Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Draft report for public consultation

Health Technology Assessment of Birth Cohort Testing for Hepatitis C

March 2021

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this health technology assessment.

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Conflicts of interest

None

List of abbreviations commonly used in this report

BIA	budget impact analysis
CC	compensated cirrhosis
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness analysis curve
CIDR	Computerised Infectious Disease Reporting
CLIA	chemiluminescent immunoassay
CSO	Central Statistics Office
CUA	cost-utility analysis
DAA	direct-acting antiviral
DBS	dried blood spot
DCC	decompensated cirrhosis
EASL	European Association for the Study of the Liver
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EQ-5D-5L	Euroqol 5-Dimension, 5-Level Instrument
GP	general practitioner
GRADE	Grading Of Recommendations Assessment, Development And Evaluation
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIPE	Hospital In-Patient Enquiry
HIQA	Health Information and Quality Authority
HIV	human immunodeficiency virus
HPSC	Health Protection Surveillance Centre
HSE	Health Service Executive
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IDU	injecting drug user
IMO	Irish Medical Organisation
IU	International unit
LT	liver transplant
MEIA	microparticle enzyme immunoassays
METAVIR	Meta-analysis of Histological Data in Viral Hepatitis
MSM	men who have sex with men
NAAT	nucleic acid amplification test

NCEC	National Clinical Effectiveness Committee
NCRI	National Cancer Registry Ireland
NHCTP	National Hepatitis C Treatment Programme
NPV	negative predictive value
NVRL	National Virus Reference Laboratory
PCRS	Primary Care Reimbursement Service
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWID	people who inject drugs
QALY	quality-adjusted life year
RCT	randomised controlled trial
RDT	rapid diagnostic test
RIBA	recombinant immunoblot assay
RNA	ribonucleic acid
RT-PCR	polymerase chain reaction
SVR	sustained virological response
TMA	transcription mediated amplification
USPSTF	US Preventive Services Task Force
WHO	World Health Organization
WTP	Willingness to pay

1 Introduction

1.1 Background to the request

The hepatitis C virus (HCV) is a blood borne virus which predominantly affects the liver. HCV is most commonly transmitted through injecting drug use (sharing of needles and other drug paraphernalia), but may also be transmitted through: inadequate sterilisation of medical equipment, blood transfusion, sex, and passed from mother to child.[1] Although 15-45% of people spontaneously clear acute infection (that is, within six months of infection), the virus may persist in the circulation of those infected which can lead to progressive fibrosis and cirrhosis of the liver.[2] Those that develop chronic HCV infection may not present with severe complications, such as liver cirrhosis and hepatocellular carcinoma (HCC), until decades after contracting the virus.

Following the adoption of a resolution on hepatitis by the World Health Assembly in May 2014, which called for an intensified global hepatitis response, the World Health Organization (WHO) estimated that there were 71 million people living with chronic HCV infection worldwide in 2015 (global prevalence: 1%).[3] Of these, an estimated 399,000 died from cirrhosis or HCC in 2015.[3] In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy for 2016–2021 on viral hepatitis which aims to eliminate viral hepatitis as a public health threat by 2030 with a particular focus on HCV infection.[4] Elimination – defined as a 90% reduction in new chronic infections and a 65% reduction in mortality compared with the 2015 baseline – would require diagnosis of 90% of those infected and treatment of 80% of those diagnosed.[4] The WHO report identified underdiagnosis of HCV infection as the main challenge to HCV elimination.[3] Advancements in treatment for HCV infection, which can cure in most cases and are more acceptable to patients, have led to a shift in HCV care policy, with the paradigm now firmly focused on elimination. Specifically, the identification and cure of those living with HCV infection that are currently undiagnosed, so that the number of people accessing treatment greatly exceeds the number newly infected, thereby reducing the infected cohort.

In Ireland, the National Hepatitis C Strategy 2011-2014 was the first published strategy relating to all those infected with HCV in Ireland.[5] The strategy contained 36 recommendations spanning surveillance, prevention, screening and treatment of HCV infection. In 2015, a Public Health Plan for the Pharmaceutical Treatment of Hepatitis C was published by the Department of Health which recommended the establishment of a multi-annual national treatment plan that would ensure the most appropriate management of access to new treatments.[6] The National Hepatitis C Treatment Programme (NCHTP) was established in 2015 to provide treatment across a range of healthcare settings to all people living with HCV infection, with the aim of

making hepatitis C a rare disease in Ireland by 2026.[7]

An Irish National Clinical Guideline for Hepatitis C Screening[8] was quality assured by the National Clinical Effectiveness Committee (NCEC) and endorsed by the Minister for Health in 2017. It included a conditional recommendation to offer one-off testing to people born between 1965 and 1985 (that is, birth cohort testing).[8] It was proposed that birth cohort testing (of approximately 1.5 million people) would be implemented in addition to, rather than in place of, other testing strategies. The 1965 to 1985 birth cohort was identified as the most suitable for HCV testing because national HCV surveillance and seroprevalence data (based on notifications to the HPSC) indicated that HCV prevalence in Ireland is highest amongst those born between 1965 and 1985 (72.5% of cases).[8-10] As birth cohort testing was anticipated to have significant funding implications, it was conditionally recommended, subject to the outcome of a full HTA.

The Health Information and Quality Authority (HIQA) agreed to undertake a HTA of implementing birth cohort testing for hepatitis C in Ireland following a formal request from the hepatitis C screening guideline development group. The aim of the HTA is to establish the clinical, cost-effectiveness and budget impact of offering testing to all people in Ireland born between 1965 and 1985.

1.2 Terms of reference

This HTA is being carried out to assess the impact of the introduction of birth cohort testing for hepatitis C of people in Ireland born between 1965 and 1985. The clinical and economic impact of birth cohort screening in addition to risk-based screening will be compared with current care, which comprises risk-based screening only. The potential organisational and ethical implications of birth cohort screening will also be assessed.

Informed by the evidence available in this HTA, a decision will be made on whether and how birth cohort testing should be implemented in Ireland. In consultation with the Department of Health, the Evaluation Team developed questions in relation to the critical information required to inform such a decision. The evidence in this HTA will inform decision-making by the Minister for Health and the Health Service Executive (HSE).

The Terms of Reference for the HTA are to:

- Describe the diagnostic tests for detection of HCV and the first-line treatments available in Ireland.
- Examine the current evidence of effectiveness and safety of testing for HCV.
- Describe the epidemiology of HCV and HCV genotypes in Ireland (including the estimated prevalence in the birth cohort).
- Review the clinical effectiveness of HCV direct-acting antiviral (DAA) treatment.
- Conduct a systematic literature review on the cost-effectiveness of HCV testing.
- Estimate the cost-effectiveness, resource implications and budget impact of birth cohort testing for HCV in the Irish cohort born between 1965 and 1985.
- Consider any wider organisational, ethical or societal implications that birth cohort testing for HCV may have for patients, the general public or the healthcare system in Ireland.
- Based on this assessment, advise on whether birth cohort testing for HCV should be implemented in Ireland.

1.3 Overall approach

Following an initial scoping of the technology, the Terms of Reference of this assessment were agreed between HIQA, the Department of Health and the HSE.

HIQA convened an Expert Advisory Group comprising representation from relevant stakeholders including the Department of Health, the HSE, the Health Protection Surveillance Centre, the National Virus Reference Laboratory, clinicians with specialist expertise in HCV screening and treatment, the National Screening Service, the National Centre for Pharmacoeconomics and two patient advocacy groups (the Irish Haemophilia Society and SAGE Advocacy). The role of the Expert Advisory Group is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group will be made available in the acknowledgements section of this report.

The Terms of Reference of the Expert Advisory Group are to:

- Contribute to the provision of high quality and considered advice by the Authority to the Health Service Executive.
- Contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate.
- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to the Authority regarding the scope of the analysis.
- Support the Evaluation Team led by the Authority during the assessment process by providing expert opinion and access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.
- Contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process upon the conclusion of the assessment.

HIQA has appointed an Evaluation Team comprising staff from the HTA Directorate to carry out the assessment.

The Terms of Reference of the HTA were reviewed by the Expert Advisory Group at its first meeting. The draft description of technology and systematic review of cost-effectiveness of HCV screening were discussed at that meeting in addition to draft findings on the epidemiology of HCV infection in Ireland, modelling approaches and the organisational implications of the implementation of birth cohort testing for chronic HCV infection. Considerations regarding the cost-effectiveness, budget impact, social and ethical implications of providing birth cohort testing in Ireland will be discussed at the second meeting of the group. Draft versions of this report will be circulated for review by the Expert Advisory Group before a final draft report will be prepared for public consultation. After the public consultation is complete, a final version of this report will be circulated for review by the Expert Advisory Group before it is submitted to the Board of HIQA for approval. The completed assessment will be submitted to the Minister for Health and the Health Service Executive as advice and published on the HIQA website.

2 Description of technology

Key points

- The hepatitis C virus (HCV) is a blood borne virus that predominantly affects the liver. At least six major HCV genotypes (genetic variations) exist, each of which has its own subtypes.
- HCV has a high degree of genetic variability due to the virus's ability to constantly mutate as it attempts to evade the body's immunological response. The variability of hepatitis C (in terms of genotypes, subtypes and quasi-species) has made it difficult to develop a vaccine that can protect against all HCV strains.
- Birth cohort testing involves offering one-time screening for HCV infection to people born during a particular period of time. No prior ascertainment of risk is undertaken, rather for this cohort, there is evidence (such as epidemiological trends) of an elevated risk of exposure relative to the general population.
- The Irish birth cohort was identified based on national HCV surveillance and seroprevalence data, which indicated that 72.5% of HCV cases were born between 1965 and 1985.
- Birth cohort testing broadly conforms to the principles of screening outlined by the World Health Organization (WHO), in the form of case-finding with the objective of detecting and treating people with chronic HCV infection.
- Given its once-off nature, birth cohort does not fulfil the principle of screening as continuous process. However, those within the birth cohort will continue to be offered risk-based screening, where appropriate.
- In accordance with the WHO criteria for effective screening programmes, a birth cohort testing programme should include mechanisms for systematic invitation and follow-up, a participation rate of over 70% from the birth cohort, adequate infrastructure and resourcing to ensure diagnosis and treatment, and a monitoring and evaluation framework.
- The structure adopted by a birth cohort testing programme will influence the acceptability and uptake, as well as effectiveness and cost-effectiveness of testing. The structure may be opportunistic or systematic in nature.

- A systematic population-based programme is likely to improve equity of access, efficiency of resources and yield a higher participation rate than opportunistic testing.
- Up until 2019, the US Centers for Disease Control and Prevention and the US Preventive Services Task Force were the only international organisations that had recommended birth cohort screening. The extent to which eligible people have availed of screening based on these recommendations is unclear.
- In 2019, the Hellenic National Plan for Hepatitis C was published in Greece which recommended birth cohort screening for all adults born between 1945 and 1980.
- Diagnosis of chronic HCV infection involves two steps: (1) detection of an anti-HCV antibody to indicate if a person has ever had acute HCV infection; and (2) a confirmatory nucleic acid test to verify active HCV infection through the detection of viral ribonucleic acid (RNA) or core antigen test to detect HCV proteins in blood or oral fluid.
- The sensitivity and specificity of antibody, RNA and antigen tests will influence the effectiveness of birth cohort testing. Sensitivity is the ability of an index test to accurately identify those who have the condition. Specificity is its ability to correctly identify those who do not have the condition.
- HCV infection is curable and highly effective treatments are available. Over 95% of patients achieve a sustained virological response (SVR) following treatment with second generation interferon-free direct-acting antivirals (DAAs).

2.1 Introduction

The hepatitis C virus (HCV), first identified in 1989, is a blood borne virus that predominantly affects the liver.[1] It is most commonly transmitted through injecting drug use (sharing of needles and other drug paraphernalia). Although HCV infection can often resolve spontaneously, chronic HCV infection may lead to fibrosis, cirrhosis and potentially fatal complications such as hepatocellular carcinoma (HCC).[2, 11-13]

The purpose of this chapter is to describe the detection and treatment of HCV infection as a tool for preventing the sequelae (long-term complications of chronic infection) and transmission of HCV infection at a population-level. To facilitate understanding, a brief description of hepatitis, the natural history of HCV infection, the six major HCV genotypes, and the immunological response to HCV infection is initially provided. The epidemiology of HCV is described in detail in Chapter 3. An overview of current screening strategies for HCV in Ireland and internationally is also provided.

2.2 Viral hepatitis

Hepatitis refers to inflammation of the liver in response to tissue injury. Inflammation can be caused by drug or alcohol use, particular medications, and certain medical conditions. In most cases, inflammation occurs as a result of a viral infection. There are five main types of hepatitis virus (referred to as types A, B, C, D, and E) that can cause acute hepatitis.[3] Important distinctions exist between these viruses in terms of their modes of transmission, clinical course and burden. Infection with hepatitis A and E rarely leads to chronic hepatitis, which is associated with progressive scarring of the liver (cirrhosis) and primary liver cancer (HCC).[3] Co-infection is possible, particularly with HBV, which may increase the burden of disease associated with HCV and complicate its management. Hepatitis A, B, D and E are summarised in Appendix 1.

2.3 Hepatitis C

Hepatitis C virus (HCV) is a blood-borne virus which infects the liver and commonly causes progressive liver disease. HCV infection can be mild, lasting only a few weeks (that is, acute HCV infection) or become a serious, lifelong illness.[14] HCV infection is often asymptomatic – only a minority of people experience mild symptoms such as fatigue, muscle and joint pain, jaundice, abdominal discomfort or itching.[15, 16] People with acute HCV infection may develop a vigorous antibody and cell-mediated immune response that spontaneously eradicates the virus. However, 55-85% of acutely infected individuals fail to clear the virus and develop chronic HCV infection.[2]

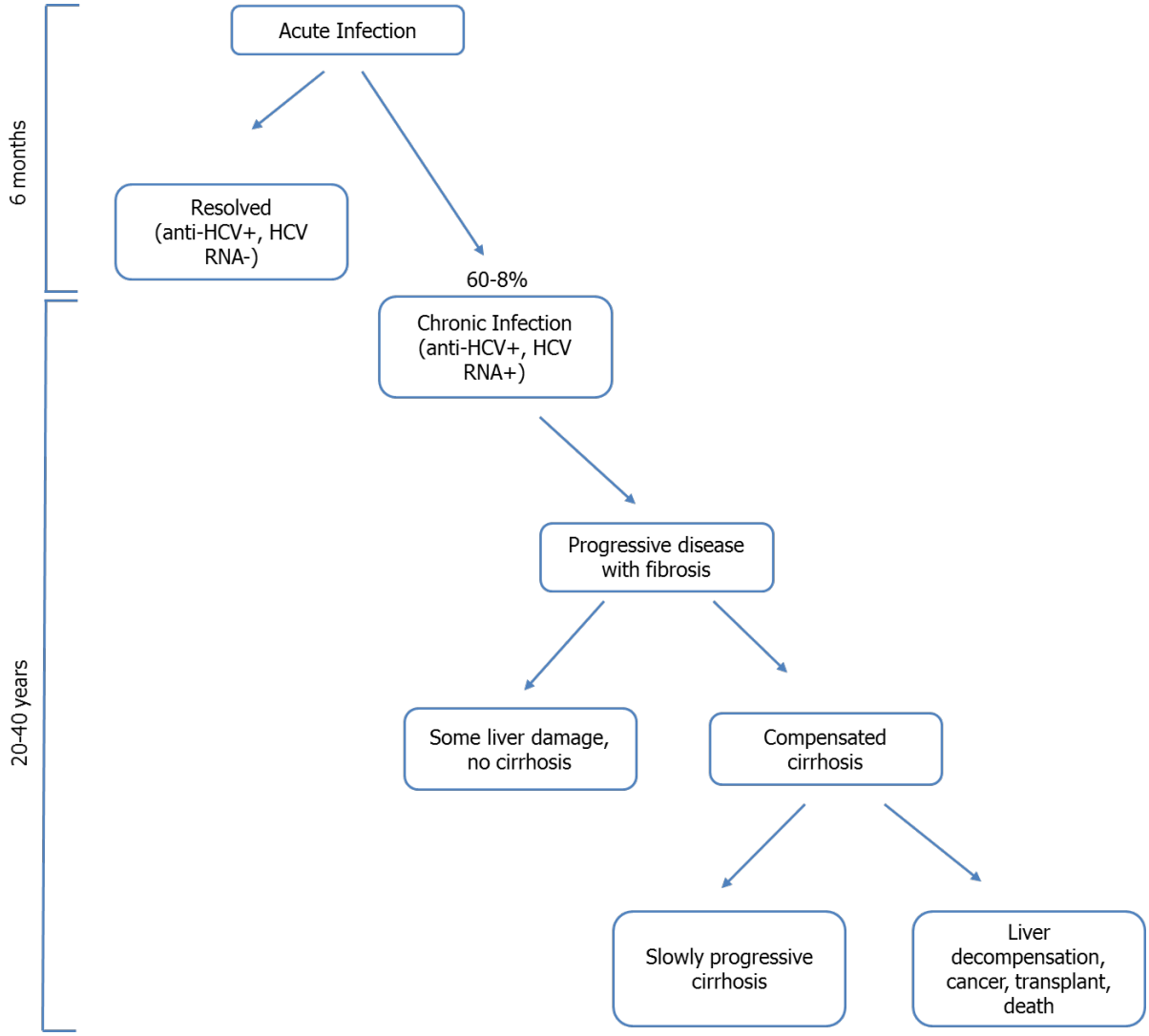
The time between exposure to HCV and the development of detectable HCV antibodies (the "window period") can range from two weeks to six months. Accordingly, chronic HCV infection is generally defined as the presence of HCV ribonucleic acid (RNA) for

more than six months.[17] Spontaneous resolution of HCV infection rarely occurs beyond six months.[8] Left untreated, chronic HCV infection can cause serious health problems including liver fibrosis and cirrhosis, HCC and death. As the transition from acute to chronic HCV infection often occurs in the absence of symptoms, considerable liver damage may occur before HCV infection is eventually diagnosed. The clinical course of HCV infection is summarised in Figure 2.1.

Fibrosis represents the wound healing process of the liver in response to injury and inflammation, and has major implications for the development of HCV-associated chronic liver diseases. Fibrosis is characterised by excessive accumulation of extracellular matrix proteins that interfere with the normal structure and function of the liver.[18] Accumulation of fibrotic tissue over a prolonged period of time compromises liver function and may eventually lead to cirrhosis and end-stage liver complications.[19] The METAVIR liver biopsy histological staging system[20] is frequently used to assess the severity of liver fibrosis. The scoring system (explained further in Chapter 3) distinguishes between successive stages from normal liver (stage F0) to cirrhosis (stage F4) based on estimates of transition rates during fibrosis progression.[20]

Cirrhosis may be compensated initially whereby the liver is scarred, but liver function is not compromised. Decompensation occurs when cirrhosis progresses to the point where liver function is impaired. People with decompensated cirrhosis have symptomatic complications, including those related to hepatic insufficiency and portal hypertension.[21] The risk of cirrhosis ranges from 15% to 35% within 25 to 30 years of acquiring HCV infection,[11, 12, 22] and it is estimated that 1-4% of individuals with cirrhosis develop HCC each year.[2, 22] Progression to advanced liver disease can be accelerated by numerous factors, including HCV acquisition at an advanced age (>40–55 years), male sex, co-infection with other viruses (for example, HBV or human immunodeficiency virus (HIV)), higher body mass index (BMI), presence of hepatic steatosis (build-up of fat in the liver) and consumption of alcohol.[16]

Figure 2.1. Clinical course of HCV infection



Key: HCV+ – hepatitis C virus antibody positive; HCV- – hepatitis C virus antibody negative; RNA+ – ribonucleic acid positive; RNA- – ribonucleic acid negative.

2.4 HCV Genotypes

HCV has a high degree of genetic variability owing to its level of viral replication, the absence of proof reading activity during replication and the virus's ability to constantly mutate as it attempts to evade the body's immunological response.[23] Different genetic variations in the RNA of HCV have emerged as a result of the viral replication and mutation processes. A genetic variation of HCV is known as a HCV genotype.

HCV genotyping, based on molecular assay,[24] categorises the genetic variations of HCV into groups based on similar genes. At least six major HCV genotypes (labelled 1 to 6), each of which has its own subtypes (labelled 1a, 1b, etc.) and quasi-species (a population of closely related genetic mutations), exist.[25] Most people are infected by a single dominant genotype, but it is possible to be infected by multiple genotypes at the same time. To date, more than 90 HCV genotype subtypes have been identified.[17]

Each genotype differs in terms of virulence (severity of harmfulness) and pathogenicity (ability to cause harm), and may influence the progression of fibrosis, the risk of steatosis (an abnormal retention of fat) and the risk of HCC.[26] However, observational data suggest that with the possible exception of genotype 3,[26-28] genotype does not influence fibrosis progression.[11, 29-31]

Historically, genotyping has been performed to inform the treatment regimen (treatment type and duration) that a person should be prescribed and to predict their response to treatment.[24] However, the availability of pangenoptypic treatments may soon remove the need for genotyping within the clinical pathway.

2.5 Immune response after HCV infection

Viral clearance of HCV infection involves multiple components of the adaptive immune system including antibody and T cell responses.[32, 33] When a person is exposed to HCV, the immune system attempts to eliminate the virus by producing neutralising antibodies (proteins) targeted against the structural and non-structural viral proteins.[34] Anti-HCV antibodies alone are insufficient to eliminate HCV infection as only a small proportion of anti-HCV antibodies are able to inhibit HCV from binding or entering host cells.[25] The presence of anti-HCV antibodies also does not prevent re-infection.[25] HCV screening tests are designed to detect the presence of anti-HCV antibodies in serum or plasma.

In general, it takes three to 12 weeks for seroconversion – the production of enough antibodies to be detectable by an antibody test – but seroconversion can take up to six months.[32, 33, 35] Consequently, it is possible for individuals with acute-stage HCV infection or those who are immunosuppressed to be missed by anti-HCV antibody screening during this window period.[17, 36] The reasons why some people spontaneously clear the virus while others develop chronic infection are unknown. Given that HCV is an intracellular virus, the cell-mediated branch of the immune system is the predominant responder to infection, and is likely to play an important role in viral clearance. HCV elimination has been associated with strong and sustained CD4+ and CD8+ T cell responses that target multiple epitopes within the different HCV proteins.[34]

Although the presence of anti-HCV antibodies indicates exposure to the virus, it does not indicate active HCV infection. This is because viral clearance may occur spontaneously and a sustained virological response (SVR) may be achieved with treatment following exposure to the virus. Once a person has been exposed to HCV, they will typically remain HCV seropositive even if the virus is cleared naturally or cured by treatment. Active HCV infection must be confirmed by direct diagnostic methods that detect viral RNA (nucleic acid tests) or proteins (core antigen testing).[17]

Therefore, diagnosis of active HCV infection involves two steps: (1) detection of an anti-HCV antibody to indicate if a person has ever had acute HCV infection; and (2) a confirmatory nucleic acid amplification test (NAAT) or HCV core antigen test to verify active HCV infection through the detection of viral RNA in blood or oral fluid.[8]

2.6 Birth cohort testing

Risk-based testing strategies pose challenges for identifying individuals with HCV infection and linking them to care. For example, individuals may be unaware of the risk factors for infection, may not recall exposure to a risk factor that occurred many years ago, may be unwilling to disclose previous risk-taking behaviour to a healthcare worker, or healthcare providers may not systematically identify behaviours that put individuals at risk of HCV infection.[3, 37] The relative importance of risk factors also varies substantially between geographical regions and populations studied.[3]

Birth cohort testing is an expanded testing strategy that involves offering one-time screening for HCV infection to people born during a particular period of time. No prior ascertainment of risk is undertaken, rather for this cohort, there is evidence (such as epidemiological trends) of an elevated risk of exposure relative to the general population. Birth cohort testing is recommended by the WHO for older persons at higher risk of infection and morbidity within populations that have an overall lower general prevalence.[2] The higher risk of infection may be because of historical exposure to unscreened or inadequately screened blood products and or poor injection safety. Compared with risk-based testing, birth cohort testing circumvents the need to identify specific behavioural risks as the basis for screening.[38]

Birth cohort testing has been suggested as a more pragmatic approach than general population testing for identifying undiagnosed cases of chronic HCV infection that may not be detected by current risk-based strategies.[39] Birth cohort testing is conditionally recommended by the WHO in easily identified age or other demographic groups known to have a HCV prevalence higher than that of the general population.[2, 38] The recommendation was based on low quality evidence.

In 2017, the WHO reported that most countries have some form of birth cohort HCV epidemic.[38] The proportion of the population living with HCV infection often increases with age, in a way that exceeds what could be expected from the cumulative risk of infection year after year.[40] This is often referred to as a "cohort effect" and occurs in populations that were infected due to factors such as unsafe healthcare related injections, which contributed to the transmission of HCV on a larger scale earlier.[38] A birth cohort may have a higher HCV prevalence due to the presence of a generalised historical exposure to a risk factor that has since been removed, such as by the introduction of routine screening of blood products and improvements in injection

safety practices.

Birth cohort testing has been advocated and endorsed by both the Centers for Disease Control[41, 42] and US Preventive Services Task Force[37, 43] due to the limited effectiveness of risk-based HCV testing approaches, rising HCV-associated morbidity and mortality, and advances in HCV care and treatment in the US.[41, 42] Birth cohort testing has been shown to increase HCV testing rates and identify persons living with HCV infection without known risk factors.[44] However, the yield from birth cohort testing may be considerably lower in healthcare settings serving lower risk populations. Hence, a significant proportion of the HCV-infected population may not be captured by birth cohort testing.

The 2017 national clinical guideline for Hepatitis C Screening conditionally recommended offering one-off screening to people in Ireland born between 1965 and 1985.[8] Key rationale highlighted by the Hepatitis C Screening guideline development group were that, compared with opportunistic testing, an organised testing programme can achieve greater equity in access to care and a more efficient use of healthcare resources by ensuring that all individuals at risk of infection are targeted within the most appropriate timeframe.

The 1965 to 1985 birth cohort was identified based on national HCV surveillance (based on notifications to the HPSC between 2004 and 2016) and seroprevalence data which indicated that in Ireland HCV prevalence is highest amongst those born between 1965 and 1985 (72.5% of cases).[8-10] As notification data can only provide information on diagnosed cases, a significant proportion of those chronically infected may be unaware of their infection status and remain undiagnosed until they present with symptoms indicative of severe liver damage.

2.7 Principles of a birth cohort testing programme

2.7.1 Definitions

Birth cohort testing for HCV involves offering one-time testing to people born within a certain timeframe to identify people with undiagnosed chronic HCV infection and link them to care. The suggested birth cohort for Ireland is those born between 1965 and 1985.

Screening is a form of secondary prevention, typically applied to a large apparently healthy population. In the context of HCV infection, screening would provide the opportunity for detection and treatment of those with unrecognised HCV infection, preventing potential disease progression and onward HCV transmission.

Birth cohort testing conforms to the concept of case-finding whereby the main

objective is to detect and treat people with chronic HCV infection. Birth cohort testing is also broadly similar to selective screening whereby large-scale population testing occurs in a selected high-risk group. In this instance, the birth cohort is only considered high-risk when compared with the low-risk of HCV infection among the general population.

Wilson and Jungner outlined the principles of screening (presented in Box 2.1) in a 1968 WHO report.[45] When examined in isolation, birth cohort testing (which involves offering a one-off test) does not fulfil the principle of case-finding as a continuous process. However, while the proposed birth cohort testing is limited to a one-off test, those within the birth cohort will continue to be offered risk-based screening where appropriate (for example: ongoing injection drug use, haemodialysis, etc.). The ninth criterion (of economic balance) is being assessed as part of this HTA. Therefore, if found to be economically balanced, birth cohort testing would meet all of Wilson and Jungner's criteria.

Box 2.1. Wilson and Jungner principles of screening[45]

- The condition sought should be an important health problem.
- There should be an accepted treatment for patients with recognised disease.
- Facilities for diagnosis and treatment should be available.
- There should be a recognisable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be an agreed policy on whom to treat as patients.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuing process and not a "once and for all" project.

2.7.2 Screening programmes

The purpose of this section is to illustrate the components and requirements of traditional screening programmes and to illustrate the extent to which these may apply to birth cohort testing.

According to the WHO, a screening programme includes all of the core components in the screening process, which ranges from inviting the target population to be screened to accessing effective treatment for individuals diagnosed with disease.[46] Screening programmes require significant healthcare resources, infrastructure and functional

health systems to be effective. Therefore, screening programmes should be undertaken only when resources are sufficient to cover nearly all of the target group; when facilities exist for follow-up of those with abnormal results to confirm diagnoses and ensure treatment; and when prevalence of the disease is high enough to justify the effort and costs of screening. When planned effectively, appropriately financed and implemented, screening programmes can reduce disease-related morbidity and mortality.

The key features of any screening programme are that:

- it identifies individuals at sufficiently high risk of disease for whom further investigation or direct therapy is warranted. Typically, a positive screening test is a precursor to a confirmatory diagnostic test
- it is offered to a target population who are asymptomatic and have not sought medical attention for the disease of interest
- the benefits outweigh the harms.

The extent to which benefits outweigh harms is subject to a variety of factors including the characteristics of the screening test, the prevalence of disease in the screened population, and the risk of disease progression if left untreated. These factors are described in Section 2.10. For those with symptomatic liver disease or with identified risk factors for HCV, the testing pathway may deviate from that of the proposed birth cohort testing strategy.

The effectiveness of birth cohort testing to reduce the incidence, morbidity and mortality from HCV-related hepatic and extrahepatic complications depends on:

- the participation or uptake rate
- the sensitivity and specificity of the screening test
- the natural history of the disease (rate of onset of decompensated cirrhosis, HCC and other liver-related complications)
- the effectiveness of treatment
- the compliance with follow-up and treatment.

The WHO has specified that an effective screening programme should have the following criteria in place:

- mechanisms for systematic invitation and follow-up for individuals identified by the screening test as having an abnormal finding (that is, call and recall mechanisms)
- participation from over 70% of the target population
- necessary infrastructure and resources to offer the test periodically and to adequately diagnose and treat those found to have the disease

- a robust monitoring and evaluation framework to assure quality.[46]

The structure adopted by a testing programme will influence the acceptability and uptake of testing, as well as its effectiveness and cost-effectiveness. A screening or testing programme may adopt one of two structures:

- Opportunistic – test is offered as part of routine care when the patient interacts with the healthcare system for a reason unrelated to the test. For example, HCV testing may be offered to a person born between 1965 and 1985 while visiting their general practitioner (GP) for an annual health check-up. That is, the healthcare consultation is initiated by the patient.
- Systematic – population-based testing organised by the healthcare system. For example, if all people born between 1965 and 1985 are invited on a call-recall basis to visit their GP for HCV testing. That is, the healthcare consultation is initiated by the healthcare system.

In contrast to opportunistic testing, organised testing can achieve greater equity in screening access and is a more efficient use of healthcare resources by ensuring that all individuals at risk are targeted within the most appropriate timeframe.[47] In addition to improving equity of access and efficiency of resources, organised testing provides better conditions for ensuring that quality assurance guidelines for screening are followed in order to achieve the greatest benefit with the least harm.[48]

Evidence on the effectiveness of organised compared with opportunistic screening programmes is limited. A 2016 systematic review[49] identified ten studies (three randomised controlled trials (RCTs), seven non-RCTs) which compared organised screening programmes with opportunistic screening programmes. None of these studies considered HCV screening and only one study considered screening for an infectious disease, chlamydia. The included studies compared various methods of organised screening, including the use of postal screening, a call-recall system and a worksite screening initiative, with opportunistic screening methods such as patients requesting screening from their general practitioner. The organised approaches involved dissemination of personalised invitation letters, information pamphlets, and telephone or letter reminders.

All three RCTs found that screening uptake was higher for organised than opportunistic screening programmes (although the difference was not statistically significant in one of the RCTs).[49] Five of the seven non-RCTs also found that organised screening was substantially more effective.[49] Overall, it would appear that uptake increases when people are enrolled in an organised screening programme – a trend which is consistent despite differences in target diseases, study methods, study populations, and characteristics of the intervention and control arms.[49] The variability in the non-RCT

findings may have been due to selection bias, differences in disease groups or contextual factors. These ten studies may not be directly applicable to HCV screening, but the findings would suggest that a systematic population-based screening programme would have a higher uptake than offering opportunistic screening. A public awareness campaign may also encourage improved uptake. However, convenience and accessibility are also likely to influence screening uptake. The model of implementation adopted (which may be multifactorial) will have implications for the acceptability and uptake of testing, as well as the effectiveness and cost-effectiveness of birth cohort testing.

For many diseases, factors such as test accuracy, prevalence and disease progression may vary with age. Important considerations in the design of any programme would therefore also include the:

- age at which screening should start (sufficient prevalence of the condition to justify screening)
- age at which screening should stop (insufficient prevalence, low risk of disease progression, or limited benefit due to life expectancy)
- test or tests to use in screening (diagnostic test accuracy)
- requirement (if any) for repeated screening and the interval between screening rounds (risk of disease progression, diagnostic test accuracy).

The age at which testing should start and stop is determined by the definition of the birth cohort. That is, people born between 1965 and 1985. The tests used and their performance characteristics are described in Chapter 4. As noted, testing would be once-off.

Irrespective of whether opportunistic testing or an organised programme was to be offered, it is expected that for ethical reasons, birth cohort testing for HCV would have to meet the WHO requirement of having adequate resources and infrastructure to treat those identified with the disease. Consideration will also be required regarding the requirement for a monitoring and evaluation framework to ensure that the test offered meets minimum performance standards and that those who avail of testing would, within defined time periods, be notified of their test result and offered follow-up healthcare and treatment, as appropriate.

Screening may result in overtreatment, that is, where infection is identified and treated, when in the absence of treatment, it would never have developed into symptomatic complications. There is also a risk that screening will identify false positives which do not require treatment, but that potentially contribute to stress and anxiety. Furthermore, there is a risk of false negative test results with any screening programme. Potential standards in relation to a testing programme are outlined in

Chapter 7. Ethical considerations in relation to screening for HCV infection are discussed in detail in Chapter 8.

2.7.3 Performance characteristics of a screening test

The diagnostic accuracy of screening reflects the performance characteristics of the screening test and describes how well the test discriminates between those who do, and do not have the target condition. To determine the diagnostic accuracy of an index test, its performance must be compared with that of a 'gold standard' diagnostic test (that is, the best available method for determining the presence of disease) in terms of sensitivity and specificity.[50]

Sensitivity is the ability of an index test to accurately identify those who have the condition: the proportion of people with the condition who receive a positive test result. As per Table 2.1, sensitivity is calculated as a/(a+c). The specificity of a screening test is its ability to correctly identify those who do not have the condition: the proportion of people without the condition who receive a negative test result. As per Table 2.1, specificity is calculated as d/(b+d). Individuals are then classified according to whether the screening test is positive or negative, and whether the 'gold standard' is positive (disease present) or negative (disease absent).

Table 2.1. Relationship between a screening test result and the occurrence of the condition

Test result	Condition present*	Condition absent*
Positive	True positive (a)	False positive (b)
Negative	False negative (c)	True negative (d)

* As determined by the gold standard diagnostic test

The positive predictive value (PPV) is the probability that when a test result is positive, that the person truly has the infection or disease. As per Table 2.1, the PPV is calculated as a/(a+b). The negative predictive value (NPV) represents the probability that a person's test result is negative, that they truly do not have the infection. As per Table 2.1, the NPV is calculated as d/(d+c). Predictive values are influenced by the prevalence of the disease within the target population. A higher prevalence increases the PPV and reduces the NPV of a test, and vice versa. A mathematical example of how the predictive values are influenced by prevalence is presented in Appendix 2.

2.8 Screening for HCV in Ireland

Since the development of innovative treatments for HCV infection, there has been a paradigm shift towards HCV elimination. The main challenge to achieving this goal is

identifying those living with HCV infection who are currently undiagnosed and eligible for treatment. With this objective in mind, a national clinical guideline for Hepatitis C Screening was published by the National Clinical Effectiveness Committee in 2017.[8] The guideline recommended that screening should be routinely offered to individuals with behaviours, exposures, and conditions that place them at increased risk of HCV infection.[8] The risk groups for which target-based screening is strongly recommended and the risk groups for which screening should be considered, but not routinely offered are presented in Table 2.2.[8] A number of other national policies relevant to HCV screening, described below, were in place before the approval of the national clinical guideline in 2017. No organised risk-based screening programme for HCV infection currently exists in Ireland.

A testing programme exists for those who were recipients of a blood transfusion (blood or blood components) in Ireland prior to October 1991. An anti-D national screening programme was initiated in 1994 to offer HCV testing to recipients of potentially contaminated anti-D immunoglobulin injected to prevent Rhesus disease in pregnant women between 1 May 1977 and 31 July 1979.[51] During this period, 4,062 vials of infectious or potentially infectious anti-D immunoglobulin were manufactured and issued by the Blood Transfusion Service Board (now the Irish Blood Transfusion Service).[8] This programme was later extended to recipients between 1 March 1991 and 18 February 1994 during which 14,946 vials of infectious or potentially infectious anti-D immunoglobulin were issued.[8] People with haemophilia, Von Willebrand's disease or other inherited coagulation disorders were particularly affected by HCV infection due to exposure to both blood and blood components for the treatment of clotting disorders.

The National Hepatitis C Database[28] was set up in 2004 to collect data on people who were identified as being infected with HCV through the receipt of contaminated blood and blood products in Ireland (n=1,694). Of the 1,694 persons known to have been infected with HCV through blood or blood components, 1,051 (62%) were infected through anti-D immunoglobulin, 418 (25%) were recipients of blood transfusions or treatment for renal disease, and 225 (13%) were people with haemophilia and other blood clotting disorders infected through clotting factors.[8, 28] The latest follow-up data are from 2013 and are available for 1,320 people, representing a participation rate of 77%.

Routinely offering screening to prisoners upon remand was recommended by the National Hepatitis C Strategy 2011-14[5] owing to a high prevalence of current or past drug use and a high prevalence of HCV amongst the prisoner population in Ireland.[52, 53] However, uptake of HCV screening by prisoners is reported to be low.[8] Testing of ex-prisoners is recommended, but a national programme has not been established.

Under the clinical guidelines for opioid substitution treatment,[54] it is recommended that all drug users (including patients who continue to inject drugs or misuse alcohol) are screened for HCV upon presentation and offered appropriate treatment, even if they are not intravenous drug users. Patients who initially test negative are offered a repeat test every six to 12 months if the patient has continued engagement with risk-taking behaviour. Compliance with this recommendation is reportedly very high (98%) according to an audit of HCV screening and referral in addiction centres in Community Health Organisation.[8, 55]

As HCV infection is associated with an increased risk for all-cause and liver-related mortality in patients on haemodialysis, the dialysis setting is recognised as a high risk environment for transmission of HCV and other blood-borne viruses.[8] Guidance on screening in the dialysis setting is outlined by the National Standing Advisory Committee on the Prevention of Transmission of Blood-Borne Diseases in the Health-Care Setting.[56] The 2014 guidance recommended that one-off testing be considered for kidney transplant patients three months post-transplant and considered for patients transplanted before the introduction of this post-transplant screening. Routine HCV screening is also recommended in patients on haemodialysis. The rationale for these recommendations is that transmission may occur during dialysis immediately prior to kidney transplant.

Finally, screening of donors of substances of human origin for HCV and other infectious diseases is regulated under EU and national legislation. In Ireland, the Health Products Regulatory Authority (HPRA) is responsible for human blood and blood components and for tissues and cells.[57, 58] The HPRA and the HSE are responsible for organs intended for transplantation.[59] Within the HSE, Organ Donation Transplant Ireland is responsible for implementation of the relevant aspects of legislation. Organ Donation Transplant Ireland has developed a framework for quality and safety of human organs intended for transplantation as required by legislation in conjunction with the HPRA.[60]

Routine screening of blood donor samples was introduced in October 1991. Laboratory testing is performed by the Irish Blood Transfusion Service for multiple disease markers on every sample, including serological testing for anti-HCV antibodies. Any donor sample that is positive for any of these disease markers cannot be used for transfusion purposes. All HCV positive donors are informed if the virus is detected in their donor sample.

All blood donated to the Irish Blood Transfusion Service is tested for anti-HCV antibodies. In addition, individual donation-NAT using a multiplex assay testing for HIV-RNA, HCV-RNA and HBV-DNA is undertaken. The Irish Blood Transfusion Service also screens tissue and cell donors with NAT. Screening of solid organ donors is done in the National Virus Reference Laboratory where combined anti-HCV antibody and

HCV antigen tests are performed for deceased donors.[8]

Table 2.2. Risk groups recommended for HCV screening in Ireland

Risk-based strategies strongly recommended in Ireland	Groups for which screening should be considered, but not routinely offered in Ireland
▪ people who have ever injected drugs (PWIDs) ▪ people known to have used unprescribed or illicit drugs administered by non-injection, where the possibility of transmission of infection by the route of administration is suspected ▪ prisoners or former prisoners ▪ homeless people who have a history of engaging in risk behaviours associated with HCV transmission, or who have had a potential HCV risk exposure ▪ migrants from a country with an intermediate to high prevalence of HCV infection (anti-HCV prevalence ≥ 2%) ▪ people who are HIV positive ▪ infants of HCV-RNA positive women ▪ men who have sex with men (MSM) ▪ people on renal dialysis or who have had a kidney transplant ▪ recipients of blood or blood components in Ireland prior to October 1991 who have not yet been tested ▪ recipients of anti-D immunoglobulin in Ireland between 1 May 1977 and the end of July 1979, and 1 March 1991 to 18 February 1994 who have not yet been tested ▪ recipients of plasma derived clotting factor concentrates in Ireland prior to 1992 who have not yet been tested.	▪ those with a tattoo, particularly those who received tattoos a number of decades ago, in non-professional settings, prisons, countries with a high prevalence of HCV, or in circumstances where infection control was poor ▪ household contacts (that is, those who share living spaces such as spouses) of a person who is HCV positive in circumstances where household transmission is more likely to have occurred (for example, if there has been a potential exposure to blood from sharing razors) ▪ recipients of solid organ transplants in Ireland prior to the introduction of routine screening ▪ recipients of blood components and blood products overseas in any country where a quality assured blood donor screening programme may not have been in place ▪ people who have received medical or dental treatment in countries where HCV is common (anti-HCV prevalence ≥ 2%) and infection control may be poor ▪ sexual partners of known HCV cases: If the case or contact is also HIV positive o If the HCV-infected case is an injecting drug user ▪ sexual contacts of persons who inject drugs, but where HCV status is unknown or where there is evidence of resolved infection ▪ commercial sex workers.

Key: HCV – hepatitis C virus; HIV – human immunodeficiency virus; MSM – men who have sex with men; PWID – people who inject drugs; RNA – ribonucleic acid.

Source: Hepatitis C Screening National Clinical Guideline[8]

2.9 International practice

Viral hepatitis is an international public health challenge that places a significant burden on communities across the globe. The global health sector strategy on viral hepatitis published by the WHO in 2016[4] recommends that each country should define the specific populations within their country that are most affected by viral hepatitis epidemics. Actions to reduce transmission and disease burden should be based on the epidemiological and social context in that country. National HCV testing policies should be informed by the best available evidence regarding the prevalence of HCV infection in the general population and within population subgroups to ensure that testing approaches are directed at high-prevalence groups.[61]

The 2017 WHO guidelines on hepatitis B and C testing [38] outline thresholds of ≥2% or ≥5% seroprevalence to indicate intermediate or high seroprevalence, respectively based on several published seroprevalence studies. In settings with an intermediate or high HCV antibody seroprevalence, it is recommended that all adults are offered HCV serological testing with linkage to prevention, care and treatment services.[2] In countries with an easily identified demographic group that has a higher anti-HCV seroprevalence than the general population, birth cohort testing should be considered. The best approach to testing outside of groups with risk behaviours or potential exposures depends on the country's unique HCV epidemiology. Therefore, the threshold used by a country will depend on country-specific considerations and the epidemiological context.[38]

A 2018 systematic review[62] identified 15 high income countries (assessed using the human development index) with HCV screening recommendations, primarily using risk-based approaches to identify those with HCV infection. In addition to risk-based testing, seven countries (Argentina, Chile, Finland, France, Greece, Japan and the US) either have an age-based testing recommendation or recommend one-time testing for all adults independent of risk factors. Of the 15 countries, only one (Japan) recommended general population screening.[63] In Japan, testing has been provided to all those aged 40-70 as part of a routine health check-up since 2002.[64, 65] In France, a decision to potentially fund universal HCV screening by the Ministry for Health is currently under review by the Haute Autorité de Santé.[66]

The US Centers for Disease Control and Prevention and the US Preventive Services Task Force were the only organisations identified that have recommended birth cohort screening for adults born between 1945 and 1965, based on prevalence estimates for that population.[41, 43] Recommendations regarding birth cohort screening in the US are underpinned by the findings of a national seroprevalence study[42] which found that the anti-HCV prevalence in this birth cohort was 3.25%, five times higher than adults born outside these years. It was estimated that between 45% and 85% of HCV

infections in the US were undiagnosed. As the 1945–1965 birth cohort is a recognised subpopulation in the US (known as the "baby boomers"), this familiarity was expected to facilitate adoption and implementation of the recommendation.[41] However, the policy response in the US has been limited with only three States (New York, Massachusetts, Connecticut) having introduced legislation that requires providers to offer HCV screening, and insufficient implementation of mechanism to monitor key metrics, such as coverage and uptake.[49, 67, 68]

Other countries (Canada, Australia and Belgium) have considered birth cohort testing, but at the time of writing, no country has introduced a similar recommendation. Following the recommendation from the US Centers for Disease Control and Prevention, the Canadian Liver Foundation[69] issued a position statement advocating for birth-cohort testing of adults born between 1945 and 1975 in addition to risk-based screening approaches. The Public Health Agency of Canada[70] subsequently updated their recommendations on HCV screening by estimating the burden, prevalence and proportion of undiagnosed cases of HCV infection in Canada,[71, 72] and by estimating the cost-effectiveness of screening.[73] The Public Health Agency of Canada recommended a risk-based HCV screening due to the uncertainty surrounding epidemiological estimates of HCV infection, and the benefits and harms of screening. At a local level, the Northwest Territories in Canada recommend one-time HCV screening for those born between 1945 and 1975. This is the only territory with a recommendation for birth cohort testing.[49]

A 2017 guideline on screening asymptomatic Canadian adults for HCV produced by the Canadian Task Force on Preventative Health Care[36] identified 11 other guidelines on testing and screening for HCV. While there was variation in the criteria for identifying those at elevated risk of HCV infection, all guidelines recommended some sort of risk-based approach to screening, ranging from routine testing of all those at high risk, to recommendations for screening in only some high-risk populations.[74] Following an extensive review of the evidence, the Canadian Task Force on Preventive Health Care recommended against screening for HCV in asymptomatic Canadian adults (including baby boomers) who are not otherwise at increased risk of HCV infection.[74] However, the Canadian Task Force stated that the recommendations may be re-evaluated if factors influencing the current recommendation change. Key reasons that the Canadian Task Force on Preventive Health Care[74] recommended against the screening asymptomatic adults not at an elevated risk of HCV infection included the:

- potential for false positives and stigma associated with diagnosis of HCV infection
- presence of knowledge gaps and system-wide barriers that would hinder population-based screening in Canada (such as high cost of treatment, limited access to publicly funded treatment and resultant health inequity)

- the potential health inequity that could arise from identifying people with HCV infection who would not qualify for drug coverage since funding for treatment was at the time limited to individuals with more advanced liver fibrosis (METAVIR fibrosis scores F2 to F4)
- estimated prevalence of HCV infection in the Canadian birth cohort (0.8%)[75] was only a quarter that of the US birth cohort (3.25%)
- uncertainty regarding screening uptake rates
- likelihood that referring individuals with screen-detected HCV for assessment would reduce access to assessment and treatment for people with clinically evident HCV.

As part of a HTA by University of Calgary in 2016,[49] a systematic review was undertaken to identify screening programmes and guidelines in other jurisdictions. There is an important distinction between countries making recommendations for screening, and countries implementing these recommendations with the introduction of screening programs. While nine countries with HCV screening guidelines were identified (Canada, US, UK, Australia, Belgium, France, Germany, the Netherlands and Saudi Arabia), only five countries had organised screening programmes (Canada, US, UK, Australia and Saudi Arabia). Of these, the US was the only country identified with guidelines that recommended screening by birth cohort.

Australian national HCV screening policy was updated in 2016.[76, 77] Risk-based screening was prioritised due to the lower proportion of undiagnosed cases of HCV infection in Australia (19%)[78] compared with the US (50%),[79, 80] access restrictions and the implementation of a public awareness programme that highlighted the risk factors for HCV infection.[81] In Belgium, a report by the Belgian Health Care Knowledge Centre[82] concluded that the lower seroprevalence estimates (possibly 0.1 to 1%) and higher screening rates in Belgium meant that the US recommendations for birth cohort testing were not generalisable to the Belgian context. The report also acknowledged a need for well-designed epidemiological research to generate reliable prevalence estimates for the general population and specific risk-groups to facilitate informed decision making.

In 2019, the Hellenic National Plan for Hepatitis C was published in Greece which recommended birth cohort testing for all adults born between 1945 and 1980 as more than three quarters of people living with HCV infection in Greece were born during this period.[83, 84] The implementation, overseen by a Committee, of the HCV National Plan in Greece is underway. The National HCV Action Plan acknowledged that prompt implementation of the recommendations would be required to optimise access to care and achieve the WHO target of HCV elimination by 2030. A list of examples of actions that could be taken by hepatologists to facilitate implementation was included in the HCV National Plan.

2.10 Diagnosis and treatment of chronic HCV infection

2.10.1 Laboratory testing for HCV infection

As noted, diagnosis of chronic HCV infection involves two steps: (1) detection of an anti-HCV antibody to indicate if a person has ever had acute HCV infection; and (2) a confirmatory NAT or core antigen test to verify active HCV infection through the detection of viral replication in blood or oral fluid.[8] The testing sequence for HCV infection is presented in Appendix 3.

Antibody testing

Screening to identify people with chronic HCV infection typically begins with an enzyme immunoassay (EIA) to detect anti-HCV antibodies in the bloodstream.[36] The purpose of an anti-HCV antibody test is to confirm that an individual has been infected with HCV infection at some point in time. However, these indirect serological tests cannot distinguish current from past infection. Therefore, a positive antibody test is insufficient to diagnose active HCV infection.[17] A positive result may indicate: current HCV infection, a false positive or past HCV infection that has resolved.

Once a person has been exposed to HCV, they will remain HCV seropositive even if the virus is cleared naturally or cured by treatment. Therefore, the presence of anti-HCV antibodies only indicates prior exposure to HCV infection. Active HCV infection must be confirmed by direct diagnostic methods that detect viral RNA (NAATs) or proteins (core antigen testing).[17] A negative antibody test result indicates that no anti-HCV antibodies were detected. As it may take up to 12 weeks for detectable anti-HCV antibodies to develop (that is, seroconversion), a negative antibody test undertaken during this "window period" is insufficient to confirm that a person has not been infected with HCV. Although the negative test result may be accurate, it can only be interpreted as evidence the person did not have the anti-HCV antibody in their blood at the time of screening. Repeat testing at least 12 weeks post exposure is necessary to confirm that the individual is anti-HCV antibody negative. For the birth cohort, repeat antibody testing is unnecessary for individuals that test anti-HCV antibody negative, as exposure is likely to have occurred many years previously.[85]

EIAs are generally recommended for HCV screening because they are easy to use, inexpensive and can be adapted to large volume testing.[17] However, it should be noted that EIA results may be negative in early acute HCV infection and in profoundly immunosuppressed patients.[8, 35] There are a variety of EIAs that can be used for HCV screening which include: enzyme-linked immunosorbent assays (ELISAs), chemiluminescent immunoassays (CLIAs) and microparticle enzyme immunoassays (MEIAs).[36] In 2008, fourth generation EIAs for detecting anti-HCV antibodies became available.[17] Fourth generation assays detect both anti-HCV antibodies and the HCV

core antigen.[86]

Rapid diagnostic tests (RDTs) can be used as an alternative to EIA testing for antibody detection, and are particularly relevant in resource-limited settings due to their lower complexity, shorter turnaround time, lower cost and the fact that specialist apparatus and technicians are not required.[86] Compared with EIAs, a 2017 systematic review and meta-analysis estimated that the pooled sensitivity and specificity of RDTs [86] were 0.98 (95% CI: 0.98-1.00) and 1.00 (95% CI: 1.00-1.00), respectively. However, the individual performance of RDTs to detect antibodies varies widely according to brand and specimen type. Near-patient tests with a pooled sensitivity of 97.46% (95% CI: 95.92-98.43%) and a pooled specificity of 99.58% (95% CI: 99.28-99.75%)[87] are also available for diagnosing HCV infection, but are not currently recommended as implementation would require substantial investment and evidence of their cost-effectiveness is limited.[35]

The use of RDTs on blood specimens is conditionally recommended in Ireland where concerns exist about hard-to-reach populations or linkage-to-care.[8] However, a quality assurance programme would need to be established before the use of RDTs for anti-HCV antibody testing could become standard practice in Ireland. Laboratory-based EIA is considered standard practice for anti-HCV antibody testing in Ireland. Key advantages of laboratory-based EIAs for large-scale screening or testing include: high accuracy and throughput, facilities for within-assay quality control and the availability of objective, automated reading of results and participation in external quality assurance schemes. Therefore, laboratory-based testing is considered the preferred antibody testing method in this HTA.

Viral load testing

A NAT (or viral load test) for detecting viral RNA is required to determine whether a person is actively infected with HCV. A NAT measures the amount of HCV RNA in the blood typically using polymerase chain reaction (PCR) technology. The presence of viral RNA indicates that the virus is actively replicating (reproducing and infecting new cells), but can also be used to predict and monitor response to treatment, and determine whether viral infection has been eradicated.[17] There is no correlation between viral load and disease progression.[17] However, the viral load can impact the likelihood of onward transmission as higher viral loads are more infective. A low viral load does not impact the decision to treat.

Antibody and nucleic acid testing can be undertaken using the same blood sample. Laboratories may adopt a reflex testing approach whereby blood samples are initially tested for the presence of anti-HCV antibodies. If positive, the sample is retested for HCV RNA.[35] If the subsequent HCV RNA test is negative, active HCV infection is effectively ruled out for most patients. If the reflex test is positive, a diagnosis of active

HCV infection has been confirmed, and the individual is referred directly for HCV care and treatment.[35] However, reflex testing is not standard practice and time restrictions apply to molecular assays. Therefore, a second blood sample may be required to confirm active HCV infection.

For new anti-HCV positive diagnoses that are RNA negative, RNA or core antigen testing is repeated and a second sample is sent for RNA testing six to 12 months later. Two repeat negative RNA or core antigen tests is considered confirmation of spontaneous clearance. RNA or core antigen testing is also repeated for anti-HCV negative individuals who are at risk of HCV re-infection.

NAAT results are reported in terms of International Units per millilitre (IU/ml). Viral loads are interpreted as high (more than 800,000 IU/ml) or low (less than 800,000 IU/mL). There are two types of NAATs:

- Qualitative – determines the presence of HCV RNA in the blood. If HCV RNA is detected, the test result is positive. If HCV RNA is not detected, the test result is negative (or undetectable). Qualitative PCR tests have a reported sensitivity to detect fewer than 50 RNA viral copies per millilitre and an estimated specificity of over 99.5%.[36]
- Quantitative – determines not only the presence of HCV-RNA, but also measures the amount of HCV-RNA in the blood. Newer quantitative real-time PCR-based assays have a reported sensitivity to detect between five and 15 IU/mL with specificity similar to qualitative tests.[36] According to guidance from the European Medicines Agency (EMA), RNA levels must be determined with a standardised CE-marked quantitative assay based on real-time PCR technology with a lower limit of detection in the order of 10-15 IU/mL.[88]

Laboratory practice may vary according to local laboratory infrastructure. It is important to note that NAAT results can vary depending on how the blood sample is handled and stored, and may even vary between laboratories. For this reason, it is recommended that NAATs are conducted by the same laboratory each time, so that results are more comparable. In addition, it is possible that the blood of an individual with an extremely low viral load may still contain HCV even though current tests are unable to measure it; that is, the virus may not have been truly eradicated from the body.

HCV core antigen testing is an alternative to NAAT for confirming diagnosis of HCV infection. The HCV core antigen is a viral protein which can be detected in the bloodstream from two weeks following infection and remains positive as long as infection persists.[8] Core antigen testing can be used to detect acute HCV infection,

confirm chronic HCV infection, and measure treatment outcomes.[36] However, HCV core antigen testing does not detect low levels of HCV (<1,000 IU/mL) and thus is mainly recommended in resource-limited settings as it is simpler to use and less expensive than viral load testing.[35] Recombinant immunoblot assays (RIBAs), which detect generation of antibodies in response to HCV antigens, were previously used as a follow-up test in people with a positive HCV EIA and a negative RNA test. However, RIBAs cannot confirm active infection and their use is not routinely recommended.[8, 17, 85]

It is recommended that initial testing should routinely incorporate HCV-antigen or HCV-RNA testing in certain patient groups (including individuals who are immunosuppressed, have previously been treated for HCV infection, or who are at risk of recent infection but in whom an antibody response may not have yet developed).[8] All individuals newly diagnosed with chronic HCV infection are referred to a consultant hepatologist or infectious diseases physician for further assessment.[85]

2.10.2 Treatment and monitoring

Viral cure of HCV infection occurs when a sustained virological response (SVR), defined as undetectable HCV-RNA in serum or plasma, is achieved.[2, 35] Long-term follow-up studies have shown that an SVR generally corresponds with a definitive cure of HCV infection with only a very low chance of relapse.[35, 89] In non-cirrhotic patients, achieving an SVR reduces mortality, prevents HCV-related liver disease and extrahepatic complications; improves health-related quality of life; and prevents onward transmission of HCV infection.[35] Successful HCV therapy can remodel liver scar tissue and return it towards architectural normality in patients with advanced fibrosis (METAVIR score F3) or cirrhosis (F4) who achieve an SVR. However, these patients remain at risk of life-threatening complications, such as hepatic failure and portal hypertension.[35] In these patients, the risk of HCC and liver-related mortality is significantly reduced, but not eliminated and surveillance for HCC must be continued.[27, 35, 90, 91]

Rapid evolution in the HCV treatment landscape has led to the development of treatment with direct-acting antivirals (DAAs) that is both curative and acceptable to patients.[8] DAAs work by blocking specific parts of the HCV structure from producing viral proteins, which serves to suppress the ongoing replication of HCV and enables the immune system to remove infected cells.[17, 35] Over 95% of patients achieve an SVR following treatment completion with second generation interferon-free DAAs.[17, 92] DAA drug combinations are generally prescribed for daily oral consumption for 8-12 weeks, but treatment may last up to 24 weeks. Second generation DAAs are well tolerated with only minor side effects compared with older interferon-based treatment regimens. Following completion of a course of DAA treatment, repeat NAT is

undertaken to determine if HCV infection has been resolved. A further blood sample is then drawn from individuals with evidence of resolved HCV infection six to 12 months later to confirm resolved infection status.[8] In accordance with recommendations of the European Association for the Study of the Liver (EASL), individuals that are HCV RNA-negative (or HCV core antigen-negative) should be re-tested for HCV RNA 12 and 24 weeks following a negative result to confirm definitive clearance and rule out interludes of undetectable HCV RNA.[35]

DAAs were licensed in Europe in 2014 and were originally prescribed according to genotype. Prior to treatment initiation, genotyping and subtyping were performed to:

1. inform the treatment regimen (treatment type and duration) that a person should be prescribed
2. predict response to treatment.[24]

Recently, pangenoptypic DAAs have become available that have demonstrated high efficacy across all six major HCV genotypes and obviate the need for genotyping.[2] The efficacy of the DAAs will be reviewed in detail in Chapter 4.

In Ireland, the National Hepatitis C Treatment Programme (NCHTP) was established in 2015 to provide treatment across a range of healthcare settings to all people living with HCV infection, with the objective of making hepatitis C a rare disease by 2026.[7, 93-95] The first- and second-line treatments reimbursed under the NHCTP are subject to an annual tender which aims to maximise value-for-money and manage HCV treatment within national budget constraints. These preferred regimens of DAA treatments are reimbursed through the Primary Care Reimbursement Service (PCRS). Reimbursement of preferred DAA treatment regimens is subject to prior-authorisation schemes. Treatment is currently dispensed through eight designated hospitals and a small number of drug treatment clinics. The estimated efficacy of first- and second-line treatments available in Ireland are described in the Clinical Effectiveness Chapter (see Chapter 4).

2.11 Discussion

The hepatitis C virus (HCV), first identified in 1989, is a blood-borne virus that predominantly affects the liver.[1] Although HCV infection can often resolve spontaneously, chronic HCV infection may lead to fibrosis, cirrhosis, liver cancer and death.[2, 11-13] As the transition from acute to chronic HCV infection is often asymptomatic, considerable liver damage may occur before HCV infection is eventually diagnosed. Highly effective treatments for HCV infection, which offer cure in most cases and are more acceptable to patients, are now available. It is well documented that treatment with second-generation direct-acting antivirals (DAAs) is safe, tolerable, highly effective and acceptable to patients.[35] Thanks to advances in the

treatment of HCV infection, there has been a recent paradigm shift in the fight to eliminate viral hepatitis towards identifying and curing people that are currently undiagnosed.

Screening methods for HCV are also well established with high rates of diagnostic accuracy documented.[86] As such, it is logical that efforts should now focus on employing new approaches for identifying people at risk of severe liver-related complications and direct them to care. Birth cohort testing has the potential to be a useful screening strategy for identifying people that have chronic HCV infection, but are currently unaware of the infection due to its asymptomatic nature. The main advantage of this approach over risk-based screening is that it circumvents the need for prior risk ascertainment. The cohort is easily identifiable as its elevated risk of exposure relative to the general population is defined by the cohort's age.

The US is the only country with guidelines[41, 43] that recommend screening by birth cohort (those born between 1945 and 1965), and the policy response to this recommendation has been limited.[49] Decision-makers need to define what trade-offs are acceptable in the fight to achieve HCV elimination, based not only on disease prevalence and the healthcare infrastructure, but also on technical, socioeconomic, cultural and behavioural considerations.[86] As people diagnosed with HCV infection may not have identifiable risk factors,[96] risk-based screening may be insufficient for identifying all people with chronic HCV infection.[36] It has been estimated that 20-30% of HCV-infected people in the US do not report any risk factors.[96-98] Birth cohort testing of adults born between 1965 and 1985 may offer a reasonable approach for identifying and treating the currently undiagnosed population with chronic HCV infection in Ireland. Adequate resources would need to be put in place to support effective implementation of a birth cohort screening programme and ensure that people identified with chronic HCV infection are provided with timely and appropriate care.

3 Epidemiology

Key points

- Acute HCV infection is generally defined as the first six months following infection with the virus. Individuals acutely infected with HCV may develop an immune-mediated response that results in spontaneous viral clearance of HCV.
- Between 55% and 85% of those acutely infected fail to clear the virus and develop chronic HCV infection, the progression of which is slow and unpredictable.
- HCV has been a notifiable disease in Ireland since 2004. From 2004 to 2018, a total of 15,266 HCV cases were notified to the HPSC. Of these, 71% (n=10,862) were from the 1965 to 1985 birth cohort.
- In 2018, 61% (n=361) of all notifications were from the 1965 to 1985 birth cohort, yielding a notification rate of 24.1 per 100,000 population. Injecting drug use was the most commonly reported risk factor for acquisition of infection.
- The estimated prevalence of undiagnosed chronic HCV infection within the 1965 to 1985 birth cohort ranges from 0.35% to 1.15%.
- There are six major HCV genotypes. From 2008 to 2018, HCV genotypes 1 (58%) and 3 (37%) were most common in the 1965 to 1985 birth cohort.
- There were 103 new cases of hepatocellular carcinoma (HCC) in 2016, but this likely represents an underestimate of the true liver cancer morbidity since more than one third of cases are reported without a subtype specification. The annual number of HCC cases has increased by 300% since 1994. Five-year net survival for cases of HCC was estimated at 32.9% between 2011 and 2015. Based on international estimates, approximately 21% of HCC cases are attributable to chronic HCV infection.
- Chronic HCV infection is associated with substantial morbidity and mortality. Of patients from the 1965 to 1985 birth cohort registered with the HSE National Hepatitis C Treatment Programme between 2018 and 2019, 15% had developed compensated cirrhosis of the liver.
- There were 128 liver transplants as a result of HCV-related complications between 2005 and 2018. A total of 176 HCV-related deaths occurred in 2016.

3.1 Introduction

This chapter describes the natural progression of HCV infection, its prevalence and associated burden of disease in Ireland. As evaluation of the cost-effectiveness of birth cohort testing requires estimation of the target population and the probability of a clinical event occurring within that population, the risk of experiencing these outcomes is also described.

3.2 Natural history of HCV

3.2.1 Description of HCV

Chronic versus acute HCV infection

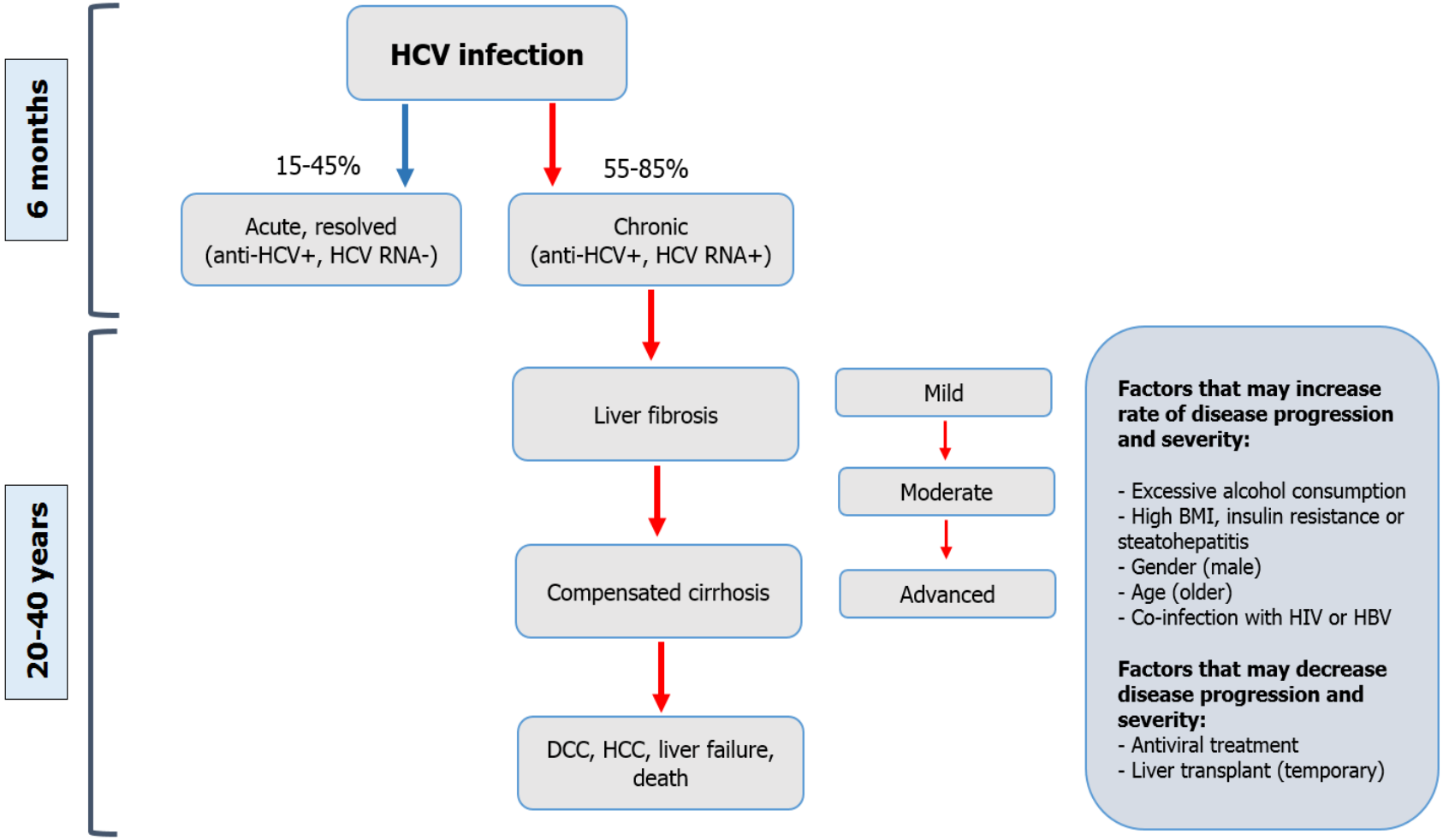
HCV is a RNA virus that can cause acute or chronic infection. HCV is acquired through exposure to blood of other HCV-infected individuals. There are six major HCV genotypes (labelled 1 to 6), as noted in Chapter 2.4.

Acute infection is generally defined as the first six months following infection with the virus.[8, 99, 100] Between 15-45% of acutely infected individuals will clear the virus spontaneously.[2, 16] The acute phase of infection is usually asymptomatic. Although mild, acute infection may be accompanied by fatigue, muscle or joint pain, fever, jaundice, rash and nausea in approximately 20% of people; hepatic failure is rare.[2]

Between 55-85% of those acutely infected with HCV fail to clear the virus and develop chronic HCV infection.[2, 16] The rate of spontaneous viral clearance in patients with chronic HCV infection is very low and those infected remain infectious as long as the virus is detectable in their blood. The progression of HCV-related disease is usually slow and unpredictable. Some patients may never develop serious liver problems. For others, chronic HCV infection leads to progressive fibrosis and cirrhosis of the liver. Given the asymptomatic nature of HCV infection, individuals who are chronically infected may only become aware of their infection status following the development of cirrhosis and its complications.[16] Hence, chronic HCV infection is sometimes called the "silent killer".[8] It is estimated that 20-30% of those chronically infected will develop cirrhosis over 20-40 years.[101]

The clinical course of HCV infection is summarised in Figure 3.1 and outlined in further detail below.

Figure 3.1. Clinical course of HCV infection



Key: BMI – body mass index; DCC – decompensated cirrhosis; HBV – hepatitis B virus; HCC – hepatocellular carcinoma; HCV – hepatitis C virus; HIV – human immunodeficiency virus; RNA – ribonucleic acid.
Source: National Hepatitis C Database 2015 report[28]

Fibrosis and cirrhosis

Hepatic fibrosis is the scarring process that occurs in response to liver injury. The accumulation of fibrosis interferes with the structure and regular function of the liver, and has major implications for the development of advanced liver diseases. The presence of liver fibrosis indicates the onset of progressive disease and ongoing damage over a prolonged period of time may eventually lead to cirrhosis and end-stage liver disease complications.[15] Patients with absent or mild fibrosis at diagnosis have a relatively low risk of developing cirrhosis over the next 20 years. However, it is noted that disease progression is faster for patients with septal fibrosis than portal fibrosis.[18, 102]

Cirrhosis results from chronic irreversible scarring of the liver. The risk of cirrhosis ranges from 5% to 20% after 20 years of chronic HCV infection, and 20% to 40% after 40 years of infection.[103] Decompensation is the progression of cirrhosis to the point where liver function is impaired and results in symptomatic complications such as hepatic insufficiency (jaundice or encephalopathy) and portal hypertension.[104-106] The latter can lead to ascites (an abnormal build-up of fluid in the abdomen) upper gastrointestinal bleeding, spontaneous bacterial peritonitis (inflammation of the abdominal wall lining), oesophageal varices, neurological complications (such as hepatic encephalopathy and hepatic coma) and hepatorenal syndrome leading to renal failure.[105, 106]

Cirrhosis may initially be compensated, but patients with chronic HCV infection can progress to hepatic decompensation, hepatocellular carcinoma (HCC) and liver failure.[16] Patients with compensated cirrhosis often remain asymptomatic, but may have evidence of portal hypertension (such as oesophageal or gastric varices). Cirrhosis can remain compensated for many years, with the annual transition to decompensation occurring at a rate of approximately 5% to 7%.[105, 106] Prognosis and survival are markedly different for patients with compensated and decompensated cirrhosis.[105, 107] The Child-Pugh classification system,[21] used to grade the severity of cirrhosis and predict the risk of mortality in cirrhotic patients, is presented in Appendix 4.

Hepatocellular carcinoma

Liver cirrhosis is the main determinant of HCC, as it rarely occurs in people with HCV infection that are not cirrhotic.[16] Pre-malignant processes take place over a period of 10-30 years, culminating in the development of HCC within five years of the onset of cell dysplasia.[108]

The cumulative five-year incidence of HCC among HCV-infected patients with cirrhosis is 10%, which corresponds to an annual incidence rate of 2.1%.[4, 109, 110] However, an annual incidence of 1-7% has been observed in patients with liver cirrhosis.[111, 112]

It is estimated that up to one third of people with cirrhosis may develop HCC over the course of their lifetime.[112] Prognosis for HCC is poor for patients with advanced disease at diagnosis due to limited treatment options.

Liver transplant

Patients with decompensated cirrhosis and HCC may undergo liver transplantation. The Irish National Liver Transplant programme began in 1993 in St. Vincent's University Hospital, the only hospital in Ireland that performs liver transplantation. Between 50 and 60 liver transplants are performed on average per annum with one-year and five-year patient survival rates of 93% and 79%, respectively.[113] A total of 116 liver transplants (18% of all liver transplants) were performed between 2005 and 2016 in people with a history of chronic HCV infection.[8, 114] A study of 4,000 transplant recipients in the US between 1981 and 1998, five-year survival was estimated at 68% among patients with decompensated cirrhosis (without HCC) secondary to chronic HCV infection.[115]

Extrahepatic manifestations

While HCV is primarily a hepatotropic virus, extrahepatic manifestations (co-morbidities directly attributable to HCV that manifest outside of the liver) may occur in patients with chronic HCV infection. Chronic HCV infection can be associated with systemic disease including cryoglobulinemia, porphyria cutanea tarda, arthralgia, membranoproliferative glomerulonephritis, Sjogren's syndrome, Raynaud's syndrome, idiopathic thrombocytopenic purpura, diabetes mellitus, chronic renal disease and non-Hodgkin's lymphoma.[2, 101, 116, 117] The prevalence of extrahepatic manifestations is generally independent of the degree of liver fibrosis.[2] Chronic HCV infection impairs patient reported outcomes (such as health-related quality of life) and work productivity in addition to clinical manifestations.[118-120]

3.2.2 Factors affecting disease progression

Liver damage and disease progression during HCV infection are driven by both viral and host factors.[32, 121] Progression is not necessarily a linear process and can be accelerated by a number of factors. These include: [29, 30, 101, 122] [29, 30, 101, 122] [29, 30, 101, 122] [29, 30, 101, 122] [29, 30, 101, 122] [29, 30, 101, 122] [29, 30, 101, 122] [29, 30, 101, 122] [29, 30, 101, 122] [6, 33-35] [6, 34-36] [6, 34-36]

- age at acquisition (older than 40 to 55 years)
- excessive alcohol consumption
- high body mass index (BMI), insulin resistance or the presence of hepatic steatosis (accumulation of fat in the liver)
- gender (being male)
- co-infection with other viruses (such as HBV and HIV) or other infectious agents

(such as schistosomiasis).[29, 30, 101, 122]

In particular, excessive alcohol consumption, HBV or HIV co-infection, and immunosuppression (due to any cause) are known to increase the risk of developing cirrhosis or HCC.[27, 123-125] HIV co-infection doubles the risk of vertical transmission of HCV,[126, 127] and is associated with higher viral loads and a lower rate of spontaneous clearance.[122, 128, 129] Approximately 1% of notified HCV cases in Ireland are co-infected with HBV.[130]

The National Hepatitis C Database,[28] was established in 2004 to collect data on people infected with HCV through the receipt of contaminated blood and blood products in Ireland. It provides evidence of the burden of liver disease associated with chronic HCV infection over several decades, including signs of liver disease (portal hypertension, varices, ascites, etc.), cirrhosis and HCC. Factors associated with having signs of liver disease by latest follow-up (2013) included:

- high alcohol intake (more than 40 units per week)
- duration of HCV-RNA positivity (longer than 20 years)
- being male
- age (older than 50 years) at follow-up
- having HCV genotype 3 (as opposed to genotype 1)
- the source of infection (blood transfusion and renal participants more likely than anti-D participants).[28]

In participants that were ever chronically infected with HCV, factors associated with a higher prevalence of cirrhosis included:

- high alcohol intake (five times more likely)
- age (50 years or older, twice as likely)
- duration of HCV-RNA positivity (more than 20 years, twice as likely)
- being male (almost twice as likely).[28]

Factors associated with the presence of HCC included:

- being male (four times more likely)
- having genotype 3 as opposed to genotype 1 (twice as likely).[28]

3.2.3 Staging

Techniques

Liver damage in patients with chronic HCV infection must be assessed to determine the severity of inflammation, risk of disease progression (prognostic) and the likely response to treatment (therapeutic). Liver biopsy, which involves the examination of

a liver tissue sample by a pathologist, is considered the gold standard for the direct histological evaluation of the severity of liver damage.[131-133] However, liver biopsy is an invasive method that has limitations, including sampling error or inter- and intra-observer variability, and low clinician and patient acceptance due to its associated morbidity and mortality.[133, 134]

An increasing number of non-invasive methods, including serum biomarkers (clotting factors, bilirubin, cholesterol, albumin and transaminases), genomics, ultrasound-based transient elastography, and magnetic resonance-based approaches are now available and widely used in clinical practice.[28, 133, 135] The purpose of these techniques is to measure the degree of inflammation (grade), extent of fibrosis (stage) and the general health of the liver.[136]

Non-invasive detection and assessment is advantageous as liver fibrosis can be monitored repeatedly and easily in the same patient.[133] All non-invasive imaging modalities are capable of distinguishing cirrhosis from less serious types of fibrosis, but performance is suboptimal when defining intermediate stages. In addition, performance of imaging-based technologies may be adversely affected by factors such as obesity, alanine aminotransferase flares, post-prandial testing or alcohol abuse.[35, 134]

Non-invasive techniques are recommended by the WHO and EASL for assessing liver disease severity prior to treatment initiation in individuals with chronic HCV infection.[2, 35] Liver biopsy may be reserved for cases of known or suspected mixed aetiologies (such as metabolic syndrome, alcoholism or autoimmunity).[35] In Ireland, the non-invasive Fibroscan® is now the preferred diagnostic tool for assessing the severity of liver disease.[8] Fibroscan® uses transient elastography (low-frequency sound waves similar to ultrasonography) to measure liver stiffness. Clinical evidence indicates that examination by Fibroscan® has excellent diagnostic accuracy for the diagnosis of cirrhosis, but is less reliable for distinguishing earlier levels of liver fibrosis (METAVIR F0 and F1).[137] Transient elastography is contraindicated in patients who are pregnant, have ascites or an implanted cardiac pacemaker.

A variety of histologic scoring systems[138-140] are available for assessing the degree of liver fibrosis and inflammation to inform the clinical management of patients. The METAVIR (Meta-analysis of Histological Data in Viral Hepatitis) scoring system is the most commonly used for interpretation of fibrosis. In clinical practice, values of liver stiffness are expressed in kilopascals (kPa), ranging from 2.5 to 75 kPa. These have been converted into corresponding degrees of the METAVIR scoring system using liver stiffness cut-off values,[35, 141-143] presented in Table 3.1. Identifying patients with advanced fibrosis (METAVIR score F3) or cirrhosis (METAVIR score F4) is particularly

important for the clinical management of patients with chronic HCV infection. Advanced fibrosis represents a definitive indication to schedule antiviral treatment.[18, 144] Cirrhosis necessitates specialist referral and treatment with antiviral therapy followed by ongoing monitoring for HCC and oesophageal varices.[18, 144] Patients with cirrhosis require continued post-treatment surveillance for HCC every six months.

Table 3.1. Interpretation of METAVIR scoring system for histologic stage of fibrosis and liver stiffness cut-off values

Score	METAVIR	Liver stiffness cut-off*	Interpretation
F0	No fibrosis	2.5-7 kPa	No or mild fibrosis
F1	Periportal fibrotic expansion		
F2	Periportal septae (>1 septum)	7.1-9.4 kPa	Moderate
F3	Portal-central septae (septal fibrosis)	9.5-14.4 kPa	Advanced fibrosis
F4	Cirrhosis	>14.5	Compensated cirrhosis

Key: kPa – kilopascal; METAVIR – Meta-analysis of Histological Data in Viral Hepatitis.
* Cut-off values are variable and may deviate slightly from those presented here.

3.3 HCV notifications in Ireland

3.3.1 HCV notifications in Ireland from 1989 to 2004

Testing for anti-HCV began in Ireland in 1989, with approximately 95% of confirmatory investigations performed by the National Virus Reference Laboratory (NVRL) over the following 15 years.[145] The NVRL's Laboratory Information Management System (LIMS) is specimen- rather than person-based. As many HCV-infected people have multiple investigations performed and given the absence of a unique health identifier in Ireland, it is not possible to count the number of unique individuals who tested HCV positive during this period using LIMS.[145] Between 1989 and 2004, 10,384 HCV cases were diagnosed (confirmed antibody positive and/or RNA positive) by the NVRL.[145] Of these, 6,637 cases (64%) were from the 1965 to 1985 birth cohort.[130]

3.3.2 HCV notifications in Ireland from 2004 to 2018

HCV has been a notifiable disease (to the Health Protection Surveillance Centre (HPSC)) in Ireland since 2004.[146] The case definition used for chronic HCV infection is the detection of HCV RNA or core antigen in serum or plasma in two samples taken at least 12 months apart.[147] Since 2012, cases known to be resolved at the time of

notification are excluded from notification.

All HCV cases not previously notified to the HPSC are notifiable. Therefore, cases first diagnosed before 2004 (but not notified) are notifiable when brought to the attention of the Department of Public Health.[130] This means that a proportion of cases notified each year may have been diagnosed a number of years prior to notification. In addition, as there is a requirement for all cases of HCV to be notified to the HPSC, cases reported may include those with known HCV who were previously diagnosed abroad. The date of original diagnosis is not routinely collected and cannot be accurately reported.[130]

Trends in HCV notification data are difficult to interpret as HCV infection is frequently asymptomatic or mildly symptomatic which means that newly diagnosed cases may have contracted HCV many years previously. Most diagnosed cases are identified as a result of risk-based testing rather than symptom presentation.[148] Therefore, notification patterns are heavily influenced by testing practices (illustrating trends in diagnoses) which may vary over time and not accurately reflect incidence.

Notifications are collated in the Computerised Infectious Disease Reporting (CIDR) System, a confidential name-based surveillance system for managing infectious disease notifications in Ireland. The notification data presented in this report were extracted from the CIDR System on May 28 2019 and July 22 2019. The data have been validated up to the end of 2018, but may differ from those previously published due to ongoing updating of notification data on the CIDR System.

3.3.3 Summary of HCV notifications from 2004 to 2018

From 2004 to 2018, a total of 15,266 HCV cases were notified to the HPSC. These figures include cases diagnosed before 2004, and may include some duplicate cases. Annual notifications of HCV peaked in 2007 (n=1,537), and have since declined by over 60% (n=589 in 2018). Given that a substantial number of prevalent cases were recorded (for the first time) in the initial years following HCV becoming notifiable in 2004,[8] the proportion of notifications that represent new cases of HCV infection is likely to be higher in more recent years. The number of HCV notifications in Ireland is presented in Table 3.2.

Table 3.2. Number of HCV notifications in Ireland by year of notification, from 2004-2018

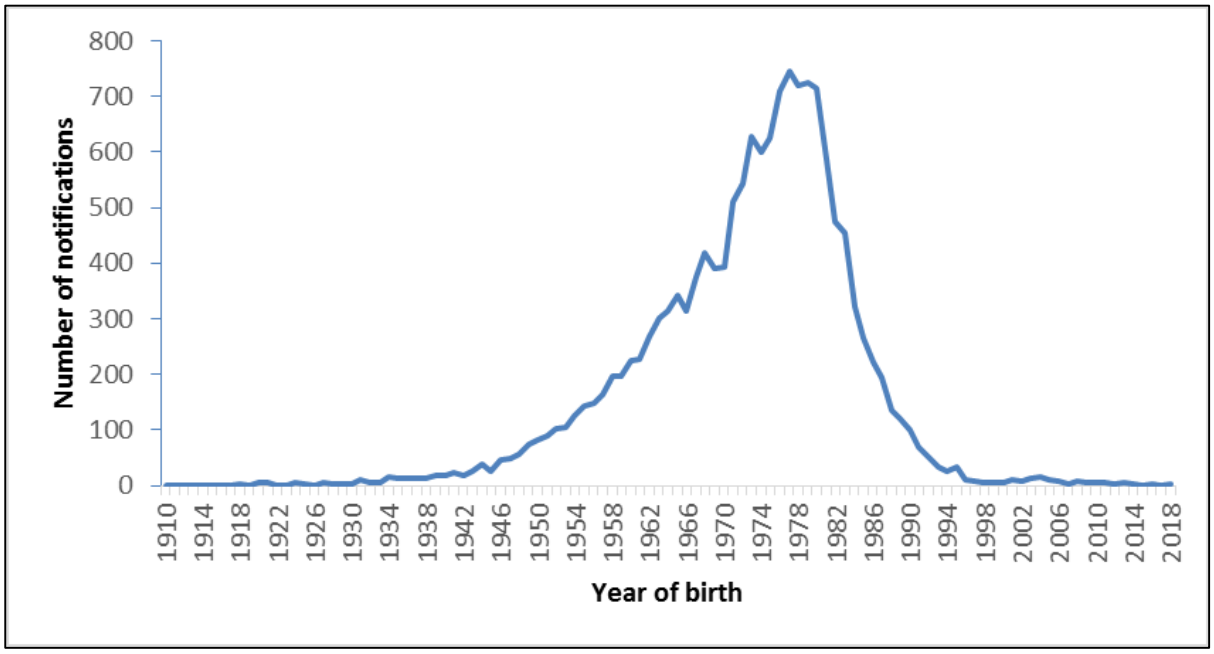
Year	All HCV notifications (n)	HCV notifications from 1965-1985 birth cohort (n)	% from birth cohort*
2004	1,119	810	72
2005	1,398	1,016	73
2006	1,208	878	73
2007	1,537	1,132	74
2008	1,503	1,126	75
2009	1,231	899	73
2010	1,214	898	74
2011	1,234	924	75
2012	874	595	68
2013	751	534	71
2014	690	462	67
2015	672	432	64
2016	639	403	63
2017	607	392	65
2018	589	361	61
Total	**15,266**	**10,862**	**71**

Source: Health Protection Surveillance Centre

* Figures are rounded to nearest whole number.

Of the 15,266 HCV notifications between 2004 and 2018, approximately 71% (n=10,862) were from the 1965-1985 birth cohort. Notifications peaked in 2007, including for the 1965-1985 birth cohort, declining since by 62% and 68%, respectively. Since 2013, the number of notifications from the birth cohort as a proportion of all HCV notifications has declined steadily. The trend in the proportion of all HCV notifications from the birth cohort over time is presented in Appendix 5. The number of HCV notifications is presented by year of birth in Figure 3.2.

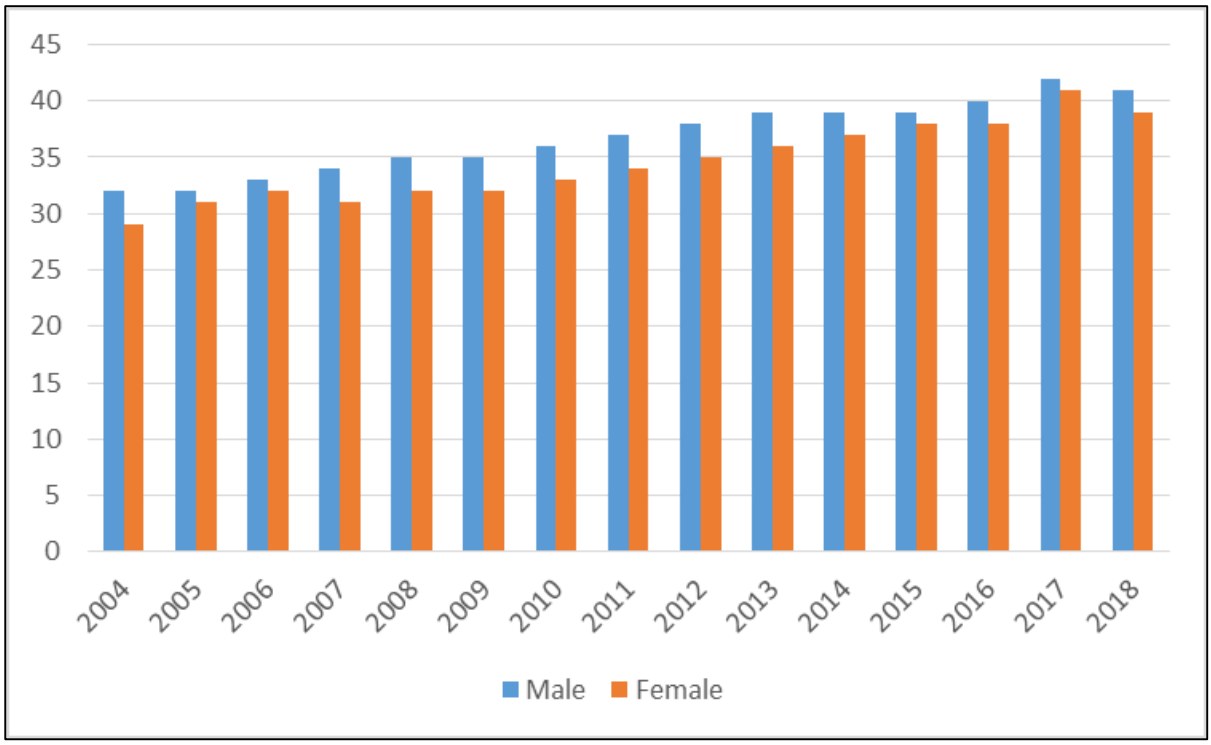
Figure 3.2. Birth year of HCV notifications in Ireland, from 2004 to 2018



Source: Health Protection Surveillance Centre

In 2018, the median age at notification among males and females was 41 and 39 years, respectively. There has been a gradual increase in the median age at notification over time. HCV notifications in Ireland from 2004 to 2018 by sex and median age at diagnosis are presented in Figure 3.3.

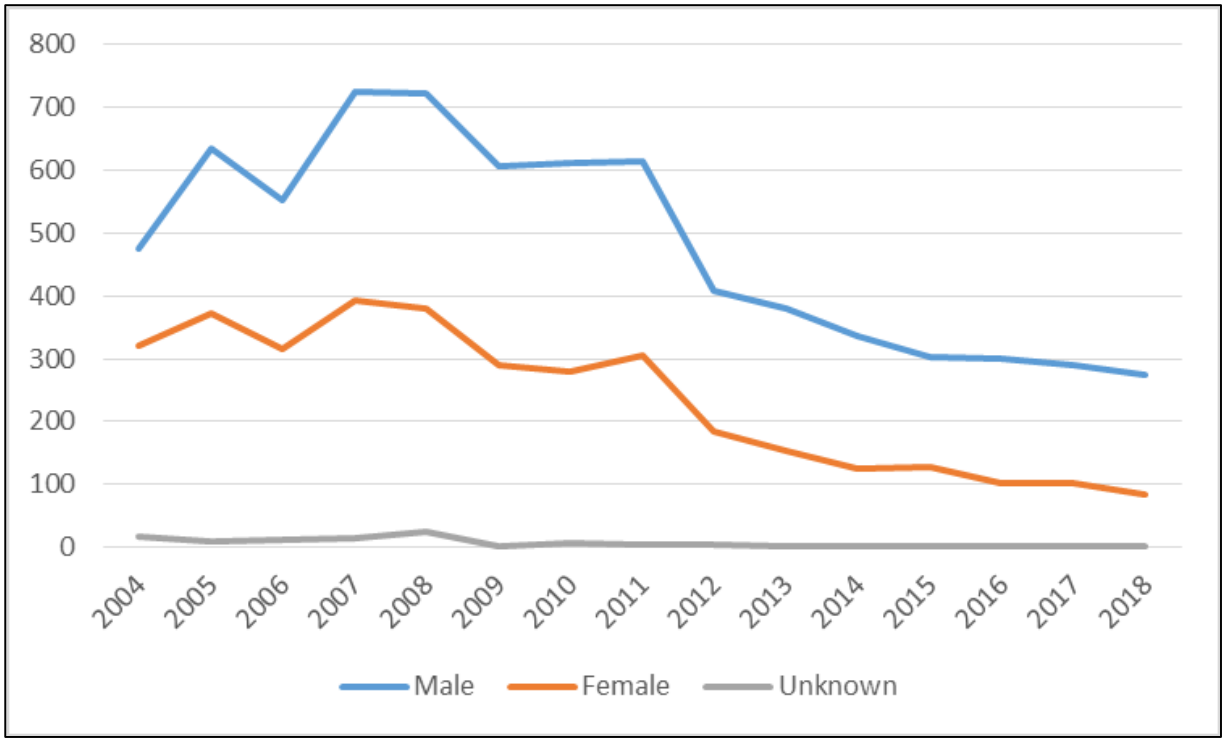
Figure 3.3. Median age of HCV notifications in Ireland by sex, from 2004 to 2018



Source: Health Protection Surveillance Centre

Of the 589 notifications in 2018, 419 (71%) were male and 168 (29%) were female. The sex was not reported in two cases (<1%). Overall, 66% of HCV notifications have been in males, with notifications in males exceeding notifications in females in each year, between 2004 and 2018. This trend is mirrored within the birth cohort, where 67% of notifications from 2004 to 2018 have been male. Since 2014, the proportion of cases that are male from the birth cohort has been above 69% each year (peaking at 76% in 2018). HCV notifications in Ireland from 2004 to 2018 by sex are presented in Figure 3.4.

Figure 3.4. Number of HCV notifications from the 1965-1985 birth cohort by sex, from 2004 to 2018



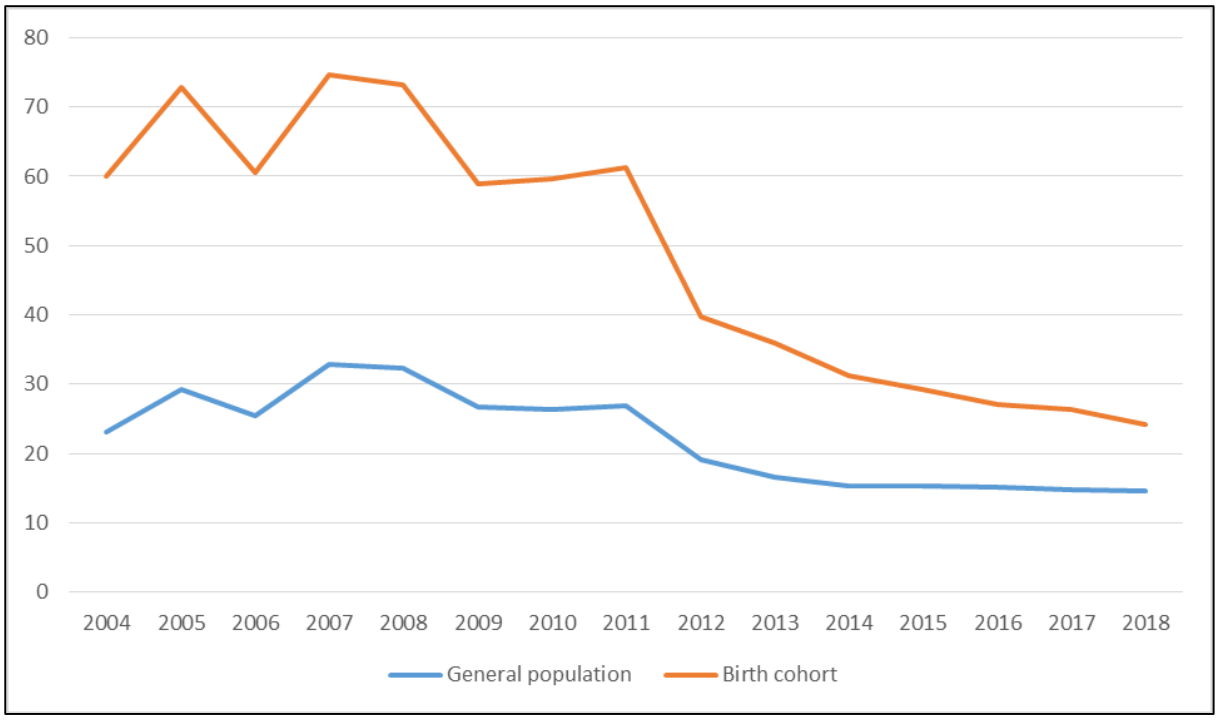
Source: Health Protection Surveillance Centre

3.3.4 HCV notification rates in Ireland from 2004 to 2018

Notification rates are expressed per 100,000 population and calculated using population data published by the Central Statistics Office (CSO).[149] The HCV notification rates in the Irish general population and 1965-1985 birth cohort are presented in Figure 3.5.

There were 589 HCV notifications in Ireland in 2018, giving rise to a notification rate of 14.6 per 100,000 population. From 2004 to 2011, the notification rate ranged from 23.0 to 32.8 per 100,000 population. Since 2012, the notification rate has decreased steadily from 19.2 per 100,000 population and appears to be stabilising at approximately 14.6 per 100,000 population. The lower notification rates reported from 2012 onwards coincide with the updated case definition outlined at the beginning of Section 3.2. It is also likely that the higher notification rates from 2004 to 2007 were a result of formal notification of known prevalent cases diagnosed prior to 2004.

Figure 3.5. Notification rates per 100,000 population in Ireland, from 2004 to 2018



Source: Health Protection Surveillance Centre

There were 361 HCV notifications from the 1965-1985 birth cohort in 2018, giving rise to a notification rate of 24.1 per 100,000 population. From 2004 to 2011, the notification rate for the birth cohort ranged from 58.9 to 74.6 per 100,000 population. Since 2012, the notification rate within the birth cohort has ranged from 24.1 to 39.8 per 100,000 population.

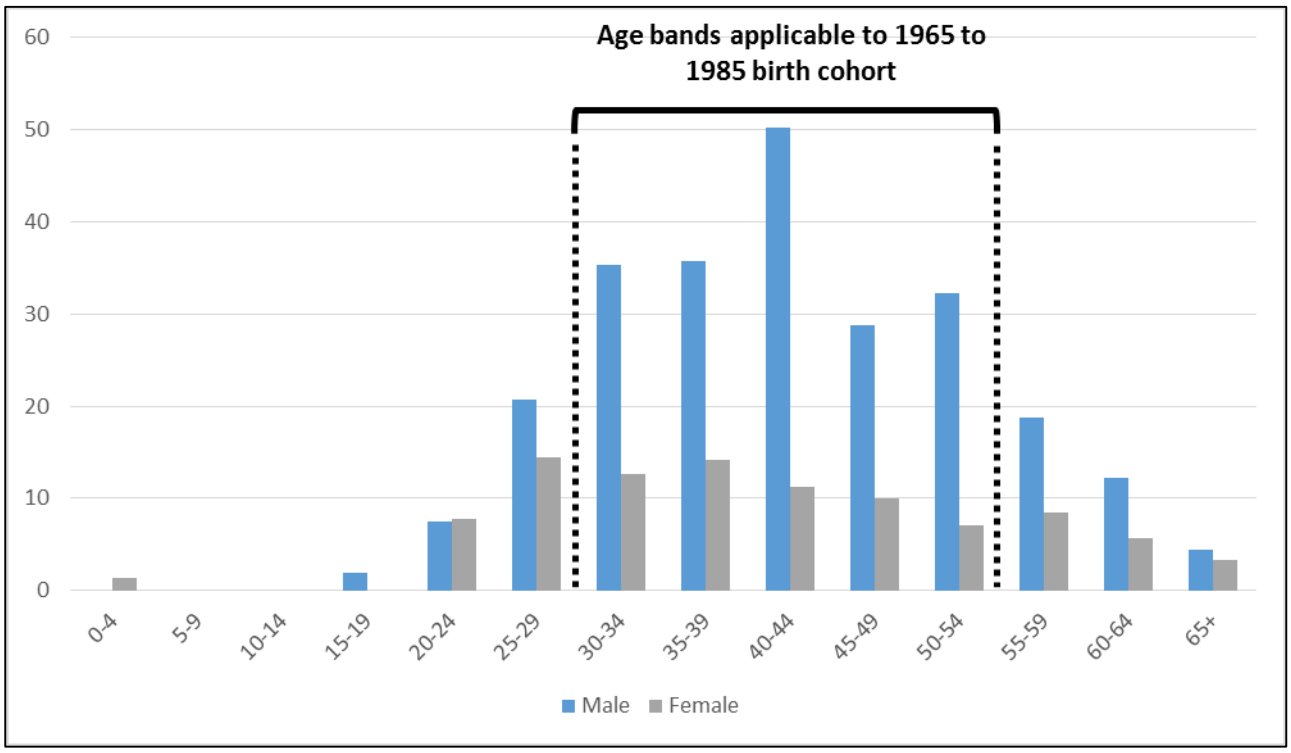
There appears to have been a more pronounced decline in the notification rate in the 1965-1985 birth cohort compared with the total population (15 per 100,000 population versus five per 100,000 population). A slower rate of decline in the notification rate is evident since 2012 and may be stabilising. This may also reflect the historical nature of the exposure to HCV within the birth cohort, and that the ongoing risk in the birth cohort is comparable to that of the general population.

In 2018, the highest notification rate (50.2 per 100,000 population) was for males aged between 40 and 44 years. This notification rate was four times that of females in this age band. For those aged 25 years or over, the notification rate was consistently higher in males than females in all age bands in 2018.

Within the five-year age groups from 35 to 54 years (applicable to the birth cohort), the notification rate in 2018 ranged from 28.8 to 50.2 per 100,000 population in males and from 7.1 to 14.1 per 100,000 population in females. This cohort comprised 55%

of all notifications in 2018. Age and sex-specific notification rates for 2018 are presented in Figure 3.6.

Figure 3.6. Age and sex-specific HCV notification rates per 100,000 population in Ireland, 2018



Source: Health Protection Surveillance Centre

3.4 Infection

3.4.1 Risk factors

HCV is acquired through exposure to blood or bodily fluids of other HCV-infected individuals. HCV infection may be transmitted via:[2, 126, 150-152]

- injecting drug use (sharing of needles and other drug paraphernalia)
- use of inadequately sterilised medical equipment during healthcare procedures such as renal dialysis or dental care
- unscreened blood transfusion
- sexual intercourse
- percutaneous procedures such as tattooing and body piercing
- needle stick injuries in healthcare workers
- vertical transmission (passed from mother to child).

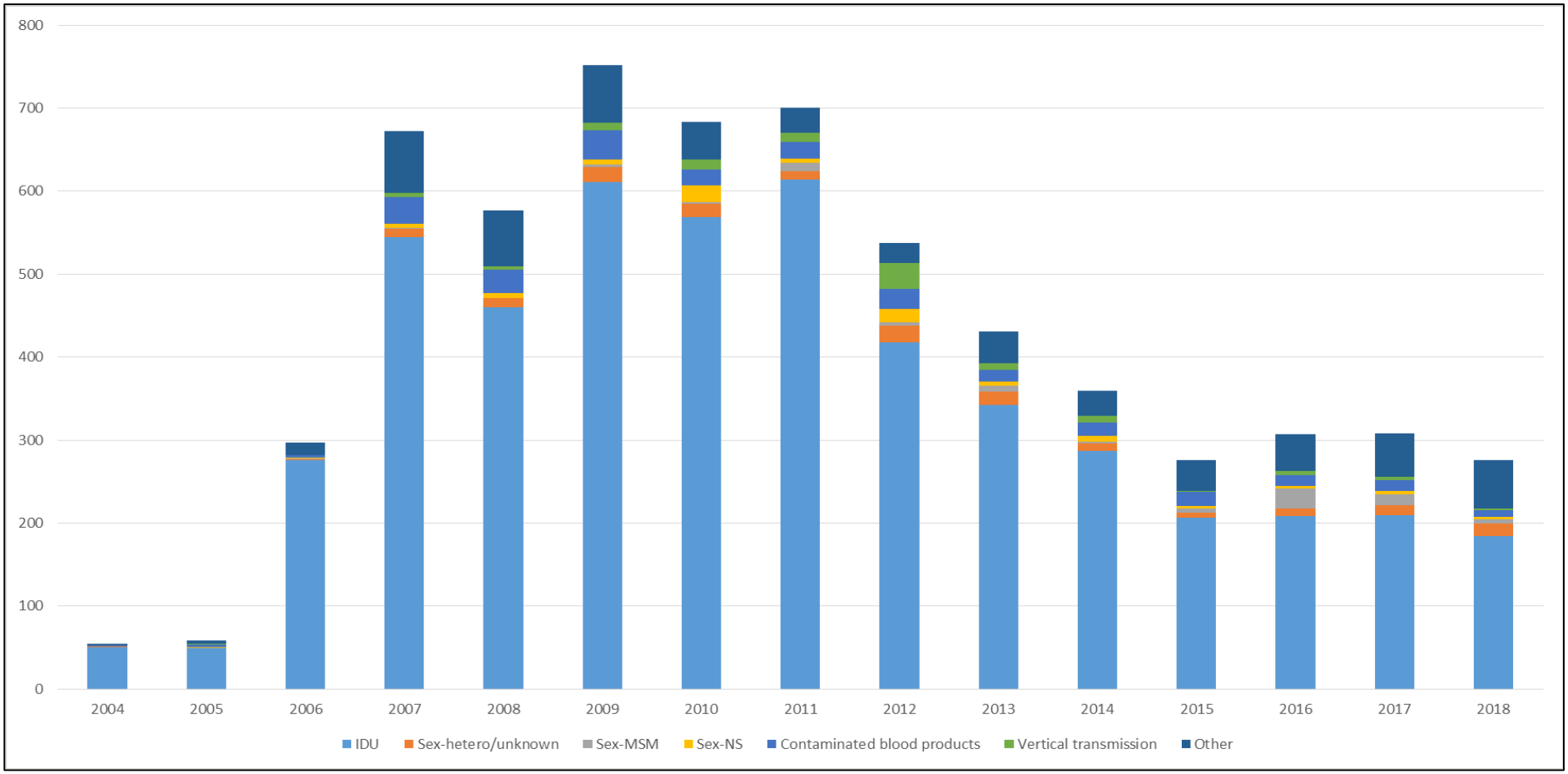
Risk factors vary globally, and no risk factor is reported in 40% of HCV cases in the Western world.[16] Healthcare associated transmission is most common in developing countries, while injecting drug use (IDU) is more common in developed countries.

Historically, the two principal modes of transmission have been blood transfusion and IDU, but since the introduction of routine blood testing in 1992, HCV infection is predominantly transmitted among people who inject drugs (PWID), accounting for 23% of new HCV infections worldwide.[3, 153] Transmission from mother to child is estimated to affect 4-8% of children born to women with HCV infection and 10-25% of children born to women with HCV/HIV co-infection.[126] Sexual transmission of HCV infection is not common among heterosexual couples, but the risk of transmission is elevated in individuals co-infected with HIV, particularly men who have sex with men (MSM).[154, 155] In Ireland, IDU is the most commonly reported likely cause of HCV infection.[9, 145]

Data on the most likely risk factor for HCV acquisition were available for 47% (n=276) of notified HCV cases in 2018. Just over two thirds (67%, n=184) of these were PWID. The proportion of cases attributed to PWID has decreased from 80% (n=342) in 2014. However, risk factor data were unavailable for over half of cases notified to the HPSC from 2014 to 2018. Increased incidence of injecting drug use in Ireland during the 1970s up to the 1990s most likely coincided with a rise in HCV acquisition. Carew et al.[9] estimated that the incidence of injecting drug use rose in the late 1980s and 1990s before peaking in 1998. The cumulative number of PWID up to the end of 2014 was estimated at 16,382, of whom 9,317 (95% CI: 8,022-9,996) developed chronic HCV infection.[9] The majority of these were young, male, lived in Dublin and injected heroin.

Nine per cent (n=24) of cases notified in 2018 were likely to have resulted from sexual transmission, including both heterosexual and men who have sex with men (MSM) populations. Figure 3.7 presents the number of notifications in Ireland by most likely risk factor from 2004 to 2018.

Figure 3.7. Number of HCV notifications in Ireland by most likely risk factor (where risk factor data available, 41%, n=6,290), from 2004 to 2018*



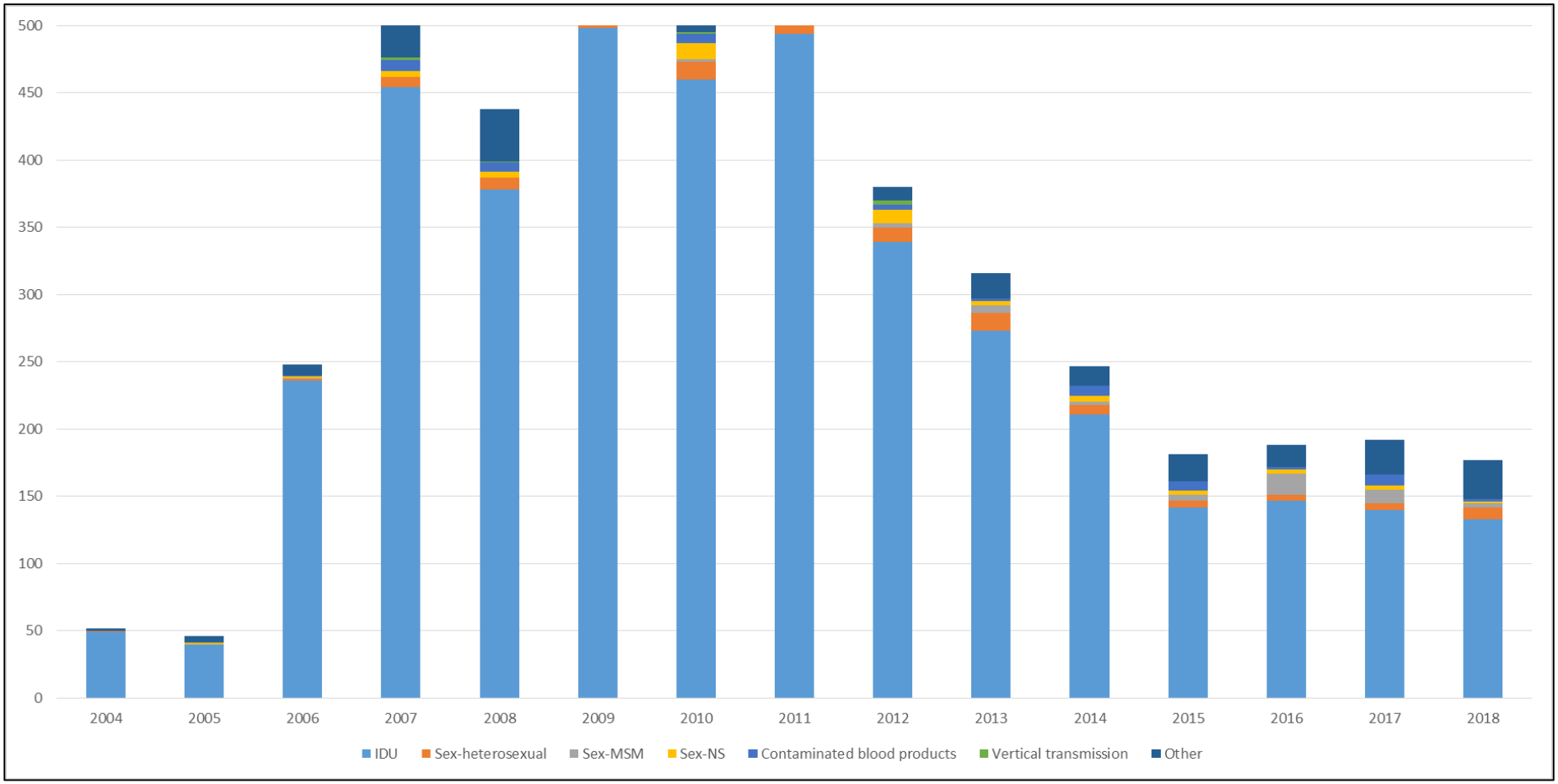
Key: IDU – injecting drug use; MSM – men who have sex with men; NS – not specified.

* Other includes surgical or dental exposure, (non-)occupational blood or needlestick exposure, tattoo, body piercing, non-IDU and cocaine drug use, renal dialysis and transplant.

Source: Health Protection Surveillance Centre

Data on the most likely risk factor for HCV acquisition were available for 49% (n=177) of cases from the birth cohort in 2018. Approximately three quarters (75%, n=133) of these were PWID. Since 2011, the proportion of cases attributed to IDU in the birth cohort has decreased from 91% (n=541) to 75% (n=133) in 2018. However, risk factor data were unavailable for just under half (46%) of cases notified to the HPSC from 2011 to 2018. In 2018, just under eight per cent (n=13) of cases were likely to have resulted from sexual transmission. Figure 3.8 presents the number of notifications in the 1965 to 1985 birth cohort by most likely risk factor from 2004 to 2018.

Figure 3.8. Number of HCV notifications in 1965-1985 birth cohort, by most likely risk factor (where risk factor data available, 43%, n=4,634), 2004 to 2018*



Key: IDU – injecting drug use; MSM – men who have sex with men.

*Other includes surgical or dental exposure, (non-)occupational blood or needlestick exposure, tattoo, body piercing, non-IDU and cocaine drug use, renal dialysis and transplant.

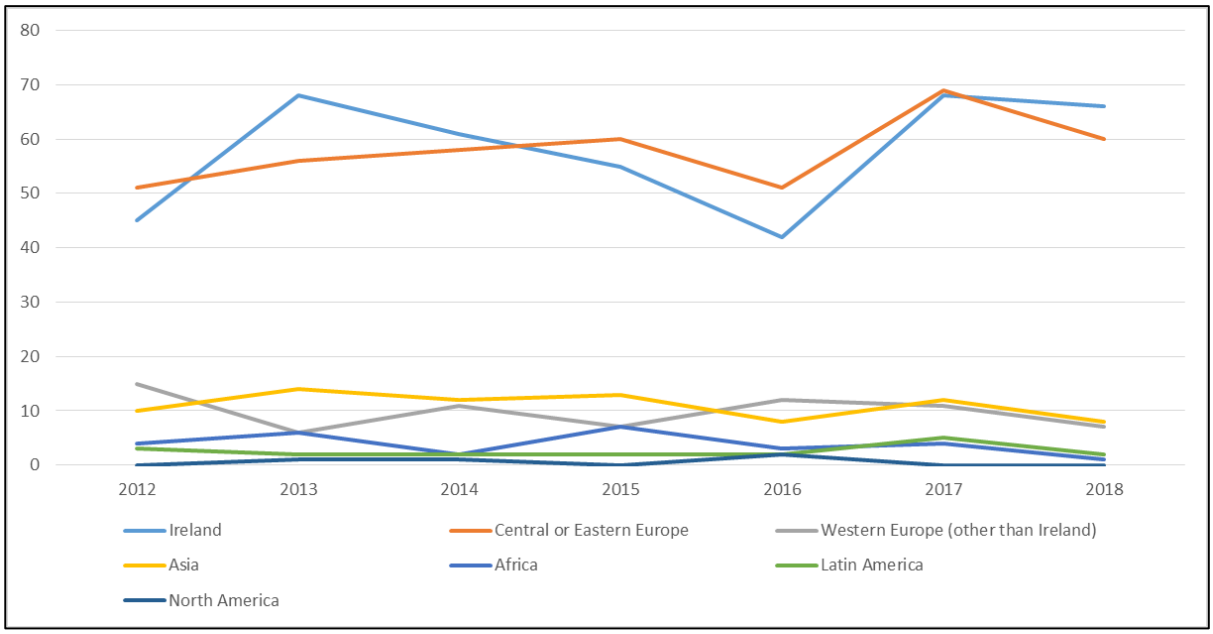
Source: Health Protection Surveillance Centre

3.4.2 Country/region of birth

Data on the region of birth were available for 40% (n=144) of HCV notifications received in 2018 from the 1965 to 1985 birth cohort. Of these, 46% (n=66) were born in Ireland, 42% (n=60) in central or Eastern Europe, 5% (n=8) in Asia, 5% (n=7) in Western European countries other than Ireland, and less than 3% (n=3) were born in Latin America or Africa.

The number of HCV notifications in the 1965 to 1985 birth cohort by region of birth and year of notification is presented in Figure 3.9. These data are incomplete and are not available for the majority of cases. However, reporting has improved; since 2012, data have been available for between 22% and 43% of HCV notifications per annum. Since 2012, the majority of birth cohort notifications have been from people born in Ireland (between 35% to 46%) and Central or Eastern Europe (between 37% to 43%) each year. The latter are overrepresented in the HCV notifications: according to the 2016 Census,[149] migrants from Central or Eastern European countries represent approximately 6% (n=81,296) of the 1965-1985 birth cohort. Of these, over half are from Poland, where the estimated anti-HCV prevalence in the general population is 0.9%.[156]

Figure 3.9. Number of HCV notifications in the 1965-1985 birth cohort by region of birth (where region of birth available, 18%, n=1,934) and year of notification, from 2012 to 2018



Source: Health Protection Surveillance Centre

3.4.3 HCV genotypes

The prevalence of HCV genotypes varies substantially across the globe. Nationally available genotype data indicate that genotypes 1 and 3 are dominant in Ireland, representing approximately 95% of HCV notifications per annum.

Of cases diagnosed by the NVRL between 1989 and 2004:

- 55% were genotype 1
- 39% were genotype 3
- 4% were genotype 2
- genotypes 4 and 5 and mixed genotypes accounted for approximately 1%.[8]

Genotype data for the period from 2005 to 2007 were unavailable at the time of writing. Genotyping results of cases diagnosed by the NVRL between 2008 and 2018 are presented in Table 3.3. The distribution is consistent with earlier data, where genotypes 1 and 3 have consistently accounted for approximately 95% of notified HCV cases in Ireland.

Table 3.3. Genotype distribution from cases diagnosed by the NVRL, 2008 to 2018*

	Genotype 1		Genotype 2		Genotype 3		Genotype 4		Other**	
Year	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
2008	326	52	16	3	264	42	16	3	2	0.32
2009	353	54	25	4	263	40	12	2	0	0.00
2010	412	53	18	2	331	43	13	2	3	0.39
2011	445	55	23	3	330	40	15	2	2	0.25
2012	401	55	14	2	289	40	14	2	9	1.24
2013	421	57	18	2	278	37	12	2	13	1.75
2014	424	57	20	3	264	36	20	3	13	1.75
2015	506	59	24	3	289	34	19	2	13	1.53
2016	557	63	20	2	285	32	14	2	10	1.13
2017	741	62	21	2	398	33	26	2	11	0.92
2018	742	64	29	3	356	31	20	2	6	0.52
Mean	**484**	**58**	**21**	**2**	**304**	**37**	**16**	**2**	**7**	**1**

Source: National Virus Reference Laboratory

* Figures represent approximations and may be subject to minor error.

** Other includes genotypes 5 and 6, mixed genotypes and unclassified samples.

3.5 Prevalence

The prevalence of HCV infection is challenging to accurately predict due to its initially asymptomatic nature. This means that people who have chronic HCV infection may have been infected many years prior to becoming symptomatic or may not become symptomatic at all.

3.5.1 Irish prevalence studies

Two studies have estimated the national prevalence of HCV infection in Ireland.[145, 157] The estimates from these studies will be used to inform the estimated prevalence of chronic HCV infection within the Irish birth cohort.

Thornton et al.

Thornton et al.[145] modelled the prevalence of HCV in Ireland by combining HCV-positive serological test data collected by the NVRL from 1989 to 2004 (10,384 cases with confirmed HCV infection) and HCV notification data from 2004 to 2009 (8,104 cases). These data were adjusted for HCV epidemiological information based on available literature. The following assumptions were made to adjust the data:

- the NVRL identified 95% of HCV diagnoses in Ireland from 1989 to 2004
- notification data from 2005 to 2009 were adjusted to account for previously diagnosed cases based on comparison of NVRL and CIDR data
- 75% of HCV infections convert to chronic infection
- 13% of people with notified chronic HCV infection had died
- 50-80% of HCV cases remained undiagnosed based on estimates from England and Scotland at the time of the analysis.

Based on the adjusted data, the number of people with chronic HCV infection in Ireland assuming levels of underdiagnosis ranging from 50-80% ranged from 19,826 (0.5% prevalence rate) to 49,565 (1.2%) by the end of 2009.

Garvey et al.

Garvey et al.[157] estimated the seroprevalence of the anti-HCV antibody and the prevalence of chronic HCV infection among the adult population (≥ 18 years) in Ireland. The cross-sectional study was based on a sample (n=3,795) of anonymised residual sera tested by the NVRL in 2016. The sampling frame included specimens from antenatal and pre-employment screening. Specimens from high-risk settings (for example, drug treatment centres and STI clinics) and populations (for example, asylum seekers) were excluded from the analysis. Overall, 33 samples were consistent with chronic HCV infection corresponding to a weighted prevalence of 0.57% (95% CI: 0.40-0.81%), presented in Table 3.4. Of the remaining specimens: 20 were

consistent with resolved HCV infection; one was from a patient with possible acute infection; 3,737 tested negative; and four were inconclusive.

There was evidence of variation in prevalence by both region and gender. Prevalence of chronic HCV infection was significantly higher in men (0.91%) than in women (0.24%). The highest prevalence was amongst men aged 40-49 years and 30-39 years from the East of Ireland, estimated at 5.2% (95% CI: 2.8-9.3%) and 3.5% (95% CI: 1.8-6.9%), respectively.[157]

Table 3.4. Estimated prevalence of HCV infection in Ireland

Group	Seroprevalence (chronic and resolved infections)		Prevalence (chronic infections only)	
	Weighted prevalence (%)	95% CI	Weighted prevalence (%)	95% CI
Female	0.42	0.25-0.71	0.24	0.12-0.49
Male	1.57	1.12-2.19	0.91	0.61-1.37
18-29 years	0.07	0.01-0.47	0	0-0
30-39 years	1.94	1.21-3.10	1.07	0.59-1.95
40-49 years	1.53	0.96-2.43	1.11	0.64-1.91
50-59 years	0.83	0.33-2.09	0.30	0.10-0.94
60-69 years	0.69	0.29-1.66	0.27	0.07-1.09
70+ years	0.50	0.16-1.57	0.50	0.16-1.57
All adults	0.98	0.73-1.31	0.57	0.40-0.81

Key: CI – confidence interval.
Source: Garvey et al.[157]

3.5.2 Estimating the prevalence of chronic HCV in Ireland

Overall, there were 15,266 HCV notifications to the HPSC between 2004 and 2018. Following the change in case definition in 2012, notifications after this point represent chronic HCV infections. From 2012 to 2018, there were 4,822 notifications of chronic HCV infections. Notifications prior to 2012 may comprise individuals that never developed chronic HCV infection. Of the 15,266 notifications, 10,444 were reported between 2004 and 2011. Assuming a conversion rate from acute to chronic infection of 70%,[2, 8, 145] the HCV cases notified between 2004 and 2011 represent approximately 7,300 chronic HCV infections. Therefore, approximately 12,100 chronic HCV infections have been notified in Ireland.

A total of 10,862 HCV infections from the 1965-1985 birth cohort were reported to the HPSC between 2004 and 2018. Of these, 7,683 were notified up to 2011. As noted, the case definition was updated in 2012 to reflect cases of chronic HCV infection only. Assuming a conversion rate of 70% from acute to chronic infection,[145] notifications up to 2011 represented approximately 5,400 chronic HCV infections. From 2012 to

2018, there were 3,179 infections from the birth cohort notified to the HPSC. Therefore, approximately 8,600 chronic HCV infections from the 1965-1985 birth cohort have been notified.

Due to procedures used by Garvey et al.[157] to anonymise individual-level data, an approximation method was required to estimate HCV prevalence by single year of age within the 1965-1985 birth cohort. This involved the use of a generalised additive model to approximate and aggregate the prevalence estimates by Garvey et al.[157] into five-year age bands applicable to the 1965-1985 birth cohort in 2015 (see technical explanation in Appendix 6). The prevalence of chronic HCV infection estimated by the generalised additive model was then extrapolated forward to estimate the prevalent number of cases of undiagnosed chronic HCV infection in the 1965-1985 birth cohort in 2021. This extrapolation included adjustment for the observed number of HCV cases notified between 2016 and 2018, the predicted number of cases notified between 2019-2020, the incidence of chronic HCV infection between 2016 and 2020 and mortality (all-cause and HCV-specific) for chronic HCV infection based on national and international data.[9, 149, 158]

The estimated prevalence of undiagnosed chronic HCV infection in the 1965-1985 birth cohort in 2021, based on the modelling exercise, is presented in Table 3.5.

Table 3.5. Estimated prevalence of undiagnosed chronic HCV in the birth cohort (in 2021)

Age group (years)	Mean (%)	LCI (%)	UCI (%)
36-40	0.27	0.10	0.53
41-45	0.73	0.26	1.45
46-50	1.14	0.51	2.01
51-56	1.00	0.46	1.74

Key: LCI – lower confidence interval; UCI – upper confidence interval.
Source: Results of generalised additive model fitted according to results presented by Garvey et al.[157] based on 2020 population estimates.[149]

3.6 Morbidity and Mortality

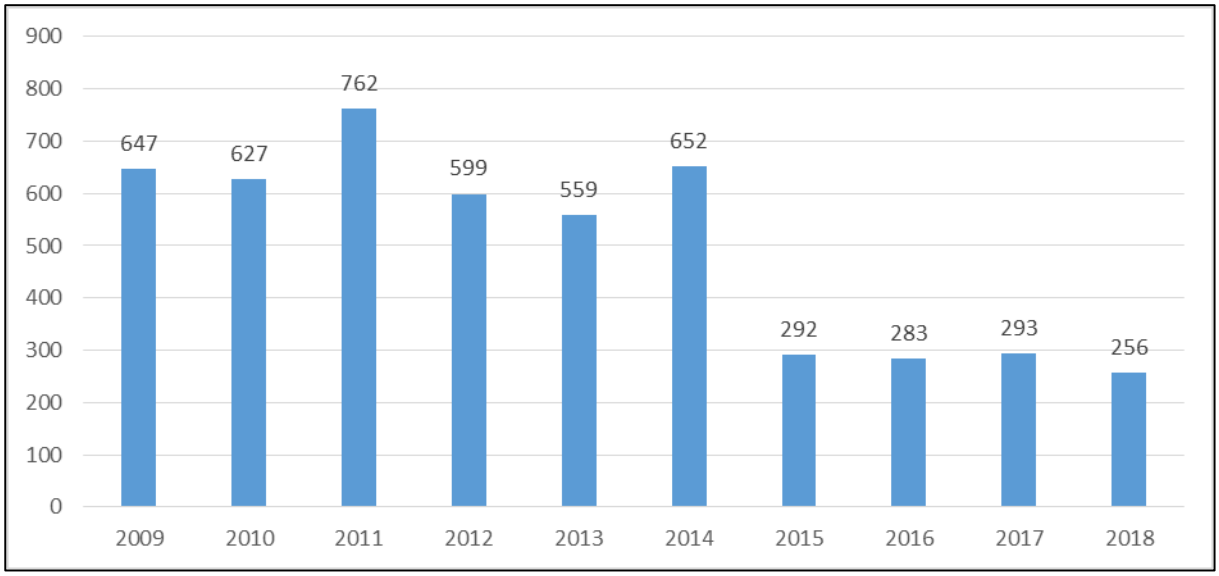
3.6.1 Outcomes data

Chronic HCV infection is a major cause of liver-related morbidity and mortality. This section aims to quantify morbidity and mortality outcomes for patients with chronic HCV infection in Ireland. The outcomes presented are based on data available from the Central Statistics Office (CSO), the Hospital In-Patient Enquiry (HIPE), the National Hepatitis C Treatment Registry (NHCTP), National Hepatitis C Database, National Cancer Registry Ireland (NCRI), and international studies. Statistics related to hospital discharge activity (HIPE) and underlying cause of death (CSO) are classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD) codes Version 10. ICD-10 codes applicable to chronic HCV infection are presented in Appendix 5.

3.6.2 Chronic HCV-associated morbidity

International studies have estimated that chronic HCV infection can reduce life expectancy by up to 12 years.[18, 159] Data from HIPE indicate that there were 4,970 admissions with a primary diagnosis of chronic HCV infection between 2009 and 2018 (Figure 3.10). Of these, 3.6% (n=178) were recorded as emergency admissions. The mean and median length of stay was one day for those discharged with a primary diagnosis of chronic HCV infection. The median age of admissions ranged from 39 to 46 years, consistently overlapping with the 1965-1985 birth cohort. These data may represent underestimates of the burden of HCV, as HCV-related fibrosis, liver cancer and cirrhosis may be coded to primary liver cancers, cirrhosis and fibrosis rather chronic HCV infection.

Figure 3.10. Admissions in Ireland with a primary diagnosis of chronic HCV infection from 2009 to 2018



Source: Hospital In-Patient Enquiry
* Admissions with a primary diagnosis of B182 (chronic viral hepatitis C)

Signs of liver disease and cirrhosis in Irish patients with chronic HCV infection

Of the National Hepatitis C Database participants that had a confirmatory HCV-RNA test (n=1,271), 64% (n=813) did not spontaneously clear the virus (as determined by testing negative at the time of first diagnosis) and became chronically infected. The median duration of HCV-RNA positivity was 31 years in those chronically infected. During this period, 29% (n=233) developed one or more clinical signs of advanced liver disease (varices, portal hypertension, ascites, etc.) and 22.3% (n=181) developed cirrhosis. Those that were chronically infected at the time of their latest RNA test (n=562) had a higher prevalence of cirrhosis (25.6%, n=144) than those with resolved HCV infection (14.7%, n=37). Only 0.4% (n=2) of those with acute HCV infection developed liver cirrhosis.

A total of 3,885 patients from the 1965-1985 birth cohort were registered with the NHCTP for HCV infection between 2012 and September 2019.[93] Staging following liver assessment was undertaken in 3,502 patients, 27% (n=1,004) of whom had compensated cirrhosis (the liver is scarred but can still perform basic functions at some level) upon registration with the NHCTP. However, those treated includes all patients (for example, people with other or ongoing risky health behaviours) identified to date and may not be representative of the undiagnosed birth cohort – an apparently healthy population with no identified ongoing risk of infection. Data from 2018 to 2019 may be more representative of the 1965-1985 birth cohort (Table 3.7) as data prior to this would contain a greater proportion of known prevalent cases and those that had clinically greater need were treated first. A total of 1,724 patients were registered with

the NHCTP between 2018 and September 2019.[93] Of the patients that were staged following liver assessment (n=1,700), 15% (n=252) had compensated cirrhosis upon registration with the NHCTP.

Table 3.7. Fibrosis distribution of the Irish birth cohort treated from 2018 to 2019, where known (n=1,700 (99%))

Age	Mild to moderate (METAVIR F0-F2) (%)	Advanced (METAVIR F3) (%)	Compensated (METAVIR F4) (%)
34-39	77	14	9
40-44	75	12	13
45-49	67	14	19
50-54	61	15	24
Overall	**72**	**13**	**15**

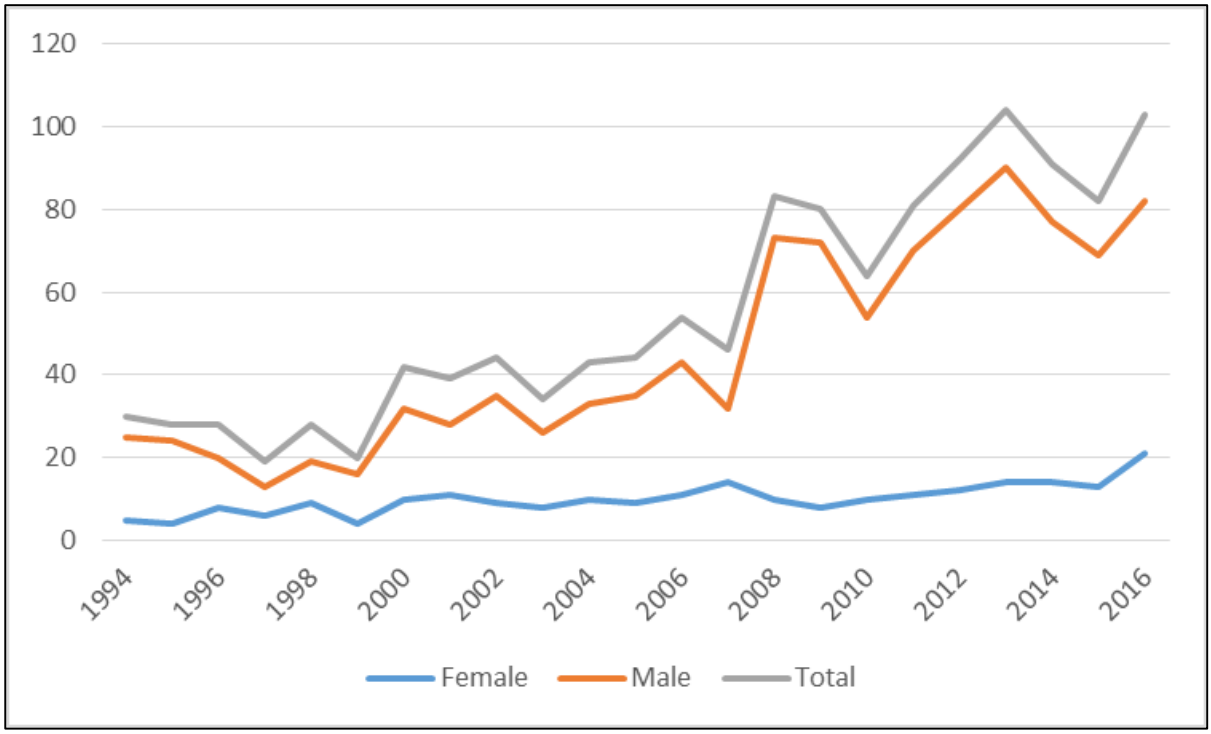
Key: METAVIR – Meta-analysis of Histological Data in Viral Hepatitis.
Source: National Hepatitis C Treatment Programme

Liver-related morbidity, risk of decompensation and risk of developing HCC are significantly reduced for HCV-infected individuals that achieve a sustained virological response (SVR) compared with those that do not.[27, 160] Overall, 90% of the patients treated from the Irish birth cohort have achieved an SVR since 2012.

Hepatocellular carcinoma

HCC is the most common histologic form of primary liver malignancy.[161, 162] Between 1994 and 2016, there were 3,568 new cases of liver cancer diagnosed in Ireland.[163] Of these, approximately 1,279 cases have received a subtype-specification of HCC. Since 1994, the annual number of HCC diagnoses has increased by over 300% (see Figure 3.11) and a significant proportion of cases with unspecified liver cancer may also have HCC. The growing number of HCC diagnoses may partly reflect the ageing Irish population, increased alcohol consumption and obesity.[164-167]

Figure 3.11. Incidence of HCC in Ireland by gender (where subtype data were available), 1994 to 2016*



Source: National Cancer Registry Ireland

* Many liver cancers are clinically diagnosed without subtype-specification. Over 30% of cases diagnosed between 2014 and 2016 were of unspecified subtype. It is likely that some of these unspecified cases represent incidence of HCC.

From a total of 268 new cases of primary liver cancer diagnosed in 2016, approximately 181 cases received a subtype specification. Of the subtyped cases, 103 received a specification of HCC, yielding an incidence rate of 2.17 HCC cases per 100,000 population (Table 3.8). The majority (82%, n=1,048) of new cases of HCC were in males. The male-to-female ratio was 3.9 in 2016 (down from 6.7 in 2012). In 2016, the median age at diagnosis of HCC was 72 and 70 years for males and females, respectively. The median age at diagnosis has been relatively unchanged in males since 1994 (range: 64-74.5 years), but has fluctuated in females (range: 54-77 years).

The proportion of patients that developed HCC as a result of chronic HCV infection is unclear. However, HBV and HCV infections have been implicated in more than 70% of HCC cases worldwide.[168] A European case-control study from 1992 to 2006 found that 20.9% of HCC cases were attributable to chronic HCV infection.[169] In the US, the population attributable factor for HCC is highest for metabolic disorders (32%), followed by HCV (20.5%), alcohol (13.4%), smoking (9%) and HBV (4.3%).[162] The risk of developing HCC was highest in those with HCV,[162, 170] and was twice as high among women than among men.[162]

Five per cent (n=44) of the chronically infected National Hepatitis C Database

participants developed HCC.[28] The median time from diagnosis of cirrhosis to HCC was three years. The median age and duration of HCV-RNA positivity at diagnosis of HCC was 62.5 years (mean: 61 years) and 29.5 years (mean: 27.7 years), respectively.

Table 3.8. Incidence of HCC in Ireland, 2004 to 2016*

	Males		Females		Overall	
	Cases (n)	**Rate per 100,000**	**Cases (n)**	**Rate per 100,000**	**Cases (n)**	**Rate per 100,000**
2004	33	1.64	10	0.49	43	1.06
2005	35	1.70	9	0.43	44	1.06
2006	43	2.03	11	0.52	54	1.28
2007	32	1.46	14	0.64	46	1.05
2008	73	3.26	10	0.45	83	1.85
2009	72	3.19	8	0.35	80	1.76
2010	54	2.39	10	0.44	64	1.41
2011	70	3.08	11	0.48	81	1.77
2012	80	3.52	12	0.52	92	2.00
2013	90	3.94	14	0.60	104	2.25
2014	77	3.35	14	0.60	91	1.96
2015	69	2.98	13	0.55	82	1.75
2016	82	3.49	21	0.88	103	2.17

Key: HCC – hepatocellular carcinoma.
Source: National Cancer Registry Ireland
* Many liver cancers are clinically diagnosed without subtype-specification. Only liver cancers with a HCC subtype-specification are presented.

The treatment of HCV-associated HCC does not differ from non-HCV-associated HCC.[17] However, treatment options are limited, particularly for patients with more advanced disease. Potentially curative therapies such as liver resection, liver transplantation or local ablative therapy are restricted to those with early-stage disease.[108]

Liver resection is the treatment of choice for non-cirrhotic patients, with an estimated five-year survival of 41% to 74%,[161, 171] but resection depends on several underlying factors such as tumour size, liver function and liver volume.[108, 161] Patients with significant portal hypertension may develop post-operative decompensation, with an estimated five-year survival of less than 50%.[161] Recurrence rates in patients resected to treat HCC are up to 70% after five years.[161]

Cirrhotic patients may be treated with laparoscopic surgery and liver transplantation. The Milan criteria[172] have been used to define patients with HCC that require liver transplantation. Four-year survival rates following liver transplant of 75% have been demonstrated.[161] However, liver cancer is often inoperable due to the size and

location of tumours that render surgery impractical and risky.

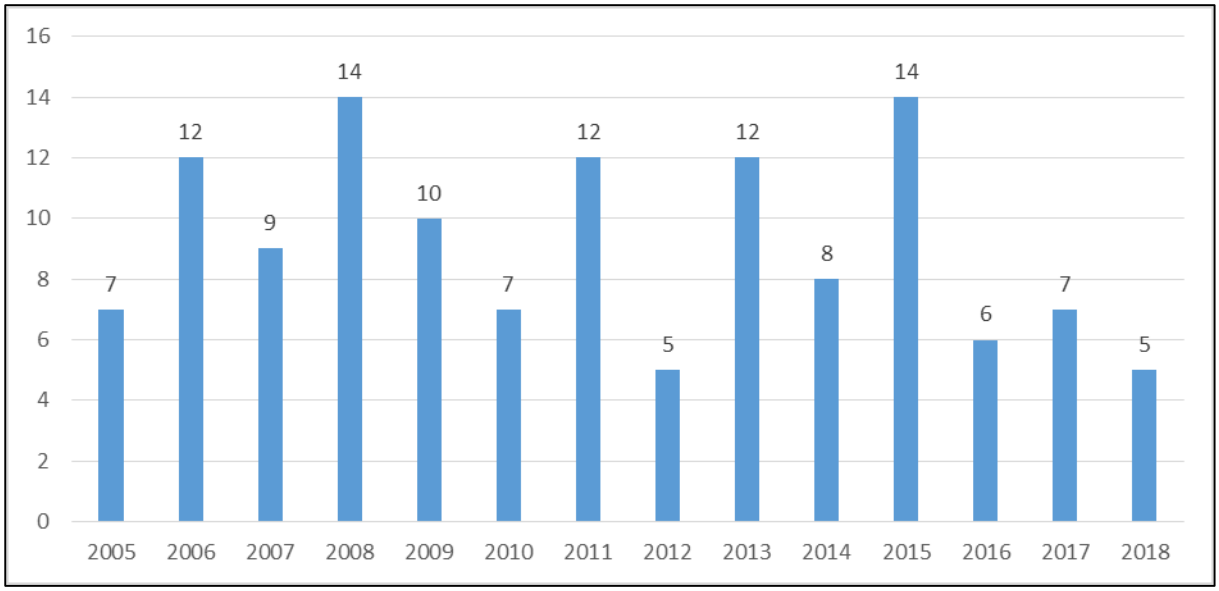
From 2009 to 2013, 31% of cases were diagnosed at stage four and it is likely that many unstaged patients were also diagnosed at a late stage of disease (see Appendix 5).[164] In 2015, 30% and 37% of patients received surgery and medical oncology (chemotherapy) for treatment of HCC, respectively (see Appendix 5).

Liver transplant

Liver transplantation, for which HCV is the main cause in developed countries,[18] is the only therapeutic option for end-stage liver disease.[173] Data from HIPE indicate that there were 128 liver transplants in Ireland as a result of HCV-related complications between 2005 and 2018 (Figure 3.12).[114] Of these, 37% (n=47) were recorded as emergency admissions. The mean and median length of stay was 28 and 19 days, respectively, for those discharged following liver transplantation as a result of HCV-related complications. The median age of admissions ranged from 49 to 62 years (55 to 69 years in 2018). The median age did not overlap with the age of the Irish birth cohort in any year.

By the end of 2013, 22 National Hepatitis C Database participants had received 25 liver transplants.[28] All transplant recipients were HCV-RNA positive at the time of transplantation. All those that were tested post-transplant (n=17) remained HCV RNA positive. The median age at transplantation was 53.5 years (range: 29-66 years) and the median duration of HCV infection at transplantation was 29 years (range: 1-39 years). In patients who remain chronically infected with HCV, by five years post-transplant, up to 30% will have developed cirrhosis of the transplanted organ. This contrasts with the average development time of 30 years for cirrhosis in chronic HCV patients that are not transplanted.[117]

Figure 3.12. Number of liver transplantations in Ireland attributable to chronic HCV infection, from 2005 to 2018



Source: Hospital In-Patient Enquiry

* Principal procedure of 9031700 (liver transplantation) with a secondary diagnosis of B182 (chronic viral hepatitis C)

3.6.3 Mortality

Chronic HCV infection

HCV-specific disease burden data in Europe are scarce.[173] In 2002, it was estimated that HCV caused more than 86,000 deaths in Europe, accounting for 35% of cirrhosis and 32% of all liver cancer deaths during that year.[173] In the US, all-cause mortality has been estimated to be 2.37 times higher in HCV-infected patients than HCV-negative patients, while liver-related mortality is 26.5 times higher.[158] Global variation in mortality rates due to cirrhosis has been linked to variation of major risk factors across different populations.[174]

There was a total of 176 HCV-related deaths recorded in Ireland in 2016.[149] Of these, 46 were aged between 30 and 54 years at the time of death yielding an overall death rate of 2.6 per 100,000 population (Table 3.9).[149] The rate of all-cause mortality in this cohort was 123.7 per 100,000 population. By the end of 2013, 260 participants in the National Hepatitis C database had died.[28] Death from liver disease occurred in 73 participants, 63 of whom were chronically infected. Among those that developed chronic HCV infection (n=813), 23% (n=185) had died compared with 8% (n=35) of those that never became chronically infected.

Table 3.9. Mortality rates in Ireland by age at death in 2016

Age group (years)	All-cause mortality rate per 100,000	HCV-related mortality rate per 100,000
30-34	60.2	0.6
35-39	57.0	2.5
40-44	106.0	2.2
45-49	162.7	2.9
50-54	257.9	5.2
Overall	**123.7**	**2.6**

* Cause of death recorded as B18 (chronic viral hepatitis), B19 (unspecified viral hepatitis), K72 (hepatic failure, not elsewhere specified), K73 (chronic hepatitis, not elsewhere classified), K74 (fibrosis and cirrhosis of liver), K76 (other diseases of liver) and R18 (ascites).
Source: Central Statistics Office

An SVR is associated with a significant reduction in all-cause mortality for patients with chronic HCV infection.[27, 117, 175] An observational cohort study conducted in Denmark between 2002 and 2013 found that achieving an SVR was associated with a reduced all-cause mortality rate of 0.68 (95% CI: 0.43-1.09) and liver-related mortality of 0.6 (95% CI: 0.36-1) in patients with chronic HCV infection.[27] The improvements in mortality may be partly attributed to resolution of extrahepatic manifestations, reduced incidence of lymphoma, and a reduced risk of type 2 diabetes and its associated complications.[117] Survival benefit is also more pronounced in cirrhotic and co-infected cohorts.[175]

The median survival for patients with compensated cirrhosis (mean age: 58 years) is approximately nine to 12 years with a five-year survival rate of 84%.[105, 109, 176] Once compensation has been established, the five-year cumulative probability of developing the first episode of decompensation (ascites, variceal bleeding or encephalopathy) is 28%, resulting in a 6.6% annual rate of decompensation.[109, 177] Survival rates decline rapidly with the onset of decompensation.[101] Five-year survival of patients with decompensated cirrhosis has been estimated at 47%.[109, 177]

Liver cancer and hepatocellular carcinoma

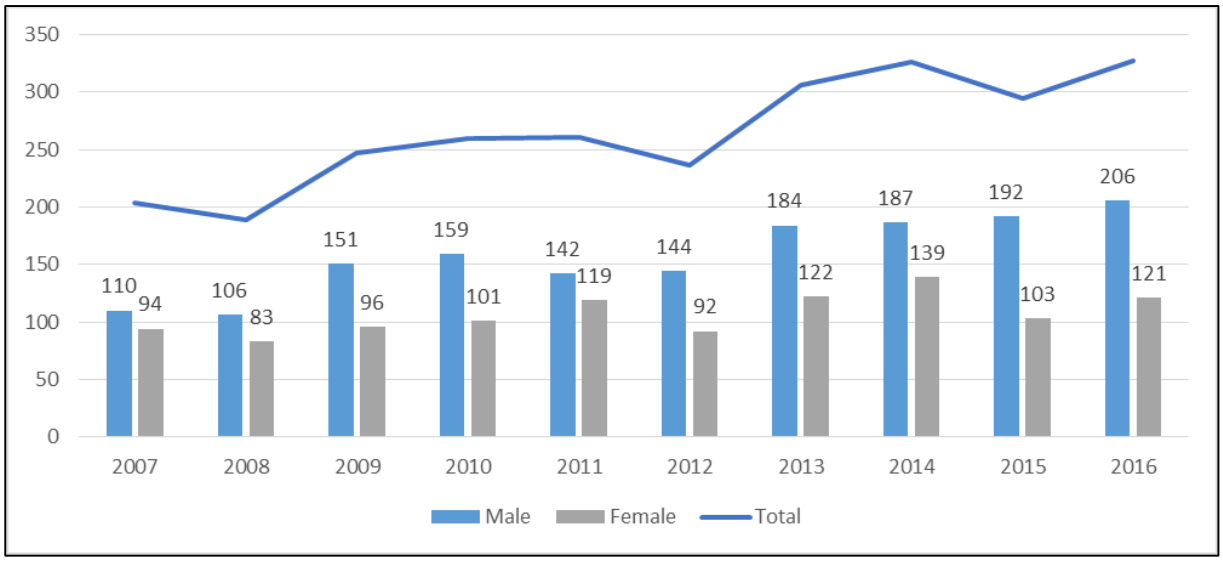
The number of deaths from liver cancers in Ireland has been increasing over time (Figure 3.13).[149] These figures include all deaths from primary liver cancer, but a significant proportion may be attributable to HCC. Since 2007, the number of deaths from liver cancer has consistently been higher in males than females. Data for 2016 indicate that, in males, liver cancer mortality was highest in those aged 70 to 74 years (n=42) while in females, it was highest in those aged 85 years and over (n=36).

Since 1990, male and female mortality rates from liver cancer have increased by an annual average of 8.9% (95% CI: 7.5-10.2%) and 10.7% (7.4-14.1%),

respectively.[164] The number of female deaths have exceeded the number of new cases of liver cancer recorded almost every year since 1994.[164] Between 2010 and 2014 in Ireland, mortality-to-incidence ratios of liver cancer averaged 1.3 in females and 0.9 in males.[164]

Prognosis for HCC is poor; three year survival without liver transplantation is estimated at 6.7%.[177, 178] However, fatality rates vary widely by country and gender.[111] From 2000 to 2004, Ireland had the lowest male and female age-standardised mortality rates for HCC in Europe at 0.78 and 0.3 per 100,000 population, respectively.[179] Of the 44 chronically infected National Hepatitis C Database participants that developed HCC, 63% (n=28) had died from liver-related causes by 2013.[28] Ireland ranked fourth best for liver cancer survival across Europe between 2000 and 2007.[164]

Figure 3.13. Total deaths from liver cancer in Ireland by gender, from 2007 to 2018



* Cause of death recorded as C22 (Malignant neoplasm of liver and intrahepatic bile ducts).
Source: Central Statistics Office

A total of 1,279 new cases of HCC were diagnosed from 1994 to 2016. The most recent (2011-2015) five-year net survival was estimated at 32.9% (Table 3.10).[164] From 1994 to 1999, survival for patients diagnosed with HCC was similar to that of all patients diagnosed with primary liver cancer (see Appendix 5). However, the improvement in survival in recent years has been much more marked for patients with a diagnosis of HCC relative to all patients with primary liver cancer. This relative improvement may be due to disproportionately fewer patients with HCC being diagnosed at advanced stages and therefore not receiving a full diagnostic work-up (that is, subtyping) and or advances in treatment being applied to patients with a more specific diagnosis.

Table 3.10. Five-year net survival (age-standardised) for HCC in Ireland

Time period	Net survival (%)	95% CI
1994-1999	4.9	2.1-11.2
2000-2005	18.1	13.4-24.4
2006-2010	17.7	13.8-22.7
2011-2015	32.9	27.3-39.7

Key: CI – confidence interval.
Source: National Cancer Registry Ireland

Liver transplant

Eleven of the 22 liver transplant patients from the National Hepatitis C Database have died since transplantation.[28] Five died from liver-related causes, five died from non-liver-related causes and no death certificate was available for the remaining patient. The median time between transplant and death for these patients was 29 months.

3.7 Discussion

The HCV-associated burden of disease is substantial. Worldwide, it is estimated that 71 million people are living with chronic HCV infection, many of whom are unaware of their infection.[1] It was estimated that 399,000 deaths occurred in 2016 as a result of HCV-related diseases, such as cirrhosis of the liver and HCC.[1] To estimate the burden of HCV-associated disease in Ireland, population-based data of HCV notifications and HCV prevalence were retrieved, including epidemiological data specific to the 1965 to 1985 birth cohort. However, limitations apply to the interpretation of these data.

Firstly, HCV infection is frequently asymptomatic which means that newly diagnosed cases may have been contracted many years previously. Therefore, notification data are heavily influenced by testing practices rather than reflecting incidence of disease. Secondly, a proportion of cases notified each year may have been diagnosed a number of years prior to notification, since HCV only became notifiable in 2004, and may include cases that were previously diagnosed abroad.[130] Thirdly, not all cases notified to the HPSC represent chronic HCV infections since resolved infections were notifiable up until 2012.[146, 147] Finally, identification of HCV cases from the birth cohort to date have been predominantly risk-based and may not be representative of the lower risk 1965 to 1985 birth cohort.

Ireland ranks at the lower end of the spectrum internationally, in terms of HCV prevalence,[180] despite high-profile outbreaks of HCV infection through receipt of contaminated blood products that were distributed during the 1970s and 1990s. The estimated prevalence of HCV infection in the 1965 to 1985 birth cohort is based on a study of residual sera specimens tested by the NVRL in 2016.[157] The estimates generated by the study may not be appropriately representative of the 1965 to 1985 birth cohort, given the small number of specimens, across the entire sample, that were consistent with chronic infection (n=33). In addition, the study may be overly representative of the East of Ireland, despite efforts to minimise bias. It is difficult to estimate the proportion of undiagnosed cases of HCV infection due to the asymptomatic nature of disease. However, comparable rates of underdiagnosis of between 40% and 60% have been previously cited.[145]

HCV-related morbidity and mortality data are limited in Ireland. Data from the NCRI demonstrates that the incidence of primary liver cancers (such as HCC) have increased in Ireland over the last two decades. However, the number of liver cancers attributable to HCV-infection is unclear. International studies have estimated the population-attributable fraction of HCV-associated HCCs at approximately 20%.[162, 169] The burden of HCV-associated liver cancers may also be underestimated, since not all HCC cases receive liver cancer subtyping. Finally, chronic HCV infection is rarely recorded as the primary cause of death.

4 Clinical effectiveness of testing and treatment

Key points

- The sensitivity and specificity of laboratory-based serological tests for detection of anti-HCV antibodies (in serum or plasma samples), compatible with a diagnosis of current or past HCV infection, is estimated at over 99% and over 96%, respectively.
- Diagnosis of chronic HCV infection is based on detection of HCV-ribonucleic acid (RNA) or HCV core antigen. The limit of detection (sensitivity) of quantitative nucleic acid amplification tests (NAAT) for HCV-RNA in serum or plasma ranges from 3.9 to 30 international units per millilitre, with a specificity of over 99%. Compared with NAAT, HCV core antigen tests have a sensitivity of 93% and a specificity of 99% in serum or plasma.
- A systematic review and meta-analysis of the diagnostic accuracy of HCV tests in dried blood spots (DBS) was undertaken given that the use of DBS may facilitate a reflex testing strategy. From 20 studies comparing the diagnostic accuracy of HCV-RNA tests in DBS with that in serum or plasma, the sensitivity and specificity were estimated at 95% (95% CI: 92% to 97%) and 98% (95% CI: 98% to 99%), respectively.
- Three first-line direct-acting antiviral (DAA) therapies are available under a reimbursable list of preferred regimens recommended by the HSE National Hepatitis C Treatment Programme. The regimens are prescribed according to HCV genotype, prior treatment status and the presence or absence of cirrhosis.
- Virological cure of HCV is defined using a surrogate outcome, sustained virological response (SVR), and considered an acceptable proxy of cure.
- Interferon-free DAA therapies are highly effective; across all HCV genotypes over 95% of patients achieve a sustained virological response (SVR).
- DAAs have a positive safety profile with very low (<5%) incidence of adverse events, serious adverse events, discontinuations due to adverse events and mortality.
- A cross-sectional study from the US reported no significant differences, in terms of sustained virological (SVR) response, between patients identified by birth cohort and risk-based testing.

4.1 Introduction

The aim of this chapter is to provide an overview of the clinical pathway applicable to birth cohort testing for chronic HCV infection in Ireland. The clinical effectiveness of the diagnosis and management of HCV is described in terms of the:

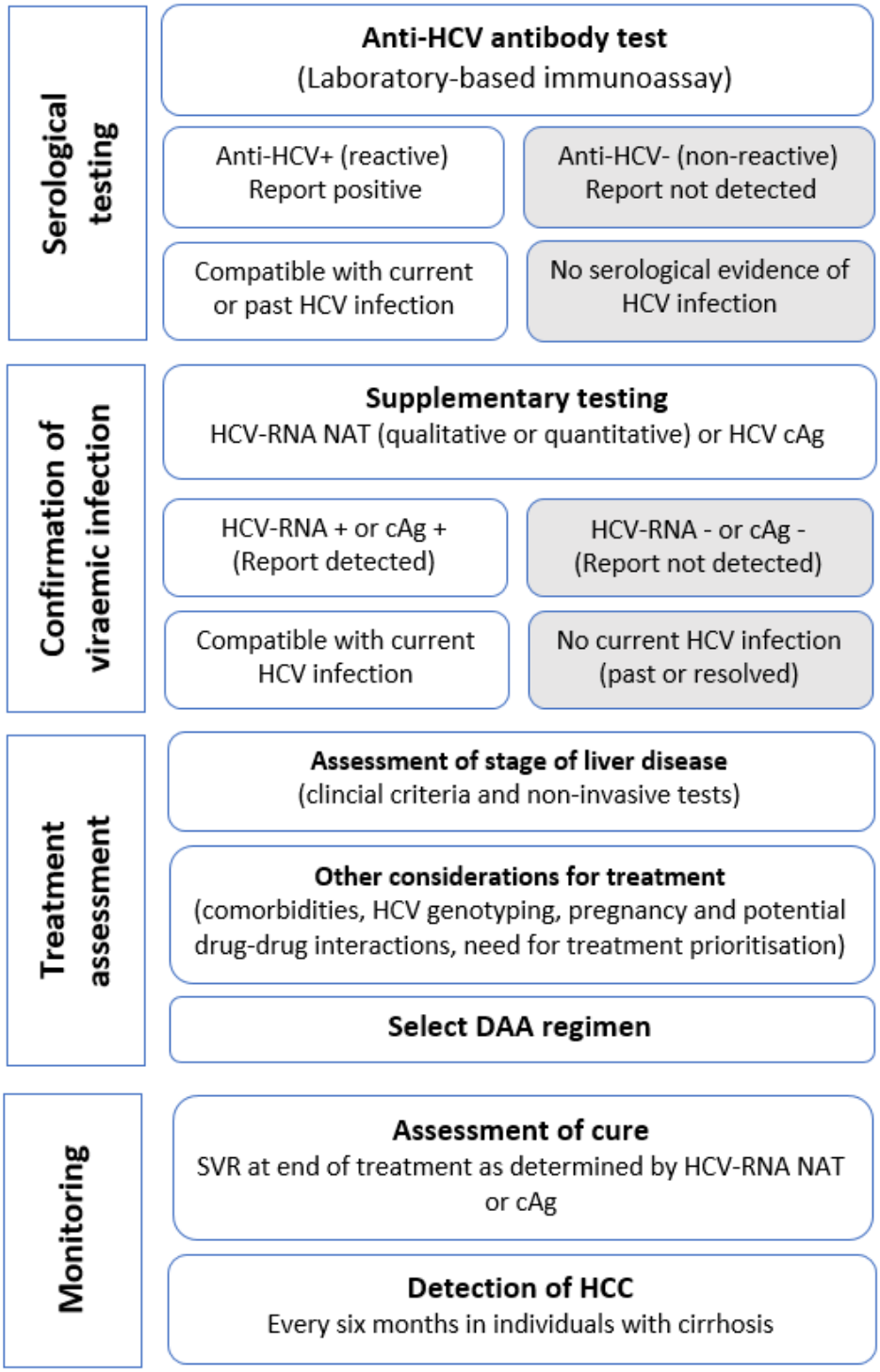
- sensitivity and specificity of tests for diagnosing chronic HCV infection
- harms and benefits associated with alternative testing pathways applicable to birth cohort testing for HCV infection
- effectiveness and safety of available treatments
- outcomes for patients with chronic HCV infection identified via birth cohort testing.

Systematic reviews of diagnostic testing accuracy (for the routine practice of HCV testing in serum or plasma) and treatment effectiveness were not undertaken given that:

- clinical evidence of testing for HCV, relative to no testing or usual care, is likely to be strongly contingent upon the testing and treatment strategies used in addition to factors that impact country-specific burden of disease
- the testing strategy described in Chapter 2 is considered the gold standard approach to laboratory-based testing for HCV
- the treatment of chronic HCV infection in Ireland is defined by an algorithm, underpinned by international evidence, which will not alter as a result of the outcome of this HTA.

An overview of the clinical pathway is presented in Figure 4.1.

Figure 4.1. Overview of clinical pathway for detection and treatment of chronic HCV infection*



Source: Adapted from WHO guidelines for the screening and treatment of chronic HCV infection[2, 61]
Key: cAg – core antigen; DAA – direct-acting antiviral; HCC – hepatocellular carcinoma; HCV – hepatitis C virus; NAT – nucleic acid test; RNA – ribonucleic acid; SVR – sustained virological response.
* No major adverse events have been recorded in pregnant patients exposed to DAAs, but common practice is stop treatment and re-commence treatment following delivery.[181]

4.2 Laboratory testing

4.2.1 Detection of HCV infection

As illustrated in Figure 4.1, laboratory detection of chronic HCV infection comprises an initial serological test for anti-HCV antibodies followed by confirmation of active infection in those that test antibody positive. The latter comprises either a nucleic acid amplification test (NAAT) to detect HCV ribonucleic acid (RNA) or a core antigen test, to detect the HCV core antigen (a marker of HCV replication).

Anti-HCV antibodies are detectable in serum or plasma in the majority of patients ever infected with HCV (see Section 2.5). While levels may decline following spontaneous or treatment-induced viral clearance, anti-HCV antibodies typically remain serologically detectable as evidence of current or past HCV infection. Seroreversion, while uncommon, has been reported.(182)

Anti-HCV antibody results may be negative in individuals with early acute HCV infection (initial six month period following exposure) and in those that are profoundly immunosuppressed. In the context of the proposed birth cohort testing, it is assumed that a decision to proceed with testing and the interpretation of the tests would consider the patient's individual context – including recent or ongoing risk-based behaviour, comorbid conditions, and the potential for immunosuppression which may confound a diagnosis. It is assumed that those identified to have recent or ongoing risky behaviour will be managed through existing risk-based testing protocols to ensure early acute HCV infection is not missed. Exposure to and acquisition of HCV many years ago is assumed for the remainder of the birth cohort.

Active HCV infection can be confirmed by a nucleic acid amplification technology (NAAT) test, which detects HCV-RNA, or a core antigen test, which detects the HCV core antigen (a marker of HCV replication), in serum or plasma. In patients with acute hepatitis C infection the HCV core antigen becomes detectable in serum or plasma a few days after HCV-RNA.(35) In rare cases, the HCV core antigen becomes undetectable in the presence of HCV-RNA.(183)

NAAT test results are reported in terms of International Units per millilitre (IU/ml). According to guidance from the European Medicines Agency (EMA), HCV-RNA levels must be determined with a standardised CE-marked[1] quantitative assay based on polymerase chain reaction (PCR) technology with a lower limit of detection in the order of 10-15 IU/ml.(88) Viral loads are interpreted as high (more than 800,000 IU/ml) or

[1] CE marking indicates conformity with health, safety and environmental protection standards for products traded in the European Economic Area. A range of laboratory-based tests which have received CE-marking in Europe for diagnosis of chronic HCV infection are presented in Appendix 7.

low (less than 800,000 IU/ml). The majority of patients with chronic HCV infection have a HCV-RNA level above 50,000 IU/ml.[184] Some studies of patients with chronic HCV infection have reported HCV-RNA levels of greater than 10,000 IU/ml in more than 95% of cases.[185, 186] In a retrospective analysis of 2,472 patients chronically infected with HCV genotype 1, only four had a HCV-RNA level below 1,000 IU/ml.[35, 187] In a Swiss cohort study (patients enrolled between 2000 and 2017) of chronically infected treatment-naïve patients that underwent quantitative HCV-RNA testing, only 3.5% (88 of 2,533) had a viral load ≤1,000 IU/ml prior to treatment-initiation.[188, 189]

4.2.2 Diagnostic accuracy of laboratory-based tests for diagnosis of chronic HCV infection in serum and plasma

As described in Chapter 2.7.3, diagnostic accuracy reflects the performance characteristics of the diagnostic test used and describes how well the diagnostic test discriminates between those who do and do not have the target condition. To determine the diagnostic accuracy of an index test, its performance must be compared with that of a 'gold standard' or 'reference standard' diagnostic test (that is, the best available method for determining the presence of disease). Sensitivity and specificity are common measures used to evaluate the performance of a diagnostic test. An overview of these measures of diagnostic accuracy is provided in Box 4.1.

Box 4.1. Overview of measures used to determine diagnostic test accuracy

	Reference standard	
Index test result	**Condition present**	**Condition absent**
Positive	True positive (a)	False positive (b)
Negative	False negative (c)	True negative (d)

- **Sensitivity** describes the proportion of those with the condition that are correctly classified as positive by the index test.
  - Sensitivity = a / (a + c)
- **Specificity** describes the proportion of those without the condition that are correctly classified as negative by the index test.
  - Specificity = b / (b + d)

As the gold standard, the diagnostic accuracy of laboratory-based tests for the detection of anti-HCV antibodies and HCV-RNA in serum and plasma (conventional blood samples) has been extensively evaluated and reported. Therefore, a systematic review of the diagnostic accuracy of these tests in conventional blood samples was not undertaken. Estimates of the sensitivity and specificity of anti-HCV antibody and HCV-RNA tests in conventional blood samples are based on a report published by the World Health Organization (WHO) in May 2019.[190]

For each CE-marked serological test for qualitative detection of anti-HCV, the sensitivity and specificity was over 99% and 96%, respectively.[190] For confirmation of viraemic HCV infection, the limit of detection (smallest concentration that could reliably be measured (analytical sensitivity)) of quantitative HCV-RNA tests ranged from 3.9 IU/ml to 30 IU/ml, with a specificity of over 99%.[190] HCV-RNA tests with a sensitivity of ≤15 IU/ml are recommended under the European Association for the Study of the Liver (EASL) 2020 recommendations.[35, 189]

Although less sensitive than HCV-RNA tests, HCV core antigen testing is simpler to use, has less stringent handling requirements and is less expensive than viral load (NAAT) testing.[35, 191] Compared with NAAT testing in serum or plasma, core antigen testing has a sensitivity and specificity of 93.4% and 98.8%, respectively.[183] A 2016 systematic review and meta-analysis comparing core antigen testing with NAAT testing was used to inform the diagnostic performance of core antigen tests for the diagnosis of chronic infection.[183] The lower sensitivity of HCV core antigen tests in serum or plasma is a function of a higher limit of detection, equivalent to between approximately 500 IU/ml and 10,000 IU/ml of HCV-RNA.[183, 189] It is estimated that more than 95% of individuals chronically infected with HCV have a viral load in excess of 10,000 IU/ml.[185, 186, 188, 189]

As highlighted in Section 2.10, HCV-RNA or core antigen testing is repeated at six to 12 months in new anti-HCV diagnoses that are HCV-RNA-negative. Current practice in hepatology units is for repeat viral load testing at baseline (pre-treatment) and post-treatment to confirm virological cure.

4.2.3 Accuracy of laboratory-based tests for diagnosis of chronic HCV infection in dried blood spot samples

As described in the preceding sections, diagnosis of chronic HCV infection typically involves (1) an initial serological test to indicate an antibody response following exposure to HCV (that is, anti-HCV positive); and (2) if anti-HCV positive, a second test to verify active HCV infection using either a NAAT test or a core antigen test. Both tests are based on venous blood samples obtained through venepuncture.[8] In order to facilitate reflex testing, whereby the second test is performed on the same sample used for the serological test, venous samples must be centrifuged and frozen within 6-24 hours of venepuncture.[38, 190] This requirement is logistically challenging and not always feasible (see Chapter 7.3.2). Dried blood spot (DBS) testing, which involves depositing finger pricks of whole blood on filter paper, can facilitate reflex testing by circumventing the need for venepuncture, centrifugation, freezing and cold-chain storage of samples.[38, 185] Accordingly, a systematic review was undertaken to compare the diagnostic accuracy of HCV tests using DBS samples with those using

conventional blood samples. A summary of the systematic review is presented below, with a focus on the use of DBS for HCV-RNA tests. The full systematic review is presented in Appendix 4A.

Methods

Review question

The systematic review question, formulated using the Population, Index test, Reference test, Diagnosis (PIRD) framework and presented in Table 4.1,[192] sought to answer:

- What is the diagnostic accuracy of laboratory-based HCV testing using DBS compared with venous blood (whole blood, serum or plasma) samples among patients with chronic or resolved HCV infection?

Table 4.1. Systematic review question defined using PIRD framework

Population	Adults exposed to, having or suspected of having chronic HCV.
Index test	DBS (obtained by finger puncture and depositing blood drops on filter paper) tested for the presence of anti-HCV antibodies, HCV-RNA or HCV core antigen in a laboratory setting.
Reference test	Venous blood (serum, plasma or whole blood) samples tested for the presence of anti-HCV antibodies, HCV-RNA or HCV core antigen in a laboratory setting.
Diagnosis of interest	Diagnosis of chronic or resolved HCV infection.

Key: DBS – dried blood spot; HCV – hepatitis C virus; RNA – ribonucleic acid.

Eligibility criteria

Cross-sectional and case-control studies which compared the index test (based on a DBS sample) with the reference test (based on a serum, plasma or whole blood sample) in the population of interest were included in the systematic review. Only studies that reported sufficient data to estimate sensitivity and specificity (that is, to construct 2x2 contingency tables to calculate the number of true positives, true negatives, false positives and false negatives) were included.

Search methods

Electronic searches were conducted in PubMed, Embase, Scopus, Web of Science, Lilacs and the Cochrane library (which includes the Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database (HTA) and the National Health Service Economic Evaluation Database) up to July 17 2020, supplemented by a grey literature search, and forward citation searching and hand-searching of the included studies.

Screening, data extraction and assessment of studies

Screening of eligible studies, data extraction and quality appraisal were undertaken independently by two reviewers, with disagreements resolved by discussion. The body of evidence was independently assessed in accordance with previously published GRADE guidance.[193-195]

Statistical analysis

Univariate and bivariate meta-analyses were used to derive pooled estimates of sensitivity and specificity. To facilitate the meta-analyses (that is, to ensure independence of the included studies), one pair of diagnostic outcomes were selected from each study. Diagnostic outcomes reported at the threshold specified by the manufacturer were included when available. Where it was unclear which of the reported data pairs should be included in the primary study analysis, a conservative approach was adopted by selecting the data pair which produced the lowest estimate of sensitivity and specificity. Subgroup analyses were undertaken to investigate the influence of heterogeneity on pooled estimates. Sensitivity analyses were undertaken to investigate the robustness of the pooled estimates. Small-study bias was assessed using Deek's funnel plot and regression test of asymmetry.[196, 197] All statistical analyses were conducted in R Studio version 4.0.2 using the *meta* and *mada* packages.

Results

Search results

Overall, a total of 1,972 citations were returned from database and grey literature searching. Of these, 322 were removed as duplicate citations. A further 1,481 citations were excluded following title and abstract screening. Of the 156 citations that underwent full-text review, 44 individual studies were included in the synthesis. Of these, 20 assessed the diagnostic accuracy of HCV-RNA tests in DBS compared with conventional blood samples.

Overview of included studies assessing diagnostic accuracy of HCV-RNA in DBS

Overall, 20 individual studies assessing the diagnostic accuracy of HCV-RNA in DBS were included in the synthesis.[198-217] The included studies were published between 2002 and 2020. Four of the studies were from Spain,[205, 210, 211, 216] two each were from Australia,[200, 201] France,[214, 217] Italy,[202, 213] UK,[198, 212] Vietnam,[208, 215] and there was one each from Denmark,[207] Germany,[209] India,[206] Pakistan,[199] Saudi Arabia,[204] and the USA.[203] Nine studies were cross-sectional,[200, 201, 205, 206, 208-211, 215] and eleven were case-control studies.[198, 199, 202-204, 207, 212-214, 216, 217]

There was a study population of 2,940 participants across the included studies, with sample size ranging from 25 to 511 participants. Ten studies reported the gender of study participants.[200, 204-206, 208, 210, 211, 214-216] The proportion of male participants

ranged from 55% to 96%, with a mean of 74%. Nine studies reported the age of study participants, with the mean or median ranging from 39 to 52 years.[200, 204-206, 208, 211, 214-216]

Sample HCV-RNA prevalence (based on the reference standard) ranged from 26% to 85%. Only two studies reported the disease severity (that is, fibrosis distribution) of participants with chronic HCV infection[200, 208] In both studies, the majority (>65%) of patients that received fibrosis staging were between METAVIR fibrosis stages F0 to F2.

The HCV genotype of HCV-infected participants was reported in 10 studies,[201, 205, 206, 208, 210-214, 217] with HCV genotype 1 and HCV genotype 3 reported in 58% and 23% of study participants, respectively. However, the reported genotype data was generally from only a subset of participants or based on a larger cohort study (for example, where oral and DBS samples were analysed as part of a larger study) therefore its applicability is limited.

Study population risk factors for HCV acquisition were reported in 10 studies.[200, 202, 203, 205, 207, 208, 210, 211, 215, 216] From these, the most commonly reported risk factors were co-infection with HBV and or HIV, and a history of injecting drug use. However, a detailed breakdown of risk factor data was often not provided. Four studies reported the treatment status of HCV-infected patients.[208, 210, 211, 214] In two of these,[208, 214] all HCV-infected patients were treatment-naïve.

Nine studies reported diagnostic outcomes for capillary DBS samples.[199, 200, 203-205, 207, 210, 211, 216] Nine studies reported diagnostic outcomes for venous DBS samples (for example, pipetting venous blood onto filter paper).[201, 202, 206, 208, 209, 212-214, 217] One study reported diagnostic outcomes for both capillary and venous DBS samples.[215] The DBS sample type was unclear in one study.[198]

The 20 included studies contributed 34 unique pairs of diagnostic outcomes (that is, sensitivity and specificity) of RNA tests in DBS to the synthesis. Twelve studies contributed only one pair of diagnostic outcomes.[198, 199, 202-209, 216, 217] Eight studies contributed multiple 2x2 data pairs.[200, 201, 210-215] The reasons for individual studies contributing multiple pairs of diagnostic outcomes included:

- reporting paired outcomes by assay principle[213]
- reporting paired outcomes by manufacturer assay[200, 214]
- DBS sample type[215]
- reporting paired outcomes by threshold applied.[201, 210-212]

The range (that is, minimum and maximum) of study-level estimates are summarised in Table 4.2.

Table 4.2. Range of study-level estimates of HCV-RNA tests using DBS*

Outcome	Lower mean estimate (95% CI)	Upper mean estimate (95% CI)
Sensitivity	0.79 (95% CI: 0.57 to 0.91)	1.00 (95% CI: 0.96 to 1.00)
Specificity	0.83 (95% CI: 0.58 to 0.95)	1.00 (95% CI: 0.98 to 1.00)

Key: CI – confidence interval; DBS – dried blood spot; HCV – hepatitis C virus; RNA – ribonucleic acid.
* Reference sample: venous blood (whole blood, serum or plasma).

The diagnostic accuracy may vary according to the type of assay used. Fourteen studies reported results using reverse-transcription polymerase chain reaction (RT-PCR),[198, 199, 202, 204-206, 208, 210-212, 214-217] and four reported results using transcription-mediated amplification (TMA),[201, 203, 207, 209] while one reported the use of both.[213] The assay principle of the assay used in one study was unclear.[200]

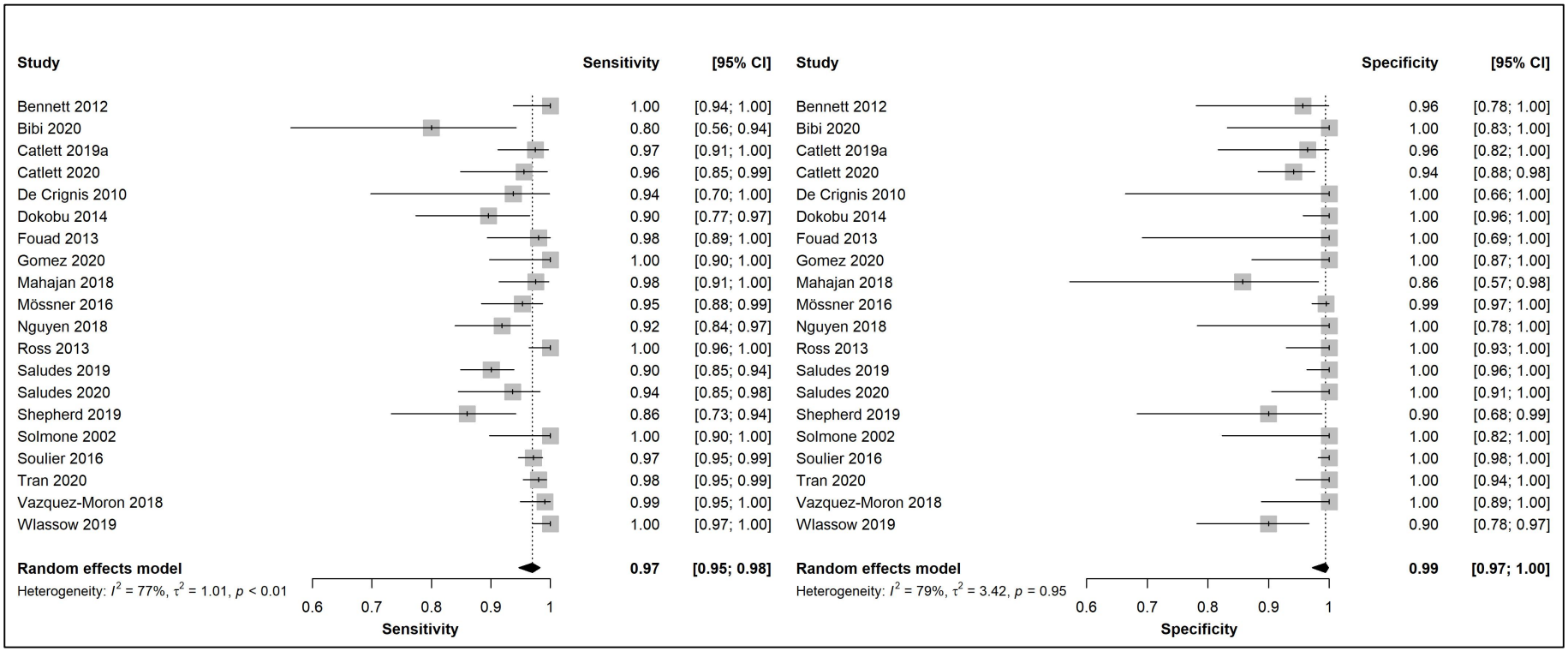
Twelve studies reported the use of a viral load threshold, reported in terms of international units per millilitre (IU/ml).[199-202, 206, 207, 209-212, 215, 217] The viral load thresholds reported ranged from 10 IU/ml to 50,000 IU/ml. The most commonly reported (n=5) threshold was a viral load threshold of ≥1,000 IU/ml.[201, 206, 210-212] Four studies reported that they interpreted the results according to the manufacturer's instructions, but the explicit threshold value used could not be identified.[199, 207, 209, 217] For studies in which an explicit threshold could be identified, it was assumed that the limit of detection was employed to interpret test results.

Meta-analysis
Across all included studies (relative to HCV-RNA in serum, plasma or whole-blood) the pooled sensitivity and specificity of HCV-RNA in DBS were estimated in the univariate meta-analysis at 0.97 (95% CI: 0.95 to 0.98) and 1.00 (95% CI: 0.97 to 1.00), respectively. The robustness of these results was investigated by subgroup and sensitivity analysis. The subgroup and sensitivity analysis included analysis:

- by assay principle (that is, RT-PCR versus TMA)
- by DBS sample type (that is, capillary versus venous)
- by study design (cross-sectional versus case-control studies)
- stratified by risk of bias
- according to common viral load threshold of 1,000 IU/ml.

The forest plot of sensitivity and specificity estimated in the univariate sensitivity analysis is presented in Figure 4.2.

Figure 4.2 Forest plot of sensitivity and specificity of HCV-RNA tests in DBS compared with in serum or plasma

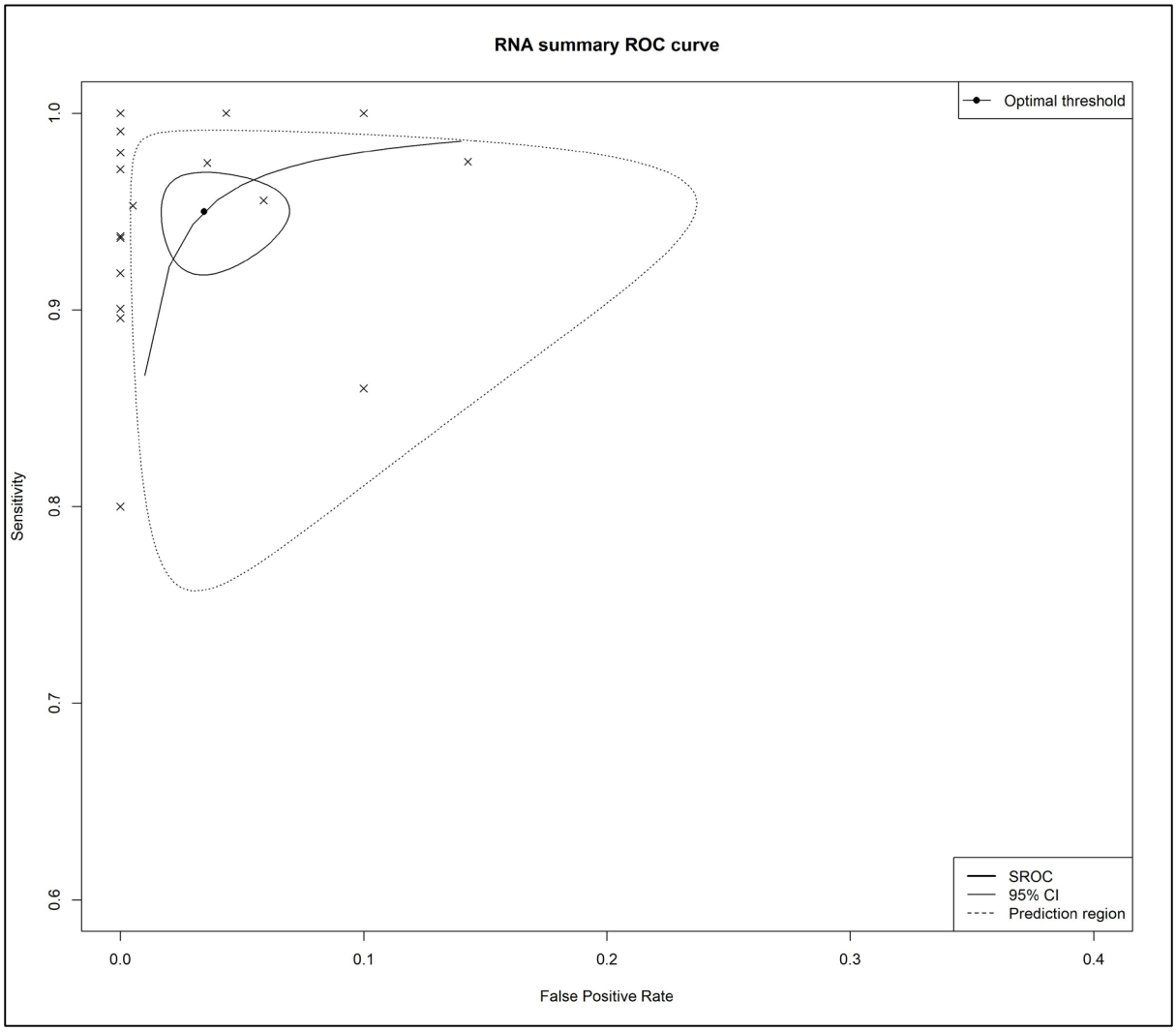


Key: DBS – dried blood spot; HCV – hepatitis C virus; RNA – ribonucleic acid.

Note: Univariate meta-analysis does not account for correlation between pairs of sensitivity and specificity.[218-220] Heterogeneity is considered the rule rather than expectation in meta-analyses of diagnostic accuracy.[218, 220] Univariate tests for heterogeneity, such as the inconsistency index (I^2) and tau^2, can be misleading.

In the bivariate meta-analysis, the pooled sensitivity and specificity were estimated at 0.95 (95% CI: 0.93 to 0.97) and 0.96 (95% CI: 0.93 to 0.98), respectively. The correlation co-efficient was 0.052, the area under the curve (AUC) was 0.982 and the Akaike information criterion (AIC) was -152.29. The summary receiver operating characteristic (SROC) curve, based on the parameters of the bivariate model, is presented in Figure 4.3.

Figure 4.3. SROC curve of HCV-RNA in DBS, compared with in serum or plasma



Key: SROC – summary receiver operating characteristic.
Note: The SROC is plotted according to the generalisation of the Rutter and Gatsonis curve.[221]

Study quality and applicability

Overall, six studies were rated as low risk of bias,[200, 201, 206, 210, 211, 215] 10 were at moderate risk of bias,[198, 199, 202-205, 208, 209, 212, 214] and four were at high risk of bias.[207, 213, 216, 217] Study quality and applicability to the Irish healthcare system are discussed in Appendix 4A.

4.3 Treatment effectiveness and safety

4.3.1 National Hepatitis C Treatment Programme

The National Hepatitis C Treatment Programme (NHCTP) is a public health programme that aims to eliminate HCV in Ireland by 2026 through the provision of treatment, across a range of healthcare settings, to all persons infected with HCV. The governance structure of the NHCTP encompasses a Programme Advisory Group and Clinical Advisory Group that develops and recommends treatment guidelines in line with international best practice.[181] The NHCTP is supported by a national HCV disease and treatment registry which collects treatment-specific and outcome data for patients treated.

Since 2015, €30 million has been allocated annually to fund HCV drug treatment in Ireland. Initially, access to treatment was prioritised for those with greatest clinical need. In January 2017, NHCTP treatment guidelines were amended to support wider access to treatment, irrespective of fibrosis stage, so that all HCV-RNA positive patients are considered for direct-acting antiviral (DAA) therapy. However, patients are still prioritised according to local cohort factors and if they meet the treatment criteria in place prior to January 2017.[181] The preferred regimens (Table 4.3) stipulated by the NHCTP are subject to an annual national procurement process to ensure that treatments with the best value-for-money are prescribed. The preferred regimens are ranked according to cost, with more expensive regimens requiring sign-off from the National Clinical Lead and or Clinical Advisory Group prior to reimbursement.

The NHCTP treatment guidelines[181] are based on the 2018 EASL treatment guidelines,[35] informed by published evidence, expert opinion and presentations at international meetings. The EASL guidelines recommend use of interferon-free, ribavirin-free, oral DAA-based treatment regimens for all patients who are willing to be treated and for whom treatment is not contraindicated.[35] This recommendation applies to both treatment-naïve and treatment-experienced patients. The DAA regimens are stratified according to genotype and the presence or absence of cirrhosis. DAA combination therapies were first approved for treatment of HCV in Ireland in December 2014.[181]

Table 4.3. Preferred regimens (2019) for HCV patients with and without cirrhosis*¥

	Sof/Led (Harvoni®)	Sof/Vel (Epclusa®)	Glec/Pib (Maviret®)	Sof/Vel/Vox** (Vosevi®)
GT1 Non-cirrhotic	8-12 weeks (treatment-naïve 1a/b, treatment-experienced 1b)	12 weeks (treatment-experienced 1a) 12 weeks (CL Approval Required)	8 weeks (CL Approval Required)	12 weeks (CAG Approval required)
GT1 Cirrhotic	12 weeks (Treatment-naïve 1a/b, treatment-experienced GT1b)	12 weeks (Treatment-experienced 1a) 12 weeks (CL Approval Required)	12 weeks (CL Approval Required)	12 weeks (CAG Approval Required)
GT2 Non-cirrhotic	-	12 weeks	8 weeks	12 weeks (CAG Approval Required)
GT2 Cirrhotic	-	12 weeks	12 weeks	12 weeks (CAG Approval Required)
GT3 Non-cirrhotic	-	12 weeks	8/12 weeks (CL Approval Required)	12 weeks (CAG Approval Required)
GT3 Cirrhotic	-	-	12 weeks (treatment-naïve) 16 weeks (treatment-experienced)	12 weeks (CAG Approval Required)
GT4 Non-cirrhotic	12 weeks (treatment-naïve)	12 weeks	8 weeks	12 weeks (CAG Approval Required)
GT4 Cirrhotic	12 weeks (treatment-naïve)	12 weeks	12 weeks	12 weeks (CAG Approval Required)
GT5/6 Non-cirrhotic	12 weeks (treatment-naïve)	12 weeks	8 weeks	12 weeks (CAG Approval Required)
GT5/6 Cirrhotic	12 weeks (treatment-naïve)	12 weeks	12 weeks	12 weeks (CAG Approval Required)

Key: CAG – Clinical Advisory Group; CL – Clinical Lead; glec – glecaprevir; GT – genotype; HCV – hepatitis C virus; led – ledipasvir; pib – pibrentasvir; RNA – ribonucleic acid; sof – sofosbuvir; vel – velpatasvir; vox – voxilaprevir.

Source: National Hepatitis C Treatment Programme

* Cirrhosis is defined as Child-Pugh A.

** The pangenotypic fixed-dose combination of sofosbuvir, velpatasvir and voxilaprevir is considered a second-line therapy which requires approval from the NHCTP's Clinical Advisory Group prior to reimbursement.

¥ Regimens are ranked according to increasing cost.

4.3.2 Considerations prior to treatment initiation

The NHCTP treatment guidelines recommend that all treatment-naïve and treatment-experienced patients with chronic HCV infection, who have no contraindications for treatment, should be offered treatment. Liver disease severity should be assessed prior to the initiation of therapy.[35] The choice of treatment regimen and post-treatment prognosis depend on the stage of fibrosis. Patients with clinical evidence of cirrhosis do not require fibrosis staging, but should be assessed for portal hypertension.

HCV genotyping, including subtyping of HCV genotype 1, and knowledge of whether the patient is treatment-experienced are used to tailor treatment regimen and duration. Highly efficacious treatments are now available for patients with detectable pre-existing resistance-associated substitutions at baseline. Therefore, systematic testing for HCV resistance prior to treatment in drug-naive individuals is not recommended.[35] However, resistance testing is recommended in patients that do not achieve a sustained virological response (SVR) following exposure to two or more classes of DAA drugs.[181]

There are few contraindications to treatment with DAAs.[35] The use of certain cytochrome P450/P-glycoprotein inducing agents (such as carbamazepine and phenytoin) are contraindicated with all regimens due to the risk of significantly reduced concentrations of DAA and associated high risk of virological failure. Sofosbuvir should be used with caution in patients with severe renal impairment if no alternative treatment option is available, as the pharmacokinetics and safety of sofosbuvir-derived metabolites in patients with severe renal dysfunction is still being ascertained.[35] Treatment regimens comprising a HCV protease inhibitor are contraindicated for patients with decompensated cirrhosis (Child-Pugh B or C) due to the substantially higher protease inhibitor concentrations in these patients and the associated risk of toxicity.[2, 35] DAA therapies do not have a negative impact on mental health or therapy evaluation drop-off in patients with mental health disorders.[222]

The guidelines highlight that patients with the following indications should be considered for treatment without delay:

- significant fibrosis (METAVIR score F2 or F3)
- compensated (METAVIR score F4) or decompensated (Child Pugh B or C) cirrhosis
- clinically significant extrahepatic manifestations (such as HCV immune complex-related nephropathy and non-Hodgkin B-cell lymphoma)
- HCV recurrence post-liver transplantation

- enhanced risk of liver disease progression due to the presence of concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, HBV co-infection, diabetes)
- high risk of transmitting HCV (PWIDs, MSM with high-risk sexual behaviours, women of childbearing age who wish to get pregnant, haemodialysis patients and people who are incarcerated).[35]

4.3.3 Virological cure of HCV

The goal of antiviral HCV therapy is to cure chronic HCV infection, defined as an SVR. An SVR corresponds to a definitive cure of infection in the vast majority of cases.[89]

It is defined as undetectable HCV-RNA in serum or plasma 12 weeks (SVR12) or 24 weeks (SVR24) post-treatment,[223] as determined by a sensitive molecular method with a lower limit of detection of ≤15 international units per millilitre (IU/ml).[35, 189] Undetectable HCV core antigen 24 weeks post-treatment can also be used to define SVR24 in patients with detectable core antigen prior to treatment.[35] Virological cure of HCV:

- prevents HCV-related liver complications and extrahepatic diseases (including hepatic necro-inflammation, fibrosis, cirrhosis, HCC, severe extrahepatic manifestations and death)
- improves health related quality of life and reduces stigma
- prevents onward transmission of HCV infection.

The validity of SVR as a surrogate outcome for viral cure of HCV is discussed in Section 4.6.

4.3.4 Treatment effectiveness

The clinical effectiveness of DAA combination therapies, in terms of SVR12 rates, is described below according to each DAA combination. A de novo systematic review was not undertaken as the effectiveness of these combination therapies has been extensively reviewed in recent years and given the consistency of findings between the published reviews. The evidence underpinning the 2018 European Association for the Study of the Liver (EASL) treatment guidelines,[35, 224] the 2018 WHO guideline for the treatment and care of people with chronic HCV infection,[2] the US Preventive Services Task Force's (USPSTF) 2020 recommendations[225] for screening for HCV infection and other relevant systematic reviews[226, 227] was considered when estimating treatment effects.

Consistent with good research practice, the systematic reviews by the WHO[228] and USPSTF[225] were quality appraised using the AMSTAR 2 tool,[229] with the results

presented in Appendix 7. The systematic review by the WHO was judged to be of low quality due to insufficient consideration of risk of bias, a lack of assessment of heterogeneity and publication bias, a lack of protocol registration and not presenting a list of excluded studies. The systematic review by the USPSTF was judged to be of critically low quality due to a lack of protocol registration, inadequate assessment of risk of bias and lack of explanation for heterogeneity. However, while acknowledging the limitations of these reviews, it was noted that both found similar results, in terms of the effectiveness of DAA therapies, and that their findings were consistent with other published literature. The effectiveness of DAA combination therapies is accepted by the clinical and scientific community.

The posology of fixed-dose DAA combination therapies for chronic HCV infection is presented by target HCV genotype in Appendix 7. The following sections summarise the effectiveness of the 2020 NHCTP preferred regimens.

Sofosbuvir and ledipasvir (Harvoni®)

Sofosbuvir and ledipasvir is recommended for treatment of HCV genotypes 1, 4, 5 and 6 in Ireland.[181] The effectiveness data for this combination are summarised in Table 4.4.

A 2015 systematic review[226] found that the pooled SVR12 fixed combination therapy with sofosbuvir and ledipasvir was 98% (95% CI: 95-100%) in patients with HCV genotype 1. In the clinical studies informing the EASL recommendations,[35] the SVR12 rates of fixed-dose combination therapy with sofosbuvir and ledipasvir ranged from 93-98% for patients with HCV genotype 1a treated for between 8 and 12 weeks (including treatment-naïve patients with and without cirrhosis). Dual therapy with sofosbuvir and ledipasvir is not recommended in treatment-experienced patients with HCV genotype 1a.[230] In patients with HCV genotype 1b treated for between 8 and 12 weeks, SVR12 ranged from 87-100% (including treatment-naïve and treatment-experienced patients with and without cirrhosis). The SVR12 rate ranged from 91-100% patients with HCV genotype 4, 5 and 6 (including treatment-naïve and treatment-experienced patients with and without cirrhosis).

The WHO's 2018 systematic review [2, 228] found that the pooled SVR12 rate exceeded 95% across HCV genotypes 1, 4 and 5 for treatment-naïve patients, based on RCTs. In the all-treatment experienced population, the pooled SVR12 rates of fixed-dose combination therapy with sofosbuvir and ledipasvir was 97% (95% CI: 96-98%) in patients with HCV genotype 1, 96% (95% CI: 93-98%) in patients with HCV genotype 4, 95% (95% CI: 89-100%) in patients with HCV genotype 5, and 90% (95% CI: 89-100%) in HCV genotype 6, based on evidence from RCTs, non-randomised trials and observational studies. The USPSTF's 2020 systematic review[225] found that the pooled SVR12 rates ranged from 95-96% in HCV genotypes 5 and 6 (see Appendix 7). Results

did not differ when stratified according to the patient's cirrhosis or treatment status at baseline.

Table 4.4. SVR12 rates for sofosbuvir and ledipasvir (Harvoni®)*

HCV genotype	EASL (2018)	USPSTF (2020)	WHO (2018)
1a	93-98	-	98%
1b	96-100%	-	
2	NA	NA	NA
3	NA	NA	NA
4	91-96%	-	96%
5**	95%	95%	95%
6**	96%	96%	97%

Key: EASL – European Association for the Study of the Liver; HCV – hepatitis C; NA – not applicable; USPSTF – US Preventive Service Task Force; WHO – World Health Organization; SVR – sustained virological response.

* Results are summarised across treatment experience and status of cirrhosis.

** Results for HCV genotypes 5 and 6 are generally based on a small number of trial participants.

Sofosbuvir and velpatasvir (Epclusa®)

Sofosbuvir and velpatasvir is recommended for treatment of HCV genotypes 1, 2, 3 (non-cirrhotic only), 4, 5 and 6 in Ireland.[181] National Clinical Lead approval is required prior to reimbursement of sofosbuvir and velpatasvir combination therapy for HCV genotype 1, other than if indicated for treatment-experienced HCV genotype 1a.[181] Fixed-dose combination therapy with sofosbuvir and velpatasvir is not recommended for cirrhotic patients with HCV genotype 3 in Ireland.[181] The effectiveness data for this combination are summarised in Table 4.5.

In the clinical studies informing the EASL recommendations,[35] the SVR12 rates of fixed-dose combination therapy with sofosbuvir and velpatasvir ranged from 95-100% across HCV genotypes 1a, 1b, 2, 4 and 6 (including treatment-naïve and treatment-experienced patients with and without cirrhosis). In patients with HCV genotype 3, the SVR12 rate was 93-98% in treatment-naive patients (with or without cirrhosis), but was only 89-91% in treatment-experienced patients (with or without cirrhosis).[35] A 2017 systematic review[227] estimated pooled SVR12 rates of 97.2% (95% CI: 94.7-98.8) in non-cirrhotic patients and 96.3% (95% CI: 92-98.7) in cirrhotic patients with HCV genotype 3.

A 2018 systematic review by the WHO[2, 228] found that the pooled SVR12 rates ranged from 84% to 98% across HCV genotypes 1 to 3 for treatment-naïve patients. In the all-treatment experience population (includes mixed or unclear treatment-experience populations), the pooled SVR12 rates exceeded 96% (95% CI: 92-100%) for all HCV

genotypes, apart from HCV genotype 3 which was estimated at 89% (95% CI: 85-93%).[228] An additional study[231] published following the WHO's data analysis found SVR12 rates of 100% for HCV genotypes 5 and 6. However, the number of patients with HCV genotype 5 (n=13) and 6 (n=20) was small.

A 2020 systematic review by the USPSTF[225] found that the pooled SVR12 rates of treatment with sofosbuvir and velpatasvir ranged from 96-100% across all HCV genotypes (see Appendix 7). Results did not differ when stratified according to the patient's cirrhosis or treatment status at baseline.

Table 4.5. SVR12 rates for sofosbuvir and velpatasvir (Epclusa®)

HCV genotype	EASL (2018)	USPSTF (2020)	WHO (2018)
1a	95-98	99%	95-96%
1b	99%	100%	
2	99-100%	96%	84-99%
3	89-98%	100%	89-98%
4	100%	100%	99%
5**	97%	97%	97%
6**	100%	99%	99%

Key: EASL – European Association for the Study of the Liver; HCV – hepatitis C; USPSTF – US Preventive Service Task Force; WHO – World Health Organization; SVR – sustained virological response.

* Results are summarised across treatment experience and status of cirrhosis.

** Results for HCV genotypes 5 and 6 are generally based on a small number of trial participants.

Glecaprevir and pibrentasvir (Maviret®)

Fixed-dose combination therapy with glecaprevir and pibrentasvir is recommended for treatment of all six major HCV genotypes in Ireland.[181] Approval from the National Clinical Lead is required prior to reimbursement of glecaprevir and pibrentasvir combination therapy for HCV genotype 1 and non-cirrhotic HCV genotype 3.[181] The effectiveness data for this combination are summarised in Table 4.6.

In the clinical studies informing the EASL recommendations,[35] the SVR12 rates of fixed-dose combination therapy with glecaprevir and pibrentasvir ranged from 98-100% across HCV genotypes 1a, 1b and 2 (including treatment-naïve and treatment-experienced patients with and without cirrhosis). In HCV genotype 3, SVR12 rates of 90-100% were observed in combined treatment-naive and treatment-experienced patients without cirrhosis treated for 8 weeks. In patients with HCV genotype 4 (including treatment-naive and treatment-experienced patients without cirrhosis), the SVR12 rates ranged from 93-100% when treated for between 8 and 12 weeks.[35] In patients with HCV genotypes 5 and 6 (including treatment-naive and treatment-experienced patients without cirrhosis), the SVR12 rates ranged from 90-100% when

treated for between 8 and 12 weeks.[35]

The WHO's 2018 systematic review[2, 228] found that the pooled SVR12 rate was 95% (95% CI: 93-97%) for treatment-naïve patients with HCV genotype 3. In the all-treatment experience population, the pooled SVR12 rates of fixed-dose combination with glecaprevir and pibrentasvir exceeded 94% (95% CI: 89-100%) for HCV genotypes 1, 2, 3, 4 and 6.[2, 228] The USPSTF's 2020 systematic review[225] found that the pooled SVR12 rates of treatment with glecaprevir and pibrentasvir ranged from 94-99% across all HCV genotypes (see Appendix 7). Results did not differ when stratified according to the patient's cirrhosis or treatment status at baseline.

Table 4.6. SVR12 rates for glecaprevir and pibrentasvir (Maviret®)

HCV genotype	EASL (2018)	USPSTF (2020)	WHO (2018)
1a	98%	99%	98%
1b	100%		
2	98-100%	98%	98%
3	90-98%	95%	95%
4	99-100%	94%	97%
5**	100%	96%	83%
6**	90-100%	97%	94%

Key: EASL – European Association for the Study of the Liver; HCV – hepatitis C; USPSTF – US Preventive Service Task Force; WHO – World Health Organization; SVR – sustained virological response.

* Results are summarised across treatment experience and status of cirrhosis.

** Results for HCV genotypes 5 and 6 are generally based on a small number of trial participants.

Sofosbuvir, velpatasvir and voxilaprevir (Vosevi®)

Sofosbuvir, velpatasvir and voxilaprevir is the only pangenotypic DAA regimen currently approved for re-treatment of patients that previously failed a DAA regimen.[2] However, it cannot be used in patients with Child-Pugh Class B or C cirrhosis.[35] In Ireland, is recommended as a second-line therapy across all six major HCV genotypes, but requires approval from the Clinical Advisory Group prior to reimbursement.[2, 181] The EASL does not recommend triple combination therapy with sofosbuvir, velpatasvir and voxilaprevir in patients with HCV genotype 1a, as non-inferiority was not demonstrated when compared with sofosbuvir and velpatasvir.[35, 232]

In two clinical studies[232] informing the EASL recommendations,[35] the SVR12 rates of fixed-dose combination therapy with sofosbuvir, velpatasvir and voxilaprevir ranged from 96-99% for patients with HCV genotype 3 treated for between 8 and 12 weeks (including treatment-naïve patients with and without cirrhosis). The WHO's 2018 systematic review[2, 228] found that the pooled SVR12 rate was 96% (95% CI: 92-100%) in HCV genotype 3 for treatment-naïve patients, based on RCTs. In the all-

treatment experience population, the pooled SVR12 rates ranged from 94-98% across all HCV genotypes.

4.3.5 Treatment safety

As of May 2018, the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) had approved 13 DAAs from four drug classes (see Table 4.7). Three pangenotypic DAA combinations (glecaprevir/pibrentasvir, sofosbuvir/ daclatasvir, sofosbuvir/velpatasvir) are available for treatment of HCV-infected individuals with and without cirrhosis.[2] The remaining DAA combinations are HCV genotype-specific.

Table 4.7. DAAs according to class

NS5A (protease) inhibitors	NS5A inhibitors	NS5B polymerase inhibitor (nucleotide analogue)	NS5B polymerase inhibitor (non-nucleoside analogue)
Glecaprevir	Daclatasvir	Sofosbuvir	Dasabuvir
Voxilaprevir	Velpatasvir		
Grazoprevir	Ledipasvir		
Paritaprevir	Ombitasvir		
Simeprevir	Pibrentasvir		
	Elbasvir		

Source: World Health Organization[2]

A 2018 systematic review[228] commissioned by the WHO identified 142 clinical studies that evaluated the safety and efficacy of these antiviral therapies for treatment of chronic HCV infection. The clinical studies included randomised and non-randomised controlled trials in addition to prospective and retrospective observational studies. Safety was evaluated with respect to discontinuations due to adverse events (anaemia, insomnia, headache, fatigue, rash and nausea), the occurrence of serious adverse events (cardiovascular events), and mortality. The DAA combinations evaluated in the review included, but were not restricted to, regimens currently recommended by the NHCTP guidelines:

- sofosbuvir and velpatasvir
- sofosbuvir and ledipasvir
- glecaprevir and pibrentasvir
- sofosbuvir, velpatasvir and voxilaprevir.

Across all DAA combinations and studies, the number of discontinuations due to adverse events ranged from 0-4%.[228] The quality of the evidence (assessed using GRADE) was moderate, with downgrading due to a lack of studies blinding patients or

outcome assessors. This may have impacted the perceived subjectivity of labelling a discontinuation as a discontinuation due to an adverse event. The incidence of adverse events were higher with DAA regimens containing ribavirin.[233] The addition of ribavirin is not recommended in the preferred regimens for treatment of HCV infection in Ireland.[181] Across all DAA combinations and studies, the pooled percentage of serious adverse events ranged from 1-5%, while the incidence of all-cause mortality ranged from 0-4%.[228] Study quality varied from moderate- to high- quality. The quality of the evidence was high, assessed using GRADE.

A 2017 systematic review by the Canadian Task Force on Preventive Health Care[234] found that interferon-free DAA combination therapies had a lower frequency of adverse events (anaemia, psychological adverse events, flu-like symptoms, neutropenia, rash) and treatment discontinuation due to adverse events compared with pegylated interferon plus ribavirin.

A 2020 systematic review[225] based on 44 trials (randomised and non-randomised clinical trials) by the USPSTF found that 73.3% (95% CI: 68.0-78.1%) of patients on interferon-free DAA regimens experienced an adverse event (anaemia, diarrhoea, fatigue, headache, insomnia, nausea, vomiting or rash). However, only 1.9% (95% CI: 1.5-2.4%) experienced a serious adverse event and withdrawal due to adverse events was only 0.4% (95% CI: 0.3-0.6%). The frequency of adverse events was generally similar when trials were stratified according to cirrhosis status at baseline and prior antiviral therapy experience. It should be noted that 10 trials in the analysis included a DAA regimen in combination with ribavirin, which as noted are associated with a higher incidence of adverse events than ribavirin-free DAA regimens. The use of ribavirin in combination with DAAs is not recommended in Ireland.[181]

4.3.6 Treatment of patients with advanced and end-stage liver disease

No treatment currently exists that can target pathological alterations within the liver to restore the integrity of the liver architecture.[235, 236] Patients with chronic HCV infection that develop decompensation risk irreversible disease, regardless of successful treatment with DAAs.[237] Therefore, management of patients with decompensated cirrhosis includes use of antivirals to prevent further progression and suppression of aetiological factors that have led to accumulation of fibrosis and cirrhosis (for example, alcohol consumption).[235] A prospective cohort study of DAA therapies in patients (n=9,895) with decompensated cirrhosis and hepatocellular carcinoma conducted in France between 2012 and 2015. The authors found that successful DAA therapy was associated with a reduced risk of all-cause mortality (adjusted hazard ratio: 0.48 (95% CI: 0.33-0.70)) and development of hepatocellular carcinoma (adjusted hazard ratio: 0.66 (95% CI: 0.46-0.93).[238]

Interferon-free DAA regimens can be offered to patients with advanced liver disease (as assessed by MELD score). However, patients with HCV-associated cirrhosis and HCC that are successfully treated maintain a high risk of HCC recurrence.[112] During the first two years following HCC treatment with curative intent and subsequent DAA therapy, patients require imaging at three- to four-month intervals, extended to six-month intervals thereafter.[112]

For patients with end-stage liver disease, the presence of HCV infection at the time of liver transplantation is not a contraindication to transplantation, but antiviral treatment is necessary following the procedure.[239] While on the waiting list for liver transplantation, the primary aim of antiviral therapy is to prevent HCV infection of the new liver. Additionally, antiviral therapy aims to improve liver function in patients that are clearing HCV, which may potentially avoid the need for liver transplant.[239]

Liver transplant is indicated in patients with end-stage liver disease (e.g., decompensated cirrhosis with a MELD score ≥18–20). [35] The presence of HCV infection is not a contraindication to transplantation, but antiviral treatment is necessary following the procedure to prevent infection of the new liver. Antiviral treatment may also be initiated if the expected transplant wait time is more than six months; treatment aims to improve liver function and may potentially avoid the need for transplant

4.4 Harms and consequences of testing and treatment

A key harm from testing for chronic HCV infection is the occurrence of false negatives. The overall testing strategy has a high diagnostic performance, in terms of positive and negative predictive values. However, false negatives are still expected to occur – an issue that is exacerbated when a mass testing approach is adopted within a low prevalence setting. Failure to detect individuals with chronic HCV may delay the opportunity to intervene prior to the development of irreversible liver damage. That said, patients with a positive serological test result, but negative HCV-RNA or antigen test result, will be re-tested after six months to confirm resolved infection, thus mitigating the potential impact of a false negative diagnosis in these patients. False negatives due to the "window period" (that is, the period before production of detectable anti-HCV antibodies) are unlikely to occur since a historical exposure to HCV is suspected in patients from the 1965 to 1985 birth cohort for whom there is no known recent or ongoing risky behaviours.

False positives represent another harm that may occur from testing for hepatitis C. Diagnosis of HCV infection is associated with stigmatisation which can lead to alienation from friends, family and workplaces, disclosure of which can cause anxiety and distress.[36] False positives cause harms, in terms of negative psychological and

social effects, that are difficult to quantify, but adversely affect quality of life.[240] False positive serological tests lead to unnecessary supplementary testing, reflecting an inefficient use of healthcare resources. People that have had an acute HCV infection will always test anti-HCV antibody positive regardless of whether the virus spontaneously resolves or the patient achieves an SVR. Patients with resolved infection are not at risk of disease progression, unless they are re-infected through subsequent exposure. HCV reinfection can occur after spontaneous or treatment-induced virological clearance. Reinfection is diagnosed based on the reappearance of HCV-RNA or HCV core antigen following virological clearance and demonstration (by sequencing and phylogenetic analysis) that HCV infection has been caused by a different or distantly related strain of the same HCV genotype from that of the initial infection.[189] Reinfection is suspected in cases where recurrence of HCV infection occurs more than 12-24 weeks post-SVR and risky health behaviours are suspected.[189]

A reflex testing strategy is likely to mitigate, but not eliminate, some of the harms caused by a positive serological diagnosis since the patient receives the results of both tests at the same time. Reflex testing also reduces the potential for loss to follow-up by decreasing the number of clinical visits required.[189] However, coordination between clinical sites and laboratories is required to ensure that implementation of reflex testing is feasible. The operationalisation of reflex testing is discussed further in Chapter 7. Individuals with positive HCV-RNA or HCV antigen test results are referred to hepatology units where a baseline HCV-RNA test is undertaken to quantify viral load prior to treatment initiation. Therefore, patients with a false positive result are unlikely to progress to treatment.

Highly effective treatment is available to successfully eliminate chronic HCV infection.[35] Through identification and treatment, birth cohort testing has the potential to prevent substantial liver-related morbidity, extrahepatic manifestations and mortality. As the majority of chronically infected individuals from the 1965 to 1985 birth cohort are asymptomatic, the benefits to patients in terms of reduced morbidity and additional life-years will occur in the future. As described in Chapter 3, chronic HCV infection can be asymptomatic, but patients may still develop long-term complications.

Overdiagnosis refers to the diagnosis of 'disease' that will never cause symptoms or death during a patient's ordinarily expected lifetime.[241] Overdetection refers to the identification of abnormalities that do not progress, that progress too slowly to cause symptoms or harm during a person's remaining lifetime, or that resolve spontaneously.[241] It is a side effect of screening for early forms of disease that can lead to investigations and treatments that may cause harm, but from which the patient has little if any potential to benefit. This may be the case for individuals identified with early disease as a result of chronic HCV infection that would never develop advanced

liver disease in the absence of treatment. These patients would potentially undergo treatment unnecessarily. However, since investigations for and treatment of HCV (see Section 4.3.5) are safe and well tolerated, it can be argued that the benefits from halting disease progression and prevention of onward transmission outweighs the harms of overdiagnosis at a societal level.

4.5 Validity of SVR, a surrogate outcome measure

Virological cure of HCV is defined using a surrogate outcome, sustained virological response (SVR). In order for a surrogate outcome to be valid, two conditions must be met:

- there should be a strong and independent association between the surrogate endpoint and patient-important outcome(s), where the association is evaluated independently for each individual patient-important outcome
- RCTs of the same or alternative drug class should independently demonstrate improvements in the surrogate endpoint consistently associated with improvements in patient-important outcomes.[242]

The validity of SVR as a patient-important outcome for patients with HCV infection has been debated following the publication of a 2017 Cochrane systematic review which concluded that there was a lack of evidence to substantiate the effectiveness of DAAs at improving morbidity, serious adverse events, quality of life and mortality.[243] The review also highlighted a lack of data from RCTs to assess quality of life, morbidity and mortality. However, other studies demonstrated the importance of achieving an SVR.

A 2017 systematic review of 59 studies (four RCTs, 15 prospective cohort studies and 40 retrospective cohort studies) found that antiviral treatment reduced the risk of developing HCC, all-cause mortality and liver-specific mortality.[244] The effects on these outcomes were stronger when an SVR was achieved (87% and 75% reduction in liver-related and all-cause mortality respectively),[244] with the magnitude of the effects demonstrating the strong relationship between SVR and patient-important outcomes.[242] Other systematic reviews have reported that treatment for chronic HCV infection is associated with reduced risk of HCC, all-cause mortality and liver-related mortality compared with no treatment or treatment failures.[160, 245] Many of these studies included interferon-based treatments, but recent systematic reviews have found no difference in clinical outcomes between patients that achieved an SVR with DAA therapies compared with those treated with older interferon-based therapies.[225, 246]

A 2018 cohort study of 40,664 patients with HCV infection (but without advanced liver disease) treated with DAAs found that patients who achieved an SVR had a significantly lower mortality rate than those who did not.[247] An association between SVR and pathological/physiological endpoints (hepatic fibrosis and portal hypertension) has also been demonstrated.[248]

With regards to extrahepatic manifestations, a 2018 systematic review of non-randomised studies found that achieving an SVR following antiviral therapy (compared with no SVR) in non-cirrhotic chronically infected patients was associated with:

- reduced extrahepatic mortality
- higher complete remissions in patients with cryoglobulinemia vasculitis
- higher objective response in those with malignant B-cell lymphoproliferative diseases
- reduced insulin resistance at follow-up
- reduced risk of major cardiovascular adverse events
- significant protective effect on the incidence of diabetes frequency at follow-up
- reduced incidence of de novo type 2 diabetes
- lower levels of fatigue.[249]

There is a lack of evidence from RCTs that DAAs lead to significant improvements in long-term, patient-important outcomes.[242, 243] However, the evidence outlined above from observational studies of interferon-based regimens and one large cohort study of patients treated with DAAs indicate a clear association between SVR, mortality and occurrence of extrahepatic manifestations.[247] Although desirable, it is unlikely that RCTs of DAAs designed specifically to demonstrate improvements in patient-important outcomes will ever be conducted, since the outcomes (that is, cirrhosis, need for transplant and mortality) take decades to develop.[242]

4.6 Outcomes of US-based birth cohort testing

The Hepatitis C Assessment and Testing (HepCAT) Project is a cross-sectional intervention study investigating risk-based and birth cohort testing strategies across urban primary care clinics in the US. At least three published HepCAT studies[44, 250, 251] have examined the effectiveness and implementation of birth cohort testing.

A cross-sectional study[251] with retrospective electronic medical record review was carried out to determine whether birth cohort testing improves identification of patients with the anti-HCV antibody. The study found that patients identified via birth cohort testing were significantly less likely to have a documented indication for HCV testing than patients identified via risk-based testing. Notably, patients identified by birth cohort testing were significantly less likely to have a documented history of

substance abuse (30.5 % versus 49.5 %, p=0.02) or elevated serum alanine aminotransferase (ALT) levels of > 40 U/L (22% versus 46.7 %, p=0.002); or a diagnosis (such as cirrhosis or HIV infection) that may trigger HCV testing (combined with any risk-associated factor [55.9 % versus 79.0 %, p=0.002]).[251]

A retrospective study examined the cascade of care for patients newly diagnosed with HCV infection by birth cohort testing compared with risk-based testing.[250] The authors postulated that birth cohort testing might lead to improved uptake of evaluation, care and treatment since patients diagnosed with HCV infection may have historically been excluded from treatment in the US due to the prevalence of risk factors, such as drug use.[250] The milestones examined included HCV viral load, specialist referral, evaluation by specialist, offer of treatment, treatment initiation and attainment of SVR. Substantial time gaps were observed between milestones along the cascade of care, without improvement for those identified by birth cohort testing. However, no significant differences in SVR were reported. The study demonstrated that increased testing for HCV does not necessarily improve treatment outcomes and highlighted the importance of improving linkage to care. Another study[44] demonstrated that physician-targeted prompts (for example, posters and reminder stickers) as part of a multi-component intervention (including educational sessions for primary care providers and staff) can further enhance HCV testing rates.

4.7 Discussion

This chapter provides an overview of the evidence underpinning the safety and clinical effectiveness of HCV testing and treatment. The accuracy of diagnostic tests for chronic HCV infection was informed by a WHO report published in May 2019.[190] These estimates were obtained from publicly available information or directly from manufacturers.

A reflex testing strategy, whereby both the initial anti-HCV antibody test and the subsequent test to diagnose chronic HCV infection are performed on the same blood sample, is modelled in the cost-utility analysis in Chapter 6. Reflex testing of conventional blood samples poses logistical challenges since blood samples must be centrifuged and frozen within 6-24 hours of venepuncture. Collection of dried blood spots (DBS) may facilitate a reflex testing strategy, therefore a systematic review and meta-analysis of the diagnostic accuracy of laboratory-based HCV tests DBS samples was undertaken. Based on the published evidence, the sensitivity and specificity of HCV-RNA in DBS were estimated at 0.95 (95% CI: 0.93 to 0.97) and 0.96 (95% CI: 0.93 to 0.98), compared with detection of HCV-RNA in conventional blood samples collected by venepuncture. However, the international evidence was of variable quality and is not directly applicable given that many of the studies were conducted in study populations at-risk of HCV acquisition in developing countries. The use of DBS would require independent validation in the healthcare setting of intended use prior to incorporation in a birth cohort testing programme.

Treatment effectiveness was mainly based on evidence underpinning the EASL treatment guidelines[35] and two relevant systematic reviews.[225, 228] The systematic reviews by the WHO[228] and USPSTF[225] were judged to be of low-quality and critically low-quality, respectively, following appraisal with AMSTAR 2.[229] However, factors that led to a downgrading of quality, such as a lack of protocol registration, do not necessarily discredit the estimates of treatment effects. The findings were also consistent across the reviews.

The current NHCTP guidelines (published May 2019) are based on the 2018 EASL treatment guidelines.[35, 181] In September 2020, the EASL published updated recommendations on the treatment of chronic HCV infection.[189] Notable changes to the EASL recommendations include:

- omitting sofosbuvir and ledipasvir combination therapy from the list of recommended DAA therapies

- recommending the use of sofosbuvir and velpatasvir in combination with weight-based ribavirin for 12 weeks in patients with HCV genotype 3 that are cirrhotic.

These updated recommendations are currently under review by the NHCTP's Clinical Advisory Group.

Safety outcomes were also based on published systematic reviews,[225, 228, 234] which demonstrated a positive safety profile for DAAs. The frequency of treatment-related harms included in these reviews is likely to be over-estimated since patients received ribavirin and interferon-based regimens in some of the included studies. Clinical evidence indicates that interferon-free and ribavirin-free DAA combinations have a superior safety profile.[35] Despite their positive safety profile,[233] it is theoretically possible that rare side-effects could occur that have not yet been identified during post-marketing surveillance, particularly when testing and treating an apparently healthy population.[2] In addition, trials were generally not designed to assess the effects on long-term outcomes, such as mortality.[225]

As we did not conduct our own systematic review, we have not formally assessed whether the patient populations included in the primary studies restrict generalisability to the 1965 to 1985 birth cohort. It is expected that patients identified by birth cohort testing will primarily be non-cirrhotic and treatment-naïve. However, the number of treatment-naïve and non-cirrhotic patients in trials was often small when stratified by HCV genotype and DAA combination. There is evidence emerging in the US that long-term outcomes for patients identified by birth cohort testing are similar to those identified by risk-based strategies.[250, 251] However, the evidence is limited in its quantity.

Finally, there is evidence to indicate that the relative effectiveness of DAA therapies may differ by HCV genotype.[252] A network meta-analysis could be used to estimate the relative effectiveness of DAA therapies by HCV genotype, however, the small number of patients across HCV genotypes would reduce the inferences that could be drawn. The preferred regimens recommended in Ireland are subject to a separate national procurement process and are not under evaluation in this HTA.[181]

5 Systematic review of economic evaluations

Key points

- A systematic review of economic evaluations identified 27 studies from 10 countries published between 2008 and 2020.
- The included studies assessed the cost-effectiveness of offering once-off testing to cohorts of the general population. However, the testing strategies varied substantially with the majority of studies assessing a variety of testing strategies.
- Sixteen studies compared birth cohort testing with either risk-based testing or no testing, nine of which reported results indicating that birth cohort testing was cost-effective.
- Eleven studies compared one-off general population testing with either risk-based testing or no testing. Of the eight cost-utility analyses (CUAs), six reported results indicating that general population testing was cost-effective.
- Eight studies (including seven CUAs) compared once-off universal testing (that is, testing the whole adult population) with either no testing or risk-based testing. Of the seven CUAs, five reported results indicating that universal testing was cost-effective.
- Key parameter data such as testing uptake rate, prevalence and disease progression of the undiagnosed cohort, diagnostic test performance were often poorly reported by studies. Where reported, uncertainty surrounding the cost-effectiveness estimates were often sensitive to changes in these parameters.
- The modelled treatment strategies, costs and effects varied substantially between studies. Treatment costs ranged from €3,331 to €115,852 per person, and effects ranged from 35% to 100%.
- Study quality and applicability were variable. Overall, six were low-quality, 17 were moderate-quality and four were high-quality. No included study was considered directly applicable to Ireland.

5.1 Introduction

This chapter reviews the existing international evidence on the cost-effectiveness of once-off age-based testing strategies for identifying people in the general population with undiagnosed chronic HCV infection that do not meet current criteria for risk-based testing.

The once-off testing strategies of interest include:

- birth cohort testing – testing is offered to an easily identified birth cohort which has evidence of an elevated risk of HCV infection relative to the rest of the general population. Most often, this cohort is defined in terms of an age range (which has a lower and upper limit) according to birth year. Therefore, people born in years outside of the birth cohort cannot age into the eligible cohort.
- general population testing – testing is offered to a subgroup of the general population, but this is not necessarily underpinned by an elevated risk of infection
- universal testing – the whole or near-whole adult population is offered testing.

It should be noted that the terminology surrounding these testing strategies is often used interchangeably in the international literature. However, in this chapter effort is made to distinguish between these strategies.

5.2 Review methodology

A systematic review was undertaken to identify the available cost-effectiveness evidence and to assess its applicability to the Irish setting. The purpose of the systematic review is to inform decision-making regarding the potential introduction of birth cohort testing in Ireland.

The proposed methods for this systematic review were outlined in a protocol which was registered with PROSPERO.[253] The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria,[254] and follows national HTA guidelines for the retrieval and interpretation of economic literature.[255]

5.2.1 Review question

The review question, presented in Table 5.1, was formulated in line with the population, intervention, comparator, outcomes, study design (PICOS) framework.

Table 5.1 PICOS for systematic review of cost-effectiveness

Population	Undiagnosed, asymptomatic, non-pregnant and treatment-naïve individuals who are not at an elevated risk of HCV infection*
Intervention	Once-off age-based testing: ▪ birth cohort testing** ▪ general population testing ▪ universal testing of the adult population.
Comparator	No testing or another testing strategy (such as risk-based testing).
Outcomes	**Primary outcomes:** Any relevant incremental ratio of costs and benefits (such as ICERs).
Study design	Full economic evaluations (CEA, CMA or CUA).

Key: CEA – cost-effectiveness analysis; CMA – cost-minimisation analysis; CUA – cost-utility analysis; HCV – hepatitis C virus; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year.
* An elevated risk of HCV infection is defined as an individual who falls into any of the risk groups identified in the Irish national clinical guideline for hepatitis C screening.[8]
** Birth cohort testing is defined as specific cohorts of older person at high risk of infection (because of historical exposure) and morbidity within populations that have an overall lower general prevalence.[38]

5.2.2 Types of studies

The review aimed to identify full economic evaluations (cost-effectiveness analysis, cost-utility analysis and cost-minimisation analysis).

5.2.3 Types of participants

The population of interest is undiagnosed, asymptomatic and treatment-naïve adults (aged 18 and above) who do not meet the criteria of risk-based testing guidelines.[8] The population may be suspected to have a high prevalence of HCV infection compared with the rest of the general population due to past generalised exposures that have since been identified and removed (such as the introduction of routine screening of blood products).[3]

5.2.4 Types of outcome measures

The main outcomes were incremental cost-effectiveness ratios (ICERs), typically expressed in terms of the cost per quality-adjusted life year (QALY) gained. However, ICERs may also be expressed in terms of disability-adjusted life years (DALYs), health or life years equivalent (LYE), cost per unit of disease-specific effect (for example, per case of hepatocellular carcinoma (HCC) avoided), or incremental net monetary benefit.

5.2.5 Exclusion criteria

The following exclusion criteria were applied:

- cost-consequence analysis, cost-benefit analysis, other types of cost analyses and comparative resource use studies
- economic evaluations of targeted risk-based testing strategies
- studies for which an English translation could not be found
- commentaries, letters, conference papers and abstracts where the full paper was unobtainable
- studies published before 2000.

5.2.6 Search strategy

All searches were run until 17 July 2020. The full search strategy can be found in Appendices 1 and 2.

Search terms were based on a 2016 systematic review which compared the cost-effectiveness of a variety of HCV testing strategies.[256] These search terms were appraised with a peer review checklist.[257] Where appropriate, the clinical search terms were combined with the relevant economic search filter for each database from the Scottish Intercollegiate Guidelines Network (SIGN).[258]

Electronic searches were carried out in Medline, Embase and the Cochrane Library (which includes the Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the National Health Service Economic Evaluation Database (NHS EED)). A grey literature search of national and international electronic sources was also undertaken. Studies included following full-text screening were hand-searched for additional literature.

5.2.7 Study identification and data extraction

Selection of studies

Citations were screened by one person to eliminate duplicates and clearly irrelevant studies. Two people independently reviewed the remaining citations as per the inclusion criteria, with disagreements resolved by discussion. Screening was undertaken using Covidence and EndNote X8 software.[259]

Data extraction and management

Data extraction was performed independently by two people, with disagreements resolved by discussion. Extracted data were recorded in Excel 2013 spreadsheets.

Assessment of quality and applicability

Quality was assessed using the Consensus for Health Economic Criteria (CHEC)-list questionnaire.[260] Applicability was assessed using the International Society for Pharmacoeconomics (ISPOR) questionnaire.[261] Quality and applicability assessments of the included studies were performed independently by two people with disagreements resolved by discussion.

Data synthesis

A narrative synthesis of the cost-effectiveness results was undertaken given the heterogeneous nature of the study data. Study-level descriptive statistics were calculated and presented, where appropriate.

Costs were presented in the 2019 Euro following adjustment for inflation and purchasing power parity in accordance with national HTA guidelines.[255, 262, 263] Where the cost year was not reported by the study authors, it was assumed that the unit costs were from two years prior to study publication (based on the average trend estimated from included studies which reported the unit cost year).

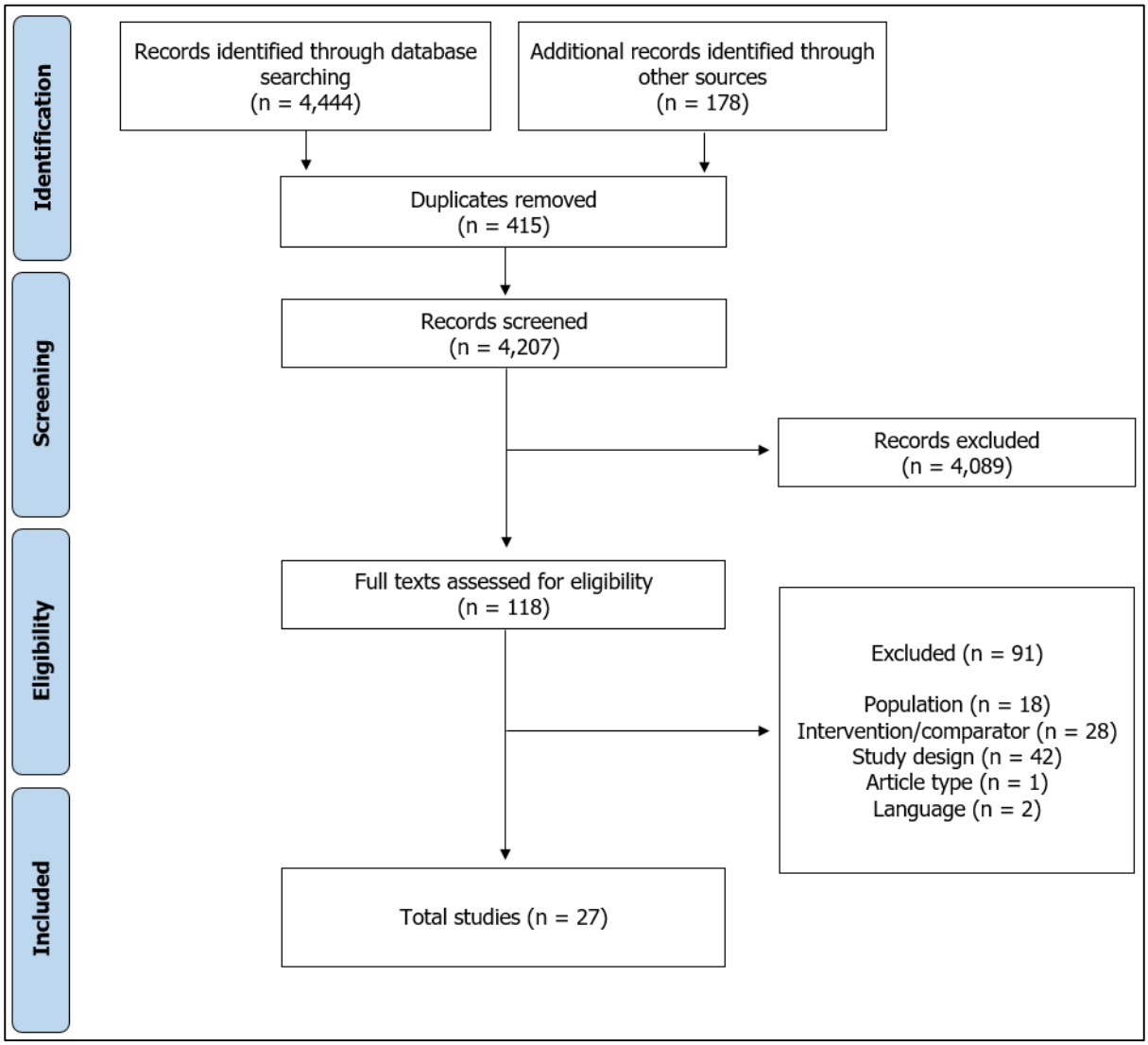
Willingness to pay (WTP) thresholds of €20,000 and €45,000 per quality adjusted life-year (QALY) gained have typically been used in Ireland as reference points for decision-making regarding the reimbursement of medicines. For the purpose of reporting in this systematic review, the cost-effectiveness of the testing strategies are interpreted by employing a WTP threshold of €45,000 per QALY.

5.3 Results

5.3.1 Search results

Overall, a total of 4,622 citations were identified from database and grey literature searching. Of these, 415 were removed as duplicate citations. A further 4,089 citations were excluded following title and abstract screening. Following full-text review, 27 studies were included in the synthesis.[65, 66, 73, 153, 177, 264-285] The PRISMA flow diagram,[254] outlining the flow of information during the systematic review process, is presented in Figure 5.1.

Figure 5.1. PRISMA flow diagram



Key: PRISMA – Preferred Reporting Items for Systematic Review and Meta-Analysis; n – number of citations.

5.3.2 Overview of study characteristics

Study characteristics of the included studies, published between 2008 and 2020, are presented in detail in Tables 5.2 to 5.6 and discussed in detail below. Of the included studies:

- nine were from the US[153, 177, 264, 266, 270, 276, 277, 281, 285]
- four were from South Korea[271-274]
- three were from Canada[73, 278, 284]
- two were from France[66, 268]
- two were from Italy[275, 282]
- two were from Japan[65, 279]
- two were from Spain[265, 267]
- one each from Belgium[280] and Bulgaria[269] and the UK.[283]

Target populations

Of the nine studies from the US,[153, 177, 264, 266, 270, 276, 277, 281, 285] six modelled the 1945-1965 "baby boomer" birth cohort,[153, 264, 266, 270, 281, 285] one modelled the 1946-1970 birth cohort (comprising an expansion of the baby boomer population),[277] one modelled those born between 1939 and 1973,[276] and one modelled testing of all those aged ≥18 years.[177]

Of the four studies from South Korea,[271-274] one study modelled those born between 1948-1977 and another modelled those born between 1953-1978.[271, 274] In the other two studies from South Korea, the alternative strategies comprised testing all those aged ≥18 years.

Of the three studies from Canada,[73, 278, 284] one modelled those born between 1945-1975,[278] one modelled alternative cohorts born between 1951-1990 and 1951-1970,[73] and the other study modelled alternative cohorts born between 1938-2002, 1953-1992 and 1953-1972.[284]

Of the two studies from France,[66, 268] one modelled the French "baby boomer" birth cohort born between 1945-1965.[66] The other modelled a range of target populations including those born between 1959-2000, 1959-1978, 1938-1978 and 1938-2000.[268]

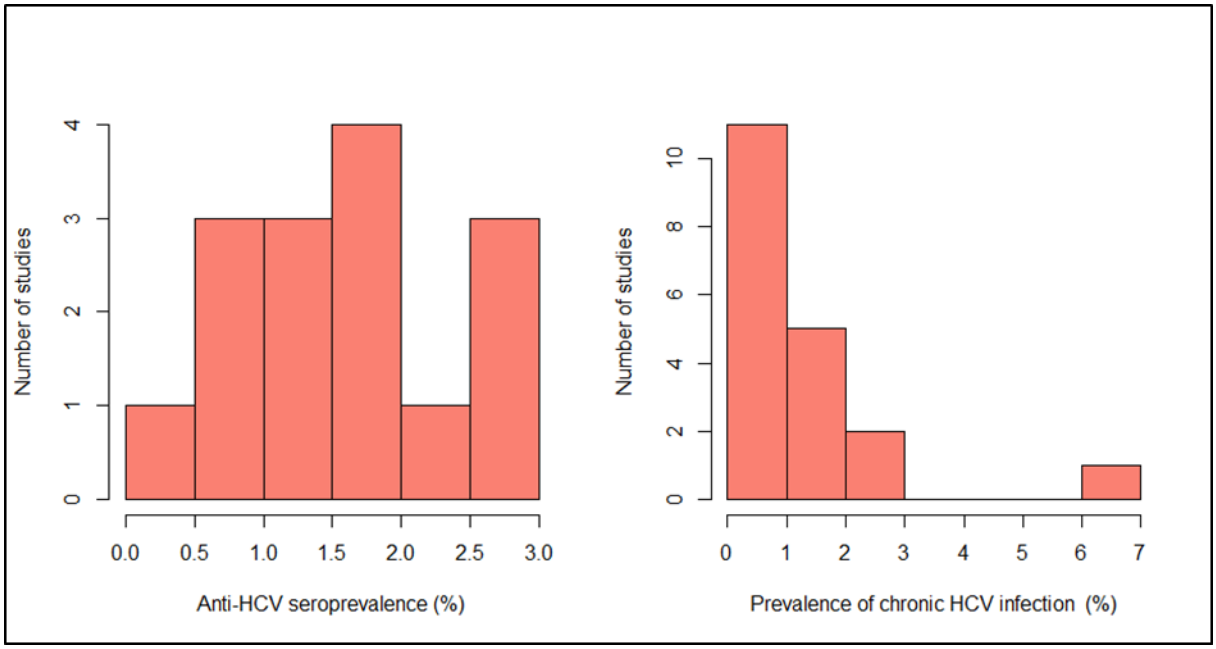
Of the two studies from Italy,[275, 282] one modelled those born between 1948-1978.[282] The other study modelled a range of target populations including those born between 1948-1977, 1958-1977, 1968-1987 and 1948-1967.[275] The two studies from Japan modelled those born between 1931-1980,[279] and 1938-1968.[65]

Of the two studies from Spain,[265, 267] one study modelled those born between 1943-1997,[267] the other modelled those born between 1938-1967.[265] The studies from

Belgium, Bulgaria and the UK modelled testing of all those aged ≥18 years,[280] those born between 1955-1980,[269] and those born between 1950-1979,[283] respectively.

The seroprevalence (that is, the presence of anti-HCV antibodies) rate of the target population was reported in 15 studies,[73, 177, 265-267, 270-274, 276, 278, 281, 284, 285] ranging from 0% to 3% in the base case. The prevalence rate of chronic HCV infection was reported in 19 studies,[65, 66, 73, 153, 265, 267, 268, 270, 272-274, 277-283, 285] ranging from 0% to 7%. A histogram of the modelled prevalence rates is presented in Figure 5.2.

Figure 5.2 Histogram of modelled prevalence rates, by number of studies*



* * Only one prevalence estimate is included per study. Where the prevalence rates were reported by subgroup and sufficient data were provided, a weighted mean estimate was calculated. Where the prevalence rates were reported by subgroup and sufficient data were not provided to calculate a weighted mean, the highest general population prevalence rate was selected.

The regional prevalence of HCV genotypes varies substantially across the globe due to country-specific and cultural factors. The HCV genotype distribution of the target population was reported in 18 studies.[65, 66, 73, 153, 177, 264, 266, 267, 271, 272, 274, 276-279, 282, 284, 285] HCV genotype 1 was the dominant genotype in each of these studies.

Disease severity of the target population, in terms of fibrosis progression, will influence the cost-effectiveness of testing strategies. The fibrosis distribution of the target population was reported in 19 studies.[66, 73, 153, 177, 265-268, 270-272, 274, 276-279, 283-285] In 17 studies,[66, 73, 153, 177, 265-268, 271, 272, 274, 276, 277, 279, 283-285] the disease severity of the target population trended towards the less progressed disease states (that is, F0-F2), but two studies trended towards the more progressed states (that is, F3-F4).[270, 278] Study population data are presented in Table 5.2.

Table 5.2. Characteristics of study populations

Study, country	Birth years*	Age range* (years)	Prevalence (%)		HCV genotype (%)						Fibrosis distribution (%)				
			Seropositive	Chronic HCV	1	2	3	4	5	6	F0	F1	F2	F3	F4
Barocas (2018), United States	1945-1965	53-73	NA	NA	79	10	10	1			NA				
	≤ 2000	≥ 18													
Buti (2018), Spain	1938-1967	50-79	1.77	0.78	NA						53		13	13	13
	1938-1997	20-79	1.11	0.44											
Coffin (2012), United States	1945-1965	47-67	1.60	NA	78	22		0	0	0	20	20	20	20	20
	1943-1992	20-69													
Crespo(2019), Spain	1943-1997	20-74	1.20	0.4	66	0	21	14	0	0	50		20	15	15
Deuffic-Burban (2018), France **	1938-1978	40-80	NA	0.19	NA						24	21	19	13	23
Dimitrova (2019), Bulgaria	1955-1980	39-64	NA	NA	NA						NA				
Eckman (2013), United States	≤ 1995	≥ 18	1.40	NA	78	22		0	0	0	20	20	20	20	20
Eckman (2019), United States	1945-65	53-73	2.60	2.03	NA						1	15	15	14	55
	≤ 1995	≥ 18***	1.00	0.78							2	18	16	14	50
Ethgen (2017), France	1945-65	52-72	NA	0.53**	62	39					33	38	17	6	6
Kim (2017), South Korea	1968-1977	40-49	0.60	NA	53	47	0	0	0	0	83				18
	1958-1967	50-59	0.80	NA											
	1948-1955	60-69	1.53	NA											
Kim (2018), South Korea	1969-1978	40-49	0.38	0.18	54	46	0	0	0	0	23	36	20	13	8
	1959-1968	50-59	0.61	0.28							15	30	21	18	18
	1949-1958	60-65	1.06	0.49							10	23	19	19	29
Kim (2019),	≤ 1999	≥ 20	0.65	0.35	NA						NA				

Study, country	Birth years*	Age range* (years)	Prevalence (%)		HCV genotype (%)						Fibrosis distribution (%)				
			Seropositive	Chronic HCV	1	2	3	4	5	6	F0	F1	F2	F3	F4
South Korea															
Kim (2020), South Korea	≤ 1980	≥ 40	0.77	0.36	54	46	0	0	0	0	8	29	33	19	12
Kondili (2020), Italy	1948-77	43-72	NA	NA	NA						NA				
Liu (2013), United States	1939-1973	40-74	2.22	NA	80	20					13	51	13	10	13
McEwan (2013), United States	1945-1965	48-68	NA	1.77	75	25		0	0	0	15	30	20	17	18
McGarry (2012), United States	1946-1970	40-64	NA	1.56	75	25		0	0	0	17	31	20	16	17
Mendlowitz (2019), Canada	1945-1975	44-74	1.80	1.33	67	9	22	1	1		5	18	20	35	23
Nagai (2020), Japan	1971-1980	40-49	0.22	NA	65	35	0	0	0	0	100				0
	1961-1970	50-59	0.35	NA							99				1
	1951-1960	60-69	0.36	NA							98				2
	1941-1950	70-79	0.60	NA											
	1931-1940	80-89	1.36	NA											
Nakamura (2008), Japan	1938-1968	40-70	NA	0.36	70	30		0	0	0	NA				
Opstaele (2019), Belgium	≥ 18	≤ 2001	0.60	NA	NA						NA				
Rein (2012), United States	1945-1965	47-67	2.84	1.79	NA						NA				
Ruggeri (2013), Italy	1983-1998	15-30	NA	2.0	66	20	6	8	0	66	NA				
	1968-1982	31-45		6.00											
	1953-1967	46-60		7.00											

Study, country	Birth years*	Age range* (years)	Prevalence (%)		HCV genotype (%)						Fibrosis distribution (%)				
			Seropositive	Chronic HCV	1	2	3	4	5	6	F0	F1	F2	F3	F4
	≤ 1952	≥ 60		5.00											
Williams (2019), UK	1950-1979	40-69	NA	0.20	NA						43		39		18
Wong (2015), Canada¥	1981-1990	25-34	0.40	0.29	67	9	22	1	1		20	36	36	5	4
	1971-1980	35-44	0.40	0.29							7	37	37	14	7
	1961-1970	45-54	0.80	0.58							1	25	25	27	22
	1951-1960	55-64	0.80	0.58							0	15	15	34	36
Wong (2017), Canada ₸	1968-2003	14-49	0.00	NA	67	9	22	1	1		16	31	15	23	15
	1953-1967	50-64	0.01	NA											
Younossi (2017), United States	1945-1965	50-70	2.73	2.09	73	13	12	1	0		Non-genotype 3:				
	≤ 1997	≥ 20	1.70	1.30							11	26	30	18	15
											Genotype 3:				
											10	24	28	17	20

Key: F – METAVIR fibrosis stage; GT – genotype; HCV – hepatitis C virus; NA – not available.
* Birth years or age range are calculated from year of publication when this could not be identified from the paper directly.
** Fibrosis distribution calculated by combining individual subgroup estimates of undiagnosed individuals which stratified by age, gender and alcohol status.
*** Fibrosis distribution in overall general population calculated by aggregating fibrosis distributions of 1945-1965 birth cohort and general population excluding 1945-1965 birth cohort.
¥ Median seroconversion of 77.5% used to calculate the prevalence of chronic HCV infection.
₸ Fibrosis distribution comprises an average across subgroups presented. Population weights were unavailable.

Testing strategies

All of the studies assessed the cost-effectiveness of offering one-time HCV testing to people in the general population. However, these strategies (presented in Table 5.3) varied substantially from study to study according to target age group and whether or not there was evidence of an elevated risk of HCV that underpinned selection of the modelled cohort.

In 17 studies, at least one testing strategy was defined by an age range where the target population was suspected of an elevated risk of infection when compared with the overall general population (that is, a birth cohort was specified).[66, 153, 264-266, 268-271, 274-278, 281, 283, 285] One study modelled graduated birth cohort testing in which testing was offered to a specific birth cohort in year one and then subsequently offered to another birth cohort in year three.[275]

In 17 studies, at least one testing strategy was defined according to an arbitrary age range (for example, those aged 18-70) or threshold (for example, those aged ≥40) for which the rationale (such as inferred risk from epidemiological data) was not described.[65, 73, 177, 264-268, 270, 272, 273, 275, 279, 280, 282, 284, 285] One of these studies modelled a catch-up programme at age 65, whereby testing was offered to those that did not attend HCV testing when initially offered.[272]

Universal testing (that is, offering testing to the whole or near-whole adult population) was modelled in 11 studies.[177, 264, 265, 268, 270, 273, 275, 278, 280, 284, 285] Overall, eight studies undertook age-based subgroup analyses to identify the age bands in which testing would be most cost-effective.[65, 267, 271, 273, 276, 279, 282, 283]

Of the 27 included studies, only two modelled a systematic testing programme where the healthcare attendance was initiated specifically for the purpose of HCV testing.[267, 268] Both studies were based on cross-sectional studies in which study participants were invited (by telephone or letter) to attend HCV testing.[267, 268]

Twelve studies modelled opportunistic testing programmes, in which HCV testing was offered to those already attending a healthcare appointment (for example, routine health examination).[65, 269, 272-274, 276, 278, 280, 281, 283-285] Testing was offered to people attending routine medical or primary care appointments scheduled for another purpose in five of these studies,[269, 276, 281, 284, 285] and to people attending an emergency department (ED) in two studies.[278, 280] Opportunistic testing was modelled as an add-on to existing national health programmes in five studies.[65, 272-274, 283] The healthcare setting and mechanism of invitation of the modelled testing programme was unclear in 13 studies.[66, 73, 153, 177, 264-266, 270, 271, 275, 277, 279, 282]

Details on the implementation and organisational implications of the proposed testing strategies were limited. Two studies specified that all testing occurred in year one,[153, 281] while two studies specified that testing took place at the outset of model simulation.[271, 276] One study assumed that 100% of the target population (those born between 1945 and 1965) would be tested in equal proportions over a five-year period.[277] In one study,[280] one testing round per year over five years was assumed with a different patient population attending the ED every year. One study specified graduated birth cohort testing whereby one birth cohort was offered testing in year one and then testing was subsequently offered to another birth cohort in year three.[275] Testing and treatment of the target population was modelled over a two-year timeframe in one study.[273]

One study was based on outcomes of a national testing strategy implemented between 2003 and 2006.[65] One study modelled "low", "intermediate" and "high" testing scenarios corresponding to rates of awareness (70%, 75% and 80%, respectively) of chronic HCV infection over a 20-year period.[66] One study specified that testing was offered at a national health check which occurs every five years, but it was unclear if HCV testing was offered repeatedly to those that declined testing at their initial health check.[283] The period over which testing was implemented was unspecified in 16 studies.[73, 177, 264-270, 272, 274, 279, 282-285]

Three studies modelled the phasing of treatment to manage capacity implications.[153, 271, 280] One study modelled that 24% of patients were treated in year one and treated in equal proportions over the subsequent 10-year period.[153] One study assumed that 60% of patients were treated in year one, with the remainder treated in equal proportions over the subsequent four years.[271] Treatment was phased over a three-year period in one study.[274] In one study, it was assumed that 70% of patients were treated in the year following diagnosis, with 85% of patients treated in each subsequent year thereafter.[280]

The testing sequence for diagnosing chronic HCV infection varied slightly between studies. Twenty-six studies modelled the use of an anti-HCV antibody test to determine if the patient was ever exposed to HCV.[65, 66, 73, 177, 264-285] Twenty-three studies also modelled the use of an HCV-RNA test to determine chronic HCV infection.[65, 66, 73, 177, 264-268, 270-279, 282-285] Only one study modelled the use of an antigen test to detect chronic HCV.[65]

Reflex testing, in which anti-HCV antibody and HCV-RNA tests are performed on the same sample, was modelled in two studies.[278, 283] Reflex testing was performed on all anti-HCV positive samples in one study,[278] and on 65% of anti-HCV positive samples in the other study.[283]

Ten studies reported the use of blood samples,[73, 265, 267, 270-274, 282, 284] one study reported the use of dried blood spots (DBS).[278] The sample type modelled in the other studies was not reported.[65, 66, 153, 177, 264, 266, 268, 269, 275-277, 279-281, 283, 285]

Table 5.3. Testing strategies of included studies

Study	Country	Testing strategy*
Barocas (2018)	United States	1) Testing those aged 53-73 (1945-1965) 2) Testing those aged ≥ 40 3) Testing those aged ≥ 30 4) Testing those aged ≥ 18
Buti (2018)	Spain	1) Testing those aged 20-79 (1938-1997) 2) Risk-based testing 3) Testing those aged 50-79 (1938–1967) and risk-based testing of those aged 20-49 (1968-1997)
Coffin (2012)	United States	1) Risk-based testing 2) Testing those aged 20-69 (1943-1992) 3) Testing those aged 47-67 (1945-1965)
Crespo (2019)	Spain	1) No testing 2) Testing those aged 20-74 (1943-1997)
Deuffic-Burban (2018)	France	1) Risk-based testing 2) Testing men aged 18-59 (1959-2000) 3) Testing those aged 40-59 (1959-1978) 4) Testing those aged 40-80 (1938-1978) 5) Testing those aged 18-80 (1938-200)
Dimitrova (2019)	Bulgaria	1) No testing** 2) Testing those aged 39-64 (1955-1980)
Eckman (2013)	United States	1) No testing 2) Testing those aged ≥ 18
Eckman (2019)	United States	1) No testing 2) Testing those aged ≥ 18 3) Testing those aged 53-73 (1945-1965)
Ethgen (2017)	France	1) No testing 2) Testing those aged 52-72 (1945-1965), with treatment restrictions 3) Testing those aged 52-72 (1945-1965), without treatment restrictions
Kim (2017)	South Korea	1) No testing 2) Testing those aged 40-69 (1948-1977)
Kim (2018)	South Korea	1) No testing** 2) Testing those aged 40-65 (1953-1978)
Kim (2019)	South Korea	1) No testing 2) Testing those aged ≥ 20 3) Testing those aged ≥ 40 4) Testing those aged ≥ 60
Kim (2020)	South Korea	1) Risk-based testing 2) Testing those aged ≥ 40 3) Testing those aged ≥ 40, with catch-up programme for non-attenders at 65
Kondili (2020)	Italy	1) Risk-based testing 2) Testing those aged 43-72 (1948-1977) 3) Testing those aged 43-62 (1958-1977)

Study	Country	Testing strategy*
		4) Testing those aged 33-52 (1968-1987) in year 1, testing those aged 53-72 (1948-1967) in year 3 5) Testing those aged 53-72 (1948-1967) in year 1, testing those aged 33-52 (1968-1987) in year 3 6) Testing the entire Italian population
Liu (2013)	United States	1) No testing** 2) Risk-based testing 3) Testing those aged 40-74 (1939-1973)
McEwan (2013)	United States	1) Risk-based testing 2) Testing those aged 48-68 (1945-1965)
McGarry (2012)	United States	1) Risk-based testing 2) Testing those aged 40-64 (1946-1970)
Mendlowitz (2019)	Canada	1) No testing** 2) Testing those aged 44-74 (1945-1975) 3) Testing those aged ≥ 15
Nagai (2020)	Japan	1) No testing 2) Testing those aged 40-89 (1931-1980)
Nakamura (2008)	Japan	1) No testing 2) Testing those aged 40-70 (1938-1968)
Opstaele (2019)	Belgium	1) No testing 2) Testing PWID 3) Testing MSM 4) Testing those aged ≥ 18
Rein (2012)	United States	1) No testing 2) Risk-based testing 3) Testing those aged 47-67 (1945-1965)
Ruggeri (2013)	Italy	1) No testing 2) Testing those aged 35-65 (1948-1978)
Williams (2019)	UK	1) No testing** 2) Testing those aged 40-69 (1950-1979)
Wong (2015)	Canada	1) No testing** 2) Testing those aged 25-64 (1951-1990) 3) Testing those aged 45-64 (1951-1970)
Wong (2017)	Canada	1) No testing** 2) Testing those aged 15-79 (1938-2002) 3) Testing immigrant population aged 15-79 (1938-2002) 4) Testing those aged 25-64 (1953-1992) 5) Testing those aged 45-64 (1953-1972)
Younossi (2017)	United States	1) Risk-based testing 2) Testing those aged 52-72 (1945-1965) 3) Testing those aged ≥ 20

Key: MSM – men who have sex with men; PWID – people who inject drugs.
* Age bands or birth years were calculated based on publication year when this could not be identified from the paper directly.
** Background rate of detection was modelled as part of the no testing comparator.

Model characteristics

Of the included studies, 24 comprised modelled cost-utility analyses (CUAs),[66, 73, 153, 177, 264-268, 270-272, 274-285] and three were modelled cost-effectiveness analyses (CEAs).[65, 269, 273]

Fourteen studies used Markov models (simulating the natural progression of disease),[65, 66, 73, 264, 267, 273-277, 281-284] 11 studies used decision tree (to simulate the costs and consequences of offering testing) and Markov model hybrids,[153, 177, 265, 266, 268, 270-272, 279, 280, 285] one study used an individual-level state-transition model (that is, a microsimulation),[278] and in one study the model structure was unclear.[269]

Twenty-five studies were conducted from the perspective of the publically-funded healthcare system,[65, 66, 73, 153, 177, 264-272, 274-280, 282-285] one study adopted a societal perspective,[281] and the perspective adopted in one study was unclear.[273]

Twenty-three studies employed a lifetime time horizon.[65, 73, 153, 177, 264-268, 270-272, 274, 276-285] Four studies reported time horizons between 11 and 33 years. [66, 269, 273, 275]

Discounting, which reflects time preferences by converting future costs and benefits to present values, was applied to costs and benefits at a rate of 3% in 12 studies.[65, 177, 264-267, 270, 273, 276, 277, 281, 285] Four studies each applied a discount rate of 3.5%,[153, 272, 282, 283] and 5%.[73, 271, 274, 284] Two studies applied discount rates of 4%,[66, 268] although the discount rate decreased to 2% after 30 years in one of these.[268] One study each applied a discount rate of 1.5%,[278] and 2%.[279] The current discount rate in Ireland is 4%.[263]

Differential discounting, which generally involves discounting benefits at a lower rate than that of costs to allow for increasing value of benefits over time,[286-288] was applied in two studies.[269, 280] One study applied discount rates of 3% and 1.5% to costs and benefits, respectively.[280] One study applied a discount rate of 3.5% to costs, but did not apply discounting to benefits.[269] Discounting was not reported in one study.[275] Differential discounting is not used in Ireland at present.

Characteristics of the modelled analyses are presented in Table 5.4.

Table 5.4. Cost-effectiveness analysis characteristics of included studies

Study	Country	Evaluation framework	Model type	Perspective	Time horizon	Discount rate
Barocas (2018)	United States	CUA	Markov	Healthcare system	Lifetime	3%
Buti (2018)	Spain	CUA	Decision tree/Markov	Healthcare system	Lifetime	3%
Coffin (2012)	United States	CUA	Decision tree/Markov	Healthcare system	Lifetime	3%
Crespo (2019)	Spain	CUA*	Markov	Healthcare system	Lifetime	3%
Deuffic-Burban (2018)	France	CUA	Decision tree/Markov	Healthcare system**	Lifetime	4%****
Dimitrova (2019)	Bulgaria	CEA	Unclear	Healthcare system	11 years	Costs: 3.5% Benefits: NR
Eckman (2013)	United States	CUA	Decision tree/Markov	Healthcare system	Lifetime	3%
Eckman (2019)	United States	CUA	Decision tree/Markov	Healthcare system	Lifetime	3%
Ethgen (2017)	France	CUA	Markov	Healthcare system	20 years	4%
Kim (2015)	Egypt	CUA	Markov	Societal***	40 years	3%
Kim (2017)	South Korea	CUA	Decision tree/Markov	Healthcare system	Lifetime	5%
Kim (2018)	South Korea	CUA	Markov	Healthcare system	Lifetime	5%
Kim (2019)	South Korea	CEA	Markov	Unclear	33 years	3%
Kim (2020)	South Korea	CUA	Decision tree/Markov	Healthcare system	Lifetime	3.5%
Kondili (2020)	Italy	CUA	Markov	Healthcare system	13 years	NR
Liu (2013)	United States	CUA	Markov	Healthcare system**	Lifetime	3%
McEwan (2013)	United States	CUA	Decision tree/Markov	Healthcare system	Lifetime	3.5%
McGarry (2012)	United States	CUA	Markov	Healthcare system	Lifetime	3%
Mendlowitz (2019)	Canada	CUA	Microsimulation	Healthcare system	Lifetime	1.5%
Nagai (2020)	Japan	CUA	Decision tree/Markov	Healthcare system	70 years	2%
Nakamura (2008)	Japan	CEA	Markov	Healthcare system	Lifetime	3%

Study	Country	Evaluation framework	Model type	Perspective	Time horizon	Discount rate
Opstaele (2019)	Belgium	CUA	Decision tree/Markov	Healthcare system	60 years	Costs: 3% Benefits: 1.5%
Rein (2012)	United States	CUA	Markov	Societal***	Lifetime	3%
Ruggeri (2013)	Italy	CUA	Markov	Healthcare system	Lifetime	3.5%
Williams (2019)	UK	CUA	Markov	Healthcare system	Lifetime	3.5%
Wong (2015)	Canada	CUA	Markov	Healthcare system	Lifetime	5%
Wong (2017)	Canada	CUA	Markov	Healthcare system	Lifetime	5%
Younossi (2017)	United States	CUA	Decision tree/Markov	Healthcare system	Lifetime	3%

Key: CEA – cost-effectiveness analysis; CUA – cost-utility analysis; NR – not reported.
* The CUA was informed by and reported as part of an observational study
** Reported as societal perspective, but only direct medical costs included in CUA. Productivity losses were not included.
*** Only direct medical costs included (no patient costs), but productivity losses were modelled.
**** Discount rate reduced to 2% after 30 years in the model simulation.

5.3.2 Summary of clinical effectiveness and cost estimates

The parameters used to represent the clinical pathway (such as testing uptake, diagnostic test accuracy, treatment uptake and treatment effectiveness) and intervention costs will influence the clinical- and cost-effectiveness of the modelled testing strategy.

The uptake of HCV testing was reported in 20 studies,[66, 73, 153, 265-269, 271-274, 277-281, 283-285] ranging from 1.5% to 100% (median: 74%). The modelled uptake rate of HCV testing was unclear in seven studies.[65, 177, 264, 270, 275, 276, 282]

The sensitivity and specificity of anti-HCV testing was reported in 10 studies.[177, 264, 267, 270, 271, 274, 276, 279, 282, 283] The sensitivity of anti-HCV testing ranged from 94% to 100% (median: 99%). The specificity of anti-HCV testing ranged from 47% to 100% (median: 99%).

The sensitivity and specificity of HCV-RNA testing was reported in only five studies.[264, 267, 271, 282, 283] The sensitivity of HCV-RNA testing ranged from 96% to 100% (median: 100%). The specificity of HCV-RNA testing was reported at approximately 100% in each of the five studies.

Eight studies modelled interferon-based treatment regimens only.[65, 153, 177, 266, 276, 277, 281, 282] The uptake rate of interferon-based treatment was reported in six of these studies,[65, 177, 266, 276, 277, 281] ranging from 24% to 100% (median: 33%). All eight studies reported the modelled rate of SVR for interferon-based treatment, ranging from 48% to 85% (median: 54%).

Nineteen studies modelled interferon-free treatment regimens, which are associated with higher efficacy and an improved safety profile.[66, 73, 264, 265, 267-275, 278-280, 283-285] The uptake rate of interferon-free treatment was reported in 12 studies,[73, 265, 270-274, 278, 279, 283-285] ranging from 35% to 100% (median: 64%). Sixteen studies reported the modelled rate of SVR for interferon-free treatment, ranging from 89% to 98% (median: 96%).[66, 73, 264, 265, 267-271, 274, 275, 278, 279, 283-285]

The cost of anti-HCV testing was reported in 23 studies,[65, 66, 73, 153, 177, 264-267, 270-274, 276-279, 281-285] ranging from €3 to €39 (median: €16). The cost of HCV-RNA testing was reported in 23 studies,[65, 66, 73, 153, 177, 264-267, 270-279, 282-285] ranging from €34 to €178 (median: €74). One study reported a combined cost of anti-HCV and HCV-RNA testing of €146.[66] The heterogeneous nature of these costs results from variability in the cost components included (for example, costs of staff time, staging and HCV genotyping) and or variability in the cost of laboratory resources (for example, equipment and staff time). These data are summarised in Table 5.5.

The costs of treatment were reported in all 27 studies. In the studies that modelled interferon-based treatment only, costs ranged from €17,181 to €71,116 (median: €84,037).[65, 153, 177, 266, 276, 277, 281, 282] In the studies that modelled interferon-free treatment, costs ranged from €4,852 to €62,962 (median: €31,259).[66, 73, 264, 265, 267-275, 278-280, 283-285] Treatment costs can vary according by country, HCV genotype, disease stage, combination therapy, duration of therapy and the source of the unit cost (for example, published list price or expert opinion). Representative costs are presented in Table 5.6. The full list of modelled therapies and treatment costs are presented in Appendix 3.

Table 5.5. Characteristics of modelled testing strategies

Study	Testing	Anti-HCV		HCV-RNA		Adjusted cost (2019 €)*	
	uptake (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Anti-HCV	HCV-RNA
Barocas (2018)	NA	100	97	89	100	16	66
Buti (2018)	100	NA	NA	NA	NA	39	96
Coffin (2012)	15	NA	NA	NA	NA	21	62
Crespo (2019)	23	99	96	100	100	5	65
Deuffic-Burban (2018)	50	NA	NA	NA	NA	NA	NA
Dimitrova (2019)	45	NA	NA	NA	NA	NA	NA
Eckman (2013)	NA	94	NA	97	NA	20	107
Eckman (2019)	NA	94	NA	97	NA	16	88
Ethgen (2017)	75	NA	NA	NA	NA	16	66
Kim (2017)	72	100	100	47	100		178**
Kim (2018)	76	98	NA	100	NA	3	124
Kim (2019)	76	NA	NA	NA	NA	3	71
Kim (2020)	72	NA	NA	NA	NA	17	126
Kondili (2020)	NA	NA	NA	NA	NA	3	35
Liu (2013)	NA	97	NA	100	NA	NA	76
McEwan (2013)	91	NA	NA	NA	NA	20***	36***
McGarry (2012)	100	NA	NA	NA	NA	30	83
Mendlowitz (2019)	50	NA	NA	NA	NA	16	77
Nagai (2020)	2	99	NA	99	NA	9	35
Nakamura (2008)	NA	NA	NA	NA	NA	11	34

Study	Testing	Anti-HCV		HCV-RNA		Adjusted cost (2019 €)*	
	uptake (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Anti-HCV	HCV-RNA
Opstaele (2019)	8	NA	NA	NA	NA	NA	NA
Rein (2012)	91	NA	NA	NA	NA	34	NA
Ruggeri (2013)	NA	100	100	100	100	11	85
Williams (2019)	48	100	100	100	100	5	85
Wong (2015)	91	NA	NA	NA	NA	10	71
Wong (2017)	90	NA	NA	NA	NA	10	70
Younossi (2017)	86	NA	NA	NA	NA	16	48

Key: anti-HCV – hepatitis C virus antibody test; NA – not available; RNA – ribonucleic acid test.
Note: figures are rounded to the nearest integer.
* Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.[262, 263] Where studies did not report the cost year, it was assumed that the cost year was two years prior to the year of publication, based on the mean observed from studies that reported the cost year.
** Includes the costs of anti-HCV testing, HCV-RNA testing, disease staging and HCV genotyping.
*** Cost of testing was reported according to whether positive or negative diagnosis observed. Assumed that negative diagnosis comprises anti-HCV test only, while positive diagnosis involves both anti-HCV and HCV-RNA tests.

Table 5.6. Characteristics of modelled treatment strategies

Study	Treatment uptake (%)*	SVR (%)*	Adjusted cost (2019 €)*¥
Interferon-free therapies			
Barocas (2018)	NA	96	58,177
Buti (2018)	82	98	31,493
Crespo (2019)	NA	96	9,122
Deuffic-Burban (2018)	NA	95	31,259
Dimitrova (2019)	NA	95	25,206
Eckman (2019)	100	94	22,083
Ethgen (2017)	NA	89	46,792
Kim (2017)	39	97	13,369
Kim (2018)	64	96	12,863
Kim (2019)	35	NA	8,422
Kim (2020)	64	NA	11,754
Kondili (2020)	NA	97	4,852
Mendlowitz (2019)	95	98	40,078
Nagai (2020)	90	97	36,011
Opstaele (2019)	NA	NA	43,974
Williams (2019)	50	92	12,393
Wong (2015)	55	94	36,048
Wong (2017)	88	94	40,903
Younossi (2017)	50	98	62,962
Interferon-based therapies			
Coffin (2012)	32	48	54,704
Eckman (2013)	28	85	70,871
Liu (2013)	33	50	25,826
McEwan (2013)	NA	72	55,236
McGarry (2012)	24	72	71,116
Nakamura (2008)	100	56	32,478
Rein (2012)	41	52	48,468
Ruggeri (2013)	NA	48	17,181

Key: NA – not available; SVR – sustained virological response.

* Representative averages have been derived to reflect study population data (such as prevalence, genotypes and disease stage) influencing treatment uptake, alternative treatment regimens, SVR rates and costs. A full list of modelled treatments is presented in Appendix 3.

¥ Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.[262, 263] Where studies did not report the cost year, it was

assumed that the cost year was two years prior to the year of publication, based on the mean observed from studies that reported the cost year.

5.3.3 Summary of cost-effectiveness results

Birth cohort testing versus no testing or risk-based testing

Sixteen studies (details of which are presented in Table 5.7) compared birth cohort testing with either risk-based testing or no testing.[66, 73, 153, 266, 268, 270, 271, 274-278, 281, 283-285] Fourteen studies reported results indicating that birth cohort testing was cost-effective when employing a willingness to pay (WTP) threshold of €45,000 per QALY gained.[73, 153, 266, 268, 270, 271, 274, 275, 277, 278, 281, 283-285] Overall, two studies found that birth cohort testing was cost-saving and more effective than risk-based testing,[270, 285] with the ICERs from the remaining studies ranging from €5,279 to €66,098 per QALY gained.

From Figure 5.3, it can be seen that the ICERs of all studies published since 2018 would be considered cost-effective at a €45,000 WTP threshold. This finding may reflect a reduction in treatment costs in recent years and the likelihood that current risk-based testing practices identifies fewer undiagnosed cases over time.

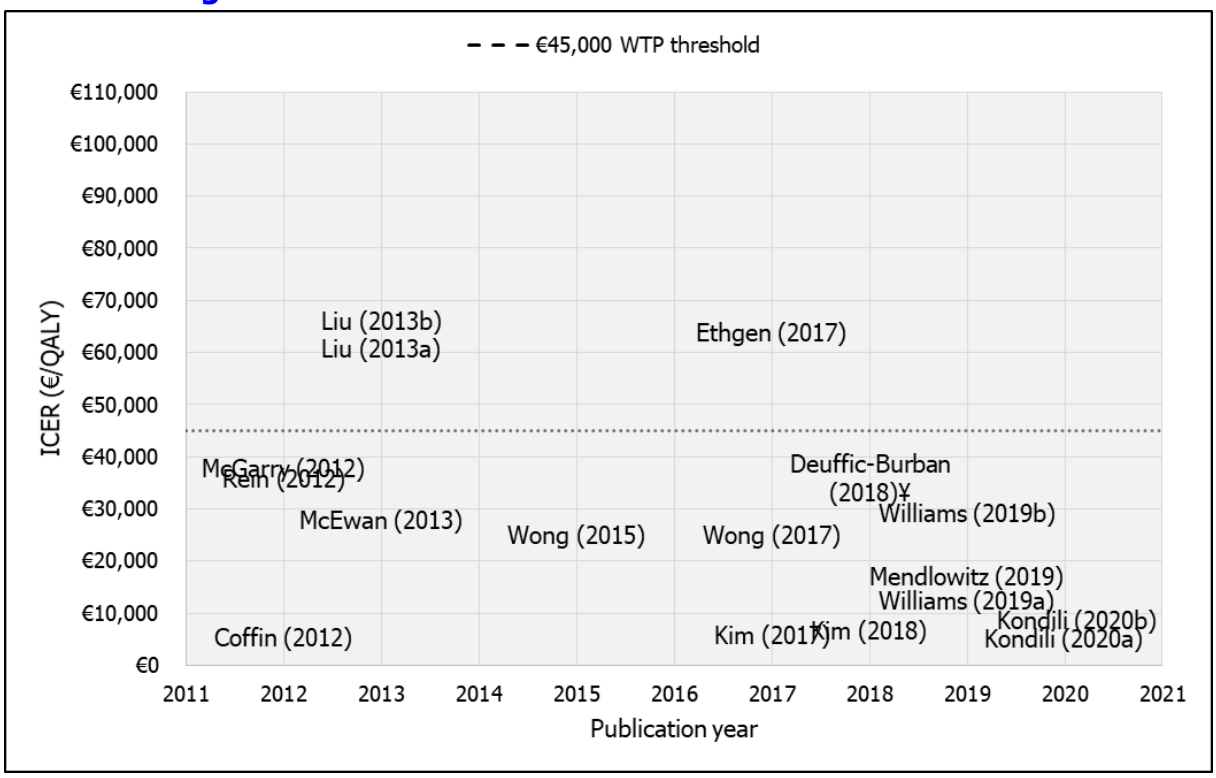
One study compared several birth cohort testing strategies with risk-based testing:

- testing those aged 43-72 (born 1948-1977)
- testing those aged 43-62 (born 1958-1977)
- testing those aged 33-52 (born 1968-1987) in year 1, and testing those aged 53-72 (born 1948-1967) in year 3
- testing those aged 53-72 (born 1948-1967) in year 1, and testing those aged 33-52 (born 1968-1987) in year 3.[275]

In each case, birth cohort testing was cost-effective when compared with risk-based testing. However, it should be noted that a fully incremental analysis (in which each strategy is ranked according to total effects and compared with the next best alternative) was not conducted.

One study reported results according to whether transition probabilities were based on a commonly cited study in the UK,[289] or an adapted version of a previously published back-calculation model that uses hospital statistics and national statistics data on decompensated cirrhosis, hepatocellular carcinoma, and HCV-related mortality to estimate the burden of HCV.[290-293] In either case, the estimated ICER was below the WTP threshold of €45,000.

Figure 5.3. ICERs comparing birth cohort testing with no testing or risk-based testing*



Key: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year; WTP – willingness to pay.

Note: Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.[262, 263] Where studies did not report the cost year, it was assumed that the cost year was two years prior to the year of publication, based on the mean observed from studies that reported the cost year. A WTP threshold of €45,000 per QALY is typically used in Ireland for reimbursement of pharmaceuticals.[263]

* Two studies found that birth cohort testing dominated no testing and risk-based testing.[270, 285] Therefore, no ICER is presented for these studies.

¥ Testing those aged 40-59 is presented here as a birth cohort strategy given consideration of all strategies evaluated in the CUA. However, it should be noted that it was unclear whether evidence of an elevated risk of HCV infection, compared with the rest of the general population, underpinned the selection of this cohort. The ICER has been calculated from study results compared with alternatives of interest and may be subject to rounding error. Finally, the strategy was weakly dominated (that is, it had a higher ICER than that of a more effective alternative) by strategies of testing those aged 40-80 and 18-80.

Table 5.7. ICERs comparing birth cohort testing with no testing or risk-based testing

Study	Country	Intervention	Adjusted ICER (€/QALY)
Coffin (2012)	United States	Testing those aged 47-67 (born 1945-1965)	€5,429
Deuffic-Burban (2018)¥	France	Testing those aged 40-59 (born 1959-1978)	€36,103
Eckman (2019)	United States	Testing those aged 54-74 (born 1945-1965)	Dominant
Ethgen (2017)	France	Testing those aged 52-72 (born 1945-1965)	€63,960
Kim (2017)*	South Korea	Testing those aged 40-69 (born 1957-1977)	€5,872
Kim (2018)*	South Korea	Testing those aged 60-65 (born 1949-1978)	€6,807
Kondili (2020a)	Italy	Testing those aged 33-52 (born 1968-1987) in year 1, testing those aged 53-72 (born 1948-1967) in year 3	€5,275
Kondili (2020b)	Italy	Testing those aged 53-72 (born 1948-1967) in year 1, testing those aged 33-52 (1968-1987) in year 3	€5,860
Kondili (2020c)	Italy	Testing those aged 43-72 (born 1948-1977)	€4,308
Kondili (2020d)	Italy	Testing those aged 43-62 (born 1958-1977)	€5,497
Liu (2013a)**	United States	Testing those aged 40-74 (born 1939-1973)	€60,912
Liu (2013b)**	United States	Testing those aged 40-74 (born 1939-1973)	€66,098
McEwan (2013)	United States	Testing those aged 48-68 (born 1945-1965)	€27,905
McGarry (2012)	United States	Testing those aged 40-64 (born 1946-1970)	€37,900
Mendlowitz (2019)	Canada	Testing those aged 44-74 (born 1945-1975)	€17,089
Rein (2012)	United States	Testing those aged 47-67 (born 1945-1965)	€35,890
Williams (2019a)*	UK	Testing those aged 47-67 (born 1945-1965)	€12,479
Williams (2019b)*	UK	Testing those aged 40-69 (born 1950-1979)	€29,404
Wong (2015)	Canada	Testing those aged 40-69 (born 1950-1979)	€25,210
Wong (2017)	Canada	Testing those aged 45-64 (born 1951-1970)	€25,056
Younossi (2017)	United States	Testing those aged 45-64 (born 1953-1972)	Dominant

Key: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year.

Note: Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.[262, 263] Where studies did not report the cost year, it was assumed that the cost year was two years prior to the year of publication, based on the mean observed from studies that reported the cost year.

* Study results were reported according to subgroup. Subgroup data have been combined to estimate the cost-effectiveness of the overall strategy. These estimates may be subject to rounding error.
** Liu (2013a) and (2013b) represent the ICER when patients receive IL-28B guided triple therapy and universal triple therapy, respectively.
¥ Testing those aged 40-59 is presented here as a birth cohort strategy given consideration of all strategies evaluated in the CUA. However, it should be noted that it was unclear whether evidence of an elevated risk of HCV infection, compared with the rest of the general population, underpinned the selection of this cohort. The ICER has been calculated from study results compared with alternatives of interest and may be subject to rounding error. Finally, the strategy was weakly dominated (that is, it had a higher ICER than that of a more effective alternative) by strategies of testing those aged 40-80 and 18-80.

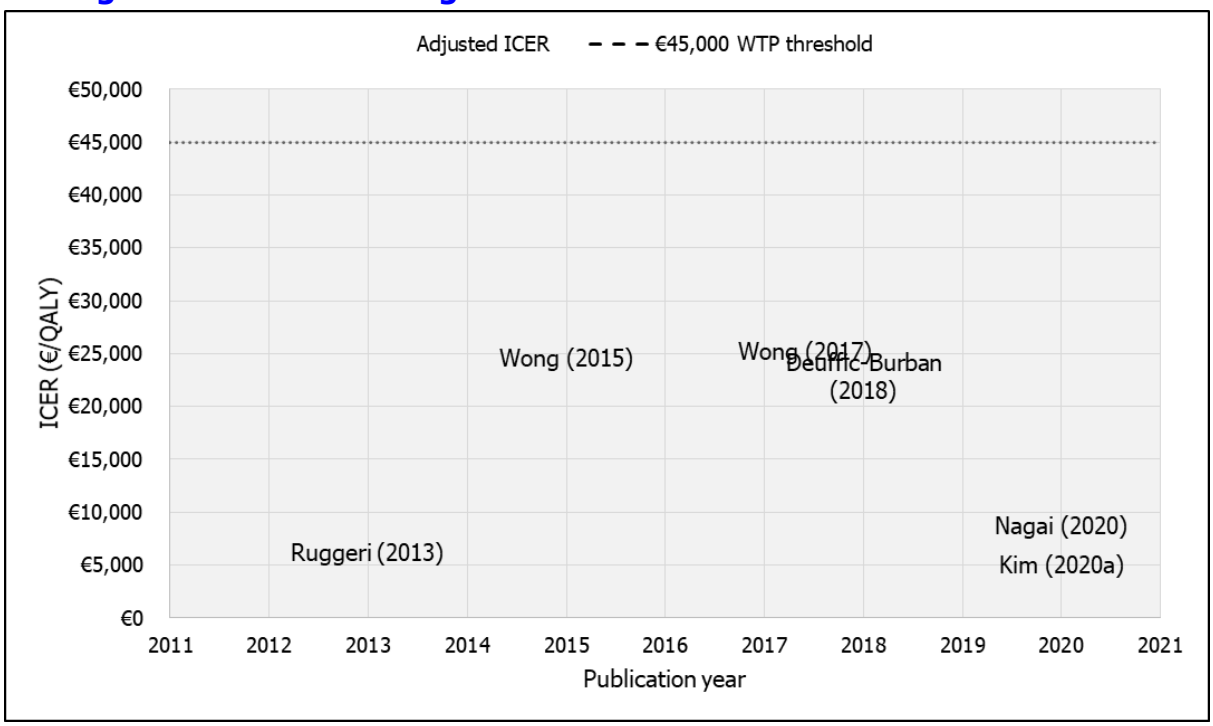
General population testing versus no testing or risk-based testing

Eleven studies (details of which are presented in Table 5.8) compared general population testing with either risk-based testing or no testing,[65, 73, 266-269, 272, 273, 279, 282, 284] eight of which comprised CUAs.[73, 266-268, 272, 279, 282, 284] Three studies comprised CEAs.[65, 267, 273]

All eight of the CUAs reported results indicating that one-off general population testing was cost-effective when employing a WTP threshold of €45,000.[73, 266-268, 272, 279, 282, 284] One study reported that general population testing was dominant,[267] while the ICERs (presented in Figure 5.4) in the other studies ranged between €5,064 and €22,895 per QALY gained. One of the CUAs modelled an additional strategy in which testing was offered to non-attendees at age 65, estimating an ICER of €4,954 per QALY gained.[272]

Of the CEAs, one study reported an ICER of €927 per life year gained,[269] one study reported ICERs ranging from €92,128 to €383,504 per infection averted and from €594,405 to €624,750 per death averted,[273] and one study reported an ICER of €2,531 per a gain in life expectancy.[65]

Figure 5.4. ICERs comparing one-off general population testing with no testing or risk-based testing*



Key: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year; WTP – willingness to pay.

Note: Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.[262, 263] Where studies did not report the cost year, it was assumed that the cost year was two years prior to the year of publication, based on the mean observed from studies that reported the cost year.

* One study, which found that general population testing dominated no testing, is not presented here.[267]

Table 5.8. ICERs comparing general population testing with no testing or risk-based testing

Study	Country	Intervention	Adjusted ICER (€/QALY unless stated)
Cost-utility analyses			
Coffin (2012)	United States	Testing those aged 20-69 (born 1943-1992)	€7,942
Crespo (2019)	Spain	Testing those aged 20-74 (born 1943-1997)	Dominant
Deuffic-Burban (2018)¥	France	Testing those aged 40-80 (born 1938-1978)	€22,895
Kim (2020a)	South Korea	Testing those aged ≥ 40 (once-off) (born ≤ 1980)	€5,064
Kim (2020b)	South Korea	Testing those aged ≥ 40, with catch-up programme for non-attenders at 65 (born ≤ 1980)	€8,797
Nagai (2020)	Japan	Testing those aged 40-89 (born 1931-1980)	€8,797
Ruggeri (2013)	Italy	Testing those aged 35-65 (born 1948-1978)	€6,272
Wong (2015)	Canada	Testing those aged 25-64 (born 1951-1990)	€24,658
Wong (2017)	Canada	Testing those aged 25-64 (born 1953-1972)	€23,852
Cost-effectiveness analyses			
Dimitrova (2019)	Bulgaria	Testing those aged 39-64 (born 1955-1980)	€1,236/LY gained
Kim (2019a)*	South Korea	Testing those aged ≥ 60 (born ≤ 1959)	€94,001 /infection averted
Kim (2019b)*	South Korea	Testing those aged ≥ 40 (born ≤ 1979)	€92,128 /infection averted
Kim (2019c)*	South Korea	Testing those aged ≥ 60 (born ≤ 1959)	€364,877 /death averted
Kim (2019d)*	South Korea	Testing those aged ≥ 40 (born ≤ 1979)	€383,504 /death averted
Nakamura (2008)*	Japan	Testing those aged 40-70 (born 1938-1968)	€2,431 /LE gained

Key: ICER – incremental cost-effectiveness ratio; LE – life expectancy; LY – life year; QALY – quality-adjusted life year.

Note: Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.[262, 263] Where studies did not report the cost year, it was assumed that the cost year was two years prior to the year of publication, based on the mean observed from studies that reported the cost year.

* Study results calculated based on presented data and may be subject to rounding error.

¥ Testing those aged 40-59 is presented here as a birth cohort strategy given consideration of all strategies evaluated in the CUA. However, it should be noted that it was unclear whether evidence of an elevated risk of HCV infection, compared with the rest of the general population, underpinned the selection of this cohort. The ICER has been calculated from study results compared with alternatives of interest and may be subject to rounding error. Finally, the strategy was weakly dominated (that is, it had a higher ICER than that of a more effective alternative) by strategies of testing those aged 40-80 and 18-80.

Universal testing versus no testing or risk-based testing

Eight studies (details of which are presented in Table 5.9) compared universal testing with either no testing or risk-based testing,[177, 265, 273, 275, 278, 280, 284, 285] seven of which comprised CUAs.[177, 265, 275, 278, 280, 284, 285] Six of the seven CUAs reported results indicating that universal testing was cost-effective at a WTP of €45,000.[265, 275, 278, 280, 284, 285] Overall, one CUA found that universal testing was dominant,[285] while the other CUAs estimated ICERs between €5,650 and €46,124 per QALY gained. The CEA estimated ICERs of €106,693 per infection averted and €497,822 per death averted.[273]

Universal testing versus birth cohort testing

Five CUAs (details of which are presented in Table 5.10) compared universal testing with birth cohort testing.[264, 265, 270, 275, 285] Four CUAs reported that universal testing was cost-effective at a WTP of €45,000.[264, 265, 270, 285] Overall, one study found that universal testing was dominant,[285] while the ICERs of the other studies ranged between €9,348 and €682,686.[264, 265, 270, 275, 285]

Table 5.9. ICERs comparing universal testing with no testing, risk-based testing or birth cohort testing

Study	Country	Intervention	Adjusted ICER (€/QALY unless stated)
Universal testing versus no or risk-based testing (CUAs)			
Buti (2018)	Spain	Testing those aged 20-79 (born 1938-1997)	€11,616
Eckman (2013)	United States	Testing those aged ≥ 18 (born ≤ 1995)	€46,124
Kondili (2020)	Italy	Testing the entire Italian population (born)	€8,197
Mendlowitz (2019)	Canada	Testing those aged ≥ 15 (born ≤ 2004)	€13,181
Opstaele (2019a)	Belgium	Testing those aged ≥ 18 (born ≤ 2001), offered during one year only	€5,650
Opstaele (2019b)	Belgium	Testing those aged ≥ 18 (born ≤ 2001), offered over five years	€5,717
Wong (2017)	Canada	Testing those aged 15-79 (born 1938-2002)	€36,452
Younossi (2017)	United States	Testing those aged ≥ 20 (born ≤ 1997)	Dominant
Universal testing versus no or risk-based testing (CEAs)			
Kim (2019a)*	South Korea	Testing those aged ≥ 20 (born ≤ 1999)	€106,693
Kim (2019b)*	South Korea	Testing those aged ≥ 20 (born ≤ 1999)	€497,822
Universal testing versus birth cohort testing (CUAs)			
Barocas (2018)	United States	Testing those aged ≥ 18 (born ≤ 2000)	€23,581
Buti (2018)	Spain	Testing those aged 20-79 (born 1938-97)	€9,706
Eckman (2019)	United States	Testing those aged ≥ 18 (born 1945-1965)	€9,348
Kondili (2020a)¥	Italy	Testing the entire Italian population	€682,686
Younossi (2017)	United States	Testing those aged ≥ 20 (born ≤ 1997)	Dominant

Key: CEA – cost-effectiveness analysis; CUA – cost-utility analysis; ICER – incremental cost-effectiveness ratio; LE – life expectancy; LY – life year; QALY – quality-adjusted life year.

Note: Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.[262, 263] Where studies did not report the cost year, it was assumed that the cost year was two years prior to the year of publication, based on the mean observed from studies that reported the cost year.

* Study results calculated based on presented data and may be subject to rounding error.

¥ Comparator comprises graduated birth cohort testing of those aged 33-52 (born 1968-1987) in year one and those aged 53-72 (born 1948-1967) in year three.

5.3.4 Quality of included studies

Study quality, assessed using the CHEC-list questionnaire,[260] was variable (see Figure 5.5). Overall, six studies were of low quality,[65, 267, 269, 273, 275, 280] 17 were of moderate quality,[66, 73, 153, 177, 264-266, 268, 270, 271, 276, 277, 279, 281, 282, 284, 285] and four were of high quality.[272, 274, 278, 283]

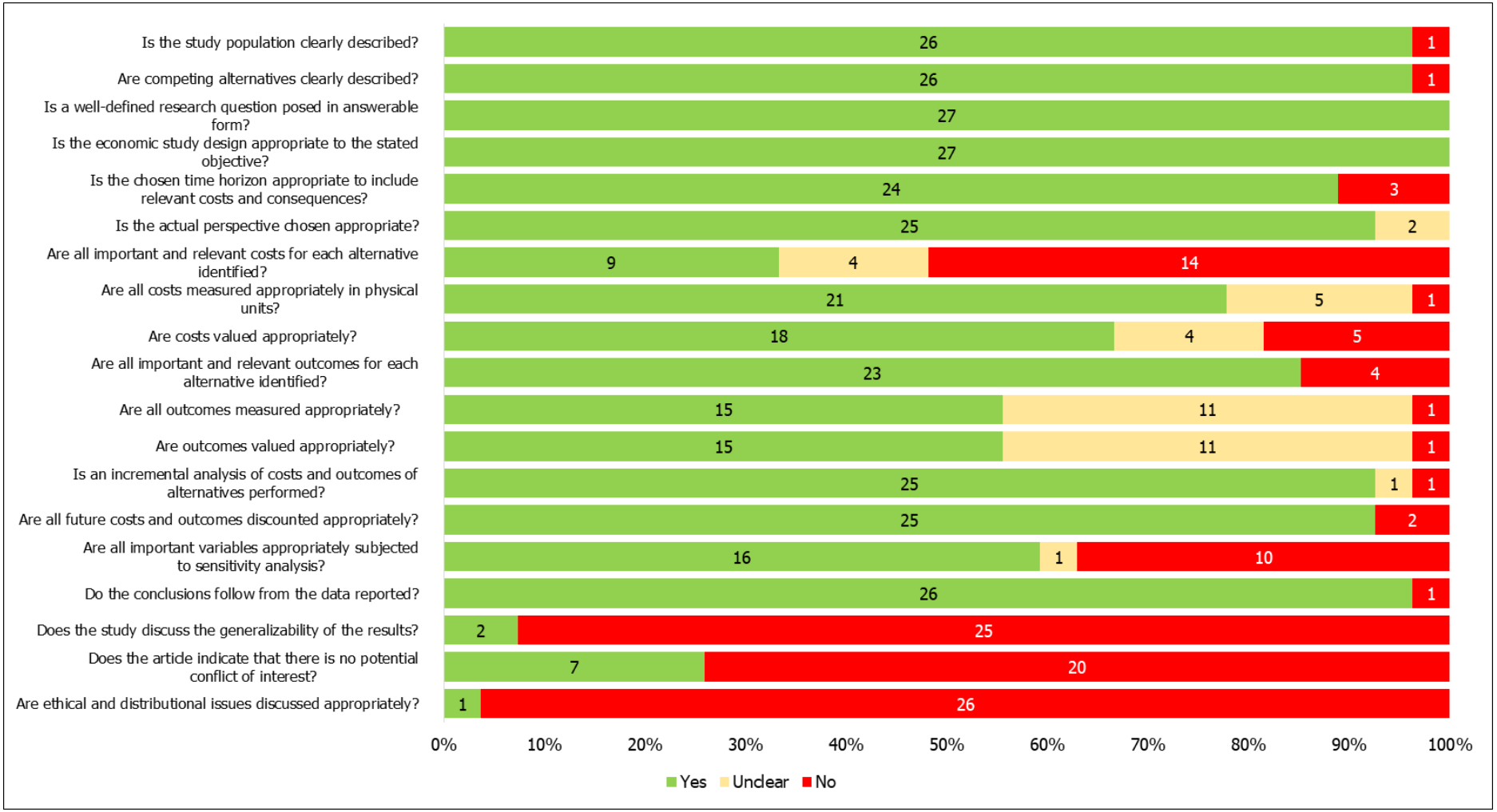
The common quality issues included:

- Perspective – the perspective unclear in one study,[273] and three studies reported that the analysis was conducted from the societal perspective,[268, 276, 281] but only direct medical costs (reflecting the healthcare system perspective). Only one of these studies estimated productivity losses.[281] None of these studies were considered sufficiently comprehensive from a societal perspective, but were adequate from a healthcare system (public payer) perspective.
- Time horizon – due to the age range of the target population, the time horizon may have been insufficient to fully capture long-term costs and benefits in four studies.[66, 269, 273, 275]
- Costs – cost issues were identified in 22 studies.[65, 66, 73, 153, 177, 264, 266-271, 273-277, 280-282, 284, 285] These included not modelling all relevant costs (for example, costs of testing, treatment-related adverse events, treatment monitoring or staging) and methods for estimating unit costs (for example, basing costs on expert opinion or using tariff-based estimates). The cost year that was used was not reported in six studies.[66, 153, 269, 275, 281, 282]
- Outcomes – the sources of and elicitation method used for deriving utility weights was generally poorly reported and without evidence of systematic identification. Preference measurement methods for deriving utility weights were not clearly reported in 13 studies.[66, 73, 264-267, 269, 271, 277, 280, 281, 284, 285] QALY outcomes were not reported in three studies.[65, 269, 273]
- Sensitivity analysis – approaches adopted for assessing parameter uncertainty were inadequate in 11 studies.[65, 66, 153, 265, 267, 269, 271, 273, 277, 280, 285] Issues related to poor reporting of methods or results of sensitivity analysis. In many cases, the bounds selected for the parameter values in the sensitivity analysis were not justified nor explained.
- Discounting – issues relating to discounting were identified in two studies.[269, 275] One of these did not apply discounting to benefits,[275] while the other did not report the use of discounting at all.[269]

- Generalisability and ethical considerations – only two studies[274, 294] discussed the generalisability of their findings to other settings and patient groups. Only one study adequately discussed ethical and distributional issues.[267]
- Conflicts of interest – authors of 20 studies were either subject to a potential conflict of interest or did not include a declaration of competing interests.[65, 66, 73, 153, 177, 265-268, 270-272, 277-282, 284, 285] The potential conflict was generally from industry sponsorship for the study or receipt of funding received for unrelated work.

All of the included studies were published in peer reviewed journals and were therefore subject to word count and other formatting restrictions. While many provided additional details in supplementary appendices, the format does not lend itself to transparent reporting. As appropriate assessment of the cost-effectiveness of HCV testing involves a holistic modelling approach encompassing diagnosis and treatment of people with HCV infection, the brevity of the reporting gives rise to challenges in identifying how the work was done, and whether it was carried out to a high standard.

Figure 5.5. Quality assessment of included studies*



Key: CHEC – Consensus on Health Economic Criteria.

* Quality assessment was undertaken with CHEC-list questionnaire.[260] Some of the CHEC-list items have been shortened for legibility.

5.3.5 Applicability of included studies

Transferability and applicability to the Irish setting were assessed using the ISPOR questionnaire.[261] The assessment of applicability is intended to determine the extent to which the findings of published economic evaluations might apply in the decision-maker's setting. In this case, the decision-maker (the Department of Health) is interested in whether birth cohort testing should be implemented to identify and treat people with chronic HCV infection born between 1965 and 1985. Overall, 23 studies were considered partially applicable,[66, 73, 153, 177, 264-268, 270-272, 274-279, 281-285] and four were not applicable.[65, 269, 273, 280]

Common applicability issues (see Figure 5.6) included:

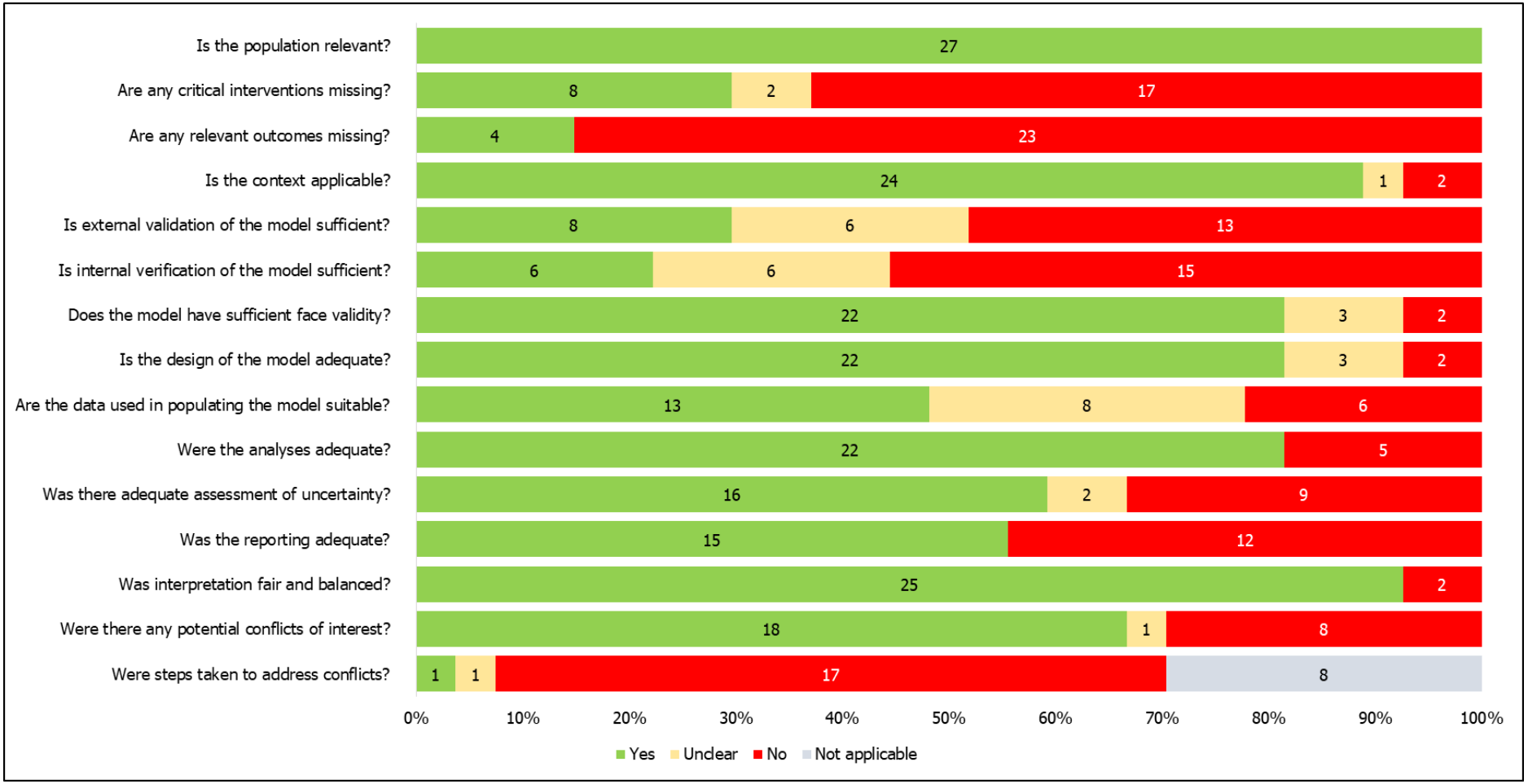
- Absence of critical interventions – eight studies modelled interferon-based therapies only.[65, 153, 177, 266, 276, 277, 281, 282] Older interferon-based therapies are associated with higher rates of adverse events, lower effectiveness and longer therapy durations.
- Model validation – only two studies reported sufficient information on external validation and internal verification.[278, 279]
- Sensitivity analysis – approaches adopted for assessing parameter uncertainty were inadequate in 11 studies,[65, 66, 153, 265, 267, 269, 271, 273, 277, 280, 285] with univariate or probabilistic sensitivity analysis often not conducted.
- Reporting quality – inadequate reported was observed in 12 studies.[153, 177, 264, 265, 267-269, 273, 275, 276, 280, 285] For example, reporting in relation to key parameter inputs (such as the diagnostic performance of testing, and the uptake rates of testing and treatment), target populations (such as prevalence, HCV genotype and fibrosis data) and reporting of results was often inadequate.
- Conflicts of interest – authors of 20 studies were either subject to a potential conflict of interest or did not include a declaration of competing interests.[65, 66, 73, 153, 177, 265-268, 270-272, 277-282, 284, 285] The potential conflict was generally from industry sponsorship for the study or receipt of funding received for unrelated work.

Discounting was applied to costs and benefits in 26 of the included studies.[65, 66, 73, 153, 177, 264-274, 276-285] However, only two studies applied the 4% rate required by Irish national HTA guidelines.[66, 263, 268] The discounting rates applied to costs and benefits may influence the estimated ICER thus restricting transferability.[263]

Due to the diverse range of populations and treatment strategies employed, it is difficult to justify applicability of these studies to Ireland. The birth cohort may differ

according to age, HCV prevalence, prevalence of HCV risk factors, HCV genotypes and disease severity.

Figure 5.6. Applicability assessment of included studies



Key: ISPOR – The Professional Society for Health Economics and Outcomes Research.

* Applicability assessment was undertaken with the ISPOR questionnaire.[261]

5.4 Discussion

This systematic review identified 27 economic evaluations of age-based once-off testing strategies for identifying people with undiagnosed chronic HCV infection who do not meet the criteria for risk-based testing. Willingness to pay (WTP) thresholds of €20,000 and €45,000 per quality adjusted life-year (QALY) gained have typically been used in Ireland as reference points for decision-making regarding the reimbursement of medicines. For the purpose of reporting in this systematic review, the cost-effectiveness of the testing strategies are interpreted by employing a WTP threshold of €45,000 per QALY.

The included studies were of varying levels of quality and applicability. Overall, six studies were low quality,[65, 267, 269, 273, 275, 280] 17 were moderate quality,[66, 73, 153, 177, 264-266, 268, 270, 271, 276, 277, 279, 281, 282, 284, 285] and four were high quality.[272, 274, 278, 283] Twenty-three studies were considered partially applicable,[66, 73, 153, 177, 264-268, 270-272, 274-279, 281-285] and four were not applicable.[65, 269, 273, 280]

The included studies compared a variety of testing strategies categorised as follows:

- birth cohort testing versus no testing or risk-based testing
- general population testing versus no testing or risk-based testing
- universal testing versus no testing or risk-based testing
- universal testing versus birth cohort testing.

Sixteen studies compared birth cohort testing with either risk-based testing or no testing,[66, 73, 153, 266, 268, 270, 271, 274-278, 281, 283-285] 14 of which reported results indicating that birth cohort testing was cost-effective.[73, 153, 266, 268, 270, 271, 274, 275, 277, 278, 281, 283-285] Focusing only on the studies of higher quality and applicability,[274, 278, 283] the ICERs ranged between €6,807 and €29,404.

Eleven studies compared one-off general population testing with either risk-based testing or no testing.[65, 73, 266-269, 272, 273, 279, 282, 284] All eight cost-utility analyses (CUAs) reported results indicating that general population testing was cost-effective. [73, 266-268, 272, 279, 282, 284] The CUA of high quality and partial applicability estimated ICERs between €4,954 and €5,064.[272]

Eight studies compared once-off universal testing (that is, testing the whole adult population) with either no testing or risk-based testing.[177, 265, 273, 275, 278, 280, 284, 285] Of the seven CUAs,[177, 265, 275, 278, 280, 284, 285] six reported results indicating that universal testing was cost-effective.[265, 275, 278, 280, 284, 285] The CUA of high quality and partial applicability estimated an ICER of €13,181.[278]

Five studies compared universal testing with birth cohort testing.[264, 265, 270, 275, 285] The four studies of moderate quality and partial applicability found that universal testing

was cost-effective.[264, 265, 270, 285] one of these studies found that universal testing was dominant (that is, it was less costly and more effective than the next best alternative),[285] with ICERs between €9,348 and €23,581 estimated in the other three CUAs.[264, 265, 270, 285]

It should be noted that the synthesis of cost-effectiveness cannot be considered an incremental analysis. In order to undertake a fully incremental analysis at the study-level, testing strategies should be ranked according to total effectiveness and then compared against the next best alternative. Given the diverse range of study populations and testing strategies assessed within studies, this systematic review summarised direct comparisons of relevance to the research question. With the observed variation in study-level data, it would be inappropriate to pool data in order to achieve a fully incremental analysis.

Overall, the quantity and quality of evidence suggested that once-off age-based testing (that is, birth cohort, general population or universal) of adults that do not meet the current criteria of risk-based testing is likely cost-effective. However, it should be noted that a large degree of heterogeneity was observed between studies, particularly in terms of the characteristics of the study populations, treatment costs and effects. The uncertainty surrounding the cost-effectiveness of testing was generally most sensitive to changes in testing and treatment uptake rates, prevalence of undiagnosed chronic HCV infection, disease progression of undiagnosed cases, treatment costs and whether or not identified HCV cases were eligible for treatment. However, as these data were often not clearly reported it is difficult to draw firm conclusions on their influence. An Irish-specific CUA is required to determine the cost-effectiveness of birth cohort testing in Ireland.

The underlying prevalence of undiagnosed chronic HCV infection and the uptake of testing in the target population will influence the cost-effectiveness of a national birth cohort testing programme. The prevalence of undiagnosed chronic HCV infection (and therefore the cost-effectiveness of testing) may fluctuate according to the specific age bands targeted by a birth cohort testing programme. The influence of these factors on cost-effectiveness and budget impact are evaluated in chapter 6, but should also be monitored during any potential implementation of a testing programme.

5.5 Conclusion

From review of the international evidence, population-based once-off HCV testing to identify people with currently undiagnosed HCV appears to be cost-effective. However, the cost-effectiveness varies according to the prevalence of undiagnosed infection within the target cohort and the observed uptake of testing and treatment. Given, the significant investment required to implement birth cohort testing in Ireland and the finding that none of the included studies were directly applicable (due to limitations in

terms of the study population characteristics, methods adopted or the absence of relevant therapies), an Irish-specific CUA is recommended.

6 Economic evaluation and budget impact analysis

Key points

- An economic model was developed to estimate the cost-effectiveness and budget impact of introducing birth cohort testing in Ireland. The analysis compared the incremental costs and health benefits of two testing programmes relative to no birth cohort testing:
    - a systematic birth cohort testing programme
    - an opportunistic birth cohort testing programme.
- The economic model comprised a closed-cohort decision tree and Markov model hybrid which tracked the 1965-1985 birth cohort from the outset of the simulation until death.
- A staggered implementation is assumed, whereby the 1965-1985 birth cohort is split into four age-based subgroups and offered testing sequentially over a four-year period.
- Both systematic and opportunistic birth cohort testing programmes were estimated to be more costly and more effective than no birth cohort testing in the base case.
- Compared with no birth cohort testing, the incremental cost-effectiveness ratio (ICER) for opportunistic birth cohort testing was estimated at €8,357 (95% CI: €843 to €19,699) per quality-adjusted life year (QALY) gained. Compared with opportunistic testing, the ICER of systematic birth cohort testing was estimated at €9,237 (95% CI: €1,384 to €21,632) per QALY. These estimates, which were robust in sensitivity analyses, are considered cost-effective at a willingness to pay (WTP) threshold of €20,000 per QALY gained.
- The ICERs were most sensitive to changes in the discount rate, the background detection rate of cases of undiagnosed chronic HCV infection (that is, the rate of detection without intervention), disease progression rates and the prevalence rate of undiagnosed chronic HCV infection.
- The incremental budget impact of introducing a systematic birth cohort testing programme was estimated at €65 million over a five-year time horizon, compared with no birth cohort testing. The budget impact was most sensitive to changes in the uptake rate of testing, prevalence of undiagnosed chronic HCV infection and the background rate of detection.

- Over a five-year period, it was estimated that systematic birth cohort testing would lead to an additional 0.6 million primary care attendances, 0.6 million anti-HCV antibody tests, 8,930 core antigen tests and 2,792 patients receiving DAA therapy over the course of four years.

6.1 Introduction

This chapter describes the cost-utility and budget impact analyses undertaken to assess the introduction of birth cohort testing for the hepatitis C virus (HCV) in Ireland. Chapter 5 highlighted that the cost-effectiveness of birth cohort testing is influenced by a number of country-specific parameters (for example, disease prevalence, testing uptake and treatment costs). Accordingly, a de novo economic model tailored to the Irish context was developed.

All of the analyses described in this chapter were conducted in line with national HTA guidelines,[262, 263, 295] reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement,[296] and undertaken in Excel 2013 and R Studio version 4.0.2.

6.2 Health economic analysis

6.2.1 Study objective

The purpose of the health economic analysis was to examine the cost-effectiveness and budget impact of introducing birth cohort testing for HCV.

6.2.2 Target population

The proposed birth cohort comprises all people living in Ireland that were born between 1965 and 1985. The aim of the intervention is to identify patients with chronic HCV infection that are currently unaware of their infection. As such, patients that have been previously diagnosed and are currently aware of their infection status are not considered in the analysis.

6.2.3 Health technology

Chapter 2 provides a detailed description of the health technology. Briefly, the proposed birth cohort testing involves offering one-off testing for HCV to all people in Ireland born between 1965 and 1985. In the analysis, a blood draw is performed by a general practitioner (GP) or general practice nurse to test for HCV. An anti-HCV antibody test and a reflex core antigen test are performed sequentially on the patient's blood sample to confirm the presence of viraemic infection. Only patient samples that test positive on the first-step anti-HCV antibody test undergo the second-step core antigen test.

The analysis adopts a staggered implementation for birth cohort testing, whereby testing is phased across four years. A systematic testing programme, in which patients are invited to attend their GP practice specifically to receive HCV testing, is assessed alongside an opportunistic testing programme in the analysis. The core components

and rollout of the systematic testing programme are described in Chapter 7.

6.2.4 Type of health economic analysis

A cost-utility analysis (CUA) was undertaken to estimate the incremental cost and health benefits associated with birth cohort testing. Health benefits are expressed in terms of quality-adjusted life years (QALYs), which reflect the impact of the intervention on patients' quality and quantity of life.[297] The analysis was undertaken within a decision-analytic framework,[298] that simulated the long-term costs, consequences and patient outcomes associated with chronic HCV infection. The primary outcome is the incremental cost-effectiveness ratio (ICER) – the incremental cost per QALY gained. In the base case analysis, the ICER is assessed relative to a willingness-to-pay (WTP) threshold of €20,000.

An incremental net monetary benefit (INMB), a summary statistic that represents the value of an intervention in monetary terms at a WTP threshold for a unit of benefit, was also estimated. A positive INMB indicates that the intervention is cost-effective relative to its comparator at the WTP threshold. That is, the cost to derive benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit.

The budget impact analysis estimates the incremental cost of implementing birth cohort testing over a five-year time horizon.

6.2.5 Perspective, time horizon and discounting

The analysis adopts the perspective of the Irish publicly-funded health and social care system, namely the Health Service Executive (HSE). Accordingly, only direct medical costs to the HSE were incorporated. Indirect costs such as productivity losses associated with morbidity and mortality, and out-of-pocket expenses incurred by individuals attending diagnostic testing were excluded from the analysis.

Incremental costs were estimated over a five-year time horizon in the BIA. In the CUA, costs and benefits were estimated over a lifetime time horizon, and discounted at a rate of 4% (varied between 0% and 10% in the univariate sensitivity analysis) as specified in national guidelines.[263] Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future.

6.2.6 Comparators

The alternatives compared in the analysis are:

- systematic birth cohort testing
- opportunistic birth cohort testing

- no birth cohort testing (that is, current practice).

Opportunistic testing comprises offering one-off testing for HCV to people from the birth cohort that are attending a GP consultation for another purpose. As such, people from the 1965-1985 birth cohort are not formally invited to attend their GP practice for HCV testing. However, it is assumed that a public awareness campaign is undertaken.

No birth cohort testing represents current practice whereby no testing programme or mechanisms to initiate birth cohort testing are implemented. Instead, patients are identified through a background rate of detection (such as by antenatal or risk-based testing) or their disease progresses to the point of symptomatic presentation. Patients can be identified by background detection or present symptomatically in each of the three modelled strategies.

6.2.7 Model structure

The decision-analytic model comprises a closed-cohort decision tree and Markov model hybrid which tracks the 1965-1985 birth cohort from the outset of the simulation until death.

A decision tree uses a branching structure in which each branch represents a future event that may take place. These branches meet at decision nodes that have a probability of an event occurring. Costs and outcomes are assigned to each segment of each branch, and combined so that the expected cost and outcome for each intervention and comparator can be estimated. The formulae used to calculate the diagnostic outcomes of testing are presented in Appendix 11.

In our analysis, the decision tree (Figure 6.1) estimates the:

- number of patients tested and identified for treatment
- testing outcomes of patients (that is, the number of true positives, true negatives, false positives and false negatives)
- cost of testing (for example, costs of GP consultation and HCV testing).

The Markov model (Figure 6.2 and Figure 6.3) simulates the natural progression of disease for patients in the birth cohort that have chronic HCV infection, and estimates the costs and consequences for patient outcomes. Natural disease progression is represented by patients transitioning between mutually-exclusive health states. Transitions between these health states are unidirectional and governed by probabilities which indicate the risk of disease progression.

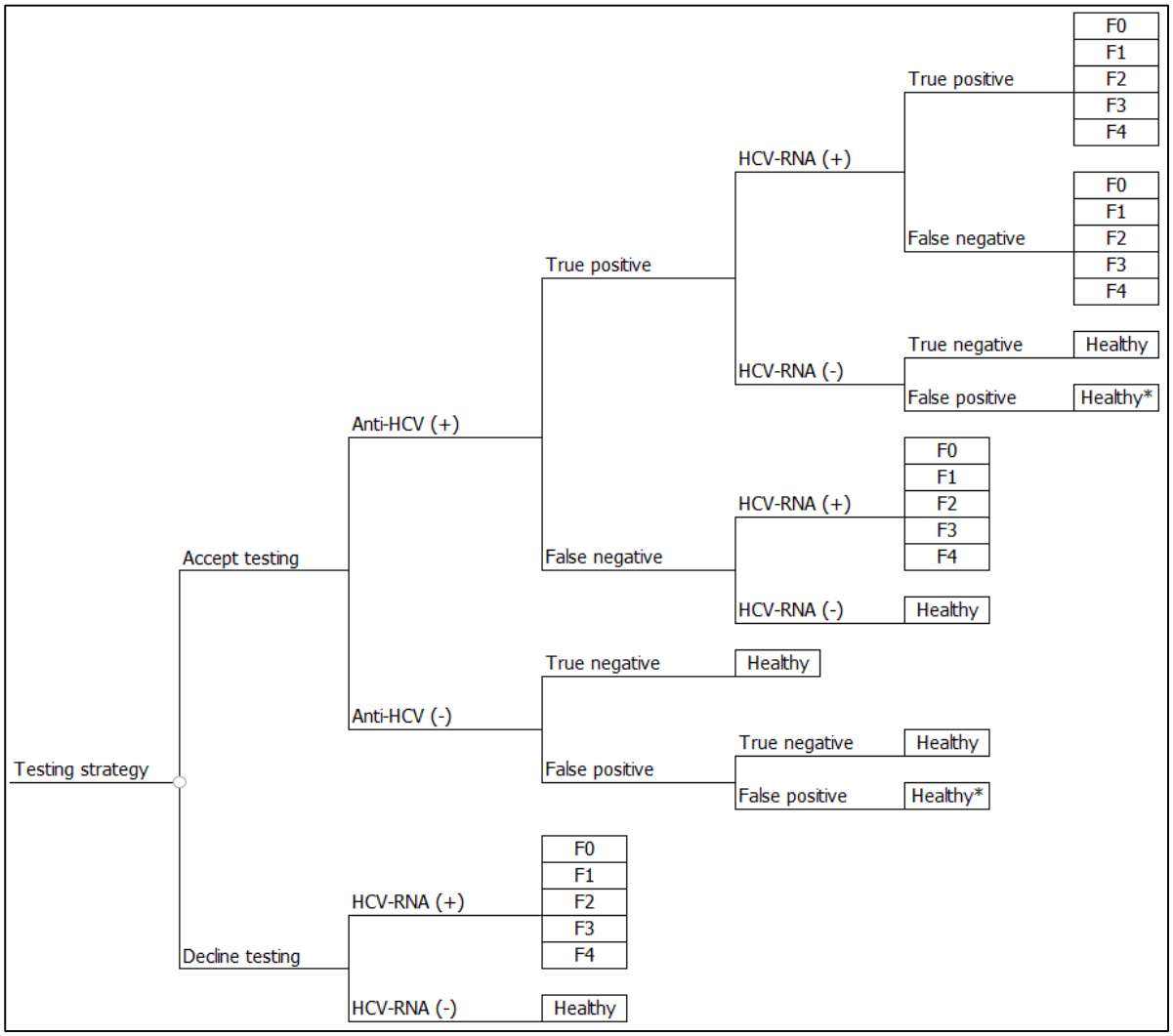
At the outset of the Markov model, patients with chronic HCV infection are distributed

across the fibrosis stages F0 to F4, according to the decision tree outcomes. Without treatment (see Figure 6.2), patients may remain in their fibrosis stage or progress to the advanced liver disease health states of decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC) and liver transplantation (LT). Patients can only stay in the LT state for one year before moving into the post-liver transplant (post-LT) health state. Patients can die from all-cause mortality at any time during the model.

The model assumes that patients identified by birth cohort testing are offered treatment which, if successful, can prevent further disease progression (see Figure 6.3). All patients that are successfully treated enter the sustained virological response (SVR) health state. Patients identified at METAVIR fibrosis stages F0 to F3 that achieve an SVR incur no further disease progression. However, patients that develop compensated cirrhosis (F4) prior to successful treatment have an ongoing risk of disease progression to the advanced liver disease states. Patients that do not achieve an SVR with a first-line direct-acting antiviral (DAA) therapy are retreated with a second-line DAA therapy. If they do not achieve an SVR upon re-treatment, they remain in the non-SVR health states and continue along the natural course of disease.

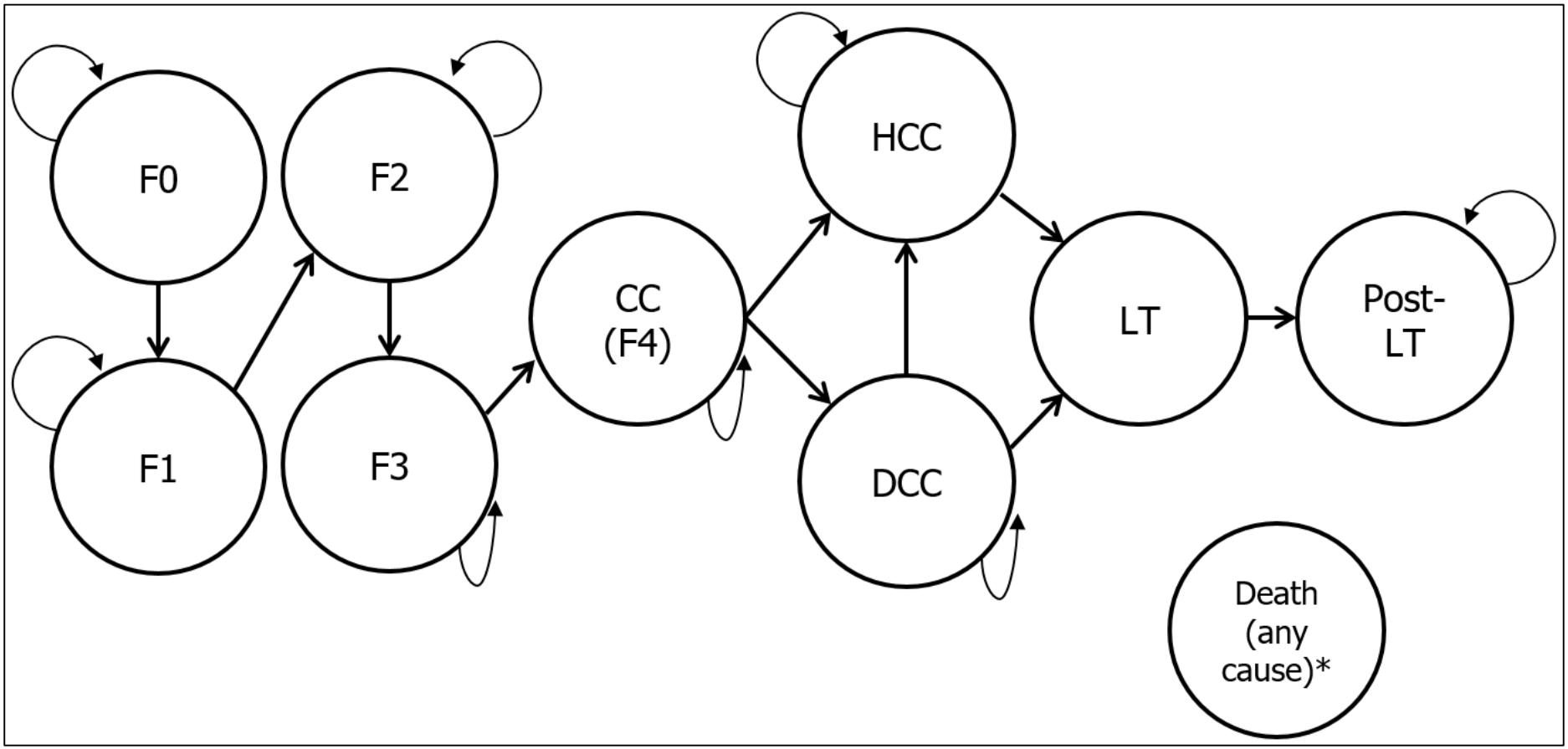
Undiagnosed patients with chronic HCV infection do not accrue health state costs until they are identified by testing or they become symptomatic (that is, they progress beyond F4 to DCC or HCC), at which point their HCV diagnosis is known. Therefore, symptomatic patients become ineligible for birth cohort testing and follow the natural course of disease.

Figure 6.1. Decision tree for HCV testing strategies**



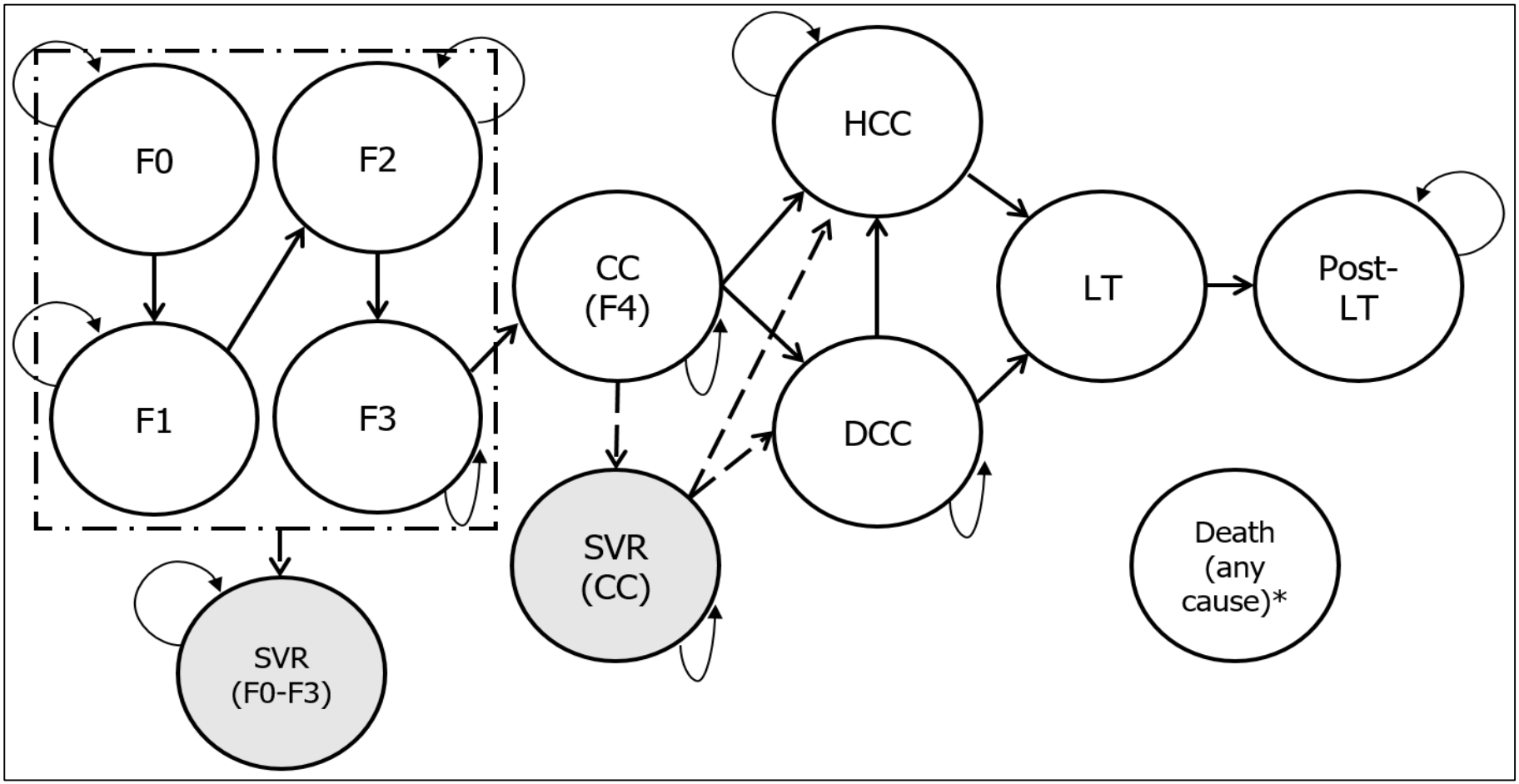
Key: F – METAVIR fibrosis stage; HCV – hepatitis C virus; RNA – ribonucleic acid.
* False positive diagnoses are identified following further testing.
** Each testing strategy followed the same decision tree pathway.
Anti-HCV (+) denotes that patients have a detectable anti-HCV antibody.
HCV-RNA (+) denotes that patients have chronic HCV infection.

Figure 6.2. Markov model of natural disease progression without treatment



Key: CC – compensated cirrhosis; DCC – decompensated cirrhosis; F – METAVIR fibrosis stage; HCC – hepatocellular carcinoma; LT – liver transplant.
* Patients can die from all-cause mortality at any stage in the model.

Figure 6.3. Markov model of treatment-modified disease progression



Key: CC – compensated cirrhosis; DCC – decompensated cirrhosis; F – METAVIR fibrosis stage; HCC – hepatocellular carcinoma; LT – liver transplant; SVR – sustained virological response.

Note: In the treatment-modified disease progression model, individuals can be treated to achieve SVR. However, those who reach the CC health state before achieving SVR have an ongoing risk of progression to DCC and HCC.

* Patients can die from all-cause mortality at any stage in the model.

6.3 Model parameters

6.3.1 Target population

The proposed target population comprises people in Ireland born between 1965 and 1985. The size of the Irish population born between those years (presented in Table 6.1) is based on the Central Statistics Office (CSO) population estimates for 2020.[149]

The base case analysis assumes that the implementation of birth cohort testing is staggered, whereby patients are divided into subgroups according to age bands and offered testing over discrete six-month intervals. Each subgroup (defined by age group) is split in two and tested over the course of one year.

Table 6.1. Size of target population in 2021

Age band (years)	Group 1	Group 2	Total population
36-40	193,232	193,232	386,464
41-45	196,846	196,846	393,691
46-50	179,254	179,254	358,507
51-56	188,705	188,705	377,409
Overall	758,036	758,036	1,516,072

Source: Central Statistics Office[149]

It is assumed that patients are offered first-line therapy in the six-month period following testing. Patients that fail first-line therapy are then offered second-line therapy in the six month period subsequent to failing first-line therapy. The sequence of testing, treatment and re-treatment adopted in the model is presented in Table 6.2.

Table 6.2. Sequence of staggered implementation

Model cycle*	Screened	Treated	Re-treated
0	51-56 (group 1)	NA	NA
1	51-56 (group 2)	51-56 (group 1)	NA
2	46-50 (group 1)	51-56 (group 2)	51-56 (group 1)
3	46-50 (group 2)	46-50 (group 1)	51-56 (group 2)
4	41-45 (group 1)	46-50 (group 2)	46-50 (group 1)
5	41-45 (group 2)	41-45 (group 1)	46-50 (group 2)
6	36-40 (group 1)	41-45 (group 2)	41-45 (group 1)
7	36-40 (group 2)	36-40 (group 1)	41-45 (group 2)
8	NA	36-40 (group 2)	36-40 (group 1)
9	NA	NA	36-40 (group 2)

Key: NA – not applicable.

* Each cycle represents a discrete six-month period.

The aim of birth cohort testing is to identify asymptomatic patients with chronic HCV infection that would not otherwise be identified by current risk-based screening methods. As described in Section 3.5.2, the prevalence of chronic HCV infection was derived by applying an approximation method to estimates by Garvey et al.,[157] and modelling the prevalent population forward to 2021, adjusting for incidence and mortality in the years following the study.[9, 149, 158]

A commonly cited seroconversion rate (conversion from acute to chronic infection) of 70% (95% CI: 55-85%) was used to back-calculate the total level of seropositivity (which includes both chronic and resolved infections) in the birth cohort based on the prevalence of chronic HCV infection.[2] Parameters related to the prevalence of HCV in the 1965-1985 birth cohort are presented by age band in Table 6.3.

Table 6.3. Prevalence of undiagnosed chronic HCV infections in the 1965-1985 birth cohort (in 2021)

	Mean (%)	95% CI (%)	Distribution	Source
Seropositivity				
Seroconversion	70	55-85	Beta	(2)
Chronic HCV				
36-40 years	0.27	0.10-0.53	Beta	(9, 149, 157, 158)
41-45 years	0.73	0.26-1.45	Beta	(9, 149, 157, 158)
46-50 years	1.14	0.51-2.01	Beta	(9, 149, 157, 158)
51-56 years	1.00	0.46-1.74	Beta	(9, 149, 157, 158)

Key: HCV – hepatitis C virus; CI – confidence interval.

From the outset of the model, patients are distributed across fibrosis stages METAVIR F0 to F4. The fibrosis distribution is based on data from the National Hepatitis C Treatment Programme (NHCTP),[93] which provided the disease stage of patients from the 1965 to 1985 birth cohort upon registration with the programme from 2012 to September 2019.

Data from patients registered with the NHCTP Registry in 2018-2019 were used to estimate the fibrosis distribution of the undiagnosed birth cohort – an apparently healthy population with no ongoing risk of infection.[299] It is unclear how applicable this fibrosis staging is to the undiagnosed patient population as patients recorded in the Registry are likely to represent people with risky health behaviours given that screening in Ireland to date has been primarily risk-based. Using estimates from high-risk patient populations introduces uncertainty as the fibrosis distribution of patients in the undiagnosed birth cohort has not been described in the Irish setting and therefore is unknown.

Due to challenges in stratifying patients that fall into METAVIR F0, F1 and F2, these

fibrosis stages are aggregated into a single group in the NHCTP Registry data. Therefore, fibrosis are grouped in the NHCTP Registry data as follows:

- F0-F2 (mild fibrosis)
- F3 (moderate fibrosis)
- F4 (compensated cirrhosis).[93]

These "mild fibrosis" data were disaggregated to facilitate the use of previously published rates of disease progression. The disaggregation was based on international evidence comparable to the fibrosis data observed in the Irish population between 2018 and 2019.[300, 301] These data were further stratified according to the applicable age bands to facilitate subgroup analysis. Uncertainty in the disaggregation was reflected by repeated simulation from a dirichlet distribution assigned to the disaggregated point estimate. The dirichlet distribution was replicated in the probabilistic sensitivity analysis (PSA) by assigning a gamma distribution to each individual fibrosis input, reducing the effective sample size to match the uncertainty observed in the international evidence.[300, 301] The estimated fibrosis distribution is presented in Table 6.4.

Table 6.4. Fibrosis distribution by age band

	Mean (%)	95% CI (%)	Distribution	Source
36-40 years				
F0	4	0-13	Gamma	(93, 300, 301)
F1	49	32-65	Gamma	(93, 300, 301)
F2	26	12-41	Gamma	(93, 300, 301)
F3	15	5-28	Gamma	(93)
F4	7	1-17	Gamma	(93)
41-45 years				
F0	4	1-11	Gamma	(93, 300, 301)
F1	47	35-60	Gamma	(93, 300, 301)
F2	25	15-36	Gamma	(93, 300, 301)
F3	11	4-20	Gamma	(93)
F4	13	6-22	Gamma	(93)
46-50 years				
F0	4	0-11	Gamma	(93, 300, 301)
F1	43	29-57	Gamma	(93, 300, 301)
F2	22	12-35	Gamma	(93, 300, 301)
F3	14	6-25	Gamma	(93)
F4	17	8-29	Gamma	(93)
51-56 years				
F0	26	14-41	Gamma	(93, 300, 301)
F1	28	16-43	Gamma	(93, 300, 301)
F2	15	6-27	Gamma	(93, 300, 301)

	Mean (%)	95% CI (%)	Distribution	Source
F3	12	4-24	Gamma	(93)
F4	19	8-32	Gamma	(93)

Key: CI –confidence interval.

The genotype distribution of the undiagnosed population was based on data available on the 1965-1985 birth cohort from the National Virus Reference Laboratory (NVRL).(302) The average across 2017 and 2018 was used as the point estimate in the model (see Table 6.5). As per previous years, HCV genotypes 1 and 3 represent approximately 95% of HCV cases.(147) A gamma distribution was assigned to each HCV genotype to replicate a dirichlet distribution in the PSA. The HCV genotypes were not stratified by age band.

Table 6.5. HCV genotype distribution in the 1965-1985 birth cohort

	Mean (%)	95% CI (%)	Distribution	Source
Genotype 1	63.1	58.7-67.7	Gamma	(302)
Genotype 2	2.1	1.4-3.0	Gamma	(302)
Genotype 3	32.1	28.9-35.4	Gamma	(302)
Genotype 4	2.0	1.2-2.8	Gamma	(302)
Genotype 5/6	0.7	0.3-1.3	Gamma	(302)

Key: CI –confidence interval.

6.3.2 Case-finding

The effectiveness of birth cohort testing to identify individuals with currently undiagnosed chronic HCV infection will depend on a number of factors including the:

- size of the target population
- prevalence of infection in the target population
- uptake of testing in the target population
- diagnostic accuracy of the testing sequence.

The size of the population and prevalence of HCV infection in the 1965 to 1985 birth cohort are described in Section 6.3.1. The uptake rate and diagnostic accuracy of testing are described below.

Uptake rates of testing

It is anticipated that all people living in Ireland born between 1965 and 1985 will be offered testing. However, it is unknown exactly how many people will accept the offer of testing (that is, the uptake rate). The uptake rate is likely to differ according to the structure, which can be systematic or opportunistic in nature, adopted by the testing programme. International data on the uptake rates of systematic and opportunistic testing programmes in the general population are limited. However, it is likely that a

systematic programme will yield a higher uptake of testing (see Section 2.7.2). As described in Chapter 8, the uptake rate will also differ according to whether two healthcare attendances are required for testing or whether reflex testing is implemented (that is, likelihood of drop-off in attendance increases when more attendances required). In the analysis, implementation of reflex testing is assumed.

The uptake of systematic testing was estimated based on the mean uptake rate observed for the BowelScreen programme between 2012 and 2017.[303] Under the National BowelScreen Programme, men and women aged between 60 and 69 years are offered screening for colorectal cancer on a two-yearly cycle. Of the 1,035,395 people invited to attend bowel screening during the period from 2012 to 2017, a total of 423,111 attended screening (yielding a mean uptake rate of 41%).

Although the BowelScreen programme is not directly comparable to birth cohort testing for HCV (due to differences in population demographics, diagnostic samples and tests, disease outcomes and the once-off nature of birth cohort testing), it represents a conservative estimate for the likely uptake of a systematic testing programme based on a pre-existing national screening programme. It is assumed that people who accept the invitation to attend their GP practice for HCV testing will go through with testing. That is, the probability that people may attend, but then decline the test following GP counselling, is not modelled. This may occur in practice if a systematic programme was rolled out, but the number of people that would decline testing having attended the appointment is likely to be low.

The lower bound of the annual uptake rate of testing was estimated based on a Scottish study where testing was offered to former or current IDUs (aged between 30-54 years) attending primary care.[304] Assuming that the uptake rate follows a normal distribution (that is, its lower and upper limits lie within 1.96 standard deviations of the mean), the 95% confidence interval lies between 31-51%. Again, this estimate is not directly comparable to the undiagnosed birth cohort (as the IDU population represent a risk group for HCV testing and because study participants were attending primary care prior to being offered HCV testing), but using this estimate allows for a wide degree of imprecision thus reflecting the uncertainty surrounding the expected uptake of birth cohort testing.

Since opportunistic testing comprises people attending a GP consultation for another purpose and being opportunistically offered HCV testing, the uptake rate for an opportunistic testing programme is based on GP utilisation rates in Ireland, specifically the Healthy Ireland survey.[305] The survey data, collected between 2014 and 2015, is adjusted by survey weights and stratified by gender (see Table 6.6) from the age of 25 to 54 years. A weighted average was calculated according to each modelled age band based on gender-specific population estimates and the Healthy Ireland GP

utilisation rates. As the Healthy Ireland survey asked whether the person had visited the GP in the previous 12 months, it is important to note that this estimate may be subject to recall bias (a systematic error that occurs when participants do not remember previous events accurately). In addition, it is assumed that GP attendance is not influenced by public awareness of birth cohort testing. In the model, the opportunistic rate is multiplied by the uptake rate observed in the observational studies described above to reflect the likelihood that the individual will accept HCV testing.

Table 6.6. GP attendance rates per annum, by gender*

	Males		Females	
Age group (years)	**Attendance (%)**	**Survey sample size (n)**	**Attendance (%)**	**Survey sample size (n)**
25-44	56	1,434	73	1,502
45-49	61	337	66	320
50-54	66	292	76	315

Key: GP – general practitioner; LCI – lower confidence interval; UCI – upper confidence interval.
* Defined as a proportion of the target population attending the GP at least once in a 12 month period.
Source: Healthy Ireland (data from 2014-15)

In the model, birth cohort testing is compared with current practice (that is, no birth cohort testing). As demonstrated by the HPSC notifications data presented in Chapter 3.3, even without formal implementation of birth cohort testing, a proportion of the 1965-1985 birth cohort will still be opportunistically identified by current screening practices. Therefore, an estimate of people with chronic HCV infection from the birth cohort that would be opportunistically identified irrespective of formalised birth cohort testing is included in the analysis. Consistent with the approach adopted by previous economic evaluations, this is estimated by inclusion of a background rate of detection.[73, 293]

The rates of background testing were estimated using data from the UK.[293] The data were used for the reported age bands (35-39, 40-44, 45-49, 50-54, 55-59, 60-64) coupled with assumptions about decreasing testing in older age bands and increased testing in 20-24, 25-29 and 30-34 year olds. It was assumed that there would be a low rate of testing in 15 to 19 year olds. The test proportions were applied to the 2017 Irish population by age band and then adjusted to reflect the observed number of HCV tests in 2017.[93] An arbitrary range of uncertainty was applied to ensure that values for each age band would include those reported in the UK study. Finally, age-specific multipliers were derived based on the observed number of HCV notifications in 2018.[306] The modelled uptake rates are presented in Table 6.7.

Table 6.7. Modelled annual uptake rates for HCV testing and rates of background detection by age band

	Mean	95% CI	Distribution	Source
Systematic testing (opt-in)	0.41	0.31-0.51	Beta	(303, 304)
Opportunistic testing (opt-in)				
36-40	0.649	0.62-0.67	Beta	(305, 307-311)
41-45	0.647	0.62-0.67	Beta	(305, 307-311)
45-49	0.639	0.58-0.69	Beta	(305, 307-311)
51-56	0.711	0.66-0.76	Beta	(305, 307-311)
Background rate of detection*				
35-39	0.06	0.00-0.19	Beta	(93, 293, 306)
40-44	0.03	0.01-0.07	Beta	(93, 293, 306)
45-49	0.02	0.01-0.04	Beta	(93, 293, 306)
50-54	0.03	0.00-0.08	Beta	(93, 293, 306)
55-59	0.03	0.00-0.11	Beta	(93, 293, 306)
60-64	0.04	0.00-0.16	Beta	(93, 293, 306)
65-69	0.04	0.00-0.25	Beta	(93, 293, 306)
70-74	0.03	0.00-0.20	Beta	(93, 293, 306)
75-79	0.02	0.00-0.10	Beta	(93, 293, 306)
80-84	0.02	0.00-0.16	Beta	(93, 293, 306)
85+	0.06	0.00-0.31	Beta	(93, 293, 306)

Key: CI – confidence interval.
* Function of background testing and prevalence.

Accuracy of diagnostic tests

As described in Section 2.7.3, the diagnostic accuracy of screening reflects the performance characteristics of the screening test and how well it discriminates between those who do (sensitivity) and do not (specificity) have the target condition. In the analysis, an anti-HCV antibody test followed by a reflex core antigen test are performed sequentially on the patient's blood sample to confirm the presence of viraemic infection. Only patient samples that test positive on the first-step anti-HCV antibody test undergo the second-step core antigen test.

The diagnostic performance of anti-HCV tests is based on the sensitivity and specificity of CE-marked devices presented in a 2019 WHO report of diagnostics for hepatitis C.[190] The diagnostic performance of core antigen testing is based on a 2016 systematic review and meta-analysis of core antigen tests for diagnosis of chronic HCV infection compared with nucleic acid amplification tests.[183] The estimated sensitivity and specificity of HCV tests was verified against data provided by the National Virus Reference Laboratory and HSE Pathology Programme.

The sensitivity and specificity of the anti-HCV antibody and HCV core antigen tests used in the model are presented in Table 6.8. It was assumed that the diagnostic test accuracy of the two tests is independent. That is, the result of the second test is unaffected by the result of the first test. More specifically, a sample that generates a false positive with the anti-HCV test is not at increased likelihood of generating a false-positive with the core antigen test.

Table 6.8. Sensitivity and specificity of tests for diagnosis of HCV

	Mean	95% CI	Distribution	Source
Anti-HCV sensitivity	0.991	0.968-0.999	Beta	(190)
Anti-HCV specificity	0.996	0.995-0.997	Beta	(190)
Core antigen sensitivity	0.934	0.899-0.962	Beta	(183)
Core antigen specificity	0.988	0.975-0.996	Beta	(183)

Key: HCV – hepatitis C virus; CI – confidence interval.

6.3.3 Treatment-related parameters

In addition to the case-finding parameters described in 6.3.3, the clinical effectiveness of birth cohort testing will depend on treatment:

- uptake
- adherence
- effectiveness.

As described in Chapter 4.3, reimbursed treatment of hepatitis C in Ireland is prescribed according to a treatment algorithm recommended by the National Hepatitis C Treatment Programme (NHCTP). The algorithm comprises two lines of direct-acting antiviral (DAA) therapies stratified according to HCV genotype and the presence or absence of cirrhosis.

Treatment uptake for first-line DAA therapies is based on a previously published economic evaluation which estimated the uptake rate of second-generation interferon-free DAAs at 90%.(284) Treatment uptake for second-line therapy is estimated at 95%, considering that patients who refuse treatment are more likely to drop-off during first-line therapy. Treatment completion of DAA therapy is estimated at 94% based on a retrospective analysis of discontinuation of second-generation DAAs among Medicare claims in patients with chronic HCV infection, conducted in the US between 2014 and 2016 (see Table 6.9).(312) This treatment completion rate is applied to first- and second-line therapy.

In the analysis, a patient that refuses first-line therapy cannot be offered second-line therapy and reverts to the natural course of disease. If a patient discontinues treatment for any reason, they are considered a treatment failure. That is, their

subsequent disease progression reflects that of an individual that does not receive any treatment. In the model, patients that fail or discontinue first-line therapy are offered second-line therapy. Patients that fail or discontinue second-line therapy follow the natural course of disease. Adverse events were not considered in the CUA, as second generation DAAs are typically not associated with severe drug-related adverse events.[265]

Table 6.9. Treatment uptake and completion

	Mean (%)	95% CI (%)	Distribution	Source
1st line uptake	90	78-98	Beta	[284]
2nd line uptake	95	89-99	Beta	Assumption
Completion	94	94-94	Beta	[312]

Key: CI – confidence interval; NA – not applicable.

Treatment effectiveness was estimated by meta-analysis of the SVR rates underpinning a systematic review undertaken to inform the WHO's 2018 treatment guideline.[2, 228] The clinical data included RCT and non-RCT studies in patients that were treatment-experienced, treatment-naïve and or patients of unknown treatment experience. To ensure sample size of sufficient strength when stratified by HCV genotype, RCT and non-RCT studies in patients of mixed treatment experience were included in the meta-analysis. However, treatment effects were similar when only RCT data in treatment-naïve patients were meta-analysed.

The random-effects meta-analysis used inverse variance methods (which weights each random variable according to its precision) to calculate a pooled estimate of the proportion of patients that achieved an SVR, stratified by HCV genotype and treatment regimen. Only treatments recommended by the NHCTP 2019 treatment algorithm were included.[181] As sofosbuvir, velpatasvir and voxilaprevir (Vosevi®) is the only second-line therapy currently recommended across all HCV genotypes, SVR rates were meta-analysed across all HCV genotypes for second-line therapy. The estimated treatment effects, presented in Table 6.10, are in line with the international evidence outlined in Section 4.3.4.

In the model, treatment effectiveness is weighted by HCV genotype distribution in the target population (see Section 6.3.1) to incorporate an absolute measure of effectiveness in the model. The mean value of this absolute effect was 0.97, and did not vary with the presence of cirrhosis.

Table 6.10. Treatment effectiveness parameters

	Mean	95% CI	Distribution	Source
First-line				
Genotype 1	0.97	0.97-0.97	Beta	(228)
Genotype 2	0.98	0.95-0.99	Beta	(228)
Genotype 3	0.96	0.86-0.99	Beta	(228)
Genotype 4	0.98	0.94-0.99	Beta	(228)
Genotype 5/6	0.97	0.90-0.99	Beta	(228)
Second-line				
Pangenotype	0.96	0.94-0.98	Beta	(228)

Key: CI – confidence interval.

6.3.4 Transition probabilities

In the Markov model, movement from one health state to the next (that is, disease progression) is governed by transition probabilities. As the model uses a six-month cycle length, annual transition probabilities from published literature sources were converted to six-month probabilities of event occurrence. Consistent with the method described by Briggs et al.,(298) probabilities were converted to instantaneous event rates and then to a six-month probability of the event occurring. This method assumes that the event rate is constant over time. Transition probabilities were based on a variety of published international evidence. Further to the point estimates described here, a calibration exercise, presented in Chapter 6.4.1, was conducted to ensure plausibility of the number of cases of HCC and liver transplantations predicted by the model.

To estimate disease progression between the fibrosis health states F0 to F4, a subgroup analysis was performed on studies(300, 301, 313, 314) from the community setting identified by a commonly cited systematic review and meta-analysis.(12) A general linear (mixed effects) model was used to meta-analyse the transition probabilities from these studies, implicitly assuming that the studies represent a random selection from a larger population of studies. An update of the systematic review and meta-analysis was published in 2019 with a subgroup analysis of fibrosis progression among patients with chronic HCV infection in the community setting.(315) However, study-level data were not provided.

The risk of progression from F4 to DCC is based on a European cohort study of patients (n=384) with compensated cirrhosis which estimated that the five-year risk of DCC and HCC was 0.18 and 0.07, respectively.(176, 316) Patients that progress to the F4 (that is, compensated cirrhosis (CC)) health state prior to achieving an SVR have an ongoing risk of progressing to the advanced liver disease states (DCC and HCC). The relative risk of progression to DCC for these patients is based on a long-term follow-up study

from five large tertiary care hospitals in Europe and Canada of patients with chronic HCV infection (n=530) which found that the risk of liver failure was 0.07 (95% CI: 0.03-0.20) compared with patients that did not achieve an SVR.[248, 293] The relative risk of progression to HCC for patients with CC is based on a 2013 systematic review of observational studies (n=18) that investigated the association between response to therapy and HCC in patients with chronic HCV infection.[160] The systematic review found that SVR was associated with a reduced risk for HCC of 0.23 (95% CI: 0.16-0.35).[160, 293] Transition probabilities between the advanced liver disease stages (DCC and HCC) were from a variety of previously published studies identified in the systematic review of economic evaluations.[65, 73, 282, 317]

In the model, patients have an elevated risk of liver-related mortality in the DCC, HCC LT and post-LT health states. Commonly cited probabilities of liver-related mortality for patients with DCC were considered in the model.[73, 109, 177, 316, 318, 319] However, inclusion of these parameters led to an underestimation at the beginning of the time horizon and an overestimation later in the time horizon when compared with the survival curves observed by more recently published clinical studies.[105, 320, 321] Therefore, a transition probability was estimated based on these observed survival curves, taking into account discounting to minimise bias in the summation of costs and QALYs. The implementation of a survival function for DCC was not considered given that it would require individual-level simulation which was not facilitated by the cohort-level Markov model structure.

Liver-related mortality from HCC was estimated from HCC-specific five-year net survival estimates from 2011 to 2015 provided by the National Cancer Registry Ireland (NCRI), presented in Chapter 3.6.3.[163] The data collected by the NCRI demonstrates that survival for HCC has improved markedly in recent years, and at a faster rate than that of overall liver cancer survival. Based on these data, it is estimated that 32.9% (95% CI: 27.3-39.7%) of patients will be alive at five-year follow-up. To ensure that the model accurately predicted this outcome, a six-month transition probability of 0.105 (95% CI: 0.09-0.12) to liver-related mortality was employed in the model. As this is used as a constant event rate in the model and because of the accelerated improvement of HCC-specific survival relative to overall liver cancer survival in recent years, it is likely that it underestimates liver-related mortality in patients during the initial years of diagnosis with HCC. The transition probability is consistent with those used by previously published studies.[65, 282]

Consistent with previously published economic evaluations, the liver-related mortality rate in the first year following liver transplant was significantly higher than in the years subsequent to transplantation.[153, 316] The age-dependent probability of all-cause mortality was based on the CSO's 2016 Irish life tables.[149] The transition probabilities are presented in Table 6.11.

Table 6.11. Six-month transition probabilities used in the economic analysis

	Mean	LCI	Distribution	Source
Without treatment				
F0-to-F1	0.07	0.04-0.10	Beta	(300, 301, 313, 314)
F1-to-F2	0.04	0.03-0.05	Beta	(300, 301, 313, 314)
F2-to-F3	0.06	0.04-0.08	Beta	(300, 301, 313, 314)
F3-to-F4 (CC)	0.08	0.05-0.11	Beta	(300, 301, 313, 314)
CC-to-DCC	0.02	0.01-0.03	Beta	(176, 316)
CC-to-HCC	0.01	0.00-0.02	Beta	(176, 316)
DCC-to-HCC	0.04	0.03-0.05	Beta	(65, 282)
DCC-to-LT	0.02	0.01-0.03	Beta	(73, 317)
HCC-to-LT	0.02	0.01-0.02	Beta	(274)
DCC-to-liver related death	0.11	0.07-0.15	Beta	(105, 320, 321)
HCC-to-liver related death	0.04	0.00-0.18	Beta	(163)
LT-to-liver related death (first year)	0.11	0.06-0.17	Beta	(153)
LT-to-liver related death (subsequent year)	0.03	0.02-0.04	Beta	(316)
With treatment				
CC-to-DCC (RR)	0.03	0.00-0.09	Beta	(293)
CC-to-HCC (RR)	0.12	0.07-0.18	Beta	(293)

Key: CC – compensated cirrhosis; CI – confidence interval; DCC – decompensated cirrhosis; F – METAVIR fibrosis stage; HCC – hepatocellular carcinoma; LT – liver transplant; RR – relative risk.

6.3.5 Quality of life estimates

In the model, health benefits are expressed in terms of quality-adjusted life years (QALYs) gained. QALYs reflect the impact of an intervention on patients' quality and length of life, estimated using self-reported utilities or health-related quality of life.[297] The utility values used to estimate QALYs in the CUA are presented in Table 6.12.

Consistent with the approach of Ara and Brazier,[322] age-based QALYs were used to approximate baseline values in the general population. Index scores were calculated based on participant data from the EQ-5D-5L survey, conducted between March 2015 and September 2016 on a representative sample of the Irish population (n=1,311).[323, 324] The EQ-5D-5L surveys self-reported health status across five domains of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) at five levels of severity. Individual scores across each domain were converted to a single index (that is, the baseline utility value), which were averaged across each age group

with uncertainty reflected in the variance of the sampling distribution. The EQ-5D-5L survey data were reported according to 10-year age band. The data were not disaggregated on the basis of the five-year age bands employed in the model. Non-parametric bootstrapping was undertaken to reflect uncertainty at the population-level as opposed to the individual-level. It should be noted that the sample size was small, particularly in the 75 years and over age groups.

A disutility multiplier of 0.98 (95% CI: 0.93-1.00) was used for people that received a false positive diagnosis of chronic HCV infection, to reflect the associated anxiety and stress, with their QALY value returning to baseline in the subsequent cycle.[277, 282, 325] As reflex core antigen testing is modelled, the number of false positive diagnoses was lower than if a two-step testing process requiring two individual blood draws was implemented (that is, only patients that test positive for the anti-HCV antibody and core antigen will receive a positive diagnosis). It is assumed that patients who receive a false positive diagnosis will be identified by baseline HCV-RNA testing at follow-up. Therefore, their utility decrement will not carry beyond the subsequent six-month cycle.

Utility values for patients with chronic HCV infection are based on an observational study of HCV patients (n=270, mean age: 45 years) treated in two hepatology units in Dublin between September 2011 and October 2012.[326] The utility values were estimated based on the index scores elicited using the EQ-5D-3L survey.[327] The utility values for F0 to F2 reported in the study were aggregated to "mild fibrosis". Therefore, the utility values attributed to patients in the F0 to F2 health states are equivalent in the model. This biases against the intervention since patients diagnosed at F0-F1 will not gain QALYs from early diagnosis compared with F2. However, the bias is small when compared with international studies that included an incremental difference.[265, 281] No treatment-related utility decrements were incorporated in the model.

Table 6.12. Health-state utility values

	Mean	95% CI	Distribution	Source
Baseline utilities in the general population				
35-44	0.93	0.91-0.94	Beta	(323, 324)
45-54	0.88	0.86-0.90	Beta	(323, 324)
55-64	0.86	0.83-0.89	Beta	(323, 324)
65-74	0.85	0.81-0.88	Beta	(323, 324)
75-84	0.80	0.75-0.85	Beta	(323, 324)
85+	0.83	0.73-0.91	Beta	(323, 324)
Disutility for false positive diagnosis				
Disutility multiplier	0.98	0.93-1.00	Beta	(277, 282, 325)
Disease-specific utilities (relative to population norm)				
Mild (F0-F2)	0.75	0.71-0.79	Beta	(326)
F3	0.74	0.69-0.75	Beta	(326)
F4	0.64	0.52-0.72	Beta	(326)
DCC	0.46	0.22-0.62	Beta	(326)
HCC	0.52	0.25-0.64	Beta	(326)
LT (first year)	0.49	0.25-0.63	Beta	(326)
Post-LT (subsequent years)	0.59	0.51-0.66	Beta	(326)
SVR	0.81	0.75-0.87	Beta	(326)

Key: CI –confidence interval; DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; F – METAVIR fibrosis stage; LT – liver transplant; SVR – sustained virological response.

6.3.6 Costs

As birth cohort testing considers the full clinical pathway, from identification of patients to treatment, four cost categories were included in the model:

- screening costs
- health state costs
- treatment-related costs
- implementation costs.

All costs presented in Table 6.13 are valued in 2019 Euro (€) currency with healthcare costs adjusted according to the CSO's consumer price index (CPI) for health.

Screening costs

In the model, a birth cohort testing programme is modelled via both a systematic testing programme and an opportunistic testing programme, and compared with no birth cohort testing (current standard). In both cases, the intervention includes the cost of a GP appointment. In the systematic testing arm, a GP visit is explicitly required for the purpose of HCV testing with the appointment reimbursed by the HSE. In the

opportunistic testing arm, HCV testing is added to an existing GP appointment (for example, an annual health check) with the cost of the appointment reimbursed by the HSE.

In the model, the cost of a GP consultation is based on the opportunity cost of the GP's time (that is, the cost of foregone alternative uses of their time), as estimated by a previous HTA.[328] In the HTA, the opportunity cost of a GP visit was a function of the number of GP visits in Ireland and the total income of GP and other services that must be funded through that income. In reality, the cost of a GP appointment for HCV testing will be subject to contract negotiations between the Irish Medical Organisation (IMO), the Department of Health and the Health Service Executive (HSE). The cost of the GP appointment also includes the cost of blood sampling consumables, as estimated by a previous HTA.[8, 329]

Diagnosis of chronic HCV infection requires an anti-HCV antibody test followed by a supplementary test to confirm chronic HCV infection. In the model, a simplifying assumption is incorporated whereby patients receive a reflex core antigen test for confirmation of chronic HCV infection. Patients may receive a core antigen or ribonucleic acid (RNA) test in reality, but core antigen (although less sensitive) is more likely to be used if birth cohort testing is implemented via a centralised programme since it permits a longer window for spinning down and freezing samples for reflex testing and is more pragmatic from a cost perspective (that is, it has a lower unit cost per test).

As described in Section 2.10, patients that are diagnosed with chronic HCV infection receive baseline (pre-treatment) and post-treatment RNA tests to confirm virological cure. In the model, patients that receive a false positive core antigen test result incur the cost of the baseline RNA test and the cost of an outpatient department appointment, but do not incur health state costs. The costs of the anti-HCV, core antigen and HCV-RNA tests are based on those previously published and verified by expert opinion.[8] The cost of an outpatient visit is €138, representing staff utilisation (medical care, administration and phlebotomy), based on the figure reported by the 2013 HSE Ready Reckoner.[330] As (contrary to healthcare inflation) the HSE Ready Reckoners published prior to 2013 indicated a downward trend in the cost of an outpatient visit, it may represent an overestimate but is broadly consistent with that found by a micro-costing study of ambulatory care for HCV in Ireland published in 2015.[331] The cost of sample transportation has not been estimated as it is assumed that existing resources will be utilised.

Costs for diagnosis of chronic HCV infections are presented in Table 6.13.

Table 6.13. Costs for diagnosis of chronic HCV infection

	Mean (€)	95% CI (€)	Distribution	Source
GP visit	50	48-53	Gamma	(328)
Blood consumables	1	1-2	Gamma	(8, 329)
Anti-HCV test	11	9-13	Gamma	(8)
Core antigen test	40	34-47	Gamma	(8)
HCV-RNA test	55	46-64	Gamma	(8)
OPD visit	138	112-167	Gamma	(330)

Key: CI – confidence interval; GP – general practitioner; HCV – hepatitis C virus; OPD – outpatient department; RNA – ribonucleic acid.

Health state costs

Health state costs (presented in Table 6.14) represent the annual healthcare cost incurred by a patient in a given health state due to the management of their HCV infection. In the model, patients with undiagnosed chronic HCV infection do not accrue health state costs until either they are identified by screening or they become symptomatic (that is, they progress beyond F4). It is assumed that once patients become symptomatic their HCV status is detected as part of clinical diagnosis. As a result, these patients become ineligible for screening and follow the natural course of disease incurring health state costs for the treatment and management of their HCV.

All of the health state costs used in the health economic analysis are based on a micro-costing study of ambulatory healthcare utilisation of patients with chronic HCV infection at two large tertiary referral hepatology services in Ireland, inflated to 2019 Euro.[331] The observational study included a micro-costing of ambulatory care and the annual cost of healthcare resource utilisation for patients with chronic HCV infection. The healthcare costs of individuals from the general population that do not have chronic HCV infection are not estimated in the model.

Table 6.14. Health state costs

	Mean (€)	95% CI (€)	Distribution	Source
F0-F2	417	353-503	Log-Normal	(331)
F3	437	352 -525	Log-Normal	(331)
F4 (CC)	1,875	1,049-3,277	Log-Normal	(331)
DCC	8,699	4,188-15,136	Log-Normal	(331)
HCC	23,042	16,055-30,671	Log-Normal	(331)
LT	143,727	142,543-144,886	Log-Normal	(331)
Post-LT	5,592	5,186-6,066	Log-Normal	(331)
SVR	46	17-75	Log-Normal	(331)

Key: CI – confidence interval; CC – compensated cirrhosis; DCC – decompensated cirrhosis; F – fibrosis; HCC – hepatocellular carcinoma; LT – liver transplantation.

Treatment-related costs

Treatment costs include the costs of first- and second-line therapy (for patients that fail first-line therapy). As described in Section 4.3, the preferred regimens reimbursed for treatment of chronic HCV infection in Ireland are subject to an annual national procurement process. The price for each regimen is agreed in confidence between the HSE Corporate Pharmaceutical Unit and the drug manufacturers. To ensure plausibility of the modelled cost predictions, the manufacturers of the DAA therapies recommended by the NHCTP's 2019 treatment guidelines were contacted to share, in confidence with the Evaluation Team, the standard regimen cost for treating a person with chronic HCV infection. The unit costs are not presented in this report due to the commercially sensitive nature of the cost data. However, the method used to include treatment costs in the analysis is described.

First, the estimated number of patients with chronic HCV infection (that is, the prevalence) was disaggregated according to age band, HCV genotype and the presence or absence of cirrhosis. Second, weights were assigned to each therapy regimen to reflect the rank order of preferred therapies. An average cost of first-line and second-line therapies was then estimated. Finally, probability distributions were assigned to each input to reflect uncertainty, and the overall average cost per line of therapy and 95% confidence intervals were estimated based on repeated simulation.

Patients will undergo HCV genotyping prior to receipt of first-line therapy, and will undergo resistance testing prior to receipt of second-line therapy. These costs, which were provided by expert opinion, are aggregated along with the costs of first- and second-line therapy to ensure that the commercially sensitive unit costs cannot be identified from the model outputs.[299] In the model, patients that accept therapy incur the full therapeutic cost, regardless of treatment outcomes. Patients that do not achieve an SVR upon re-treatment remain in the non-SVR health states and continue along the natural course of disease and incur management costs related to their

diagnosis.

Implementation costs

Implementation costs are relevant to birth cohort testing in terms of:

- the set-up and running costs for a testing programme
- an accompanying public awareness campaign.

Training costs may also be relevant to ensure that healthcare staff are adequately resourced to perform phlebotomy and package samples for transport appropriate for reflex testing. However, these costs have not been estimated.

As described in Chapter 7.3.1, set-up and running costs will be attributable to birth cohort testing if it is implemented via a systematic testing programme. Implementation of a systematic programme would aim to improve patient care, assist service planning and enable quality assurance and evaluation.

The resources required (see Table 6.15) to set-up and run such a programme and database registry are based on the 2019 business case submitted to the HSE for the set-up of a National Diabetes Registry. However, it is acknowledged that these estimates may not be directly applicable given that the diabetic retinopathy programme comprises a live register while birth cohort testing involves one-off testing.

Salary costs (presented in Table 6.16) were estimated in line with national HTA guidelines, adjusting for pay-related social income (PRSI), overheads and pension contributions. Uncertainty was reflected by non-parametric bootstrapping based on the HSE salary scales for each grade. The running costs of the programme are only included during the initial ten years of the time horizon in line with efforts to eliminate HCV in Ireland.[7, 93-95]

Table 6.15. Resource requirements for systematic programme

Job title	WTE	Grade	Annual cost*	Source
Clerical Officer	1.0	Clerical officer	€43,028	(332)
ICT Developer	0.5	VI (clerical)	€70,841	(332)
Data architect	1.0	VII (clerical)	€77,130	(332)
Project manager ICT	1.0	VII (clerical)	€77,130	(332)
Project Manager Business	1.0	VII (clerical)	€77,130	(332)
Specialist in Public Medicine	0.5	Specialist in Public Health Medicine	€159,066	(332)

Key: ICT – Information Communications Technology; LCI – lower confidence interval; UCI – upper confidence interval; WTE – whole time equivalent.
* Annual salary costs are based on non-parametric bootstrapping of HSE salary grades and adjusted for pension, pay-related social insurance and overheads.(262, 263)

It is assumed that implementation of a birth cohort testing programme, whether systematic or opportunistic in nature, will be accompanied by a public awareness campaign aimed at encouraging uptake of testing. The costs of a public awareness campaign are very difficult to quantify, since it will depend entirely on the approach adopted to reach the target audience. However, the National Screening Service was able to provide broad estimates of the cost ranges that may be applicable to the individual components of a public awareness campaign.(299)

The individual components that will determine the cost of a public awareness campaign include:

- qualitative research – investigation of the target audience's knowledge, awareness levels, information gaps and or misconceptions
- creative development – campaign development based on the findings from the qualitative research which will vary according to the type of media campaign required (for example, radio and press), and require the involvement of creative agencies and analysts
- focus testing – testing of creative routes (for example, focus groups)
- media plan – the duration of the media campaign.

To include these costs in the analysis, the midpoint of the estimated ranges were assumed as the mean and a standard deviation was estimated from the lower and upper bounds of the estimated ranges. The total cost of the individual components was then used as a single model input to allow for a wide range of uncertainty in the estimate. It has been demonstrated that aggregating individual cost components better reflects correlation between the individual components.(333)

Table 6.16. Implementation unit costs

	Mean (€)	95% CI (€)	Distribution	Source
Clerical Officer	43,028	32,475-55,043	Gamma	(332)
ICT Developer	70,841	64,212-77,792	Gamma	(332)
Data architect	77,130	67,948-86,885	Gamma	(332)
ICT PM	77,130	67,948-86,885	Gamma	(332)
Business PM	77,130	67,948-86,885	Gamma	(332)
Specialist in Public Medicine	159,066	128,850-192,418	Gamma	(332)
Public awareness campaign	508,804	228,455-899,739	Gamma	(333)

Key: CI – confidence interval; ICT – Information Communications Technology; PM – project manager.

6.4 Handling of uncertainty and model verification

6.4.1 Sensitivity analysis

Parameter uncertainty, relating to the imprecision of the model inputs, was assessed using probabilistic sensitivity analysis (PSA). PSA involves assigning statistical distributions to each of the input parameters and simultaneously drawing a random sample from the plausible range for each parameter. These random samples are drawn repeatedly in a Monte Carlo simulation (where the model was run 10,000 times) with different sets of inputs simulated. The statistical distribution assigned to each parameter was based on published recommendations for economic evaluation in health care.(334-336) The mean value and variance across the model replications were then recorded. The uncertainty is presented via a scatterplot of point estimates from the model replications on the cost-effectiveness plane. The cost-effectiveness acceptability curve (CEAC), which illustrates the probability that an intervention is cost-effective at different willingness-to-pay (WTP) thresholds, was also plotted based on the PSA outputs.

There is no stated universal WTP threshold in Ireland below which an intervention is considered cost-effective. In previous evaluations in Ireland, willingness-to-pay thresholds of between €20,000 and €45,000 per QALY have typically been used as reference points. An international study generated estimates for Ireland suggesting that the WTP threshold is closer to €20,000 per QALY than €45,000 per QALY.(337) A 2016 framework agreement between the Irish Pharmaceutical Healthcare Association (IPHA) and the HSE for the supply and pricing of medicines sets out €20,000 per QALY and €45,000 per QALY as reference points for decision-making in regards the reimbursement of medicines (excluding vaccines).(338) The agreement also sets out five-year budget impact thresholds for the level of HSE authority required in decision-making.

Structural uncertainty was assessed using deterministic univariate sensitivity analysis

and scenario analysis (see Section 6.4.4). Univariate sensitivity analysis shows how influential each parameter is by itself and how sensitive the model outputs are to fluctuations in each input value. To identify the key model inputs, each parameter is assigned a lower and upper limit (that is, a 95% confidence interval) based on empirical evidence. Each parameter is then individually fixed at the lower and upper bounds of their plausible ranges, and the impact on the model output recorded. The uncertainty of model outputs according to extreme variation in model inputs is presented in a tornado diagram.

Sensitivity analysis to investigate potential influence of correlation between modelled subgroups

In the base case analysis, prevalence and the rate of background detection are modelled independently according to subgroup. In the real-world, the prevalence or rate of background detection within one subgroup may be correlated with that of another subgroup. Independence assumes that the prevalence in one age group is unrelated to the prevalence in other age groups. Correlation assumes that they are related; that is, if prevalence is high in one it will likely be high in the others too. The potential influence of this correlation on the cost-effectiveness of the technology was assessed in a sensitivity analysis.

As described in section 6.3.1, in the base case analysis these parameters were estimated using a generalised additive model that simulated data from a variety of sources. The simulation outputs from the generalised additive model were used as the basis for estimating plausible correlations between the subgroups. That is, the model outputs of an individual simulation (in terms of prevalence or detection across age bands) were selected at random and modelled directly in the CUA, with the cost-effective estimates recorded for each iteration of the simulation (n=10,000). All other parameters in the CUA were fixed at their mean value during this process.

6.4.2 Subgroup analysis

Subgroup analysis of the CUA and BIA were conducted in the following groups, those aged:

- 36-40 years
- 41-45 years
- 46-50 years
- 51-56 years.

The subgroup analysis is presented according to the assumptions of the base case analysis. That is, the results are underpinned by the assumption that implementation of birth cohort testing adopts a staggered implementation over a five-year period with testing first offered to the oldest cohort.

6.4.3 Scenario analysis

Scenario analysis was conducted to assess structural uncertainty in the model. A number of scenarios were modelled:

- *scenario 1:* reverse ordering of the staggered implementation, whereby testing is first offered to the youngest cohort (that is, people aged 36-40) and sequentially offered to the older age groups
- *scenario 2:* the consequences in terms of costs, health benefits and capacity implications if the observed uptake rate of HCV testing is much higher than that modelled in the base case analysis; in this scenario the modelled uptake rate is based on observational studies conducted in Ireland across a variety of healthcare settings
- *scenario 3:* since the data informing disease progression rates in the base case analysis is not directly applicable to the undiagnosed 1965-1985 birth cohort (given that disease progression rates are based on individuals diagnosed with disease that may have exhibited other risk factors), alternative (that is, marginally lower) fibrosis progression rates for patients with chronic HCV infection were modelled to estimate its influence on costs and health benefits; the disease progression data are based on a 2018 systematic review and meta-analysis of treatment-naïve patients
- *scenario 4:* as per scenario 3, given that the fibrosis distribution (that is, the current disease progression of the birth cohort) informing the base case analysis may not be directly applicable to the undiagnosed birth cohort, the initial fibrosis distribution at the outset of the model simulation was tested by arbitrarily weighting towards the less advanced fibrosis stages (F0-F3) and the more advanced fibrosis stages (F1-F4)
- *scenario 5:* the unit costs of the advanced liver disease health states was arbitrarily reduced to investigate the impact of downstream healthcare costs on the cost-effectiveness of birth cohort testing
- *scenario 6:* a disproportionate number of HCV-RNA positive samples from the Garvey study were from the antenatal population (that is, a bias is assumed).

The structural assumptions and model inputs used to conduct these analyses are presented alongside the results of each scenario in Section 6.5.

6.4.4 Threshold analysis

A threshold analysis estimates the conditions above or below which the model output may become cost-effective, by substituting the point estimate for a wide sequence of values and recording the variation in model outputs. Both univariate and multivariate approaches were adopted in the threshold analysis.

The following parameters were assessed by threshold analysis:

- cost of antibody test
- cost of core antigen test
- prevalence of chronic HCV infection
- uptake rate of systematic testing.

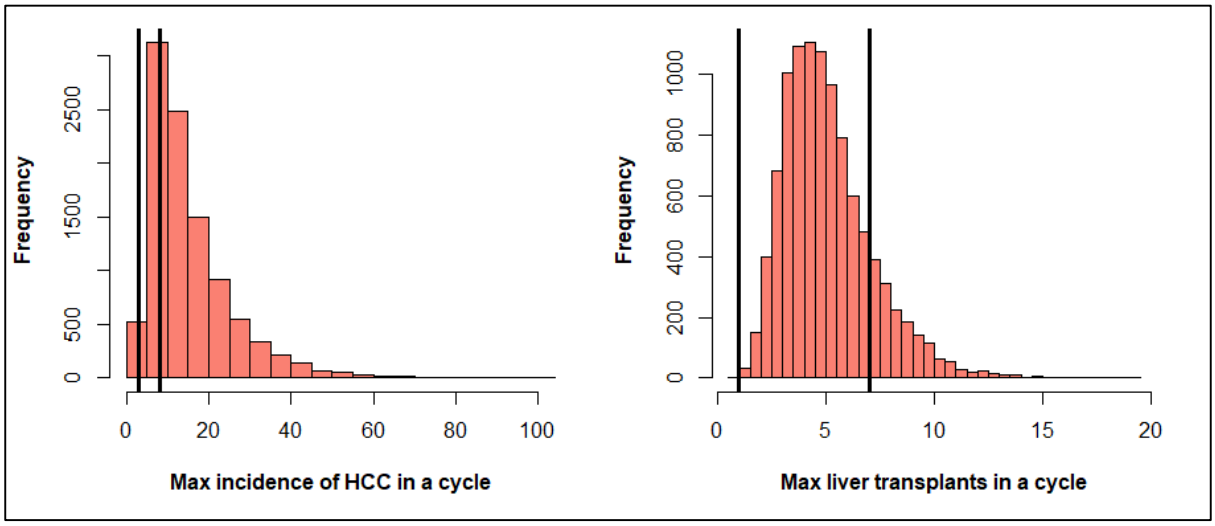
6.4.5 Model validation and calibration

Internal validation, pertaining to the mathematical logic of the model, was conducted in accordance with HIQA's internal Quality Assurance Framework. All model inputs, calculations and model outputs were reviewed by a second economic modeller. Cross verification of the clinical predictions was performed for both the decision tree and Markov model by replicating the inputs and outputs from published studies.[316, 339] A subset of the model parameters were further calibrated against the expected incidence of hepatocellular carcinoma (HCC) and liver transplantation (LT) cases.

It was assumed that between 60% and 90% of all liver cancers are due to HCC,[340-343] and that between 20% and 40% of HCC cases are due to chronic HCV infection.[162, 168, 169] Applying these ranges to the incidence of all liver cancers for people aged between 35 and 54 years from 2006 to 2015 produces an incidence of between three and eight HCC cases per model cycle.[164] It was assumed that there should be an incidence of between three and seven LT cases per cycle based on the epidemiological data presented in Section 3.6.2.

Monte Carlo simulation – which involves drawing a random value from a probability distribution for each model input – was undertaken for the "no birth cohort testing" comparator using 10,000 model iterations. For each simulation, all model inputs along with the estimated incidence of HCC and LT cases over a five-year time horizon were recorded. This demonstrated that only 23% of the model predictions were within the predefined plausible incidence range (see Figure 6.4). This issue was more pronounced in the projections of HCC than that of LT. Overestimating the incidence of HCC and LT would bias in favour of birth cohort testing since the associated health-state costs are substantial and the health-state utilities are considerably lower than those for the fibrosis health states in which patients are offered testing.

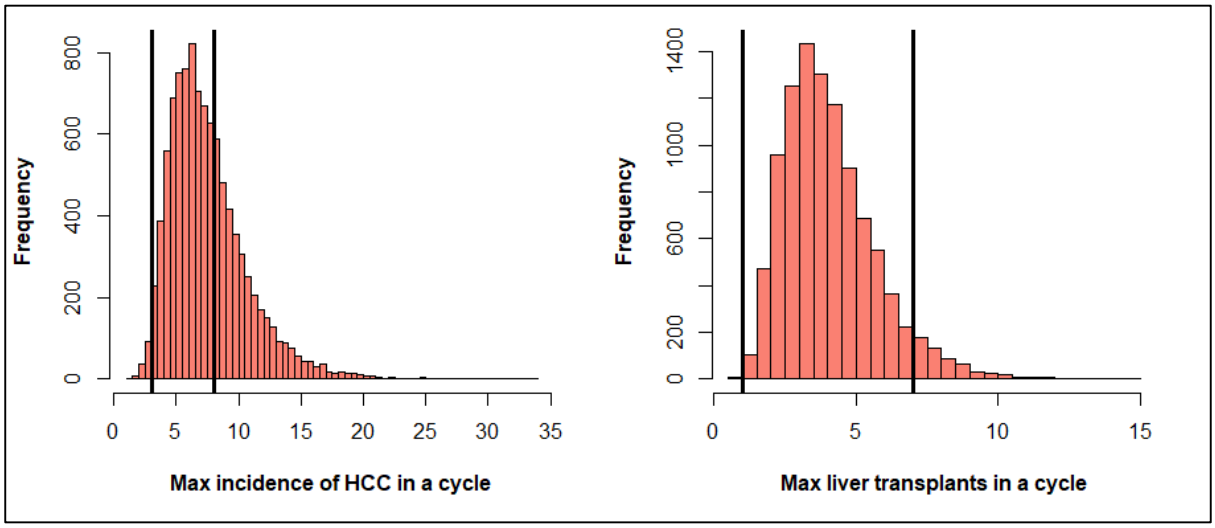
Figure 6.4. Modelled incidence of HCC and LT prior to calibration



Key: HCC – hepatocellular carcinoma; LT – liver transplantation.

Logistic regression (implemented using a generalised linear model with a binomial error distribution and logit link function) identified which model inputs had a statistically significant effect on the modelled incidence of HCC and LT cases. The parameter distributions were re-estimated based on the values that resulted in simulations that generated plausible outputs for incidence of HCC and LT cases. This iterative process (from Monte Carlo simulation through to logistic regression) was repeated until at least 50% of the modelled incidence of HCC and LT was within the predefined plausible limits.

Figure 6.5. Modelled incidence of HCC and LT following calibration



Key: HCC – hepatocellular carcinoma; LT – liver transplantation.

The transition probabilities from CC-to-DCC and CC-to-HCC, based on previously published international studies,[176, 316] had a significant influence on the modelled incidence of HCC and LT. Following downward calibration of these parameters, the

proportion of modelled incidence of HCC and LT within the expected range was 62% (see Figure 6.5). The updated parameters are presented in Table 6.17.

Table 6.17. Six-month transition probabilities updated during calibration

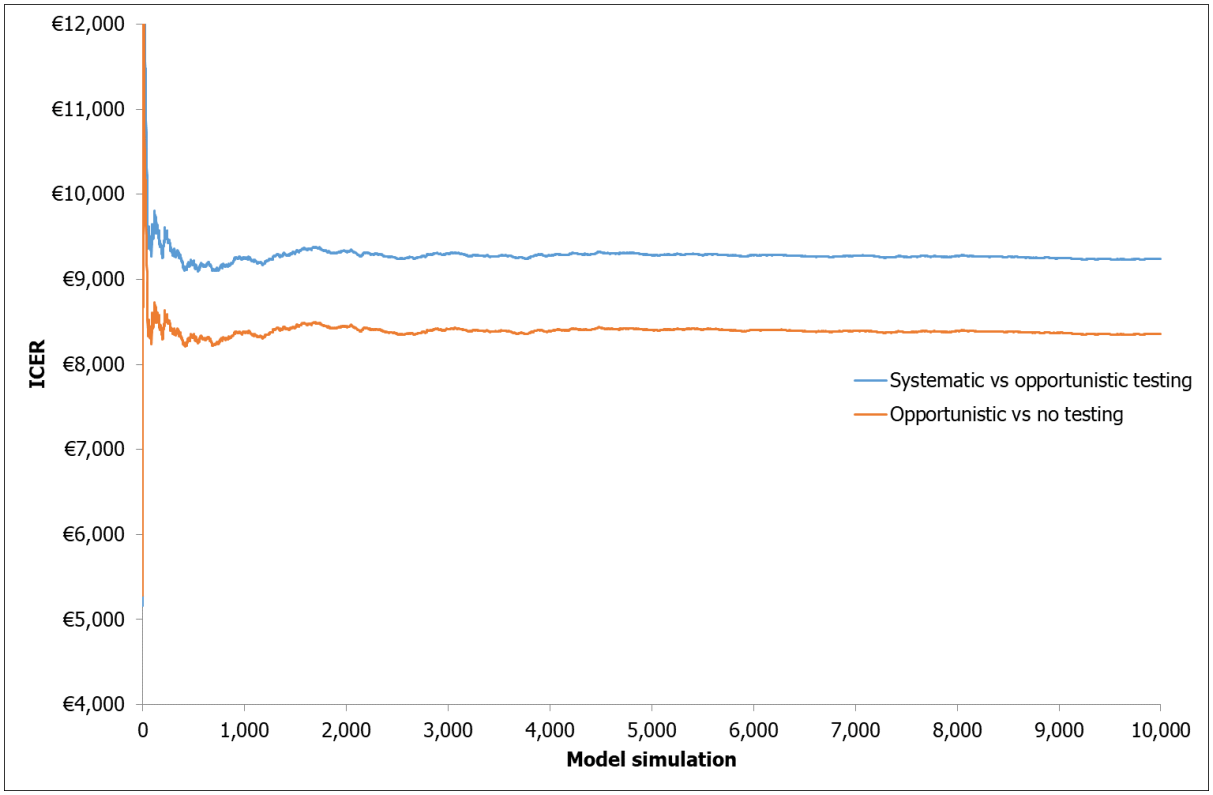
	Original values		Calibrated values	
	Mean	**95% CI**	**Mean**	**95% CI**
CC-to-DCC	0.020	0.01-0.03	0.019	0.011-0.029
CC-to-HCC	0.007	0.00-0.02	0.003	0.000-0.006

Key: CC – compensated cirrhosis; CI –confidence interval; DCC – decompensated cirrhosis; F – METAVIR fibrosis stage; HCC – hepatocellular carcinoma; LT – liver transplant; RR – relative risk.

6.5 Results

The model was run for 10,000 Monte Carlo simulations to estimate the costs and consequences of each strategy in the economic model. To determine if the model had converged on a result, the mean incremental cost-effectiveness ratio (ICER) was monitored across simulations (Figure 6.6). After 1,000 simulations, the estimated mean ICERs were consistently within 1% of the overall mean ICER estimated after 10,000 simulations. Due to the computational burden of running the model, scenario analyses were based on 2,000 simulations.

Figure 6.6. Analysis of convergence



Note: Cumulative mean incremental cost-effectiveness ratio by model simulation is presented.

6.5.1 Cost-utility analysis – base case analysis

Overview of findings

The introduction of birth cohort testing (whether systematic or opportunistic) was cost-effective when compared with no birth cohort testing at a willingness-to-pay (WTP) threshold of €20,000 per quality-adjusted life year (QALY) gained. It was estimated that implementation of a systematic or an opportunistic birth cohort testing programme would lead to increased costs, but also increased benefits. A summary of the CUA results are presented in Table 6.18.

Table 6.18. Cost-effectiveness incremental findings*

	Costs	QALYs	ICER	INMB
Versus no birth cohort testing				
Opportunistic testing (95% CI)	€1,573 (€202 to €3,017)	0.21 (0.10 to 0.34)	€8,357 (€843 to €19,699)	€2,597 (€31 to €5,671)
Versus opportunistic birth cohort testing				
Systematic testing (95% CI)	€847 (€160 to €1,611)	0.10 (0.05 to 0.16)	€9,237 (€1,384 to €21,632)	€1,166 (-€98 to €2,565)

Key: ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality-adjusted life year.

* In an incremental analysis of costs and effects, the alternatives under assessment are ranked according to total health effects (that is, QALYs) and the incremental costs and effects are calculated relative to the next best alternative. As systematic birth cohort testing led to the greatest total effects, its ICER is calculated relative to the next best alternative (that is, opportunistic birth cohort testing).

A target population of 11,779 (95% CI: 7,742 to 16,560) undiagnosed cases of chronic HCV was estimated.

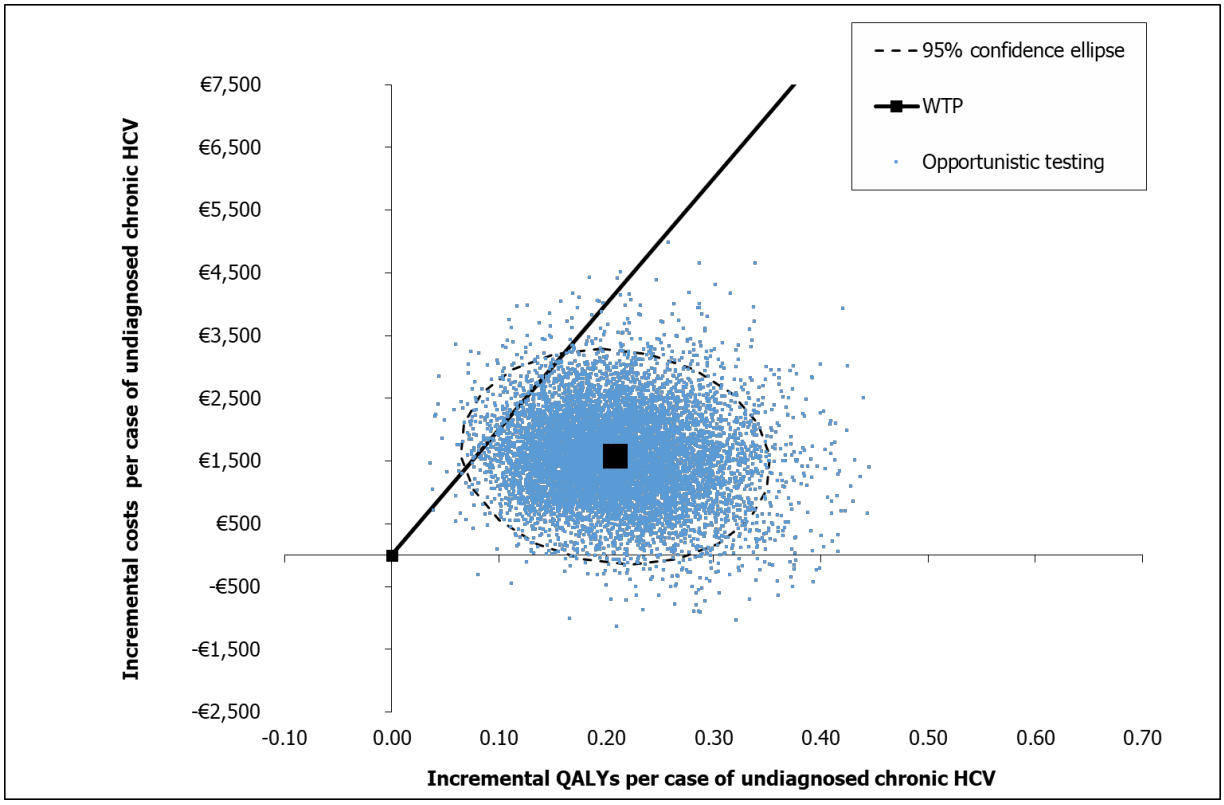
Over a lifetime time horizon, the incremental cost of opportunistic birth cohort testing per undiagnosed case of HCV was estimated at €1,573 (95% CI: €202 to €3,017), and the incremental QALY gained was estimated at 0.21 (95% CI: 0.10 to 0.34), compared with no birth cohort testing. The ICER was estimated at €8,357 (95% CI: €843 to €19,699) per QALY gained. The INMB was estimated at €2,597 (95% CI: €31 to €5,671) using a WTP of €20,000.

Over a lifetime time horizon, the incremental cost of systematic birth cohort testing per undiagnosed case of HCV was estimated at €847 (95% CI: €160 to €1,611), and the incremental QALY gained was estimated at 0.10 (95% CI: 0.05 to 0.16), compared with opportunistic birth cohort testing. The ICER was estimated at €9,237 (95% CI: €1,384 to €21,632) per QALY gained. The INMB was estimated at €1,166 (95% CI: --€98 to €2,565) using a WTP of €20,000. As systematic birth cohort testing produced the greatest overall QALYs and had an ICER below the WTP threshold, it would be considered the most cost-effective of the three alternatives evaluated in this HTA.

Cost-effectiveness plane

The cost-effectiveness plane, which illustrates the incremental costs and benefits estimated in the probabilistic analysis, comparing opportunistic birth cohort testing with no birth cohort testing is presented in Figure 6.7. Although there was considerable uncertainty in the estimated costs and benefits, the vast majority of the point estimates fall into the north-east quadrant of the cost-effectiveness plane (where the intervention is more costly, but also more effective), indicating that opportunistic birth cohort testing is cost-effective at a WTP of €20,000 per QALY gained.

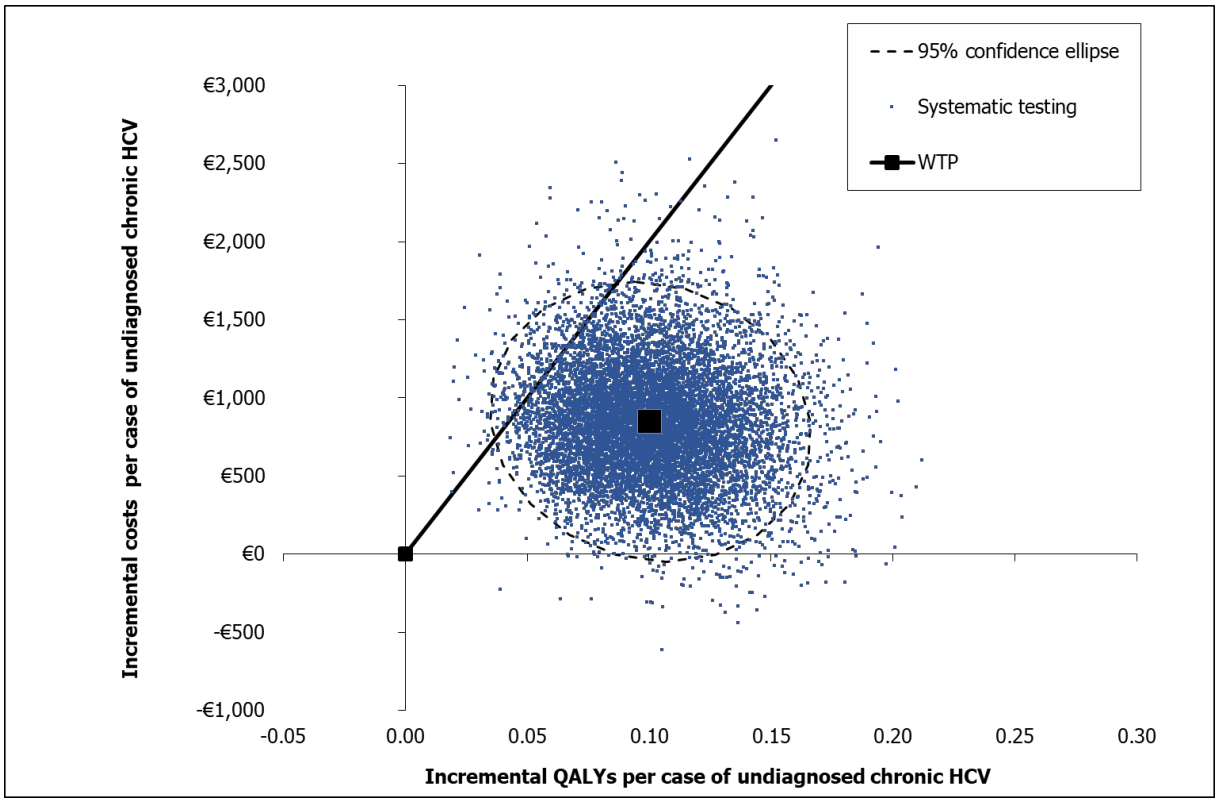
Figure 6.7. Cost-effectiveness plane of opportunistic birth cohort testing compared with no birth cohort testing



Key: HCV – hepatitis C virus; QALY – quality-adjusted life year; WTP – willingness to pay threshold.

The cost-effectiveness plane comparing systematic birth cohort testing with opportunistic birth cohort testing is presented in Figure 6.8. Although there was considerable uncertainty in the estimated costs and benefits, the vast majority of the point estimates fall into the north-east quadrant of the cost-effectiveness plane (where the intervention is more costly, but also more effective), indicating that opportunistic birth cohort testing is cost-effective at a WTP of €20,000 per QALY gained.

Figure 6.8. Cost-effectiveness plane of systematic birth cohort testing versus opportunistic birth cohort testing

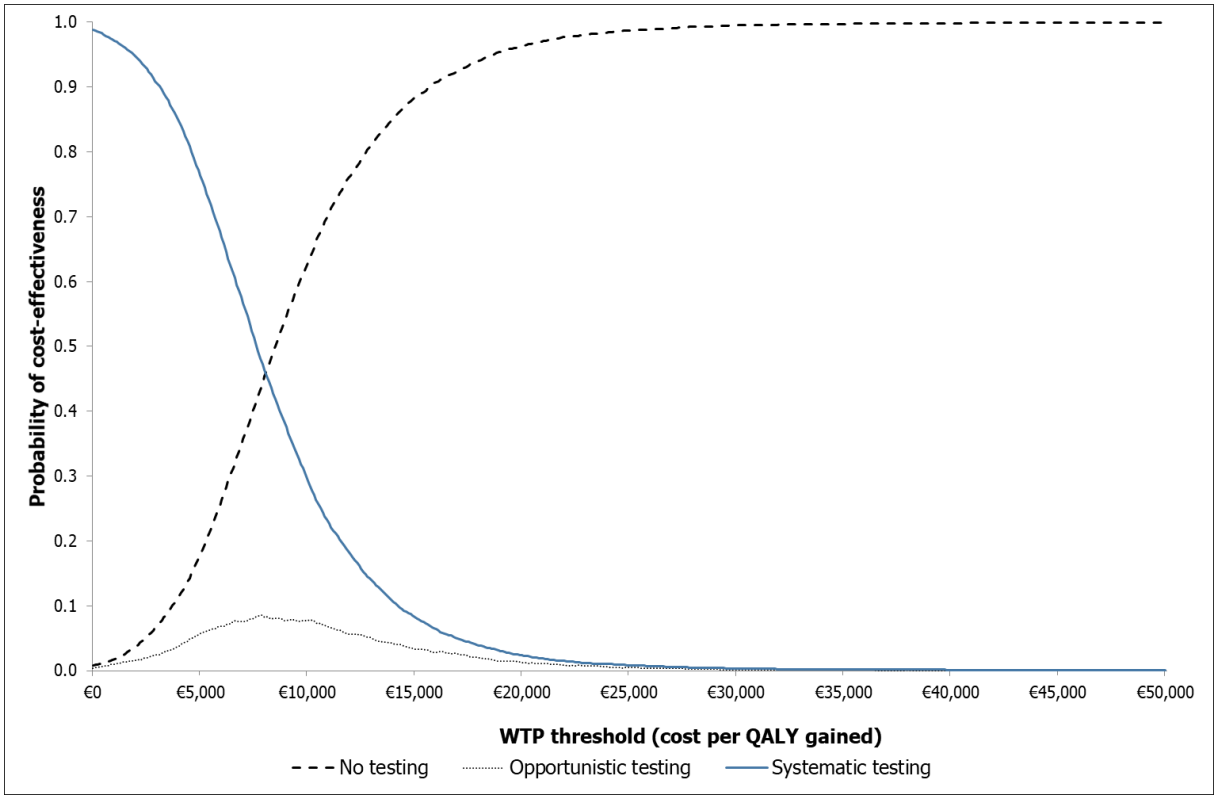


Key: HCV – hepatitis C virus; QALY – quality-adjusted life year; WTP – willingness to pay threshold.

Cost-effectiveness acceptability curve

The cost-effectiveness acceptability curve (CEAC) summarises the impact of uncertainty on the finding of the economic evaluation by plotting the net monetary benefit (which expresses the intervention's value in monetary terms) at alternative WTP thresholds. From Figure 6.9, there is a clear trend in favour of the introduction of systematic birth cohort testing at WTP thresholds above €10,000. At WTP thresholds of €20,000 and €45,000, the probability of systematic birth cohort testing being cost-effective was 0.96 and >0.99, respectively.

Figure 6.9. Cost-effectiveness acceptability curve of mutually exclusive alternatives under assessment in CUA



Key: CEAC – cost-effectiveness acceptability curve; CUA – cost-utility analysis; QALY – quality-adjusted life year; WTP – willingness to pay.

Note: The CEAC is based on total net monetary benefit (a summary statistics representing the value of an intervention in monetary terms) of each testing strategy at the specific WTP threshold.

6.5.2 Cost-utility analysis – univariate sensitivity analysis

In the univariate sensitivity analysis, each parameter was individually set at the lower and upper limits of its 95% confidence interval while all other parameters were held constant at their mean values. Through this analysis, the impact of parameter uncertainty on decision uncertainty can be explored.

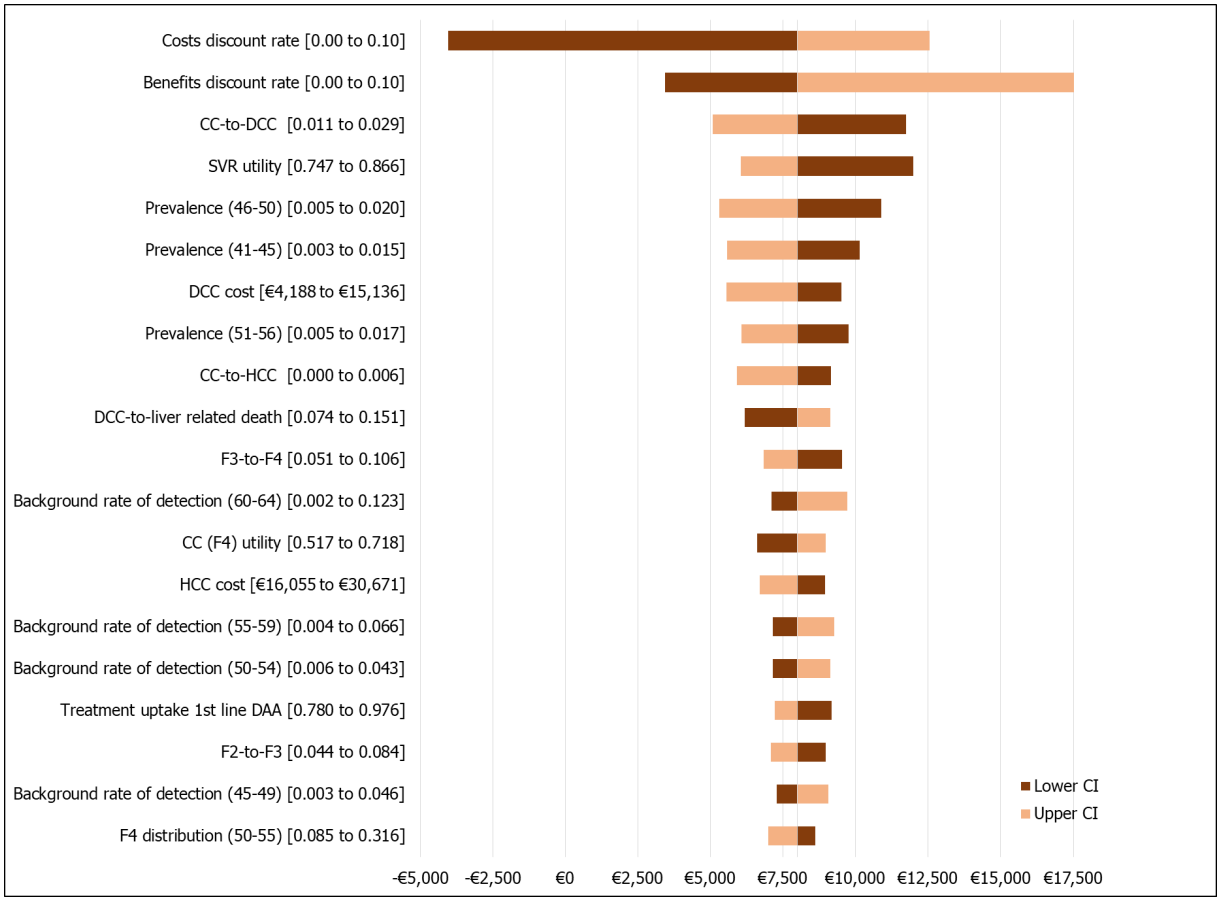
Opportunistic testing versus no testing

The cost-effectiveness of opportunistic birth cohort testing, compared with no birth cohort testing, was most sensitive to changes in the following:

- discount rate applied to costs and benefits
- transition probability for patients progressing from CC-to-DCC
- utility derived in the SVR health state.

The ICER of opportunistic birth cohort testing did not exceed the WTP of €20,000 per QALY gained in the univariate sensitivity analysis. The summary results of the univariate sensitivity analysis comparing opportunistic birth cohort testing with no birth cohort testing are presented in Figure 6.10

Figure 6.10. Tornado plot of univariate sensitivity analysis (ICER of opportunistic birth cohort testing versus no birth cohort testing)*



Key: CC – compensated cirrhosis; CI – confidence interval; DAA – direct-acting antiviral; DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; SVR – sustained virological response.
Note: In the base case analysis, the prevalence of HCV infection in each subgroup
* In the interests of legibility, only the 20 parameters that, when set at their upper and lower bounds, resulted in the largest change in the ICER, are presented.

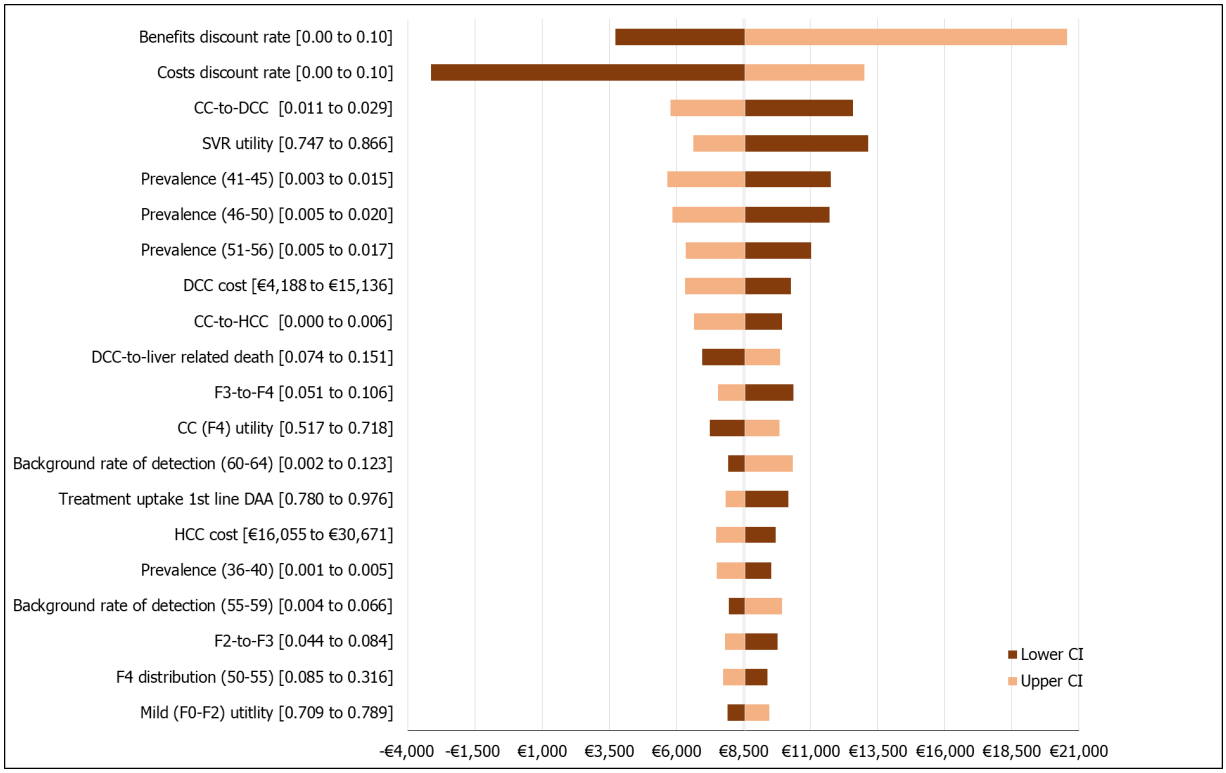
Systematic testing versus opportunistic testing

The cost-effectiveness of systematic birth cohort testing, compared with opportunistic birth cohort testing, was most sensitive to changes in the following:

- discount rate applied to costs and benefits
- transition probability for patients progressing from CC-to-DCC
- utility derived in the SVR health state.

The ICER (comparing systematic birth cohort testing with opportunistic birth cohort testing) increased to €20,567 when applying a discount rate of 10% to costs, but otherwise did not exceed the WTP of €20,000 per QALY gained in the univariate sensitivity analysis. The summary results of the univariate sensitivity analysis comparing systematic birth cohort testing with opportunistic birth cohort testing are presented in Figure 6.11.

Figure 6.11. Tornado plot of univariate sensitivity analysis (ICER of systematic birth cohort testing versus opportunistic birth cohort testing)*



Key: CC – compensated cirrhosis; CI – confidence interval; DAA – direct-acting antiviral; DCC – decompensated cirrhosis; HCC – hepatocellular carcinoma; NA – not available; SVR – sustained virological response.

* In the interests of legibility, only the 20 parameters that, when set at their upper and lower bounds, resulted in the largest change in the ICER, are presented.

Sensitivity analysis to investigate potential influence of correlation between modelled subgroups

In the base case analysis, prevalence of chronic HCV infection and the rate of background detection are modelled independently according to subgroup. In the real-world, the prevalence or rate of background detection within one subgroup may be correlated with that of another subgroup. The potential influence of this correlation on the cost-effectiveness of the technology was assessed in a sensitivity analysis.

As described in section 6.3.1, in the base case analysis these parameters were estimated using a generalised additive model that simulated data from a variety of sources. The simulation outputs from the generalised additive model were used as the basis for estimating plausible correlations between the subgroups. That is, the model outputs of an individual simulation (in terms of prevalence or detection across age bands) were selected at random and modelled directly in the CUA, with the cost-effective estimates recorded for each iteration of the simulation (n=10,000). All other parameters in the CUA were fixed at their mean value during this process.

The results of this analysis are presented in Table 6.19. The estimated ICERs were not significantly different from those estimated in the base case analysis (that is, the mean estimates remained within the confidence bounds of those originally estimated). In the base case, the ICERs comparing opportunistic with no birth cohort testing and systematic with opportunistic birth cohort testing were estimated at €8,357 (95% CI: €843 to €19,699) and 9,237 (95% CI: €1,384 to €21,632) per QALY gained, respectively. Since only the correlated parameters (that is, prevalence and background detection) were varied in this analysis, the imprecision (that is, the 95% CIs) in the ICERs represents the uncertainty of these estimates in the individual simulations.

Table 6.19. Cost-effectiveness incremental findings

Intervention	Comparator	Costs (95% CI)	QALYs (95% CI)	ICER (95% CI)
Correlated prevalence of chronic HCV				
Opportunistic testing	No testing	€1,553 (€1,393 to €1,921)	0.20 (0.14 to 0.23)	€7,872 (€5,954 to €13,843)
Systematic testing	Opportunistic testing	€831 (€781 to €953)	0.10 (0.07 to 0.11)	€8,606 (€7,115 to €13,410)
Correlated background rate of detection				
Opportunistic testing	No testing	€1,553 (€1,393 to €1,921)	0.20 (0.14 to 0.23)	€7,872 (€5,954 to €13,843)
Systematic testing	Opportunistic testing	€831 (€781 to €953)	0.10 (0.07 to 0.11)	€8,606 (€7,115 to €13,408)

Key: HCV – hepatitis C virus; ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; QALY – quality-adjusted life year.

6.5.3 Cost-utility analysis – subgroup analysis

A subgroup analysis was performed to estimate the cost-effectiveness of birth cohort testing for HCV according to each modelled age band. The structural assumption of a staggered implementation as per the base case was retained in the subgroup analysis, the results of which are summarised in Table 6.20.

When comparing opportunistic birth cohort testing with no birth cohort testing, the ICERs ranged from €5,803 (95% CI: -€1,933 to €18,659) in the 46-50 years age band to €37,262 (95% CI: €10,348 to €104,000) in the 36-40 years age band.

When comparing systematic birth cohort testing with opportunistic birth cohort testing, the ICERs ranged from €6,104 (95% CI: -€2,157 to €20,294) in the 46-50 years age band to €40,671 (95% CI: €11,748 to €111,029) in the 36-40 years age band.

The ICER estimated for the 36-40 year olds subgroup exceeds the WTP threshold of €45,000 when comparing opportunistic birth cohort testing with no birth cohort testing. These results indicate that systematic birth cohort testing of those aged 36-40 is not cost-effective, but this finding is subject to a significant range of uncertainty, which is unsurprising given that the estimated prevalence (0.27% (95% CI: 0.1-0.53%)) is lowest in this age group. When excluding the 36-40 age band from the deterministic incremental analysis, the ICER of opportunistic birth cohort testing reduced to €6,097 per QALY gained compared with no birth cohort testing.

Table 6.20. ICERs estimated in subgroup analysis

Age group	Opportunistic vs no testing	Systematic vs opportunistic testing
36-40 years (95% CI)	€37,262 (€10,348 to €104,000)	€40,671 (€11,748 to €111,029)
41-45 years (95% CI)	€11,092 (€170 to €34,904)	€11,679 (-€11 to €37,134)
46-50 years (95% CI)	€5,803 (-€1,933 to €18,659)	€6,104 (-€2,157 to €20,294)
51-56 years (95% CI)	€7,147 (-€1,788 to €22,473)	€7,150 (-€2,342 to €23,710)

Key: ICER – incremental cost-effectiveness ratio.

6.5.4 Cost-utility analysis – threshold analysis

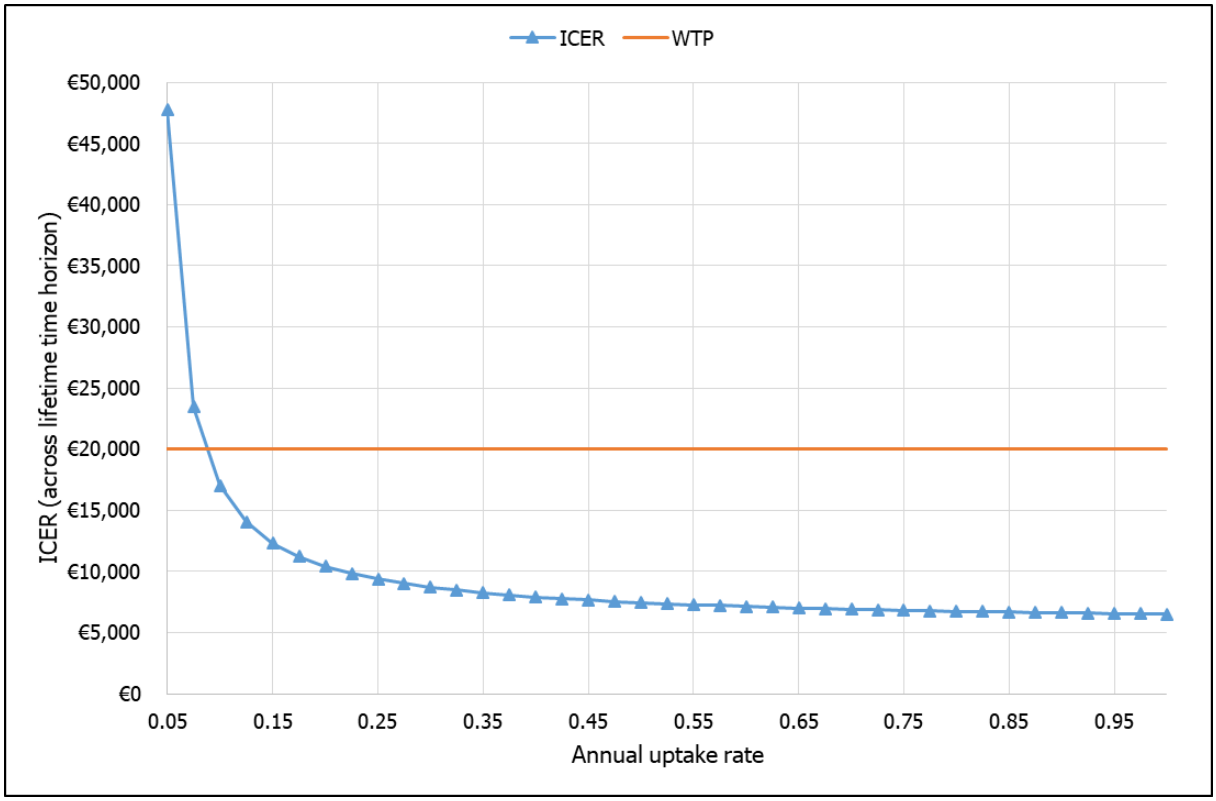
A deterministic threshold analysis was conducted to identify conditions under which the cost-effectiveness of an opportunistic birth cohort testing for HCV may change, when compared with no birth cohort testing.

Univariate analysis

The influence of the annual uptake rate of HCV testing and the prevalence of undiagnosed chronic HCV infection were investigated in the univariate analysis. All other parameters were held at their mean value during the analysis.

The ICER exceeded the WTP threshold of €20,000 per QALY gained (that is, not cost-effective) when the uptake of HCV testing was set at approximately 8% or less, but remained cost-effective at uptake rates above this value (see Figure 6.12). Accordingly, birth cohort testing is cost-effective at low uptake rates (for example, 10%), likely due to the lack of additional capital investment required.

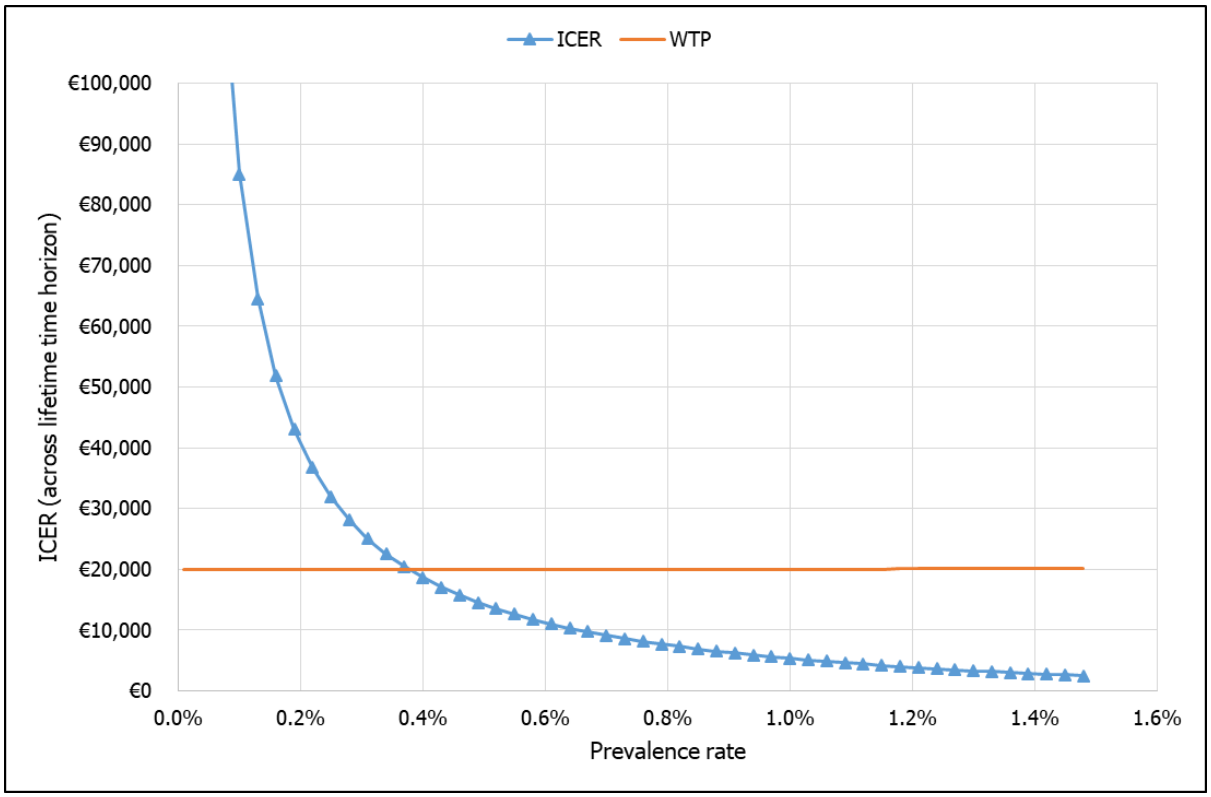
Figure 6.12. Threshold analysis of annual uptake rate on ICER, comparing opportunistic birth cohort testing with no birth cohort testing



Key: ICER – incremental cost-effectiveness ratio; WTP – willingness to pay threshold of €20,000 per QALY gained.

The ICER was higher than the WTP threshold of €20,000 per QALY gained (that is, not cost-effective) when a uniform prevalence rate of undiagnosed chronic HCV infection in the birth cohort was set at approx. 0.4% or less, but was cost-effective at prevalence rates above this value (see Figure 6.13).

Figure 6.13. Threshold analysis of prevalence rate on ICER, comparing opportunistic birth cohort testing with no birth cohort testing



Key: ICER – incremental cost-effectiveness ratio; WTP – willingness to pay threshold of €20,000 per QALY gained.

Bivariate analysis

The influence of the annual uptake rate of HCV testing and the prevalence of undiagnosed chronic HCV infection were also investigated in a bivariate analysis (or two-way sensitivity analysis), whereby both parameters were varied simultaneously. All other parameters were held at their mean value during the analysis.

The ICER for opportunistic birth cohort testing exceeded the WTP threshold of €20,000 per QALY gained (that is, not cost-effective) when both the annual uptake rate for HCV testing and the overall prevalence rate of undiagnosed chronic HCV infection in the birth cohort were low. For example, an uptake rate of 16% and an overall prevalence of 0.35% yielded an ICER of €28,192 per QALY gained. In contrast, opportunistic birth cohort testing dominated (that is, it was cost-saving and more effective) no birth cohort testing when uptake and prevalence were high. For example, an uptake rate of 60% and a prevalence of 3.78% led to a cost saving of €1,751.

The results of the bivariate threshold analysis are presented in Figure 6.14.

Figure 6.14. Heat map of bivariate threshold analysis of annual uptake rate and prevalence rate of undiagnosed chronic HCV infection, comparing opportunistic birth cohort testing with no birth cohort testing

Uptake \ Prevalence	0.35%	0.42%	0.51%	0.61%	0.73%	0.88%	1.06%	1.27%	1.52%	1.82%	2.19%	2.63%	3.15%	3.78%
16%	€ 28,192	€ 23,069	€ 18,800	€ 15,243	€ 12,278	€ 9,808	€ 7,750	€ 6,034	€ 4,605	€ 3,413	€ 2,421	€ 1,594	€ 904	€ 330
18%	€ 26,830	€ 21,911	€ 17,811	€ 14,395	€ 11,548	€ 9,176	€ 7,199	€ 5,551	€ 4,179	€ 3,035	€ 2,081	€ 1,287	€ 625	€ 73
20%	€ 25,668	€ 20,921	€ 16,965	€ 13,668	€ 10,921	€ 8,631	€ 6,724	€ 5,134	€ 3,809	€ 2,705	€ 1,785	€ 1,019	€ 380	-€ 153
22%	€ 24,673	€ 20,071	€ 16,237	€ 13,041	€ 10,378	€ 8,159	€ 6,310	€ 4,770	€ 3,486	€ 2,416	€ 1,524	€ 781	€ 162	-€ 354
24%	€ 23,817	€ 19,339	€ 15,608	€ 12,498	€ 9,907	€ 7,748	€ 5,949	€ 4,449	€ 3,200	€ 2,159	€ 1,291	€ 568	-€ 35	-€ 537
27%	€ 23,079	€ 18,707	€ 15,063	€ 12,026	€ 9,496	€ 7,387	€ 5,630	€ 4,166	€ 2,945	€ 1,929	€ 1,081	€ 375	-€ 213	-€ 704
30%	€ 22,444	€ 18,159	€ 14,589	€ 11,614	€ 9,135	€ 7,069	€ 5,347	€ 3,912	€ 2,717	€ 1,721	€ 890	€ 199	-€ 378	-€ 858
33%	€ 21,896	€ 17,686	€ 14,177	€ 11,253	€ 8,817	€ 6,787	€ 5,095	€ 3,685	€ 2,510	€ 1,531	€ 715	€ 35	-€ 532	-€ 1,004
37%	€ 21,426	€ 17,277	€ 13,819	€ 10,937	€ 8,536	€ 6,535	€ 4,868	€ 3,478	€ 2,320	€ 1,355	€ 551	-€ 119	-€ 677	-€ 1,142
41%	€ 21,024	€ 16,924	€ 13,507	€ 10,660	€ 8,287	€ 6,310	€ 4,662	€ 3,289	€ 2,145	€ 1,192	€ 397	-€ 265	-€ 816	-€ 1,276
45%	€ 20,714	€ 16,649	€ 13,261	€ 10,438	€ 8,086	€ 6,126	€ 4,493	€ 3,131	€ 1,997	€ 1,052	€ 264	-€ 392	-€ 939	-€ 1,395
49%	€ 20,449	€ 16,411	€ 13,046	€ 10,242	€ 7,905	€ 5,958	€ 4,336	€ 2,984	€ 1,857	€ 918	€ 135	-€ 517	-€ 1,060	-€ 1,513
54%	€ 20,227	€ 16,208	€ 12,859	€ 10,068	€ 7,743	€ 5,805	€ 4,190	€ 2,844	€ 1,723	€ 788	€ 9	-€ 640	-€ 1,180	-€ 1,631
60%	€ 20,045	€ 16,037	€ 12,698	€ 9,915	€ 7,596	€ 5,664	€ 4,053	€ 2,712	€ 1,593	€ 661	-€ 115	-€ 762	-€ 1,301	-€ 1,751

6.5.5 Cost-utility analysis – scenario analysis

Staggered implementation, beginning with youngest cohort

A scenario analysis was performed to estimate the cost-effectiveness of birth cohort testing where HCV testing is first offered to the youngest age group (36-40 year olds) and then sequentially offered to the older age groups. Accordingly, this scenario represents a reversal of the staggered implementation incorporated in the base case. The sequence of the staggered implementation in terms of screening and treatment over the initial five-year period is presented in Table 6.21.

Table 6.21. Scenario analysis – sequence of staggered implementation

Model cycle*	Screened	Treated	Re-treated
0	36-40 (group 1)	NA	NA
1	36-40 (group 2)	36-40 (group 1)	NA
2	41-45 (group 1)	36-40 (group 2)	36-40 (group 1)
3	41-45 (group 2)	41-45 (group 1)	36-40 (group 2)
4	46-50 (group 1)	41-45 (group 2)	41-45 (group 1)
5	46-50 (group 2)	46-50 (group 1)	41-45 (group 2)
6	51-56 (group 1)	46-50 (group 2)	46-50 (group 1)
7	51-56 (group 2)	51-56 (group 1)	46-50 (group 2)
8	NA	51-56 (group 2)	51-56 (group 1)
9	NA	NA	51-56 (group 2)

Key: NA – not applicable.

* Each cycle represents a discrete six-month period.

Compared with no birth cohort testing, the ICER for opportunistic birth cohort testing was estimated at €9,592 (95% CI: €1,313 to €22,697) per QALY gained. Compared with opportunistic birth cohort testing, the ICER for systematic birth cohort testing was estimated at €10,108 (95% CI: €1,858 to €23,502) per QALY gained. The ICERs were marginally higher than in the base case analysis, but would still be considered cost-effective at a WTP of €20,000.

Alternative HCV testing uptake rate

In the base case, the uptake rate of HCV testing was estimated at 41% (95% CI: 31% to 51%) based on the uptake rate observed in the National BowelScreen Programme.[303] A number of observational studies provide informative data for estimating an alternative uptake rate.[307-311] This scenario assesses the impact of modelling an alternative uptake rate based on these Irish studies, described below. As the uptake rate is significantly higher than that in the base case, this would be considered an upper limit of the plausible range for uptake of HCV testing implemented via a systematic testing programme.

Universal antenatal screening was piloted in the Rotunda Hospital between June 2007

and 2008, where women were routinely offered HCV testing.[307] Of the 9,121 women that were eligible for the study, 98.4% (n=8,976) agreed to anti-HCV testing. An opt-out testing strategy for blood-borne viruses was piloted across four primary care centres in Dublin between September 2014 and February 2015.[309] All patients aged 18 years or older who presented for routine blood tests were offered an additional blood test to screen for three blood-borne viruses: HBV, HCV and HIV. Patients (n=1,188) were given an information leaflet before testing and given the choice to opt-out of having the additional blood test. Overall, 89.5% (n=1,063) of patients accepted testing. Of these, 61.8% (n=657) were female and 38.2% (n=406) were male with a median age of 54 years. There was no significant difference in age or sex of those that accepted or declined testing.

A universal opt-out HIV, HBV and HCV testing programme for emergency department (ED) patients undergoing phlebotomy was piloted in St. James's Hospital between March 2014 and January 2015.[308] Patients were advised that an additional serum sample would be taken for bloodborne virus testing. A total of 8,839 unique patient test results were eligible, with an uptake rate of 50.1% (n=4,508) obtained. The study was repeated for the period from July 2015 to June 2018.[310] Of those that attended the ED and underwent phlebotomy (n=88,854), 61.7% (n=54,817) accepted screening. Opt-out testing for blood-borne viruses was also piloted in University Hospital Galway between January and November 2016.[311] Patients attended the acute medical unit and also received a blood draw were eligible for the study. Overall, 40.4% (n=1,936) consented to an additional blood sample for bloodborne virus testing.

The results of these studies were combined in a random-effects meta-analysis (see Table 6.21), with a pooled estimate of 78% (95% CI: 49% to 96%). Although conducted in the Irish context, the generalisability of these studies is limited by the nature in which patients are offered testing. In all of the studies, patients that were already undergoing phlebotomy were asked if they would consent to an additional blood test. Therefore, the test was opportunistic in nature and did not require an additional healthcare attendance. Additionally, the studies were conducted across a variety of settings, with clinical and statistical heterogeneity restricting their applicability.

Table 6.22. Summary of testing uptake rates from Irish observational studies

Study	Setting	Participants (n)	Uptake rate (%)
Allen (2019)	AMU	4,793	40
Grant (2019)	ED	88,854	62
Lambert (2013)	Antenatal	9,121	98
O'Connell (2016)	ED	19,980	50
O'Kelly (2016)	Primary care	1,188	89
RE meta-analysis (95% CI)		**123,936**	**0.78 (0.45-0.94)**

Key: AMU – acute Medical Unit; CI – confidence interval; ED – emergency department; RE – random effects.

Note: the uptake rate represents the likelihood of a patient accepting the invitation of HCV testing during a GP consultation.

Compared with no birth cohort testing, the ICER for opportunistic birth cohort testing was estimated at €7,162 (95% CI: -€227 to €17,867) per QALY gained. Compared with opportunistic birth cohort testing, the ICER for systematic birth cohort testing was estimated at €8,040 (95% CI: €61 to €20,639) per QALY gained.

These estimates are marginally lower than the ICERs estimated in the base case analysis, demonstrating that the higher uptake rate of HCV testing the more cost-effective the intervention.

Alternative disease progression rates

In the base case, fibrosis progression (that is, transition probabilities governing progression from F0 through to F4) of undiagnosed cases of chronic HCV infection in the birth cohort was based on a meta-analysis of studies from the community setting.[12, 300, 301, 313, 314]

In this scenario analysis, alternative transition probabilities are modelled from a 2018 meta-analysis of fibrosis progression rates in treatment-naïve patients with chronic HCV infection. These updated transition probabilities (see Table 6.22) are marginally lower than those used in the base case, thus reflecting slower disease progression in the 1965-1985 birth cohort.

Table 6.23. Six-month transition probabilities used in scenario analysis

	Mean	95% CI	Distribution	Source
Without treatment				
F0-to-F1	0.06	0.05-0.06	Beta	(315)
F1-to-F2	0.04	0.04-0.05	Beta	(315)
F2-to-F3	0.06	0.06-0.07	Beta	(315)
F3-to-F4 (CC)	0.06	0.05-0.07	Beta	(315)

Key: CI – confidence interval; F – METAVIR fibrosis stage.

Compared with no birth cohort testing, the ICER for opportunistic birth cohort testing was estimated at €9,055 (95% CI: €1,575 to €21,055) per QALY gained. Compared with opportunistic birth cohort testing, the ICER for systematic birth cohort testing was estimated at €9,949 (95% CI: €1,835 to €22,490) per QALY gained.

These estimates represent a marginal increase on the ICERs estimated in the base case analysis, but would still be considered cost-effective at a WTP of €20,000.

Alternative fibrosis distribution

As described in section 6.3.1, cases of undiagnosed chronic HCV infection in the birth cohort are distributed across fibrosis stages METAVIR F0 to F4 at the outset of the simulation. In the base case, the initial distribution of these cases was based on data from the NHCTP of patients from the 1965 to 1985 birth cohort registered with the programme between 2018 and September 2019.(93) It is unclear how generalisable this fibrosis staging is to the undiagnosed birth cohort.

To investigate the impact of the initial fibrosis distribution on the cost-effectiveness results, alternative fibrosis distributions were generated by arbitrarily weighting the proportion of the undiagnosed cohort towards: (1) the less advanced fibrosis stages; and (2) the more advanced fibrosis stages. These proportions were not varied during Monte Carlo simulation. The alternative fibrosis distributions modelled in this scenario are presented in Table 6.24.

Table 6.24. Fibrosis distribution by age band

	Lower progression (%)	Advanced progression (%)
35-39 years		
F0	49	0
F1	26	4
F2	15	49
F3	11	26
F4	0	21
40-44 years		
F0	47	0
F1	25	4
F2	11	47
F3	17	25
F4	0	24
45-49 years		
F0	43	0
F1	22	4
F2	14	43
F3	21	22
F4	0	31
50-55 years		
F0	28	0
F1	15	26
F2	12	28
F3	45	15
F4	0	31

Key: F – METAVIR fibrosis stage.

Compared with no birth cohort testing, the ICER for opportunistic birth cohort testing was estimated at €13,254 (95% CI: €4,312 to €28,672) per QALY gained when modelling the less advanced fibrosis distributions. Compared with opportunistic birth cohort testing, the ICER for systematic birth cohort testing was estimated at €14,394 (95% CI: €4,698 to €32,802) per QALY gained when modelling the less advanced fibrosis distributions.

Compared with no birth cohort testing, the ICER for opportunistic birth cohort testing was estimated at €4,017 (95% CI: -€2,313 to €12,301) per QALY gained when modelling the more advanced fibrosis distributions. Compared with opportunistic birth cohort testing, the ICER for systematic birth cohort testing was estimated at €4,689 (95% CI: -€1,881 to €13,366) per QALY gained when modelling the more advanced fibrosis distributions.

In both analyses, the ICERs remained below the WTP of €20,000. However, this

analysis demonstrated that there is more to gain, in terms of cost-effectiveness, the more advanced the disease progression of the undiagnosed birth cohort since these cases will soon become symptomatic and incur healthcare costs associated with the advanced liver disease states. Additionally, the 95% confidence intervals of the ICERs in the less advanced disease scenario cross the WTP threshold demonstrating decision uncertainty under this scenario.

Reduced costs of advanced liver disease health states

As illustrated by the results of the univariate sensitivity analysis, the costs of the advanced liver disease health states (that is, DCC, HCC and LT) have a significant influence on the cost-effectiveness of birth cohort testing. This is largely due to the substantial downstream savings incurred as a result of identifying cases of undiagnosed chronic HCV infection before they become symptomatic. To investigate the implication of a reduction in these health state costs, a scenario analysis was undertaken in which the costs of these health states were halved.

Compared with no birth cohort testing, the ICER for opportunistic birth cohort testing was estimated at €13,139 (95% CI: €6,109 to €25,476) per QALY gained. Compared with opportunistic birth cohort testing, the ICER for systematic birth cohort testing was estimated at €13,987 (95% CI: €6,518 to €26,874) per QALY gained.

As expected, the ICERs increased compared with those estimated in the base case analysis. Although these estimates remained below the WTP of €20,000, their 95% confidence intervals cross this threshold demonstrating decision uncertainty under this scenario.

6.5.6 Budget impact analysis – base case analysis

A budget impact analysis (BIA) addresses the affordability of the health technology, that is, the net annual financial cost of adopting the technology over the next five years. The incremental budget impact is presented relative to the current standard of no birth cohort testing for HCV. The annual budget impact is presented in Table 6.25.

Table 6.25. Annual incremental budget impact of birth cohort testing versus no birth cohort testing (in millions)

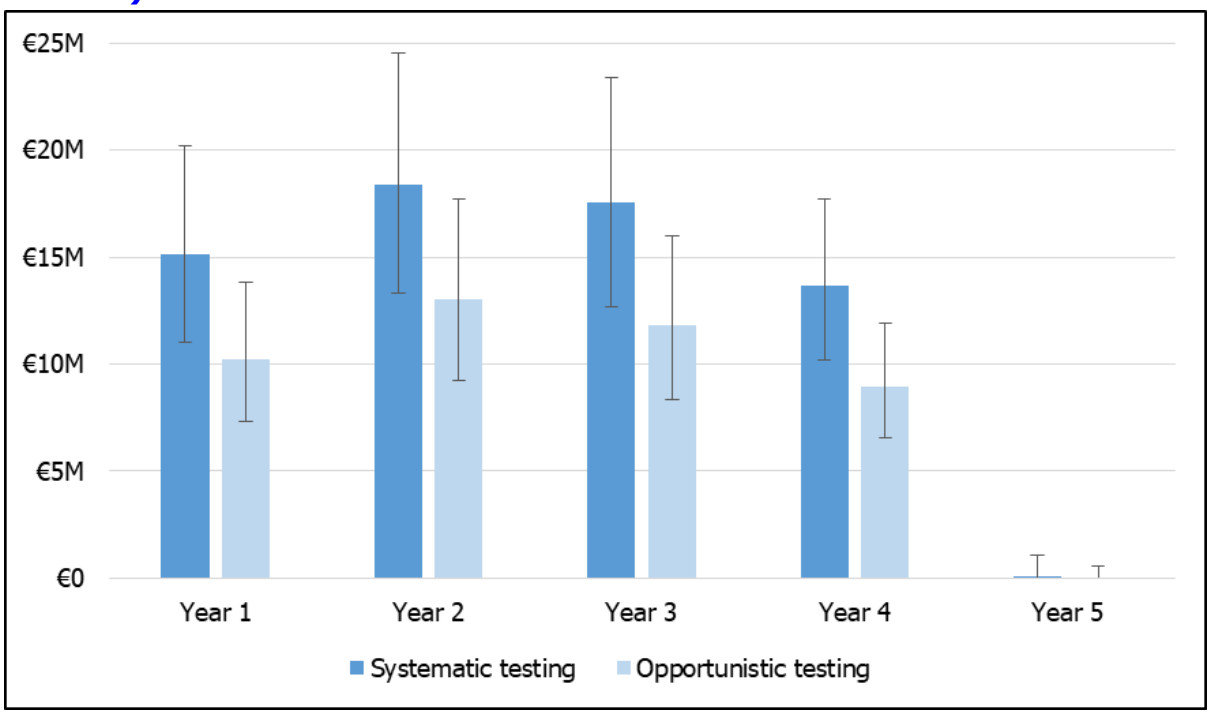
Year	Systematic testing (€)	Opportunistic testing (€)
Year 1 (95% CI)	€15.1 (€11.0 to €20.2)	€10.2 (€7.3 to €13.8)
Year 2 (95% CI)	€18.4 (€13.3 to €24.6)	€13.0 (€9.3 to €17.7)
Year 3 (95% CI)	€17.6 (€12.7 to €23.4)	€11.8 (€8.3 to €16.0)
Year 4 (95% CI)	€13.6 (€10.2 to €17.7)	€8.9 (€6.5 to €11.9)
Year 5 (95% CI)	€0.1 (-€1.0 to €1.1)	-€0.2 (-€0.9 to €0.5)
Total (95% CI)	**€64.8 (€49.2 to €82.3)**	**€43.8 (€32.6 to €56.6)**

Key: LCI – lower confidence interval; UCI – upper confidence interval.

The incremental budget impact of systematic and opportunistic birth cohort testing was estimated at €64.8 (95% CI: €49.2 to €82.3) million and €43.8 (95% CI: €32.6 to €56.6) million, respectively, over a five-year time horizon. As the modelled testing programmes are phased over a four-year period, the incremental cost is significant from years one to four of the time horizon. However, the incremental cost decreases substantially thereafter. The five-year budget impact is presented in Figure 6.15.

In the systematic testing programme, the majority of the total cost over the five-year time horizon was divided between health states and treatment costs (48% (95% CI: 34-65%)), implementation costs (42% (95% CI: 33-54%)) and testing costs (8% (95% CI: 6-11%)). The proportion of total cost over a five-year time horizon due to implementation and testing costs associated with an opportunistic testing programme were lower (37% (95% CI: 27-49%) and 7% (95% CI: 5-10%), respectively), with health states and treatment costs representing the majority of costs (54% (95% CI: 39-74%)).

Figure 6.15. Incremental budget impact versus no birth cohort testing (in € millions)



Note: Error bars represent the 95% confidence intervals estimated in the probabilistic sensitivity analysis.

It was estimated that systematic birth cohort testing would lead to an additional 0.62 (95% CI: 0.47 to 0.77) million primary care attendances, 0.62 (95% CI: 0.47 to 0.77) million anti-HCV tests, 8,930 (95% CI: 5,713 to 13,252) core antigen tests and 2,792 (95% CI: 1,708 to 4,188) patients receiving DAA therapy over the course of four years.

In comparison, opportunistic birth cohort testing would lead to an additional 0.41 (95% CI: 0.31 to 0.51) million anti-HCV tests, 5,942 (95% CI: 3,790 to 8,823) core antigen tests and 2,008 (95% CI: 1,196 to 3,065) patients receiving DAA therapy over the course of four years. The prevalence of undiagnosed chronic HCV infection was estimated at 11,779 (95% CI: 7,742 to 16,560).

A breakdown of the estimated number of additional tests and patients treated with DAA therapies from implementation of birth cohort testing are presented in Table 6.26.

Table 6.26. Additional tests from implementation of birth cohort testing for HCV over four-year time period

	Systematic testing			Opportunistic testing		
	Anti-HCV	**Core antigen**	**DAAs**	**Anti-HCV**	**Core antigen**	**DAAs**
Year 1 (95% CI)	153,950 (117,056 to 191,223)	2,724 (1,414 to 4,678)	546 (235 to 992)	103,931 (78,829 to 129,995)	1,815 (933 to 3,127)	381 (161 to 698)
Year 2 (95% CI)	145,993 (110,991 to 181,362)	2,853 (1,446 to 4,957)	1,017 (566 to 1,616)	102,391 (77,503 to 128,053)	1,981 (1,001 to 3,466)	748 (408 to 1,203)
Year 3 (95% CI)	160,286 (121,851 to 199,095)	2,202 (1,057 to 3,996)	830 (424 to 1,371)	103,971 (78,705 to 130,476)	1,410 (676 to 2,552)	599 (303 to 1,000)
Year 4 (95% CI)	157,376 (119,682 to 195,477)	1,151 (660 to 1,854)	399 (157 to 745)	102,092 (77,275 to 128,070)	736 (420 to 1,190)	279 (107 to 534)
Total **(95% CI)**	617,605 (469,544 to 767,172)	8,930 (5,713 to 13,252)	2,792 (1,708 to 4,188)	412,385 (312,980 to 514,738)	5,942 (3,790 to 8,823)	2,008 (1,196 to 3,065)

Key: DAA – direct antiviral therapy; HCV – hepatitis C virus; CI –confidence interval.

6.5.7 Budget impact analysis – univariate sensitivity analysis

Systematic birth cohort testing versus no birth cohort testing

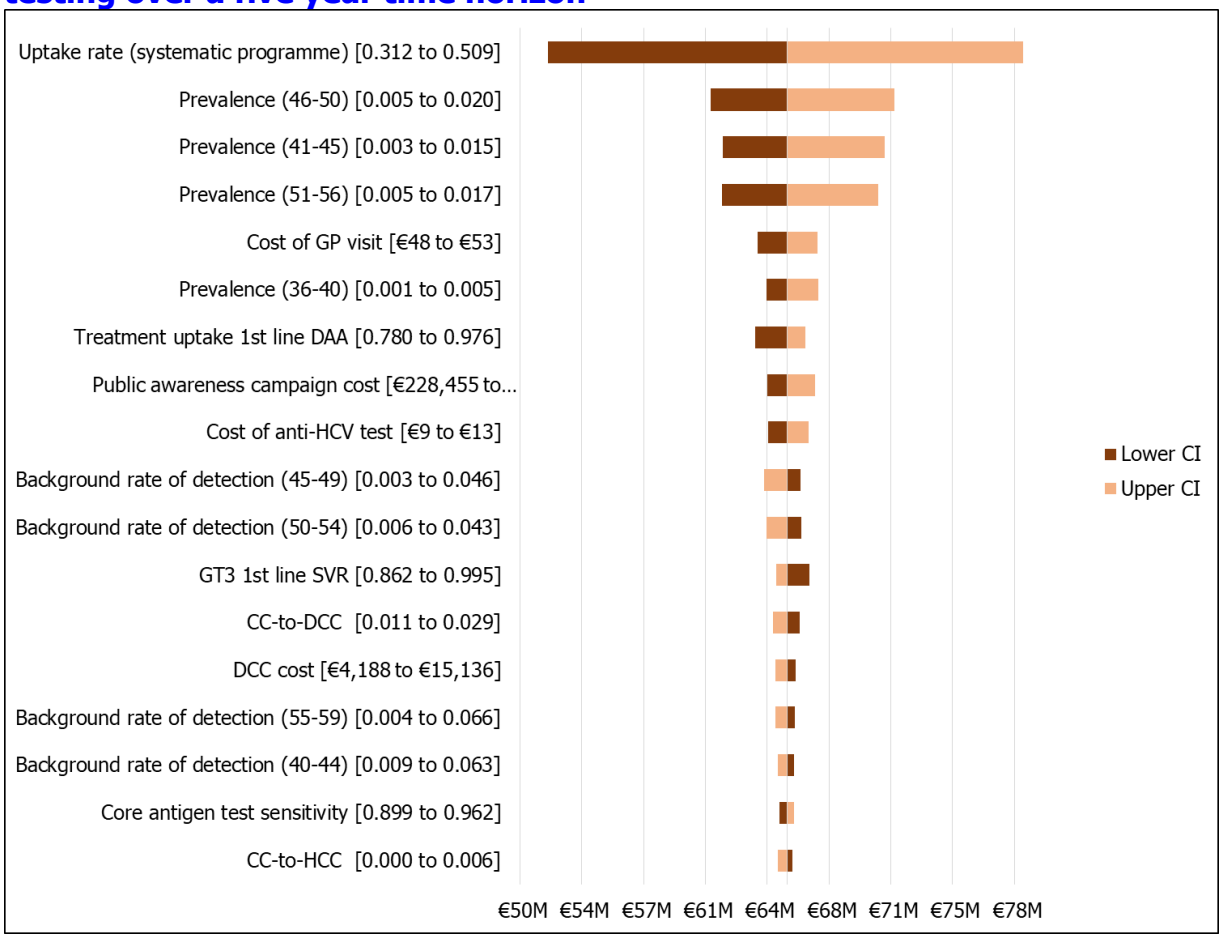
In the univariate sensitivity analysis, each parameter was individually set at the lower and upper limits of its 95% confidence interval while all other parameters were held at their mean values. Through this analysis the impact of parameter uncertainty on decision uncertainty can be explored. The summary results of the univariate sensitivity analysis comparing systematic birth cohort testing with no birth cohort testing are presented in Figure 6.16.

The incremental budget impact of systematic birth cohort testing compared with no birth cohort testing was most sensitive to changes in the following parameters:

- uptake rate of testing
- prevalence of undiagnosed chronic HCV infection in the 36-40, 41-45, 46-50 and 51-56 age bands
- cost of a GP visit.

The uptake rate of a systematic birth cohort testing programme had the greatest influence on the estimated budget impact. At its plausible limits, the budget impact ranged from €51.6 million to €78.5 million.

Figure 6.16. Univariate sensitivity analysis comparing the incremental budget impact of systematic birth cohort testing with no birth cohort testing over a five year time horizon*



Key: CC – compensated cirrhosis; DAA – direct-acting antiviral; DCC – decompensated cirrhosis; GP – general practitioner; GT – genotype; HCV – hepatitis C virus; SVR – sustained virological response.
* All parameters were varied in the analysis. For legibility, only 18 of the 20 most influential parameters are presented. Treatment costs have been removed from the tornado plot due to commercial sensitivity.

Opportunistic birth cohort testing versus no birth cohort testing

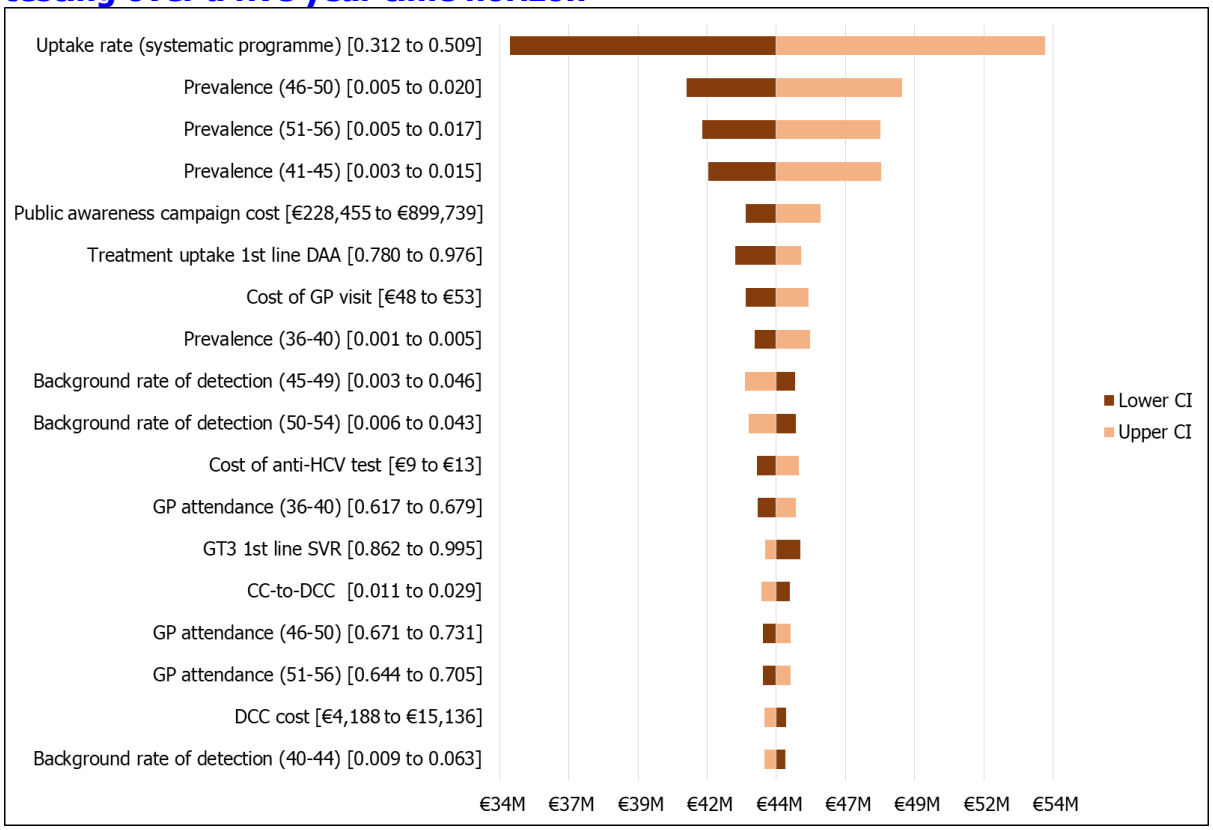
The summary results of the univariate sensitivity analysis comparing opportunistic birth cohort testing with no birth cohort testing are presented in Figure 6.17.

The incremental budget impact of opportunistic birth cohort testing compared with no birth cohort testing was most sensitive to changes in the following parameters:

- uptake rate of testing
- prevalence of undiagnosed chronic HCV infection in the 40-44, 45-49 and 50-55 age bands
- cost of the public awareness campaign.

The uptake rate of a systematic birth cohort testing programme had the greatest influence on the estimated budget impact. At its plausible limits, the budget impact ranged from €34.4 million to €53.7 million.

Figure 6.17. Univariate sensitivity analysis comparing the incremental budget impact of opportunistic birth cohort testing versus no birth cohort testing over a five year time horizon*



Key: CC – compensated cirrhosis; DAA – direct-acting antiviral; HCC – hepatocellular carcinoma; HCV – hepatitis C virus.

* All parameters were varied in the analysis. For legibility, only 18 of the 20 most influential parameters are presented. Treatment costs have been removed from the tornado plot due to commercial sensitivity.

6.5.8 Budget impact analysis – subgroup analysis

A subgroup analysis was performed to estimate the incremental budget impact of birth cohort testing for HCV, compared with no birth cohort testing, according to each modelled age band. The structural assumption of a staggered implementation as per the base case was retained in the subgroup analysis. The results of the subgroup analysis are summarised in Table 6.27.

The estimated budget impact was lowest in the 36-40 age band and highest in the 46-50 age band, representing approx. 20% and 28% of the total five-year budget impact for introduction of systematic birth cohort testing, respectively. These age bands represented approx. 19% and 29% of the total five-year budget impact for introduction of opportunistic birth cohort testing, respectively.

Table 6.27. Subgroup analysis – total budget impact over first five years

Age group (years)	Systematic vs no testing (€ - millions)	Opportunistic vs no testing (€ - millions)
36-40 (95% CI)	€12.8 (€9.6 to €16.3)	€8.2 (€6.1 to €10.6)
41-45 (95% CI)	€16.7 (€11.7 to €23.5)	€10.9 (€7.4 to €15.6)
46-50 (95% CI)	€18.1 (€12.5 to €25.5)	€12.9 (€8.7 to €18.5)
51-56 (95% CI)	€17.3 (€12.2 to €23.8)	€11.9 (€8.2 to €16.7)
Overall (95% CI)	**€64.8 (€49.2 to €82.3)**	**€43.8 (€32.6 to €56.6)**

6.5.9 Budget impact analysis – two-way sensitivity analysis

A two-way sensitivity analysis was conducted to identify the effect of varying the key input parameters on the five-year incremental budget impact associated with introduction of systematic birth cohort testing (compared with no birth cohort testing). A two-way sensitivity is conducted by varying pairs of parameters simultaneously, holding all other parameters at their mean values.

The influence of the following pairs of parameters were investigated:

- annual uptake rate of HCV testing and the cost of a primary care consultation to undergo HCV testing
- annual uptake rate of HCV testing and the prevalence of undiagnosed chronic HCV infection.

In the base case, the uptake rate of HCV testing and the cost of a GP visit to undergo testing were estimated at 41% and approximately €50, respectively. With increasing uptake and increasing cost of attendance, it is expected that the budget impact will increase. For example, assuming an uptake rate of 54% at a cost of €62 per GP attendance would lead to a net budget impact of €162 million over a five-year time horizon.

In the base case, the uptake rate of HCV testing and the prevalence of undiagnosed chronic HCV infection were estimated at 41% and 0.78%, respectively. With increasing uptake and prevalence of chronic HCV infection, it is expected that the budget impact will increase (as a result of increased testing and treatment capacity implications). For example, assuming an uptake rate of 60% and a prevalence of 1.27% would lead to a net budget impact of €108 million over a five-year time horizon.

These figures compare to the incremental budget impact of approx. €64.8 million over a five-year time horizon, estimated in the base case. The results of the two-way sensitivity analysis are summarised in Figure 6.18 and Figure 6.19.

Figure 6.18. Heat map of two-way sensitivity analysis of annual uptake rate and cost of GP attendance, comparing systematic birth cohort testing with no birth cohort testing

Uptake \ Cost of GP visit	€ 35	€ 39	€ 42	€ 47	€ 51	€ 56	€ 62	€ 68	€ 75	€ 83	€ 91	€ 100
18%	€ 49,055,060	€ 50,917,715	€ 52,966,635	€ 55,223,109	€ 57,697,779	€ 60,427,898	€ 63,424,112	€ 66,728,994	€ 70,358,510	€ 74,349,913	€ 78,740,457	€ 83,572,716
20%	€ 53,599,974	€ 55,669,591	€ 57,946,169	€ 60,453,362	€ 63,202,996	€ 66,236,464	€ 69,565,590	€ 73,237,682	€ 77,270,479	€ 81,705,372	€ 86,583,755	€ 91,952,933
22%	€ 58,517,996	€ 60,817,571	€ 63,347,103	€ 66,132,874	€ 69,188,024	€ 72,558,544	€ 76,257,574	€ 80,337,678	€ 84,818,564	€ 89,746,224	€ 95,166,651	€101,132,406
24%	€ 63,823,050	€ 66,378,134	€ 69,188,727	€ 72,284,028	€ 75,678,640	€ 79,423,663	€ 83,533,698	€ 88,067,147	€ 93,045,911	€ 98,521,091	€104,543,789	€111,172,407
27%	€ 69,525,413	€ 72,364,396	€ 75,487,278	€ 78,926,503	€ 82,698,295	€ 86,859,433	€ 91,426,140	€ 96,463,307	€101,995,269	€108,078,804	€114,770,693	€122,135,826
30%	€ 75,630,561	€ 78,784,988	€ 82,254,858	€ 86,076,220	€ 90,267,102	€ 94,890,590	€ 99,964,711	€105,561,565	€111,708,191	€118,467,677	€125,903,112	€134,086,596
33%	€ 82,137,890	€ 85,642,810	€ 89,498,222	€ 93,744,182	€ 98,400,719	€103,537,930	€109,175,844	€115,394,573	€122,224,160	€129,734,703	€137,996,300	€147,089,064
37%	€ 89,039,351	€ 92,933,708	€ 97,217,501	€101,935,236	€107,109,168	€112,817,183	€119,081,534	€125,991,237	€133,579,670	€141,924,721	€151,104,277	€161,207,352
41%	€ 96,318,109	€100,645,175	€105,404,947	€110,646,878	€116,395,693	€122,737,935	€129,698,329	€137,375,779	€145,807,376	€155,079,659	€165,279,170	€176,504,815
45%	€103,205,448	€107,965,223	€113,200,974	€118,967,101	€125,290,801	€132,267,270	€139,923,707	€148,368,906	€157,643,667	€167,843,183	€179,062,651	€191,410,865
49%	€110,352,412	€115,588,166	€121,347,496	€127,690,239	€134,646,312	€142,320,432	€150,742,517	€160,032,241	€170,234,483	€181,453,956	€193,795,377	€207,378,420
54%	€117,724,540	€123,483,873	€129,819,139	€136,796,160	€144,447,845	€152,889,382	€162,153,681	€172,372,383	€183,594,855	€195,936,283	€209,511,854	€224,453,209

Key: GP – general practitioner.

Figure 6.19. Heat map of two-way sensitivity of annual uptake rate and prevalence rate of undiagnosed chronic HCV infection, comparing systematic birth cohort testing with no birth cohort testing

Uptake \ Prevalence	0.35%	0.42%	0.51%	0.61%	0.73%	0.88%	1.06%	1.27%	1.52%	1.82%	2.19%	2.62%	3.15%
16%	€ 23,319,219	€ 24,175,180	€ 25,202,333	€ 26,434,916	€ 27,914,017	€ 29,688,937	€ 31,818,841	€ 34,374,726	€ 37,441,787	€ 41,122,261	€ 45,538,828	€ 45,538,828	€ 57,198,564
18%	€ 25,479,021	€ 26,432,343	€ 27,576,330	€ 28,949,114	€ 30,596,455	€ 32,573,265	€ 34,945,435	€ 37,792,040	€ 41,207,965	€ 45,307,075	€ 50,226,007	€ 50,226,007	€ 63,211,982
20%	€ 27,865,509	€ 28,924,353	€ 30,194,965	€ 31,719,699	€ 33,549,381	€ 35,744,998	€ 38,379,739	€ 41,541,428	€ 45,335,455	€ 49,888,286	€ 55,351,683	€ 55,351,683	€ 69,775,046
22%	€ 30,500,891	€ 31,673,726	€ 33,081,128	€ 34,770,011	€ 36,796,669	€ 39,228,660	€ 42,147,048	€ 45,649,113	€ 49,851,592	€ 54,894,565	€ 60,946,132	€ 60,946,132	€ 76,922,266
24%	€ 33,409,197	€ 34,704,710	€ 36,259,325	€ 38,124,863	€ 40,363,509	€ 43,049,884	€ 46,273,533	€ 50,141,912	€ 54,783,967	€ 60,354,432	€ 67,038,989	€ 67,038,989	€ 84,686,214
27%	€ 36,616,344	€ 38,043,305	€ 39,755,657	€ 41,810,481	€ 44,276,268	€ 47,235,213	€ 50,785,947	€ 55,046,828	€ 60,159,884	€ 66,295,550	€ 73,658,349	€ 73,658,349	€ 93,096,133
30%	€ 40,150,195	€ 41,717,280	€ 43,597,781	€ 45,854,383	€ 48,562,305	€ 51,811,812	€ 55,711,219	€ 60,390,508	€ 66,005,653	€ 72,743,827	€ 80,829,635	€ 80,829,635	€ 102,176,162
33%	€ 44,040,588	€ 45,756,144	€ 47,814,812	€ 50,285,213	€ 53,249,695	€ 56,807,072	€ 61,075,924	€ 66,198,547	€ 72,345,694	€ 79,722,269	€ 88,574,158	€ 88,574,158	€ 111,943,138
37%	€ 48,319,343	€ 50,191,087	€ 52,437,180	€ 55,132,492	€ 58,366,865	€ 62,248,114	€ 66,905,612	€ 72,494,608	€ 79,201,404	€ 87,249,558	€ 96,907,341	€ 96,907,341	€ 122,403,881
41%	€ 53,020,237	€ 55,054,868	€ 57,496,425	€ 60,426,293	€ 63,942,135	€ 68,161,144	€ 73,223,956	€ 79,299,329	€ 86,589,776	€ 95,338,311	€ 105,836,552	€ 105,836,552	€ 133,551,901
45%	€ 57,666,091	€ 59,852,601	€ 62,476,412	€ 65,624,985	€ 69,403,273	€ 73,937,218	€ 79,377,951	€ 85,906,831	€ 93,741,486	€ 103,143,071	€ 114,424,971	€ 114,424,971	€ 144,209,178
49%	€ 62,714,246	€ 65,055,365	€ 67,864,707	€ 71,235,918	€ 75,281,370	€ 80,135,913	€ 85,961,364	€ 92,951,905	€ 101,340,553	€ 111,406,929	€ 123,486,579	€ 123,486,579	€ 155,376,844
54%	€ 68,193,513	€ 70,689,961	€ 73,685,699	€ 77,280,585	€ 81,594,447	€ 86,771,081	€ 92,983,042	€ 100,437,395	€ 109,382,616	€ 120,116,881	€ 132,997,997	€ 132,997,997	€ 167,004,133
60%	€ 74,133,738	€ 76,783,655	€ 79,963,556	€ 83,779,436	€ 88,358,492	€ 93,853,360	€ 100,447,200	€ 108,359,807	€ 117,854,935	€ 129,249,088	€ 142,922,068	€ 142,922,068	€ 179,018,724

6.6 Discussion

A de novo economic model was developed to estimate the cost-effectiveness and budget impact of introducing birth cohort testing for HCV in Ireland. The birth cohort comprises all people living in Ireland that were born between 1965 and 1985. The aim of the intervention is to identify patients with chronic HCV infection that are currently unaware of their infection. An incremental analysis compared the costs and health benefits of two programmes relative to no birth cohort testing:

- a systematic birth cohort testing programme
- an opportunistic birth cohort testing programme.

In the base case, staggered implementation of birth cohort testing is assumed over a four-year period. The staggered implementation, sequenced by age band starting with those aged 50-55, is adopted to control the volume of activity and the implications on healthcare capacity across the clinical pathway. The analysis assumes implementation of reflex testing whereby patient samples that test positive on the first-step anti-HCV antibody test undergo the second-step core antigen test. Implementation of reflex testing mitigates against potential drop-off due to repeated healthcare attendance.

The economic model comprised a closed-cohort decision tree and Markov model hybrid which tracked the 1965-1985 birth cohort from the outset of the simulation until death. The decision tree modelled the short term costs and consequences of offering one-off testing to the birth cohort, while the Markov model simulated the natural progression of disease according to whether or not HCV testing was accepted. The parameters used in the economic model were derived from a wide variety of sources based on national and international data. Benefits were measured in terms of quality-adjusted life years (QALYs).

6.6.1 Summary of main findings

Cost-utility analysis

In the cost-utility analysis (CUA), both systematic and opportunistic birth cohort testing programmes were estimated to be more costly and more effective than no birth cohort testing. Compared with no birth cohort testing, an ICER of €8,357 (95% CI: €843 to €19,699) per QALY gained was estimated for opportunistic birth cohort testing. Compared with opportunistic testing, an ICER of €9,237 (95% CI: €1,384 to €21,632) per QALY gained was estimated for systematic birth cohort testing. In a fully incremental analysis, systematic birth cohort testing would be considered the cost-effective option of the three alternatives evaluated in this HTA.

Probabilistic sensitivity analysis (PSA), univariate sensitivity analysis, scenario analyses

and threshold analyses were undertaken to investigate the findings of the CUA. In the univariate sensitivity analysis, the ICER was most sensitive to changes in the discount rate, the disease progression rates and health-state utility derived by patients that achieve a sustained virological response following direct-acting antiviral (DAA) therapy. However, the ICER remained below the willingness to pay (WTP) threshold of €20,000 when parameters were set at extreme values, demonstrating the robustness of the finding of cost-effectiveness.

In the subgroup analysis, it was found that the ICER comparing opportunistic birth cohort testing with no birth cohort testing in the 36-40 year olds age band exceeded the €20,000 WTP threshold (with the ICER estimated at €37,262 (95% CI: €10,348 to €104,000)). This finding is unsurprising given that the estimated prevalence of chronic HCV infection is lowest (estimated at 0.27% (95% CI: 0.1-0.53%)) in this age band. When excluding the 36-40 age band from the deterministic incremental analysis, the ICER of opportunistic birth cohort testing reduced to €6,097 per QALY gained compared with no birth cohort testing.

The scenario analysis demonstrated that the ICER was sensitive to changes in the healthcare costs associated with the advanced liver disease health states and the fibrosis progression of the undiagnosed birth cohort. However, the finding of cost-effectiveness was robust (that is, the point estimate of the ICER remained under the WTP threshold).

Budget impact analysis

In the budget impact analysis (BIA), the incremental cost of a systematic birth cohort testing programme was estimated at €64.8 (95% CI: €49.2 to €82.3) million over a five-year time horizon, compared with no birth cohort testing. The majority (48% (95% CI: 34-65%)) of the total costs were healthcare and treatment costs, while implementation costs (42% (95% CI: 33-54%)) were also considerable. The incremental cost of opportunistic birth cohort testing was estimated at 43.8 (95% CI: €32.6 to €56.6) million over a five-year time horizon, compared with no birth cohort testing. The majority (54% (95% CI: 39-74%)) of the total costs were healthcare and treatment costs.

As the modelled testing programmes are phased over a four-year period, the incremental budget impact is significant from years one to four of the time horizon. However, the annual incremental cost decreases substantially thereafter as the number of people offered one-off testing decreases. Over a four-year period, it was estimated that systematic birth cohort testing would lead to an additional 0.62 (95% CI: 0.47 to 0.77) million primary care attendances, 0.62 (95% CI: 0.47 to 0.77) million anti-HCV antibody tests and 8,930 (95% CI: 5,713 to 13,252) core antigen tests, and an additional 2,792 (95% CI: 1,708 to 4,188) patients receiving DAA therapy. In

comparison, opportunistic birth cohort testing would lead to an additional 0.41 (95% CI: 0.31 to 0.51) million anti-HCV tests and 5,942 (95% CI: 3,790 to 8,823) core antigen tests, 2,008 (95% CI: 1,196 to 3,065) patients receiving DAA therapy. In the stochastic analysis, the prevalence of undiagnosed chronic HCV infection was estimated at 11,779 (95% CI: 7,742 to 16,560).

A range of sensitivity analyses were undertaken to investigate the findings of the BIA. In the univariate sensitivity analysis, the budget impact was most sensitive to changes in the uptake rate of testing, prevalence of undiagnosed chronic HCV infection, and the cost of GP attendance. The two-way sensitivity analysis demonstrated that the budget impact of birth cohort testing will increase significantly with a higher uptake and higher cost of primary care visit to undergo HCV testing. In the base case, the mean uptake rate and cost of a primary care visit were estimated at 41% and €50, respectively. Assuming an uptake rate of 54% and a cost per visit of €62, the incremental budget impact of a systematic birth cohort testing programme would increase to €162 million over a five-year time horizon.

As per the findings of the CUA's subgroup analysis, the budget impact of offering systematic birth cohort testing only to those born between 1965 and 1980 (that is, excluding youngest age band) was investigated. In this analysis, the incremental budget impact of systematic birth cohort testing reduced to €52 million compared with no birth cohort testing.

6.6.2 Strengths and limitations

This economic analysis is a synthesis of the best nationally and internationally available evidence on the detection and treatment of hepatitis C. It is the first comprehensive analysis of offering one-off birth cohort testing in Ireland, and as far as we are aware it is the first full economic evaluation to assess implementation of a systematic national testing programme. However, important limitations exist in relation to the currently available evidence and the findings of the economic analysis must be interpreted in light of these limitations.

Firstly, there are a number of key parameters that are influential on the results of the economic analysis which are subject to uncertainty. Without question, the cost-effectiveness of birth cohort testing will be heavily influenced by the prevalence of undiagnosed chronic HCV infection in the 1965-1985 Irish birth cohort. The modelled prevalence, estimated at 11,779 (95% CI: 7,742 to 16,560), is based on an Irish cross-sectional study published in 2017.[157] The study was based on a random sample (of residual sera collected between April 2014 and February 2016) representative of the adult general population. Although effort was made to ensure that the study sample was representative of the general population, the prevalence estimates of the

undiagnosed HCV infection are imprecise and subject to a large degree of uncertainty due to the study sample size (n=3,795) and the low number of observed chronic HCV infections (n=33). The influence of this imprecision was investigated in several ways and these analyses demonstrated the robustness of the finding that implementation of birth cohort testing was cost-effective.

Furthermore, the disease progression of the undiagnosed cohort is subject to considerable uncertainty. The economic model does not simulate when a person was infected with HCV, therefore it does not know how long a person has had chronic HCV infection. This fact is handled by distributing prevalent cases across the fibrosis health states at the outset of the simulation to reflect varying degrees of disease progression. In the base case, the initial fibrosis distribution of these cases was based on the fibrosis data of patients born between 1965 and 1985 birth cohort upon registration with the National Hepatitis C Treatment Programme between 2018 and September 2019.[93] It is unclear how applicable this fibrosis staging is to the undiagnosed birth cohort. The alternative fibrosis distributions modelled in the scenario analysis demonstrated that birth cohort testing would be considered less cost-effective in undiagnosed patients with less advanced disease progression. In the scenario analysis, the upper bound of the 95% confidence interval of the ICER reached approximately €29,000. However, the mean estimate (approx. €13,000) was still well below the WTP threshold of €20,000 per QALY. The economic analysis is strengthened by the calibration against independent data to ensure that the modelled disease outcomes are plausible.

The uptake rate of HCV testing will have a direct implication on the cost-effectiveness and budget impact of birth cohort testing. The modelled uptake rate was estimated at 41% (95% CI: 31-51%) based on the mean uptake rate observed for the BowelScreen programme between 2012 and 2017.[303] These data may be of limited applicability due to differences in population demographics, diagnostic samples and tests, disease outcomes and the once-off nature of birth cohort testing; however, it presents a conservative estimate for the likely uptake of a systematic testing programme based on an existing National Screening Programme with an uptake rate that is in line with rates reported in primary studies of general population and birth cohort testing in Spain and the US.[68, 344] The pooled estimate of the uptake rate observed in Irish observational studies was much higher at 78% (95% CI: 49% to 96%),[307-311] but its applicability is limited by the opt-out nature of the interventions assessed in these studies and the heterogeneous healthcare settings in which testing was offered. If systematic birth cohort testing is implemented, an opt-in provision is anticipated whereby patients will attend their GP practice specifically to receive HCV testing.

In the base case, the ratio of testing to detection of undiagnosed prevalent cases is determined on a pro-rata basis, that is, if 41% of the birth cohort receives HCV testing then 41% of undiagnosed cases will be identified (assuming 100% diagnostic testing

accuracy). A differential uptake, whereby testing uptake is higher or lower in different groups of people with chronic HCV infection, is plausible.[345, 346] For example, HCV prevalence may be higher in people with lower socioeconomic status, therefore if uptake is low amongst those with low socioeconomic status then the yield from testing will be low. However, evidence to this effect is scarce and the direction of the effect is unclear.[347-349] That said, those at risk of HCV infection as a result of lifestyle risk factors (such as injecting drug use) was taken into account in the economic model via the incorporation of a background rate of detection, informed by a combination of UK and Irish data.[93, 293, 306]

The implementation costs of birth cohort testing are subject to uncertainty. In the base case, a per-item fee of €50 (95% CI: €47 to €53) is assumed for people to attend their GP practice and receive testing. If a decision is taken to implement primary-care based birth cohort testing, then it is assumed that, consistent with other service development and reforms, negotiations would be undertaken between the Department of Health, the HSE and the Irish Medical Organisation (IMO) to agree the terms of any contract.[350] In addition, while the estimated resourcing costs of systematic birth cohort testing are based on an existing business case for a National Registry, it is difficult to accurately predict the ongoing costs of a testing programme without appropriate planning of the resources that would be required to run and oversee a national testing programme.

Secondly, the economic model exhibited several structural limitations worth noting. A closed cohort model was used to project the costs and health consequences of the currently undiagnosed cohort over a lifetime time horizon. Adopting this approach means that the model does not account for either new (incident) infections or re-infection in this undiagnosed cohort. A dynamic transmission model, which can be challenging to parameterise and computationally burdensome, would be required to characterise these non-linear interactions.[351] In the case of birth cohort testing, the additional complexity introduced by modelling non-linear interactions is unwarranted given the low rates of incidence and (conflicting evidence of) re-infection with chronic HCV.[9, 352-355]

The economic model assumes the implementation of reflex testing in the modelled alternatives (systematic birth cohort testing and opportunistic birth cohort testing). As described in Chapter 7.2, the standard clinical pathway in Ireland requires two separate blood samples that are collected during sequential healthcare attendances. In the comparator of "no birth cohort testing", the costs of additional healthcare attendances to confirm diagnosis and potential for drop-off along the cascade of care are not modelled. This structural assumption biases in favour of the comparator and therefore represents a conservative approach to addressing decision-maker uncertainty.

To undergo reflex testing, serum samples must be centrifuged and frozen within 6-24 hours of phlebotomy to ensure stability of the sample.[302, 356] However, this is logistically challenging to accomplish and may not be feasible in rural settings. A micro-costing of the diagnostic pathway would be required to reflect the cost implications of adopting reflex testing for birth cohort testing. Such a micro-costing has not been undertaken and is a clear limitation of the analysis.

Finally, the economic model assumes independence between the diagnostic outcomes of sequential diagnostic tests in the diagnostic pathway. It is plausible that there could be a correlation between the diagnostic outcomes of the results between the first-step anti-HCV antibody test and the second-step confirmatory test. For example, patient samples which receive a false positive anti-HCV antibody test result may be more likely to receive to a false positive core antigen test result. This correlation was not modelled due to a lack of empirical evidence to inform such an association.

6.6.3 Conclusions

Based on the economic evaluation and budget impact analysis, the currently available evidence indicates that, although the expected five-year budget impact is significant, birth cohort testing for HCV represents a value-for-money investment. From published evidence, it is clear that the available:

- diagnostic tests used to detect chronic HCV are highly sensitive and specific
- treatments are very effective.

Accordingly, the key question is whether birth cohort testing merits the significant upfront investment required to implement the intervention. Given the substantial downstream healthcare costs associated with treating the long-term complications of chronic HCV infection, offering one-off birth cohort testing to people in Ireland born between 1965 and 1985 is highly likely to be cost-effective. International modelled projections estimate that, based on current rates of diagnosis, Ireland will not achieve its elimination target of 90% diagnosis coverage and 80% treatment coverage until 2050.[357] The National Hepatitis C Treatment Programme (NHCTP) has noted that the downward trend in cases in Ireland since 2015 despite increased testing. If current trends persist, the WHO elimination target may be achieved by 2030. Either way, identifying and treating those currently undiagnosed and chronically infected from this cohort will go some distance to improving Ireland's chances of achieving the HSE's current elimination target by 2026. However, any decision to implement birth cohort testing must be balanced with concerns regarding affordability. While highly cost-effective, the five-year budget impact is substantial and it is noteworthy that while high uptake of HCV testing will maximise cost-effectiveness, it will also have direct budgetary implications.

As considerable decision uncertainty exists in relation to key parameter data, further research on the likely uptake of testing (for example, surveying a representative sample of the birth cohort) would be sensible. In addition, rollout of birth cohort testing could initially pursue a pilot programme which could be phased into wider practice over time according to the observed yield of testing (that is, the coverage and identification of HCV diagnoses). Given the low prevalence, the sample size will be very important to ensure that a sufficiently large patient population is captured to provide a statistically meaningful power of effect. The collection of cost data associated with the logistical challenges, highlighted in this HTA, from sample collection and transportation to laboratory analysis could be incorporated as part of a pilot study.

Finally, while this economic evaluation provides a clear answer to whether the introduction of birth cohort testing delivered via primary care would be cost-effective, alternative models of implementation (for example, offering testing in other healthcare settings) could be further explored to ensure that the most cost-effective model of implementation is adopted. Such investigation would be prudent given the large upfront investment required to implement birth cohort testing.

7 Organisational issues

Key points

- A systematic or opportunistic structure could be adopted for a birth cohort testing programme. A systematic programme would comprise a population-based programme where participants are invited to attend testing. An opportunistic programme would involve offering once-off testing as part of routine care when the patient interacts with the healthcare system for another reason, unrelated to testing (for example, an annual health check-up).
- In this health technology assessment (HTA), it is assumed that implementation of one-off birth cohort testing will require a primary care consultation where a blood sample is drawn by a general practitioner (GP) or practice nurse. It is assumed that a single blood sample will be used for both the initial serological test and any subsequent confirmatory testing (that is, reflex testing).
- Implementation of a systematic birth cohort testing programme could lead to a 0.8% relative increase in existing primary care activity over a four-year period, based on a testing uptake rate of 41%. If a higher uptake of testing is observed, then the demand on primary care capacity will be larger.
- To undergo reflex testing, serum samples must be centrifuged and frozen within 6-24 hours of phlebotomy to ensure stability of the sample. Additional storage and labour capacity would be required in hospital laboratories to meet the requirements of preparing and storing up to 160,000 additional samples per year over four years.
- Alternative testing technologies include dried blood spot testing, rapid diagnostic tests (RDTs) and oral fluid tests. These tests have the potential to increase testing coverage, but at the expense of reduced diagnostic accuracy, implementation of additional quality assurance procedures, and, in the case of RDTs and oral fluid tests, increased risk of loss to follow-up as there is no evidence of these tests being used to diagnose chronic HCV infection, thus preventing the use of reflex testing.
- Quality assurance mechanisms in accordance with best medical practice would be required to establish any testing programme. If implemented, guidance on testing and pathways for patient referral and follow-up should be developed in conjunction with the National Programmes for Pathology and Hepatitis C. Responsibility for communicating testing results to programme participants should be clearly defined.

- General information services, including information leaflets, Freephone services and public awareness campaigns, could be used to support implementation of birth cohort testing. Physician-targeted prompts and educational interventions could also be used to enhance testing uptake rates.
- Consideration could be given to the implementation of a pilot programme, targeting areas known to have a high prevalence, given concerns regarding the feasibility and uptake of a national testing programme. The pilot programme would need to be of a suitable scale to allow identification of a sufficient volume of cases so that the findings are informative for national policy.

7.1 Introduction

The aim of this chapter is to provide an overview of the potential organisational challenges associated with introduction of birth cohort testing for chronic HCV infection in Ireland. The challenges relate to the clinical pathway, logistical issues of testing, set-up and running of a testing programme, and resourcing implications. Measures that could be introduced to control potential capacity issues are also considered.

A birth cohort testing programme for chronic HCV infection was modelled in the cost-utility analysis (CUA). The modelled programme assumes that testing is offered in the primary care setting and involves a blood test that undergoes laboratory analysis. However, alternative models for implementation exist, comprising other healthcare settings and novel testing technologies, which could be adopted for birth cohort testing. These alternatives are described in this chapter.

7.2 A birth cohort testing programme for HCV

The core features of a testing programme are discussed in Chapter 2.7.2 in accordance with the World Health Organization's (WHO) criteria for effective screening programmes.[46] Birth cohort testing for HCV aims to identify and link infected individuals to appropriate care and treatment, thereby reducing HCV-related incidence, morbidity and mortality by providing direct-acting antiviral (DAA) therapy to those in need, and monitoring their response to therapy with appropriate follow-up. As outlined in Chapter 2.7, one of two different approaches to birth cohort testing could be adopted: systematic testing or opportunistic testing.

A systematic testing programme comprises a population-based programme organised by the healthcare system. A systematic birth cohort testing programme would involve inviting all people living in Ireland born between 1965 and 1985 to attend their GP to undergo HCV testing. In this instance, the healthcare interaction is initiated by the Health Service Executive (HSE) using a systematic process for inviting participation in the (opt-in) programme. One US-based study found that the implementation of a primary care-based systematic testing programme increased the uptake rate in the 1945-1965 "baby boomer" population by 137%.[68] The set-up of a population register would be required to monitor and evaluate coverage of a systematic testing programme.

An opportunistic testing programme would involve offering HCV testing as part of routine care when the patient interacts with the healthcare system for another reason, unrelated to HCV testing (for example, an annual health check-up). In this instance the health interaction is initiated by the patient. Therefore, participation in HCV testing is considered opportunistic in nature. A population register would not be a requirement for an opportunistic testing programme, but the lack thereof would make it difficult to

establish coverage and uptake of the testing programme. Based on data collected between 2014-2015 in the Healthy Ireland survey,[305] GP attendance rates range from 56-76% for people aged between 25 and 54 years (corresponding with the birth cohort) attend a GP at least once per annum.

Chapter 2.7 outlined that the structure adopted by a testing programme, whether systematic or opportunistic in nature, will influence the acceptability and uptake of testing, as well as the effectiveness and cost-effectiveness of birth cohort testing for HCV. Both a systematic testing programme and an opportunistic testing programme for one-off birth cohort testing for HCV in the primary care setting are modelled in Chapter 6.

The advantages of systematic testing programmes are outlined in Chapter 2.7. In summary, organised testing can achieve greater equity in access and is considered a more efficient use of healthcare resources by ensuring that all individuals at risk are targeted within the most appropriate timeframe.[47] Appropriate quality assurance mechanisms, clear referral and follow-up procedures as well as call and recall processes are all necessary to optimise the effectiveness and safety of the testing programme regardless of structure. Guidance on testing and pathways for patient referral and follow-up could be developed in conjunction with the HSE National Programmes for Pathology and Hepatitis C, respectively. Organised testing may offer better opportunities to optimise quality assurance.

7.2.1 Quality assurance and evaluation

Given its once-off nature, the concept of case-finding is more applicable to birth cohort testing than conventional screening which involves a continuous process of testing. However, due to parallels between birth cohort testing and conventional population-based screening, the features of a screening programme are described below.

Typical features of an organised population-based screening programme includes development and use of a set of programme standards, against which performance is measured. Quality assurance systems and risk management strategies that are embedded in the programme from the outset facilitate formal, ongoing evaluation and audit. Examples of organised population-based screening programmes in Ireland include BowelScreen, BreastCheck, CervicalCheck and Diabetic RetinaScreen.[303]

The WHO has specified that an effective screening programme should have the following criteria in place:

- mechanisms for systematic invitation and follow-up for individuals identified by the screening test as having an abnormal finding (that is, call and recall mechanisms)

- participation from over 70% of the target population
- necessary infrastructure and resources to offer the test periodically and to adequately diagnose and treat those found to have the disease
- a robust monitoring and evaluation framework to assure quality.[46]

These criteria are discussed below in the context of a systematic birth cohort testing programme. However, criteria in relation to informed consent, test performance, communication of results and timely follow-up and treatment would also be applicable to an opportunistic testing programme.

1. Mechanisms for invitation and follow-up

An organised testing programme would require mechanisms for invitation and follow-up to enable people from the 1965 to 1985 birth cohort to participate in the programme. In an organised testing programme, all eligible patients would be issued an invitation to participate in the programme. Such organised programmes are typically accompanied by a public awareness campaign to promote testing (see section 7.5.1). A systematic invitation system would include invitations to HCV testing and follow-up, and issuing of results. Accordingly, a population frame, from which participants can be identified by the programme and invited to attend HCV testing, would be required.

The process for compilation of a population frame can vary. For BowelScreen, the target population is identified using data extracted from the Department of Social Protection and self-registrants. The Diabetic RetinaScreen register is compiled from national health schemes, such as the Medical Card Scheme, Drugs Payment Scheme and Long-term Illness Scheme, and is continuously updated by GPs who can register eligible patients (all persons with diabetes aged 12 years and older) with the programme. Development and management of the population frame must comply with the relevant legislation on data protection including the General Data Protection Regulation (GDPR).

If established, consideration could be given to linking such a comprehensive birth cohort testing registry and invitation system with: (1) the National Medical Laboratory Information System (MedLIS) to prevent unnecessary duplication of laboratory testing; and (2) the National Hepatitis C Treatment Programme (NHCTP) to provide access to records of those eligible to attend screening and treatment, and to monitor patient outcomes in the testing programme.[93, 358]

2. Participation in testing

A quality standard for coverage by invitation could be used to measure the proportion of the eligible population from the 1965 to 1985 birth cohort that has been invited to attend HCV testing. Indicators could include coverage (receipt of invitation), invitation

uptake (GP attendance to discuss undergoing testing) and testing uptake (undergoing testing). A high participation rate in a testing programme increases the likelihood of identifying prevalent cases.

In the CUA, an uptake rate of 41% was modelled based on that observed for the BowelScreen programme between 2012 and 2017.[303] Although the BowelScreen programme is not directly comparable to birth cohort testing for HCV (due to differences in population demographics, diagnostic samples and tests, disease outcomes and the once-off nature of birth cohort testing), it represents a conservative estimate for the likely uptake of a systematic testing programme based on a pre-existing national screening programme. The results of threshold analysis on the impact of alternative uptake rates is also presented in Chapter 6.5.

3. Infrastructure and resources

If implemented, birth cohort testing for HCV in Ireland should be supported by adequate resources to allow all those diagnosed to access appropriate treatment across the continuum of care. The potential capacity issues associated with birth cohort testing are considered in Chapter 7.4.

To operationalise an organised testing programme, resources would be required to invite participation, collect key performance data, and measure programme performance against quality standards. Consideration could be given to providing a Freephone service to answer patient queries, consistent with the approach adopted with other national screening programmes, such as BowelScreen and Diabetic RetinaScreen.[303] Development of a comprehensive birth cohort testing registry would enable the following functions:

- patient care – facilitate review and recall, structured care and monitoring of patient groups
- quality assurance and improvement – relevant and reliable data is required to assure quality and measure improvement at a service-level
- planning and evaluation – public health policy can be informed through surveillance, service planning and evaluation
- research – facilitate population health services research to address current questions and challenges.[359]

If a registry is developed, then its design should be aligned with conceptual, technical and service delivery priorities and opportunities identified via Sláintecare, the e-Health agenda, the evolution of the National Electronic Health Record, the Individual Health Identifier, the E-Chart blueprint, and data re-association methodologies and governance processes. As such, the set-up of a birth cohort registry would also require:

- agreement with HSE leadership and key stakeholders regarding the purpose of such a registry
- agreement with HSE leadership and key stakeholders on consent, governance structures and data processes
- development of guidelines and frameworks for register development and maintenance
- development of data standards in line with HIQA guidance[360]
- designated personnel that will be tasked with maintaining and checking data quality, and undertaking data analyses
- development of a business case for staffing and information communications technology (ICT) requirements to progress through HSE procurement processes.[359]

In addition, the long-term maintenance of the registry beyond the lifespan of the testing programme would have to be considered. This may be justified under certain circumstances, such as for long-term outcome measurement or to grant non-attendees the option to avail of testing.

The resources required (see Table 7.1) to set-up and run an organised testing programme and database registry were based on the 2019 business case submitted to the HSE for the set-up of a National Diabetes Registry. These estimates may not be directly applicable given that the National Diabetes Registry comprises a live register while birth cohort testing involves one-off testing. The steps outlined above would need to be undertaken to refine the resourcing estimates. The linking of a birth cohort testing register with the treatment registry would allow tracking and follow-up of patient outcomes. Data gathered through the birth cohort testing programme could be used to inform process implementation of any future one-off testing programmes.

Table 7.1. Resource requirements for systematic programme

Job title	WTE	Grade	Source
Clerical Officer	1.0	Clerical officer	[332]
ICT Developer	0.5	VI (clerical)	[332]
Data architect	1.0	VII (clerical)	[332]
Project manager ICT	1.0	VII (clerical)	[332]
Project Manager Business	1.0	VII (clerical)	[332]
Specialist in Public Medicine	0.5	Specialist in Public Health Medicine	[332]

Key: ICT – Information Communications Technology; LCI – lower confidence interval; UCI – upper confidence interval; WTE – whole time equivalent.

4. Monitoring and evaluation

As noted, criteria established by the WHO for an effective screening programme include specifications for programme monitoring and evaluation. While not directly applicable to birth cohort testing since it is limited to a one-off test, the criteria provide

a useful framework when considering how to quality assure the testing programme and ensure it gives rise to the best possible outcomes. Consideration should be given to development of key performance indicators (KPIs) to monitor the testing process and provide an indirect evaluation of the impact of the testing programme. KPIs can be used to identify and respond to problems that may arise, and address the human and financial costs of testing.

Consistent with a number of national screening programmes, consideration should be given to the establishment of a quality assurance committee, comprising a multidisciplinary team of experts prior to the launch of any birth cohort testing programme. For BowelScreen, the quality assurance committee has overall responsibility for continuing oversight of quality within the programme. Within this remit, the committee is responsible for reviewing international standards, recommending best practice, and monitoring and evaluating performance against quality standards.

Development of quality standards with KPIs addressing the following areas could be considered to enable performance measurement:

- programme invitation, coverage and testing uptake
- communication of findings to patient
- test performance
- compliance with and linkage to care.

If programme coverage is used as a KPI, then targets would need to be set for inviting people from the eligible population to participate in the testing programme within a given timeframe. An important quality metric will be measurement of the proportion of invitees that participate and receive HCV testing. Appropriate follow-up would be required for those that do not accept the offer of testing or do not attend for testing.

Communication of test findings is a critical component of a testing programme in order to mitigate unnecessary stress and anxiety regarding test results among programme participants, to link diagnosed patients with healthcare services for appropriate HCV staging, work-up and treatment, and to ensure public trust in the programme. KPIs would be required to ensure that results are communicated in a time-efficient manner including oversight of the time from invitation acceptance, through GP attendance, laboratory testing, communication of results to the patient and follow-up with the hepatology programme where relevant.

For existing screening programmes in Ireland, responsibility for communication and follow-up differs by programme. For BreastCheck (which comprises a mammogram delivered directly by the programme), screening participants receive a letter with their mammogram results within three weeks of breast screening. The results are also sent

to the screening participant's GP (if provided by the participant). For BowelScreen (which comprises a self-administered bowel sample that is sent by Freepost for laboratory analysis), the programme communicates directly with the patient, with a copy of the result also sent to the participant's GP (if provided). For CervicalCheck, where the screening sample is taken by a registered provider (GP or practice nurse), the results are sent to the provider, who then liaises with the participant. Whether the communication of findings to participants is the responsibility of the participant's GP or the testing programme would need to be clearly defined and communicated to participants in the testing programme. In the CUA, a primary care-based testing programme is modelled. In practice, people that are not registered with a GP may need to access testing via an alternative route (such as a public health clinic).

The effectiveness of the test is an important consideration in any testing programme. Key indicators include the sensitivity and specificity of the test in addition to the positive predictive value (PPV) and negative predictive value (NPV). The results of any subsequent tests that lead to identification of false positive diagnoses, such as independent laboratory verification of positive tests or baseline HCV-RNA testing at treatment initiation, should be recorded. As described in Chapter 4.2, sensitivity and specificity of anti-HCV antibody testing were estimated at over 99% and 96%, respectively, while sensitivity and specificity of the HCV core antigen test were estimated at 93% and 99% in serum or plasma compared with HCV-RNA tests, respectively.

As described in Chapter 2.7.3, the PPV and NPV are influenced by the prevalence of disease within the target population. That is, a higher prevalence leads to higher PPV and reduces NPV, and vice versa. Therefore, it is still important to confirm that diagnostic test performance is optimal. False positives increase the burden on both the patient and healthcare system (in terms of patient anxiety and worry, incidence of potential side-effects from treatment, healthcare capacity, resourcing and treatment costs). False negatives have the potential to increase patient disease burden and could have economic consequences in terms of the escalation of healthcare costs for management of their disease progression. Furthermore, trust in the test is paramount to ensuring patients engage with the programme. Processes for dealing with false positives and false negatives would need to be developed under a comprehensive testing programme.

In an organised testing programme consideration must be given as to how testing is coupled with mechanisms to ensure that those identified with chronic HCV infection are linked to care. Important quality metrics in a testing programme are likely to include waiting time for hepatology services, the proportion of patients that access treatment and the proportion treated that achieve a sustained virological response (SVR). Knowing the number of people accessing treatment and its outcome, at both

local and national levels would provide important data to support monitoring of Ireland's progress towards HCV elimination. Linking with the existing NHCTP Registry would allow these data to be captured for patients identified by the introduction of a birth cohort testing programme. If a testing programme is implemented, data collected as part of a testing programme should be aligned with that of the NHCTP Registry in the interest of data continuity.

7.3 Clinical pathway

7.3.1 Overview of clinical pathway

Throughout this health technology assessment (HTA), it is assumed that implementation of birth cohort testing will require a primary care consultation where a blood sample will be drawn by a general practitioner (GP) or general practice nurse. It is also assumed that a single blood sample will be used to make a diagnosis of chronic HCV infection. As described in Chapter 2.10, laboratory detection comprises an initial serological test for anti-HCV antibodies confirming past exposure to HCV followed by a supplementary test to confirm chronic infection. The latter may involve either a nucleic acid amplification test (NAAT) to detect HCV ribonucleic acid (RNA) or a core antigen test, to detect the HCV core antigen (a marker of HCV replication). The sensitivity and specificity of laboratory tests for diagnosis of chronic HCV infection are outlined in Chapter 4.2.

Testing can be undertaken in hospital laboratories; however, many laboratories currently send HCV-RNA tests to the National Virus Reference Laboratory (NVRL) for testing. The NVRL is also used for verification of borderline results and supplemental testing on anti-HCV positive specimens.[302, 356]

Following confirmation of chronic HCV infection, patients should be linked to care to undergo baseline HCV-RNA testing (which is used to monitor treatment effectiveness), HCV genotyping, fibrosis staging, treatment initiation and follow-up.

7.3.2 Implications for current pathway

Two alternative laboratory-based approaches (presented in Figure 7.1) may be adopted for diagnosis of chronic HCV infection:

- anti-HCV and confirmatory tests are performed on the same sample (reflex testing)
- anti-HCV and confirmatory tests are performed on two separate samples (current standard).

Currently, samples sent to HSE pathology laboratories for HCV testing are typically stored at room temperature with serological tests performed the next working day

following receipt of the sample. Where samples are received on a Friday, the serological test may not be undertaken until the following Monday (that is, up to 72 hours later).

To enable reflex testing, serum samples must be centrifuged (spun down) and frozen (which prevents sample degradation) within 6-24 hours of venepuncture. This time constraint means that the original serology clotted blood sample is often unsuitable for reflex testing.[302, 356] Samples therefore need to be spun down and frozen upon arrival in order to be suitable for reflex testing.

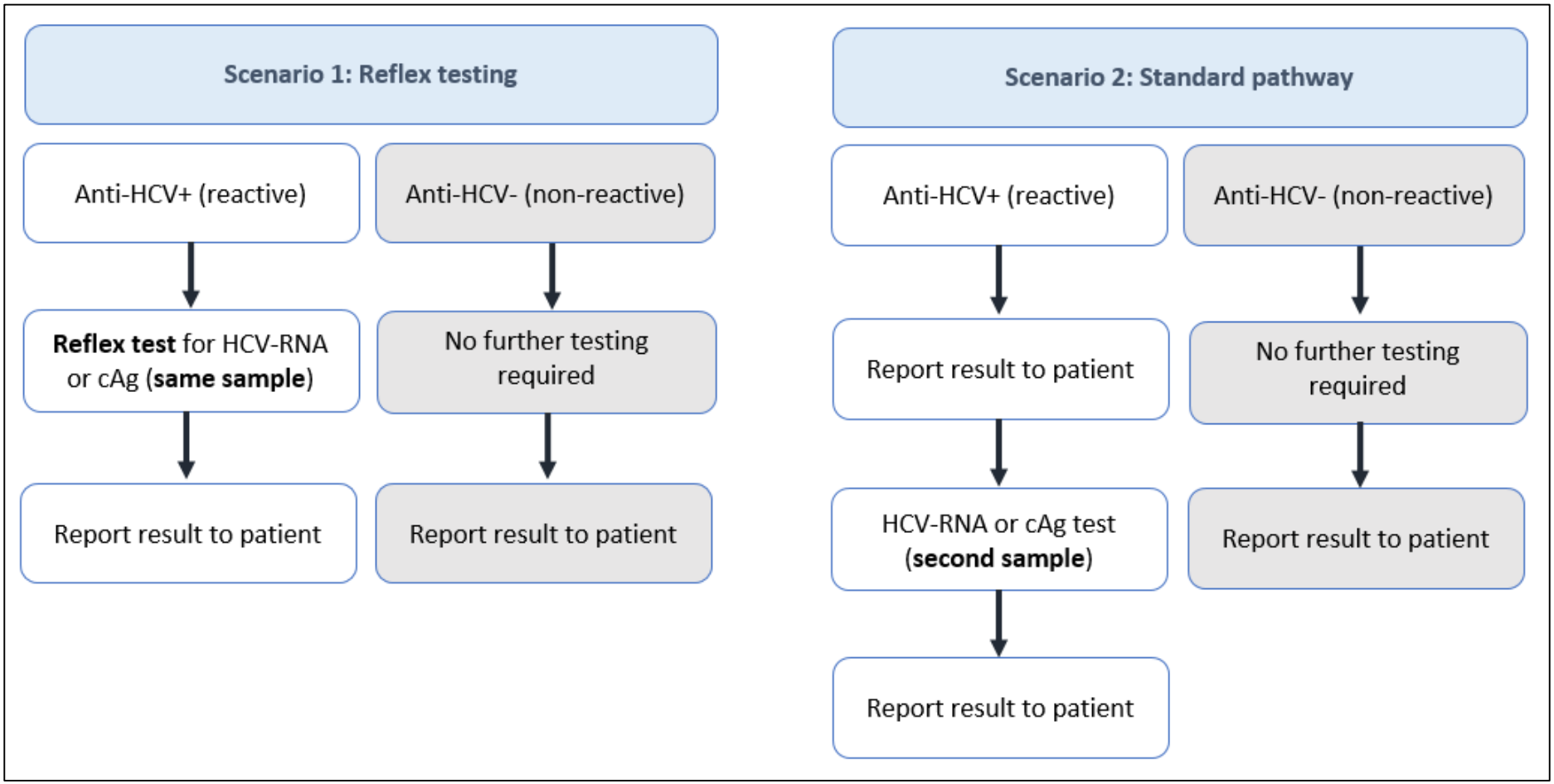
Reflex testing is assumed in the CUA as it lowers costs and avoids the risk of non-compliance with a second GP visit for confirmatory testing. Reflex testing allows the patient to receive both test results at the same time, mitigating the stress and anxiety caused by a positive anti-HCV diagnosis (indicating prior exposure) in those whose infection has resolved and who are therefore not at risk of HCV-related disease sequelae.[361] However, reflex testing is not currently considered standard practice and the logistical challenges noted would need to be considered in light of any implementation decision.[85, 356]

It may be feasible for laboratories to implement a policy of freezing part of all birth cohort samples upon receipt, but this would represent a logistical challenge which would require additional laboratory staffing and freezer storage capacity, particularly if uptake in the birth cohort was high and samples required long term storage (as tested specimens may be stored for up to two years).[356] In the budget impact analysis (BIA) (see Chapter 6.5.6), it was estimated that a testing uptake rate of 41% in a systematic testing programme would lead to between 146,000 and 160,000 anti-HCV antibody tests per annum (on average) representing a significant logistical challenge to ensure that adequate capacity and storage resources are in place for laboratories.

It was highlighted by the HSE Pathology Programme that many in-house serology and polymerase chain reaction (PCR) testing options are validated for serum only or plasma only, respectively. This would be problematic for reflex testing of single serum or plasma samples. Sample volume may also be an issue as the testing algorithm of some laboratories requires repeat anti-HCV testing when the serum sample is reactive. Under such a testing algorithm, it would be problematic to perform HCV-RNA testing (which requires one millilitre of serum) on the remaining sample volume. Therefore, sufficient sample volume will be required to ensure that reflex testing is practical.

Compared with opportunistic testing, implementation of a systematic programme would allow the volume of activity across the clinical pathway to be managed. In Chapter 7.4, it is described how implementation could be phased over four years to minimise potential capacity issues across the clinical pathway.

Figure 7.1. Alternative pathways for laboratory-based diagnosis of chronic HCV infection



Key: cAg – core antigen; HCV – hepatitis C virus; RNA – ribonucleic acid.

7.4 Capacity implications

7.4.1 Overview of the population

The proposed target population comprises people living in Ireland born between 1965 and 1985. In total, this represents approximately 1.5 million people (see Table 7.2).[149] Chapter 6.3.1 outlined that the CUA assumes a staggered implementation of birth cohort testing whereby patients are divided into subgroups according to age bands and offered testing over discrete six-month intervals. The purpose of the staggered implementation is to reduce the impact on healthcare capacity across the clinical pathway.

Table 7.2. Target population and prevalence by age group in 2021

Age band (years)	Total population	Chronic HCV prevalence*	
	N	%	N
36-40	386,464	0.27%	1,054
41-45	393,691	0.73%	2,889
46-50	358,507	1.14%	4,087
51-56	377,409	1.00%	3,761
Overall	**1,516,072**	**0.78%**	**11,791**

Source: Central Statistics Office population estimates 2020[149]
* Predicted number of undiagnosed based on estimates by Garvey et al.,[157] as described in Chapter 3.5.2.

7.4.2 Coverage, uptake and clinical pathway implications

To incorporate the phased implementation approach in the CUA, each subgroup is split in two and HCV testing is rolled out over the course of one year (see Table 7.3). The model assumes that patients with chronic HCV infection that are identified by testing are offered first-line therapy in the six-month period that follows testing. Patients that fail first-line therapy are then offered second-line therapy in the six month period subsequent to failing first-line therapy. The model also assumes that phased implementation begins with testing the oldest cohort and working down through to the younger age groups. This approach was adopted given the assumption that older cohorts are likely to have been infected for a longer period and the assumption that progression of HCV-related disease increases over time.

The sequence of testing, treatment and re-treatment adopted in the model over a five-year period is presented in Table 7.3. According to this proposed sequence, by the end of implementation year five, each cohort will have been offered birth cohort testing and treatment. This is in line with the National Hepatitis C Treatment Programme's (NHCTP) target of HCV elimination by 2026.[7, 93-95]

Table 7.3. Sequence of staggered implementation of modelled testing programme

Model cycle*	Tested	Treated	Re-treated
1	50-55 (group 1)	NA	NA
2	50-55 (group 2)	50-55 (group 1)	NA
3	45-49 (group 1)	50-55 (group 2)	50-55 (group 1)
4	45-49 (group 2)	45-49 (group 1)	50-55 (group 2)
5	40-44 (group 1)	45-49 (group 2)	45-49 (group 1)
6	40-44 (group 2)	40-44 (group 1)	45-49 (group 2)
7	35-39 (group 1)	40-44 (group 2)	40-44 (group 1)
8	35-39 (group 2)	35-39 (group 1)	40-44 (group 2)
9	NA	35-39 (group 2)	35-39 (group 1)
10	NA	NA	35-39 (group 2)

Key: NA – not applicable.
* Each cycle represents a discrete six-month period.

If a systematic testing programme is implemented with an uptake rate of 41% as estimated in the CUA, the following number of people approximately would receive HCV testing in each year:

- 154,000 in year one
- 146,000 in year two
- 160,000 in year three
- 157,000 in year four.

Importantly, the implementation of birth cohort testing would have capacity implications for:

- primary care
- laboratories
- treatment services.

Primary care capacity

There are approximately 3,000 GPs in Ireland, working across group practices, primary care centres, single practices and health centres.[362] It is estimated that there are approximately 20 million patient visits to GPs each year, with 73% of adults visiting their GP in 2018.[328, 363] Based on 2014-2015 Healthy Ireland data, it is estimated that between 56% and 76% of people from the 1965-1985 birth cohort visit their GP every year, with GP attendance consistently higher in females than males (see Table 7.4).

Table 7.4. Percentage of people attending the GP over a 12-month period in Ireland, 2014-2015

	Males		Females	
Age group (years)	**Attendance (%)**	**Total population (n)**	**Attendance (%)**	**Total population (n)**
35-39	56	150,500	73	162,062
40-44	56	192,086	73	197,952
45-49	61	178,122	66	180,428
50-54	66	187,896	76	189,429

Key: GP – general practitioner; LCI – lower confidence interval; N – number; UCI – upper confidence interval.
Source: Healthy Ireland, Central Statistics Office[149]

As described in Chapter 6.3.2, the uptake rate of a systematic testing programmes is modelled at 41%. Implementation of a systematic testing programme involves invitation to attend a primary care centre specifically for the purpose of HCV testing. Capacity would be required to provide an additional 0.62 million GP consultations over a four-year period in a systematic testing programme, representing a relative increase in existing activity of approximately 0.8% per annum. The anticipated number of additional GP visits per annum is presented in Table 7.5.

Table 7.5. Total (average) number of additional GP visits over a four-year period*

Time period	Systematic testing programme (n)	Opportunistic testing programme (n)
Year 1	153,950	103,931
Year 2	145,993	102,391
Year 3	160,286	103,971
Year 4	157,376	102,092
Total	**617,605**	**412,385**

Key: GP – general practitioner.
* The presented figures represent the predicted average. Substantial uncertainty exists in relation to the likely uptake of testing (see Chapter 6 for further discussion).

As part of the GP consultation, it is expected that patients would complete an initial questionnaire to confirm that they do not fall into any of the other risk categories, outlined in Chapter 2.8. The purpose would be to rule out potential recent exposure to HCV and to identify if the patient has previously undergone HCV testing.

Within the 1965-1985 birth cohort, there will be subgroups who, at the time of invitation to attend for testing, will have received HCV testing in the previous 12 months. These subgroups include (but are not limited to): patients known to have chronic HCV and those with test results consistent with having been previously exposed, but having cleared the virus; people that are currently active blood donors

and have not experienced any type of HCV risk exposure since their most recent blood donation (since HCV testing is undertaken as part of the blood donation process); patients that have initiated immunosuppressant therapy (where HCV testing is often recommended at therapy initiation); and those that have received occupational-related testing (for example, healthcare workers). These people may therefore reasonably decline testing on the grounds that they are at low risk of infection and have been recently tested.

If a decision is taken to implement birth cohort testing, and a primary-care based model of care is chosen for testing, then it is assumed that, consistent with other service development and reforms, negotiations would first be undertaken between the Department of Health, the HSE and the Irish Medical Organisation (IMO) to agree the terms of any contract, irrespective of whether the testing programme is opportunistic or systematic in nature.[350]

Laboratory capacity

As of 2013, there were at least 13 laboratories nationally carrying out HCV testing on behalf of the HSE, including 12 hospital-based laboratories and the National Virus Reference Laboratory (NVRL) which is sub-contracted by other hospitals to provide HCV testing on a fee-for-service basis (and carries out over 50% of all HCV tests annually).[8, 364] The estimated number of anti-HCV antibody tests performed annually and the number of annual number of cases of viraemic infection that were notified in Ireland between 2014 and 2019 is presented in Table 7.6. As described in Chapter 3.3, since 2012 only cases of chronic HCV infection (determined by the detection of HCV-RNA or core antigen in serum or plasma) are notified in Ireland.

Table 7.6. Anti-HCV antibody tests and notifications per annum in Ireland, 2014-19

Year	Anti-HCV antibody tests*	HPSC notifications
2014	99,647	690
2015	108,465	671
2016	117,427	637
2017	120,738	607
2018	128,197	585
2019	137,342	474

Key: HCV – hepatitis C virus; HPSC – Health Protection Surveillance Centre.
Source: National Hepatitis C Treatment Programme and Health Protection Surveillance Centre. [93, 365, 366]

* Based on the number of anti-HCV antibody tests performed annually from the four main Health Service Laboratories (between the NVRL, Cork University Hospital, University Hospital Galway and the Rotunda Hospital) involved in testing from 2014 to 2019. Between them, these laboratories are estimated to carry out approximately 90% of all anti-HCV tests in Ireland.

In the CUA, it is assumed that confirmatory testing will be done with a core antigen test rather than HCV-RNA as time constraints in terms of sample processing (that is, time to centrifuge and freezing) are less restrictive and the cost per test is lower. Over the course of a four-year period it is anticipated that a systematic testing programme would lead to an additional 618,000 anti-HCV antibody tests and 8,900 core antigen tests. In comparison, an opportunistic programme would lead to an additional 412,000 anti-HCV antibody tests and 5,900 additional core antigen tests (see Table 7.7).

Table 7.7. Number of additional HCV tests required over a four-year period

Time period	Systematic		Opportunistic	
	Antibody	Core antigen	Antibody	Core antigen
Year 1	153,950	2,724	103,931	1,815
Year 2	145,993	2,853	102,391	1,981
Year 3	160,286	2,202	103,971	1,410
Year 4	157,376	1,151	102,092	736
Total	617,605	8,930	412,385	5,942

Key: HCV – hepatitis C virus.

Treatment services

Consistent with criteria established for screening programmes and best medical practice, it is assumed that implementation of any birth cohort testing for HCV in Ireland would be supported by adequate resources to allow all those diagnosed to access appropriate care and treatment. The NHCTP is currently structured to provide treatment for HCV through one of eight hospitals, five of which are located in Dublin:

- Beaumont Hospital (Dublin)
- Mater Hospital (Dublin)
- Our Lady's Hospital Crumlin (paediatric cases only) (Dublin)
- St James's Hospital (Dublin)
- St Vincent's Hospital (Dublin)
- Galway University Hospital
- Cork University Hospital
- St Luke's Hospital, Kilkenny.[367]

Linkage to care has been identified as a key issue in the implementation of testing and treatment of chronic HCV infection, and there is growing support for the delivery of care in the community.[368] While investigation and oversight would be provided through the dedicated secondary care sites, a pilot programme is currently being rolled out whereby treatment can be accessed in drug treatment clinics and primary care.[93, 366]

In the BIA, it was estimated that a systematic birth cohort testing programme would lead to detection of an additional 2,792 (95% CI: 1,708 to 4,188) patients receiving

DAA therapy over the course of four years. In an opportunistic testing programme it was estimated that an additional 2,008 (95% CI: 1,196 to 3,065) patients would receive DAA therapy over four years. Using the number of notified cases in Ireland as a proxy for those accessing treatment, on average 612 patients received HCV treatment each year from 2016-2018.

As the ability to manage additional patients may differ by treatment centre, consideration may need to be given to the potential requirement for additional resources on a centre-by-centre basis. Implementation of birth cohort testing for HCV has the potential to increase health inequity if treatment is not accessible to all those who are diagnosed. It is expected that most HCV-infected persons will be able to start treatment immediately following detection of chronic HCV infection, and, consistent with the ethical considerations during the set-up of a testing programme (outlined in Chapter 8), should be offered treatment as soon as feasibly possible to reduce the potential for loss to follow-up and burden of morbidity that may occur with delays in starting treatment.

7.5 Information and awareness

7.5.1 Public awareness campaign to support rollout

In the cost utility analysis (CUA), it is assumed that implementation of a birth cohort testing programme, whether systematic or opportunistic in nature, will be accompanied by a public awareness campaign with the aim of encouraging a higher uptake of testing. The individual components that will determine the cost of a public awareness campaign could include:

- qualitative research – investigation of the target audience's knowledge, awareness levels, information gaps and or misconceptions
- creative development – campaign development based on the findings from the qualitative research which will vary according to the type of media campaign required (for example, radio and press), and require the involvement of creative agencies and analysts
- focus testing – testing of creative routes (for example, focus groups)
- media plan – the length of the required media campaign.[299]

7.5.2 General information services

If a birth cohort testing programme is established, it is assumed that general information services would be made available to members of the 1965 to 1985 birth cohort. This could include information leaflets detailing HCV infection, risk factors for acquisition of infection, testing procedures, treatment, risk of false diagnoses, communication of results and onward referral which could be sent to members of the

birth cohort when invited to attend HCV testing.

Consideration could also be given to establishing a new freephone service or to link in with existing freephone services that support National Screening Programmes in Ireland, to answer queries and concerns regarding testing and treatment. For example, individuals who wish to participate in the Bowelscreen programme can call a freephone customer information line to consent to participation. Clear communication on the risks associated with HCV testing (that is, the risk of a false diagnosis) is crucial to ensuring trust in and engagement with the testing programme among the general public.

As noted in Section 7.4.2, it is assumed that patients would complete a pre-testing questionnaire to ensure that they do not fall into any of the current risk-based screening categories when undergoing testing for HCV. Some patients may also have recently donated blood and already have been tested for HCV. Such a questionnaire could be used by the GP in addition to the patient's records as part of any consultation to inform a decision to test.

7.5.3 Physician-targeted interventions to support rollout

If an opportunistic testing programme was to be established, consideration could be given to physician-targeted interventions that trigger the GP to offer HCV testing with the aim of encouraging uptake. One US study found that physician-targeted prompts (for example, posters and reminder stickers) as part of a multi-component intervention (including educational sessions for primary care providers and staff) can enhance HCV testing rates.[44]

Consideration may also be given to educational brochures and the creation of training materials to assist GPs and practice nurses. One Scottish study found that awareness raising campaigns were insufficient in the absence of accompanying educational initiatives.[369] A mixed-methods service evaluation in the UK found that computer prompts and GP education on whom to test aid HCV case-finding.[370] A systematic review of observational and randomised controlled studies found that physician-targeted interventions were effective in increasing uptake of anti-HCV antibody testing.[371, 372] However, the contrasting health system funding models between Ireland and the UK should be noted. In Ireland, a fee-per-item payment is often used to reimburse GPs in this context (and modelled in the CUA).

A 2018 systematic review by the European Centre for Disease Prevention and Control (ECDC) found that combining a public awareness campaign with educational brochures and training for GPs can result in improved testing uptake.[373] One study found that this approach led to a three-fold increase in people being tested, compared with a 1.4-fold increase in testing when only a public awareness campaign was

implemented.[374]

7.6 Alternative testing options and settings for birth cohort testing for HCV

This HTA assessed the costs and benefits of a birth cohort testing programme for HCV where tests are collected in the primary care setting prior to laboratory analysis. Assumptions around the structure of a birth cohort testing programme were based on equity of access, the potential uptake of the intervention and acceptability to the birth cohort, based on expert opinion. However, there are other novel testing interventions and healthcare settings in which testing for HCV may be considered to maximise yield of testing and efficiency of healthcare resources.

7.6.1 Novel testing initiatives

Common testing strategies for HCV include universal screening, birth cohort testing or risk-based testing. In light of the World Health Organization's effort to eliminate viral hepatitis by 2030,[3] new technologies and strategies for implementation of testing have been developed which may be incorporated in national testing strategies and programmes. The European Centre for Disease Prevention and Control (ECDC) conducted a 2018 systematic review to identify testing approaches in healthcare and community settings across a variety of patient populations.[373, 375]

Testing initiatives across primary care and community settings, hospital and other healthcare settings, and multiple/unspecified settings were included in the systematic review. Overall, the systematic review found that the effectiveness of interventions to improve HCV testing coverage in primary care was limited, with testing interventions focused mainly on risk groups, such as migrants and the homeless. The systematic review concluded that the optimal approach for increasing testing coverage and identification of the undiagnosed fraction may involve a combination of a diverse set of testing opportunities and national testing strategies.

Novel testing initiatives for HCV in primary care and community settings identified in the systematic review included oral sampling and dried blood spot (DBS) testing, with evidence indicating that, although less accurate, these technologies facilitate increased testing coverage and are highly acceptable to users and testing staff.[373]

Dried blood spot (DBS) testing and self-testing

DBS testing, which involves depositing blood drops on a filter paper, is increasingly used for HCV testing. Advantages of DBS testing include:

- the sampling process avoids the need for venepuncture
- removes the need to separate plasma samples

- reduced workforce requirements
- requires smaller volumes of blood and components (plasma and serum) compared with venepuncture
- high sample stability at room temperature
- can be used for detection of anti-HCV antibodies and HCV-RNA
- reduced sample transportation requirements
- avoids the requirement for centrifugation and frozen storage of test samples to facilitate reflex testing.[185, 376-378]

A systematic review and meta-analysis was undertaken to assess the diagnostic accuracy of laboratory-based tests for detecting HCV in DBS (see Chapter 4A). In the meta-analysis, the sensitivity and specificity of anti-HCV tests in DBS were estimated at 0.95 (95% CI: 0.92 to 0.97) and 0.98 (95% CI: 0.98 to 0.99), respectively, compared with anti-HCV in serum, plasma or whole-blood. The sensitivity and specificity of HCV-RNA in DBS was estimated at 0.95 (95% CI: 0.93 to 0.97) and 0.97 (95% CI: 0.94 to 0.98), respectively, compared with HCV-RNA in serum, plasma or whole-blood. The sensitivity and specificity of core antigen in DBS was estimated at 0.87 (95% CI: 0.80 to 0.91) and 0.99 (95% CI: 0.96 to 1.00), respectively, compared with HCV-RNA in serum, plasma or whole-blood. These results are consistent with those of previously published systematic reviews.[376, 379] Therefore, these tests may provide a useful alternative in situations where reflex testing of conventional blood samples is not logistically feasible. However, it should be noted that the generalisability of these findings to low-prevalence settings is limited due to the characteristics of the study populations and methodological limitations of the included studies.

Commercially available DBS cards are primarily used in newborn screening and preclinical drug development by highly proficient personnel within controlled clinical and laboratory environments. DBS samples are susceptible to contamination by the user, patient, environment, equipment and contact with other cards.[377] Health-care workers also have a risk of exposure to potentially infectious agents until blood is dried and contained in secure packaging. However, most of these risks can be mitigated through standard operating procedures and accessories. DBS testing is recognised as a useful sample type for hard-to-reach populations and has been validated for human immunodeficiency virus (HIV), but there is evidence that it can be messy and uncomfortable for individuals in the self-testing setting.[299]

Newborn blood spot screening is currently in place in Ireland which screens from a number of conditions, but not HCV, by heel-prick.[380] In the UK, DBS testing is offered in the primary care setting to at-risk infants born to hepatitis B virus (HBV) positive mothers.[381] Several drops of blood are obtained by heel-prick and applied to dedicated filter paper (Guthrie cards) which are air dried and posted for laboratory analysis. Under the service, criteria and control measures have been established for

testing, and training materials have been developed for personnel administering testing. The initial three-year audit data reported that 98% of the testing was undertaken in primary care (66% in GP practices, 18% were home-visits and 15% in community immunisation clinics).[382]

DBS typically requires minimal formal training as healthcare practitioners already typically take blood with automated lancets (for example, for assessing management of diabetes mellitus); however roll-out of a DBS programme would ideally include development of online resources to help ensure healthcare practitioners are competent and confident in their ability to carry out the procedure.[383] In the UK programme, only one sample out of 2,027 was inadequate for HBV antigen testing, indicating excellent user technique and ease of sampling by DBS. The introduction of DBS testing in specialist drug service centres has had the greatest impact on efforts for improving diagnosis of HCV in Scotland (see Chapter 7.6.2).[384]

Self-sampling and self-testing represent relatively new testing modalities, which have been authorised for use in a limited number of countries for detection of HIV,[385] with the potential to improve testing coverage. One study identified in the ECDC systematic review reported coverage rates for self-sampled DBS postal testing kits for HIV self-testing at a sexually transmitted infection (STI) clinic for men-who-have-sex-with-men (MSM) for the first 30 users of the service at 53.3%.[386] No evidence of self-testing for HCV was identified in the ECDC systematic review.[373] One study published in 2020 which assessed the feasibility of DBS for HCV-RNA self-sampling at home in the Netherlands found a high correlation (r=0.958) between HCV-RNA in laboratory-spotted DBS and self-sampled DBS.[387] Self-sampled DBS was also used in a cross-sectional study in France that aimed to estimate the prevalence of chronic HBV and HCV infections in the general adult population in 2016.[388]

Rapid diagnostic tests (RDT), near-patient tests and oral sampling

Rapid diagnostic tests (RDTs), on-site tests with single day results, can be used for antibody detection, and are particularly relevant for mass screening initiatives and in resource-limited settings due to their lower complexity, shorter turnaround time, lower cost and the fact that specialist apparatus and technicians are not required.[86] As described in section 2.10.1, the sensitivity and specificity of RDTs for anti-HCV detection may be as high as 98% (95% CI: 98-100%) and 100% (95% CI: 100-100%), respectively.[86] However, the individual performance of RDTs to detect antibodies varies widely according to brand and specimen type.

As described in section 2.10.1, near-patient tests that detect anti-HCV antibodies with a pooled sensitivity of 97.5% (95% CI: 95.9-98.4%) and a pooled specificity of 99.6% (95% CI: 99.3-99.8%) are also available.[87] The use of RDTs on blood specimens is conditionally recommended in Ireland where concerns exist about hard-to-reach

populations or linkage-to-care.[8] However, a quality assurance programme would need to be established before the use of RDTs or near-patient testing could become standard practice in Ireland. Laboratory-based enzyme immunoassay (EIA) is considered standard practice for anti-HCV antibody testing in Ireland. In addition, as RDTs and near-patients tests are not currently available to detect chronic HCV infection, they do not facilitate the use of reflex testing. Given these limitations, the cost-effectiveness of these technologies was not modelled in this HTA.

The 2017 National Clinical Effectiveness Committee (NCEC) National Clinical Guideline for Hepatitis C Screening recommended against performing diagnostic testing for HCV infection on oral fluid samples due to low sensitivity, low PPV and a lack of commercial assay validation with oral fluid samples. Since the publication of the NCEC National Clinical Guideline for Hepatitis C Screening, a 2017 WHO systematic review has been published, which estimated that the sensitivity and specificity for detection of anti-HCV antibodies using oral fluids was 94% (95% CI: 93-96%) and 100% (95% CI: 100-100%), respectively.[86] Evidence identified in the ECDC systematic review indicates that oral sampling is acceptable to patients in community settings.[373] In community drug services in the UK, onsite oral sampling of drug users to identify bloodborne viruses reported coverage of 100%, compared with 7.4% for standard serological testing at a sexually transmitted infection (STI) clinic.[389] No evidence was reported for the use of oral samples to diagnose chronic HCV infection. Therefore, the use of oral samples would not facilitate the use of reflex testing and for this reason, the cost-effectiveness of this approach was not modelled in this HTA.

Alternative healthcare settings

As described in Chapter 6.3.2, a number of opt-out testing strategies for bloodborne viruses have been piloted in emergency department (ED) and acute medical units (AMU) in Ireland.[308, 310, 311] These studies involved opportunistically offering an additional blood draw for bloodborne virus testing (HBV, HCV and HIV) to patients that were already undergoing phlebotomy. The cost-effectiveness of these strategies is yet to be determined and may vary by geographical region, as demonstrated by the difference in observed uptake rates between sites (61.7% in Dublin versus 40.4% in Galway). Two studies on universal testing in EDs identified by the ECDC systematic review reported lower positivity rates compared with other strategies.[373] However, such strategies could be important for case-finding in areas that are known to have a high prevalence and or burden of disease, or where injecting drug use is prevalent.

7.6.2 The Scottish experience

A HCV elimination plan was launched in Scotland in 2006.[384, 390, 391] The overarching aim of the plan was to improve services to prevent transmission of infection, identify those infected and ensure that those diagnosed received treatment. The plan was

underpinned by significant additional funding – £100 million of investment was allocated to services between 2008 and 2015 – which has had a major impact on tackling HCV elimination.[384, 392] Notably, between 2006 and 2018:

- an estimated 45% reduction (38,000 down to 21,000) in those living with chronic HCV infection was achieved
- an estimated 55% reduction (23,500 to 10,500) in the number of people unaware of their infection
- approximately 16,000 people have been treated, of whom an estimated 80% (n=12,800) have achieved a SVR.[392]

The action plan has predominantly focused on implementation of risk-based screening strategies undertaken in hospital and primary care settings, but has expanded into prison settings in recent years. The cost-effectiveness of a birth cohort testing strategy using a population-based screening approach (potentially with restriction to high-prevalence geographical regions) is currently under evaluation. An important element of the Action Plan is the creation of a highly developed HCV service infrastructure. A multidisciplinary workforce of hundreds – guided by nationally agreed guidelines, standards and targets – has been trained and integrated to promote awareness levels among both general and at-risk populations.

As part of the drive towards HCV elimination in Scotland, DBS testing strategies in community pharmacies and community drug services have shown promise in their ability to increase testing coverage for people who inject drugs (PWID).[390, 391, 393] One study found that HCV case-finding for PWID via DBS in specialist addiction services and prisons was cost-effective.[394] The introduction of DBS testing in community drug settings has been credited with the most significant increase in new diagnoses.[391]

7.7 Pilot programme of birth cohort testing for HCV

Chapter 6 suggests that the implementation of birth cohort testing for HCV is likely to be cost-effective under the range of assumptions and scenarios tested in this HTA. However, the budget impact and associated opportunity cost of birth cohort testing are significant. There is a lot of uncertainty surrounding key model inputs, such as the prevalence of the undiagnosed birth cohort and the uptake of testing in addition to the feasibility of a primary care-based programme that utilises reflex testing. These could have important implications for the cost-effectiveness and affordability of birth cohort testing.

This chapter has identified several logistical issues that would need to be addressed if a decision were made to implement birth cohort testing. A systematic testing programme would require substantial effort to establish (in terms of identifying the population, ensuring adequate laboratory capacity, quality assurance, etc.). If uptake

is poor, the programme may be considered a failure since the one-off nature of the programme would not provide the opportunity to capture non-attendees.

Taking all of these factors into account, it is reasonable to suggest that implementation could initially pursue a pilot programme, which could be phased into wider practice over time. The programme could be informed by the preliminary learnings from the pilot to optimise coverage and identification of HCV diagnoses. Similar studies have been undertaken in France and Spain to inform national policy.[344, 388] Given the low prevalence, the sample size will be very important to ensure that a sufficiently large patient population is captured to provide a statistically meaningful power of effect. The practicalities of a pilot study, in terms of the time required to plan and run a study, as well as the budget required to provide a sufficiently large sample size, should be considered. If few cases are picked up in a pilot then it may not be particularly informative for policy.

Given that the prevalence of HCV is highest in the East of the country (see Chapter 3.5.1), it would make sense for a proposed pilot to take place in the Dublin area. Such a pilot could be undertaken with the caveat that it would present a biased view of the underlying prevalence of HCV infection across the country, but would have the best prospect of identifying necessary information to inform policy. The pilot should be designed to investigate policy-relevant variables, such as testing uptake, prevalence, disease progression of the undiagnosed population and logistical issues relating to the taking and transport of samples, laboratory analysis and linkage to treatment services.

7.8 Discussion

The potential introduction of birth cohort testing for HCV will have capacity implications across the clinical pathway including primary care, laboratory testing, linkage to care and treatment services. The main capacity implications will be in primary care and hospital laboratories since it is estimated that, over a four year period, birth cohort testing may require (on average) 0.62 million additional primary care visits, 0.62 million additional laboratory tests and an additional 2,800 people accessing treatment. A staggered implementation was adopted in the base case cost-utility analysis (CUA) to assess the impact of spreading the potential burden on the healthcare system over a period of four years.

A reflex testing strategy, whereby positive anti-HCV antibody tests receive confirmatory core antigen testing for diagnosis of chronic HCV infection using the same blood sample, was modelled in the CUA. Reflex testing represents a deviation from the current laboratory testing pathway for HCV and would require centrifuge and freezing of test samples from the birth cohort. Additional storage and labour capacity would be required in hospital laboratories to ensure that samples are spun down and frozen within recommended time constraints (between 6-24 hours depending on the

assay). Dried blood spot (DBS) testing circumvents the need for centrifuge and freezing of samples, but would require the development of training materials for personnel administering tests, clinical validation in the setting in which it is to be used and the establishment of standard operating procedures to integrate this method into routine practice.

Other settings outside of primary care, such as Emergency Departments (ED) and Acute Medical Units (AMU), have been suggested as alternative means of opportunistically identifying patients with undiagnosed chronic HCV. However, the cost-effectiveness and organisational implications of birth cohort testing in these settings have not been assessed in this HTA, which focuses on the introduction of a primary care-based testing programme. Other approaches, such as oral sampling for anti-HCV detection, could be used in community settings and may be acceptable to patients, but would require clinical validation in the settings in which they will be used as well as the development of a quality assurance programme prior to implementation. Such techniques would also require an additional healthcare visit involving a blood draw as the currently available tests are not validated for use in this sample type for identifying patients with chronic HCV infection.

Capacity implications will vary according to the geographical spread of undiagnosed chronic HCV within the 1965 to 1985 birth cohort. A prudent initiative may be to roll-out a pilot programme which targets the areas known to have a high prevalence density, particularly if there are concerns regarding the affordability of a national testing programme. However, the proposal of a pilot study would need to address the practicalities and associated trade-off of such a study – that is, the time required to construct and undertake the study, and the cost of such a study to provide a sufficiently large sample size given the low prevalence of HCV – to ensure that the findings adequately address the uncertainty surrounding prevalence and testing uptake to inform national policy.

The once-off nature of birth cohort testing means that the concept of case-finding is more applicable than screening, but the principles of screening would still be relevant to a population-based testing programme. A quality assurance system would need to be embedded in any population-based testing programme from the outset. The resource requirements for the set-up and running of a testing programme, whether systematic or opportunistic, and linkage with existing registries for patient follow-up will need to be considered in light of any decision to implement a birth cohort testing programme. Similarly, public awareness and physician-targeted initiatives should be considered.

8 Ethical Considerations

Key points

- In terms of the benefit-harm balance, the proposed testing programme would involve testing a large cohort with the knowledge that only approximately 1% will benefit directly through having HCV infection detected and treated.
- Due to the stigma often associated with HCV, birth cohort testing will have to be carried out in a manner that is sensitive to the stigma and ensure best uptake and treatment completion.
- Birth cohort testing could, over a relatively short period of time, identify a large number of people infected with HCV relative to those detected through other means, such as risk-based testing. The additional cases could create challenges for managing the timely treatment of all patients within capacity constraints.
- The health service utilisation generated by birth cohort testing could displace other care, particularly in the primary care setting. The testing programme could create additional demand for primary care of 1.5% to 2.2% per year, with consequences for the availability of services.
- Testing such a large cohort to identify a relatively small number of cases may be a very inefficient use of resources that could be used more efficiently elsewhere in the system. The use of opportunistic testing may improve efficiency but may also adversely impact on the successful identification of those infected with HCV.
- A number of important ethical considerations including issues relating to benefit-harm balance, acceptability and equity of access could be addressed by requiring any birth cohort testing to meet WHO criteria for effective screening programmes (it should include mechanisms for systematic invitation and follow-up, a participation rate of over 70%, adequate infrastructure and resourcing to ensure diagnosis and treatment, and a monitoring and evaluation framework).

This chapter discusses the ethical issues that should be considered in relation to the introduction of birth cohort testing for chronic hepatitis C virus (HCV) in Ireland. This chapter was developed broadly in line with the structure described in the European network of HTA (EUnetHTA) Core Model.[395] The ethical issues associated with a technology must be assessed in relation to the prevalent social and moral norms relevant to the technology. This section also examines the ethical issues related to the technology assessment itself.

8.1 Terminology

A consideration in relation to the proposed technology is how it should be defined (see Chapter 2.7.1). Mass testing of the population is often referred to as screening. However, in the context of hepatitis C and given the nature of the available tests, it may be more appropriate to consider it as case-finding. Ordinarily, a screening test is not intended to be diagnostic, but rather a means to identify those at elevated risk who are then referred for diagnosis.[45] In case-finding, the main object is to detect disease and initiate clinical management and treatment.[45]

The literature on the ethics of screening and case-finding is generally focused on screening. In lieu of the limited body of literature specific to case-finding, the following sections will draw on published literature relating to both case-finding and screening.

For simplicity, in the subsequent text, the intervention will be referred to as testing rather than case-finding. The intervention is also considered here as a programme rather than a one-off test. The concept of a programme entails the need for appropriate governance and metrics of performance in relation to the management of individuals who present for testing and follow-up for those who test positive.

8.2 Overview of population testing

Disease detection often occurs when a person is symptomatic and presents to their doctor seeking diagnosis. The intention of screening and case-finding is to support early disease detection and treatment, potentially before the patient becomes symptomatic. Early detection can lead to less intensive treatment and improved clinical outcomes. Wilson and Jungner[45] proposed criteria for appraising the validity of a screening programme which were subsequently modified by the World Health Organization (WHO), presented in Box 8.1.

Box 8.1. Criteria for appraising the validity of a screening programme

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Source: Wilson and Junger,[45, 396] Andermann et al.[45, 396]

In relation to hepatitis C, the first four criteria can be assessed on the basis of the description of the technology (Chapter 2), the burden of disease (Chapter 3), and the clinical effectiveness (Chapter 4). Criteria five to nine are features of the programme design, while the tenth criterion must be based on a holistic assessment of the programme. The benefits and harms must encompass both the individual and the population, and both clinical and economic perspectives (Chapter 6).

In the original Wilson and Jungner criteria, there was a criterion that stated that: "case-finding should be a continuing process and not a 'once and for all' project." This was removed during the 2008 update of the criteria, although no specific justification was provided. It may be that where eradication of a disease is a realistic goal, continued case-finding may become obsolete. It could also be argued that the criterion of programme evaluation means that a programme is constantly re-assessed and modified or stopped if it no longer meets the other criteria.

The principles set out by Wilson and Jungner and subsequently updated by the WHO are by no means the only principles described for screening. A 2018 systematic review identified 41 sets of principles which encompassed 367 unique principles.[397] Approaches to diagnostics and screening have evolved markedly since the original principles were outlined, particularly with the advent of genetic testing and the increased emphasis on programme design and governance. Based on a synthesis of the 41 sets of principles they identified, Dobrow et al.[397] proposed 12 principles, grouped into three domains relating to the disease, intervention and system (see Table

8.1). The synthesised set of principles are similar to the 2008 WHO criteria with the addition of explicit consideration for economic evaluation, which was included in the original Wilson and Jungner criteria. In accordance with the WHO criteria for effective screening programmes, birth cohort testing should include mechanisms for systematic invitation and follow-up, a participation rate of over 70% from the birth cohort, adequate infrastructure and resourcing to ensure diagnosis and treatment, and a monitoring and evaluation framework.[46]

Table 8.1. Refined set of consolidated principles, by domain

Domain	Consolidated principle
Disease/condition	▪ epidemiology of the disease or condition ▪ natural history of disease or condition ▪ target population for screening.
Test/intervention	▪ screening test performance characteristics ▪ interpretation of screening test results ▪ post-screening test options.
Program/system	▪ screening program infrastructure ▪ screening program coordination and integration ▪ screening program acceptability and ethics ▪ screening program benefits and harms ▪ economic evaluation of screening program ▪ screening program quality and performance management.

Source: Dobrow et al.[397]

8.3 Benefit-harm balance

The benefit from testing that accrues to the individual is highly context-specific. Typically, many people need to be tested (and exposed to potential harms) for a minority to benefit. The benefits to the few must counter the harms to the many, however they might be assessed. The distinction between benefits to the community and to individuals needs to be borne in mind when considering recommendations to participate in organised population-based screening programmes. As screening programme participants are ostensibly healthy people, a programme should be able to demonstrate evidence of an overall population benefit and also minimal risk that certain individuals may be disadvantaged by the programme.[398] In terms of HCV testing, the purpose is to identify and treat people with undiagnosed chronic HCV infection.

The benefits and harms of birth cohort testing should be considered in relation to both testing and treatment. In the absence of this testing, those with chronic HCV infection will go undetected until such time as they become symptomatic, perhaps due to severe liver damage, or if they are otherwise tested for HCV. Later detection will still entail treatment, although potentially with the patient having permanent liver damage and

the associated treatment and quality of life impacts. This section places a greater emphasis on testing, as it is assumed that most people in the 1965-1985 birth cohort with chronic HCV infection will eventually be identified, and undergo treatment irrespective of the implementation of birth cohort testing.

8.3.1 Safety of testing

As outlined in Chapters 2 and 3, the reference standard screening for chronic HCV infection requires one or possibly multiple blood draws for testing. Although rare, cases of unsafe phlebotomy can occur, ranging from pain or bruising at the site of puncture, to fainting, nerve damage and haematoma.[399] A systematic review of adverse events in diagnostic venepuncture in adults found that bruising occurred in 10.3% of cases while pain and haematoma each occurred in 2% of patients.[400] More serious adverse events, such as nerve injuries, were found to be very rare and published in the form of case-reports. The reported common adverse reactions are likely to be mild in nature and have very short term consequences. The impact of such events needs to be considered relative to the potential to benefit. It is estimated that the prevalence of chronic HCV infection in the birth cohort is approximately 1% (see Chapter 3, Section 3.5.2), so 99% of those tested will not benefit but will be exposed to the potential, albeit minor, harms of testing.

Issues can also arise when a blood sample is poorly collected, stored or transported, leading to inaccurate test results or the need for repeat testing.[400] Inaccurate results that lead to the need to provide a second sample could give rise to anxiety for the individual tested. Unless a blood sample is considered unacceptable for testing, there is a risk that a damaged sample may generate an incorrect test result giving rise to false-positive and false-negatives.

8.3.2 Stigma

Stigma arises when an individual is considered by others to be undesirably different, and is subjected to exclusion, rejection, blame or devaluation.[401] Stigmatisation has serious consequences for the individual in terms of mental and physical health. Stigma is associated with a number of chronic infectious diseases (e.g., leprosy, tuberculosis, human immunodeficiency virus (HIV)) including hepatitis C.[402] The perception of stigma linked with hepatitis C is most likely due to its association with injecting drug use.[401]

The stigma associated with HCV infection impacts adversely on initiatives to prevent its transmission, seeking treatment, uptake and adherence of testing and treatment, and on quality of life.[401] People diagnosed with HCV infection may be unwilling to attend clinics or put themselves in a position where they may be identified as having

HCV infection. In the context of birth cohort testing for HCV, stigma will impact on whether people avail of testing and, if they test positive, whether they will avail of and complete treatment. Here, the definition of treatment includes follow-up testing to determine if a sustained virological response (SVR) has been achieved.

To maximise the benefits of birth cohort testing for HCV, steps should be taken to ensure that blood sample taking, communication of results, and treatment all take place in an environment that recognises the sensitive nature of HCV and protects the privacy of the individual.[403] A failure to acknowledge the perception of stigma in the design and delivery of an organised birth cohort testing programme may undermine the willingness of people to participate.

Depending on the context for a given individual diagnosed with HCV infection, it may be recommended to undertake contact tracing. An individual may not want the fact that they have HCV to be known to others. The requirement for contact tracing should not be perceived as a threat to the infected individual, such that they may be reluctant to engage with health services (either to facilitate contact tracing or for treatment).

One point to note is that cases identified through birth cohort testing have potentially not been previously considered as being at elevated risk for HCV infection. Although tested individuals have consented to participate and therefore should appreciate that there is a possibility of testing positive, they may not accept the test results if they are positive as they may not identify or accept that they had an exposure in the past. In part due to the stigma associated with HCV, there is a risk that they will fail to seek or complete treatment. Again, it is essential that birth cohort testing is designed in a manner that each step is supportive of participants and ensures that those identified as HCV positive receive treatment.

8.3.3 Timely intervention

As birth cohort testing is intended to achieve early detection of prevalent cases of chronic HCV infection, a key benefit is to initiate early treatment. The complications associated with chronic HCV infection create a considerable burden of morbidity and mortality. As was apparent from the review of epidemiology (see Section 3.2.1), patients with chronic HCV infection are likely to develop liver fibrosis. If untreated, scar tissue builds up in the liver and eventually the liver becomes cirrhotic. Retrospective studies of the natural course of hepatitis C suggest that, in the absence of treatment, end stage liver disease is common with cirrhosis and liver cancer taking 20 and 30 years, respectively to develop.[404]

The current drugs for treating chronic HCV infection, direct acting antivirals (DAAs), are highly effective at achieving an SVR. From the assessment of clinical effectiveness

(see Section 4.3.4), interferon-free DAA therapies are highly effective with over 95% of patients achieving a SVR across all HCV genotypes. Early successful treatment can prevent further damage to the liver. As the liver can regenerate, those who undergo successful treatment are also likely to experience a reversal of liver damage. Indeed, by avoiding severe liver damage the treatment of chronic HCV infection reduces demand for liver transplantation and also increases the pool of potential donor organs.[405] In terms of treatment safety, 73% of patients on interferon-free DAA regimens experienced a minor adverse event (anaemia, rash, fatigue, headache, insomnia, nausea, diarrhoea, vomiting or rash) and 1.9% experienced a serious adverse event. Those serious adverse events can result in persistent disability, hospital admission, or death.[404]

There is a risk that follow-ups opportunities may be lost and those diagnosed with HCV infection will not commence or complete treatment. In the economic model, there was an assumption that 10% of cases would not complete the first course of treatment. A low rate of treatment completion would reduce the benefits of the programme. Treatment completion will have to be monitored as part of programme performance and steps taken to ensure that completion is maximised, such as identifying if there are specific barriers to access.

Successful treatment of chronic HCV infection reduces the risk of onward transmission in the population, thereby reducing incidence of HCV infection. The effectiveness of new HCV treatments has enabled the shift towards elimination of HCV.[406] Successful treatment of HCV also prevents the development of extra-hepatic manifestations.[35] The programme of testing is intended to identify prevalent cases of HCV infection in the birth cohort. However, it is unclear how much the birth cohort contributes to incidence. If all prevalent cases in the birth cohort are identified and successfully treated, it may do little to address incidence of HCV infection. The birth cohort has been identified on the basis of being the broad population subgroup with the highest prevalence rather than incidence of HCV infection. Bearing in mind the goal of eliminating HCV infection, it will be critical that a programme of birth cohort testing does not take away from the need to manage the incidence of HCV infection.

8.3.4 Over-treatment

Not all people with chronic HCV infection will develop cirrhosis or signs and symptoms indicative of chronic liver disease. Quantifying the magnitude of risk of progression to cirrhosis and HCC with time is difficult as outcomes are influenced by presence of the population risk factors known to accelerate disease progression. Therefore, screening may lead to over-diagnosis and over-treatment of the disease.

However, as the birth cohort are aged between 35 and 55, even the oldest members

of the cohort have an average life expectancy of 27 and 29 years for males and females, respectively. Even if an individual became infected only shortly before testing, development of cirrhosis of the liver could still occur well within life expectancy and therefore, a benefit would be derived from treatment. It is also worth considering the improved quality of life due to reduce hepatic and extra-hepatic manifestations of chronic HCV and also the benefits of preventing onward transmission.

8.3.5 Prevalence within the birth cohort

It was noted in the analysis of burden of disease (Chapter 3) that the estimated prevalence of HCV infection is markedly higher in males than females, and that there is also substantial regional variation across Ireland. It is arguable that a more targeted approach, for example limiting testing to males in the birth cohort in the greater Dublin region, could potentially identify the majority of cases with much greater efficiency. By limiting the programme to a specific birth cohort, there is already an explicit attempt to focus testing on a subgroup with maximum prevalence. However, adopting an overly narrow focus could undermine the goal of eliminating HCV as a further reduction in population coverage is likely to lead to a reduction in the number of identified cases. The inclusion of additional eligibility criteria could also be perceived as discrimination. Members of the birth cohort infected with HCV are as entitled to avail of testing and receive treatment irrespective of where they live in the country.

8.4 Acceptability

Until a person has a positive test result and commences treatment, they are not a patient, but an otherwise healthy member of the population. Population-based screening or testing generates patients that were not patients prior to participation. People may therefore be hesitant to participate if they do not believe they could have the disease or condition (and consequently do not stand to benefit) or if the population testing programme is unacceptable due to its structure. The success of the programme will be impacted by the uptake of testing. If uptake is low then few cases of HCV infection will be identified and treated, and the goal of elimination is unlikely to be achieved. Participation in a screening or testing programme is typically voluntary, and to maximise uptake the programme must be acceptable to participants. Acceptability can be considered in terms of the testing and the treatment.

8.4.1 Testing

Some people experience blood test anxiety, and may be unwilling to submit for a blood test, particularly if they perceive limited personal opportunity to benefit. Although the birth cohort has been defined based on a high incidence of HCV infection relative to the general population, in the absence of other risk factors any given individual may perceive that their own risk of HCV infection is very low. The use of dry blood spot

testing could be a potentially acceptable alternative for those with blood test anxiety as it requires a finger-prick rather than syringe to extract blood. While other sampling techniques are possible, such as oral sampling, they may be associated with lower diagnostic test accuracy and would not necessarily facilitate a reflex test. However, if there is evidence of poor uptake due to the unacceptability of the sample collection method, then alternative approaches may be worth pursuing.

In relation to finger-prick sampling, studies were identified that specifically investigated the acceptability of this approach for people who inject drugs undergoing HCV testing.[407, 408] Finger-prick testing was considered acceptable to participants, and one study suggested that it was considered preferable to venepuncture.[407] It is important to note that the preferences identified in those studies may not be applicable to the general population in the birth cohort. In particular, the stated preferences may reflect the context of a group who may undergo regular screening tests rather than a one-off test.

There is evidence that simplified testing strategies are more desirable among participants. A values and preferences survey across 43 countries found strong support from patient groups for simplified and rapid turnaround testing strategies that would improve access to testing, including for high-risk groups.[409] Simple and fast approaches were considered as preferable to reduce loss to follow-up. There was also a preference for tests based on capillary blood to facilitate use in point-of-care settings, even at the expense of test sensitivity.

The uptake of testing may be influenced by who carries out the testing and undertakes the associated tasks such as obtaining consent, providing counselling and delivering test results). A study of HIV testing in an ED environment, for example, found marked differences between counsellor-led and provider-led testing.[410] From the perspective of a GP practice-based testing programme, consideration may have to be given to whether a practice nurse-led approach may lead to a different uptake of testing to a GP-led approach.

8.4.2 Treatment

Four identified studies investigated the preferences of HCV-infected persons regarding HCV treatment regimens.[2] For persons infected with HCV, the likelihood of a cure and the lack of adverse events are the most important considerations related to treatment regimens, though factors such as a shorter (for example, eight-week) course of treatment were also valued. Therefore, use of pangenotypic regimens would be acceptable.

The effectiveness of treatment was estimated based on SVR measured at short-term

follow-up. As highlighted in Section 4.5, the validity of SVR as a patient-important outcome for HCV has been debated given the lack of long-term follow-up data from randomised trials. Based on current evidence, an SVR is considered an acceptable proxy of cure given evidence from large prospective studies indicating both the durability of an SVR and the association between SVR and reduced mortality and occurrence of extra-hepatic manifestations from HCV. For patients with advanced disease at the time of treatment for HCV, they may experience further disease progression during or after treatment. There is the possibility that long-term adverse effects might eventually be identified, although seems this implausible once the short-term treatment course has ceased.

8.4.3 Autonomy and shared decision-making

Those invited to participate in testing should be provided with adequate information so that they understand what is involved. That is, they should understand what is involved in the test procedure, and the implications of a positive test result. The participants will all be adults and so will, with few exceptions, be able to exert autonomy. For those who lack the capacity to consent, such as due to intellectual disability, consent must be given by a legal guardian.

A test can be described by the characteristics of sensitivity and specificity. Sensitivity is a measure of how well a test identifies true positives as positive. Specificity is a measure of how well a test identifies true negatives as negative. Sensitivity and specificity are typically negatively correlated, as there is a trade-off between the two. Screening tests tend to be minimally invasive and generally have a high sensitivity (to ensure that all true positive cases are identified), but at the expense of specificity (that is, many true negatives may be initially thought to be positives).

The screening test identifies potential cases where a more invasive diagnostic test is required to formally identify those with the disease or condition of interest. The consequence of poor specificity is a high rate of false-positives on the initial test. Depending on how birth cohort testing is offered, there could be a delay between the initial positive screening result and a subsequent diagnostic test to determine whether the person genuinely has the disease or condition. That period can be one of significant anxiety and stress due to the uncertainty associated with potentially being positive.

In the case of birth cohort testing for HCV, a single blood sample can be used for both the initial antibody test and confirmatory test (that is, reflex testing). That means that a positive test triggers the reflex test which must also be positive for the person to be notified that they may have chronic HCV. This removes concern that would arise for those previously exposed to HCV (antibody positive), but who have cleared the virus

and are not currently at risk. Although the rate of false-positives for the two-step reflex test is low at approximately one in 10,000 tests, due to the large number in the cohort that will still likely translate into over 100 false positives.

The implications for a false positive are referral to hepatology clinic for further testing and treatment as necessary, at which point all or almost all false-positives should be identified. For those with false-positive test results, there is likely to be an impact on quality of life between the initial test results and confirmatory testing. Consideration will have to be given to how best to manage that period and how to convey the information to manage the concerns of the individual. The use of relevant key performance indicators (KPIs) that define the maximum length of time between positive test detection and follow-up for confirmatory testing would help to mitigate against the risk of prolonged stress and anxiety.

The concepts of sensitivity and specificity are challenging to explain to a lay audience. The information provided to participants will have to clearly outline the testing process and the implications of a positive test result in terms of further testing and the potential for false-positive results. As it is thought that birth cohort testing will be structured around a blood sample taken in a primary care setting, there is the opportunity for interaction and discussion with the general practitioner (GP) or practice nurse. However, that implies that the participant has to initiate contact either by making an appointment following an invitation to participate in the birth cohort testing programme, opportunistically while attending the GP practice, or they must proactively make contact. It is therefore important that sufficient information is provided to the individual in the invitation to participate to adequately understand the benefits and harms of participation.

To ensure public confidence in HCV birth cohort testing, it is important that information on its effectiveness is made available. Such information is often in relation to KPIs (for example, percentage tests completed over a given time period). Regular monitoring and evaluation of birth cohort testing outcomes is also vital to ensure that effectiveness is maintained and improved where possible. Clear information about the accuracy of the tests, along with prospective evaluation and reporting, can ensure public confidence and lead to good uptake. As birth cohort testing for HCV is a one-off, evaluation of the effectiveness may occur once at the end of the programme and reported retrospectively. If testing is rolled out on a phased basis as proposed in this evaluation, then prospective reporting will be possible. Quality standards, against which a birth cohort testing programme can be evaluated, are discussed in Chapter 7.3.1.

The need to respect autonomy and support shared decision-making also extends to treatment for those who are identified as HCV positive. The pathways for the

treatment of HCV are well-established in Ireland and will not change if HCV birth cohort testing is introduced. As with testing, it is important that those offered treatment are given clear information on the benefits and harms of treatment.

8.5 Justice and equity

Access to healthcare is considered a basic human right applying equally to men, women and children, regardless of gender, race, sexual preference, socioeconomic status or behavioural practices, including drug use, and is in accordance with the United Nations Universal Declaration of Human Rights.[411, 412]

The proposed birth cohort testing does not discriminate between participants other than to restrict the included age range to those born between 1965 and 1985. The people in the birth cohort are not at risk because of when they were born, but due to the fact that HCV prevalence is highest in that cohort (based on national surveillance and prevalence data).[8-10] Accordingly, there is no shared risk of exposure that is common to the entire birth cohort. However, the modelled programme includes a staggered approach to testing age groups within the birth cohort as a means to balance demand and capacity. The consequence of a staggered approach is that some within the birth cohort will be tested sooner than others, and thereby stand to gain more through earlier treatment. While the modelling approach considered starting with youngest first and oldest first, from an ethical point of view it is unclear how the choice should be made. The older members of the cohort may have had HCV infection for longer, and by delaying diagnosis and treatment further it may reduce the prospect of a good outcome. The younger members of the cohort, on the other hand, could potentially gain more healthy life years by earlier treatment.

From an equity perspective, testing a large cohort when it is known that only a small percentage will be HCV-positive is a questionable approach. The birth cohort contains 1.5 million people, of which, approximately 1% may be infected with HCV. The resources required (or opportunity cost) to carry out testing are significant, and it may reasonably be asked whether a more targeted approach to identifying cases is possible. A significant source of costs relates to the testing itself (between primary care consultation, sample collection and laboratory testing of the samples).

A more efficient approach could involve targeting those within the birth cohort at higher risk of having chronic HCV infection due to historic exposure to known risk factors. However, without a common exposure that can be easily identified, such an approach may not exist. A US study found that patients identified by birth cohort testing were significantly less likely to have a documented indication for HCV testing than patients identified via risk-based testing.[251] In the context of HCV elimination, which focuses on identifying those currently unaware of their chronic infection, a key

attraction of the birth cohort testing concept is that it circumvents the need to identify specific risk factors as the basis for testing.[38, 39]

There is substantial uncertainty regarding the likely uptake of testing, with few sources of data to support assumptions. An issue will arise if those with HCV infection are less likely to avail of birth cohort testing. There are a variety of reasons why this situation could occur, and the consequence would be that birth cohort testing would fail to capture the intended individuals, but would still incur the costs of testing a large number of individuals. It is therefore essential that those most likely to have HCV face minimal barriers to accessing a testing programme. For the purposes of the economic model, it was assumed that there would be no association between uptake and prevalence in the tested population. That is, a reduction in uptake would result in a proportional reduction in the absolute number of cases identified. In terms of prevalence by risk group, there is evidence that prevalence is higher in people with lower socio-economic status.[413, 414] However, from a limited number of identified studies reporting data on uptake of cancer screening services, there was mixed evidence regarding variation in uptake by socio-economic status.[415, 416] As such, it is unclear that uptake will be markedly lower in those at higher risk of HCV infection. While it is possible that those at highest risk may be less likely to engage with a formal programme, they may also be more likely to be diagnosed through background testing.

It is probable that there will be insufficient capacity in the system to complete testing of the entire cohort in one year. A reasonable alternative is to stagger the roll-out of birth cohort testing, possibly by age group. Individuals who have chronic HCV infection who are tested earlier have the potential to gain more than those tested later on the basis of starting treatment at an earlier stage of disease progression. The other consideration is whether a staggered roll-out should commence with the oldest members of the cohort or the youngest. Alternative approaches, such as random sampling to determine which individuals are invited first, may not be feasible as they may create difficulties for clarity of message in any public awareness campaign. The approach taken could be selected on the basis of maximising health gain and minimising inequities.

The health service utilisation generated by birth cohort testing could displace other care. Testing will be carried out in a primary care setting, either by a GP or a practice nurse. GPs in Ireland provide in excess of 17 million consultations a year. Depending on uptake, HCV birth cohort testing could generate an additional 1.0 to 1.5 million consultations. Even if the visits are staggered over four years that would imply an additional demand of 1.5% to 2.2% per year, which will clearly displace care to some extent. It may be possible to consider a hybrid of systematic and opportunistic testing, whereby a patient is invited to participate, but can do so at their next GP appointment.

While this approach would create challenges for estimating the rate at which tests will be carried out and when birth cohort testing would be complete, it would potentially reduce displaced care and testing costs. The full burden of the programme on primary care is challenging to assess. The interface between primary care and the programme will need to be carefully managed to ensure a consistency of approach and that there is no ambiguity for those participating in the programme in terms of who is responsible for the various elements of communication. Laboratory capacity will also be affected by the large number of additional tests that would need to be carried out. The ability to manage and schedule the volume of tests could be important from a logistical point of view. In the event that reflex testing is used, samples will have to be retained for the second test, contrary to the current process.

Finally, depending on uptake, prevalence and the rate at which people are invited to testing, the number of cases identified could potentially exceed capacity to treat. This would raise equity issues as to who, in such a case, should be given priority: cases who presented symptomatically or those who were detected through birth cohort testing? Those who are detected symptomatically may stand to gain a more immediate benefit from treatment as it may alleviate symptoms. The HSE NHCTP clinical advisory group recommends that treatment should be prioritised based on clinical criteria and mode of infection. However, there is a potential that this would be distorted if a testing programme had KPIs requiring that those identified through the programme should be offered follow up and treatment within a defined period. Protocols for how to manage capacity constraints and prioritise treatment would need to be set out in advance of implementing a testing programme.

8.5.1 Factors influencing access

It is assumed that birth cohort testing for HCV would be offered to every member of the 1965-1985 birth cohort. However, the manner in which testing is implemented may create barriers to access for some in the cohort.

A fundamental aspect of birth cohort testing that will affect access is whether implementation of a testing programme adopts a systematic or opportunistic approach. A systematic programme will identify and contact all people in the birth cohort and invite them to participate. Opportunistic testing will be based on promotion through advertising and prompts from clinicians (for example, in a GP consultation). The choice of programme design could have implications for who in the cohort becomes aware of availability of birth cohort testing. A systematic programme should, in theory, lead to everyone in the cohort at least being invited to participate. That is, of course, contingent on creating a comprehensive database of everyone in the country in the birth cohort. This can be challenging for ethnic minorities or other hard-to-reach groups. While opportunistic testing does not require a list of all eligible

people, it needs sufficient promotion to ensure that there is public awareness and acceptable levels of uptake. People who do not have contact with a clinician, such as a GP, during the period that a birth cohort testing programme is active, may not be offered the opportunity to participate. It must also be recognised that not all members of the birth cohort will be registered with a GP. Some subgroups of the population, such as medical card holders and non-nationals, may face greater difficulties than others in getting registered with a GP, with implications for equity of access to testing.

As already stated, the information provided as part of the invitation to participate should not be in a format that excludes certain groups. The information should be presented in sufficient translations and in a manner that is understandable given the varying levels of health literacy in the birth cohort. As described in Chapter 7.5, any information awareness strategy should be underpinned by a thorough investigation of the target audience's information needs.

If birth cohort testing is implemented in a primary care setting, there needs to be an awareness that access to primary care varies across the country. Particularly in more rural areas, there may be a substantial travel cost associated with attending the GP. Strategies can be considered to reduce this potential burden for individuals, such as ensuring that testing can occur as part of a routine GP visit and having a wide time window in which to avail of the programme. Given the large number of GP practices in the country, it is unlikely that any other setting could provide better accessibility for those availing of birth cohort testing while also being acceptable for taking blood samples. However, there may be scope for alternative approaches to improve access for some hard to reach groups, such as the use of mobile phlebotomy clinics.

Another point to note is whether those who miss testing when invited should be allowed to present for testing in a subsequent testing round. This may bias against those who are called in the final screening round, unless the opportunity to avail of testing is left open for a number of years after completion of inviting all members of the birth cohort. The considerations may be different for an opportunistic programme where it is clear that not all members of the birth cohort will attend a GP in a given year, and hence making the programme available for an extended period may improve overall uptake. Ongoing evaluation of uptake would enable a prospective assessment of when the programme might reasonably be discontinued.

Distinct from the testing component is the treatment of identified cases of HCV infection. The National Hepatitis C Treatment Programme (NHCTP) is currently structured to provide treatment for HCV through one of eight hospitals, six of which are located in the East of Ireland.[367] The requirement for travel and the accessibility of treatment centres may create a significant barrier for some. Initiatives to ensure that patients can avail of treatment and follow-up care may be important in some

regions. Hospitals with distributed rural populations may already have experience of how to overcome accessibility issues for patients being treated for HCV infection, and that knowledge can be used to support the effectiveness of birth cohort testing for HCV. In addition to geographic access, there is also the issue of timely access to treatment. Existing screening programmes have key performance indicators in relation to the time between diagnosis and treatment being offered. It should be borne in mind that the cohort with HCV identified through the testing programme were not patients prior to attending testing, and they should not be disadvantaged because of that in their access to timely treatment.

8.5.2 Use of resources

The significant resource consumption associated with birth cohort testing may reduce or delay access to assessment and treatment for people with clinically evident chronic HCV infection, if adequate resources are not put in place to ensure capacity to treat all cases of chronic HCV infection. The counter-argument could also be made that since HCV notifications have declined steadily since 2011, perhaps capacity exists to accommodate the additional cases that will be generated by birth cohort testing. While notifications do not necessarily represent incidence, they may act as a proxy measure when the rate of background testing is relatively constant. If birth cohort testing is introduced as a structured programme and on a phased basis, there will be the prospect of staggering the roll-out sufficiently to ensure there is sufficient capacity. Using a systematic approach to the programme offers a better prospect of controlling volume of testing and treatment than opportunistic testing. With a systematic programme, the flow of invites can be managed in response to uptake of testing and the prevalence of detected HCV infections. The likely uptake of testing is subject to substantial uncertainty. With a systematic programme it will be possible to monitor uptake and use that information to update the volume of programme invites being distributed.

The economic evaluation considered the costs and benefits of a HCV testing programme from the perspective of the publicly funded healthcare system. The cost-utility of a health intervention provides an estimate of value-for-money in a way that facilitates comparison across interventions and disease areas. As we operate in a fixed budget system, if a new intervention is introduced that requires resources, those resources must come from elsewhere in the system. If the new intervention is good value for money then it may be an efficient use of resources. However, if the intervention is not good value-for-money, then it is implied that it would be an inefficient use of resources to fund. The point at which an intervention is considered good value-for-money is referred to as the willingness-to-pay (WTP) threshold. In Ireland, there is no defined WTP for public health interventions, but thresholds of €20,000 and €45,000 per quality-adjusted life year (QALY) have been used as

reference points to support decision-making. On the basis of the economic evaluation, birth cohort screening (whether opportunistic or systematic) is cost-effective at a WTP threshold of €20,000 per QALY. The budget impact is also a relevant consideration, as it supports an assessment of affordability. An intervention may be good value-for-money but unaffordable. The converse is also true, as an intervention that is not considered good value for money may be affordable on account of few people being eligible for treatment.

8.6 Ethical consequences of HTA

The purpose of this section is to outline specific ethical issues that relate to the conduct of this HTA, including choice of outcomes, data sources and timing of the assessment.

8.6.1 Choice of outcomes

In carrying out a HTA, a technology is evaluated on the basis of one or more clinical outcomes. That is, how do the outcomes based on the intervention of interest compare to those achieved using a comparator, such as standard care? In this case, standard care is no birth cohort testing. While it is recognised that some cases would still be detected through one of the risk-based screening strategies in place, the focus of this assessment is on members of the birth cohort that would not otherwise be tested for HCV infection.

Common issues for clinical outcomes, particularly for chronic conditions, is the length of follow-up available from trial evidence and whether the measured outcomes are final, intermediate or surrogate endpoints. Sufficient follow-up is required to determine whether there is a real difference in outcomes and whether that difference is sustained. A final endpoint is the outcome of interest (for example, mortality). For an intermediate or surrogate outcome, a clear, plausible and demonstrated association with the endpoint of interest is necessary. Virological cure of HCV is defined using a surrogate outcome, sustained virological response (SVR).[242] The validity of SVR as a surrogate endpoint for successful treatment of chronic HCV infection is discussed in Chapter 4.6.

As previously outlined, patients with chronic HCV infection can remain asymptomatic for years and may never develop serious liver problems. Some patients with chronic HCV infection only become aware of their infection status once they have already developed cirrhosis and its complications.[16] As with any economic model, simplifying assumptions must be made to ensure that a highly complex set of possible pathways can be meaningfully represented with the available data. For example, a dynamic transmission model that could incorporate the benefits of reduced onward transmission was not used. In developing a model, a balance must be struck between accuracy and complexity. The standard approach to managing and evaluating the

impact of structural assumptions is to test them through sensitivity and scenario analyses (see Chapter 6).

This HTA assesses a programme of testing. While the cost of treatment is included, it is implicitly assumed that treatment will be available to all those who test positive. The cost of birth cohort testing is distinct from treatment, and the two costs are likely to be managed as two distinct budgets. If the budget for treatment were to run out before testing had been completed, for example, then there would be an ethical issue that has not been accounted for in the modelling process.

8.6.2 Timing of the assessment

A HTA is carried out at a point in time, and the timing of the assessment can be important. For many health interventions, the evidence base is dynamic as populations and interventions change. For example, an ageing population can have implications for the comorbidities amongst patients and treatment response. Costs for testing and treatment change over time, as do disease incidence and prevalence. As a consequence, the results of the cost-effectiveness analysis will change depending on when it is carried out. As the assessment is based on a fixed birth cohort, as that cohort ages the cost-effectiveness of the birth cohort testing may change: the potential benefits may reduce (e.g., due to shorter life expectancy with increasing age) while the costs may stay largely the same or even increase with inflation. In the context of HCV testing, timing has been important in terms of the availability of direct-acting antivirals (DAAs): they are effective and well-tolerated with a good evidence base, and for which systems have been introduced to dramatically reduce the price, making treatment affordable.

From a HTA perspective, over time it is generally anticipated that the evidence-base improves for a given intervention. The effect of improved evidence is often, but not always, to reduce uncertainty. With further trials, for example, our understanding of treatment effect often improves and the precision associated with the treatment effect increases. At the time of this evaluation, there is strong evidence around the diagnostic test accuracy of HCV testing, and in relation to the efficacy and cost of treatment. Much of the uncertainty in the analysis stems from the limited data available on the prevalence of undiagnosed HCV in Ireland, and the likely uptake of a birth cohort testing programme.

8.6.3 Data sources

The analyses included both Irish and international data. While high-quality Irish data existed for some of the parameters, epidemiological evidence related to disease progression were only available using international data with unknown applicability.

Given the substantial estimated budget impact of the testing programme, the limited evidence regarding the set-up and running costs of the programme should be noted. The development of a detailed implementation plan may facilitate a more detailed assessment of costs.

From an ethical standpoint, recommendations were made in the absence of complete Irish data; it is possible that this would make a difference to the interpretation of the results. However, through extensive sensitivity analysis using alternative values, the results are relatively robust and hence it is believed that it should not greatly impact the conclusions from an ethical perspective.

8.7 Discussion

This chapter considered the ethical issues that might arise with the introduction of a birth cohort testing programme for HCV in Ireland. In terms of the benefit-harm balance, the proposed testing programme would involve testing a large cohort with the knowledge that only approximately 1% will benefit directly through having HCV infection detected and treated. However, the risk of harms associated with testing are considered low. The testing approach has high sensitivity and specificity so the risk of false-positives and false-negatives are relatively low. Due to the stigma associated with HCV, birth cohort testing will have to be carried out in a manner that is sensitive to the stigma and ensure best uptake and treatment completion.

Birth cohort testing could, over a relatively short period of time, identify a large number of people infected with HCV compared to those detected through other means. The additional cases would create challenges for managing the timely treatment of patients within capacity constraints.

A number of important ethical considerations including issues relating to benefit-harm balance, acceptability and equity of access could be addressed by requiring any birth cohort testing to meet WHO criteria for effective screening programmes. That is, that it should include mechanisms for systematic invitation and follow-up, a participation rate of over 70% from the birth cohort, adequate infrastructure and resourcing to ensure diagnosis and treatment, and a monitoring and evaluation framework.

The other important ethical consideration regards the efficient use of resources. The birth cohort are not at higher risk than the rest of the population because of when they were born *per se*. Those who are at higher risk of HCV infection happen to be in that birth cohort and defining the cohort by year of birth simplifies identification of cases. However, testing such a large cohort to identify a relatively small number of cases may be a very inefficient use of resources that could be used more efficiently elsewhere in the system. The use of opportunistic testing may improve efficiency but may also adversely impact on the successful identification of those infected with HCV.

9 Discussion

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The aim of the HTA was to establish the clinical, cost-effectiveness and budget impact of offering one-off hepatitis C testing to all people in Ireland born between 1965 and 1985. This HTA considered the following domains:

- description of technology
- epidemiology
- clinical effectiveness and safety
- systematic review of the cost-effectiveness literature
- economic evaluation
- organisational issues
- ethical issues.

9.1 Background to the assessment

In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy for 2016–2021 on viral hepatitis which aims to eliminate viral hepatitis as a public health threat by 2030 with a particular focus on (hepatitis C virus) HCV infection. Elimination was defined as a 90% reduction in new chronic infections and a 65% reduction in mortality compared with the 2015 baseline. In Ireland, the National Hepatitis C Strategy 2011-2014 was the first published strategy relating to all those infected with HCV in Ireland. In 2015, a Public Health Plan for the Pharmaceutical Treatment of Hepatitis C was published by the Department of Health which recommended the establishment of a multi-annual national treatment plan that would ensure the most appropriate management of access to new treatments. The National Hepatitis C Treatment Programme (NCHTP) was established in 2015 to provide treatment across a range of healthcare settings to all people living with HCV infection with the aim of making hepatitis C a rare disease in Ireland by 2026.

An Irish National Clinical Guideline for Hepatitis C Screening was endorsed by the Minister for Health in 2017. It included a conditional recommendation to offer one-off testing to people born between 1965 and 1985 (that is, birth cohort testing). It was proposed that birth cohort testing (of approximately 1.5 million people) would be implemented in addition to, rather than in place of, other testing strategies. As birth cohort testing was anticipated to have significant funding implications, it was conditionally recommended, subject to the outcome of a full HTA.

The Health Information and Quality Authority (HIQA) agreed to undertake a HTA of implementing birth cohort testing for hepatitis C in Ireland following a formal request from the hepatitis C screening guideline development group. The aim of the HTA is to establish the clinical, cost-effectiveness and budget impact of offering once-off HCV testing to all people in Ireland born between 1965 and 1985.

9.2 Description of the technology

Birth cohort testing involves offering one-time testing for HCV infection to people born during a particular period of time. No prior ascertainment of risk is undertaken. Rather, for this cohort, there is evidence (such as epidemiological trends) of an elevated risk of exposure relative to the general population. The Irish birth cohort was identified based on national HCV surveillance and seroprevalence data which indicated that 72.5% of HCV cases were born between 1965 and 1985.

Birth cohort testing broadly conforms to the principles of screening outlined by the World Health Organization (WHO). However, given its once-off nature, birth cohort does not fulfil the principle of screening as a continuous process and therefore can be considered case-finding, which, although similar, is conceptually distinct from screening. The objective of case-finding is to identify people previously exposed to HCV in order to detect and treat those who have developed chronic HCV infection, rather than waiting for those people to present with symptoms of infection. Those within the birth cohort will continue to be offered risk-based screening for HCV, where appropriate (that is, in accordance with clinical guidance).

In accordance with the WHO criteria for effective screening programmes, a birth cohort testing programme should include mechanisms for systematic invitation and follow-up, a participation rate of over 70% from the birth cohort, adequate infrastructure and resourcing to ensure diagnosis and treatment, and a monitoring and evaluation framework. The structure, which may be systematic or opportunistic in nature, adopted by a birth cohort testing programme will influence the acceptability and uptake, as well as effectiveness and cost-effectiveness of testing. A systematic population-based programme is likely to improve equity of access, efficiency of resources and yield a higher participation rate than opportunistic testing.

Up to 2019, the US Centers for Disease Control and Prevention and the US Preventive Services Task Force were the only international organisations that had recommended birth cohort testing. In 2019, the Hellenic National Plan for Hepatitis C was published in Greece which recommended birth cohort testing for all adults born between 1945 and 1980. The extent to which eligible people have availed of testing based on these recommendations is unclear.

Diagnosis of chronic HCV infection involves two steps: (1) detection of an anti-HCV

antibody to indicate if a person has ever had acute HCV infection; and (2) a confirmatory nucleic acid test to verify active HCV infection through the detection of viral ribonucleic acid (RNA) or a core antigen test to detect HCV proteins in blood or oral fluid. The diagnostic accuracy of anti-HCV antibody, RNA and antigen tests will influence the effectiveness of birth cohort testing. Sensitivity is the ability of an index test to accurately identify those who have the condition. Specificity is its ability to correctly identify those who do not have the condition.

Early-stage HCV infection is curable and highly effective treatments are available. Over 95% of patients achieve a sustained virological response (SVR) following treatment with second generation interferon-free direct-acting antiviral (DAA) therapies. Successful DAA therapy reduces the risk of developing HCC, all-cause mortality and liver-specific mortality.

9.3 Epidemiology

HCV is a blood borne virus that predominantly affects the liver. At least six major HCV genotypes exist, each of which has its own subtypes. HCV has a high degree of genetic variability due to the virus's ability to constantly mutate as it attempts to evade the body's immunological response. The variability of the hepatitis C virus (in terms of genotypes, subtypes and quasi-species) has made it difficult to develop a vaccine that can protect against all HCV strains.

Acute HCV infection is generally defined as the first six months following infection with the virus. Individuals acutely infected with HCV may develop an immune-mediated response that results in spontaneous viral clearance of HCV. Between 55% and 85% of those acutely infected fail to clear the virus and develop chronic HCV infection, the progression of which is slow and unpredictable.

HCV has been a notifiable disease in Ireland since 2004. From 2004 to 2018, a total of 15,266 HCV cases were notified to the HPSC. Of these, 71% (n=10,862) were from the 1965 to 1985 birth cohort. In 2018, 61% (n=361) of all notifications were from the 1965 to 1985 birth cohort, yielding a notification rate of 24.1 per 100,000 population. Injecting drug use was the most commonly reported risk factor for acquisition of infection. The estimated prevalence of undiagnosed chronic HCV infection within the 1965 to 1985 birth cohort ranges from 0.35% to 1.15%. From 2008 to 2018, HCV genotypes 1 (58%) and 3 (37%) were most common in the 1965 to 1985 birth cohort.

There were 103 new cases of hepatocellular carcinoma (HCC) in 2016, but this likely represents an underestimate of the true liver cancer morbidity since more than one third of cases are reported without a subtype specification. The annual number of HCC cases has increased by 300% since 1994. Five-year net survival for cases of HCC was

estimated at 32.9% between 2011 and 2015. Based on international estimates, approximately 21% of HCC cases are attributable to chronic HCV infection. Chronic HCV infection is associated with substantial morbidity and mortality. Of patients from the 1965 to 1985 birth cohort registered with the HSE National Hepatitis C Treatment Programme (NHCTP) between 2018 and 2019, 15% had developed compensated cirrhosis of the liver. There were 128 liver transplants as a result of HCV-related complications between 2005 and 2018. A total of 176 HCV-related deaths occurred in 2016.

9.4 Clinical effectiveness

The sensitivity and specificity of laboratory-based serological tests for detection of anti-HCV antibodies, compatible with a diagnosis of current or past HCV, is estimated at over 99% and over 96%, respectively.

Diagnosis of chronic active HCV is based on detection of HCV-RNA or HCV core antigen. The limit of detection (sensitivity) of quantitative nucleic acid amplification tests (NAAT) for HCV-RNA ranges from 3.9 to 30 international units per millilitre, with a specificity of over 99%. Compared with NAAT, HCV core antigen tests have a sensitivity of 93% and a specificity of 99%.

Three first-line DAA therapies are available under a reimbursable list of preferred regimens recommended by the HSE NHCTP. The regimens are prescribed according to HCV genotype, prior treatment status and the presence or absence of liver cirrhosis.

Virological cure of HCV is defined using a surrogate outcome, sustained virologic response (SVR), and considered an acceptable proxy of cure. Interferon-free DAA therapies are highly effective; across all HCV genotypes over 95% of patients achieve an SVR. DAAs have a positive safety profile with very low (<5%) incidence of adverse events, serious adverse events, discontinuations due to adverse events and mortality. A cross-sectional study from the US reported no significant differences, in terms of SVR, between patients identified by birth cohort and risk-based testing for HCV.

9.5 Systematic review of economic evaluations

A systematic review of economic evaluations identified 18 studies from seven countries, published between 2012 and 2018. All were modelling studies that assessed the cost-effectiveness of birth cohort and or general population testing.

Treatment strategies included first and second generation direct-acting antiviral combinations and older interferon-based regimens. The cost per treatment regimen ranged from €4,852 to €71,116. The treatment duration, SVR rate and rate of adverse events varied substantially according to the treatment strategy employed. Of the

studies which modelled second generation DAAs, the rate of SVR ranged from 91-100% according to HCV genotype.

The level of uncertainty surrounding the cost-effectiveness of HCV testing was most sensitive to changes in population- and treatment-specific parameters. Population-specific parameters included the prevalence of chronic HCV infection, proportion of undiagnosed chronic HCV cases, fibrosis score of undiagnosed cases, age of the population and the test uptake rate. Influential treatment-specific parameters included the uptake rate, costs and efficacy of treatment.

Identifying and treating people with chronic HCV infection at an earlier age and or stage of infection generally led to improved cost-effectiveness as a result of better patient outcomes. Cost-effectiveness generally improved with the use of newer DAA combination therapies and a reduction in treatment eligibility restrictions. The estimated incremental cost-effectiveness ratios (ICERs) from 14 of the 16 studies that compared birth cohort testing with no testing or risk-based testing would be considered cost-effective at a willingness-to-pay (WTP) threshold of €45,000 per QALY gained. Study quality was variable, and none of the included studies could be considered directly applicable to Ireland.

9.6 Economic evaluation

An economic model was developed to estimate the cost-effectiveness and budget impact of introducing birth cohort testing in Ireland. The analysis compared the incremental costs and health benefits of systematic and opportunistic birth cohort testing programmes to the current approach of no formal birth cohort testing programme.

The economic model comprised a closed-cohort decision tree and Markov model hybrid which tracked the 1965-1985 birth cohort from the outset of the simulation until death. A staggered implementation is assumed, whereby the 1965-1985 birth cohort is split into four age-based subgroups and offered testing sequentially over a four-year period.

Both systematic and opportunistic birth cohort testing programmes were estimated to be more costly and more effective than no birth cohort testing in the base case. Compared with no birth cohort testing, the ICER for opportunistic birth cohort testing was estimated at €8,357 (95% CI: €843 to €19,699) per quality-adjusted life year (QALY) gained. Compared with opportunistic testing, the ICER of systematic birth cohort testing was estimated at €9,237 (95% CI: €1,384 to €21,632) per QALY. These estimates, which were robust in sensitivity analyses, are considered cost-effective at a willingness to pay (WTP) threshold of €20,000 per QALY gained.

The incremental budget impact of introducing a systematic birth cohort testing programme was estimated at €65 million over a five-year time horizon, compared with no birth cohort testing. The budget impact was most sensitive to changes in the uptake rate of testing, prevalence of undiagnosed chronic HCV infection and the background rate of detection. Over a five-year period, it was estimated that systematic birth cohort testing would lead to an additional 0.6 million primary care attendances, 0.6 million anti-HCV antibody tests, 8,930 core antigen tests and 2,792 patients receiving DAA therapy over the course of four years.

The ICERs were most sensitive to changes in the discount rate, the background detection rate of cases of undiagnosed chronic HCV infection (that is, the rate of detection without intervention), disease progression rates and the prevalence of undiagnosed chronic HCV infection.

9.7 Organisational issues

A systematic or opportunistic structure could be adopted for a birth cohort testing programme. A systematic programme would comprise a population-based programme where participants are invited to attend testing. An opportunistic programme would involve offering once-off testing as part of routine care when the patient interacts with the healthcare system for another reason, unrelated to testing (for example, a health check-up). Implementation of a systematic birth cohort testing programme could lead to a 1% relative increase in existing primary care activity over a four-year period, based on a testing uptake rate of 41%. If a higher uptake of testing is observed, then the demand on primary care capacity will be larger.

In this health technology assessment (HTA), it was assumed that implementation of one-off birth cohort testing will require a primary care consultation where a blood sample is drawn by a general practitioner (GP) or practice nurse. It is assumed that a single blood sample will be used for both the initial serological test and any subsequent confirmatory testing (that is, reflex testing). To undergo reflex testing, serum samples must be centrifuged and frozen within 6-24 hours of phlebotomy to ensure stability of the sample. Additional storage and labour capacity would be required in hospital laboratories to meet the requirements of preparing and storing approximately 160,000 additional samples per year over four years.

Alternative testing approaches include the use of an alternative test type (for example rapid diagnostic tests (RDTs) to detect anti-HCV antibody) or specimen type (HCV-RNA or antigen testing based on dried blood spots or oral fluid). These approaches have the potential to increase testing coverage, but at the expense of reduced diagnostic accuracy and implementation of additional quality assurance procedures. Furthermore, testing approaches that involve collection of specimens that are not

amenable to reflex testing have the potential of increased loss to follow-up.

Quality assurance mechanisms in accordance with best medical practice would be required to establish any testing programme. If implemented, guidance on testing and pathways for patient referral and follow-up should be developed in conjunction with the National Programmes for Pathology and Hepatitis C. General information services, including information leaflets, Freephone services and public awareness campaigns, could be used to support implementation of birth cohort testing. Physician-targeted prompts and educational interventions could also be used to enhance testing uptake rates.

A pilot programme, targeting areas known to have a high prevalence, may be considered if there are concerns regarding the feasibility, uptake and affordability of a national testing programme. The pilot programme would need to be of a suitable scale to allow identification of a sufficient volume of cases, so that the findings are informative for national policy.

9.8 Ethical considerations

In terms of the benefit-to-harm balance, the proposed testing programme would involve testing a large cohort with the knowledge that only approximately 1% will benefit directly through having HCV infection detected and treated. Testing such a large cohort to identify a relatively small number of cases may be a very inefficient use of resources that could be used more efficiently elsewhere in the system.

Birth cohort testing could, over a relatively short period of time, identify a large number of people infected with HCV relative to those detected through other means, such as risk-based testing. However, the additional cases could create challenges for managing the timely treatment of all patients within capacity constraints. The health service utilisation generated by birth cohort testing could displace other care, particularly in the primary care setting. The testing programme could create additional demand for primary care in excess of 1% per year, with consequences for the availability of services.

Due to the stigma often associated with HCV, birth cohort testing will have to be carried out in a manner that is sensitive to this stigma and ensure best uptake and treatment completion.

A number of important ethical considerations including issues relating to benefit-harm balance, acceptability and equity of access could be addressed by requiring any birth cohort testing to meet WHO criteria for effective screening programmes.

9.9 Conclusions

International targets have been established to ensure that viral hepatitis is eliminated as a public health threat. In Ireland, the Health Service Executive (HSE) aims to make hepatitis C a rare disease by 2026. The National Hepatitis C Treatment Programme (NHCTP) has noted that the downward trend in cases in Ireland since 2015 despite increased testing.

People living in Ireland born between 1965 and 1985 have been identified as the target population for birth cohort testing based on nationally available epidemiological data (that is, prevalence is highest within this cohort). Implementation of birth cohort testing will improve Ireland's chances of achieving the HSE's elimination target. However, any decision to implement birth cohort testing must be balanced with concerns regarding affordability. While it is estimated that birth cohort represents value-for-money in terms of the incremental cost per incremental health gain, the five-year budget impact is substantial and a high uptake of testing would have direct budgetary and health service capacity implications.

From published evidence, it is clear that the diagnostic tests used to detect chronic HCV are highly sensitive and specific, and that the currently available treatments are very effective. That said, adherence to the World Health Organization's criteria for effective screening programmes, particularly in terms of quality assurance and monitoring processes, will be key to successful implementation of a birth cohort testing programme. These criteria include obtaining high coverage and testing uptake rates in addition to monitoring of linkage to follow-up care and treatment outcomes.

A systematic testing programme adopting a staggered implementation would provide mechanisms for monitoring of programme performance and evaluation against pre-defined quality metrics in addition to managing the expected capacity implications across the clinical pathway. In the short term, the main capacity implications will fall on primary care and laboratory testing. The use of reflex testing may reduce the capacity implications on primary care and reduce the likelihood of patient drop-off, but reflex testing may not be logistically feasible from a laboratory perspective without the use of alternative sample collection such as dried blood spots which circumvent the need for centrifuge and freezing of samples. In addition, the rollout of a primary care-based testing programme would require general practitioners to opt in to the testing programme in order for patients to receive testing.

As considerable decision uncertainty exists in relation to key parameter data, further research on the likely uptake of testing (for example, surveying a representative sample of the birth cohort) would be sensible. In addition, in light of affordability concerns, the rollout of birth cohort testing could initially pursue a pilot programme

which could be phased into wider practice over time according to evaluation of the observed prevalence and yield of testing (that is, the coverage and identification of HCV diagnoses).

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