevalence or above, whilst if only 30% of patients were contacted at the same HCV antibody cost, a 0.5% HCV RNA prevalence or above would be required for the intervention to be cost-effective.

*Figure 8: Contour plot for the threshold prevalence of virus required to achieve cost-effectiveness at a £20,000 willingness to pay threshold for different contact rates (y axis) and costs of screening test (x axis) for A) hepatitis C and B) hepatitis B*




Values to the left of the contour line represents inputs combinations in which the intervention is cost-effective at the stated prevalence (at £20,000 per QALY willingness to pay). Values to the right of the contour line represent combinations of inputs in which the intervention is not cost-effective at the stated prevalence

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## 10.6 Summary of modelling studies categorised, based on their approach to modelling the background probability of testing (Research Paper 4, Section 8.2.4)

Table 10-1: Economic evaluations, categorised depending on the approach taken to modelling the background probability of testing

| Study | HCV Testing Population or Setting | Country |
|---|---|---|
| **No background testing in any other settings outside of the intervention** | | |
| Nakamura 2008[1] | General population screening, risk-based screening | Japan |
| Ruggeri 2013[2] | Age-based screening | Italy |
| Kim 2015[3] | General population screening | Egypt |
| Mohamed 2020[4] | Prisoners | UK |
| **Fixed background rate of testing for counterfactual** | | |
| Miners 2014[5] | Migrants | UK |
| Flanagan 2019[6] | Migrants | UK |
| Buchanan 2020[7] | Pharmacy testing (PWID or any risk factor) | UK |
| Manca 2020[8] | PWID (Needle exchange, substance misuse services, and community pharmacies) | UK |
| Helsper 2012[9] | General population testing, or PWID testing | Netherlands |
| **Differential background rate of testing in infected vs. uninfected people** | | |
| Castelnuovo 2006[10] | PWID (Prisons, general practice, drug services) | UK |
| Wong 2015[11] | Age-based screening | Canada |
| Coffin 2012[12] | General population screening | United States |
| Rein 2012[13] | Age-based screening | United States |
| McGarry 2012[14] | Age-based screening | United States |
| **Differential background rate of testing between populations, based on HCV risk** | | |
| Ward 2019[15] | PWID (in an outreach service) | UK |
| Macgregor 2021[16] | MSM | UK |
| Martin 2016[17] | Prisoners | UK |
| Ward 2020[18] | PWID (in drug clinics) | UK |
| Deuffic-Burban 2018[19] | Age-based screening | France |
| Assoumou 2018[20] | General population vs. PWID testing (in adolescents or young adults) | United States |

### 10.6.1 References


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## 10.7 Narrative literature review search strategy (Research Paper 4, Section 8.3)

### 10.7.1 Embase

| # | Search |
|---|---|
| 1 | exp hepatitis/ |
| 2 | exp hepatitis c/ |
| 3 | exp Hepatitis C virus/ |
| 4 | exp hepatitis b/ |
| 5 | exp Human immunodeficiency virus/ |
| 6 | exp Human immunodeficiency virus infection/ |
| 7 | exp tuberculosis/ |
| 8 | (hepatitis or hcv or hbv or hepacivirus*).ti,ab. |
| 9 | (HIV or hiv-1 or hiv-2* or human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus).ti,ab. |
| 10 | (Tuberculosis or TB).ti,ab. |
| 11 | exp sexually transmitted disease/ |
| 12 | (sex* adj4 (infect* or disease*)).mp. |
| 13 | (STI or STD).mp. |
| 14 | exp Chlamydia trachomatis/ |
| 15 | (chlamydia or trachomatis).ti,ab. |
| 16 | exp Gonorrhoea/ |
| 17 | exp Neisseria gonorrhoeae/ |
| 18 | Gonorrh*.ti,ab. |
| 19 | exp Syphilis/ |
| 20 | (syphilis or Treponema pallidum).ti,ab. |
| 21 | or/1-20 |
| 22 | exp economic evaluation/ |
| 23 | hidden markov model/ |
| 24 | (economic evaluation* or (cost adj2 (effective* or benefit or minimi#ation or utilit* or outcom*))).mp. |
| 25 | ((economic or disease or transmission or patient or health* or decision or markov) adj5 model*).mp. |
| 26 | or/22-25 |
| 27 | ((background or probability or rate or control* or counterfactual or comparator*) adj5 (screen* or test* or case finding or case detection or rescreen*)).mp. |
| 28 | 21 and 26 and 27 |
| 29 | limit 28 to english language |

### 10.7.2 MEDLINE

| # | Search |
|---|---|
| 1 | exp hepatitis/ |
| 2 | exp hepatitis C, Chronic/ |
| 3 | exp hepatitis B, Chronic/ |
| 4 | exp HIV/ |
| 5 | exp HIV infections/ |
| 6 | exp Tuberculosis/ |
| 7 | (hepatitis or hcv or hbv or hepacivirus*).ti,ab. |
| 8 | (HIV or hiv-1 or hiv-2* or human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus).ti,ab. |
| 9 | (Tuberculosis or TB).ti,ab. |
| 10 | exp sexually transmitted disease/ |
| 11 | (sex* adj4 (infect* or disease*)).mp. |
| 12 | (STI or STD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 13 | exp Chlamydia trachomatis/ |
| 14 | exp Chlamydia infections/ |
| 15 | (chlamydia or trachomatis).ti,ab. |
| 16 | exp Gonorrhea/ |
| 17 | exp Neisseria gonorrhoeae/ |
| 18 | Gonorrh*.ti,ab. |
| 19 | exp Syphilis/ |
| 20 | (syphilis or Treponema pallidum).ti,ab. |
| 21 | or/1-20 |
| 22 | exp models, economic/ |
| 23 | Markov Chains/ |
| 24 | (economic evaluation* or (cost adj2 (effective* or benefit or minimi#ation or utilit* or outcom*))).mp. |
| 25 | ((economic or disease or transmission or patient or health* or decision or markov) adj5 model*).mp. |
| 26 | or/22-25 |
| 27 | ((background or probability or rate or control* or counterfactual or comparator*) adj5 (screen* or test* or case finding or case detection or rescreen*)).mp. |
| 28 | 21 and 26 and 27 |
| 29 | limit 28 to english language |

### 10.7.3 Econlit

| # | Search |
|---|---|
| 1 | (economic evaluation* or (cost adj2 (effective* or benefit or minimi#ation or utilit* or outcom*))).mp. |
| 2 | ((economic or disease or transmission or patient or health* or decision or markov) adj5 model*).mp. |
| 3 | ((background or probability or rate or control* or counterfactual or comparator*) adj5 (screen* or test* or case finding or case detection or rescreen*)).mp. |
| 4 | (1 or 2) and 3 |

### 10.7.4 Web of Science

| # | Search |
|---|---|
| 1 | TS=(hepatitis or hbv or hcv or hepacivirus*) |
| 2 | TS=(HIV or hiv-1 or hiv-2* or human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus) |
| 3 | TS=(Tuberculosis or TB) |
| 4 | TS=(sex* near/4 (infect* or disease*)) |
| 5 | TS=(STI or STD) |
| 6 | TS=(chlamydia or trachomatis) |
| 7 | TS=(Gonorrh*) |
| 8 | TS=(syphilis or Treponema pallidum) |
| 9 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 |
| 10 | TS=((economic or disease or transmission or patient or health* or decision or markov) near/5 model*) |
| 11 | TS=(economic evaluation* or (cost NEAR/2 (effective* or benefit or minimi?ation or utilit* or outcom*))) |
| 12 | #10 or #11 |
| 13 | TS=((background or probability or rate or control* or counterfactual or comparator*) NEAR/5 (screen* or test* or “case finding” or “case detection” or rescreen*)) |
| 14 | #9 and #12 and #13 |