Cost effectiveness analysis of hepatitis C case finding strategies using direct linkage into care

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This work is dedicated to my wife Tanya,

who has helped me at every stage and been so patient.

I cannot wait to close this fantastic chapter and start the next

even more amazing one!

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Declaration of Originality

I declare that the work within this thesis is my own and all else is appropriately referenced.

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Abstract

It is estimated that more than 50% of persons with hepatitis C in the UK remain undiagnosed, which should be considered a failure of current screening processes. Further, treatment uptake is poor and linkage and retention to care is a significant barrier to virus elimination.

In this thesis we demonstrate the impact of long term linkage to care using the example of hepatocellular carcinoma surveillance. We demonstrate that in scenarios where patients are required to followed up long term, there are currently significant shortfalls in maintaining linkage to specialist services. In at least 40% of cases, lack of linkage was not due to patient related factors and were institutional failures. We also evaluated the impact of hepatitis C cirrhosis on hospital admissions. Patients who did not achieve SVR were associated with more frequent admission events and more days of admission. Whilst it is unclear if this was primarily associated with greater likelihood of advanced liver disease solely it does provide a compelling argument for treatment at earlier stages of disease. After demonstrating the burden of disease, health economic evaluation was performed comparing real-life screening and treatment outcomes in a drug-treatment unit, antenatal screening service and a homeless shelter. In all scenarios the screening was followed by direct linkage into specialist services aiming to increase retention. Finally a exploratory analysis was performed on a UK birth cohort screening programme using real-world age distributions of hepatitis C patients. All health economic analysis was performed using a validated hepatitis C natural history Markov modelling model.

Hepatitis C screening at varying viraemic prevalences as seen in the drug treatment unit (41%) and antenatal screening (0.16%) are demonstrably cost-effective as long as patients are appropriately linked up to care with specialist services to reap the benefits of SVR at earlier stages of disease and minimise onward virus related liver complications.

Abbreviations

AASLD	American Association for the Study of Liver Diseases
ALD	Alcoholic liver disease
Au	Australia antigen
BC	Base case
BCLC	Barcelona Clinic Liver Cancer classifications
BOC	Boceprevir
CDC	Centers for Disease Control and Prevention
cDNA	Complimentary deoxyribonucleic acid
CEA	Cost effectiveness analysis
CLIA	Chemiluminescence immunoassay
CT	Computed tomography
DAA	Direct acting antiviral
DBS	Dry blood Spot
DTU	Drug treatment unit
EAP	Early access programme
EASL	European Association for the Study of the Liver
EIA	Enzyme-linked immunosorbent assay
eRVR	Extended rapid virologic response
ESLD	End stage liver disease
FDA	US Food and Drug Administration
HAV	Hepatitis A virus
HBV	Hepatitis B virus

HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
ICER	Incremental cost-effective ratio
ICHNT	Imperial College Healthcare NHS Trust
IDU	Injection drug use
IFN	Pegylated-interferon alpha
ITU	Intensive Care Unit
FSS	Fatigue Severity Score
GT4	Genotype 4
HAI	Health Action International
HPA	Health Protection Agency
HQRL	Health-related quality of life
LDV	Ledipasvir
LMIC	Lower and Middle Income Countries
LPGW	Lowest paid unskilled government worker
LYG	Life year gained
NASH	Non-alcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Clinical Excellence
NWDAS	North Westminster Drug and Alcohol Service
MELD	Model of endstage liver disease
MONARCH	Modelling the natural history and cost effectiveness of hepatitis C
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
PCP	Primary care providers

PCR	Polymerase chain reaction
PWID	Person who inject drugs
QALY	Quality-adjusted life-year
Q-Q	Quantile- quantile
RBV	Ribavirin
RIBA	Recombinant immunoblot assays
RNA	Ribonucleic acid
RT-PCR	Real-Time polymerase chain reaction
RVR	Rapid virologic response
SA	Sensitivity analysis
SMV	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virologic response
TACE	Transarterial chemoembolization
TVR	Telaprevir
UAM	Unlinked Anonymous Monitoring
USA	The United States of America
USPSTF	United States Preventative Services Task Force
UKELD	United Kingdom Model for End-Stage Liver Disease
USS	Ultrasound scan
WHO	The World Health Organisation

Publications arising from this thesis

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1 General Introduction

1.1 Hepatitis C Virus

Hepatitis C virus (HCV), a hepacivirus from the Flaviviridae family, was first described in 1989 following the isolation of complimentary deoxyribonucleic acid (cDNA) from chimpanzee serum [1]. Until the 1970's the only recognised forms of viral hepatitis were hepatitis A virus (HAV) [2] which was spread faeco-orally and hepatitis B which was initially denoted as Australia (Au) antigen after being identified in the blood of an aborigine [3].

In 1974 the existence of a third form of viral hepatitis was shown when epidemiological studies demonstrated that the majority of transfusion associated hepatitis did not identify either hepatitis A nor B [4, 5]. Subsequently a new disease, denoted as non-A, non-B hepatitis was identified. Chimpanzee studies demonstrated a 60nm transmissible virus [6] that caused both acute and chronic hepatitis [7, 8].

Following the isolation of cDNA by Choo and colleagues, the encoded protein reacted with antibodies from patients with non-A, non-B hepatitis which led to the development of anti-HCV antibody serological assays [9]. HCV was characterised as a 3000 amino acid polyprotein encoded from a single-stranded positive sense ribonucleic acid (RNA) virus [10]. Subsequently HCV was discovered as an important cause of post transfusion hepatitis.

1.2 Transmission and epidemiology

Hepatitis C is a blood-borne virus and is transmitted from person to person via blood-to-blood contact from an infected person. In developed countries the most common route for transmission of hepatitis C is intravenous drug use, and historically through blood transfusions [11]. The latter of which has become rare since 1990 with the onset of HCV screening in blood [12]. In a case control study from the United States of America, 2316 blood donors that tested positive for HCV were assessed for likely routes of acquisition. They were compared to 2,316 seronegative donors matched for age, sex and race/ethnicity [13]. The associations to following exposures were:

- Intravenous drug use – odds ratio 49.6
- Blood transfusion – odds ratio 10.9
- Sex with an intravenous drug user – odds ratio 6.3
- Having been in jail more than three days – odds ratio 2.9
- Pierced ears or body parts – odds ratio 2.0

Deaths related to hepatitis C are increasing. It is estimated that there were 333,000 deaths globally in 1990 due to HCV, increasing to 499,000 in 2010 and 704,000 in 2013 [14]. This is likely to be a reflection of widespread transmission in the 1940's and 1950's following iatrogenic procedures and injecting drug use behaviours [15]. Following it's discovery, the incidence appears to have declined from the 1990's as a result of better awareness and safer practices both in healthcare scenarios and amongst persons who inject drugs (PWID). However, persons infected in the last 30-60 years are now increasingly presenting with HCV cirrhosis and hepatocellular

carcinoma (HCC) and this is projected to be an on-going problem for several more decades [16-18].

In the UK it estimated by Public Health England that around 214,000 individuals are chronically infected with HCV and injecting drug use remains the most important risk factor. In England, within this high risk population it is reported that testing rates are rising year on year. However in 2014 in an Unlinked Anonymous Monitoring (UAM) survey, only 52% that were HCV positive were aware that they were HCV positive and only 18% have received any therapy for HCV. Whilst hospital episode statistics and death certification commonly underestimates true numbers of admissions and deaths, HCV was attributed to 950 hepatocellular carcinomas in 2004 which rose to 2,658 in 2013. HCV related deaths in 2004 were recorded at 190 compared to 424 in 2013. There were 45 liver transplant registrations due to HCV cirrhosis in 1996 and 175 in 2014. It is projected that by 2025, if up-scaling of treatment is not introduced, there could be up to 12,510 patients with HCV related cirrhosis or hepatocellular carcinoma. [19].

Recent estimates conversely suggest that the global prevalence of HCV may be lower than previously thought. A 2013 systematic review estimated that 185 million persons are HCV antibody positive i.e. history of exposure, of which 130-150 million are chronically infected [20]. However more recently a systematic review that excludes older studies estimates only 80 million have chronic infection [21]. These lower estimates are thought to reflect both improved transmission prevention but also improved testing with lower false positive rates. These figures still reflect an important global problem and should not distract from the on-going burden of disease

caused by manifestations of end stage liver disease (ESLD) and HCC. However, if correct the potential lower numbers of infected persons provides encouragement that global eradication may be a relatively less daunting feat than previously envisaged.

Owing to the shared routes of transmission, those infected with HIV have a greater risk of co-infection with HCV and vice versa. Whilst it is frequently cited that 4 millions persons are co-infected, there are no reliable sources for this estimation.

HCV has a highly variable genome and 6 predominant genotypes each with various subgenotypes [22] which have variable responses to treatment. These distribution of genotypes is highly variable in different global areas as demonstrated in Figure 1.1. Genotype 1 accounts for 46.2% of HCV infections and is the most common, followed by genotype 3 which accounts for 30.1%.

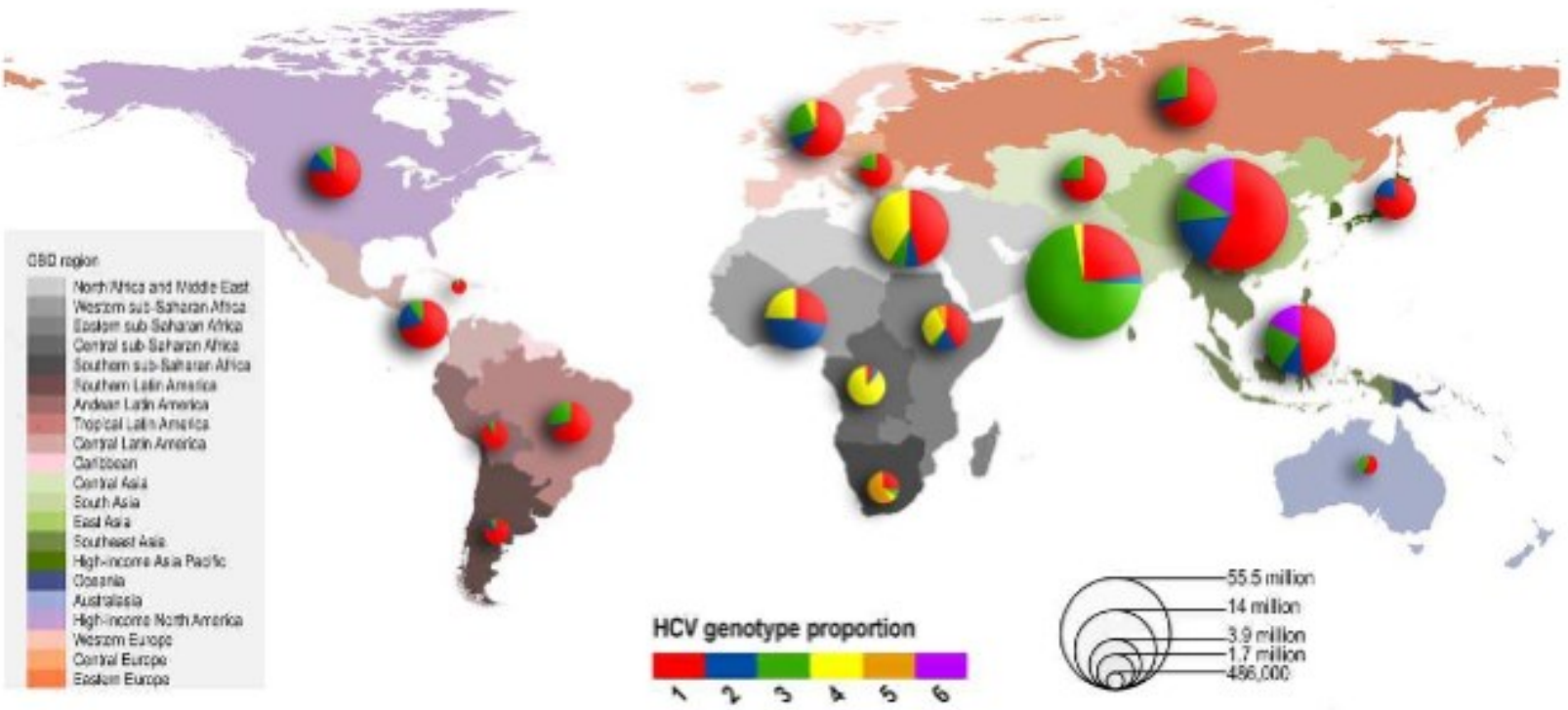


Figure 1.1 Global distribution of genotypes of HCV [23] with genotype 1 (red); genotype 2 (blue); genotype 3 (green); genotype 4 (yellow), genotype 5 (amber) and genotype 6 (purple) proportions demonstrated per region.

1.3 Diagnosis and Virological markers

Screening for HCV is primarily performed using an anti-HCV antibody (anti-HCV Ab) assay. This is performed using enzyme-linked immunosorbent assay (EIA) or chemiluminescence immunoassay (CLIA) [24, 25]. However anti-HCV Ab are often undetectable for the first 45-68 days in which recombinant immunoblot assays (RIBA) may help confirm diagnoses [26, 27]. Presence of HCV ribonucleic acid (RNA) is a highly sensitive diagnostic marker of chronic HCV infection if detected 6 months after exposure but is too expensive to initiate as first line screening [24-26]. Multiplex bead assays and Dried Blood Spot (DBS) testing in high-risk groups enable a low-cost and accurate screening method. However, point of care HCV RNA testing still requires further advancements. Whilst increasingly testing kits are demonstrating improving sensitivity and specificity, cost remains a barrier for use in nationwide screening programmes [28].

1.4 Natural history of chronic hepatitis C

Persons infected with hepatitis C develop an acute hepatitis which is commonly minimally or asymptomatic and therefore often goes unnoticed. Chronic hepatitis C is defined as the presence of active replicating virus 6 months following infection. It is widely believed that chronic infection develops in 70-80% of infected individuals with 10-20% progressing to liver cirrhosis within 20 years [29]. These figures were derived from post-transfusion hepatitis C, but other outbreaks due to iatrogenic causes included contaminated rhesus immunoglobulin in the 1970's [30, 31]. In these,

predominantly younger women, demonstrated a milder course with rates of chronicity between 55-60% and rates of cirrhosis of around 5% after 15-20 years.

Liver related disease progression is driven by immune response against infected hepatocytes which are the primary locus for the virus. Fibrosis develops as a consequence of chronic inflammation. There is variability in fibrosis progression, although in immunocompetent individuals progression to advanced fibrosis occurs over a period of decades. Factors that are associated with more accelerated fibrosis include patient age, age at acquiring of infection, male sex, metabolic syndrome, immunosuppression, HIV and history of excess alcohol consumption [32, 33].

The progression of HCV through stages of fibrosis tends to occur without any symptoms or occult symptomology. However the development of cirrhosis represents irreversible parenchymal damage which infers a more severe prognosis and often the development of overt symptoms. Compensated cirrhosis (where despite irreversible liver parenchymal fibrosis overall liver function is preserved) is attributed to an estimated annual mortality or transplant rate of 4.6% [34]. Cirrhosis progresses from a state of compensation to a state of decompensation (where liver function is impaired) or end-stage liver disease (ESLD) at a rate of 2-4% per year [35]. HALT-C a large prospective follow-up of hepatitis C patients with cirrhosis suggests that once progression of cirrhosis from a compensated state to decompensated there is a 13% risk of complication, 3% risk of hepatocellular carcinoma and 10% risk of mortality annually. 5-year mortality in patients with compensated cirrhosis is 91% but once decompensated is up to 50% per year [36]. Summarising this natural history data,

prevention of cirrhosis and particularly decompensation is critical if hepatitis C related complications are to be avoided in a patient's lifetime.

1.5 Impact of HCV at a societal level

The impact of hepatitis C at societal and work productivity level has been extensively reported but many of the studies have significant limitations. To date the majority of the evidence for impact of HCV on work productivity is based on qualitative data gathering from clinical trials. Many of these studies are post hoc analyses and the trial populations studied are unlikely to be representative of "real world" scenarios. Analyses are conducted on observed data and given that subjects report their findings at study visit time-points and not in real time means that results are subject to recall bias.

The CDC report an estimated 4 work loss days in a 12 month period in 2007 for US employed adults aged 18-64 regardless of health history [37]. It is reported that for 0.75 days per month, sufferers of hepatitis C are unable to work, suggestive of a significant burden of disease [38]. A post hoc analysis of 1147 patients who enrolled in a phase 3 clinical trial 22% reported unemployment at baseline. Of which 38% attributed their work status to health reasons, and those unemployed were significantly more likely to have more disabling fatigue, as measured by Fatigue Severity Scale (FSS). Approximately 7% of all employed patients reported worked shorter hours, and 9% reported that work based productivity was lower due to hepatitis C related health issues. During treatment with telaprevir, pegylated interferon and ribavirin increased levels of unemployment, inability to work until 24-

48 weeks post completion of treatment where values returned to baseline. After controlling for baseline characteristics (i.e. race, age, gender and fibrosis stage) the only predictor for inability to work within the preceding 4 weeks during treatment was baseline Fatigue Severity Score [39]. It is suggested that achievement of SVR12 leads to significant improvement in patient related outcomes and work productivity. However, interferon is associated with negative patient related outcomes during the course of the treatment which returns to baseline by the end of 12 weeks post treatment. Despite interferon causing significant work productivity losses during treatment neither treatment regimen was associated with an increased likelihood of stopping working [40].

In Spain data collected from national registries between 2007-2011 was used to estimate productivity losses due to premature deaths attributable to hepatitis C infection. During the period studied it was estimated that over €1 billion of total productivity loses could be attributable to HCV infection [41]. In a recent study based on data provided during an interferon free phase 3 clinical trial of genotype 1 hepatitis C, absenteeism (inability to attend work) and presenteeism (attendance at work but with reduced productivity) of persons involved in the trial were used to model at a US population level. Within the study population 7.83% exhibited absenteeism and 2.57% presenteeism before initiation of therapy. It was estimated that respectively the cost was $3,706 and $1,248 per patient per year. As a result if extrapolated to a population level this would incur an annual societal cost of $7.1 billion when only considering genotype 1 hepatitis C in the USA. Furthermore the interferon free treatment studied (ledipasvir and sofosbuvir) led to 93% SVR within the trial study

population of 1,923 US patients with an estimated $2.7 billion productivity loss saving over the first year time horizon [42].

1.6 Paradigm shift in treatment availability and acceptability

A key driver of interest in improving case finding of HCV is the emergence of the newer direct acting antiviral (DAA) agents which allow for treatment with shorter durations, higher efficacy, reduced adverse events, and therefore greater acceptability [43]. For more than a decade standard treatment has been based on pegylated interferon and ribavirin for 24 or 28 weeks with sustained virologic response (SVR) rates between 40 to 80% at best [44]. The more recent emergence of protease inhibitors such as boceprevir and telaprevir for genotype 1 patients only enhanced chances of SVR from 40% to 80% but at the expense of poorer tolerability due to significant adverse events [45]. More recently a variety of protease inhibitors, polymerase inhibitors and NS5A inhibitors have received Food and Drug Agency and European Medicines Agency approval. A major limitation to wide-scale use and up-scaling of therapies, to date, is relatively increased treatment costs. However the introduction of competitive tiered pricing and generics is facilitating a progressive increase in their use in developed countries. More recently emerging new medications potentiate a once daily, all oral, pan-genotypic treatment for 12 weeks with near universal SVR regardless of fibrosis stage, decompensation, and genotype [46-48].

1.7 Cost Effectiveness Analysis (CEA)

Allocation of costly medicines is a perennial challenge with complex ethical and economic implications. Various principles have been proposed, including morally relevant values such as treating people equally, giving priority to the worst off and saving the most lives [49]. From a public health perspective the ideal would be to make treatment universally accessible. In the UK, the National Institute for Health and Clinical Excellence (NICE) uses economic analyses for the evaluation of medicines, diagnostic techniques and healthcare technologies [50].

Decision modelling uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated. Such models provide probabilities of consequences allowing evaluation of expected cost and expected outcomes of each evaluated option. For a given option the expected cost is the sum of the costs of each outcome weighted by the probability of that outcome. A key aspect in such modelling is allowance for variability and uncertainty with all decisions [51].

Economic evaluation in health considers impact of cost and health outcomes of new interventions either compared to current standards or compared to no intervention at all [52]. In the context of healthcare, measures of outcome and improvement can be variable. Specific examples include percentage blood cholesterol reduction in those at risk of ischaemic heart disease or improvement in peak flow rates in asthmatics [53, 54]. Screening strategies can also be evaluated with regards the immediate impact of a positive diagnosis found where the natural history of the disease is that of rapid

onset of symptoms and risk of mortality, for example breast cancer true positive cases picked up through screening [55]. However when considering screening in conditions which evolve over longer periods of time, the relevance of a positive outcome may be minimal when only looking at short term measures. Furthermore increasingly in an era of resource allocation, cost effectiveness analyses are based on measures that are comparable across different evaluations. In particular quality-adjusted life-year (QALY) is the most frequently used measure for this purpose.

Using health-related quality of life (HQRL) metrics, a patient's quality of life per year is assigned a "quality weight" or value between 0 and 1 which represents the individual's health utility for that year [56, 57]. A perfect year of health being assigned a value of 1. In a cost effective analysis QALY is used as a measure of effect [52]. The use of QALY primarily reflects health related quality of life but also acts as a surrogate marker of the impact of an intervention on length of life.

Standard cost-effectiveness analysis involves comparison of differences in costs between interventions assessed whilst also comparing the differences in benefits. Interventions that cost less and generate greater effects than comparative interventions are considered unequivocally cost-effective, and in these situations are referred to as being "dominant". If an intervention incurs additional cost but with sufficient additional benefits it may still be considered cost effective. In such a situation the incremental cost and effects are compared with those of other uses of healthcare resources. The question for policy makers is whether the QALYs generated outweigh the cost incurred. In order to provide comparison across a range of interventions a

simplified calculation of the incremental cost-effective ratio (ICER) is used my many policy makers when assessing the economic benefits of an intervention. The ICER is calculated as:

$$\text{ICER} = \frac{\Delta \text{ Cost between interventions}}{\Delta \text{ QALYS between interventions}}$$

In the UK, the National Institute of Clinical Excellence (NICE) undertakes economic appraisal of new technologies and a willingness to pay threshold of between £20,000 to £30,000 is commonly applied [58]. Cost effectiveness literature has been based on arbitrary value assignment to utility gain, with unclear origins of practice. Specifically, the £20,000 or $50,000 willingness to pay per QALY is not based on any specific economic science. In it's essence they were originally derived as a mechanism for comparison of interventions, however with time policymakers have used fixed values and willingness to pay thresholds for formal policy making. To put in context the value of willingness to pay is irrespective of the utility used (i.e. same financial willingness to pay for a QALY compared to life year gained) [59]. Further these figures are independent of the total or proportion of budget available at a given time that could be focused on a specific resource.

1.8 Current hepatitis C screening strategies

UK HCV testing comprises screening all donated blood units and those with increased risk such as injecting drug users, prisons, healthcare workers, and migrant populations from high HCV prevalence countries according to NICE guidelines [60]. In the UK, screening is aimed at high-risk individuals as prevalence of HCV in the general population is low. It is not considered currently to be cost effective to screen outside of such high risk populations [61].

Whilst cost is an important consideration for a screening programme, screening committees apply stringent requirements to be satisfied to ensure that the benefits of screening outweigh negative effects. The WHO criteria for screening as described by Wilson and Junger require the following points to be satisfied [62]:

- The condition should be an important health problem.
- Accepted treatment for patients recognised with disease
- Facilities for diagnosis and treatment
- There should be a test or examination for the condition and treatment, with an agreed policy on whom to treat
- Facilities for diagnosis and treatment should be available.
- There should be a latent stage of disease and the natural history understood
- The cost of case finding 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

Various strategies of hepatitis C screening have been evaluated previously. Broadly speaking screening has been evaluated within general populations, birth cohorts – with the aim of identifying high risk age groups, screening within high risk groups such as prisoners and patients with injecting drug use (PWID) and antenatal populations. Systematic review highlights that cost effectiveness within screening are dependent on input parameters of population groups being screened, prevalence and understanding of disease incidence [63].

1.8.1 Screening High risk groups

Currently UK screening is focussed on high-risk populations such as persons who inject drugs, prisoners and blood donors. Various cost effectiveness analyses have been used to evaluate these measures.

1.8.2 Prisons

Global estimates for prevalence of hepatitis C in Prisons varies considerably, in Western Europe it is estimated to be 30% [64]. In the UK, HCV testing in prisons is meant to be "opt-out" although actual rates of testing remain variable and in the main suboptimal. In Scotland, a review of practice since 2009 demonstrates that treatment outcomes of prisoners with HCV, who are not being transferred or release during therapy, can be comparable to matched cases treated in the community [65].

A technical cost effectiveness evaluation, estimated that doubling of prison testing rates with current interferon based therapies would result in an ICER of £19,850 per QALY. When considering a situation where those eligible would be given 8-12 weeks

of DAA only regimes whilst in prison could improve cost effectiveness with ICER of £15,090. In both scenarios it was assumed that the mean referral rate for treatment in prison was 2.5%. In both scenarios if treatment rates increase, there is an exponential decline of ICER up to about 10-15% treatment rates and then a more gradual improvement of ICERs. If current treatment strategies were used, testing was doubled and 15% were treated in prison then with current therapies the ICER would be approximately £10,000 per QALY and £5000 per QALY with DAA only 8-12 week regimens [66].

Tan and colleagues performed cost effectiveness analysis of the potential prison population in the US, based on natural history data for general population HCV [67]. They used Markov simulation, combining treatments with interferon and ribavirin in a US prison population compared to no treatment. They assessed cost of liver biopsy and sub-analysed for age groups and fibrosis stage within their modelling. Liver transplantation costs were not considered in this population. The demographics were based on a US prison population being 87.3% male, with a genotype 1 prevalence of 78% and SVR of 42%. Looking at a target population of 40-49 year olds they report $41,321 saving with a QALY gain of 0.75 when comparing treating prisoners with HCV compared to no treatment. Within the sensitivity analyses, only genotype 1 patients with no fibrosis aged 40-49 were deemed non cost effective with $3,367 increased cost with 0.01 QALY gain i.e. ICER of $336,700. Limitations within this study was the lack of prospective data for treatment outcomes in a prospective cohort of prisoners. Major limitations for treatment of prisoners in real-life practice is inability to treat during incarceration and therefore practical difficulties of linkage into care. The natural history of HCV in the prison population has also not been

studied extensively. Within this study, no account was made for the higher prison population of African Americans who have been shown to have reduced treatment efficacy outcomes [68].

In UK prisons HCV prevalence has been quoted to be more modest and in one study as low as 7% [69]. Cost effectiveness work using two hypothetical models comparing screening of all individuals on reception into prison followed by possible later screening in the community compared to those only tested and treated in the community at a later date was not demonstrated to be cost effective by Sutton and colleagues [70]. However probabilistic sensitivity analysis demonstrated extensive uncertainty about the estimate of cost per QALY of £54,852.

Further real life UK prison studies performed in Dartmoor prison and Isle of Wight Prison has shown uptake of screening to be low 8.5-12%, albeit with up to 30% seropositivity. Furthermore, linkage in to care was shown to be poor with high rates of attrition. Despite the high incidence of HCV within these populations less than 7% actually underwent treatment. In both papers the authors concluded that it was not clear how eradicating HCV in prisoners could be improved.

1.8.3 Persons who inject drugs

Injecting drug use remains the most important risk factor for HCV infection in the UK. In England, it is estimated by Public Health England that 50% of persons who inject drugs (PWID) are positive for HCV antibody with regional prevalences in PWID populations ranging from 29% to 66%. Whilst it appears testing in this

population is becoming more common place with 61.2% tested in 2013/14 compared to 18.1% in 2006/7 only 18% report any previous treatment for HCV [19]. A systematic review of treatment uptake in PWID suggests similar issues in other developed countries with less than one in three identified undergo antiviral therapy [71]. It has been reported that when relying on attendance to hospitals or specialist clinics high drop out rates are problematic in the PWID population [72].

Previous economic modelling has suggested that providing antiviral therapy to PWID is cost-effective in settings where prevalence is at least 20%. It is believed that modest increases in treatment uptake within PWID populations (26/1000 annually) could reduce HCV prevalence by up to 86% over a 10 year period [73]. It is projected that within higher resource settings the prioritisation of treatment in PWID will substantially impact on incident infection, and reduce the numbers of infections from 600 cases in 2015 to less than 50 cases per year within a decade, assuming treatment uptake is doubled [74].

Four separate cost effectiveness analyses have been published in PWID evaluating screening compared to no screening demonstrating costs per QALY gained between £9,300 and £28,000 [69, 75-77]. Stein et al. performed a technical analysis using a decision tree model followed by Markov modelling for screening with ELISA followed by PCR and treatment using pegylated interferon and ribavirin. It was estimated that 49% would accept screening. The decision tree, relied on acceptance of a liver biopsy (assumed at 77% of those tested positive), and that treatment would only be initiated in those with moderate disease. In this study it was assumed that 50% of those that were eligible for treatment, i.e. with moderate disease, would accept

treatment. In the modern era, the use of interferon based therapy and thresholds to treat are lowering. This strategy was estimated to incur a cost of £28,000 per QALY. The authors report that the findings were sensitive to proportions of HCV positive people that accepted biopsy and then treatment. At a threshold of biopsy acceptance above 50% the ICER remained at a relatively constant level between £25,000 to £30,000 per QALY. However exponential increase in QALY was incurred at lower proportions, approximately £40,000 per QALY at 30% to £75,000 per QALY at 10% [76]. It can be extrapolated from this that cost effectiveness of screening is contingent in treatment uptake rates.

Castelnuovo et al. evaluated the effectiveness of testing for HCV amongst former injecting drug users using a decision analytic model to investigate the impact of case finding and treatment progression in a hypothetical cohort of 1000 people, compared to no testing. The authors evaluated screening within the setting of drug treatment units (DTU), primary care and UK prisons. Whilst overall it determined that screening and treatment of this population would be cost effective at a cost of £16,514 per QALY. However whilst this technical report concludes that testing in DTUs is likely to be the most cost effective on account of high prevalences, it assumes acceptance of testing at only 49%. The study also assumes that 77% of those testing positive from a DTU would have appropriate referral with only 20% attending specialist services. Within the modelling assumptions made in this study progression to treatment is contingent on having a liver biopsy [69].

Other UK cost effectiveness strategies of screening IDUs include in primary care suggests a cost effective approach with an ICER of £16,000 per QALY. Whilst

theoretically this approach may have merit, it is unclear how practical such a screening approach will be given that many currently injecting drug users may have limited interaction with primary care and those that were previously IDUs may not necessarily be identified by traditional risk base screening in primary care [77].

1.8.4 Birth Cohort Screening

In the United States of America, population screening has been introduced offering all persons born between 1945-1965 a one-time screening for HCV regardless of risk factors or symptoms. Various birth cohort screening studies have assessed implantation in the United States [78-80]. The Centers for Disease Control and Prevention (CDC) guidelines advocating one time testing in the United States for HCV for all persons between 1945 and 1965 [81]. Compared to risk based testing this has been shown to be cost effective although projected costs for this strategy in the United States equate to $1.9 billion in testing costs. However projected costs of treatment are around $25.9 billion for an extra 551,800 cases diagnosed. In the context of the United States population, these costs are outweighed by the costs of chronic hepatitis C with calculated ICERs of $4,200 to $28,602 [78, 82]. Sensitivity analyses in this population demonstrated greater costs when treating older patients with lower QALY gain than treating younger patients. Outside of the USA, birth cohort screening to date has not been widely evaluated within the published literature.

1.9 Other novel screening strategies

1.9.1 Antenatal screening of hepatitis C

The National Screening Committee has robust criteria for disease screening in the UK. Currently infectious disease in pregnancy screening is confined to Hepatitis B, Human Immunodeficiency Virus, Rubella and Syphilis. Thus far the National screening committee in the UK have ruled that screening for hepatitis C in pregnancy is not warranted. Thus far there has been a lack of evidence for cost effectiveness [83]. Ribavarin, the backbone of treatment for over a decade is a teratogen. However the introduction into clinical practice of newer direct antiviral agents against hepatitis C mean that ribavirin may in the future be no longer required in treatment and treatment durations may be as short as 8-12 weeks. This brings the theoretical possibility of treating mothers in the second and third trimesters of pregnancy and curing them of the virus and therefore preventing the vertical transmission of the virus.

To date there have been only a few reported cost effective analyses of antenatal hepatitis C screening with limited quality publications. In 2000, Ward et al. published data from a cohort of antenatal screening of women at St Mary's Hospital that were offered HCV screening [84]. Between 1997 and 1999, a total of 4825 women attended antenatal care at St Marys. Ninety eight per cent of women opted in for HCV testing of which the overall prevalence of HCV was 0.8%. Of these the majority (69%) were new diagnoses and 73% of these new cases had no identifiable risk factors. This programme allowed linkage into care with newly diagnosed women seen in joint

antenatal and family clinics to provide multidisciplinary care for mother, child and contacts.

Antenatal HCV testing provides an opportunity for asymptomatic women with a chronic disease to benefit from therapy. From the original cohort in this study 83% of infected women attended follow-up and further investigations. This is highly favourable compared to other settings where there is a high incidence of non-attendance. Antenatal screening may therefore identify infected women that are motivated and receptive to medical treatment. Their profile of being young and generally fit makes them also more favourable in terms of likelihood to respond well to treatment. This publication did not report on the overall treatment outcomes for the newly infected mothers and also any analysis into the cost effectiveness of treatment.

Similar work has been performed in Vienna and Dundee looking at universal screening compared to targeted screening of high risk mothers during the antenatal period. Interestingly the Vienna group reported no major differences in pick-up rates between the two groups [85]. Perhaps less surprisingly, the Dundee cohort demonstrated significantly higher pick-up in pregnant women who were injecting drug users (41%). However they still reported an overall HCV prevalence of 0.3% in the women who were screened without high-risk behaviour [86].

Of interest both the St Mary's and Vienna studies demonstrated a significant pick-up of women that had no discernable risk factors (73% and 21% respectively). This would mean that these women may never have been diagnosed until symptomatic from their hepatitis C.

Plunkett et al. have performed cost effectiveness work on antenatal screening of hepatitis C, and report estimated $1.17 million per quality adjusted life year (QALY) [87]. They evaluated cost effectiveness from the point of view of mother and child. Given the low vertical transmission rates of 3% this is likely to account for their findings of non-cost effectiveness. Secondly their model does not seem to account for the young age and therefore potentially longer durations of infection with subsequent increased likelihood of progression of disease. Finally, this study evaluates as one of it's strategies to use caesarean section for mothers with HCV which in a US healthcare system is a costly measure. It is now understood that caesarean section does not reduce rates of vertical transmission.

Urbanos et al. more recently published cost effective results in a Dutch cohort. Similar to previously reported the HCV prevalence within the Dutch pregnant population was 0.3%. Overall out of 4,563 screened 15 were diagnosed with HCV and only 2 were Dutch and 1 other western ethnicity with the remaining 12 from non western countries. Their group published calculated incremental cost effective ratio (ICER) of €52,473 which is above the European accepted threshold of €50,000 [88]. Within their modelling they seem to understate the transition rates from asymptomatic to symptomatic. Further, outcome rates do not seem to be adjusted for the younger age and better responses in this population with likelihood of shorter treatment durations. Finally, the costs of screening quoted are higher than would be expected in the UK. The final output was based on incremental cost effectiveness ratio on life year gained. However given that screening would detect HCV infected women years earlier it would prevent severe complications in later life when the disease would have

progressed from the asymptomatic phase. Therefore the more commonly used health related quality of life (QALY) would seem a more appropriate output in this situation.

In contrast to the outcomes of the 2 antenatal screening cost effectiveness studies described above, assessments of general population screening in the USA, Japan and Italy have all demonstrated cost effectiveness [82, 89, 90]. These studies also demonstrated increased cost effectiveness in younger populations. By accounting for age these studies better represent the greater burden of disease in the lifetime of people infected at a younger age.

1.9.2 General Population Screening:

The National Health and Nutrition Examination Survey (NHANES) suggest that 49% of the general population infected with hepatitis C are unaware of their diagnosis [91]. Furthermore, separate studies have demonstrated that up to 75% of chronic hepatitis C infected patients have no discernable high risk factors [84, 85]. This supports the notion of universal population based screening.

In the United States general population one time screening of the adult population (aged 20-69) was considered with a one time intervention in a decision analytic modelled followed by a Markov model defining the natural history, costs and quality adjusted life years (QALYs) of chronic hepatitis C [82]. The decision analytic model reflects the screening strategy algorithms based on a conservative estimate that 15% of the general population would be screened. The Markov model followed a person 45 years of age with annual transitions and standard mortality. Fibrosis was fairly

evenly distributed among each stage, and stratified by genotype 1 or 2/3. The model allows patients who fail treatment before developing cirrhosis to be retreated when cirrhotic.

Direct medical costs were only considered and based on 2010 Medicare prices. The model estimated costs and lifetime QALYs and was discounted at the recommended rate of 3%. The authors report if 15% of the general population were screened an incremental cost effective ratio (ICER) of $7900 would be achieved. However, screening 60% of the population would increase the proportion of detected cases from 58% to 80% with a consequent ICER of $10,900.

A separate Italian study model used a hypothetical enrolment of 100,000 people in the general Italian population [89]. A two-arm Markov model compared screening of the general population and subsequent treatment of subjects testing positive with a no screening strategy. Within this model progression monitored from chronic infection to cirrhosis and then complications of cirrhosis. No account was made for progression to HCC from a non cirrhotic state. The costs described in the study were also comparatively low and did not incorporate the use of protease inhibitors such as telapravir or boceprevir which at the time of publication had not been priced in Italy. The strategy cost was €25,341 per patient yielding 27.3 QALYs compared to €15,661 against 25.4 QALYs in the no-screening arm. Therefore the calculated ICER was $5,171. During sensitivity analysis it was noted that ICER tended to increase with cohort age with reduced QALY gain, although at €10,432 it is still below the accepted level of £20,000 to £30,000.

A separate Japanese study evaluated screening using the HCV core antigen test in the general population from the age of 40 to 70 and in high risk groups over 40 years of age [90]. High risk in this study were defined as high level of aminotransferase, having undergone a major operation or receiving a blood transfusion in childbirth which vary when compared to Western populations. Markov modelling was again used which allowed for progression to HCC from chronic hepatitis C and cirrhosis. Transplantation costs were not factored in this model. The prevalence of genotype in this population was assumed to be 70% with 30% genotype 2 or 3. Only direct costs were considered in this model and were converted to US dollar as of 2007 exchange rates. Out of 99,001 people screened in the general population 345 (0.36%) were detected as having hepatitis C. When compared to screening of high risk groups ICERs up to $4,825 per life expectancy gained.

In contrast, Loubiere et al. cost effectiveness of four strategies: no screening and no treatment, initiation of treatment after diagnosis of cirrhosis, and compared them to the French strategies of either two Enzyme linked immunosorbent assays (EIA) or EIA followed by HCV polymerase chain reaction (PCR) [92]. They assumed three separate populations: injecting drug users with a prevalence of 80% with half being under the age of 30 years; transfusion recipients and the general population with a prevalence of 1.2% and 53% of the diagnosed population being under the age of 45. 1998 prices were used, with significantly high screening costs quoted with a PCR test costing €80 and EIA €23. Screening the general population with EIA followed by PCR was demonstrated to be cost effective with an ICER of €4,933, however the authors suggest from their analysis that the wait and treat policy was even more cost

effective at €3,476. As well as comparatively high screening costs documented in this study, there SVR rates in the general population was low at only 45%.

1.10 Linkage into care

Linkage to care is non specific nomenclature. In the context of HIV in Low and Middle Income settings it was used to evaluate effectiveness of community health treatment centres, defined as visiting a community clinic to obtain blood results [93]. At the time of index diagnosis a given person with hepatitis C can be at various stages of liver fibrosis. The natural history of hepatitis C is a slow evolution of fibrosis over decades but various factors such as age, gender, genotype of virus, IL-28B status, co-morbidities, BMI and alcohol consumption can all have impact on rate of progression. In patients without evidence of advanced fibrosis and cirrhosis, a sustained virologic response which in most people can be considered equivalent to cure, is associated with a termination of hepatitis C related fibrosis and in some cases it is possible for disease regression [94]. In order to reach this goal persons need to be identified with the virus, linked to specialist services that can both work up patients for treatment and then deliver treatment. Traditional treatment was with 48 weeks of pegylated interferon and ribavirin with a failure rate of up to 80% in certain groups. Re-treatment would therefore be the only option unless liver disease was so severe that liver transplantation was necessary. Figure 1.2 demonstrates the multiple points in a patient's disease state and treatment pathway to SVR that can lead to loss to follow-up resulting in failure to be linked into care. Without the completion of therapy and SVR these patients will continue to progress through the natural history of HCV mediated fibrosis.

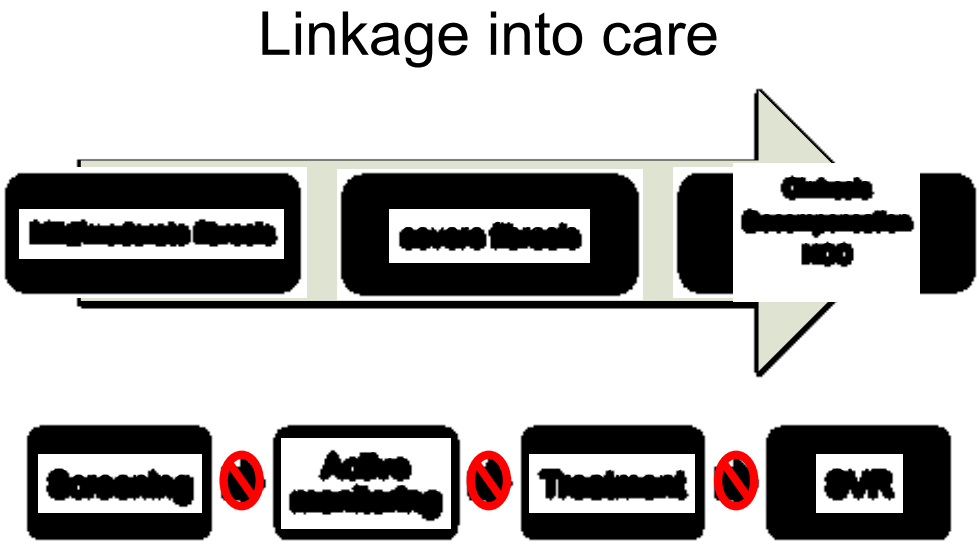


Figure 1.2 demonstrates the various time points at which patients can be unlinked from specialist care and lost to follow-up. Until patients have achieved SVR they continue to progress through the stages of fibrosis until potentially cirrhosis with or without decompensation events, cancer, transplantation and death.

Whilst research into measures that improve linkage into care in hepatitis C is limited, both anecdotal and some low quality evidence exists to suggest that point of care testing can improve linkage into care [95]. Whilst efforts to increase case finding are currently the topic of much research and clinical interest due to the availability of DAAs. Historical barriers to cure have been poor access to therapy for those identified with the virus. Established barriers to treatment, especially in vulnerable communities include reliance on primary care to arrange follow-ups and centralisation of treatment services [72]. It is postulated that by point of care testing and direct access to specialist services by either direct referral or treatment in the community can improve linkage into care, retention of identified persons within specialist services and therefore increase uptake to therapy. An important consideration in the current

climate of health resource prioritisation is if these measures remain cost effective within the thresholds acceptable to policy makers.

Within this thesis linkage to care is defined simply to mean capturing newly screened patients for follow-up appointments to be able to counsel of their new diagnosis of HCV. However, more robust metrics could be argued to be ensure linkage of care until SVR. However, given the practical issues of treatment and multiple confounders to starting interferon therapy, which was the main stay of treatment during the study period of this thesis, this metric would be subject to too much bias.

1.11 Hypothesis

- Direct linkage of care following hepatitis C screening strategies will result in high uptakes of treatment
- Strategies involving screening and direct linkage into care will be cost effective over varying degrees of hepatitis C prevalence

1.12 Aims

1. Assess cost effectiveness and linkage into care analysis of screening in traditional high-risk settings where hepatitis C prevalence is >20%.
2. Assess cost effectiveness and linkage into care analysis of screening in novel lower risk settings where hepatitis C prevalence is <20%.
3. Identify the local burden of disease associated with hepatitis C end stage liver disease

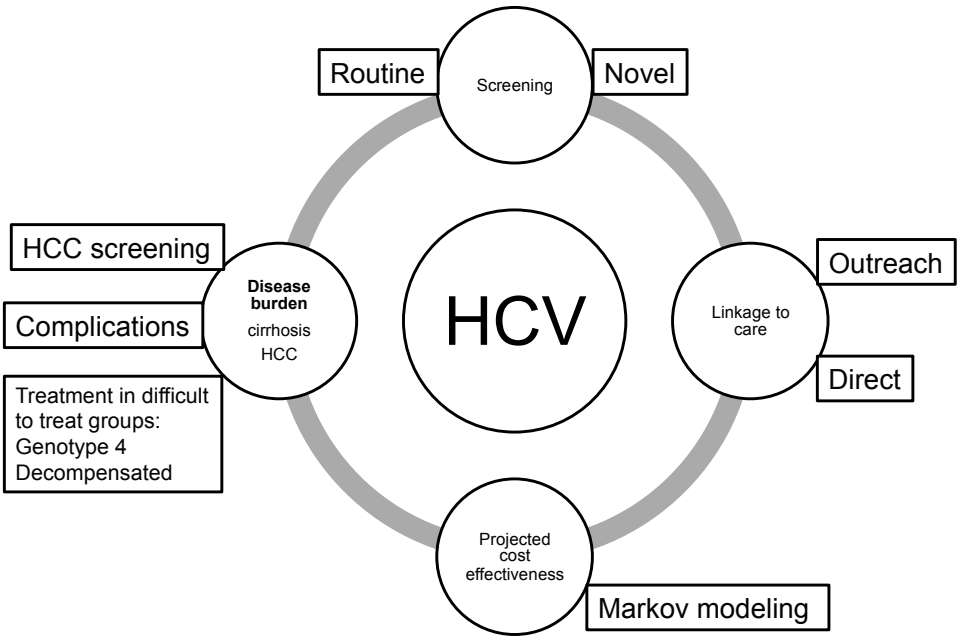


Figure 1.3 demonstrates the overall schematic of the studies of this thesis. Initially the burden of disease within the study population will be defined, in order to assess the potential impact of screening, early treatment and hopefully early intervention before the progression to cirrhosis and its complications. Traditional "high risk" groups will be assessed and compared to novel strategies to assess impact of linkage into care, and treatment outcomes. Using these outcomes health economic analysis will be performed to assess the economic impact of such interventions.

Screening projects outline

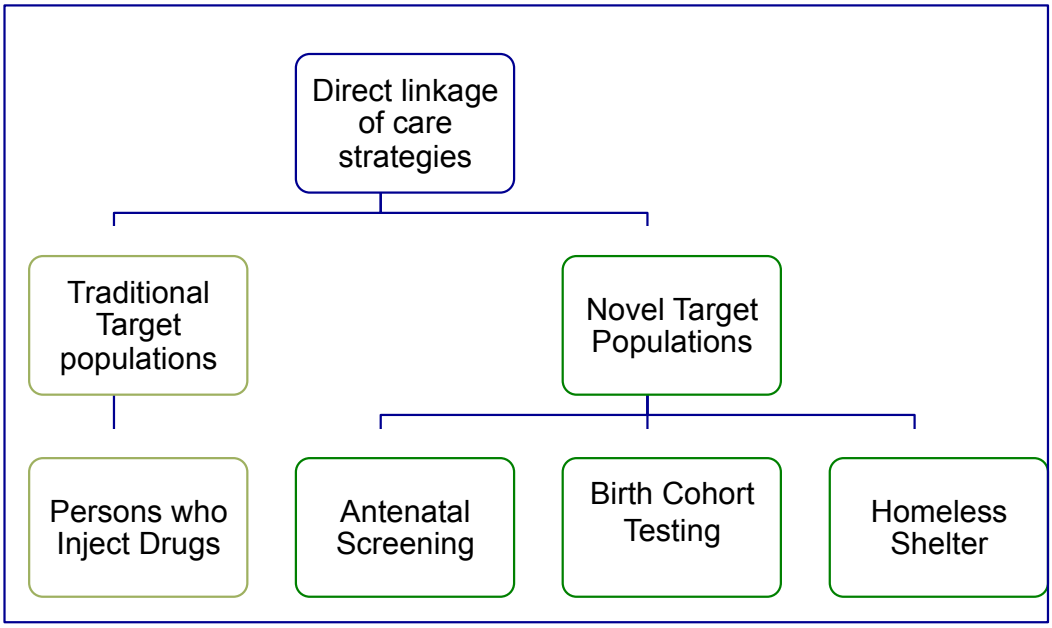


Figure 1.4 demonstrates the various strategies that will be used for comparison of traditional HCV screening targets compared to novel strategies that are proposed to be feasible and cost effective strategies for HCV screening. Historically prevalence of HCV in drug treatment units is above 20%. It is proposed that the three novel target populations screened: antenatal screening, a national birth cohort system and screening in homeless shelters is likely to be below the 20% prevalence threshold.

2 Cost Effectiveness Analysis Overview and Methodology

Cost-effectiveness analysis (CEA) is a formal method of evaluation of health outcomes and costs of medical interventions. It aims to objectively demonstrate the cost impact or benefit of an intervention to aid policy makers when evaluating the economic merits. In the UK, the National Institute of Clinical Excellence (NICE) uses such evaluations in the assessment of healthcare interventions [96]. Six basic steps when constructing such an analysis include [97]:

1. Define the intervention: The nature of the intervention needs to be defined in comparison to both the natural history of the disease without any treatment and also commonly with a comparative intervention, commonly the "gold standard" treatment in use.
2. Identifying relevant costs: These usually include direct medical costs but also may include indirect costs such as social costs (lost earnings, patient time).
3. Identify relevant benefits: These include the net benefit in patient health, after accounting for any adverse events associated with treatment. Where possible and quantifiable indirect benefits such as greater productivity can be included for analysis.
4. Measure costs: The entails placing a monetary value on medical inputs. Where costs may be incurred in the future discount rates are typically applied to convert all costs to present value terms. Greater weight is therefore applied to costs incurred sooner.

5. Measure benefits: In many CEA, benefits are converted to a single utility metric (e.g. quality adjusted life years). Cost benefits are analysed within a monetary currency and can be used to determine the cost to gain a single utility metric. Where health benefits are likely to occur in the future, a discount rate is commonly used to convert all benefits into present value terms. Greater weight is therefore applied to health benefits that are likely to be incurred sooner.

6. Account for uncertainties: The robustness of conclusions to uncertainties in the measurement of costs can be assessed using univariate and multivariate sensitivity analyses or Monte Carlo simulations.

2.1 Utilities

In order to assess both baseline health and wellbeing of an individual or population and assess impact of medical intervention, "utilities" are used as an objective surrogate. An intervention that prolongs life is often considered ideal and can be assessed using "Life Years Gained" (LYG). However, it may not be considered beneficial to an individual or society to have longer, yet poor quality of life. It is therefore more common in CEA to consider Quality Adjusted Life Years (QALYs). This concept was recommended by Fanshel and Bush in 1970, and has since been used widely in health economics literature [98]. This utility integrates mortality and morbidity to express a functional equivalent of well years of life. On this scale, a perfect year of health is denoted as 1, then as years of life become less than optimal

they are scored proportionately between 0 and 1. When considering a treatment of a condition it is important to consider the following concepts:

1. Does the medical condition or the treatment affect the life expectancy of the patient?
2. Does the condition or treatment affect the quality of the patient's life and if so by how much?
3. The duration of the effects: how much life is lost and how long is the duration of undesirable effects?

Health outcomes can be determined using different measures, such as using health-related quality of life (HRQL) questionnaires to measure impact on quality of life. These tend to be disease specific and attempt to describe aspects of health that are most pertinent to patients with the specific condition. Others attempt to offer generic description of health states. HRQL can be used to assign weights to different aspects of health to reflect the rate of each possible health states relative to full health (with a score as a fraction of 1). Within the weighting patient preferences can be considered, for example how much time in full health would people be willing to give up in order to avoid time in a particular health state. By assigning such preferences not only are the different aspects of HRQL weighted, but also allows length of life to be considered with quality of years lived. Where natural history data is available for a chronic disease, transition models can be constructed. These incorporate health utility estimates for incidence of complications, age related decrement, adverse events and treatment related disutilities using available natural history data.

In broad terms if a patient has an expected life expectancy of 80, but due to an illness the life expectancy is 60 then the disease is associated with 20 lost years. Therefore if an intervention increases life expectancy to 70 then this would be associated with 10 LYG per person. However if the quality of the extra 10 years was associated with 0.2 QALY per year then per individual then that individual will have an associated 2 QALY gain, significantly less dramatic than when considering LYG only. When extrapolating this to a population then if 100 people have the condition ascribed above then the total lost years would be multiplied by 100, in this case 2,000 years. If 50 people were eligible for the treatment ascribed in this example then these 50 would have an extra 10 years of life with 0.2 QALY per year. Therefore this population would gain 500 LYG and 100 QALYs. Furthermore, if a further intervention boosts a patient's health from 0.2 QALY to 0.4 QALY then this produces the equivalent of an incremental 0.2 QALY gain. Therefore in order to ascertain the cost effectiveness of an intervention, the natural history of the disease needs to be established with an understanding of the QALYs associated. The QALYs associated with the treatment itself, followed by the effects of the intervention will inform a calculation of the level of QALYs gained or lost by the intervention.

Finally the costs of the intervention can be used to calculate the cost required to reflect a gain in health utility. Costs of both interventions and management of treatment adverse events are off-set by the costs incurred by the specified disease process following the course of it's given natural history.

2.2 The incremental cost effectiveness ratio (ICER)

The introduction of a medical intervention can be considered using a graphical illustration Figure 2.1 boxes A-F. A screening intervention will require lab test costs (Box A). This may lead to an intervention that will alter use of health care resources (Box B) and non health care resources (Box C).

The purpose of the intervention is to improve health or delay health deterioration. Improvement can be measured in QALYs (Box D). The potential economic impacts include the inherent value of health measure in monetary terms, such as the maximum willingness to pay for certain health states (Box E). On the whole, willingness to pay is arbitrarily set as a cost per utility (commonly QALY) that a policy maker is willing to spend on an intervention. It is therefore characterising a given intervention as being cost effective, or in other words deemed to be economically acceptable. Secondly changes in health status can affect a patients work productivity (Box F). Finally changes in health status often result in change in the subsequent use of resources.

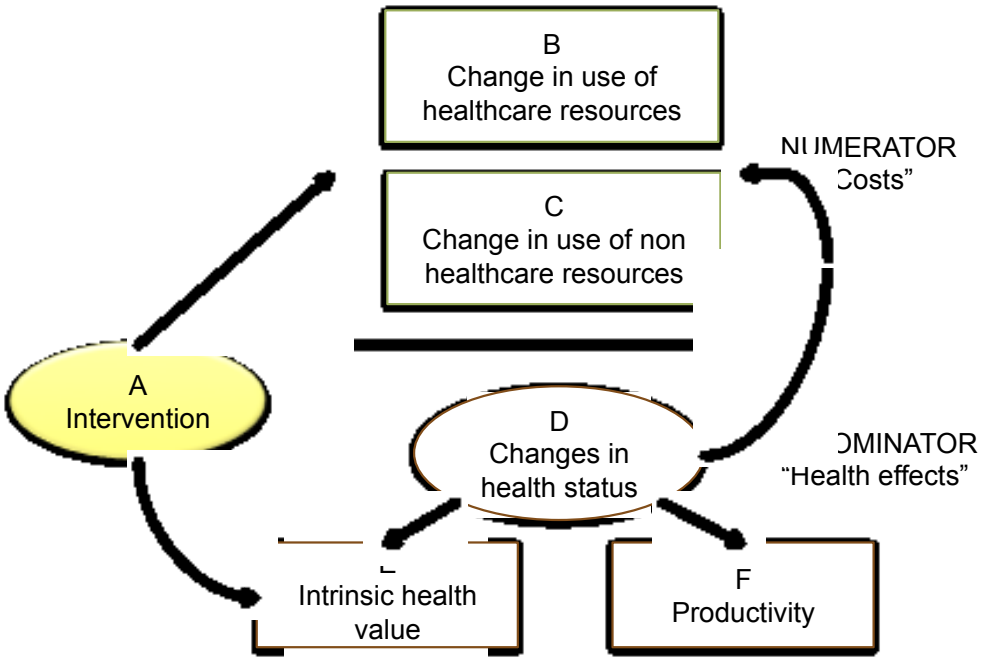


Figure 2.1 The cost effectiveness ratio

The cost effectiveness analysis identifies the consequences of adopting a medical intervention including the use of resources, and the magnitude of each change is measured. These changes are valued into a monetary cost for each input. The incremental difference in input and production costs form the basis for the cost element of the CEA. The changes in life expectancy and quality are converted into QALYs. The ratio of the increment in the cost summary to the increment of the effect measure (QALY) is the cost effectiveness ratio.

In the 1970's cost analyses for dialysis in end stage renal disease were calculated comparing centres offering dialysis compared to no dialysis which at the time demonstrated outcomes ranging $25-30k per life year gained. Studies reported a QALY gain from dialysis [99]. Policymakers based current willingness to pay thresholds based on the original data from these dialysis cohorts. These have

remained relatively unadjusted despite more recent estimations suggesting currently ICERs of $125-150k per QALY would be more appropriate [100]. However, as yet no significant rises in thresholds have be made.

2.3 Discounting

In any health economic model the effects of interventions are generated over time, and therefore it is necessary to establish a relative weight on outcomes in the future compared to any immediate impacts. In hepatitis C, eradication of the virus may provide some immediate benefits, particularly on fatigue and productivity. However, many of the benefits such as prevention of cirrhosis and cancer will likely occur in future periods. Thus, the cost savings offered for these benefits will only be realised in the future by the healthcare payer.

From a payer's point of view, one needs to separate healthcare benefits from real life economic rationalisation. When analysing resource allocation, healthcare payers could, instead, invest elsewhere in the economy which may provide a positive rate of return, which in turn could be re-invested in to healthcare with greater immediate effect. This means that costs incurred in the near future are more important than those incurred in the more distant future [101]. NICE consider a real rate of return (r) of 3.5% per annum. At this level healthcare costs of £1million incurred today (t=0) could otherwise be invested to provide extra income. For example in 10 years (t=10) if invested with a interest return of 3.5% per annum a further £410,599 could be invested at that time:

$$£1\text{million}\ (1 + r)^{t} = £1\text{m}\ (1+0.035)^{10} = £1{,}410{,}599$$

An important question regarding CEA in health economics is whether health should be discounted at the same level. Unlike other economic scenarios healthcare provides

no real opportunity to invest directly elsewhere at the same rate of return. Indeed many of the decisions in health care are related to resource allocation and whether to commit resources now or later depending on the impact on current and future health [102].

Given that health care resources in essence impact on the health of a population, if we discount health care resources then we also discount health effects. Different countries vary reasonably widely on the levels of discounting that is applied. Returning to our previous example above where an intervention costs £1million now, if it were to generate 100 QALYS in t=10, then instead of discounting health to its present value we would express it as equivalent value in t=10. Therefore by committing £1million now in t=10 the cost per QALY would be 100 QALYs per £1,410,599 and therefore £14,106 per QALY. Another way of expressing this would be to discount the same health benefits at t=10 back to their present value at t=0 (70.9 QALYs) comparing them to the costs occurring in that period [103].

Using the parameters described above one can construct a health economic model which relies on a good understanding of the natural history of the disease in question and also critically the impact and alteration incurred by an intervention such as treatment.

2.4 Natural history of hepatitis C and transition rates

Overall when considering an appropriate model structure, the influence of the condition and intervention and impacts need to be considered. The CEA should include [51]:

- Whether the disease is acute or chronic, and if chronic the possible health-related events that could occur over time
- Whether the risk of events are constant or alter over time
- Whether the effectiveness of the intervention, relative to usual care, can be assumed to be constant over time or whether it is time-limited
- When treatment is stopped or fails, appropriate assumptions about future impact on health
- Whether the probability of health-related events over time is dependent on prior patient events e.g. Mode of acquisition of illness or co-morbidities.

In order to inform cost effectiveness analysis of hepatitis C treatments, it is important to consider the natural history of the virus and it's the progression of liver related fibrosis and associated complications. It is understood that hepatitis C induces a dynamic progression of liver fibrosis described histologically using the Metavir scoring system that ranges from F0 (no fibrosis) to F4 (advanced fibrosis/cirrhosis). Generally speaking persons with F4 disease are at highest risks of complications of end stage liver disease, which include decompensation events, hepatocellular carcinoma and liver related causes of death.

Thein et al. [104] performed a systematic review including 111 reports involving 33,121 persons with chronic HCV to help provide transition probabilities between

stages of liver fibrosis. Annual stage specific transition probabilities were derived, and the impact of potential covariates were evaluated using meta-regression. Duration of infection was the most consistent factor significantly associated with progression of fibrosis. The estimated prevalence of cirrhosis was 16% after 20 years of chronic infection. Estimated mean stage-specific probabilities were: F0➔F1 0.117 (0.104-0.130); F1➔F2 0.085 (0.075-0.096); F2➔F3 0.120 (0.109-0.133); and F3➔F4 0.116 (0.104-0.129). As part of the analysis of this systematic review most evaluated covariates were significantly associated with advanced fibrosis except male gender, HIV positivity and excess alcohol use. In a meta regression analysis duration of HCV infection was independently associated with all stages of fibrosis. Using backward regression the authors modeled each stage of progression to provide equations that could be used to calculate stage specific progression rates:

F0 to F1	$\exp[-2.0124 - (0.07589 \times HCVD) + (0.3247 \times Design) + (0.5063 \times Male) + (0.4839 \times GT1)]$
F1 to F2	$\exp[-1.5387 - (0.06146 \times HCVD) + (0.8001 \times Alcohol)]$
F2 to F3	$\exp[-1.6038 + (0.0172 \times HCV\ Age) - (0.05939 \times HCVD) + (0.4539 \times Alcohol)]$
F3 to F4	$\exp[-2.2898 + (0.01689 \times HCV\ Age) - (0.03694 \times HCVD) + (0.5963 \times IDU) + (1.1682 \times BT) - (0.4652 \times GT1)]$

Figure 2.2 HCV transition rates between F0 to F4. Abbreviations: exp, exponential function; HCV, hepatitis C virus; HCV D, hepatitis C duration; IDU, injection drug use; BT, blood transfusion

Duration of HCV infection (years); study design: cross-sectional/retrospective = 1; retrospective-prospective =0; male proportion: 0 to 1; genotype 1 proportion: 0 to 1; age at HCV acquisition (years); excess alcohol proportion: 0 to 1; risk of HCV acquisition: IDU proportion 0 to 1; blood transfusion proportion 0 to 1

The reason for using an analytical Markov model of this nature was that it allows the potential for contrasting the likely progression of individual patients subject to their individual characteristics. Previously transition rate estimates were derived from mean estimates at population level. In studies, as within this thesis, where the sample sizes may be smaller than technical analyses required for population assessments this approach allows more accurate transition rates per subjects within given cohorts.

2.5 Developing a CEA

In it's basic essence individual health related events have a probability of occurrence. This given event will be associated with an expected value, i.e. an implied cost associated with that occurrence. Figure 2.3 provides illustration:

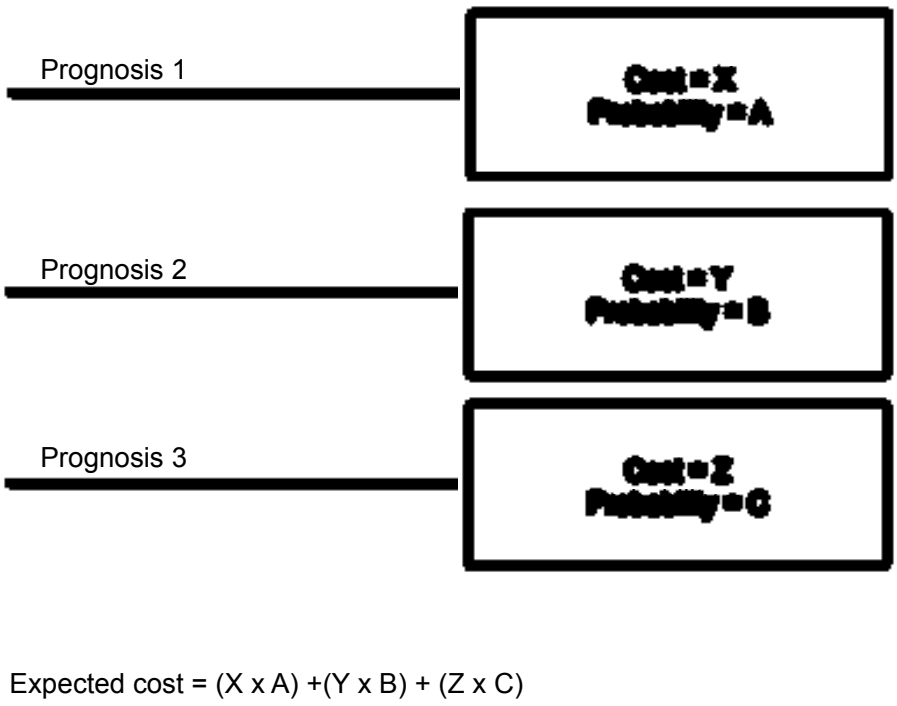


Figure 2.3 Calculating expected costs between interventions – adapted from [51]

The Markov model is commonly used approach for CEA. It allows for complex modelling options with multiple consequences to be considered compared to more basic tools such as decision tree modelling. Such models have been used in the evaluation of screening programmes [105] and therapeutic interventions [106]. The

added advantage of Markov modelling is it is structured around disease states that are mutually exclusive, representing the possible consequences of evaluated options. Therefore complex disease states can be modelled as a set of transitions between disease states over a number of cycles or discrete time periods. Costs and effects are modelled into these models as a mean per value per state per cycle and expected values are calculated by adding the costs and outcomes across each state according to the expected time that the patient remains within each transition state [51].

As aforementioned HCV has a relatively slow progressive course at early stages of disease with dynamic transitions between fibrosis stages but the development of cirrhosis is associated with a variety of disease specific complications. Figure 2.4 provides a representative example of an HCV lifetime Markov model. Within this model progression through various states of fibrosis are modelled with assigned yearly progression rates and utilities. The model calculates the probability of progression to liver specific complications for those that progress to the F4 state including liver related death. It is not however assumed that everyone will either progress to this state nor die of liver specific causes and the majority will be modelled to progress over a lifetime and die of non-liver related causes. Those between F0-F3 are subject to standard all cause mortality rates while those that transition to F4 incur additional liver specific mortality rates. The presence of SVR allows transition into a separate pathway that reflects that patients no longer progress through fibrosis stages.

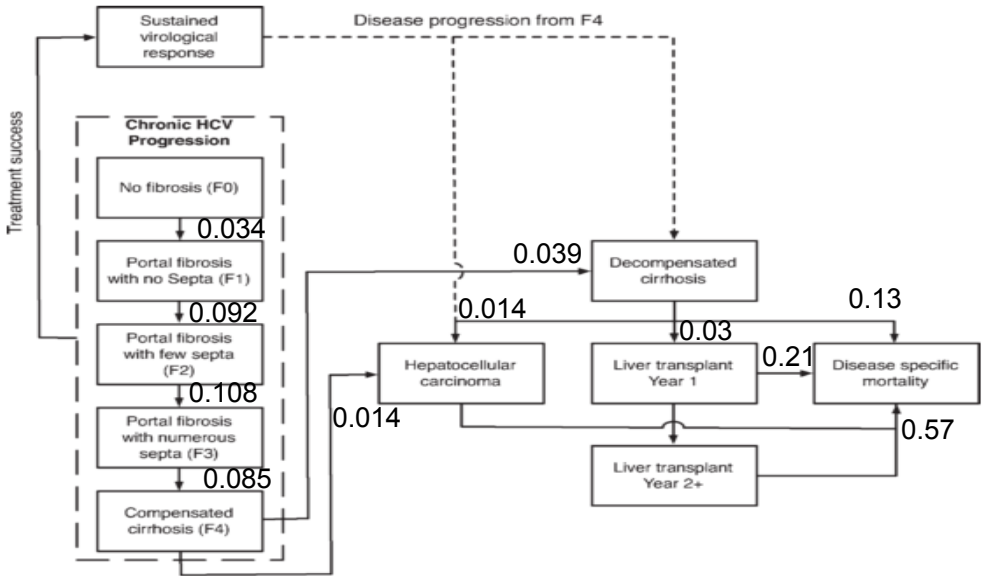


Figure 2.4 HCV lifetime Markov Model with demonstrative transition rates

The transition probabilities governing the direction and speed of transition states represented by examples above demonstrate a 1-year cycle. These transition rates as outline above are based from data from previous systematic review are reported in Table 2.1. Calculation of stage specific transition rates incorporates patient characteristics such as age, gender, duration of HCV, mode of acquisition and alcohol consumption.

Transition	Functional form		Source
F0 to F1	$\exp[-2.0124 - (0.07589 \times HCVD) + (0.3247 \times Design) + (0.5063 \times Male) + (0.4839 \times GT1)]$		[104]
F1 to F2	$\exp[-1.5387 - (0.06146 \times HCVD) + (0.8001 \times Alcohol)]$		
F2 to F3	$\exp[-1.6038 + (0.0172 \times HCV\ Age) - (0.05939 \times HCVD) + (0.4539 \times Alcohol)]$		
F3 to F4	$\exp[-2.2898 + (0.01689 \times HCV\ Age) - (0.03694 \times HCVD) + (0.5963 \times IDU) + (1.1682 \times BT) - (0.4652 \times GT1)]$		
Transition	**Mean**	**SE**	**Source**
F4 to DC	0.039	0.010	[107]
F4 to HCC	0.014	0.010	
DC to HCC	0.014	0.010	
DC to LT	0.030	0.012	
DC to Death	0.130	0.010	
HCC to LT	0.030	0.012	
HCC to Death	0.430	0.030	
LT (Yr 1) to Death	0.210	0.046	
LT (Yr 2+) to Death	0.057	0.012	

Alcohol, defined as alcohol consumption of more than 20g/day; BT, the proportion of individuals that were newly diagnosed with HCV at blood donor screening; DC, decompensated cirrhosis; Design, set to 0 if the study design is cross-sectional and set to 1 if the study design is retrospective-prospective; GT1, set to 1 for genotype 1 or 0 for non-1; HCC, hepatocellular carcinoma; HCV Age, age at cohort initiation; HCVD, length of time from the presumed date of infection to the date of liver biopsy; IDU, the proportion of individuals that acknowledged intravenous drug use (IDU) as the main risk factor for HCV infection; LT, liver transplant; SE, standard error; Yr, year.
The proportion of patients consuming excess alcohol and with a history of IDU were assumed to be 100% in line with the high risk status of the study population.
The average duration of infection was not recorded thus the mean profiles from the UK studies reported in Thein 2008 were used as proxies.
Information on patient sex was not available, thus a 50:50 male:female ratio was utilised.

Table 2.1 Disease state transition rates [108]

At stages F1 to F3 treatment of HCV would provide a treatment effect that assumes a reduced relative risk of transitioning to a worse state. Examples of how cycles are calculated are demonstrated in Figure 2.5. The annual costs associated with each state varies and therefore how total costs/QALYS are calculated by probability of time spent in each state and the cost evaluated as per Figure 2.3.

The calculation of expected costs and outcomes within the cohort model incorporates addition of costs and outcomes of all possible outcomes which are weighted by a probability of occurrence. Within the HCV Markov model this involves a calculation of low long patients spend in each state of liver fibrosis and/or complication such as hepatocellular carcinoma. For the purpose of illustration if we consider 2 cycles (i.e. 2 years) following a cohort of 10,000 patients below:

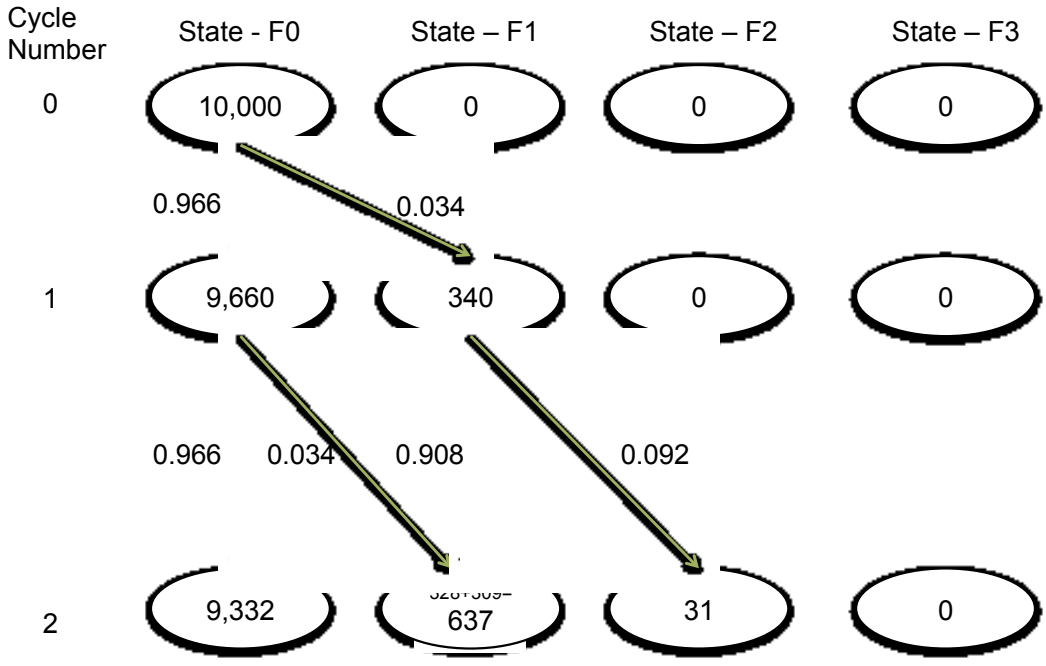


Figure 2.5 Progression of a cohort through yearly cycles based on probabilistic progression. Each year spent in each state (or fibrosis group) is associated with a cost per year, in the case of hepatitis C specific costs this is outlined in Table 2.2.

	Cost parameters			Health utility parameters		
	Mean (£)	**SE (£)**	**Source**	**Mean**	**SE**	**Source**
Disease State (annual)						
F0/F1	177.47	35.01	[109]	0.77	0.015	[70, 109]
F2/F3	922.08	97.82		0.66	0.031	
F4	1,463.50	297.45		0.55	0.054	
DC	11,728.61	1,954.09		0.45	0.031	
HCC	10,451.58	2,456.09		0.45	0.031	
LTx (Year 1)	47,310.55	6,843.48		0.45	0.031	
LTx (Year 2+)	1,781.15	456.57		0.67	0.066	
SVR from F0/F1*	333.08	62.05		0.82	0.043	
SVR from F2/F3*	922.08	97.74		0.72	0.048	
SVR from F4*	1,463.50	288.07		0.72	0.048	

* Applied in the first year only.

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LTx, liver transplant; SE, standard error; SMV, SVR, sustained virologic response.

Table 2.2 Cost and health utility parameters [108]

The proportion of living cohort per cycle are added across all the cycles. The number of cycles will determine the duration of the model that is studied. The models assume movement from one state to another. It therefore demonstrates 'no memory' of the patient and at which point they transferred disease state. As it is assumed that all transitions take place at the start of the cycle, deaths occurring during a cycle are not accounted for as being alive for any proportion of the cycle. Therefore, an unbiased estimate of life expectancy would assume deaths to occur halfway through the cycle and where possible apply a half-cycle correction for both life expectancy and expected costs incurred. In the context of a CEA, which is focussing specifically on incremental costs between interventions, it is unlikely that half cycle corrections will make any meaningful impacts on outcomes unless the cycle length is long proportionate to the models time horizon.

2.6 Developing a transition matrix

In order to build a Markov model, to simulate probability of progression of an individual or a cohort over a lifetime of cycles, a transition matrix is calculated in order to represent the proportions of persons in each state per cycle. The matrix is an accumulation of probabilities for a transition through the various stages. Each row accounts for all possible probabilities and therefore will total 1. For example, Table 2.3 outlines a one year cycle transitioning patients:

Fibrosis stage	F0	F1	F2	F3	F4
Probability = 1	Po	Pi	Pii	Piii	Piv
Transition	F0 – F1	F1 - F2	F2-F3	F3-F4	F4-F4
Transition rate	0.034	0.092	0.108	0.085	1

Table 2.3 Demonstrative table of transition rates of F0-F4

$\Sigma P_{o,iv} = 1$

When expanding on our hepatitis C model, for purpose of demonstration we can consider a transition matrix of fibrosis from states F0-F4 demonstrated in Table 2.4. For demonstration purposes in this example we limit progression to a conclusion at fibrosis stage F4. Within the model assumptions made include:

- Patients can not progress through more than one fibrosis stage per given year
- Patients can not spontaneously regress in fibrosis stage i.e. the probability of going backwards in fibrosis staging is 0
- Due to HCV being a long-term chronic condition, a model time horizon of 80 years is considered reasonable and it is commonly assumed, for simplicity, that all patients will die by the time they are 100.

When considering progression from F0 to F4 a 5 x 5 matrix is therefore constructed

	F0	**F1**	**F2**	**F3**	**F4**	**Σ**
F0	1-(pF0-F1)	pF0-F1	0	0	0	1
F1	0	1-(pF1-F2)	pF1-F2	0	0	1
F2	0	0	1-(pF2-F3)	pF2-F3	0	1
F3	0	0	0	1-(pF3-F4)	pF3-pF4	1
F4	0	0	0	0	1	1

Table 2.4 Constructing a 5 x 5 transition matrix

When using the transition rates described in Table 2.3 the following matrix is constructed using demonstrative mean transition rates (Table 2.5):

	F0	F1	F2	F3	F4	Σ
F0	0.966	0.034	0	0	0	1
F1	0	0.908	0.092	0	0	1
F2	0	0	0.892	0.108	0	1
F3	0	0	0	0.915	0.085	1
F4	0	0	0	0	1	1

Table 2.5 Calculated transition rates within the 5 x 5 matrix

This matrix provides a by building block to constructing a Markov Chain from which the basis of the Markov model is constructed. As discussed earlier the chain ascribes probabilities per cycle. As each step is conditional on the previous step the following conditional probability P=(AIB) is calculated for each step. For the purpose of demonstration, Table 2.6 considers transition from F0-F2 over a 2-year cycle where

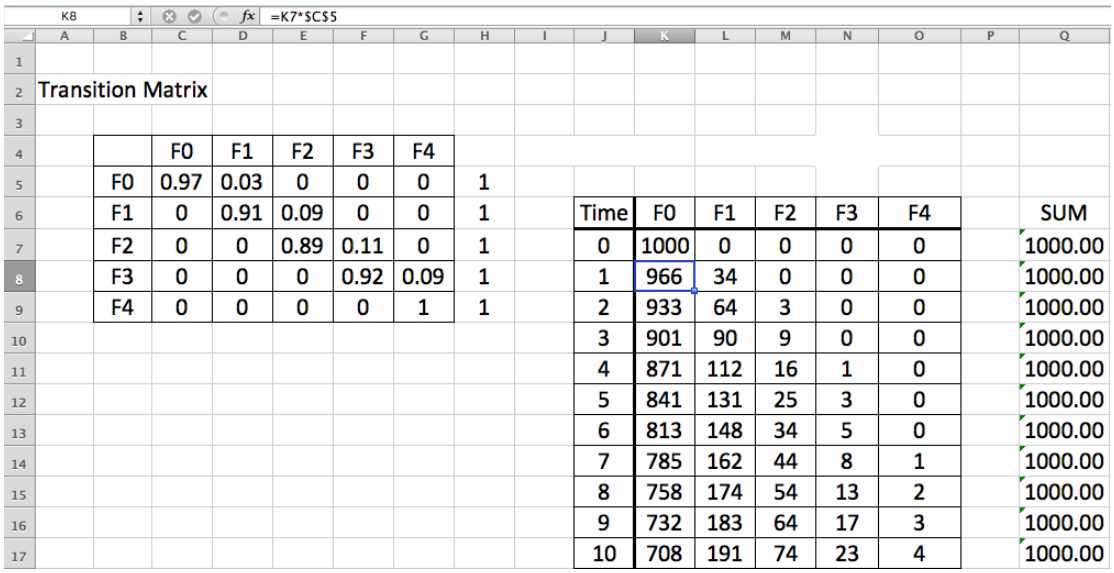
"p" represents probability; Yr represents cycle year (y-axis) and Fx-Fy represents transition from fibrosis state x to state y. This would be demonstrated with the formulae below:

Year (Yr)	F0	F1	F2
0	Yr0 F0	0	0
1	Yr0F0*p[F0-F0]	Yr0F0*p[F0-F1]	Yr0F0*p[F0-F2]+Yr0[F1-F2]+Yr0p[F2-F2]
2	Yr1F0*p[F0-F0]	YrF1*p[F1-F1]+YrF1*p[F0-F1]	Yr1*p[F2-F2]+Yr1*[F1-F2]+Yr1*p[F0-F2]

Table 2.6 Calculating transition rates within a transition matrix using Microsoft Excel equations

Using Microsoft Excel, the model can be developed using this matrix. For the purpose of demonstration the following examples will simulate the progression of 1000 persons at Year 0 with F0 fibrosis until a maximum stage of F4. Firstly a 5 x 5 transition matrix, as defined above, is constructed. Following this we populate Column J with year cycles, Column K demonstrates the population with F0 disease to Column O which is populated with those with F4 disease. Given 1000 persons start in stage F0, at time 0 no persons will be F1-4. In Year 1, as described above the probability of progression (pF0-F1 =0.034) and staying within the same fibrosis stage (pF0-F0=0.966). Using the transition matrix the probability of progression to each next state is then multiplied by the number of persons in the preceding state in the previous cycle (Figure 2.6):

Cycle 1:



Transition Matrix

	F0	F1	F2	F3	F4	
F0	0.97	0.03	0	0	0	1
F1	0	0.91	0.09	0	0	1
F2	0	0	0.89	0.11	0	1
F3	0	0	0	0.92	0.09	1
F4	0	0	0	0	1	1

Time	F0	F1	F2	F3	F4	SUM
0	1000	0	0	0	0	1000.00
1	966	34	0	0	0	1000.00
2	933	64	3	0	0	1000.00
3	901	90	9	0	0	1000.00
4	871	112	16	1	0	1000.00
5	841	131	25	3	0	1000.00
6	813	148	34	5	0	1000.00
7	785	162	44	8	1	1000.00
8	758	174	54	13	2	1000.00
9	732	183	64	17	3	1000.00
10	708	191	74	23	4	1000.00

Figure 2.6 Cycle 1 of a 5 x 5 transition matrix advancing a cohort from Metavir F0 over 10 cycles

Persons will either remain in F0 or progress to F1. Cell C5 denotes the probability of remaining in F0 and D5 denotes the progression to F1. Cells E5 to G5 denotes later fibrosis stages which from F0 are ascribed a probability of 0. In Excel the use of $ before the cell letter and number functions to anchor a set cell as a constant for all future formulae. Therefore once a base formula has been set, I edit, copy and paste the formula to rows below it will ensure that a specific value, in this case transition probability, will remain constant. Therefore using the example above cells:

K8 represents F0-F0. =(K7*C5)

L8 represents F0-F1. =(K7*D5)

M8 represents F1-F2. =(K7*E5)

N8 represents F2-F3. =(K7*F5)

O8 represents F3-F4. =(K7*G5)

Figure 2.7 demonstrates that as cycles progress, an accumulation of the results of previous cycles requires all probability states to be accounted, using the original transition matrix:

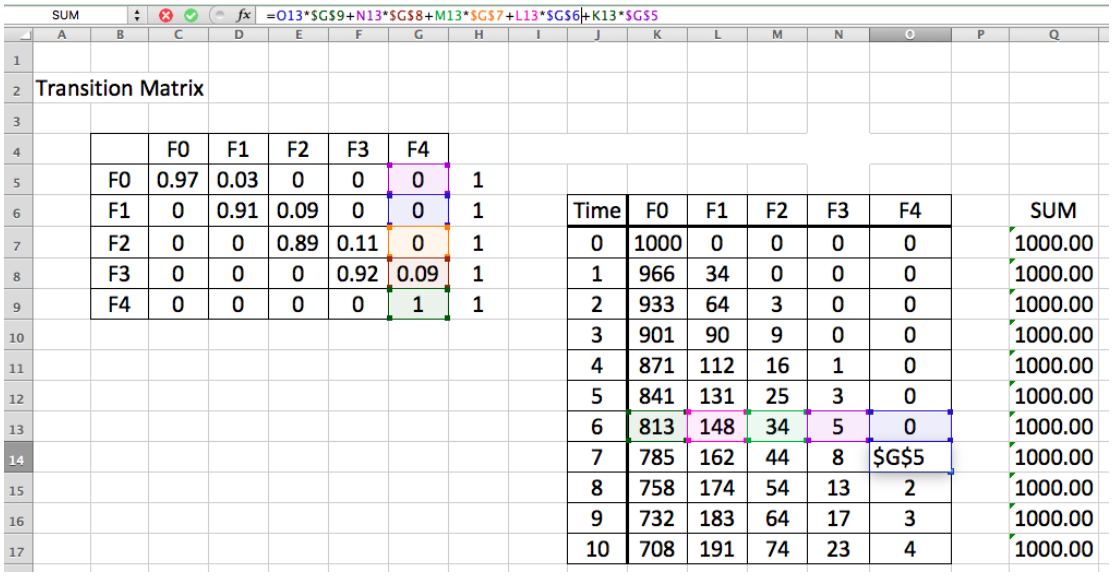


Figure 2.7 Demonstrating the serial calculations required to progress the cohort through cycles of a transition matrix, in this example in cycle 7

For example for cell O14 (number of F4 in the 7th year cycle) the 5x1 matrix in column G is calculated against row 13 (cycle 6). Therefore the number of persons with F4 disease after 7 years (cycles) would be:

[P(F4-F4)*Yr6F4] + [P(F3-F4)*Yr6F3] + [P(F2-F4)*Yr6F2] + [P(F1-F4)*Yr6F1] + [P(F0-F4)*Yr6F0]

=((O13*G9)+(N13*G8)+(M13*G7)+(L13*G6)+(K13*G5))

As represented in this example each cycle should have a total of 1000 persons in a model such as this where there is no progression to complications such as death and the number of cycles is limited to be within a normal lifetime. Having created this

Markov chain of events, costs and utilities can then be incorporated to ascertain cost effectiveness. For the purpose of demonstration if the following simple costs and utilities are described for each fibrosis stage:

	COST (£)	Utility (QALY)
f0	1	5
f1	2	4
f2	3	3
f3	4	2
f4	5	1

Each is multiplied by the total number in each state per cycle to consider a lifetime cost and a lifetime utility. In Figure 2.8 the costs for year 1 would be calculated as:

cost of F0 x number in F0 + cost of F1 x number in F1 + cost of F2 x number in F2 + cost of F3 x number in F3 + cost of F4 x number in F4

Or: =((K8*H13)+(L8*H14)+(M8*H15)+(N8*H16)+(O8*H17))

i.e. (966 x 1) + (34 x 2) + (0 x 3) + (0 x 4) + (0 x 5)

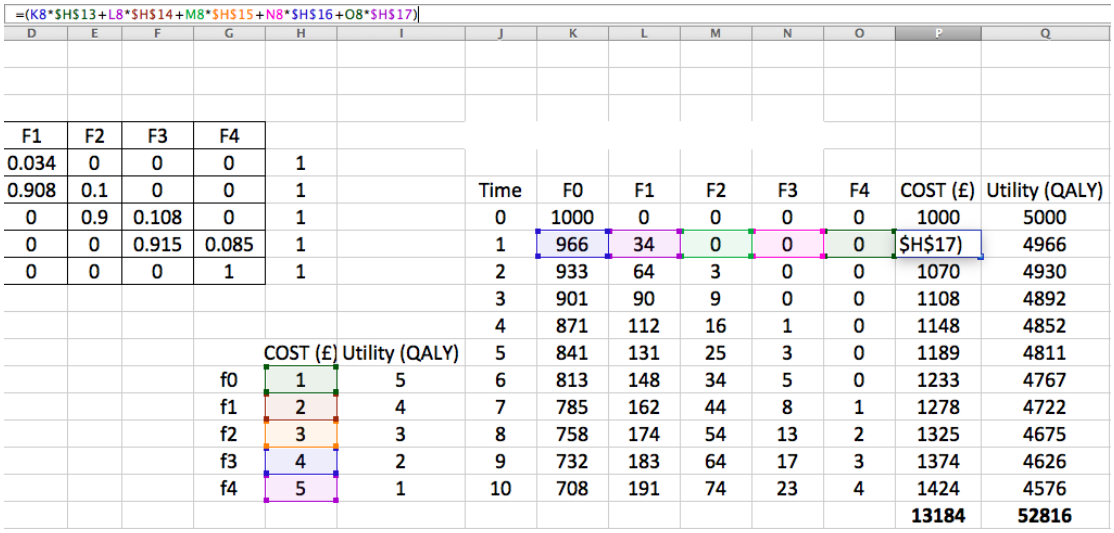
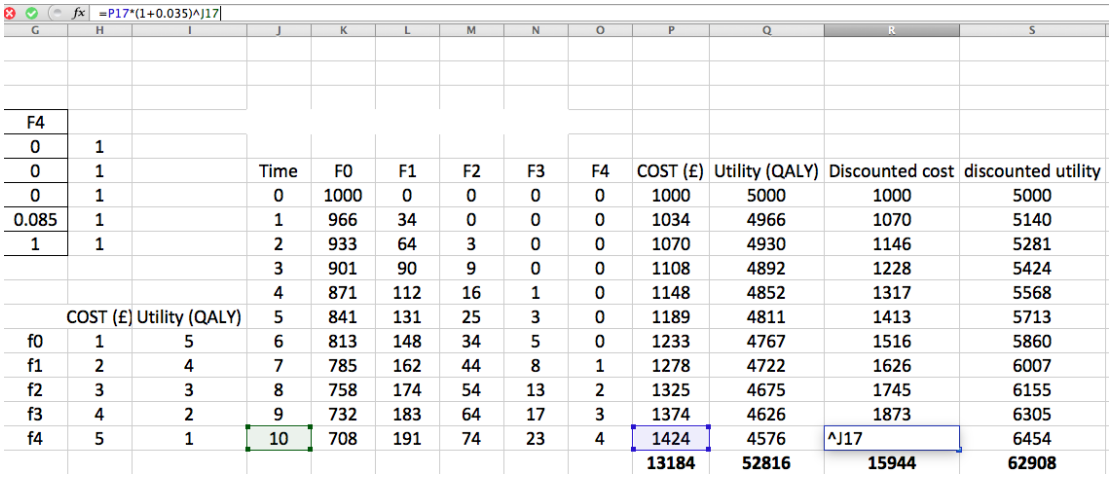


Figure 2.8 Introducing costs and utilities within a Markov Model to output health economic outcomes

Using the same function utilities acquisition (QALYS gained) in year 1 would be calculated:

=((K8*I13)+(L8*I14)+(M8*I15)+(N8*I16)+(O8*I17)

Over the course of 10 cycles the total costs and utilities can be added, in this example the costs incurred are £13,184 and utilities gained 52,816. However, these values represented undiscounted figures and in order to represent value as per the standard discounted level of 3.5% these need to be included in the analysis using the formula $(1 + r)^t$



=P17*(1+0.035)^J17

F4												
0	1											
0	1		Time	F0	F1	F2	F3	F4	COST (£)	Utility (QALY)	Discounted cost	discounted utility
0	1		0	1000	0	0	0	0	1000	5000	1000	5000
0.085	1		1	966	34	0	0	0	1034	4966	1070	5140
1	1		2	933	64	3	0	0	1070	4930	1146	5281
			3	901	90	9	0	0	1108	4892	1228	5424
			4	871	112	16	1	0	1148	4852	1317	5568
	COST (£)	Utility (QALY)	5	841	131	25	3	0	1189	4811	1413	5713
f0	1	5	6	813	148	34	5	0	1233	4767	1516	5860
f1	2	4	7	785	162	44	8	1	1278	4722	1626	6007
f2	3	3	8	758	174	54	13	2	1325	4675	1745	6155
f3	4	2	9	732	183	64	17	3	1374	4626	1873	6305
f4	5	1	10	708	191	74	23	4	1424	4576	^J17	6454
									13184	**52816**	**15944**	**62908**

Figure 2.9 Introducing discounting to costs and utilities

i.e. for each cost and utility total per year the (cost +1.035)^year

In the example above (Figure 2.9) the discount is applied to the 10 year (cycle) cost therefore:

(year 10 undiscounted cost) x 1.035^{10} = 1424 x 1.411 = 2009

Having constructed the Markov model, all parameters can be varied to satisfy the assumptions made in each base case scenario to model variations and ascertain impacts made by interventions to calculate the differences in costs between two strategies and differences in utilities in order to calculate a cost effectiveness ratio.

2.7 Dealing with assumptions

In conducting a CEA, assumptions are required to be made in order to evaluate the desirability of an intervention combining information on the natural history of the disease and treatment, clinical effectiveness of regimes, costs of intervention and sequelae. For certain aspects the level of uncertainty regarding the correct value or the relationship effects necessitates the use of estimations that may be impact on outputs.

The standard method of dealing with uncertainty is to conduct sensitivity analyses. Some critical components in the calculation is changed by a meaningful amount or using a best and worst case scenario to determine the effect on the cost effectiveness ratio. The resulting impact on the ICER provides an indication of how sensitive the results are to a plausible change in the given parameter. If there is little variation then the CEA can be considered robust or insensitive to the working assumptions made with regards that given parameter.

Typically two common methods can be used. Firstly, univariate sensitivity analysis, where input parameters are varied by an arbitrary amount (e.g. 20%). This is used to assess the variability in model outcomes as a function of specific model input parameters i.e. it is used to assess which parameters are most influential under the current model structure. Secondly, probabilistic sensitivity analysis, in which all parameters are varied simultaneously by a meaningful measure of variation (usually the standard error of the mean). Input parameters are sampled from appropriate distributions and varied randomly in line with their mean and standard error values (typically beta distributions are used for values that need to be between 0 and 1,

gamma distributions are used for values that need to be 0 or greater and normal distributions are used for values that may be any negative or positive number). A large number of simulations are then performed, each with a different set of randomised inputs and the results of each simulation recorded [51]. Within this thesis, it was deemed to be more reliable to use univariate sensitivity analyses, as key assumptions were clearly defined and being able to specify variation in these assumptions would be more accurate than would be possible using probabilistic sensitivity analysis.

There are limitations to the usefulness of sensitivity analyses. Firstly the analysis is dependent on the judgement of which variables are assessed. Secondly the amount of variation around the base value needs to be considered within clinically meaningful ranges. Finally, the analyst needs to determine the level of variation from the base case that can be considered acceptable and robust. It is therefore subjective as to the interpretation of the sensitivity results as a marker of robustness.

Additionally, it is possible to assess what potential extra cost could be spent on an intervention to maintain a cost effectiveness. This is useful in demonstrating to policymakers the likely applicability of results when considering other settings that may have differing infrastructure costs. Further, it is useful for demonstrating the likely significance or insignificance of sensitivity analysis results by demonstrating the scope of delta costs that could be incurred. In order to do this the calculation for ICER is rearranged to calculate the amount that could be spent to maintain a given ICER (usually £20,000 per QALY). For example:

Arm A total cost = ICER (e.g. £20,000) X (QALY Arm A – QALY Arm B) + Arm B cost

In order to calculate the extra that could be spent to reach the ICER threshold (in this case £20,000 per QALY, the actual cost of arm A is subtracted from the projected total cost:

Arm A total cost – Arm A actual cost

2.8 The MONARCH (MOdelling the NAtural histoRy and Cost effectiveness of Hepatitis C Markov Model

For the purposes of cost effectiveness analyses performed using the MONARCH model courtesy of Dr Phil McEwan, Health Economics and Health Outcomes Research, Cardiff, UK. This is a proprietary cohort based Markov lifetime simulation model created in Microsoft Excel. The MONARCH model is a previously published and validated HCV disease progression and cost-effectiveness model designed to progress a cohort of subjects in annual cycles through METAVIR fibrosis stages and potentially end-stage liver disease (ESLD) complications and death [78, 108, 110, 111]. Patients in METAVIR fibrosis stages F0–F4 incur an annual probability of all-cause mortality [112] whilst patients suffering from ESLD complications incur disease-specific mortality rates [113, 114]. Disease progression is modelled over a lifetime assuming a maximum age of 100 years. Total costs, quality-adjusted life-years (QALYs), and numbers of predicted ESLD complications and deaths are estimated over the simulated period.

Fibrosis stage transition probabilities were informed by characteristics of the screened population with respect to age, sex, HCV genotype and source of infection. Transition rates are incorporated using previously reported rates from a previously published systematic review [104].

Therapeutic intervention is modelled using a decision tree, and is capable of comparing two treatment strategies e.g. treatment vs. no treatment. The decision tree allows the characterisation of adverse events, therapy cessations, therapy outcomes, costs of therapy and monitoring and any disutility incurred. The achievement of SVR is considered equivalent to cure, except in the F4 state where progression to decompensated cirrhosis and hepatocellular carcinoma can still occur.

3 Evaluating the burden of disease of Hepatitis C cirrhosis and linkage to care of these patients

3.1 Introduction

Hepatitis C virus is associated with short term and long-term health sequelae. Whilst in general it is considered to be asymptomatic in the early stages of disease, it associated with fatigue, arthropathy, arthralgia and extra-hepatic complications associated with diabetes, porphyria cutanea tarda and cryoglobulinaemia [115]. Whilst associations with non-hodgkins lymphoma is established, increasingly it is being suggested from epidemiological data that presence of HCV increases risk of many solid organ cancers [116]. As described in Chapter 1 the main long-term sequelae of hepatitis C is related to progression of liver fibrosis and it's associated hepatic complications [104]. Presence of advanced liver disease (Metavir F3 or F4) is associated with complications of cirrhosis, decompensation and hepatocellular carcinoma with increased risk of death [117, 118]. Treatment and SVR is associated with reduced complications and liver related morality [119, 120].

Within health economic analysis treatment of conditions such as hepatitis C with long natural histories does not generally favour early treatment. When considering pure economics, if a fixed budget for hepatitis C treatment was provided then the most cost effective strategy would be to invest the money in something with a higher rate of interest return and treat only at the point before developing advanced fibrosis. This

would therefore account for the fact that not all persons with HCV will develop complications and also increase resource allocations over a longer period of time. However, this theoretical strategy has a number of limitations in the real world. Firstly, there currently isn't a robust and accurate strategy of being able to screen and identify persons likely to transition between F2 and F3 liver fibrosis (an ideal time point for treatment). Secondly, strategies of long term monitoring and follow-up in clinic increases the chances of long term breaks in linkage to care which both potentially increases risk of onward transmission and risk of late presentation with complications. Finally, and more difficult to quantify from an economic point of view is the psychological impact of diagnosing patients with a stigmatising condition and withholding treatment that they may be keen to use.

When considering the impact of treatment of hepatitis C, simplistically it is reasonable to consider that those treated prior to progression to cirrhosis and that achieved sustained virologic response at least 12 weeks after completion of therapy, is generally a durable response [121], and can be considered equivalent to cure. SVR is associated with improvement in liver inflammation and fibrosis [122], estimated increases in work based productivity [123, 124] and likely positive psychological impact to the individual and their family. From healthcare analysis perspectives the effect of SVR prior to developing cirrhosis is purely focused on health effects associated with amelioration of liver injury. In the main extra hepatic, psychosocial and work based productivity are not feasible to be incorporated within the analysis. That said, conflicting data about the effect of SVR suggests that in some populations the effect of treatment can be variable and co-morbidities and lifestyle practices may impact on overall health outcomes [125, 126]. In Scotland in particular data suggests

overall mortality in patients with hepatitis C irrespective of whether they are spontaneous clearers or treatment responders or non responders is ultimately determined by other lifestyle practices, such as alcohol [127]. It is important to recognise that specific populations will have variances in their population lifestyle, behaviours and hazards and it is beyond the scope of the health economic modeling used within this thesis to fully address these. However, when collating all the results within a systematic review patients that do not achieve SVR following treatment have demonstrably worse prognoses with increased all cause mortality, particularly those that have HIV co-infection or presence of cirrhosis [128].

Persons with cirrhosis, whether due to HCV or not, are at risk of complications and require regular monitoring within speciality services:

- Hepatocellular carcinoma: 6 monthly imaging surveillance
- Variceal haemorrhage: 1 to 3 yearly surveillance endoscopy
- Liver transplantation
- Increased risk of decompensation events that may or may not require hospital admissions
- Limited treatment options of HCV, in particular contraindication of interferon in persons with advanced cirrhosis with portal hypertension.

Whilst extensive population based literature is available pertaining to the points above, within this chapter we assess the local burden of hepatitis C related disease. Given that all the screening and treat strategies will be based on single centre experience (Imperial College Healthcare NHS Trust). In this chapter we will assess

the economic impact HCV related cirrhosis and also investigate long term "linkage of care" in patients with cirrhosis. In Chapter 3.2 we assess compliance to recommended 6 monthly surveillance for HCC as a surrogate for linkage to care and the impact of loss to follow up with regards HCC. In Chapter 3.3 we assess the impact of HCV cirrhosis with regards hospital admissions. Whilst it is suggested that SVR has a positive impact on mortality, it is still unclear what the true impact is in those with compensated and decompensated cirrhosis. By looking at admissions, instead of overall mortality, we aim to assess as a surrogate an objective single measure of quality of life.

3.2 Hepatocellular carcinoma surveillance, linkage into care and costs of screening and HCC complications

3.2.1 Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and third commonest cause of death due to cancer [129, 130]. Whilst at an international level, the major burden of disease is in developing countries due to hepatitis B virus (HBV), it is a rapidly evolving problem in Western Countries due to rising trends of hepatitis C virus (HCV), alcoholic liver disease (ALD), and non-alcoholic steatohepatitis (NASH) [130, 131]. In the United Kingdom HCC is responsible for approximately 1500 deaths per year and in the United States it is reported that approximately 20,000 people a diagnosed per year with HCC [130, 132]. Cirrhosis is a major risk factor for development of HCC, with 80-90% of HCCs present in those

with cirrhosis [130]. This reflects the importance in reducing rates of cirrhosis in order to reduce onward risk of HCC.

To date the natural history of post treatment HCV in cirrhotics and those with previous HCC is not fully understood. Reports from Italy suggest that treatment with DAAs in patients with HCV cirrhosis did not reduce risk of future HCC occurrence particularly in those with decompensated cirrhosis [133]. Of greater worry were reports from Spain that demonstrated an unexpectedly high rate and pattern of tumour recurrence from a small cohort of 58 patients with prior HCC who received DAAs. Recurrence was reported in 27% in a short follow-up period with median follow-up of 5.7 months [134]. Of more reassurance, French national registry data retrospectively evaluated outcomes in 189 patients with previously treated HCC who had treatment with DAAs for HCV compared to 78 who did not receive treatment. Whilst this was not a randomized control trial, and thus confounders are likely to impact on the demographics of the two groups, the authors reported no significant difference in the HCC recurrence rates between those treated with DAAs and those that weren't [135].

Randomised control trial data on HCC surveillance in persons with cirrhosis is limited. The only such randomised study was performed in a population of 18,816 Chinese patients with chronic hepatitis B. Patients were randomised 1:1 to 6 monthly screening with AFP and ultrasound versus non screening. This study demonstrated that death from HCC was significantly lower in the screened group compared to control (83.2/100,000 compared to 131.5/100,000) [136]. In persons with cirrhosis, regular surveillance improves the chances of detecting HCC at earlier stages.

Detection and therefore treatment of HCC at early stages is offers individuals affected a greater chance of being offered curative treatments [137]. Tumours picked up at early stage which are suitable for curative therapies have up to a 70% 5 year survival [138], conversely those with advanced tumours have poor outcomes with approximately a 12% 5 year survival [130]. In a United States retrospective cohort of 4482 patients with HCC listed for liver transplantation overall 5-year survival was 62%, however in those with more advanced cancers 5-year survival was 38% [139]. Whilst cost effectiveness data for 6 monthly HCC screening has limited cost effectiveness data available, it appears to be a cost effective strategy [140]. International guidelines have been introduced to guide clinicians in the practice of HCC surveillance. The European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) currently recommend screening of high-risk individuals using abdominal ultrasound scan (USS), at 6 monthly intervals [141, 142].

However, this reliance of early detection with 6 monthly screening requires a commitment from both patients and institutions to maintain lifelong linkage into secondary care services. This poses additional significant financial and also healthcare burden on a population of persons who already will have numerous other likely healthcare needs owing to their cirrhosis. In the context of considering the barriers of linkage to care for screening and treatment of hepatitis C, the longer term outcomes in linkage of care of those with established hepatitis C cirrhosis poses an interesting insight into downstream management issues related to late stage hepatitis C in those either left untreated or who have not been able to achieve SVR at an early enough stage of disease.

In a recent meta-analysis including 47 studies evaluating 15,158 patients, it was suggested that only 41% of HCCs are detected via surveillance. Patients detected with HCC on surveillance were twice as likely to receive curative therapy with better survival rates [138]. Thus far, the small number of studies assessing HCC surveillance specifically demonstrate low utilisation rates for HCC surveillance in patients with cirrhosis [143]. Aetiology, male gender and extremes of age groups have been implicated in the negative likelihood for adherence to screening for HCC [143].

To date, European outcome data for HCC surveillance screening adherence are relatively limited. This study aims to provide the largest single cohort analysis into surveillance utilisation, from a UK perspective. The main aim being to provide an insight into the current burden of HCV cirrhosis from the point of view of screening and HCC outcomes and any indicators for barriers to linkage to care.

3.2.1.1 Hypothesis

This study aims to evaluate the economic and health impact of requiring long term linkage of care in patients that have progressed to hepatitis C cirrhosis by evaluating the real-life utilisation of a hepatocellular surveillance programme in a 6 month cycle

3.2.1.2 Aims

- To evaluate the proportion of patients that have appropriate utilisation of the hepatocellular carcinoma surveillance programme suggesting appropriate linkage to care
- To evaluate the costs required to undertake this programme in Hepatitis C cirrhosis
- To compare utilisation rates to other disease processes causing cirrhosis
- To describe the impact of hepatocellular carcinoma in the study population described

3.2.2 Methods

3.2.2.1 Identifying the cohort of patients with cirrhosis

A retrospective analysis was performed to create a database of all patients with liver cirrhosis at Imperial College Healthcare NHS Trust. The electronic clinic letter database was used to compile a list of patients with documented evidence of cirrhosis from St. Mary's, Hammersmith and Charing Cross hospitals. Patients diagnosed with cirrhosis before 1st October 2013 were identified for inclusion in this cohort. The search term [CIRRHO] was used to detect all clinic letters containing the descriptors 'cirrhosis' and 'cirrhotic'. Only letters dated after January 2012 were included for inspection. Each clinic letter was examined individually to confirm a diagnosis of cirrhosis.

Inclusion Criteria:

1. Histological diagnosis of cirrhosis as determined by an Ishak score of ≥ 5; metavir stage F4 or histopathologist summary description of features in keeping with established cirrhosis
2. Fibroscan > 15KPa
3. Documented clinical evaluation of cirrhosis and established intention to treat patient as established cirrhosis

Exclusion Criteria:

1. Medical reports do not confirm or categorically exclude cirrhosis
2. Duplication of patient or hospital records
3. Patients deceased before 1st October 2013

3.2.2.2 HCC Screening utilisation

HCC screening was assessed through analysis of hospital radiology reporting software. All scans were considered for review per patient dated between 1st October 2013 and 1st April 2014. Scans done within this time frame were categorised as to whether the indication was performed specifically for screening or for alternative indications. Screening scans were classed as 'routine' if performed within the 6-month window and if not 'overdue'. Where it could not be confidently deciphered the scan was listed as "unknown".

Possible explanations for patients falling into the 'overdue' category from hospital records were identified and then broadly grouped into patient and hospital related

factors. Data on liver disease aetiology, Child-Pugh status, presence/absence of HCC and patient demographics were also documented.

We reviewed information on clinic letters and investigation request forms for each patient to establish the intention of each scan to ensure that all scans were correctly attributed to screening or for other indications. Computed tomography (CT) and magnetic resonance imaging (MRI) scans that were explicitly requested for screening were therefore also included for analysis.

All patients with suspected tumours were assessed by the Imperial College Healthcare Liver Cancer Multidisciplinary Team. Hepatocellular carcinoma diagnosis was based on EASL criteria using a 4-phase multi-detector CT scan or dynamic contrast enhanced MRI with typical hallmark of HCC (hypervascular in the arterial phase with venous washout) or histology in indeterminate cases [139]. We defined ablation, surgical resection and liver transplant as curative treatments in line with Barcelona Clinic Liver Cancer classifications (BCLC) [144]. Childs-Pugh classification and BCLC staging at the time of diagnosis were ascertained retrospectively using information gathered from clinical letters and hospital reporting software.

3.2.2.3 Costs of screening and impact of HCC diagnosis

Costs were calculated using Imperial College Healthcare NHS Trust (ICHNT) Tariffs for 2014 (personal communication). Where data could not be collected BUPA tariffs were used (http://codes.bupa.co.uk/procedures).

Modality	Unit Price (£)	Source
Diagnostic ultrasound	44	ICHNT
Liver MRI	188	ICHNT
CT Triple Phase	88	ICHNT
MRI Ablation	4,568	ICHNT
TACE	4,568	ICHNT
Liver Transplant	47,310.55	[108]
Liver Resection	8,334	BUPA
Sorafenib	17,882	British National Formulary

Table 3.1 Costs for diagnostic and treatment modalities associated with an HCC surveillance programme

3.2.2.4 Statistical analysis

Univariate analysis was performed using Wald chi-square tests to assess the significance of potential predictor categorical variables. We used independent samples t-test to compare mean ages between 'routine' and 'overdue' groups and a Mann-Whitney U test to compare distances travelled from home to hospital. Comparison between HCC treatments between those found on "surveillance" and those with "incidental" findings was made using two tailed Fisher exact testing.

Multivariate regression analysis to investigate the influence of these variables was considered in all factors with a $p<0.1$ on univariate analysis.

3.2.3 Results

3.2.3.1 Patient characteristics

1,721 patients were identified using the search term to identify potential cirrhotic patients. Post-exclusion, demonstrated in Table 3.2, we identified 898 patients eligible for HCC surveillance in the study period. The median age of the cohort was 60 years (range 20 to 91 years) and the majority of patients (67%) were male. Table 3.2 summarises patient demographics in this study group. 240 (27%) had underlying HCV cirrhosis

Screened	1721			
Excluded by study criteria	823			
Inclusion for analysis	898			
Reasons for exclusion				
No evidence of cirrhosis	655			
Incomplete clinical documentation	66			
Duplicated cases (between 2 hospitals)	57			
Death (prior to study period)	45			
Demographic variable	**All patients (n=898)**	**Routine (n=587)**	**Overdue (n=311)**	**p-value**
Age (y)*	59.7 (20.6 - 91.6)	59.5 (23.5 - 91.6)	60.0 (20.6 - 91.1)	0.52
<40, *no.* (%)	44 (4.9)	29 (4.9)	15 (4.8)	
40-55, *no.* (%)	287 (32.0)	198 (33.7)	89 (28.6)	
56-70, *no.* (%)	395 (44.0)	248 (42.3)	147 (47.3)	
>71, *no.* (%)	172 (19.1)	112 (19.1)	60 (19.3)	
Male sex, *no.* (%)	599 (66.7)	392 (66.7)	207 (66.6)	0.95
Distance to centre (miles) #	3.6 (0.9 - 232.0)	3.6 (0.9 - 232.0)	3.5 (0.9 - 140.0)	0.65
<10.0, *no.* (%)	773 (86.1)	506 (86.2)	267 (85.9)	
10.1-50.0, *no.* (%)	105 (11.7)	69 (11.8)	36 (11.6)	
>51.0, *no.* (%)	19 (2.2)	12 (2.0)	8 (2.5)	
Aetiology of liver disease, *no.* (%)				
ALD	305 (34.0)	201 (34.2)	104 (33.4)	0.51
Hepatitis C mono-infection	240 (26.7)	165 (28.1)	75 (24.1)	0.59
Other viral hepatitis	98 (10.9)	70 (11.9)	28 (9)	0.77
Autoimmune	42 (4.7)	28 (4.8)	14 (4.5)	0.62
Metabolic	20 (2.2)	9 (1.5)	11 (3.5)	0.15
NAFLD	52 (5.8)	31 (5.3)	21 (6.8)	0.73
Other	32 (3.6)	15 (2.6)	17 (5.5)	
Mixed	109 (12.1)	68 (11.6)	41 (13.2)	0.12
Hepatic compensation, *no.* (%)				
Child-Pugh A	682 (75.9)	444 (75.6)	238 (76.5)	0.81
Child-Pugh B	124 (13.8)	99 (16.9)	25 (8.0)	**0.0002**
Child-Pugh C	63 (7.0)	40 (6.8)	23 (7.4)	0.78
Indeterminate	29 (3.3)	4 (0.7)	25 (8.0)	**<0.0001**
* expressed as mean (range)				
# expressed as median (range)				

Table 3.2 Study population derivation and comparison of patient characteristics and demographics between 'routine' and 'overdue' screening groups

3.2.3.2 Outcomes of the surveillance programme

Of the 898 patients eligible for inclusion, 532 (59%) had an abdominal USS for HCC surveillance within the 6 months study period. When only including investigations where the intention was explicitly for surveillance purposes alone, an additional 55 patients were found to have received surveillance MRI or CT scans (25 MRI and 30

CT). Hence 65% of patients overall underwent HCC screening appropriate to guidelines. 12 patients were identified within the cohort to have clinical comorbidities that precluded them from undergoing surveillance. Allowing for the fact that some decompensated patients with cirrhosis within the cohort may have been too unwell to undergo surveillance, only 444 of the 587 (76%) Child-Pugh A patients with cirrhosis had HCC surveillance as per guidelines. When assessing the 240 persons with HCV cirrhosis, 165 had routine HCC surveillance within the defined 6-month cycle and 75 had overdue surveillance.

Within the overall cirrhosis population reasons for failure to complete surveillance within the recommended 6-month period are summarised in Figure 3.1. The majority of overdue cases (42%, n=131) were found to be due to patient-related factors with the most common being unexplained patient non-attendance for scheduled scans (n=119). The remaining 12 patients were not surveyed due to documented clinical reasons by the responsible clinician that the patient was not for on going screening due to medical co-morbidities. Hospital-related factors accounted for a further 40% (n=125) of patients being overdue, with 116 due to scans not being booked by physicians and 9 due to cancellations by the radiology department. It is possible that some of the 116 scans not booked by clinicians may have due to appropriate medical reasons that were not clearly stated in the notes. In 8 (3%) cases an appropriate surveillance scan was booked but later than guideline recommendations. 3 overdue patients were found to have died during the study period. Across the whole cohort we identified 638 (71%) patients had been under HCC surveillance when the interval was increased to one year.

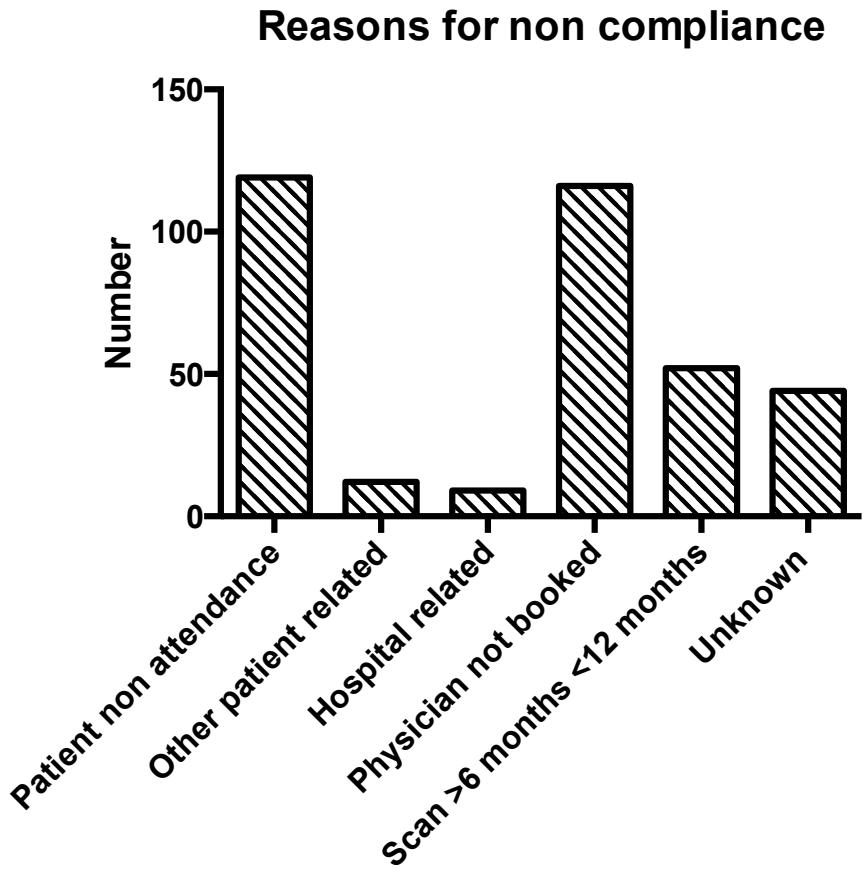


Figure 3.1 Diagrammatic representation for reasons for non-adherence to 6 monthly HCC surveillance within the study cohort.

3.2.3.3 Predictors of surveillance

Potential predictors of surveillance were investigated from a range of socio-demographic data retrieved from patient clinic letters. We found no statistically significant relationship between age (p=0.521) or gender (p=0.947) and the likelihood of a patient being overdue HCC surveillance. Whilst there were significantly more patients with Child-Pugh B cirrhosis in the routine screening group (p=0.0002), overall hepatic decompensation did not reveal any significant difference (p=0.767). The distance travelled to surveillance centre (p=0.647) and aetiology of underlying liver disease (including alcoholic (p=0.509) viral (p=0.166), autoimmune (p=0.624), metabolic (p=0.150), non-alcoholic fatty liver (p=0.736) and mixed aetiology

cirrhosis (p=0.120)) were not significantly associated with rates of HCC surveillance. Multivariate analysis was not performed due to the lack of significance on univariate analysis.

3.2.3.4 HCC detection and outcomes

61 (6.8%) patients were diagnosed with HCC during the study period, table 3.3 outlines underlying aetiologies of cirrhosis. Of these, we noted that 38 cases had been picked up as a direct result of a surveillance scan compared to 9 cases detected incidentally. Method of detection could not be identified from the notes for the remaining 14 cases. Liver biopsy was required for histological confirmation of HCC in 2 cases. Of these 61 HCCs detected 27 (44%) patients had underlying HCV cirrhosis.

	Surveillance group	**Incidental group**	**Unknown group**
Hepatitis C	22 (9%)	2 (1%)	3 (4%)
Alcohol	5 (2%)	1 (1%)	3 (3%)
Non alcoholic fatty liver	0(0%)	1 (3%)	2 (10%)
Other viral hepatitis	1 (1%)	2 (3%)	1 (4%)
Autoimmune	3 (7%)	0 (0%)	1 (7%)
Metabolic	0 (0%)	0 (0%)	2 (18%)
Mixed	7 (6%)	3 (4%)	2 (5%)

Table 3.3 demonstrates the distribution of underlying liver cirrhosis aetiologies in those diagnosed with HCC. In brackets denotes the values as percentages compared to the number screened for each aetiology per group as outlined in Table 3.2

Figure 3.2 demonstrates treatment outcomes between screening and incidentally picked HCCs. Despite a numerical trend towards more curative outcomes in the screening group, statistical significance was not achieved. Out of the 38 cases picked up on surveillance 21 had surgical resection, ablation or transplant, 12 transarterial chemoembolization (TACE) – of which 10 were for palliation and 2 were neoadjuvant, 5 patients were treated with palliative therapy of which 2 received Sorafenib. In the incidentally diagnosed group 2 had curative surgery or ablation, 4 had TACE with palliative intent and 2 further patients were treated with palliative therapy of which 1 received Sorafenib. In this group one patient's treatment outcome could not be accurately ascertained from the data available.

Within the HCV cirrhosis cohort 27 patients were identified with HCC of which 22 were picked up on surveillance, 2 were picked up incidentally and in 3 cases it could not be determined whether diagnosis was through surveillance or not. Of the 22 picked up on surveillance 14 were treated with curative intent (4 resection; 9 ablation; 1 transplant), 7 were treated with TACE and 1 had sorafenib palliative therapy. A further 2 cases were picked up incidentally, i.e. outside of surveillance, of which one had transplant and the other was palliated. 3 cases it was not clear from the documentation whether they were picked up on standard surveillance or incidentally.

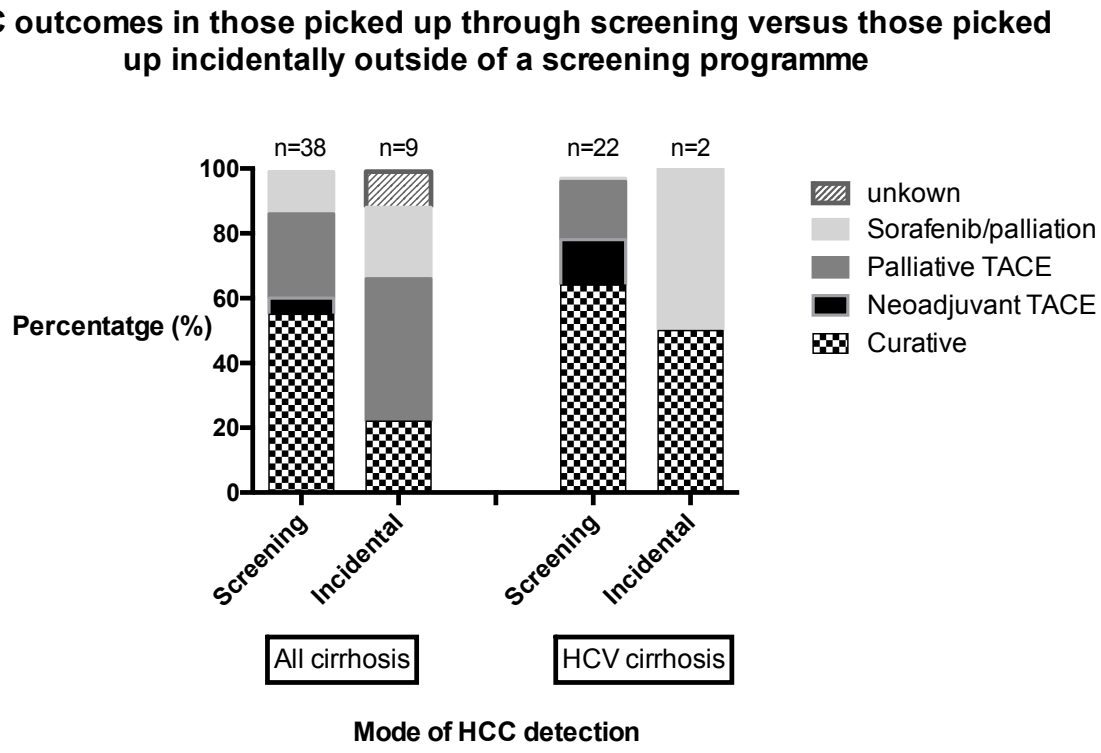


Figure 3.2 HCC outcomes comparison between those diagnosed following screening and those diagnosed incidentally outside of the screening programme

BCLC staging			Child-Pugh Score		
	Surveillance	Incidental		Surveillance	Incidental
0	7	2	A	29	7
A	16	0	B	8	0
B	12	4	C	1	2
C	2	0			
D	1	2			

Table 3.4 Comparison of BCLC and Child-Pugh scores between HCCs identified through surveillance and those identified incidentally.

3.2.3.5 Costs of screening and impact of HCC diagnosis

When considering basic costs within the studied 6-month cycle for screening in persons with HCV cirrhosis, confirmatory imaging for HCC and treatment costs of HCCs detected is approximately £233,560. This only accounts for direct costs and doesn't include infrastructure and overhead costs.

Modality	Number	Cost (£)
Diagnostic ultrasound	170	7,480
Liver MRI	24	4,512
CT Triple Phase	30	2,640
Ablation	9	41,112
TACE	7	31,976
Liver Transplant	2	94,621
Liver Resection	4	33,336
Sorafenib	1	17,883

Table 3.5 Estimated costs of HCC screening within the study cohort population

3.2.4 Discussion

3.2.4.1 HCC surveillance utilisation – an established model of long term linkage to care

HCC screening in patients with liver cirrhosis is an example of a resource intensive complication of progression of liver disease. It requires a life-long commitment from the treating physician, institution and patient in order maintain interval scans in order to gain the benefits of the process. In hepatitis C, in the current era of widely available efficacious treatments it should also be considered a system failure if patients have not been identified and treated before the development of cirrhosis. Overall, the utilisation of HCC screening amongst persons with HCV cirrhosis within this cohort was disappointing. It mirrored the overall population with cirrhosis. When considering the intention to screen within the whole cohort it was estimated that only 12 patients (1.3%) had pre-existing decisions not to undergo screening. Whilst literature in this field is limited, these results appear to support previously reported experiences from many countries that HCC surveillance may not be practiced as efficiently as expected. A previous UK audit of 184 persons with cirrhosis from a single centre reported that 52% of patients received six-monthly surveillance appropriately [145]. However, in the UK and Europe little information exists on HCC surveillance utilisation. However, in other developed healthcare states it appears that sub-optimal linkage to care for HCC surveillance is also experienced.

In the USA, differences in the healthcare system structure mean that non-gastroenterologists may be responsible for HCC surveillance. In a cohort of 1,873 patients identified with HCC with prior diagnosis of cirrhosis, only 29% of patients

were identified to have undergone regular surveillance. Being seen by a gastroenterologist/hepatologist ensured a 4.5 fold increased chance of receiving regular surveillance and 2.8 fold if seen by a physician with academic affiliation [146]. In our cohort, all patients with cirrhosis were under the care of gastroenterologists or hepatologists in university teaching hospitals, which may in part explain the superior utilisation rates in comparison. In a single-centre study at the University of Michigan in 2010 out of 160 cirrhotic patients routine surveillance was performed in 75%. However, it should be noted that the authors deemed that routine ultrasound surveillance be done yearly as opposed to 6 monthly as used in our study [147]. When using these parameters 71% of our study patients were surveyed. Indeed, a worrying population-based systematic review of HCC screening literature in 2012 suggested that fewer than 20% of patients at high risk of developing HCC undergo any form of regular surveillance [143].

3.2.4.2 Barriers to HCC surveillance

When considering causes for under utilisation of HCC screening, it is possible to identify potential factors that prohibit linkage to care on a more general healthcare level too. Where possible we obtained reasons for cases failing to adhere to surveillance guidelines. As discovered in previous studies, our analysis suggested that potential points of failure in the service appeared to fall into two main groups: patient-related factors and hospital-related factors [148, 149]. We found that non-attendance at scheduled USS appointments was the most common patient-related reason for individuals being overdue surveillance (42% of cases). This may be because patients are wilfully choosing not to attend but could also occur if patients are forgetting appointments. Co-morbities such as encephalopathy, cognitive impairment and

depression, which are all associated with cirrhosis, may in part contribute to this [150]. However, continued patient reinforcement and education can only further improve chances of improved patient participation which has been shown to have a positive impact on HCC surveillance adherence [147].

The main system-related factor appeared to be failure to schedule USS appointments. A 3-year audit cycle looking into HCC surveillance in 22 viral hepatitis patients in Adelaide, Australia identified doctor education as one of three key areas for improvement and demonstrated a 100% improvement in adherence to routine surveillance at completion compared to baseline [151]. Improving physician awareness, especially of non-hepatologists, of international guidelines may therefore reduce the number of missed scans. Given 25% of UK gastroenterologists surveyed were unaware of HCC surveillance guidelines this demonstrates the on-going need to reinforce the guidelines amongst those required to be responsible for surveillance [140]. Similar issues of limitations in healthcare provider attitudes impeding adequate HCC surveillance have also been recognised in the United States. A web-based survey of 131 primary care providers (PCP) in Dallas demonstrated only half believed that HCC screening reduced mortality. Furthermore incorrect perceptions of appropriate surveillance were demonstrated. 45% believed clinical examination was effective, 59% liver enzyme testing and 89% believed AFP alone were effective tests [152]. It must be appreciated as well that unbooked scans by physicians may also be reflective of time pressures or clinical decisions that may not have been captured within the remit of this study.

Our study found no association between any socio-demographic factors and the likelihood of receiving routine guideline-recommended surveillance. Whereas previous studies have demonstrated possible associations between aetiologies such as viral hepatitis and increased likelihood for utilisation of HCC screening no such association was noted between the various aetiologies in this study [147].

3.2.4.3 HCC outcomes

To date cost effective analyses has suggested that HCC surveillance is cost effective when pick up incidence is at least 1.5% to 6% per year [153]. Within this study cohort 61 (6.8%) new HCC cases were picked up overall within the 6-month surveillance period studied. 38 out of 587 (6.5%) patients that underwent routine screening were diagnosed with HCC. At least 62% of HCCs within this study period were identified as a direct result of screening which compares favourably to previously published literature [138].

Interestingly, it appeared that HCV was an important cause for HCC. Whilst statistically it is not possible to make any clear conclusions HCV was an underlying cause in 27 of 61 (44%) of HCCs identified within this cohort. Whilst overall rates of adherence to screening within the total HCV cohort were similar to other aetiologies, the majority of HCCs picked up were in those that attended for screening scans. It is estimated that approximately £233,560 was spent on direct screening and treatment costs for persons with HCC cirrhosis within this surveillance programme. This is likely to be a significant underestimation as it does not factor in overhead costs.

HCCs picked up during surveillance were associated with a 61% chance of curative therapy compared to 25% in those picked up incidentally which supports the findings

elsewhere [154]. Whilst this study did not demonstrate a statistically improved chance of curative therapy with HCCs picked up through screening it must be emphasised that this was not the primary endpoint of the study and the total number of HCCs were too small to make any categorical conclusions.

To our knowledge this is the largest study to date on HCC surveillance utilisation in cirrhotic patients within the UK. However limitations of the study are related to the retrospective nature of data collection. Missing or incomplete data capture from clinical letters introduces the risk of measurement bias. Patients were identified as having cirrhosis by different modalities. Although very few would have had a diagnosis based solely on a fibroscan reading it is possible that patients with cirrhosis could have been missed given our inclusion criteria of 15KPa. In HCV specifically, fibroscan has demonstrated reasonable validity in predicting cirrhosis in persons with liver stiffness values greater than 12.4KPa. In other aetiologies, particularly cholestatic disorders the evidence base is more limited and possibly higher readings of 17.3KPa are required to demonstrate cirrhosis [155]. Given that we were evaluating patients with all aetiolgies of liver diseases, and appreciating that there is heterogeneity in validity of fibroscan to diagnose cirrhosis an arbitrary cut off of 15 KPa was used. The study design aimed at including only patients with categoric cirrhosis that fulfilled the criteria for HCC screening and we aimed to include those with very likely cirrhosis as opposed to advanced fibrosis.

Furthermore, data was not collected on co-morbidities or performance status as this could not be consistently measured in a standardised way between individual clinic

letters. This may explain why clinicians, who may have failed to make their intentions clear in the clinic letters, did not survey those patients. We may therefore have under-represented the surveillance utilisation from a true intention to screen perspective. This study only looked at one cycle of HCC screening, it is possible that consistent surveillance rates (i.e. over multiple 6 monthly cycles) may be lower. The study population, being inner city London teaching hospitals, may not truly reflect both national or European practice and patient demographics per se. Further collaborative work with multicentre registry studies may better answer the question of how effectively HCC screening is being performed at an international level. In terms of assessment of outcomes no randomised clinical trials have been performed evaluating whether patients with cirrhosis that undergo surveillance versus no surveillance have a superior outcome, but this study certainly supports the notion that it does.

HCC surveillance in patients with cirrhosis is sub optimally adhered to despite evidence that HCC detection during surveillance is more likely to be at an early enough stage to be treated curatively. Whilst patient non-attendance is a significant factor, physician and hospital related factors are equally important to be addressed. To date the literature has demonstrated that we pick up less than half of HCC on surveillance. This study suggests that a major reason is that the guidelines are not being adhered to and that probably more formalised processes and infrastructure are required to ensure that surveillance is performed more adequately. Importantly, it emphasises the benefit in early treatment of HCV prior to the development of cirrhosis, both to reduce subsequent risk of HCC and also to reduce the burden of ensuring long term linkage to specialist services that are required in patients with cirrhosis.

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3.3 Impact of hepatitis C related cirrhosis and analysis of effect associated with treatment

3.3.1 Introduction

The premise of this thesis is to examine the economic and health impacts of early diagnosis through improvement of screening strategies. In order to understand the potential benefits of such strategies, we examine the impact of current practices where unfortunately many patients with hepatitis C progress to cirrhosis. Furthermore, we aim to examine what impact treatment at late stages of liver disease have on both the patients and also health care providers as a result of morbidity requiring hospital admissions.

Infection with hepatitis C virus is generally considered asymptomatic in early stages of disease, although fatigue, mood disturbances and extra hepatic complications often present in patients with HCV. Whilst difficult to quantify they are implicated in reduced work based productivity [124]. The most tangible and quantifiable effects of hepatitis C tend to be following the development of cirrhosis and it's associated complications. Extra hepatic manifestations are also relevant and are an important cause of morbidity and mortality [156]. Untreated HCV is associated with greater economic and healthcare burdens. Recent Italian cohort data suggests that in persons with compensated HCV cirrhosis, achievement of SVR is associated with levelling of survival curves comparable to that of the general non-HCV population [126].

Conversely, many studies have demonstrated that failure to achieve SVR is associated with negative outcomes.

A Danish registry study followed up 178 patients with acute non-A, non-B hepatitis from 1969 to 1987. Assessment for death certificates and diagnoses at discharge following all somatic admissions. After 23 years, 71 (40%) had died. Mortality due to cirrhosis and accidents were significantly higher compared to those of an age and sex matched Danish population. Cirrhosis was diagnosed in 9% [157]. Similarly records in Scotland of 20,969 patients with hepatitis C between 1991 and 2006 demonstrate the long-term impact of HCV due to complications of developing cirrhosis. 995 individuals were admitted to hospital with first presentation of decompensated cirrhosis with 63 deaths during follow-up (median 5.2 years). The number of new cases increased between 1996-2005 on average by 11% per annum. Risk of developing decompensated cirrhosis was greater for men, those with co-infection with HIV, those with a prior alcohol related admission and with increasing age. [158]

In the United States paid claims data for commercial insured patients were used to identify 2 matched cohorts of 8861 patients with and without HCV. This study excluded patients with cirrhosis. Costs of treating matched patients with HCV was $37,390 compared to $13,575 without. Incremental costs were associated with higher costs of ambulatory care, hospital services and HCV was associated with significantly higher risk of hospitalisation (odds ratio = 2.5) [159]. A separate US study of admissions with complications of cirrhosis between 1998 and 2003 demonstrated presence of HCV was associated with up to 23.7% of admissions. In-patient mortality

was 2.1 per 100,000. Average hospital charge per HCV patient $29,539 and total yearly costs up to £2.11 billion [160].

Currently, it is widely accepted that treatment of HCV prior to the development of cirrhosis is associated with durable viral clearance and reduction of liver related risk [161]. Furthermore it is suggested that fibrosis regression may ensue [122]. However, the development of cirrhosis poses a number of challenges. Firstly, interferon based regimens may not be safe in patients with more advanced liver disease [162]. Therefore patients with decompensated cirrhosis may need to considered for liver transplantation as a definitive treatment to reduce their risk of cirrhosis related complication. This is obviously associated with significant healthcare cost and also many patients may not be eligible for liver transplantation. More recently the advent of interferon free regimens has provided a true paradigm shift and these patients are now being offered treatment of hepatitis C [163-165]. However, it is too early to know what the true impact of such treatments are on the natural history of patients with decompensated cirrhosis.

Secondly, the presence of cirrhosis, even following successful eradication of the virus is associated with on-going risk of decompensation and HCC [166-168]. In a retrospective cohort study including 33,005 patients previously treated with interferon-based therapies, the most significant risk factor for developing hepatocellular carcinoma was the presence of cirrhosis (HR 6.69; 95% CI 4.32-10.35) [169]. In this study the overall background yearly prevalence of HCC was 0.33% rising to 1.39% in those with cirrhosis. Some smaller retrospective cohorts have suggested improvement in HCC and liver related mortality associated with interferon

based therapies [170]. However the consensus is that HCC surveillance should still continue in persons with cirrhosis irrespective of HCV treatment outcomes [142].

Some controversy has been assigned to the benefits of SVR attributed to extrapolated data from both prospective and systematic reviews of patients who had failed interferon therapies. A prospective study assigning low dose interferon for 3.5 years after treatment failure compared to placebo. Within this study it was concluded that despite viral decline on treatment progression of liver disease did not differ compare to placebo [171]. A systematic review assessing the benefits and harms of interferon monotherapy retreatment in chronic hepatitis C also concurred that no difference in outcomes were noted and in fact long term interferon therapy may be harmful [172]. Subsequently these findings have been extrapolated as part of an argument to suggest that SVR has not got a validated and proven beneficial effect in patients with hepatitis C [173]. These findings are in contradiction to data sets that primarily look at effects of SVR from short term treatment options and caution should be placed in extrapolating the observations seen while administering long term interferon therapy [94, 174, 175].

To date the largest systematic review of data looks at the all-cause mortality in patients who had been treated with interferon based therapies and comparing outcomes between those that achieved SVR and those that did not achieve SVR [161]. The authors cite the use of all cause mortality as the defined end-point to both examine the effects of extra-hepatic causes of HCV related effects and also to improve applicability of findings to low and middle income countries where liver transplantation is not an available option. The authors report that from the evidence

based on 33,360 patients that 5-year mortality was reduced by 50% in general cohort SVR vs. No SVR and 74% in those with cirrhosis. Whilst supportive of the benefits of SVR and at earlier stages of disease, there are limitations of such a study. By nature of methodological design ther is potential bias when considering differences in data reporting, quality and impact of multivariate analyses. The analysis also only considered treatment experienced patients and compared those who achieved SVR to those who didn't. It is conceivable that patients that did not achieve SVR may have inherent baseline characteristics or co-morbidities that offer a reduced survival advantage.

The aim of this study is to assess the burden of HCV cirrhosis. Whilst SVR may provide a survival advantage compared to no HCV, it is not clear whether actual complications and quality of life of these patients are impacted by the presence of cirrhosis differently. Whilst life year gained (LYG) is an important metric in health economics, the rationale for preference of use of QALYs is to justify an intervention that improves quality of life and not just quantity. We investigate the impact of SVR compared to treatment experienced by patients who did not achieve SVR and also those that never received treatment before. We study hospital admissions as an objective metric of morbidity as a surrogate for QALYs. Hospital admissions both have per patient quality of life implications but also direct cost impacts to health payers making it a interesting metric to study in this scenario.

3.3.1.1 Hypotheses:

Hospital admissions events and corresponding admission days in patients with hepatitis C cirrhosis are likely to be less frequent in those who have previously achieved SVR compared to those who have not achieved SVR. Treatment of decompensated cirrhosis patients is likely to provide beneficial effect by reducing chance of admissions subsequent to treatment.

3.3.1.2 Aims:

- To evaluate hospital admissions for all patients with hepatitis C cirrhosis over a one and two year time horizon.
- To evaluate outcomes of decompensated liver cirrhosis treated with direct acting antivirals, comparing the admission rate the year before and after treatment.
- To compare all cause admissions, liver related and non-liver related admission days and separate admission events
- To evaluate predictors of admissions in persons with hepatitis C cirrhosis

3.3.2 Methods

The study was conducted analysing hospital admission data in patients with confirmed HCV cirrhosis starting from 1st June 2013. Using the methods of identification of the cirrhosis cohort described in Chapter 3.2.2.1 240 with HCV were included for analysis of hospital admissions. The primary analysis was performed assessing 1-year follow-up in patients who were not on active HCV treatment between 1st June 2013 and 1st June 2014. In June 2014, access to DAA treatments became available to patients in this study cohort who had evidence of decompensated liver cirrhosis as part of the Early Access Programme (EAP). A secondary analysis was performed looking at 2-year admission rates. Recognising the bias that would be incurred by analysing outcomes of these patients on DAA regimes with decompensated cirrhosis the secondary analysis was split into two sub-analyses. As all patients on active treatment at the time of study analysis were excluded the 2 year follow-up analysis essentially analysed patients with compensated cirrhosis between 1st June 2013 to 1st June 2015. To measure the effect in decompensated cirrhosis the second sub-analysis looked at admission rates in the 1 year preceding initiating DAA therapy and compared it to one-year post completion of DAA therapy. Events during the twelve-week duration of therapy were excluded from analysis. 40 patients were included for analysis as patients treated as part of the Early Access Programme (EAP) between June 2014 to October 2015. Data was collected in this cohort until January 2016, which was the date one-year post completion of treatment for the last patient within the cohort that was treated with DAA therapies. Patients that were transplanted during treatment and who were continuing treatment at the time of transplant had

admissions measured post cessation of the therapy. Figure 3.3 demonstrates the outline for timelines of analysis.

3.3.2.1 Study Inclusion Criteria

Patients were included for analysis if they were aged above 18 years of age, had medical records indicating blood results or clinical assessment at the study centre after March 2013, and evidence of cirrhosis as outlined in Chapter 3.1. Patients were excluded if there was evidence of co-infection with HIV or hepatitis B and/or if they had deceased prior to June 2013.

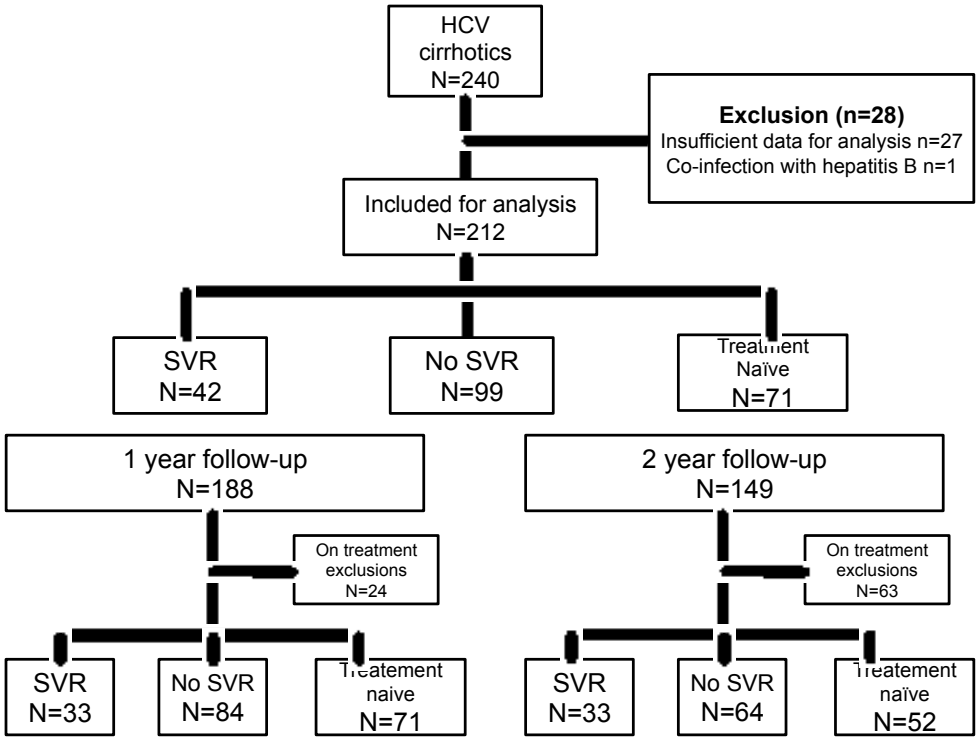


Figure 3.3a is a flow diagram demonstrating the numbers for inclusion within the 1 year and the two year follow-up studies.

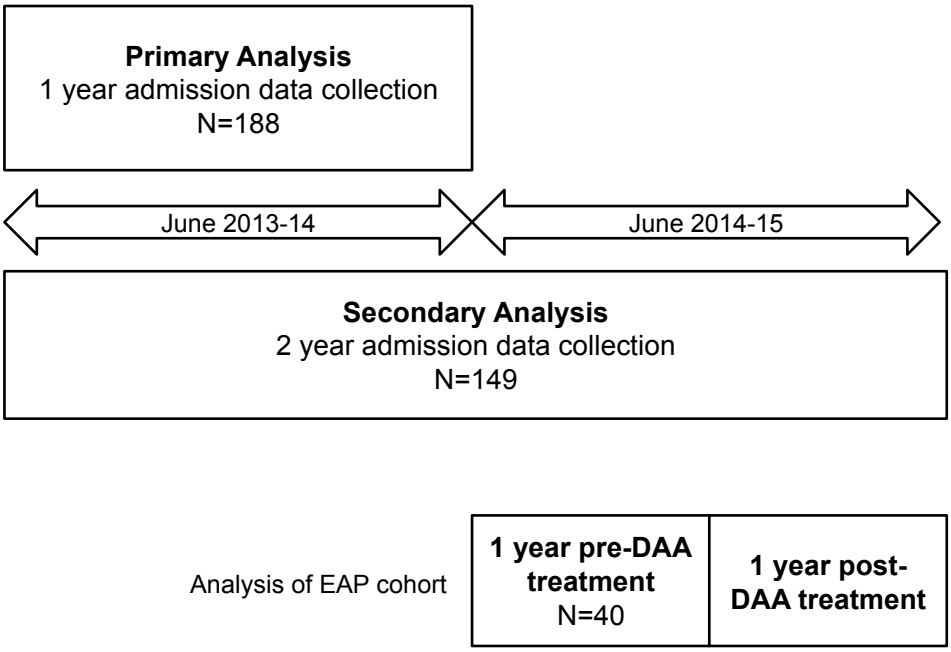


Figure 3.3b Study outline demonstrates the primary analysis of 1 year follow-up looking at number of hospital admissions between 2013-14. The Secondary analysis reports hospital admissions from 2013-15. Finally a sub-study of EAP patients review the hospital admissions one year pre and then post treatment with DAAs in persons with decompensated HCV cirrhosis.

3.3.2.2 Data Collection

As described in Chapter 3.2, hospital electronic databases were used to compile data on patient demographics such as date of birth, gender and ethnicity. HCV specific data included first date of HCV diagnosis, treatment dates, duration and outcome. Data was also collected on documented date of cirrhosis and co-morbidities. Blood tests including liver function tests, full blood count, prothrombin time and renal function were also collected and used to calculate MELD and UKELD scores at baseline and then calculated for 6 monthly intervals. Liver histology and Fibroscan data were collected.

Three separate groups were analysed: those who had previously had treatment and achieved SVR (SVR group), those who did not achieve SVR following therapy (No SVR group), and those that were treatment naïve (Treatment Naïve group). The primary data for hospital admissions were collected from Trust discharge summaries. Presenting cause for admission was listed as well as data on liver transplantation, HCC and death. Data on hospital admissions included number of admission events, number of days per admission including days on ITU and reason for admission. Hospital admissions were then defined as liver related if evidence of variceal bleeding, sepsis with or without spontaneous bacterial peritonitis, ascites, encephalopathy or HCC. Admissions deemed to be unrelated to underlying liver disease were classified non-liver related. All data was compiled in an anonymised Microsoft Excel spreadsheet.

3.3.2.3 Statistical Analysis

Baseline characteristics were compared between the three groups using Kruskall-Wallis. To compare the significance between 2 individual groups Mann-Whitney U test was performed where the data was continuous and Chi-Squared where data was categorical. For each analysis hospital admissions were evaluated as both admission events and admission days as Kruskall-Wallis testing between the three groups and Mann-Whitney U test for admission days and admission events.

Predictors of admissions was analysed using Mann-Whitney U tests for the following variables: genotype, platelets, albumin, MELD and UKELD. Chi Squared testing was applied to cohort type, ethnicity and gender. Multivariate analysis using binary logistic regression was performed on independent variables that demonstrated significance with a p-value of <0.1. To evaluate effect of SVR independent of severity of underlying cirrhosis, adjustments for MELD, at a cut off of 15, and UKELD of 49 were also performed. These cut-off values were used based on the values used as criteria for transplantation [176, 177]. All Kruskall-Wallis, Mann-Whitney U tests and Chi Squared tests were performed using Prism 6 and multivariate analysis was performed using IBM SPSS version 22.

3.3.3 Results

Table 3.6 demonstrates the baseline characteristics for the study cohort. Of the 212 patients included for analysis 73.1% were male and 47.2% were Caucasian. Genotype 1 and 3 were the most common genotypes. Forty-two (19.8%) had previously been treated and achieved SVR, 99 (46.7%) had prior treatment but failed to achieve SVR and 71 (33.5%) were treatment naïve. Of those who had prior treatment and failed to achieve SVR with interferon based therapies 52% were null responders and 47% were relapsers and 1% due to intolerance to treatment (drug allergy).

	SVR	No SVR	Treatment Naive	*p-value*
Total Patients	42	99	71	
Age (Range)	54 (39 – 76)	57 (35 – 75)	60 (37 – 87)	**0.0044**
Gender (%)				
Male	28 (67)	75 (76)	52 (73)	
Female	14 (33)	24 (24)	19 (27)	0.54
Race (%)				
Caucasian	20 (48)	49 (49)	31 (44)	
Black	8 (19)	17 (17)	14 (20)	
Asian	2 (5)	9 (9)	13 (18)	
Other	12 (28)	24 (25)	13 (18)	0.33
Genotype (%)				
1	16 (38)	36 (36)	24 (34)	
2	3 (7)	4 (4)	5 (7)	
3	15 (36)	38 (38)	18 (25)	
4	1 (2)	19 (19)	15 (21)	
Unknown	7 (17)	2 (2)	9 (13)	**0.014**
Null Responders (%)	0 (0)	51 (52)	0 (0)	
Relapse Patients (%)	0 (0)	47 (47)	0 (0)	
Stopped Treatment* (%)		1 (1)		
Time Since Last Treatment (Months)	48 (24, 78)	60 (36, 96)		0.23
Fibroscan Score (kPa)	14.6 (9.9, 18.5)	15.5 (12.7, 26.6)	35.3 (20.6, 61.8)	**0.0017**
Albumin (g/L)	40 (37.5, 43)	37 (33.8, 40)	34 (28.8, 37)	**<0.0001**
Bilirubin (µmol/L)	12 (9, 18.8)	14 (10, 21)	16.5 (11.8, 31.5)	**0.014**
Prothrombin Time (s)	11 (10, 12)	11 (11, 12)	12 (11, 14)	**0.042**
Platelet Count (x10^9/L)	144 (111, 211)	130 (87, 166)	103 (65, 160)	**0.04**
Creatinine (µmol/L)	70 (63, 90.5)	72 (64, 84)	75 (66, 104)	0.19
UKELD Score	47 (46, 50)	49 (46, 51)	49 (47, 52)	0.079
MELD Score	14 (12, 17)	15 (13, 17)	18 (15, 21)	**0.0021**
Co-Morbidities: Presence of: (%)				
Recorded Mental Health	2 (4.8)	5 (5.1)	7 (9.9)	
CVD/Metabolic Syndrome	7 (16.7)	20 (20.2)	21 (29.6)	
Organ Dysfunction	6 (14.3)	11 (11.1)	10 (14)	

Numbers represent median and in brackets is percentage or IQR
***patient stopped treatment at week 6 due to allergic reaction*
CVD (Cardiovascular Disease)
Statistical differences denoted between groups were noted between treatment naïve and the other 2 groups. Significant differences only noted between SVR and No SVR Group for albumin

Table 3.6 Baseline Characteristics

3.3.3.1 One Year Follow-up

After exclusion of 24 patients who were undergoing treatment during this study period, 188 patients were included for analysis. Those included for analysis were subdivided into three groups (SVR, No SVR and treatment naïve) with a view to comparing hospital admission outcomes as a function of their treatment status. Of these, 33 (17.5%) had achieved SVR (SVR group), 84 (44.7%) had not achieved SVR following treatment (No SVR group) and 71 (37.8%) were treatment naive. At baseline age, genotype, prothrombin time, albumin, bilirubin, creatinine, fibroscan and MELD scores were significantly higher in the treatment naïve group compared to the other two groups. Table 3.7 reports admission days per group for both 1-year and 2-year follow-up.

Total hospital admission days: Days spent in hospital for all causes were significantly different between the three groups (p=0.042). When comparing admissions between the SVR group and the treatment naïve group there were significantly reduced admissions (p=0.014). No other significant differences were noted between No SVR group and the SVR group nor the treatment naïve group.

Liver related admission days: When assessing for liver specific admissions a significant difference in admissions was noted between the 3 groups (p=0.018). Achievement of SVR was associated with no liver related admissions compared to 113 admission days and 203 admission days in the No SVR and treatment naïve groups. This represents 0 admission days per person in the SVR group, 1.35 days per person in the No SVR group and 2.86 days per person in the treatment naïve group. Liver related hospital admissions were significantly lower in the SVR group compared to the No SVR group (p=0.0093) and treatment naïve groups (p=0.0049)

Non-Liver related admission days: No significant difference was observed between the three groups (p=0.5212).

1 year follow-up	**Admission Days (days per patient per year)**			**p-values**		
	SVR	No SVR	Treatment Naive	SVR vs. No SVR	SVR vs. Treatment Naive	No SVR vs. Treatment Naive
Total Admission Days	8 (0.24)	148 (1.76)	330 (4.65)	0.078	**0.014**	0.22
Liver related admission Days	0 (0)	114 (1.35)	203 (2.86)	**0.0093**	**0.0049**	0.65
Non-Liver admission days	8 (0.24)	35 (0.42)	127 (1.79)	0.50	0.78	0.27
2 year follow-up						
Total Admission Days	45 (0.68)	147 (1.15)	441 (4.24)	0.19	**0.0003**	**0.0024**
Liver related admission Days	0 (0)	88 (0.69)	221 (2.13)	**0.029**	**0.0015**	0.12
Non-Liver admission days	45 (0.68)	59 (0.46)	220 (2.12)	0.72	0.077	**0.012**

Table 3.6 Comparison of Admission days per cohort and paired statistical analysis.

3.3.3.2 Two Year Follow-up

After excluding those on treatment during this period 23 patients from the original study period remained excluded and one patient who in the first study period was on interferon based treatment was treated with DAAs as part of the EAP and therefore was included in analysis separately as part of the EAP analysis, which included a further 39 patients. Of the EAP cohort 21 were treatment experienced and 19 were treatment naïve.

Total hospital admission days: In a 2-year period the SVR group had a total of 45 admission days, the No SVR group 147 days and the treatment naïve group 441 days which was significantly different (p=0.0003). This corresponded to 0.68, 1.15 and 4.24 admission days per patient respectively. Being treatment naïve was significantly more likely to have admission days compared to SVR (p=0.0003) and treatment experienced but no SVR (p=0.0024)

Liver related admission days: As per the 1-year analysis there were no liver related admissions in the SVR group. In the No SVR group there were 88 admissions and in the treatment naïve group 221, corresponding to 0.69 and 2.13 admission days per patient respectively. In this analysis presence of SVR conferred significantly less chance of liver related admissions compared to no SVR (p=0.029) and treatment naïve (p=0.0015). No statistical difference was seen between No SVR and treatment naïve patients.

Non-Liver related admission days: When assessing for non liver related admissions the treatment naïve group appeared to have more admission days than the other two groups: 220 days compared to 45 in the SVR group (p=0.077) and 59 in the No SVR group (p=0.012).

3.3.3.3 Liver Related Hospital Admission Events

In order to investigate whether the number of separate admissions were different between the three groups a separate analysis was performed on the number of liver related admission events.

1-year follow-up: there were a total of 25 admissions in the No SVR group (range 0-6) and in the Treatment Naïve group 31 admission (0-7). This corresponded to 0.30 and 0.44 events per person respectively.

2-year follow-up: there remained no admissions in the SVR group, 24 in the No SVR group and 31 in the Treatment Naïve group. This corresponded to 0.38 admissions per patient in the No SVR group and 0.60 admissions per patient in the treatment naive group. Table 3.8 demonstrates that liver related admission events were significantly lower in the SVR group compared to both No SVR and Treatment Naïve groups.

	Liver Related Hospital Admission Events		
	SVR vs. No SVR	**SVR vs. Treatment Naive**	**No SVR vs. Treatment Naïve**
1 Year Follow-up	**0.011**	**0.0049**	0.61
2 Year Follow-up	**0.029**	**0.0015**	0.15

Table 3.7 Comparison of statistical outcomes between individual cohorts with regards to number of discrete liver related hospital admission events

3.3.3.4 Analysis of Baseline predictors of admission

Baseline demographic, HCV related and markers of severity were analysed to look for predictor of admission within the primary analysis:

- MELD **p = 0.0301**
- Albumin **p < 0.0001**
- UKELD **p < 0.0001**
- Platelet **p = 0.0013**
- Cohort (SVR vs. No SVR vs. Treatment Naïve) **p=0.0006**
- Genotype p = 0.5542
- Ethnicity p =0.7459
- Gender p = 0.1462

All factors with a p-value <0.1 were entered into multivariate analysis, demonstrated in Table 3.9 which demonstrated UKELD was a significant predictor of hospital admissions. Treatment experience with SVR and platelets appear to have an effect but did not reach significance.

Predictors of admission	Odds Ratio	Confidence Interval	p-value
MELD	0.95	0.84-1.49	0.47
UKELD	1.29	1.07-1.57	0.009
Albumin	0.88	0.77-1.00	0.042
Platelets	0.99	0.99-1.01	0.44
Cohort	1.54	0.60-3.93	0.37

Table 3.8 Results of multivariate analysis using binary logistic regression to evaluate predictors of liver related hospital admissions

3.3.3.5 Adjustment for UKELD

Results of multivariate analysis suggest UKELD is a significant independent predictor of liver related admissions. Patients are deemed eligible for consideration for liver transplantation at a UKELD score threshold of 49. Therefore an analysis of admission events was performed correcting for patients with a UKELD less than 49. As a result analysis was performed on 130 patients in the 1-year analysis (SVR: n=27, No SVR: n=56, Treatment Naïve: n=47) and 111 patients in the 2-year analysis (SVR: n=27, No SVR: n=46, Treatment Naïve: n=38). Table 3.10 appears to demonstrate when adjusting for UKELD there appears to be a significant difference in liver related admission days and events when comparing those that achieved SVR with those that were treatment naïve.

1 Year Follow-up	UKELD adjusted p-values		
	SVR vs. No SVR	**SVR vs. Treatment Naive**	**No SVR vs. Treatment Naïve**
Total Admission Days	0.58	0.085	0.13
Liver Related Admission Days	0.17	**0.045**	0.15
Non-Liver Related Admission Days	0.38	0.93	0.26
Liver related Events	0.17	0.055	0.36
2 Year Follow-up			
Total Admission Days	0.38	**0.0042**	**0.0016**
Liver Related Admission Days	0.079	**0.0035**	0.091
Non-Liver Related Admission Days	0.61	0.25	0.063
Liver related Events	0.079	**0.0038**	0.11

Table 3.9 demonstrates results of adjustment of UKELD scores for 1 and 2 year Follow-up

3.3.3.6 Effect of Time since treatment on outcomes

The UKELD adjustment suggested that there was little difference in outcomes for patients that achieved SVR and those that were treated but that did not achieve SVR. When comparing baseline characteristics of these two groups they were well matched prior to UKELD adjustment with only significant difference in albumin 40 (37.5,43) in the SVR group compared to 37 (33.8-40) in the No SVR group. When considering whether duration since HCV therapy may have a role on outcomes in the SVR group 37% had achieved SVR greater than 5 years ago prior to June 2013 and in the No SVR group 59% had first treatment greater than 5 years prior. Comparison was made in those that achieved SVR within the preceding 5 years to June 2013 compared to those that achieved SVR greater than 5 years ago. In the No SVR group time since first treatment failure less than or greater than 5 years was also assessed. There was no evidence of impact on either total admissions nor liver related admissions when considering time since treatment when using Fishers exact testing on 2x2 comparisons of evidence of admission versus no evidence of admission.

3.3.3.7 Reasons for Admission

Liver related admissions were most commonly due to variceal bleeding and ascites. On admission, HCC was newly identified in 1 patient during the 1-year follow-up and 2-year follow-up in the No SVR group, compared to 0 patients in the SVR group. In the treatment naïve group 1 patient in the 1-year follow-up and 2 patients in the 2-year follow-up had newly identified HCC on admission. Tables 3.11 and 3.12 demonstrate reasons for admission in the 1 and 2 year follow-up cohort.

Clinical Indication	SVR [n=33] (%)	No SVR [n=84] (%)	Treatment Naïve [n=71] (%)
Variceal Bleeding	0 (0)	4 (4.8)	4 (5.6)
Ascites	0 (0)	3 (3.6)	5 (7.0)
Encephalopathy	0 (0)	2 (2.4)	3 (4.2)
Sepsis/SBP	0 (0)	3 (3.6)	2 (2.8)
HCC	0 (0)	1 (1.2)	1 (1.4)

Table 3.10 Clinical indications for liver related admissions on presentation within the 1 year follow-up arm

Clinical Indication	SVR [n=33] (%)	No SVR [n=64] (%)	Treatment Naïve [n=52] (%)
Variceal Bleeding	0 (0)	2 (3.1)	3 (5.8)
Ascites	0 (0)	2 (3.1)	5 (9.6)
Encephalopathy	0 (0)	1 (1.6)	2 (3.8)
Sepsis/SBP	0 (0)	4 (6.3)	2 (3.8)
HCC	0 (0)	1 (1.6)	2 (3.8)

Table 3.11 Clinical indications for liver related admissions on presentation within the 2 year follow-up arm

	1 Year Follow-up			2 Year Follow-up		
Death	**SVR [n=33] (%)**	**No SVR [n=84] (%)**	**Treatment Naïve [n=71] (%)**	**SVR [n=33] (%)**	**No SVR [n=64] (%)**	**Treatment Naïve [n=52] (%)**
All	0 (0)	1 (1.2)	0 (0)	2 (6.1)	2 (3.1)	8 (15.3)
Liver Related	0 (0)	1 (1.2)	0 (0)	0 (0)	2 (3.1)	3 (5.8)
Non-Liver Related	0 (0)	0 (0)	0 (0)	2 (6.1)	0 (0)	2 (3.8)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (5.8)
On admission	0 (0)	1 (1.2)	0 (0)	1 (3.0)	1 (1.2)	2 (2.8)

Table 3.12 Causes for death per cohort in the 1 and 2 year follow-up arms.

Table 3.13 demonstrates the overall number of deaths in the 1 and 2 year follow-up analyses. In the No SVR group 2 deaths were attributed to liver failure, including one who died during admission following presentation with a variceal bleed. In the treatment naïve group there were 3 liver related deaths, due to decompensated liver disease. One patient from the treatment naïve group died during admission due to a variceal bleed and there were 2 non-liver related deaths due to renal failure and the second died of a stroke. Figure 3.4, outlines all causes for liver related complications in all 212 patients included for analysis as a combined 2 year analysis. Each patient may have had more than one complication or more than one complication during admission. Ascites and variceal bleeding were important causes for admissions.

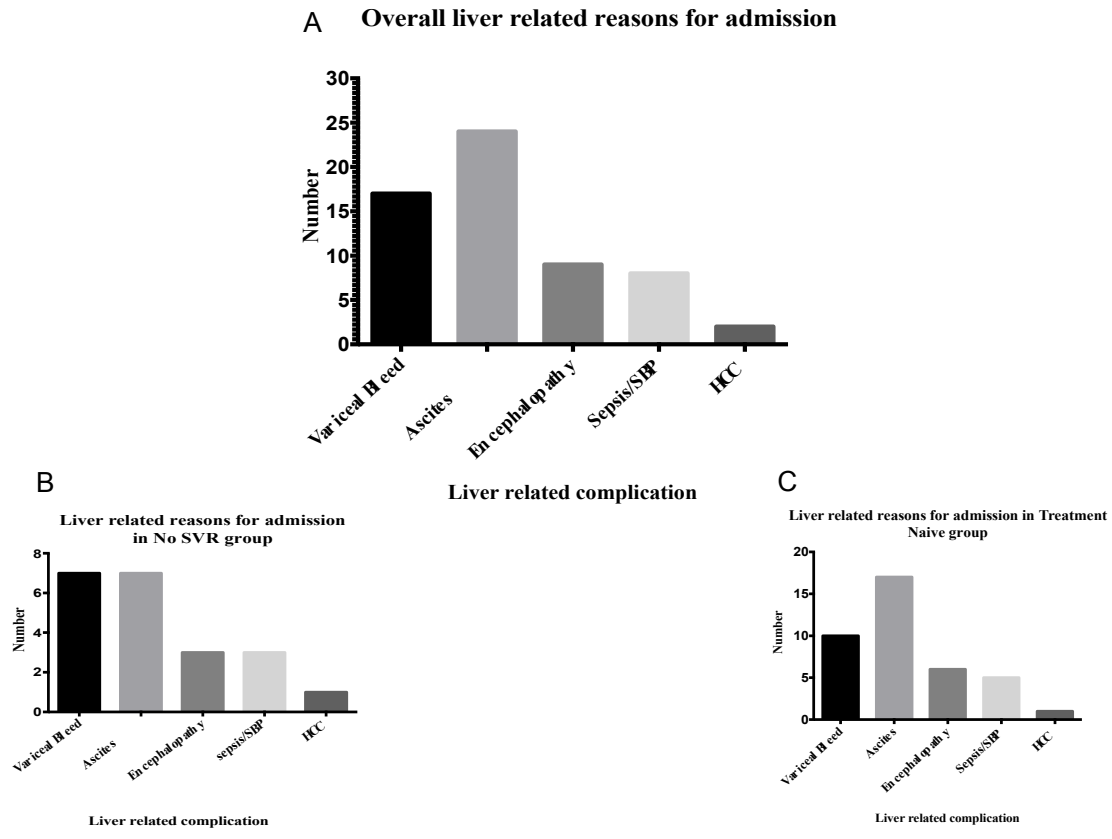


Figure 3.4 Liver related complications noted during admissions per group. Note more than one complication is possible per admission

3.3.3.8 ITU Admissions

There were no reported ITU admission in the SVR group, 4 admissions in the No SVR group and 3 in the Treatment Naïve Group. Figure 3.5 shows ITU admissions per cohort when considering all patients over the full duration of the study.

1-Year Follow-up: In the No SVR groups there was a 20 day admission for a patient due to a variceal bleed with acute kidney injury. In the treatment naïve group 1 patient had an 8 day ITU admission following a variceal bleed.

2-Year Follow-up: In the No SVR group an additional patient died one day after admission with a variceal bleed in ITU. In the treatment naïve group one patient had a 7 day admission due to ascites and another had a 21 day admission following a road traffic accident which was not believed to have been related to his HCV.

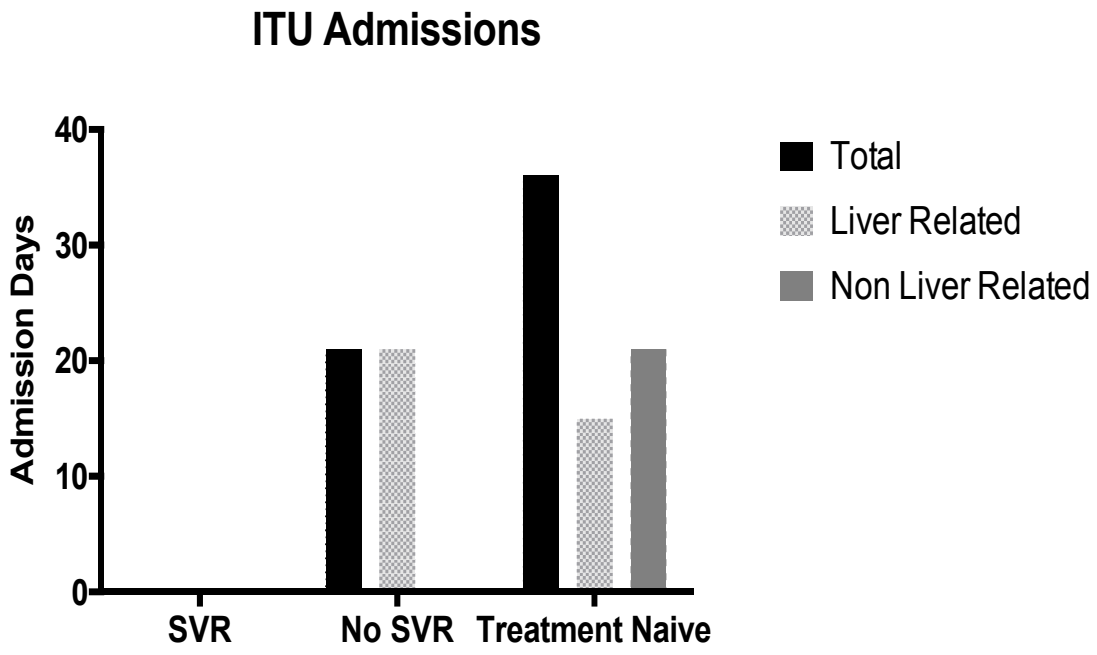


Figure 3.5 ITU admission days per cohort

3.3.3.9 Early Access Programme of Treatment of Decompensated cirrhotics with Direct-Acting Antivirals

A sub-study was performed looking specifically at hospital admission outcomes one year before and after treatment with DAAs during the Early Access Programme. All patients had decompensated cirrhosis and were at entry Child Pugh B7 or greater. Forty patients were included for analysis who had decompensated liver disease treated with DAAs between June 2014 and October 2014, described in Table 3.14. Admission numbers for this cohort were collated for the year prior to treatment and for the year following completion of 12 weeks of treatment. Within this cohort 33 (83%) were male and 22 (55%) were Caucasian. 18 (45%) were genotype 1 and 11 were genotype 3 (27.5%). Within this group the average baseline UKELD was 51 (44-54) and MELD 18 (13-25). Overall in this group 37 (92.5%) achieved SVR, 1 relapsed (2.5%) and 2 died whilst on treatment (5%). In both cases the reason for death was liver failure. Two further patients died in the year subsequent to treatment one due to liver failure and the other due to metastatic colorectal carcinoma. Treatment on this programme however significantly reduced hospital admissions when comparing the year pre-treatment compared to the year post treatment ($p=0.028$). When comparing liver related admissions this reduction in admission days was also significant ($p=0.0006$) as were liver events ($p=0.0013$) as demonstrated in Figure 3.6. No difference was observed when accounting for non-liver related admission days ($p=0.32$).

Total Patients	40
Age (Range)	54 (47 – 61)
Gender (%)	
Male	33 (83)
Female	7 (18)
Race (%)	
Caucasian	20 (48)
Black	8 (19)
Asian	2 (5)
Other	12 (28)
Genotype (%)	
1	18 (45)
2	2 (5)
3	11 (27.5)
4	7 (17.5)
Unknown	2 (5)

Table 3.13

Baseline characteristics of Early Access Programme cohort

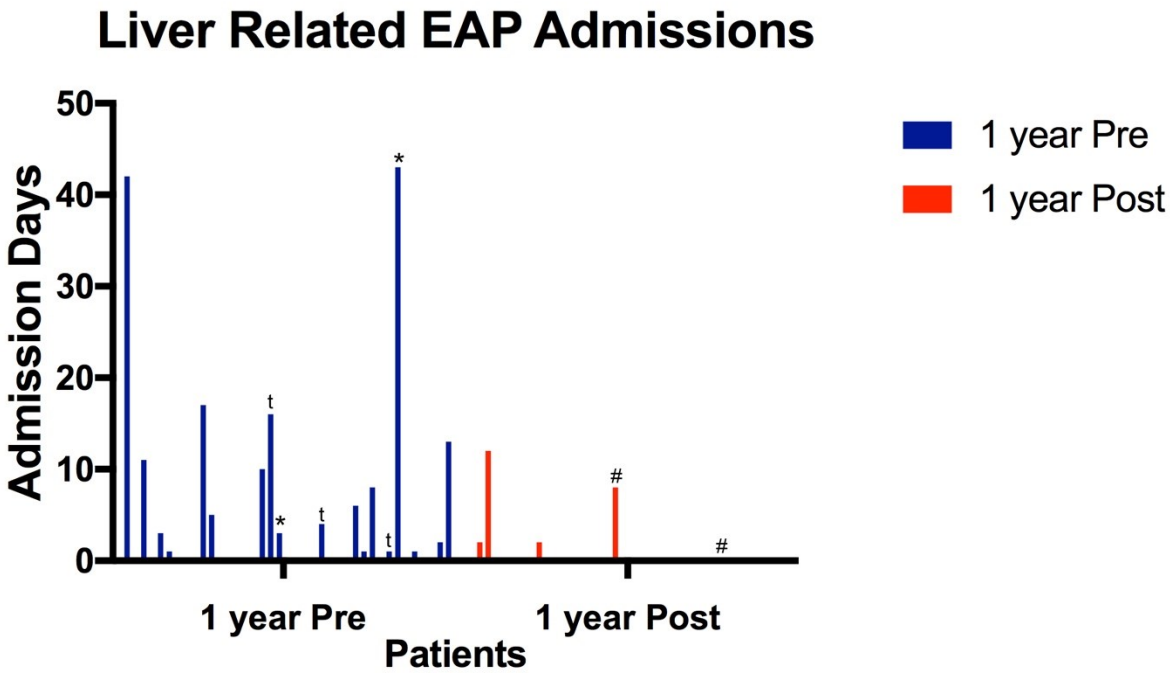


Figure 3.6 Liver related admission days for each patient on the EAP 1 year pre and post completion of 12 weeks of treatment with direct acting antivirals

* patients that died during treatment

patients that died after completion of DAA therapies

t patients that had liver transplantation during treatment

3.3.4 Discussion

This study evaluates admission rates in patients with HCV cirrhosis comparing those who have previously undergone treatment and achieved SVR and compared them to the outcomes of those that have previously failed to achieve SVR following treatment and those that never underwent treatment. This study is the largest reported single centre cohort experience of hospital admission outcomes in persons with HCV cirrhosis. Unlike most previous studies, we compare outcomes with a treatment naïve group. Patients who had been treated and achieved SVR appeared to be associated with reduced admissions to hospital compared to the other two groups when analysing both 1 and 2-year follow-up outcomes. This supports the findings of Innes and Colleagues who reported that in 1215 patients that underwent interferon therapy, there was a four-times reduced likelihood of hospitalisation or death from liver related causes than non-SVR patients. Within their cohort 14% were cirrhotic and all compensated [125].

Ongoing HCV viraemia appears to increase likelihood of liver related complications. In a US nationwide inpatient study in 2011 liver related complications were compared between hepatitis B virus (HBV), HCV and alcoholic liver disease (ALD). Whilst HBV was associated with significantly higher proportions of HCC and acute liver failure, HCV was associated with high liver cirrhosis related admission complications 83.9% vs. 69.1% in HBV and 80.9% in ALD [178].

Within our analysis we wanted to establish how relevant SVR was to chance of hospital admissions. On univariate analysis presence of SVR was significant as well

as albumin, platelets, UKELD and MELD. On multivariate analysis only UKELD demonstrated significance in prediction of hospital admission risk OR 1.29 (CI 1.07-1.57). Interestingly there did appear to be some effect in the presence of SVR with OR 1.54 (CI 0.604-3.933) however it did not reach statistical significance. Given the relatively small numbers included in this analysis it is possible that this may have impacted on statistical outcomes. In support of this is that adjustment for UKELD appeared to demonstrate that presence of SVR did indeed reduce liver related admission days and events in the 1 and 2 year analyses when compared to patients that were treatment naïve. However following UKELD adjustment there was no discernible difference in hospital admissions when comparing treatment experienced patients whether they achieved SVR or not. One possible explanation for this could be that the initiation of treatment with interferon for a period of 24 to 48 weeks either provides a period of amelioration for liver cirrhosis progression or has other immunological effects that confer longer term protection when compared to those that never underwent treatment. Interestingly the length of time since treatment did not seem impact on liver or all cause admissions suggesting that the differences seen between the SVR group and No SVR group are not simply related to temporal biases incurred by the study design not controlling for duration of follow-up since therapy. However no definite conclusions can be made on the basis of the data from this analysis.

Surprisingly MELD was not a demonstrable predictor of admission rate in this cohort. It is possible that the inclusion of sodium in the UKELD score has an impact in prediction of morbidity. Sodium is both a reflection of nutritional status, renal function, and can be impacted by diuretic use associated with ascites. Refractory

ascites in itself is a negative predictor of mortality with a 50% 2 year mortality [179], and patients with refractory ascites often require recurrent admissions for paracentesis. This is reflected by the fact that overall 40% of liver related admissions were related to ascites. It would appear prudent not to make definitive conclusions based on this data set and further work to validate these findings would be required given the extensive validation of MELD in prognostication for mortality in the context of transjugular intrahepatic portal shunts and liver transplant.

Previous studies have suggested that achievement of SVR confers similar survival as the general population [126] and achieving SVR in advanced fibrosis and early cirrhosis has beneficial effects on liver related mortality [180]. This is certainly reflected in the results of our reported study cohort that achieved SVR. However, interestingly we evaluated decompensated liver disease patients who previously could not be treated due to lack of antiviral treatment options. The dawn of direct acting antivirals as a treatment for these patients reflects a huge advance in the field. However, it is not clear if this translates into clinical benefit. A short term and relatively small analysis of 40 patients treated in this manner indeed suggests that there is a benefit of treatment with reduced liver related admission events and admission days in the year subsequent to treatment compared to the year previous to starting treatment.

Whilst this study adds to the current data providing specific impact of SVR in HCV cirrhosis, there are a number of limitations to this study. Firstly this is a retrospective analysis and data collection of certain fields were therefore not always possible. In particular we were unable to collect reliable data on alcohol consumption which has a

significant impact of driving disease progression in patients with HCV [127]. Further, SVR in a population of mainly non-cirrhotics in Scotland, resulted in reduced hepatic and non-hepatic events it was thought there was an association with SVR and behavioural events leading to healthier lifestyles [175]. However this aspect was not possible to be addressed within our study as we had not included any patient lifestyle questionnaires as part of the study design. Data was only collected for admissions to Imperial College Healthcare NHS Trust. Whilst patients were excluded if they had moved out of area or had not had evidence of care at the Trust in the three months prior to data collection, it is still conceivable patients had admissions elsewhere that could not be data captured. Adjustment for UKELD was a crude measure of adjustment of the three groups although it remains difficult to assess if further confounders may have impacted on cirrhosis severity between the three groups. With this regards patients within this cohort had not been tested for IL-28B which has impacts on both interferon response and fibrosis progression in certain subgroups [181].

Presence of SVR appears to be associated with improved outcomes with regards to admissions. During the 2-year follow-up phase there were no liver related admissions nor ITU admissions in the No SVR group. In the No SVR and Treatment naïve groups there were 0.69 and 2.86 days of hospital admissions per patient per year and liver related ITU admission for 21 days and 15 days respectively. Whilst a descriptive study, this helps conceptualise the rationale for early diagnosis and treatment in preventing progression to more advanced disease that may incur increased patient related morbidity and healthcare related economic impact.

4 Cost Effectiveness of Outreach Screening and Treatment in a Drug Treatment Unit

4.1 Introduction

Chronic infection with hepatitis C virus (HCV) is believed to affect up to 160 million people worldwide [182, 183]. In the UK it is estimated that 214,000 individuals are chronically infected with HCV, of which 90% are infected with genotype 1 or genotype 3 [19]. In developed countries people who inject drugs (PWID) either currently or previously are generally the highest risk groups. It is estimated that 35-50% of PWID in England and Wales are infected [19, 73]. Unfortunately, at least 50% are estimated to still remain undiagnosed [19]. Higher prevalence rates have been reported elsewhere with a 67% prevalence reported in New York between 2006-13 amongst PWID [184].

Chronic HCV infection is associated with increased risk of long-term complications, particularly liver cirrhosis and hepatocellular carcinoma [185-187]. Presence of other risk factors for liver disease, such as high alcohol intake, increases the risk of development of such complications [188]. In a study of autopsied PWID, approximately a third of those infected with HCV for more than 25 years had developed septal fibrosis or cirrhosis, and were associated with increased liver related mortality [189].

Previous economic modelling has suggested that providing antiviral therapy to PWID is cost-effective in settings where prevalence is at least 20% [73]. It is believed that modest increases in treatment uptake within PWID populations (26/1000 annually) could reduce HCV prevalence by up to 86% over a 10 year period [73]. Scotland, for example, have recognised the impact of HCV treatment in PWID and have instituted a national action plan to formalise screening and treatment within this population [190]. It is projected that within this resource-rich setting the prioritisation of treatment in PWID will substantially impact on incident infection, and reduce the numbers of infections from 600 cases in 2015 to less than 50 cases per year within a decade, assuming treatment uptake is doubled [74]. However, the majority of developed countries do not have similar strategies or infrastructure.

To date the largest challenge for treatment within the PWID population has been the linkage to specialist care post-diagnosis. It has been reported that when relying on attendance to hospitals or specialist clinics high drop out rates are problematic in the PWID population [72]. Increasingly, "outreach" clinics are being evaluated for the screening and treatment of blood borne viruses by providing specialist care in the community setting of Drug Treatment Units (DTU). Whilst historically and anecdotally, concerns over efficacy and compliance to therapy by PWID have been raised, the evidence does not support this notion of inferior outcomes in HCV antiviral therapy [71, 191, 192]. However, high levels of variability have been observed with regards to linking PWID to care in order to provide treatment. A systematic review of treatment uptake in PWID suggests that less than one in three identified undergo antiviral therapy [71].

Based on the outcomes of a HCV screening and treatment outreach programme implemented within a Central London DTU, the objective of this study was to assess the cost-effectiveness of such a programme for PWID.

The objectives of this study were to assess the feasibility of a HCV screening and treatment outreach programme within a Central London DTU, and to assess the cost-effectiveness of such a programme.

4.1.1 Hypothesis

Outreach screening and treatment in Drug Treatment Units is feasible and cost effective

4.1.2 Aims

- Define a single cohort from a specified DTU
- Identify HCV prevalence
- Assess rates of Viraemia (and therefore eligibility for treatment)
- Assess linkage into care
- Assess overall HCV treatment outcomes
- Assess cost effectiveness of this outreach “screen and treat” programme

4.2 Methods

4.2.1 Screening and treatment

Between 1st April 2012 and 1st November 2014, all persons attending the North Westminster Drug and Alcohol Service (NWDAS) were offered blood borne virus screening using dry blood spot (DBS) testing. DBS has previously been demonstrated as an effective HCV screening tool and has demonstrated cost-effectiveness in this setting [193]. All persons with a positive diagnosis of hepatitis C mono or co-infection were then reviewed at NWDAS by a nurse practitioner from the Imperial College Healthcare NHS Trust Liver and Antiviral Unit. An "outreach" clinic was provided with weekly visits by a specialist nurse with expertise in viral hepatitis under the supervision of a consultant hepatologist. Persons identified with HCV were offered confirmatory blood testing, as well as a full work-up for disease staging and treatment as per standard of care, which included blood tests, HCV genotype and viral load as well as non-invasive fibrosis assessment with Fibroscan (transient elastography). Over the study period linkage to care was assessed by (a) proportion of patients that attended follow-up appointments for counselling and assessment (b) proportion of patients that initiated treatment. Treatment modalities and outcomes were recorded for all patients that initiated treatment by 1st August 2015, from the original cohort identified up until November 2014. Costs of the screening programme were calculated utilising observed resource use and are presented in Table 4.1. The costs of screening and the estimated cost of treatment following positive diagnosis were used to inform a cost-effectiveness analysis of the screening programme.

Screening Component	Unit cost (£)	Resource use	Total cost (£)
Consultant/nurse time			
Nurse time	£150/half day	Half day per clinic (71 clinics)	£10,650
Consultant time	£2,500/year	3 years	£7,500
Testing			
Dry blood kits	£12.50	1 kit for each patient tested (216 patients tested)	£2,700
First consultation	£150	Cost of initial hospital visit for patient scheduled for HCV treatment (29 patients)	£4,350
Repeat patient episode	£25	Cost of initial hospital visit for patient scheduled for HCV treatment (375 visits)	£9,375
Fibroscan	£125	Cost per fibroscan (56 performed)	£7,000
Liver biopsy	£800	Cost per liver biopsy (5 performed)	£4,000
HCV anti-body test	£5.91	Cost per HCV anti-body test (216 performed)	£1,276.56
PCR test	£47	Cost per PCR test (71 initial tests performed based on positive HCV antibody testing, 5 confirmatory re-tests performed for those that initially had a negative PCR test result)	£3,337 + £235 = £3,572
Genotype testing	£44.50-126.66	Cost per genotype test performed (66 tests performed)	£8,360*
Liver screening	£150	Cost per liver screening test performed (66 tests performed)	£9,900
Total cost	-	-	**£68,683**

*So as not to bias towards the screening program, the larger cost (£126.66) was utilised HCV, hepatitis C virus; PCR, polymerase chain reaction

Table 4.1 Unit costs required for screening of HCV in this study cohort

4.2.2 Cost-effectiveness model

As described in Chapter 2.8, the MONARCH Markov model was utilised to simulate lifetime progression within this cohort and estimate associated costs and utilities. The cohort of subjects treated in this DTU transition through annual cycles through METAVIR fibrosis stages and potentially end-stage liver disease (ESLD) complications and death. The model flow diagram is presented in Figure 2.4 and transition rates applied in the model are reported in Table 2.1. Disease progression is modelled over a lifetime assuming a maximum age of 100 years. Total costs, quality-adjusted life-years (QALYs), and numbers of predicted ESLD complications and deaths are estimated over the simulated period.

Fibrosis stage transition probabilities were informed by characteristics of the screened population with respect to age, sex, HCV genotype and source of infection. Initially, patients' disease stage was reported as either mild, moderate or severe. To inform the initial distribution of patients across fibrosis stages, it was assumed that mild, moderate and severe disease corresponded to fibrosis stages F0–F1 and F2–F3, and F4 respectively. Further, due to the high-risk nature of the screened population, it was assumed that the likely route of HCV infection was through injection drug use (IDU). Alcohol consumption was based on data collected during initial screening visits by the clinical team.

The outcomes of the screening programme were used as the basis of a cost-effectiveness analysis using the MONARCH model. The additional costs of screening were compared to the benefits of identifying new cases and the opportunity for treating them, in terms of future quality of life, survival and cost implications of long-

term HCV complications. The results of modelling were used to determine an upper threshold for the cost of screening. The UK advisory body, the National Institute of Health and Care Excellence (NICE), considers an intervention cost-effective at a threshold of £20,000 to £30,000 per QALY gained [58].

A healthcare payer perspective was taken and only direct medical costs considered. Patient and societal costs, such as increased productivity among working adults, were not included. HCV-specific treatment and monitoring costs were derived from weekly estimated costs, accommodating duration of treatment by HCV genotype. Testing costs were based on cost tariffs at Imperial College Healthcare NHS Trust, as demonstrated in Table 4.1. Costs associated with the screening programme included the costs of identifying patients through the use of both HCV antibody and confirmatory testing amongst all patients; those subsequently identified as having HCV antibodies underwent viral load, genotype and baseline liver screening. Costs associated with liver biopsy were applied to the limited number of patients that underwent the procedure, whilst patients that were treated incurred antiviral therapy-related costs. All health state and treatment costs, along with health utility estimates (measured as QALYs), presented in Table 4.2, are independent of age and were discounted annually at a rate of 3.5%. All costs were inflated to 2013 values using the Health and Social Care index [194]. Patients received treatment with a mixture of HCV-related therapies as part of standard care, including pegylated-interferon alpha and ribavirin (IFN/RBV), telaprevir (TVR) and IFN/RBV, boceprevir (BOC) and IFN/RBV, simeprevir (SMV) and IFN/RBV and sofosbuvir and ledipasvir (SOF+LDV); and unlicensed DAA therapies as part of clinical trials. It was assumed that these currently unlicensed DAA therapies had price parity with SOF+LDV. In

addition to the base case analysis, a hypothetical analysis was performed in which all patients were treated with DAA only regimes. It was assumed that the DAA therapy, under the hypothetical scenario, resulted in an SVR rate of 95% across all patients and was associated with a cost equal to that of SOF+LDV.

	Cost parameters			Health utility parameters		
	Mean (£)	**SE (£)**	**Source**	**Mean**	**SE**	**Source**
Disease State (annual)						
F0/F1	177.47	35.01	[109]	0.77	0.015	[70, 109]
F2/F3	922.08	97.82		0.66	0.031	
F4	1,463.50	297.45		0.55	0.054	
DC	11,728.61	1,954.09		0.45	0.031	
HCC	10,451.58	2,456.09		0.45	0.031	
LTx (Year 1)	47,310.55	6,843.48		0.45	0.031	
LTx (Year 2+)	1,781.15	456.57		0.67	0.066	
SVR from F0/F1*	333.08	62.05		0.82	0.043	
SVR from F2/F3*	922.08	97.74		0.72	0.048	
SVR from F4*	1,463.50	288.07		0.72	0.048	

	Weekly cost (£)	**Duration (weeks)**	
		Genotype 1	**Genotype 3**
Treatments			
IFN/RBV	191.35	48	24
TVR+IFN/RBV	TVR: 1,866.50, IFN/RBV: 191.35	TVR: 12, IFN/RBV: 48	NA
BOC+IFN/RBV	BOC: 700, IFN/RBV: 191.35	BOC: 44, IFN/RBV: 48	NA
SMV+IFN/RBV	2,057.85	12	NA
SOF+IFN/RBV	3,106.60	NA	12
DCV+SOF+RBV	5,025.35	NA	24
SOF+LDV	3,248.33	Assumed 12 weeks of SOF+LDV for both genotypes	

* Applied in the first year only.

BOC, boceprevir; DC, decompensated cirrhosis; DCV, daclatasvir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, pegylated interferon α; LDV, ledipasvir; LTx, liver transplant; RBV, ribavirin; RNA, ribonucleic acid; SE, standard error; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TVR, telaprevir.

Table 4.2 Cost and health utility parameters

Conservative assumptions around drug cost were made. Any bias introduced by this assumption would be against the screening strategy. Amongst all treated patients, there was no evidence of significant anaemia or dose reduction and no blood or platelet transfusions; as such, the costs of treating any adverse events were not modelled. Therapy-specific disutility was not modelled.

4.2.3 Analysis

The base case analysis investigated the following scenarios:

Scenario 1:	No screening and no treatment
Scenario 2:	Screening and treatment, as observed within the study population
Scenario 3:	Screening and treatment, assuming all patients treated with hypothetical DAA therapy with an SVR rate of 95%

In each scenario, the identification of patients for treatment was modelled as observed in the study centre. In order to assess the incremental cost-effectiveness of screening, scenario 2 and 3 were compared to scenario 1.

4.2.4 Sensitivity analysis

A series of sensitivity analyses (SA) were conducted, to evaluate the impact of uncertainty in the following areas on modelled base case results:

1) Adjusting the rate of discounting to 0% and 6%
2) Increasing and decreasing patient age by 10 years
3) Adjusting the sex of patients such that, either all patients were male, or all patients were female
4) Adjusting the cost of disease management by ±20%
5) Adjusting the health state utility estimates by ±20%
6) Adjusting the rates of disease progression by ±20%
7) Assuming all patients had either genotype 1 or genotype 3 infection
8) Adjusting the prevalence of HCV by ±20%
9) Adjusting treatment uptake by ±20%
10) Adjusting treatment costs by ±20%

Prevalence of HCV and treatment uptake affects the cost-effectiveness of screening and treatment. Treatment uptake is historically low in the PWID population, whilst HCV prevalence is commonly higher than that observed in the general population [195-199]. Therefore, an additional analysis was undertaken to investigate the relationship between HCV prevalence and the minimum treatment uptake at which screening and treatment remained cost-effective, assuming a £20,000/QALY threshold; base case parameter values were utilised.

4.3 Results

4.3.1 Results of the screening and treatment programme

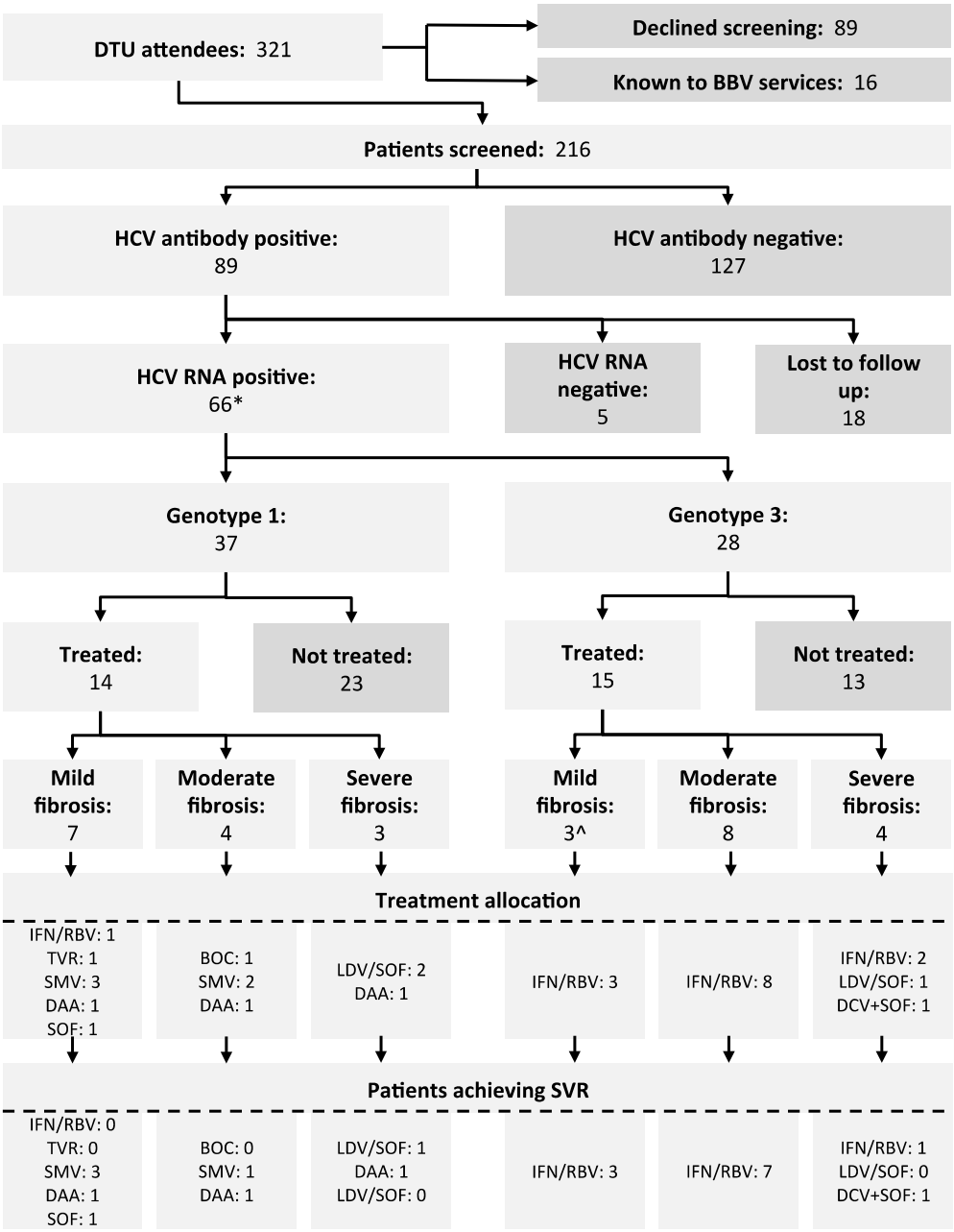
During the study period a total of 321 persons were eligible for screening at NWDAS. A total of 216 were screened, 89 (28%) persons declined testing and 16 (5%) were already known to BBV services. Of those that underwent screening, 89 (41%) persons tested positive for HCV antibodies on DBS testing, and 66 (31%) were confirmed to be viraemic on subsequent PCR testing. A total of 3 persons were co-infected, 1 with hepatitis B and 2 with HIV. Evidence of spontaneous clearance was seen in 5 persons with evidence of HCV antibody positivity but undetected HCV viral load. Throughout the study 18 (8%) persons were lost to follow-up and therefore did not undertake confirmatory blood tests or counselling. All patients had genotype 1 or 3 (56% genotype 1) infection.

Within the study period 29 patients initiated HCV treatment. One patient underwent subsequent treatment with DAAs due to failure to achieve SVR with an initial treatment of BOC+IFN/RBV. This patient subsequently achieved SVR12 with sofosbuvir, ledipasvir and ribavirin, although, for consistency, the re-treatment encounter was not included in the cost-effectiveness analyses. Of the treated patients, 14(48%) were genotype 1 and their mean age was 45 years with a range of 31-61 years. By the end of the study all patients had completed 12 weeks of follow-up beyond the end of treatment and 21 (72%) had achieved SVR12 following their initial course of treatment. A summary of patient baseline characteristics in the group that underwent treatement compared to those that didn't is presented in Table 4.3. Of the 29 patients that underwent treatment, 21 were on opiate substitution therapy at the time of treatment. Four were assessed to have excess alcohol intake and 8 had

evidence of on-going illicit substance use. Figure 4.1 demonstrates results of the screening pathways as well as treatment outcomes per genotype and liver fibrosis severity.

	Treated viraemic group N = 29	Untreated viraemic group N=37	P-value
Age	45 (31-61)	44 (24-58)	0.99
Male	22 (75%)	22 (60%)	0.20
Caucasian	27 (93%)	34 (92%)	0.99
Genotype 1 1a 1b 3	 2 (7%) 12 (41%) 0 15 (52%)	 8 (22%) 16 (43%) 1 (3%) 12 (32%)	 0.74
Prior HCV treatment	2 (7%)	1 (3%)	0.58
Reasons for non treatment Medical Mental Health Declined interferon Non engagement Moved location Rehab Deceased Unknown		 3 (8%) 1 (3%) 7 (19%) 9 (24%) 4 (11%) 1 (3%) 2 (5%) 10 (27%)	
Substance use	9 (31%)	19 (51%)	0.07
Alcohol consumption	3 (11%)	5 (14%)	**0.05**
Prescribed opiate substitution	19 (66%)	26 (70%)	0.24
HBV co-infection	1	0	0.44
HIV co-infection	0	3	0.25
F0-F1 fibrosis	11 (38%)	10 (27%)	0.23
F2-F3 fibrosis	12 (41%)	5 (14%)	0.53
F4 fibrosis	6 (21%)	2 (5%)	0.69
Unknown fibrosis stage	0	20 (54%)	
Haemoglobin (g/dL)	13.9 (10.3-16.4)	13.5(8-16.4)	0.34
Platelets (10^9/L)	191(46-427)	221(116-353)	**0.04**
INR	1.1(1-1.6)	1.1(1-1.4)	0.60
ALT (iU/L)	102(18-428)	58(8-145)	**0.02**
Albumin (g/dL)	39(26-45)	37(15-43)	**0.04**
Bilirubin (mmol/L)	13(4-49)	10(3-59)	**0.01**
Sodium (mmol/L)	139(132-143)	138(133-144)	0.75
Creatinine (µ/L)	77(54-259)	66(42-83)	0.16
HCV Viral Load (iU/mL)	$8x10^6$ ($1.23x10^5$-$152x10^6$)	$1.6x10^6$(1771-$17x10^6$)	**0.03**

Table 4.3 Baseline patient, viral, fibrosis and treatment characteristics



BOC, boceprevir + pegylated interferon alpha + ribavirin; DAA, direct-acting antivirals; DCV+SOF, daclatasvir + sofosbuvir; IFN/RBV, pegylated interferon alpha + ribavirin; LDV/SOF, ledipasvir + sofosbuvir; SMV, simeprevir + pegylated interferon alpha + ribavirin; SOF, sofosbuvir + pegylated interferon alpha + ribavirin; TVR, telaprevir + pegylated interferon alpha + ribavirin.

*1 patient identified as HCV RNA positive had an unknown genotype, however was not treated.

^1 genotype 3 patient achieved SVR with IFN/RBV therapy but had an unknown fibrosis severity at initiation, thus it was assumed that they had mild fibrosis, the most conservative assumption.

Figure 4.1 Flow diagram showing screening and treatment outcomes within this cohort

4.3.2 Cost effectiveness Results

The total cost of screening and confirmation of diagnoses was estimated to be £68,683. This translates to £318, £1,041 and £2,368 per individual screened, newly diagnosed and treated at the study centre, respectively.

Results of the cost-effectiveness analysis are presented in Table 4.4. It was predicted that under base case assumptions, screening and treatment would result in average per patient QALY gain of 4.10 and an average cost saving of £2,498, when compared to no screening and treatment, due to reductions in complication incidence. Similarly, when considering a hypothetical scenario in which all patients are treated with DAA therapies, per patient QALY gains of 5.34 were predicted alongside an average incremental cost of £5,494, as a consequence of more expensive treatment, resulting in an incremental cost effectiveness ratio (ICER) of £1,029 per QALY gained.

Result per patient	No screening and treatment	Screening and treatment (base case)		Screening and treatment (all treated with DAAs)	
	Total	**Total**	**Incremental (versus no screening and treatment)**	**Total**	**Incremental (versus no screening and treatment)**
Screening cost (£)	0	2,368	2,368	2,368	2,368
Treatment cost (£)	0	22,716	22,716	38,980	38,980
Complication cost (£)	43,360	15,778	-27,583	7,506	-35,854
Total cost (£)	43,360	40,862	-2,498	43,360	5,494
Life years	14.02	17.48	3.46	18.45	4.42
QALYs	7.94	12.03	4.10	13.27	5.34
ICER: £/life year	-	-	-723	-	1,242
ICER: £/QALY	-	-	-610	-	1,029

DAAs, direct-acting antivirals; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 4.4 Cost Effectiveness results

4.3.3 Sensitivity analysis

Sensitivity analyses, as presented in Figure 4.2 demonstrate that ICER estimates are relatively insensitive to alternative parameter assumptions. Under the majority of scenarios, the base case comparison remained cost saving, the exceptions being an increase in the rate of discounting to 6% and reducing health state costs and increasing treatment costs each by 20%; ICERs ranged from -£2,291 (dominant) to £1,430 per QALY gained. When assuming all patients are treated with a DAA therapy, ICERs ranged from minus £1,542 (dominant) to £3,892 per QALY gained.

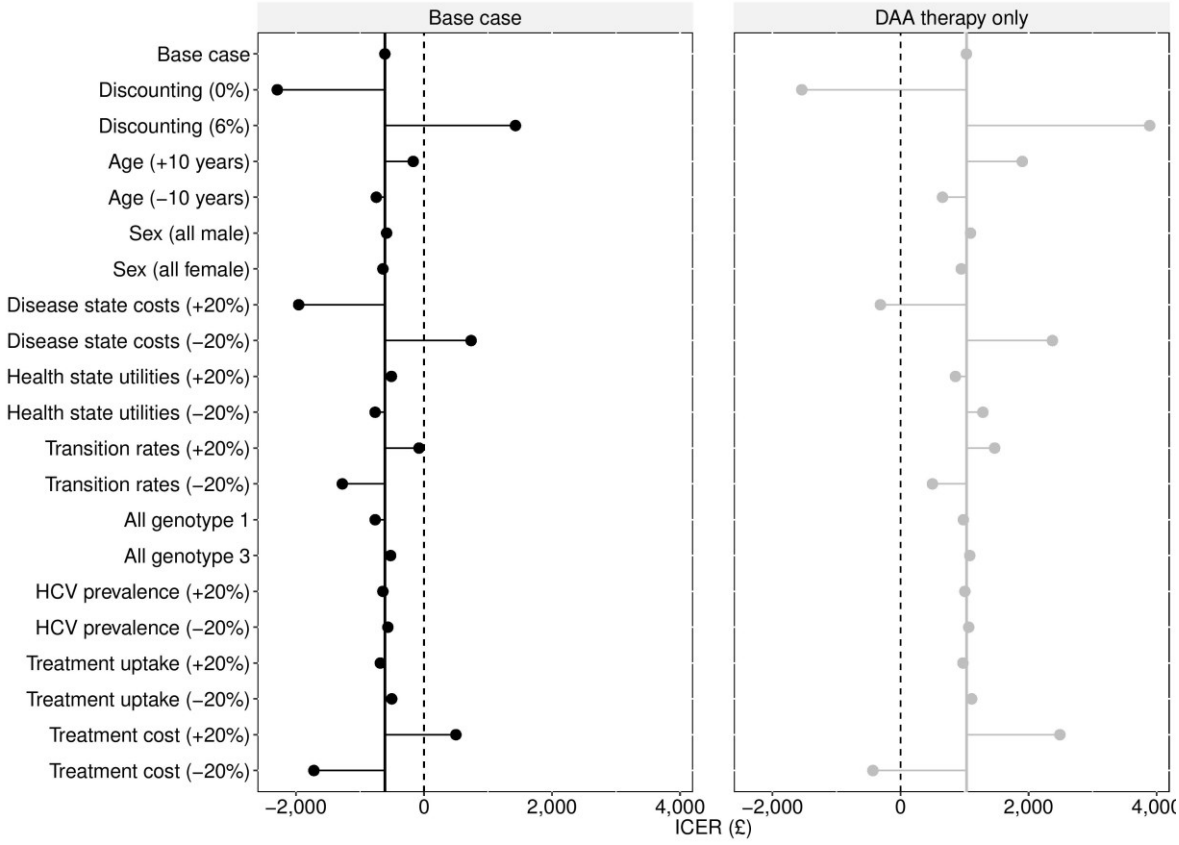


Figure 4.2 Sensitivity analyses

Figure 4.3 presents a graphical representation of the treatment uptake rate at which comparisons are no longer cost-effective, assuming a £20,000 per QALY gained threshold. As prevalence decreases, the proportion of patients that need to be treated to maintain cost-effectiveness increases. Once an HCV prevalence of approximately 4% is achieved, the proportion of patients partaking in treatment required to maintain cost-effectiveness begins to plateau. When considering a scenario where treatment uptake was increased by treating all with DAA therapies there would be a progressive, though mild improvement of cost effectiveness compared to the base case scenario. If 75% of diagnosed viraemic patients were treated in this manner this would incur £893 per QALY and if all 66 were treated this would cost £845 per QALY.

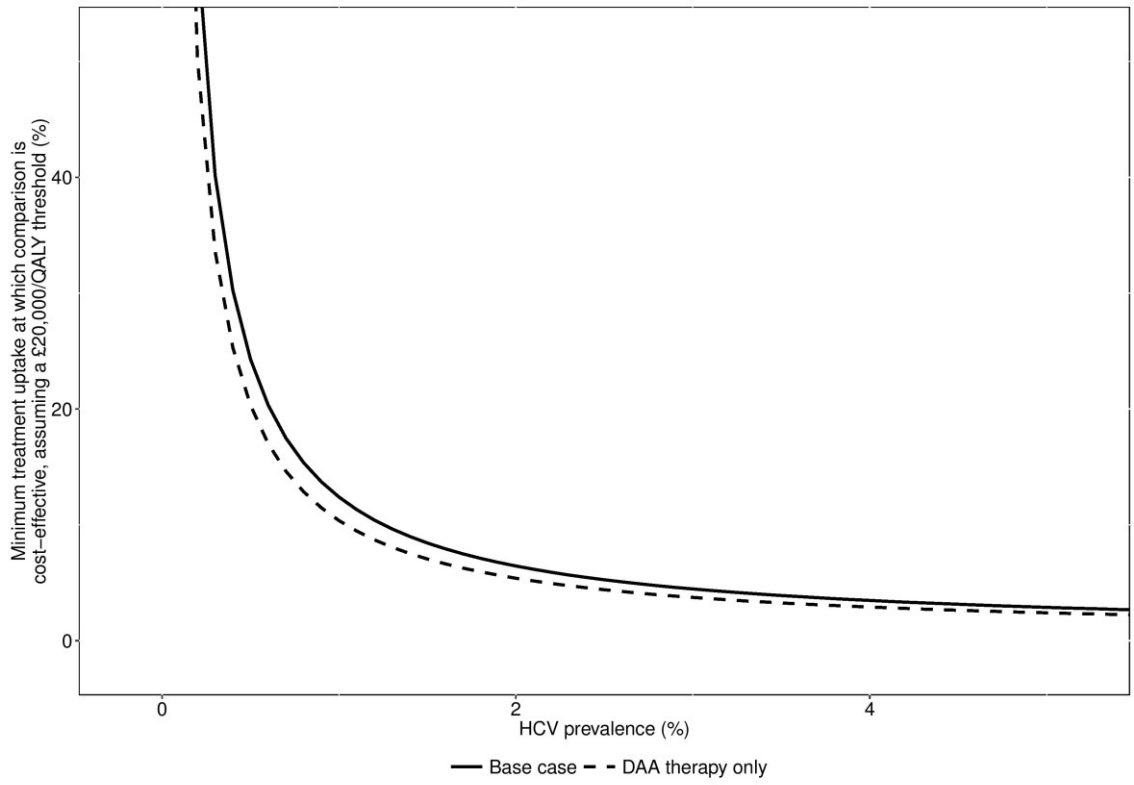


Figure 4.3 The treatment uptake rate at which comparisons are no longer cost-effective, assuming a £20,000 per QALY threshold

None of the observed patients demonstrated evidence of re-infection during the relatively short study period. In 161 Scandinavian PWID treated for HCV, reinfection was demonstrated to be an important complication with incidence of 1.7/100 person years [200]. We undertook additional analysis to assess the proportion of patients that would have to become re-infected before each comparison was no longer cost-effective, assuming a threshold of £20,000 per QALY gained. Assuming no treatment after re-infection, up to 87.2% of successfully treated patients could be re-infected before the base case comparison is no longer cost-effective. Similarly, up to 71.0% of successfully treated patients could be re-infected before the comparisons of DAA therapies are no longer cost-effective.

4.3.4 Additional per patient resource to maintain cost effectiveness

When considering the base case scenario, at a willingness to pay threshold of £20,000 per QALY an extra £84,418 could be spent per treated patient. In order to remain dominant (i.e. cost of benefits outweigh cost of intervention) within the base case scenario £2,498 could be spent per patient.

In the hypothetical all DAA treated scenario, an additional £101,243 could be spent per treated patient to maintain cost effectiveness within a £20,000 per QALY willingness to pay threshold.

4.4 Discussion

This study demonstrates a "real world" cohort experience of outreach testing and treatment of HCV in a DTU to be both feasible and cost-effective. Further, the analysis demonstrates that, from a healthcare payer perspective, this programme is likely to provide QALY and life year gains whilst also providing a cost saving, compared to a scenario of no screening and treatment. The range of sensitivity analyses performed indicate that these findings may be considered relatively robust. Withstanding any geographic variation in HCV prevalence in PWID populations and treatment uptake, results of this analysis demonstrate that, even after significant variation in prevalence and treatment uptake, the outreach screening and treatment programme remains cost-effective. This study provides evidence from a real world cohort for cost effectiveness in addition to well documented public health benefits.

In developed countries DTUs are likely to have high rates of HCV prevalence. In the past, illicit drug use was considered a barrier to treatment with concerns regarding tolerability and adherence to IFN/RBV [195]. Multidisciplinary approaches to the management of persons with substance misuse with prevention, needle exchange, safe injection and opiate substitution programmes can all help improvement in the care of PWID and improve chances of successful HCV treatment [201, 202]. Outreach programmes help improve retention into specialist service and in turn increase the likelihood of those identified as HCV positive commencing HCV treatment. Previous published literature suggests that PWID populations are good target populations for HCV screening, due to high risk behaviours and consequent likelihood of high HCV

prevalence [203]. This study provides evidence from a real world cohort to support such claims as well as support the cost-effectiveness of such a strategy.

Furthermore, recent data confirms that high SVR rates, above 95%, can be achieved with DAAs in PWID populations on opiate substitution therapy [204]. Within this commercial clinical trial cohort, despite 28% having evidence of on-going active substance misuse, it did not appear that this had a significant impact on adherence or negatively affect overall SVR rates. Sensitivity analyses performed in our study demonstrated a modest cost per QALY when assuming all patients were treated with DAAs. This strategy was estimated to be highly cost-effective and well below the acceptable threshold set by policy makers. Whilst the majority of persons in this cohort were safely treated with IFN/RBV, it is conceivable that uptake to therapy would be higher in a setting where interferon-free regimens were more widely accessible. Whilst increasing treatment costs, our estimations of the effect of increasing uptake rates to 75% and 100% demonstrate on-going cost effectiveness owing to the improvement in quality of life years.

Whilst PWID are often referred to as a "difficult to treat" population, outcomes in this cohort were equivalent to those that would have been expected in a non-PWID population. Outcomes with IFN/RBV appear comparable to that described in initial registration studies [205-207]. One patient was successfully retreated within this cohort with DAAs following initial treatment failure with boceprevir, interferon and ribavirin. Re-treatment has not however been considered in the cost effectiveness analysis, and this patient who was retreated was only considered from the point of view of initial treatment outcome. Due to the high rates of SVR observed in the study,

it is unlikely that re-treatment would significantly affect cost-effectiveness conclusions, even when assuming failure to achieve SVR.

Previously published studies have looked at the cost-effectiveness of either screening or treatment of PWID populations. Several studies assume 100% uptake of screening, clinical work up and commencement of antiviral therapy with assumed prevalence rates as high as 80% [76, 92]. This study encompasses both with "real world" data to inform base case analyses. However, it is subject to a number of limitations relating to both modelling assumptions and the underlying characteristics of the study centre and population. The study centre is based in Central London, although it is conceivable that it remains representative of other drug treatment units both nationally based on previous published data [73]. The outreach programme was provided by a teaching hospital based liver unit team and therefore required little additional support, in terms of infrastructure and staff requirements, to implement such a programme; further resources may be required to initiate such a programme in units less suitable to the programmes needs. The additional per treated patient cost that could be attributed to a screening programme and it remain cost-effective at a £20,000/QALY threshold was estimated to be £84,418 and £101,243 for the base case and DAA only scenarios, respectively; an estimated additional £2,498 could be attributed in the base case and the programme remain dominant.

This study demonstrates the numerous challenges in treatment of PWID. Firstly, 28% eligible for screening declined prior to engagement with the study team. Data was not collected from this group and therefore it is not clear what interventions could have improved screening uptake. Secondly, despite outreach testing 20% with HCV Ab

were lost to follow-up and 56% of viraemic patients were not treated. Of those that did not undergo treatment 27% had medical contraindications or declined IFN therapies. A major limitation within this study was that during the study period DAA therapies were not widely available to these patients as standard of care. This may have limited treatment uptake. The study demonstrates reasonable treatment uptake given the nature of the population but with clear room for improvement. It further serves to reinforce the real life complexities in treatment within this population. In an era of greater access to DAAs it is conceivable that further up-scaling of treatment maybe feasible, and sensitivity analyses project this to remain cost-effective.

Public health benefits of HCV screening in PWID populations have been recognised by policymakers. This study adds weight to support cost effectiveness of outreach screening and treatment. However, in order to decrease future prevalence, further efforts are required in order to increase rates of SVR and on-going prevention of infection. It is envisaged higher treatment rates and/or vaccination would be needed [208].

Sensitivity analyses, performed assuming all patients were treated with 12 weeks of DAA therapy only did not take into account that many of the patients within this cohort would have been eligible for an 8-week duration of therapy [209]. As a result, it is likely that the relative cost-effectiveness benefits of such a scenario have been underestimated. However, given that this was already a demonstrably cost-effective strategy, the conclusions of the analysis are unlikely to have been significantly altered. This study did not evaluate the potential impact of reduction of onward transmission, as this data would have been based on assumptions in the absence of

available data. Within this cohort at least 9 of 29 patients undergoing treatment had evidence of on-going substance misuse and were therefore potentially at risk of onward transmission. This study therefore likely underestimates the wider healthcare benefits of reducing onward transmission from those that were successfully treated within this PWID population.

This study supports the on-going recommendation for HCV screening within PWID populations with predicted high rates of HCV prevalence. In order to improve linkage into care and treatment uptake, outreach services are feasible and likely cost-effective. In an era of interferon-free therapies, it is projected that the additional costs associated with the use of such therapies would remain within the acceptable thresholds set by policymakers and may possibly further increase uptake and linkage into care on account of greater acceptability and tolerability.

This chapter was adapted and has been accepted for publication Selvapatt N et al. The cost impact of outreach testing and treatment for hepatitis C in an urban Drug Treatment Unit. Liver International (In Press)

5 Cost Effectiveness of Antenatal Screening for hepatitis C

5.1 Introduction

Antenatal screening for several infectious diseases, including HIV and hepatitis B virus (HBV), is performed routinely in many countries including the UK [210]. This is commonly motivated by the risk of perinatal transmission; this is estimated at 6% amongst HCV patients [211, 212]. However, in the absence of interventions available to prevent HCV transmission, routine screening for HCV in pregnancy has not been recommended in most countries [210]. Successful identification and treatment of HCV-infected individuals is associated with improved long-term health, through the avoidance of ESLD, and increased life expectancy [104, 213].

HCV is only screened for in the antenatal setting in mothers considered to be "high risk" for acquisition. Risk based screening may not be effective for three main reasons: firstly, in the primary care setting, HCV risk factors are often not fully explored [214, 215]; secondly, patients do not always report transient behaviours (e.g. injecting drug use) that occurred years or decades ago; thirdly, many acquire infection iatrogenically in their country of origin and are unaware of exposure risk.

Previous studies have shown benefit in the adoption of a routine antenatal screening programme for HCV over risk based testing strategies [84, 85, 216]. These studies demonstrate that up to 75% of newly diagnosed mothers have no reported "high risk" behaviour. Whilst many of these women were born in countries with a higher

prevalence and risk of infection, screening of migrants would potentially be stigmatising. Women screened and diagnosed with HCV during the antenatal period are generally healthy and motivated, with high rates of attendance to follow-up observed [84]. Given that testing for HCV antibodies can be carried out using the same laboratory samples taken for routine antenatal virology screening for HIV and HBV, minimal additional resource use is required. The costs of diagnostic confirmation and the treatment of newly identified patients pose potentially significant costs, but these may be offset against the potential future costs of late diagnosis and the treatment of complications, should these women be diagnosed only when the disease has progressed.

This study aims to evaluate the cost-effectiveness of routine screening for HCV antibodies in the antenatal population of a London hospital, based on data from a ten-year screening programme, using a previously published and validated simulation model of HCV.

5.1.1 Hypothesis

Antenatal Screening of HCV with direct linkage to care to specialist liver services is feasible and cost effective

5.1.2 Objectives

- Define a single cohort from a specified antenatal service
- Identify HCV prevalence
- Assess rates of Viraemia (and therefore eligibility for treatment)
- Assess linkage into care
- Assess overall HCV treatment outcomes
- Assess cost effectiveness of this antenatal screening service

5.2 Methods

5.2.1 Screening and treatment

Between 1st November 2003 and 1st March 2013, all pregnant women attending the antenatal clinics at St Mary's Hospital, Imperial College Healthcare NHS Trust, London for their "booking in" visit were offered HCV antibody testing as part of their screening. All positive results were directly reported from the virology lab to a specialist midwifery team trained in the management of patients with viral hepatitis. All mothers in which HCV antibodies were identified were referred to a named consultant hepatologist working closely with the antenatal team. Mothers with initial

undetectable viral load results had a further viral load assessment after the pregnancy to confirm spontaneous resolver status, before being discharged from follow-up. Mothers with identified viraemia were counselled in the antenatal hepatology clinic and reviewed in a family clinic following delivery, with their child, by the same hepatologist and a paediatric consultant with specialist interest in infectious diseases. All children of infected mothers were tested serologically for HCV at 15 months. These mothers were then offered regular hepatology follow-up and worked up for treatment per standard practice.

Antenatal and medical records were reviewed to evaluate the service provided to these women over the last ten years and their outcomes. Individual patient data were anonymised. Data were managed using REDCap electronic data capture tools [217] demonstrated in Figures 5.1-5.4. Information recorded included patient demographics, antenatal data, maternal HCV status and their risk factors, dates of hepatology appointments, outcomes of work up and, if relevant, treatment records and outcomes.

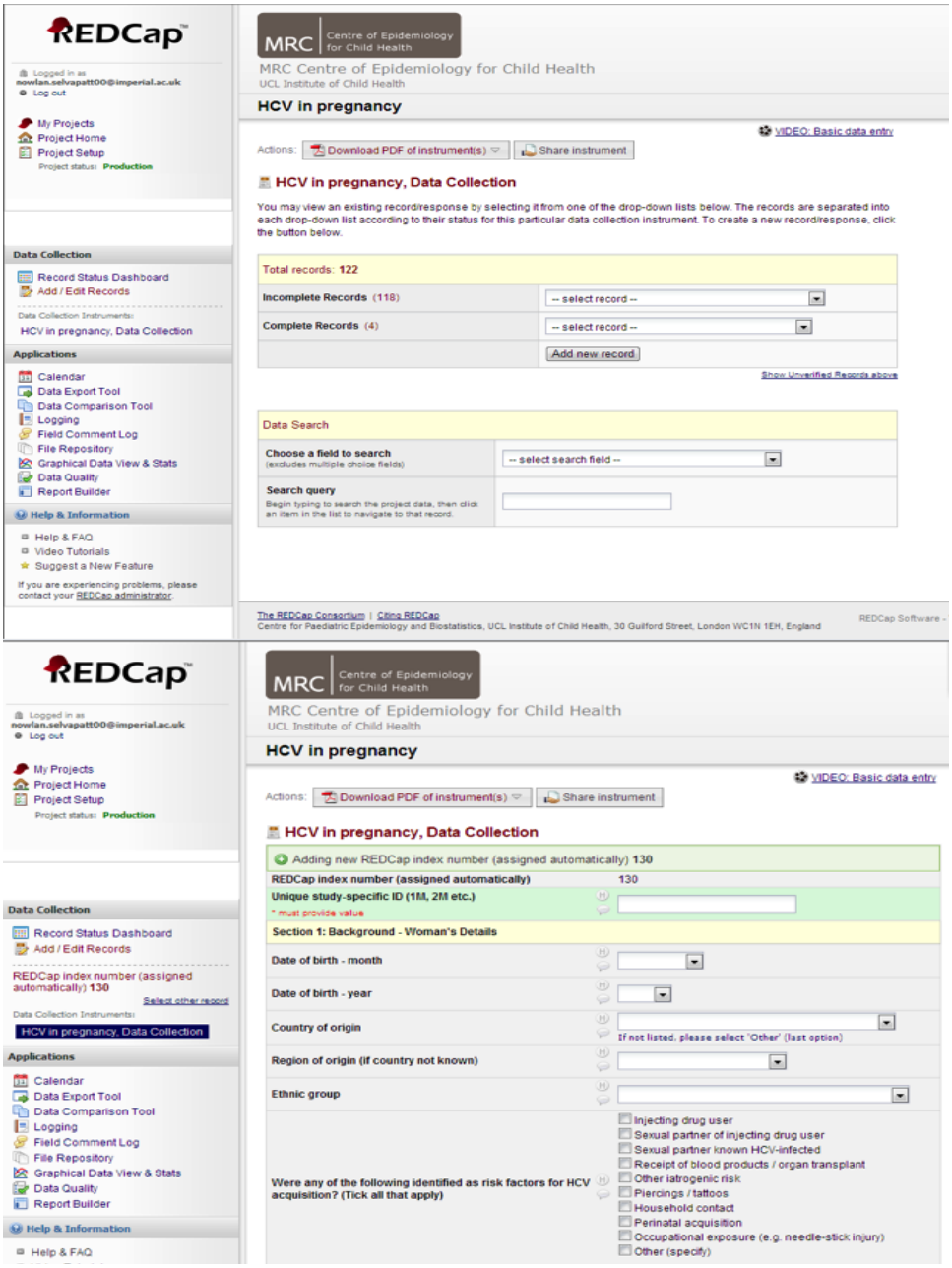


Figure 5.1 Screenshot of REDCap data collection fields (1)

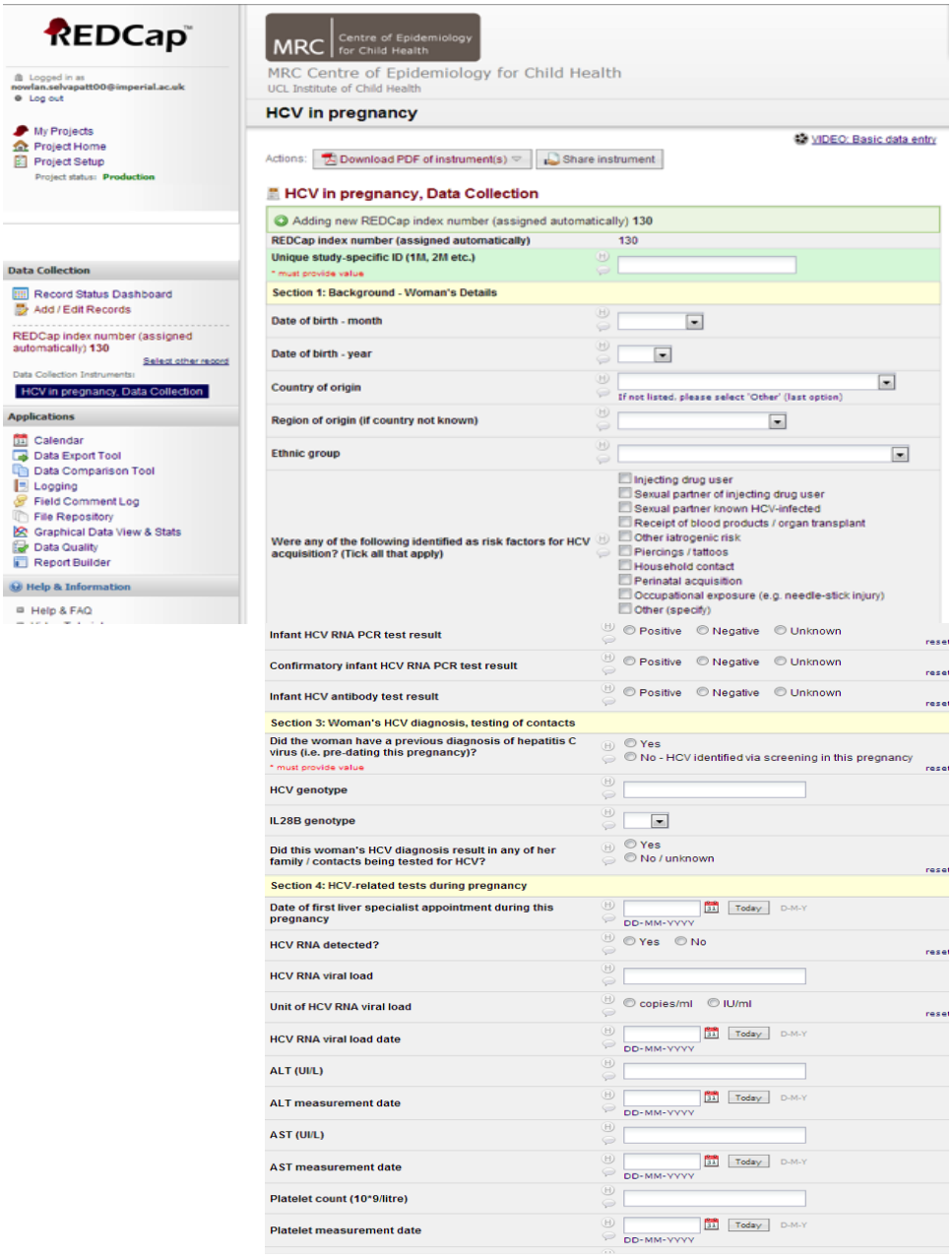


Figure 5.2 Screenshot of REDCap data collection fields (2)

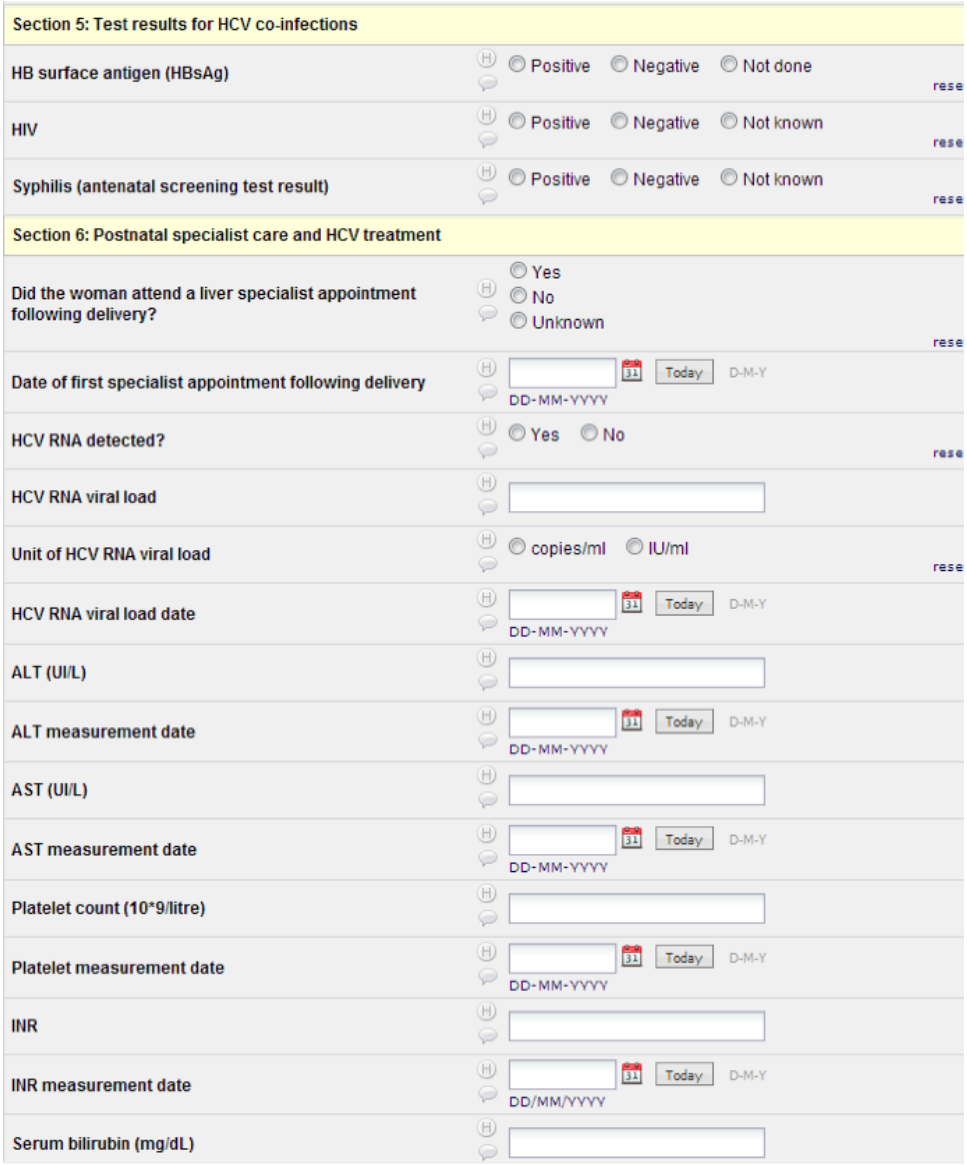


Figure 5.3 Screenshot of REDCap data collection fields (3)

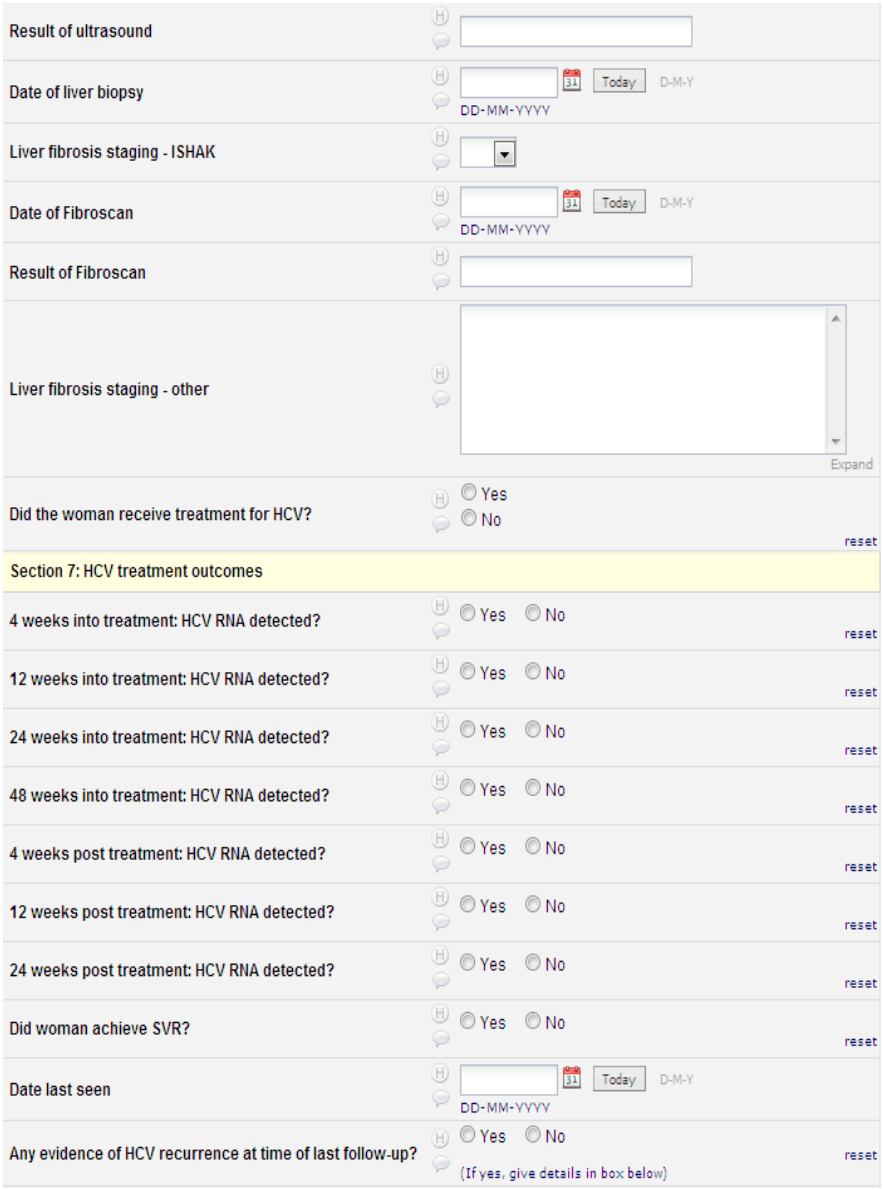


Figure 5.4 Screenshot of REDCap data collection fields (4)

5.2.2 Cost-effectiveness model

The MONARCH model was used to progress the HCV antenatal cohort in annual cycles through METAVIR fibrosis stages and potentially to ESLD complications and death [78, 108]. Figure 2.1 shows the model flow diagram and Table 2.1 reports the

transition rates applied in the model. Disease progression is modelled over a lifetime assuming a maximum age of 100 years. Total costs, quality-adjusted life-years (QALYs), and numbers of predicted ESLD complications and deaths are estimated over the simulated period.

Fibrosis stage transition probabilities were informed by characteristics of the screened population with respect to age, sex, HCV genotype and source of infection. Initially, patients' disease stage was reported as either mild, moderate or severe. To inform the initial distribution of patients across fibrosis stages, it was assumed that mild and moderate disease corresponded to fibrosis stages F0–F1 and F2–F3, respectively.

The outcomes of the screening programme were used as the basis of a cost-effectiveness analysis using the MONARCH model. The additional costs of screening were compared to the benefits of identifying new cases and the opportunity for treating them, in terms of future quality of life, survival and cost implications of long-term HCV complications. The results of modelling were used to determine an upper threshold for the cost of screening. The UK advisory body, the National Institute of Health and Care Excellence (NICE), considers an intervention cost-effective at a threshold of £20,000 to £30,000 per QALY gained [58]; in the US, the threshold is $50,000 per QALY gained [218], and a previous European evaluation of an antenatal HCV screening programme applied a threshold of €20,000 to €50,000 [88].

A healthcare payer perspective was taken and only direct medical costs considered. Patient and societal costs, such as increased productivity among working adults, were not included. HCV-specific treatment and monitoring costs were derived from weekly

estimated costs, accommodating duration of treatment by HCV genotype. Testing costs were based on cost tariffs at Imperial College Healthcare NHS Trust, as demonstrated in Table 5.1.

Screening Component	Unit Cost	Resource Use	Source
HCV antibody test	£5.91	1 per screened patient	Imperial College Healthcare NHS Trust
HCV RNA test	£47	2 per PCR negative, 1 per PCR positive	
Genotype	£44.50 - £126.66*	1 per diagnosed patient	
Liver biopsy	£750	16 patients	
Liver baseline blood test	£150	1 per diagnosed patient	

***cost range relates to conduct of genotype testing within Imperial College Healthcare NHS trust or from external NHS hospitals. The higher cost was implemented in the base case; any bias introduced by this assumption would be against the screening strategy.**
HCV, hepatitis C virus; RNA ribonucleic acid; PCR, polymerase chain reaction

Table 5.1 Unit costs and resource use of screening cost components

Costs associated with the screening programme included the costs of identifying patients through the use of both HCV antibody and confirmatory testing amongst all patients; those subsequently identified as having HCV antibodies underwent RNA, genotype and baseline liver screening. Costs associated with liver biopsy were applied to the patients that underwent the procedure, whilst patients that were treated incurred antiviral therapy-related costs. All costs and health utility estimates (measured as QALYs), presented in Table 5.2, are independent of age and were discounted annually at a rate of 3.5%, to reflect their present value. All costs were inflated to 2013 values using the Health and Social Care index [194].

	Cost parameters			Health utility parameters		
	Mean	**SE**	**Source**	**Mean**	**SE**	**Source**
Disease State (annual)						
F0/F1	£177.47	£35.01	[107]	0.77	0.015	[114]
F2/F3	£922.08	£97.82		0.66	0.031	
F4	£1,463.50	£297.45		0.55	0.054	
DC	£11,728.61	£1,954.09		0.45	0.031	
HCC	£10,451.58	£2,456.09		0.45	0.031	
LTx (Year 1)	£47,310.55	£6,843.48		0.45	0.031	
LTx (Year 2+)	£1,781.15	£456.57		0.67	0.066	
SVR from F0/F1	£333.08	£62.05		0.82	0.043	
SVR from F2/F3	£922.08	£97.74		0.72	0.048	
SVR from F4	£1,463.50	£288.07		0.72	0.048	
Treatments						
IFN/RBV	£191.35/week	NA	[219]	0.109*	0.010	[220]
SOF+IFN/RBV	£1,519.81/week	NA		0.148*	0.010	[221]

***These values represent therapy-specific disutilities.**

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN/RBV, pegylated interferon α and ribavirin; LTx, liver transplant; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response

Table 5.2 Disease state utilities and costs

In the base case, the identification and treatment of patients was modelled as observed in the women in our study centre treated with pegylated-interferon alpha and ribavirin (IFN/RBV) only. It was assumed that patients infected with HCV genotypes 1 and 4 received 48 weeks of treatment, and those with HCV genotypes 2 and 3 received 24 weeks of therapy. Conservative assumptions around drug cost were made; it was assumed no patients ended treatment early due to discontinuation or extended rapid virologic response (eRVR). Any bias introduced by this assumption would be against the screening strategy. Amongst all treated patients, there was no evidence of significant anaemia or dose reduction and no blood or platelet transfusions; as such, the costs of treating any adverse events were not modelled. Therapy-specific disutility was applied to patients whilst receiving treatment, upon completion of treatment no further disutility was incurred.

Two additional scenarios were modelled relating to the introduction of new generation DAAs: as either the initial treatment option or as subsequent treatment for patients failing to achieve SVR with IFN/RBV; to illustrate this, a treatment success rate (SVR) of 95% for 12 weeks of sofosbuvir triple therapy (SOF + IFN/RBV) was applied across all genotypes and fibrosis stages, estimated from results of recent phase 3 trials [222, 223]. In these additional scenarios, the identification of patients for treatment was modelled as observed in the study centre.

5.2.3 Sensitivity analysis

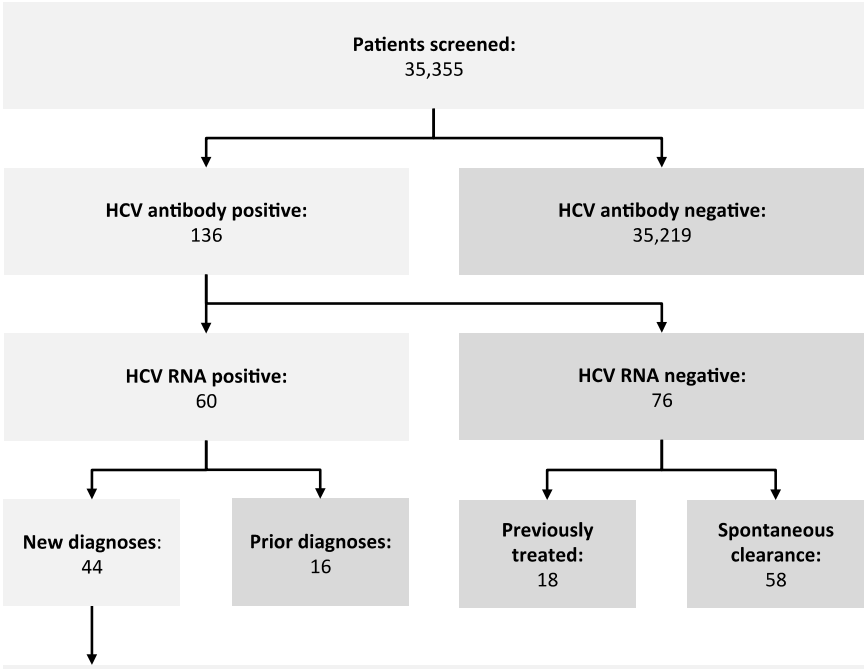
A series of sensitivity analyses (SA) were conducted, to evaluate the impact of uncertainty in the following areas on modelled base case results:

11) (a) Increasing and (b) decreasing the age at diagnosis by five years.
12) Adjusting SVR rates associated with IFN/RBV to reflect the consensus literature; i.e., 52% in HCV genotype 1 patients [206], 75% in HCV genotype 2 patients [224], 75% in HCV genotype 3 patients [224], and 48% in HCV genotype 4 patients [225].
13) Treatment of all newly diagnosed patients.
14) HCV prevalence amongst the screened population of (a) 0.1% and (b) 0.6%.

5.3 Results

5.3.1 Results of the screening and treatment programme

During the ten-year period evaluated, a total of 35,355 women underwent antenatal HCV screening at St Mary's Hospital. A total of 136 (0.38%) HCV antibody positive results were confirmed (). Overall, 44 women (0.12%) were newly diagnosed with chronic HCV. Of the remaining 92 women with positive HCV antibody results, 34 had received prior diagnosis and 58 had sequential negative HCV viral loads, indicating spontaneous clearance of the virus.



	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Unknown
Total:	21	4	11	6	2
F0-F1	5	2	4	2	0
F2-F3	2	0	1	0	0
Unknown	14	2	6	4	2
Treated with IFN/RBV*	9	2	5	3	0
Achieved SVR:	7	2	4	1	0

*During the manuscript review phase an additional three patients were treated, two of whom achieved SVR through use of unlicensed therapies and one through the use of boceprevir combined with IFN/RBV. These patients have not been incorporated within the analysis.

Figure 5.5 Flow diagram showing the results of the numbers tested and the number of new diagnoses of HCV based on antenatal screening and outcomes of treatment within the cohort.

Of the 44 newly diagnosed women, the majority were HCV genotypes 1 and 3 (figure 2), with a median age of 33 years (range 23–46) at diagnosis. None were co-infected with either HIV or HBV. Subsequently, a total of 19 women underwent treatment for HCV with IFN/RBV, of which 14 (74%) achieved SVR. Three additional women

were treated and achieved SVR, one genotype 1 with IFN/RBV and boceprevir and two genotype 4 patients with DAAs as part of a clinical trial.

Of the 44 newly diagnosed women, 14 were born in the UK, 14 in Eastern Europe, 3 in Western Europe, 4 in Africa and 9 in Asia. The likely source of HCV infection was identified as blood transfusion for one mother, whilst 11 out of the 44 mothers had a prior history of injecting drug use. Of these 11 women, one spontaneously cleared the virus the year after diagnosis and two underwent treatment, with one successful SVR. On review of the reasons for not undertaking treatment, eight mothers did not attend clinic follow-up due to complex social factors.

Five (11%) children born to mothers newly diagnosed with HCV had evidence of HCV antibodies when tested. One child had a weak antibody response but never had detectable HCV RNA, and a second child who had a viral load of 7 $x10^6$ IU/mL at the age of 4 months had spontaneously cleared the virus by the age of 12 months. Three children (6.8%) are under active follow-up with vertically acquired HCV, all with HCV genotype 3a, one of which is undergoing treatment with IFN/RBV at the time of writing. At least ten other cases were also identified as result of contact tracing as a consequence of mothers being diagnosed.

5.3.2 Cost-effectiveness results

The total cost of screening and confirmation of diagnoses was estimated to be £240,641. This translates to £6.81, £5,469 and £12,665 per individual screened, newly diagnosed and treated at the study centre, respectively.

Base case results are presented in Table 5.3 and compare a screening and treatment strategy to a no screening and no treatment strategy. These results were based on the 19 patients who were treated with IFN/RBV following screening at the study centre. When comparing treatment versus no treatment, the cost offsets associated with avoided HCV-related complications provide a relative cost-saving in patients with HCV genotypes 1, 2 and 3. Patients with genotype 4 infection incurred a greater cost, due to the relatively low observed rate of SVR, but remained cost-effective with an incremental cost-effectiveness ratio (ICER) of £4,054 per QALY gained. Across all treated patients, treatment is dominant over no treatment; that is treatment provides greater health benefits at a lower overall cost.

	Base case: IFN/RBV	DAA scenario 1: All SOF+IFN/RBV	DAA scenario 2: SOF+IFN/RBV in IFN/RBV failures
No treatment			
Total cost (£)	20,749	20,749	20,749
Total QALYs	15.39	15.39	15.39
Total life years	22.13	22.13	22.13
Treatment			
Total cost (£)	14,233	38,630	18,723
Total QALYs	17.95	18.73	18.82
Total life years	23.07	23.33	23.37
Cost-effectiveness results of treatment versus no treatment			
Δ Cost (£)	-6,516	17,881	-2,027
Δ QALY	2.56	3.34	3.43
Δ Life years	0.94	1.19	1.24
ICER (£/QALY)	**Dominant**	**£5,350**	**Dominant**
Cost-effectiveness of screening programme			
Δ Cost (£)	6,149	30,546	10,639
Δ QALY	2.56	3.34	3.43
ICER (£/QALY)	**2,400**	**9,139**	**3,105**
Maximum cost of screening program to remain cost-effective at £20,000/QALY (£)			
Total	1,097,531	930,390	1,340,402
Per screening	31.04	26.32	37.91

DAA, direct acting antiviral, ICER, incremental cost-effectiveness ratio; IFN/RBV, pegylated interferon α and ribavirin; QALY, quality-adjusted life year; SOF, sofosbuvir.

Table 5.3 Base case (BC) cost-effectiveness results (per treated patient)

After factoring in the additional costs associated with screening, additional healthcare expenditure is incurred as a result of the total screening and treatment strategy. However, when compared to the improvement in QALYs achieved in treated patients, the associated ICER of £2,400 (approximately €3,072/$3,840 USD) remains well below the accepted thresholds. Based upon screening this population of 35,355 women, it was estimated that the cost associated with screening each individual could

be increased up to £31.04 and still remain cost-effective at the £20,000/QALY gained threshold.

Table 5.3 demonstrates the potential impact of DAA use upon the cost-effectiveness of a HCV screening programme. Whilst incurring increased therapy-related costs, the improved SVR rates associated with SOF+IFN/RBV generated significant increases in QALYs and life expectancy (DAA scenario 1). A similar relationship was observed when IFN/RBV treatment failure was followed by SOF+IFN/RBV treatment (DAA scenario 2). These scenarios resulted in ICERs of £9,139 (approximately €11,697/$14,622) and £3,105 (approximately €3,974/$4,968) respectively.

Lifetime cost-effectiveness	Base case (BC)	SA 1a: **Age 28**	SA 1b: **Age 38**	SA 2: **Historical SVR %**	SA 3: **Treat all**	SA 4a: 0.1% HCV **Treat BC %**	SA 4a: 0.1% HCV **Treat all**	SA 4b: 0.6% HCV **Treat BC %**	SA 4b: 0.6% HCV **Treat all**
No treatment									
Total cost (£)	20,749	21,440	19,840	21,749	20,837	20,749	20,837	20,749	20,837
Total QALYs	15.39	15.90	14.80	15.39	15.38	15.39	15.38	15.39	15.38
Total life years	22.13	22.89	21.25	22.13	22.13	22.13	22.13	22.13	22.13
Treatment									
Total cost (£)	14,233	14,417	13,993	16,604	14,152	14,233	14,152	14,233	14,152
Total QALYs	17.95	18.63	17.17	17.56	17.96	17.95	17.96	17.95	17.96
Total life years	23.07	23.95	22.06	22.92	23.08	23.07	23.08	23.07	23.08
Cost-effectiveness of treatment versus no treatment									
Δ Cost (£)	-6,516	-7,024	-5,847	-4,146	-6,685	-6,516	-6,685	-6,516	-6,685
Δ QALY	2.56	2.73	2.37	2.17	2.59	2.56	2.59	2.56	2.59
Δ Life years	0.94	1.05	0.81	0.79	0.95	0.94	0.95	0.94	0.95
ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
Cost-effectiveness of screening programme									
Δ Cost (£)	6,149	5,642	6,818	8,520	-1,216	19,198	4,419	-124	-3,925
Δ QALY	2.56	2.73	2.37	2.17	2.59	2.56	2.59	2.56	2.59
ICER (£/QALY)	2,400	2,065	2,881	3,922	Dominant	7,492	1,707	Dominant	Dominant
Maximum cost of screening to remain cost-effective at £20,000/QALY (£)									
Total	1,097,531	1,171,480	1,010,514	904,304	2,572,019	497,477	1,165,817	2,984,863	6,994,903
Per patient	31.04	33.13	28.58	25.58	72.75	14.07	32.97	84.43	197.85

BC, base case; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SA, sensitivity analysis; SVR, sustained virological response.

Table 5.4 Sensitivity analysis results (per treated patient)

5.3.3 Sensitivity analysis

The screening strategy remained cost-effective under all sensitivity analyses performed, as presented in Table 5.4. The cost-effectiveness of screening was most significantly impacted by the prevalence of HCV infection amongst the screened women and the proportion of identified women treated. Compared to a screening cost threshold of approximately £31/person in the base case, varying the underlying HCV prevalence to 0.1% and 0.6% lead to thresholds of £14.07 and £84.43, respectively. The most cost-effective measure is expected to be ensuring the treatment of all diagnosed viraemic patients. Results suggest that treating all identified patients within the screening programme would have been dominant over no screening. Furthermore, after adjusting the prevalence of HCV infection to 0.1% or 0.6%, treatment of all positively diagnosed women would remain a more cost-effective scenario than treating a proportion as in the base case.

Conversely, age and changes in SVR were less influential. Increasing the age at which patients were diagnosed, however, proved to decrease cost-effectiveness of the screening programme. Utilising alternative SVR rates had a minor impact on the cost-effectiveness of screening, increasing the estimated ICER to £3,922. A summary of ICER and screening cost threshold results are presented in Figure 5.6, where the dashed line represents the estimated cost per person screened incurred at the study centre.

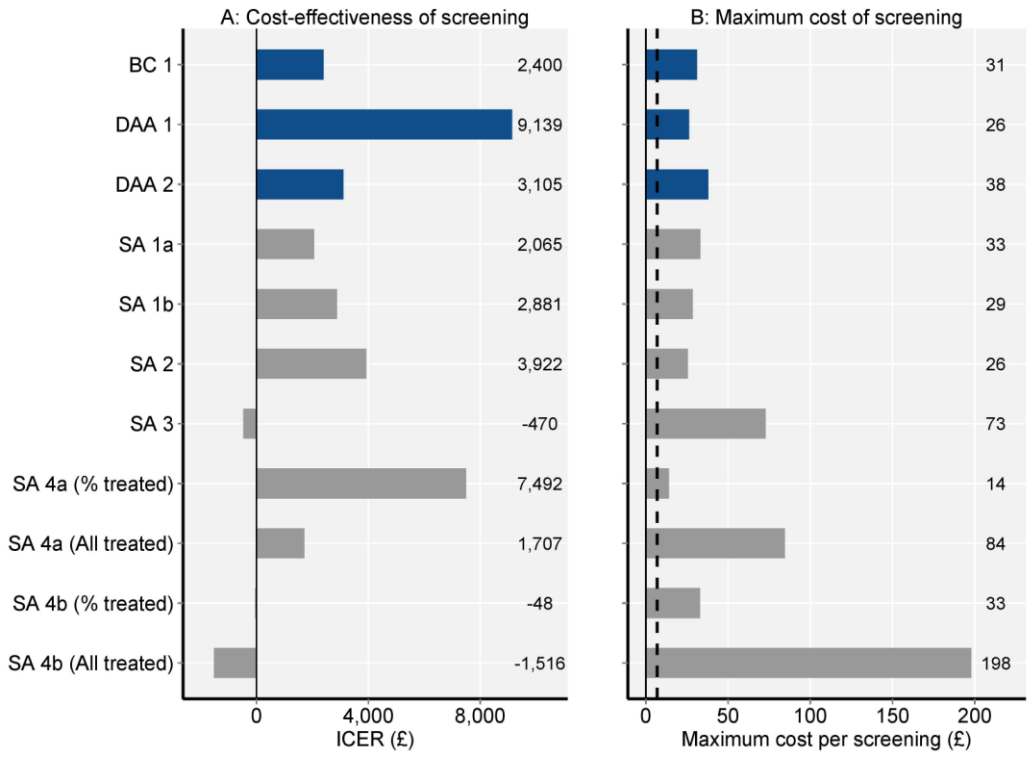


Figure 5.6 Incremental cost-effectiveness ratios and estimated maximum cost per patient screened, assuming a maximum cost-effectiveness threshold of £20,000/QALY. The dashed line represents the estimated cost per person screened incurred at the study centre

Additional analyses were undertaken relating to the most influential parameters for cost-effectiveness; i.e., the prevalence of HCV viraemia amongst the screened population and the uptake of treatment amongst those positively diagnosed. In each case, base case parameter values were utilised, whilst the prevalence of HCV or the rates of treatment uptake were contrasted over sensible ranges to investigate the effect upon cost-effectiveness. Results are presented in Figure 5.7, where the solid black line represents the £20,000/QALY threshold and the dashed black line represents the base case ICER of £2,400.

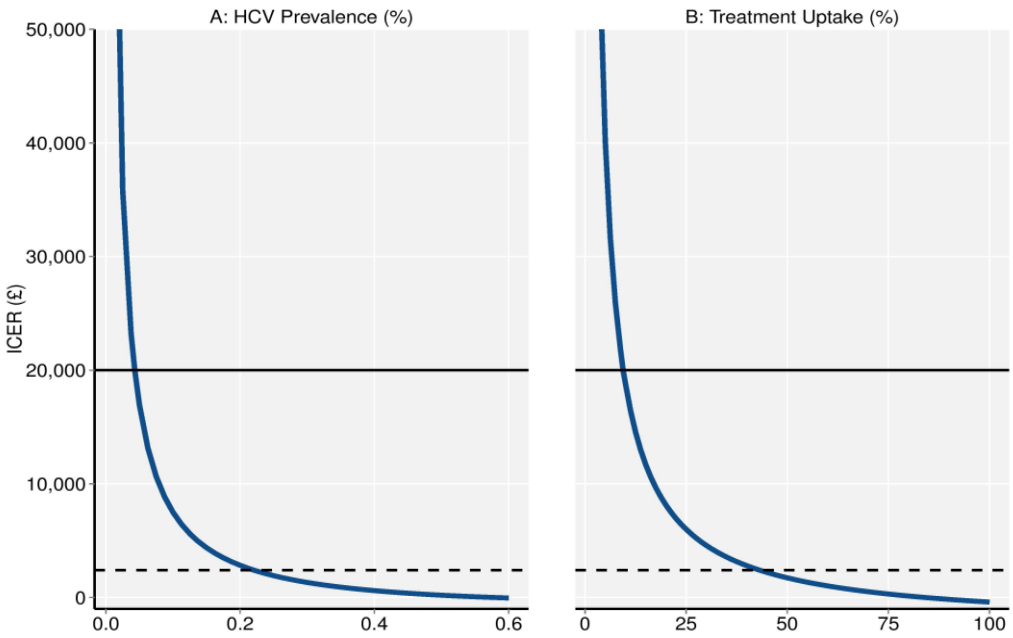


Figure 5.7 The relationship between the cost-effectiveness of screening: and the prevalence of HCV amongst screened patients; and the treatment uptake amongst those newly identified as HCV positive. The solid black line represents the £20,000/QALY threshold and the dashed black line represents the base case ICER of £2,400.

5.4 Discussion

Within the population of this study, addition of HCV screening and treatment was expected to be cost-effective. These findings are driven by the relatively low additional costs required to implement HCV antibody testing alongside existing antenatal screening tests. Overall, the incidence of newly diagnosed HCV was 0.12%, whilst seemingly low, it is comparable to the prevalence of new HBV (0.16%) and HIV (0.04%) diagnoses observed amongst antenatal screenings in England in 2013 [226]. This study has demonstrated that cost-effectiveness improves when the prevalence of HCV is increased assuming that costs and treatment uptake are comparable to those observed in this study. In countries, such as Egypt where antenatal HCV prevalence have been reported at up to 2.4% [227], the benefits of screening would potentially outweigh the additional cost incurred if the same assumptions were made. Furthermore, within that particular cohort, 90% of viraemic mothers were previously unaware of their infection and over 10% of infected patients would have been missed when undertaking screening based upon identification of risk factors. This supports the rationale for universal antenatal screening of HCV, akin to HBV and HIV. It provides the mother an opportunity to access treatment with a view of achieving SVR. At the time of writing, 22 of 44 newly diagnosed women are in position to have future pregnancies without risk of vertical transmission.

Amongst patients considered in the analysis, the observed effectiveness of conventional interferon-based dual therapy in the antenatal population with HCV genotypes 1–3 compared favourably to historical data. However, sensitivity analyses showed cost-effectiveness results were robust to deviations from the observed SVR

rates. Since the analysis in this study was undertaken, an additional three patients were treated and achieved SVR: one was treated with IFN/RBV and boceprevir for 28 weeks and two further patients were treated with interferon-free DAA regimens as part of clinical trials; potentially resulting in an underestimation of cost-effectiveness. The costs of identification and treatment of these chronically infected women were shown to be offset by the reduced risk of future sequelae of HCV-related disease. Women, and their children, who may have been identified at a later stage are more likely to be symptomatic, more difficult to treat and at increased risk of developing complications and incurring higher costs. Improved cost-effectiveness estimated in younger patients further highlights the importance of early detection. Consideration of societal costs or costs incurred by patients, such as lost productivity were not accounted for, potentially underestimating the benefits of this screening programme.

Screening strategies are receiving increasing emphasis, given the associated morbidity associated with HCV and the emergence of more efficacious treatments. Other focussed strategies, such as birth cohort screening, have been demonstrated to be cost-effective and have been implemented in the US to augment screening strategies in high risk patients [78]. This strategy offers screening to all Americans born between 1945 and 1965, a birth cohort that is estimated to contain 75% of unidentified HCV infected persons [81]; however, uptake rates for this programme have not yet been reported. Risk-based screening strategies will inevitably miss cases, and by design the birth cohort-screening programme in the US is likely not to capture 25% of HCV infections. Antenatal screening may offer a highly cost-effective strategy to identify HCV infection amongst a population that is most likely to benefit from treatment, due to demonstrated high rates of efficacy and therapy adherence.

Urbanus et al. reported that screening for HCV in Amsterdam's antenatal population was not cost-effective [88]. Two aspects that differ between the Urbanus study and this study, are (a) the inclusion of relatively high costs associated with screening and treatment within the Dutch population, and (b) the inclusion of life-years within the ICER calculation rather than QALYs. Indeed, when sensitivity analyses were performed with lower treatment costs, the Dutch screening programme was shown to be cost-effective, at a threshold of €20,000/QALY gained. The derivation of ICERs utilising life-years underestimates the benefit of treatment in relation to improved quality of life. This study demonstrated that antenatal screening has the potential to provide morbidity benefits as a result of detecting HCV-infected women earlier than they would normally be and thus preventing complications of HCV in later life.

This study is subject to a number of limitations relating to both modelling assumptions and the underlying characteristics of the study centre and population. The study centre is based in London, and, as demonstrated in the patient demographics, may have an overrepresented migrant population. Further cost may be incurred to provide a comparable programme, although centres undertaking routine antenatal HBV screening will undoubtedly have established infrastructure that would minimise costs of incorporating new HCV diagnoses too. When considering base case assumptions, it was estimated that an additional £856,890 could have been spent within this programme whilst maintaining cost-effectiveness at a threshold of £20,000 per QALY, when using base case assumptions.

Application of UK rates of alcohol consumption, in the absence of study-specific data, may have affected the derivation of fibrosis stage transition rates; however, this is unlikely to have made any significant difference to modelling results. Additionally, age-dependent health utility estimates were not considered within the modelling analysis; however, when considering the young age of the modelled cohort compared to the average UK HCV patient, and that health state utility estimates are representative of patients of differing ages, such an assumption is not likely to introduce significant bias. Given the relatively high rate of HCV antibody positive but PCR negative patients within our study population, 58 of 35,355 women (0.16%) would have experienced a brief negative impact on quality of life until their spontaneously cleared status was confirmed. Mothers that were given a new positive diagnosis in the antenatal period but were not offered treatment may also incur a decrement in quality of life. We suggest, however, that the overall gain associated with early diagnosis and improved treatment outcomes is likely to outweigh this. The assumption that in the absence of screening women would not be otherwise diagnosed or treated until symptomatic may lead to overestimations of the benefit of screening; however, given that the majority of identified patients would likely not be screened due to their "low" risk status, and in the absence of additional supporting data, this is an appropriate assumption.

The study did not evaluate the costs or benefits of the testing and treatment of children perinatally exposed. Three vertical transmissions from 44 newly diagnosed mothers were observed. There is little information available relating to the modelling of perinatally acquired HCV. Contact cases were not incorporated within the analysis, as the patient records could not be reliably used to assess contact tracing and

treatment outcomes. Whilst not considered from an economic point of view, the detection of these cases has potentially allowed for appropriate and timely management preventing further morbidity and possibly further transmission.

To date, HCV screening is reserved for individuals with elevated risks of infection, such as injecting drug use and presence of other blood borne viruses. Despite higher prevalence rates in such groups treatment uptake is suboptimal and is of limited cost efficiency [69, 76, 228]. Due to complex social factors eight mothers did not attend clinic follow up and thus did not undertake treatment. This highlights an area in which service development can be optimised further.

Antenatal screening for hepatitis C is demonstrably cost effective, whether considering use with base case interferon based therapies or as per sensitivity analyses considering DAA therapies. The established Blood Borne Virus pathways in the antenatal setting ensure good linkage to care and treatment uptake rates were high. It would be envisaged in an era of DAA therapies, uptake rates may even increase and potentially treatment could be undertaken in the third trimester akin to hepatitis B and HIV. It is hoped that committees responsible for national antenatal screening programmes will re-evaluate the need for HCV screening in the light of the evidence provided by this study.

This chapter was adapted and published Selvapatt N et al. Is antenatal screening for hepatitis C virus cost effective? A decade's experience at a London centre. Journal of Hepatology 2015(15)342-6.

6 Real-life outcomes for treatment with interferon based regimes in genotype 4 patients: Evaluation of a "difficult to treat group"

6.1 Introduction

Total numbers treated with pegylated-interferon and ribavirin following HCV antenatal screening outlined in chapter 5 were relatively small. However, the trends appeared to suggest that outcomes were at least, if not better than expected for genotypes 1-3. Amongst the three genotype 4 patients treated with pegylated-interferon and ribavirin only one achieved SVR. As it is not possible to draw any firm conclusions on the real life outcomes of patients within this cohort centre from such small numbers, we look more carefully at overall outcomes of persons treated at our study centre with hepatitis C virus genotype 4 (HCV GT4). Further, the basis of cost effectiveness analyses used by policymakers such as NICE rely on Phase 3 data when considering treatment outcomes. Within this thesis our cost effectiveness analyses are performed based on real life data. As such we compare the real life outcomes of this difficult to treat group of patients to ensure non inferiority of our real world outcomes compared to Phase 3 registration trial data.

Among the six major HCV genotypes, 90% of infected persons in developed countries have genotypes 1–4. HCV GT4 is more prevalent in Egypt, the Middle East

and Sub-Saharan Africa [229, 230]. In Europe, due to immigration and spread through injecting drug use HCV GT4 infection is becoming more prevalent [230]. Over a 4-year period, from 23 sentinel UK centres, 242 HCV GT4 patients were identified confirming that HCV GT4 is less common in the UK [231]. However, unlike other countries, no published data exists for post marketing GT4 HCV treatment outcomes in the UK. To date the standard treatment options include pegylated-interferon and ribavirin, usually for 48 weeks. Patients achieving a rapid virological response (RVR) have demonstrated improved chances of sustained virological response (SVR) and should be considered for shortening of treatment duration to 24 weeks [229, 232].

Registrations studies, with relatively small numbers of genotype 4 patients, with pegylated interferon and ribavirin demonstrated relatively limited success. In patients treated with pegylated interferon alpha-2a with ribavirin 10/13 (77%) achieved SVR compared to 4/11 (36%) with interferon alpha-2b and ribavirin compared to 4/9 (44%) with pegylated interferon alpha-2a alone [205]. In a separate registration study 16 patients were given high dose pegylated interferon and 12 low dose. In this study genotype 4, 5 and 6 were grouped together. Within this combined cohort 8/16 (50%) achieved SVR with high dose pegylated interferon and 4/12 (33%) with low dose [207].

New direct acting antiviral agents (DAAs) have demonstrated SVR rates of 89-100% in recent phase 3 clinical trials involving many thousands of patients with HCV genotypes 1–3 [223, 233-236]. These studies suggest that previously considered obstacles to SVR such as presence of cirrhosis, prior treatment failure, interleukin (IL)-28B TT polymorphism have been overcome with these new agents. There is

evidence that HCV GT4 patients also respond favourably to these new regimens, however numbers of patients in published studies are comparatively small [222, 237].

Whilst licenced for use in many countries, most patients in most countries currently still have no access to the use of DAAs. Pegylated interferon and ribavirin for the treatment of HCV GT4 patients remains the standard of care. It is recognised that when comparing clinical trial data to "real-life" outcomes discrepancies can occur. Inferior outcomes can be expected, as patients do not conform to the strict parameters used in clinical trial study protocols for inclusion and exclusion criteria of subjects treated. Health economic evaluations, used by policy makers such as NICE, rely on assumptions made following Phase 3 clinical trial data. In order to assume that such estimations remain valid in real-life settings it is important that real-life outcomes mirror that seen in the setting of Phase 3 Clinical Trials. Treatment with interferon based regimens in GT4 is widely acknowledged to be a harder to treat population than genotype 2 and 3 or genotype 1 since the advent of protease inhibitors. Therefore in establishing the efficacy of real-life treatment in such a population, if comparable to registration trials, would support that assumptions made within HCV cost effectiveness literature are applicable to the setting of this study centre. We report the largest published single centre European "real-life" observational study of treatment outcomes with pegylated interferon and ribavirin at our treatment centre in London, UK.

6.1.1 Hypothesis:

Treatment outcomes as reported, measured as achievement of SVR in genotype 4 patients treated at Imperial College Healthcare NHS Trust is non inferior to those reported in registration studies.

6.1.2 Aims:

- Assess overall SVR
- Assess for any effect of gender, age <45 or mild liver fibrosis (as seen in antenatal population)
- Assess effects on SVR of region of origin, co-infection with HIV, genotype sub-typing, Treatment duration and dose reductions

6.2 Methods

All patients with virologically confirmed HCV GT4 from 1st March 2002 to 1st October 2014 were included for analysis. All patients were assessed and treated under the care of the Department of Hepatology at St Mary's Hospital, part of Imperial College Healthcare NHS Trust in London. Patient selection for treatment was based on standard of care practice, although overall at the discretion of the individual treating physician based on clinical indications and patients' decisions. Retrospective analysis of available data included: patient age, sex, region of origin, co-infection with HIV, pre-treatment liver biopsy histological assessment, genotype subtyping (where available), treatment duration, dose reductions, and corresponding rates of SVR. Treatment outcomes were assessed comparing patients treated between 2002-2008 to 2009-2014 to evaluate any potential effect of treatment experience within our centre on patient outcomes. Patients who were lost to follow-up or who had insufficient results to be able to establish if successful eradication of HCV, determined by an SVR at least 24 weeks post treatment, were not included for analysis.

Patients were initiated with treatment involving pegylated interferon alpha-2a (180μg/week) and weight adjusted ribavirin (1,000 or 1,200 mg/day) for 48 weeks. Patients undergoing dialysis were treated with ribavirin 200mg three times per week. Shortening of treatment duration to 24 weeks was performed on patients within this cohort on the basis of achievement of rapid virologic response (RVR). However, this was at the discretion of the individual treating physician and some patients were treated for 36 or 48 weeks despite having achieved RVR. Standard dose reductions of

interferon or ribavirin were performed in the event of anaemia, neutropenia or thrombocytopenia.

SVR was defined as undetectable HCV RNA 24 weeks after the completion of therapy. Negative outcomes were classified as per standard definitions of response as those who were either intolerant (if they stopped treatment due to side effects), non-responders, relapsers and those with breakthrough.

HCV viraemia was quantified by Abbot HCV Real-Time polymerase chain reaction (RT-PCR) assay (Abbot Molecular Inc., Des Plaines, Illinois, USA) assay and genotypes were determined by phylogenetic analysis of the NS5B region (Micropathology Ltd, Warwick, UK). Histological assessment of pre-treatment liver biopsies were performed by specialist hepatology histopathologists. Ishak staging scores were used to determine fibrosis scores ranging from 0 to 6 [238].

6.2.1 Statistics

Univariate analysis was performed to assess effect of pre-treatment viral load and histological staging, region of origin, age, gender, presence of co-infection of HIV and genotype subtyping on SVR. Mann-Whitney U testing was performed to assess effect of viral load. Region of origin was subdivided into Egyptians, non-Egyptian Africans, Middle Eastern, Western Europeans, Eastern Europeans and Asians. When assessing for difference between all populations one-way ANOVA testing was used. All other parameters were compared for outcomes in 2 x 2 testing and Chi square testing was used to assess for statistical significance.

Factors related to SVR identified from univariate analysis with a $P < 0.1$ were tested using multivariate logistic regression analysis. Odds ratios were estimated from the model and given with their 95% confidence intervals.

6.3 Results

During the study period 219 patients were diagnosed with HCV GT4, of which a total of 118 patients were treated in the period assessed, with 57 achieving SVR (48%). There was no difference in SVR rates in those treated between 2002-2008 and those treated between 2009-2014. Six patients were intolerant, 25 were non responders, 3 developed breakthrough, 18 were relapsers, 3 are currently undergoing treatment and 6 were either lost to follow-up or had missing data fields. Table 6.1 demonstrates pre-treatment and demographic data for patients that underwent treatment with pegylated interferon and ribavirin.

Total new diagnoses		**219**
Total treated		118
Region of origin	Western Europe	33 (28%)
	Eastern Europe	7 (6%)
	Egypt	34 (29%)
	Non-Egyptian Africa	18 (15%)
	Saudi Arabia	15 (13%)
	Asia	4 (3%)
Sex	Male	85
	Female	33
Median age at onset of treatment (range)		44 (6-66)
Median Pre-treatment viral [iU/mL] (IQR)	SVR	122,048 (18,088-750,908)
	No SVR	984,976 (236,745-2,039,000)
Pre-treatment Ishak histological staging	0	0
	1-2	24
	3-4	28
	5-6	20
Treatment duration	<24 weeks	15
	24 weeks	16
	25-48 weeks	5
	48 weeks	79
	>48 weeks	3

Table 6.1 Demographic data and pre-treatment clinical viral loads and histological staging for patients treated with hepatitis C virus genotype 4 infection.

6.3.1 Non inferiority assessment

Non inferiority within this study cohort was compared against two registration studies that evaluated genotype 4 patients [205, 207]. A third registration study only included genotypes 1, 2 and 3 [206]. In order to be included in analysis we only used those that were treated with pegylated interferon and ribavirin which included 41 patients (of which a small proportion were in fact genotype 5 and 6) of which 22 achieved SVR (p=0.15). A second anlaysis was performed looking at outcomes of only those with high dose pegylated interferon which included 29 patients of which 18 achieved SVR (p=0.30). When pooling analysis, genotype 4 outcomes in this real-world study cohort is not significantly different to those demonstrated in the original registrations studies.

6.3.2 Assessing predictors of response

Six patients were treated for acute HCV, all of whom were co-infected with HIV, and all achieved SVR. Six patients had rapid virologic response (RVR) and 5 of these patients had their treatment duration shortened in response. Three patients were treated for 24 weeks having had a RVR, of which 2 achieved SVR and one was lost to follow-up having achieved SVR 12 weeks post treatment. Two patients were treated for 36 weeks and both achieved SVR. A sixth patient who achieved a RVR was treated for 48 weeks and also achieved SVR.

Three patients were treated for longer than 48 weeks (up to 72 weeks) none of which achieved SVR. Subtyping analysis was performed in 35 patients of which 10 were 4a,

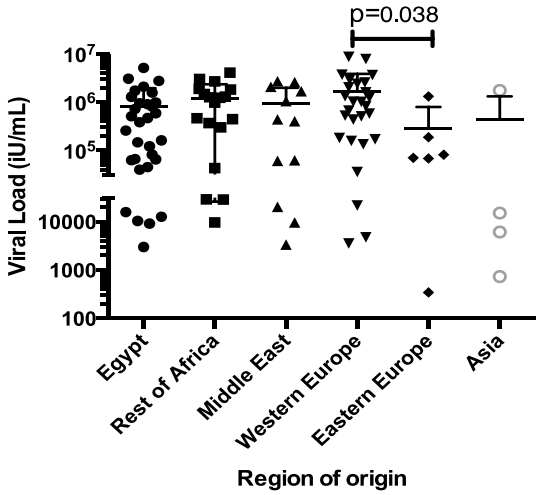
of which 50% achieved SVR, and 13 had the 4d subtype (54% SVR). Seventeen patients were co-infected with HIV with 11 achieving SVR (65%). Fifteen of these patients were from Western Europe, of which eleven were from the UK. Within this group 11 achieved SVR (65%). One patient got re-infected post SVR but spontaneously cleared hepatitis C and did not require further treatment. Of the 7 treatment failures 2 were intolerant of the treatment (severe anaemia and sepsis), 1 relapsed, 3 were non-responders and 1 relapsed into illicit drug use and stopped treatment at 4 weeks. Three HCV monoinfected patients were treated while on renal dialysis, with 2 achieving SVR.

Thirty-eight patients (32%) required interferon dose adjustments and 8 (7%) patients required ribavirin dose adjustments. When excluding patients that had dose adjustment due to renal dialysis no significant difference was noted in response between patients that had dose reduction of interferon and/or ribavirin during treatment compared to patients that had no dose reductions (P = 0.8).

Figure 6.1 demonstrates the impact of pre-treatment viral load as an independent predictor of treatment response to pegylated interferon and ribavirin. When assessing country of origin 33 were from Western Europe (of which 17 from the UK), 34 were Egyptian, 18 non-Egyptian African, 15 from The Middle East, 7 from Eastern Europe and 4 from Asia. SVR rates varied from 86% amongst Eastern European patients treated to 56% amongst Egyptians and 46% in Western Europeans to 22% in Sub-Saharan patients treated. All four Asian patients achieved SVR. On univariate analysis there were significant differences noted between treatments outcomes of patients depending on their regions of origin as demonstrated in Figure 6.2. Of note

Asian patients were not included within this analysis owing to the small number within this subgroup.

a) **Viral load comparisons between regions of origin**



b) **Comparison of pre-treatment viral loads**

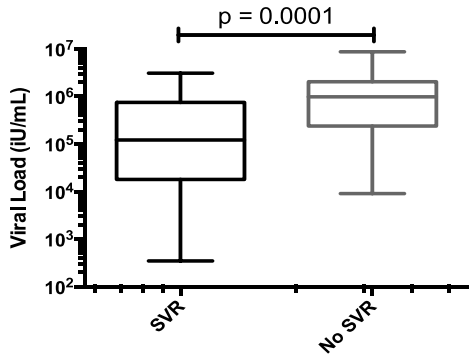
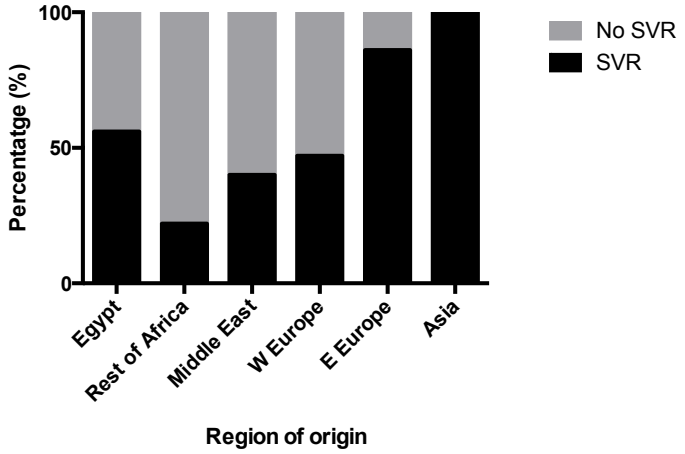


Figure 6.1 Comparison of pre treatment viral loads (a) between different regions of origin (b) between SVR and no SVR groups

a) **Regional comparisons in treatment responses**



b)

	Egypt	Rest of Africa	Middle East	W Europe	E Europe
Egypt		**<0.0001**	**0.0235**	0.2029	**< 0.0001**
Rest of Africa			**0.0059**	**0.0002**	**< 0.0001**
Middle East				0.3181	**< 0.0001**
W Europe					**< 0.0001**
E Europe					

Figure 6.2 a) Percentage of patients achieving SVR versus no SVR between different regions of origin b) Comparison of response rates for treatment between regions of origin.

Seventy-two patients had liver biopsy prior to treatment with outcomes demonstrated in Figure 6.3. None of the patients had fibrosis score of 0, 24 had Ishak staging 1-2 of which 58% achieved SVR, 28 had stage 3-4 fibrosis with 57% achieving SVR, 20 patients were treated with stage 5-6 disease on liver biopsy with significantly inferior SVR outcomes of only 20% ($P<0.001$) compared to those with Ishak scores 1-4. The

median age at the start of treatment was 48 years (range 6 years to 66 years). Age 45 years and above was also negatively associated with treatment outcomes (P<0.001) compared to those under 45 years old.

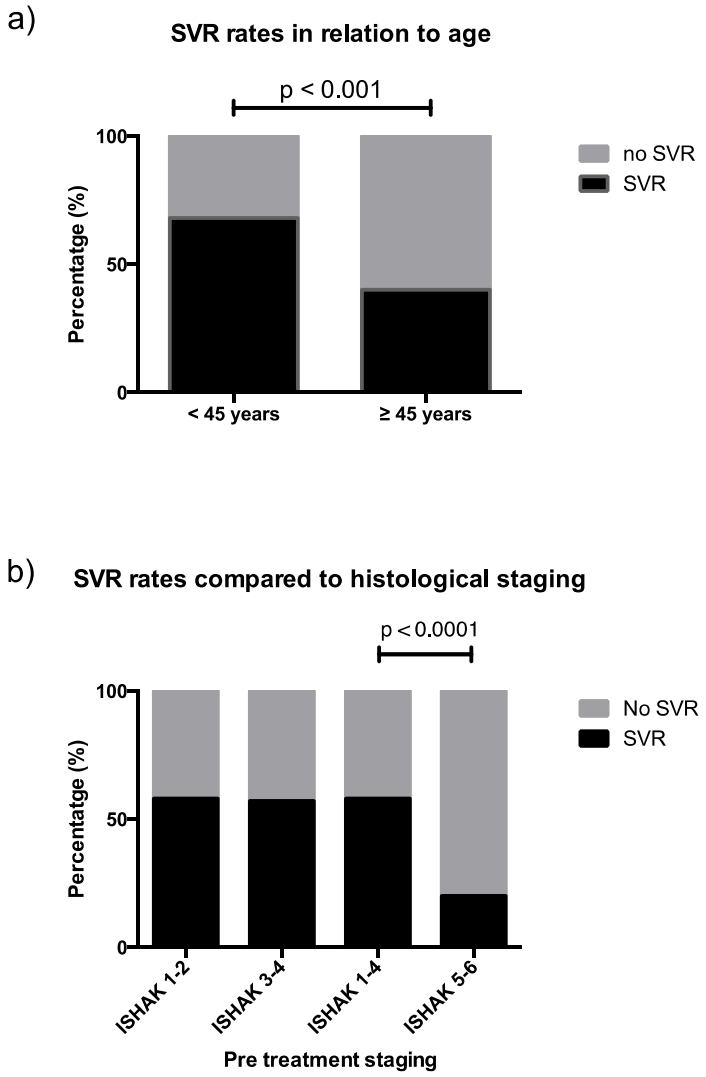


Figure 6.3 a) Proportion of SVR between patients aged above and below 45 years old b) Comparison of SVR response between pre-treatment histological (Ishak) staging scores.

Univariate predictors of response with P values <0.1: age at treatment <45 years old; pre-treatment viral load; pre-treatment histology staging and those from Eastern Europe or non Egyptian Africans compared to other regions of origin were assessed. On multivariate analysis viral load (P=0.0005); Ishak staging (P=0.0031) and age (P=0.0003) were associated with SVR but not region of origin (P=0.0645).

6.4 Discussion

This study provides a "real-life" account of treatment of HCV GT4 from a European treatment centre viewpoint. This study aims to assess if interferon based outcomes in genotype 4 are inferior to registration trial data as suggested in the small cohort treated following antenatal screening. To date, apart from the initial registration studies, the majority of "real-life" data originates from Egypt and Saudi Arabia [229. SVR in HCV GT4 has been reported to be as high as 66-75% in these groups [Kamal, 2011 #402, 239]. The literature appears to suggest that Egyptians with HCV GT4 have superior SVR rates compared to other African and Saudi Arabian populations. Differences in subtypes notably 4a versus 4d have been cited as a potential explanation for this [240].

Our data concurs with the current body of evidence that Egyptians appear to have a superior response to interferon and ribavirin compared to people infected from other parts of Africa and The Middle East. Within our cohort we did not demonstrate any difference in SVR rates between patients identified with the 4a or 4b genotypes. Whilst Western Europeans also had significantly improved outcomes compared to non Egyptian Africans, they had an equivalent response to Egyptians and patients from The Middle East. Eastern Europeans however demonstrated significantly improved SVR rates compared to the other populations on univariate analysis. However, when combing viral load, age, fibrosis score and nationality on multivariate analysis the impact of region of origin did not appear to be significant.

The presence of severe fibrosis, defined as Ishak histological staging of 5-6, was a good negative predictor of response with SVR of 20% compared to 57.5% in patients with Ishak staging 1-4. Of the 20 patients identified with Ishak stage 5-6 disease only 3 were European, the rest were Middle Eastern or from Africa. The overall high proportion of moderate to severe liver disease is most probably reflective of the fact that most patients were treated at a relatively late age with only 22 (19%) of the patients being under the age of 45 at the time of starting treatment. It is possible these could explain the differences in SVR outcomes initially seen on univariate analysis between different regions of origin. We can speculate that generalised differences in acquisition of virus in different geographical locations may relate more to length of disease prior to treatment than necessarily due to genetic variations. Many of the infected patients from Africa and The Middle East would presumably have acquired their disease at an earlier age, probably iatrogenically and many in childhood, compared to Europeans for whom many may have acquired the virus as a result of high-risk behaviours in adulthood. Given the inferior responses to interferon-based treatments compared to genotypes 1-3, earlier identification, possibly through screening programmes, of patients with HCV GT4 in particular would be beneficial in order to offer treatment at an earlier stage.

Patients with HIV co-infection and those receiving renal dialysis had surprisingly good outcomes in this cohort. HIV co-infection with HCV GT4 has previously had reported SVR between 15-34% when treated with pegylated interferon and ribavirin [229]. Seventeen patients within this cohort were co-infected with HIV with 65% achieving SVR overall and 2 out of the 3 patients treated on renal dialysis achieved SVR. In the context of limited options for these patient groups at this time, these

results hopefully re-affirm confidence in treating patients considered “hard to treat” with existing pegylated interferon and ribavirin regimes in the absence of available alternatives.

Whilst this is the largest single centre European cohort reported in the literature to our knowledge, given the overall numbers there is a risk of bias when performing small subgroup analysis. Being retrospective and given the duration of time of the study period it has meant that early sub-typing data is not available and IL-28B status is unknown. It has been demonstrated previously that response to interferon therapy in HCV GT4 patients is significantly improved in the presence of the IL-28B CC genotype [241]. In the absence of this subtyping data, it therefore needs to be considered that the geographical variations noted in this study in responses to interferon based therapy may have potentially have been due to underlying regional variations in IL-28B genotypes [242]. However, on multivariate analysis viral load, age and histological status appear to be the most significant factors for interferon based response and the regional variations in response may have been confounded by more advanced disease in certain regions where patients may have had a longer exposure to HCV infection. This study provides an insight into the outcomes of HCV GT4 from a European perspective that differs from that reported from previous reported real life experiences from Africa and The Middle East.

A significant proportion of patients identified with HCV GT4 (101 out of 219) did not embark on treatment. The reasons are multifactorial and reflect the transient nature of the population, issues with linkage into care and also reluctance to embark on interferon based therapies. Improved tolerability associated with newer DAAs may

help overcome this. The findings in our centre are comparable to previous inferior overall response rates in French and Greek cohorts [239, 243]. These results demonstrate sub-optimal treatment response rates compared to treatment with interferon-based regimes in genotypes 1-3. The emergence of DAA therapies with superior response rates will likely negate the differences in SVR rates related to interferon therapies. However, what this study does demonstrate that real life outcomes appear similar to registration studies.

When considering the antenatal population the major differences in the overall study cohort were that this cohort was predominantly male (85%) and older (median age 44). If anything these should be negative predictors of response to therapy compared to the antenatal population. An additional interesting observation from this study was the relatively large proportion of patients with advanced fibrosis and cirrhosis and associated poor responses to therapy. Given the impact of cirrhosis, as outlined in Chapter 3, this study lends further support for the necessity for earlier diagnosis and treatment to avoid poorer treatment response rates and HCV related complications of cirrhosis.

This chapter was adapted and published Selvapatt N, Habibi M, Brown A. A European Single Centre Experience of Management of Hepatitis C Virus Genotype 4 infection with pegylated-interferon and ribavirin. Journal of Medical Virology 2015;87(10)1716-21

7 Outreach screening and treatment in a homeless shelter using rapid point of care testing

7.1 Introduction

Minimal data exists for UK prevalence of HCV in homeless populations. Whilst anecdotal evidence suggests that injecting drug use is prevalent in such populations, poor quality data exists to support this [244-246]. Reports from other developed countries do certainly point towards increased IDU behaviours amongst homeless populations [247, 248]. Conversely amongst a cohort of 1,405 current and former IDUs in Baltimore, USA homelessness appeared to be a predictor of injection related risk behaviour or risk of relapse into such behaviours [249]. A systematic review and meta-analysis of HIV, tuberculosis and HIV prevalences in 43 studies involving 59,736 homeless persons found that HCV had the highest prevalence 4.3-36.2% compared to 0.2-7.7% for TB and 0.3-21.1% for HIV [250]. A 2003 study by Sherriff et al. is the only reported study reporting prevalences of HCV in a homeless population in England [251]. Of 98 individuals tested 26 (26.5%) had positive detection of HCV antibodies. However, the authors do not explain how many were subsequently tested for active viraemia nor was any evidence that these persons were attempted to be linked into care for treatment of hepatitis C.

Point of care testing is a term used to describe diagnostic testing at the time and place of patient care. The use of finger prick blood or oral fluid testing requires less staff training and potentiate increase up-scaling of screening [252]. Currently, although there are many commercially available rapid diagnostic tests, there are currently three HCV antibody serological assays that have been pre-qualifed by WHO, two of which remain laboratory based serological tests [253]. Tests requiring laboratory testing for screening, whilst accurate, do incur a reporting delay of results and the need for specialist laboratory access. This poses a further barrier to linkage to care as in the absence of robust system safeguards, such delays increase the possibility of losing hepatitis C persons to healthcare services [254]. Whilst cost effectiveness of oral fluid based strategies have not been assessed, finger prick methods compared traditional venepuncture in the context of the US baby-boomer screening population is found to be equally cost effective [255]. To date, HCV point of care testing is not in widespread use, but is increasingly being considered, especially in the context of up-scaling screening by organisations such as the World Health Organisation. In HIV point of care HIV testing has demonstrated increasing retention to care and reduced time to assessment for eligibility of initiation antiretroviral therapies [256]. In the UK, national guidance from the British HIV Association recommends point of care testing in [257]:

- Clinical settings where a rapid turnaround of testing results is desirable
- Community testing sites
- Urgent source testing in cases of exposed incidents
- Circumstances in which venepuncture is refused

The OraQuick HCV Rapid Antibody Test (OraSure Technologies Inc., Bethlehem, PA, USA) has been developed and approved by the US Food and Drug Administration (FDA) for use with whole venous blood (2010) and fingerstick blood (2011) in those aged 15 years or older [258]. It can also detect anti-HCV antibodies from saliva and has been investigated as a point of care screening tool [259]. The OraQuick assay uses indirect lateral flow immunoassay to detect antibodies against the recombinant core as well as NS3 and NS4 antigens with synthetic HCV peptides. The test procedures allow results to be interpreted after 20 to 40 minutes with built in procedural control and external quality controls [260]. Oral fluid based point of care tests confer practical advantages. Firstly sampling does not require staff training in venepuncture. Secondly in patients populations where venous access my be technically challenging, such as those with longstanding IDU practices, this non invasive sampling may be conducive to greater acceptability for screening. A study looking at 129 adults under the age of 30 who were active PWID demonstrates wider acceptability of OraQuick compared to standard phlebotomy, with the rapidity of results and lack of venepuncture being cited as key reasons for preference [261].

In a meta-analysis, with meta-regression modelling of seven point of care tests evaluated (OraQuick, Genedia, SDBioline, TriDot, Chembio, Spot, Multiplo), OraQuick performed consistently the best. In whole blood it had pooled sensitivity of 99.5% and specificity of 99.8%. Using oral fluid it maintained sensitivity 95.9% and specificity 99.4%. It does appear that oral testing has lower sensitivities compared to blood based tests, possibly due to lower concentration of oral fluid HCV antibodies compared to blood. Presence of oral pathology, mouthwash or acidic beverages may also affect results [262].

As homeless shelters are highly transient populations, we believed that it would be likely to benefit most from a screening strategy that provided results whilst the clients were still in the clinical area. This would enable instant counselling of results and may increase the likelihood of linkage into care.

7.1.1 Hypotheses

Outreach screening and treatment in a homeless hostel is feasible and cost effective. Oral swab testing is feasible and correlates with serology.

7.1.2 Aims

- Define a single cohort from a specified homeless shelter
- Identify HCV prevalence
- Assess rates of Viraemia (and therefore eligibility for treatment)
- Assess linkage into care
- Assess overall HCV treatment outcomes
- Assess cost effectiveness of this homeless screening service

7.2 Methods

A study site for hepatitis C screening of homeless persons was selected as St Mungo's Centre for the Homeless, London. St Mungos is a single site day centre open 10am to 6pm on weekdays. It functions as a day self referral drop in centre with limited daily capacity of between 20 and 30 operating on a first come basis. It provides a range of services that attendees can voluntarily use without appointment including sexual health, optician, yoga, exercise programmes, benefits advisor, mental health, housing, drug and alcohol liaison. There are also facilities for showers and laundry.

Prior to set up of a hepatitis C screening clinic a basic questionnaire (Figure 7.1) was circulated to persons attending St Mungo's aimed at anonymously assessing the level of understanding of hepatitis C, the role of screening and if previous screening had been performed. Following on from this a series of talks were provided to both the staff and clients of St Mungo's to explain the rationale for HCV screening and to increase awareness of the pilot screening programme to allow open and voluntary access for any homeless persons that wished to be tested for hepatitis C using oral swab testing. All participants were screened by voluntary processes and no direct recruitment attempts were made. In order to improve acceptability and to encourage as much as possible to collect data from as many clients as possible for prevalence rate estimation we intentionally collected minimal data from those that wished to be tested. The idea where possible, given that instant results would be provided, was to reduce data gathering that may be considered a barrier to acceptance of testing. Those that accepted screening provided date of birth and gender, in order to create a hospital

number if later required, but no other data was collected on demographics or baseline characteristics.

Hepatitis C screening was performed by a Specialist Hepatitis Nurse fortnightly. The OraQuick HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, USA) was used. Oral fluid was collected in accordance to manufacturers instructions. This oral swab testing kit provides a visual result within 20 minutes as demonstrated in Figure 7.1. As this was a proof-of-concept study the duration was screening was limited to 100 OraQuick assays that were used in all sequential voluntary attenders starting on the 28th July 2014 which lasted until 22nd January 2015.

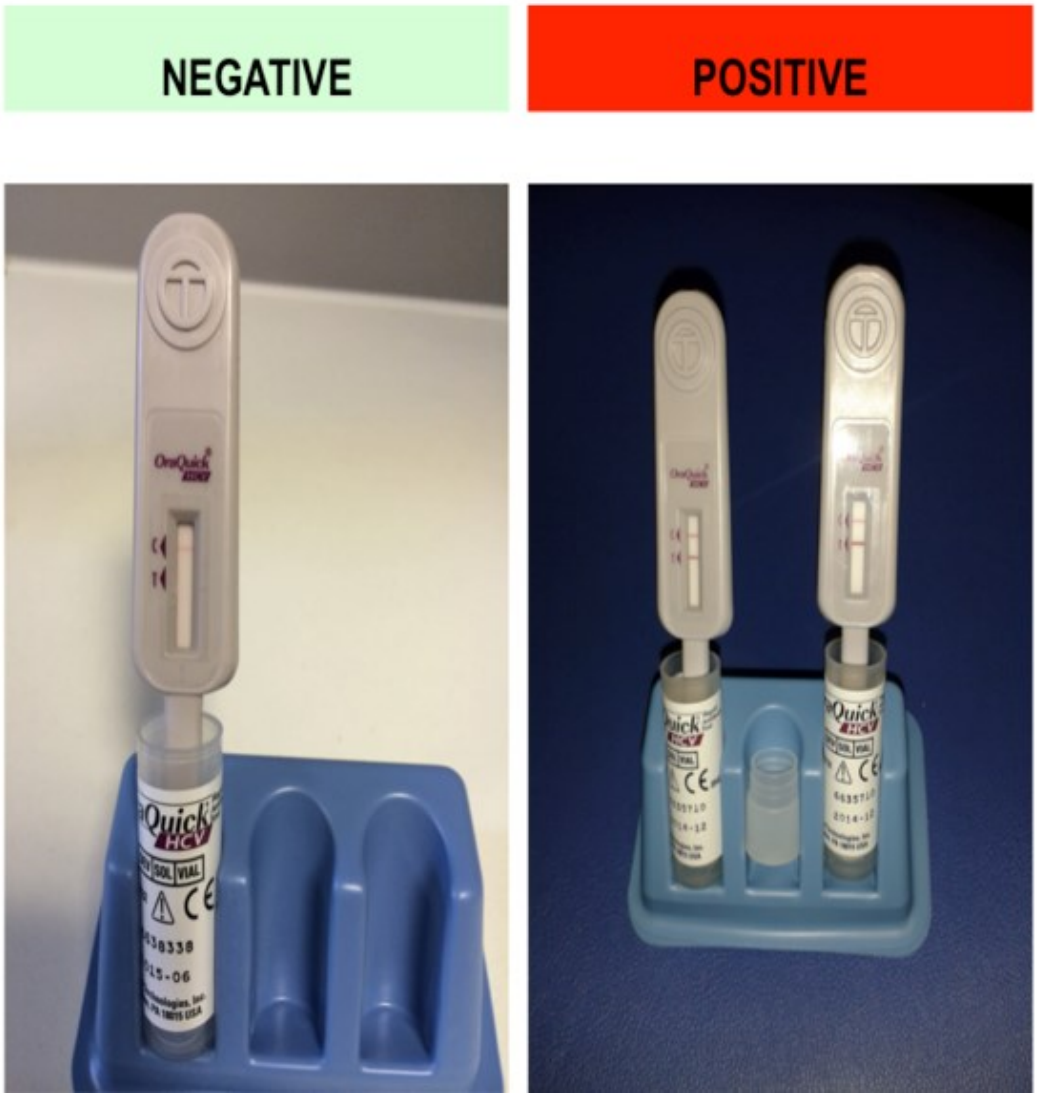


Figure 7.1 OraQuick testing kit demonstrating negative result (one band) and positive result (double band)

All patients with positive results were counselled at the time of screening by the specialist nurse and had confirmatory blood tests, HCV viral load and genotype testing. These clients were then offered follow-up appointments at St Mary's Hospital Liver and Antiviral Unit or St Mungo's Homeless shelter. Data was collected on rates of linkage to care, HCV genotype, liver fibroscan or liver biopsy assessment of fibrosis and treatment outcomes.

Data from this would be used to inform a base case scenario for health economic assessment of this screening strategy using the previously validated MONARCH Markov model for hepatitis C.

7.3 Results

Thirty two clients completed the questionnaire: 22 (69%) reported that they had heard of HCV previously; 14 (44%) had been tested before; 29 (91%) would agree to screening. 29 (91%) reported oral swab testing was acceptable form of testing and 31 (97%) would consider treatment if offered (Figure 7.2).

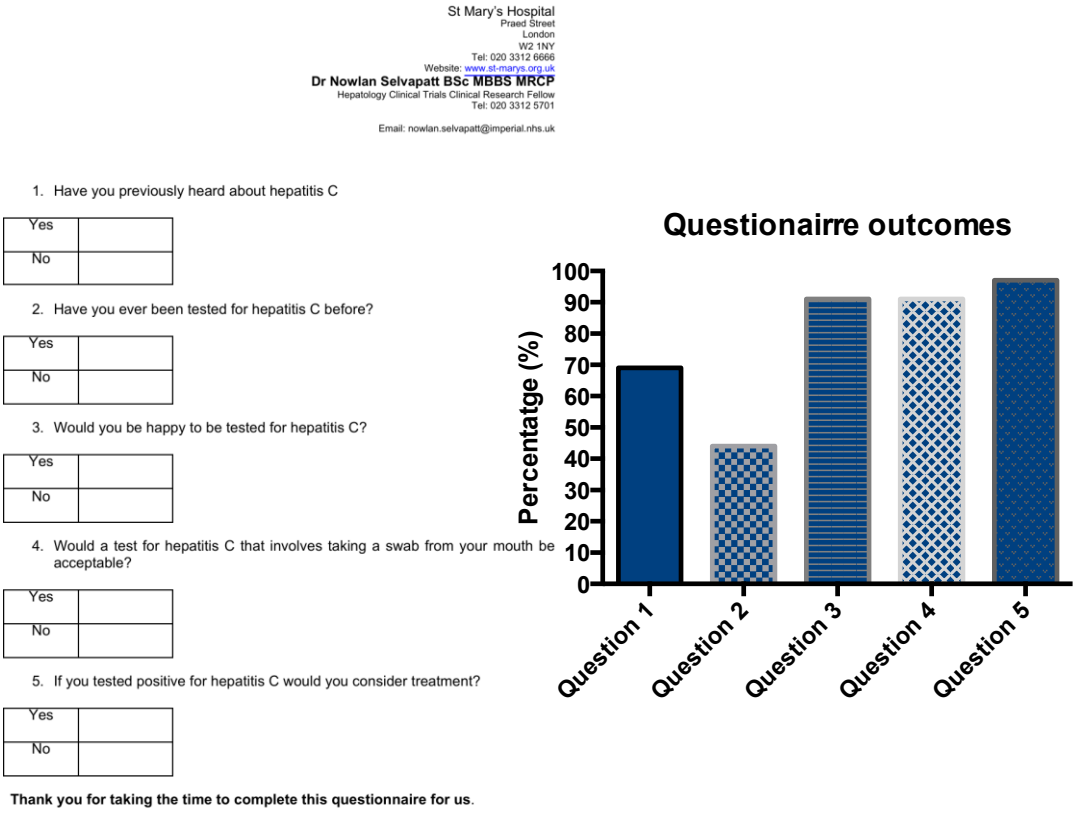


Figure 7.2 Pre-initiation questionnaire to evaluate potentially acceptability of a screening programme for hepatitis C amongst persons in a homeless shelter

During the study period 209 persons were recorded to have attended the centre on the days that HCV testing was being performed. It is not possible to decipher from the data how many were repeat attendees. 95 clients underwent HCV testing, of which

79 (83%) were male. The average age was 44 (21-74). Overall 6 (6.3%) clients tested positive for hepatitis C antibody. Figure 7.3 outlines the outcomes of these clients that were positive for HCV antibody on OraQuick testing. Of these 2 admitted current injecting drug use, 3 reported prior IDU and 1 denied any history of IDU. On confirmatory testing 4 patients were identified with HCV mono-infection, 1 patient HIV co-infection, none with hepatitis B co-infection and 1 patient was HCV antibody positive on serological antibody testing but PCR negative on sequential testing suggestive of spontaneous clearance. All 5 viraemic patients attended follow-up within 14 days of diagnosis. 3 patients were Caucasian British, 1 Latvian and 1 Russian. One patient was co-infected with HIV, both were new diagnoses. To date one patient started treatment with pegylated interferon and ribavirin (genotype 3A) but developed virologic breakthrough at week 12 and therefore stopped. Another patient has been offered treatment but has elected to wait for interferon therapies free and three are currently being worked-up for treatment.

7.3.1 Linkage to care

Of 5 patients identified with HCV viraemia, and eligible for treatment, 4 attended initial follow-up visits. All 5 were new diagnoses. One patient underwent treatment, and despite being a breakthrough on interferon and ribavirin for 16 weeks, has been retained to follow-up and is awaiting further therapy. A second patient also remains under the care of the Liver services at ICHNT and is awaiting therapy with interferon free regimes, as per patient choice. Two patients have attended follow-up, but have moved out of area and have their care formally transferred to local services. Only one

patient was lost to follow-up after attending one repeat appointment. It has not been possible to make contact.

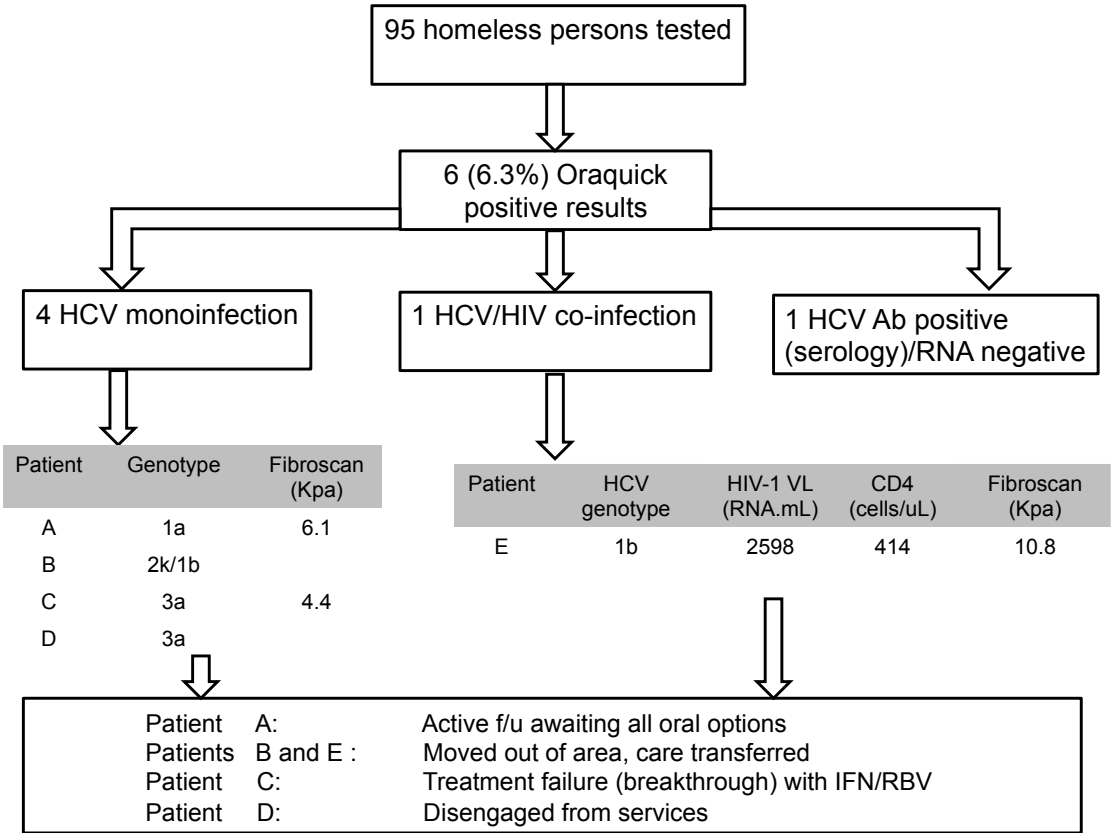


Figure 7.3 Flow chart demonstrating the outcomes of screening , hepatitis C genotypes of those positively identified with evidence of HCV antibody and outcomes of follow-up

7.4 Discussion

Oral swab testing was an acceptable tool in this homeless person's outreach pilot study. Within this study of an Inner London Homeless shelter hepatitis C antibody prevalence was 6.3%, which whilst significantly higher than the general population is lower than previously reported UK data [251]. The pathways for use as an outreach screening tool appear feasible and whilst patient numbers were limited it appears at least short term linkage to care is satisfactory especially when accounting the nature of this population. There appears to be good concordance between oral swab positive antibody results and confirmatory serological results in keeping with previous validation data. Whilst providing an interesting platform for further work, owing to the overall low numbers of patients eligible for treatment and lack of treatment outcome data it was not feasible to perform health economic analysis as the assumptions that would have been required would likely bias outcomes.

A recent study involving screening with OraQuick saliva testing in homeless people in Dublin, Ireland using the Safetynet primary healthcare services reported 26% HCV antibody positivity amongst the 460 people screened. Of these 12 (9.6%) were new diagnoses. Within this population 23% reported previous injecting drug use, 15% current and 40 were referred for assessment to specialist care services to assess suitability for treatment. The authors report however poor linkage to care with only 6 out of 40 attending appointments at the hospital for evaluation [263].

The strengths of this study are based on the novel nature of this study. Whilst point of care testing is gaining an increasing recognition as a mechanism for increasing HCV

case finding, oral swab testing remains a relatively novel strategy. This study demonstrates that amongst the most transient of populations that it is feasible, acceptable and probably owing to it's instant results offers a method of increasing the chances of linking newly diagnosed patients and keeping them linked into care. Compared to the Dublin study, which appeared to demonstrate higher prevalences, it appears that outreach testing and screening offers a possible advantage with regards linkage to care.

This study, whilst not providing any definite conclusions regarding the prevalence of HCV in homeless populations, adds to the very limited data in the UK setting and in particular London. This study has major limitations owing to the design as a proof of concept study. Firstly whilst demonstrating good correlation with serological testing this study did not assess false negative rates in this population. No assessment was made of oral health and hygiene and how that may have impacted on results, as this was outside of the remit of this study. Secondly, owing to the limited number of tests that could be offered and the significantly lower rate of HCV prevalence compared to both previous UK and international data from meta-analysis, the total number of persons identified were too small to form a base case for economic evaluation. Within the overall population screened, no data was collected on high-risk behaviours and previous or on-going injecting drug or intranasal cocaine use. Whilst this was in order to improve acceptability of testing and engagement in the pilot screening service, this limited our ability and understanding of whether practices and risk patterns in this population are different to those reported previously. In Oxford where 57% of participants admitted to being injecting drug users on a daily basis either then or previously and 34% admitting on-going injecting drug use at the time of the study

[251]. Within that study population 41% reported to sharing needles, which given that it was over a decade ago may in itself reflect a change in demographic with much improved opiate substitution and needle exchange programmes being widely available. Finally the setting of the study may not be wholly representative of an inner London homeless population. Given that it was a day centre that required attendees to self present in the morning, there may have been a selection bias within the population favouring those with greater motivation and possibly less chaotic behavioral patterns. Ideally, a screening project encompassing a wider variety of homeless settings would be needed to understand if findings have more generalizable.

Further work is required to elucidate prevalence of HCV in a homeless setting is in keeping with our findings. Whilst 6% prevalence still provides a viable strategy for screening, it is not known if this would represent a cost effective strategy. The initial outcomes for linkage into care suggest that with appropriate testing, counseling and outreach services screening of homeless persons is a potentially viable strategy that warrants further evaluation.

8 An Exploratory analysis into a birth cohort screening strategy in the UK

8.1 Introduction

Birth Cohort testing describes screening confined to a specific age distribution which has an established probability of positive diagnosis pick up. A variety of strategies such as census data collection or central laboratory data have been used to establish prevalences per age group in many countries [264-266]. Various studies have modelled the projection of prevalence and disease burden over the next 20-30 years [18, 267, 268]. Whilst these models have also evaluated the potential impact of increasing treatment on projected disease burden, very few publications have addressed the cost effectiveness of birth cohort screening as a strategy for improving early diagnosis of hepatitis C.

The United States of America (USA) have adopted a one time screening for all persons born between 1945-1965, based on data from the National Health and Nutrition Examination Survey (NHANES). NHANES provides a series of cross sectional national surveys of non-institutionalised civilians. It was estimated that 1.3% of the population in the USA (equivalent to 4 million persons) are anti-HCV antibody positive. Prevalence was noted to be higher in men than women (1.6% vs. 1%) and non-Hispanic Blacks compared to non-Hispanic Whites (2.6% vs. 1.3%). It is estimated that approximately 75% of persons with HCV infection were born

between 1945 and 1965 with a peak prevalence of 4.3% in persons aged between 40 to 49 years old [269]. A limitation of the NHANES data is that it underestimates the impact of populations such as PWID, homeless and incarcerated populations which as previously discussed are likely to have much higher prevalences [270, 271].

In keeping with other developed countries, it is estimated that in the USA 50% of HCV infected persons remain undiagnosed, and of those that have been detected less than 40% are referred for care and around 10% receive treatment [272, 273]. In the USA it's projected that by 2030 45% of persons with HCV will have cirrhosis. It is anticipated that complications of cirrhosis, decompensation and HCC will have a peak incidence amongst women aged 71-87 years old and men aged 64-80 years [274]. Hepatitis C related complications remain a significant issue in the USA with doubling of cirrhosis and decompensation prevalences between 1996 and 2006 and 20-fold increase in HCC from 0.07% to 1.3% in the same time period [275]. It can be extrapolated from this that current screening and treatment strategies have not been effective.

Following on from the identification of the 1945-1965 birth cohort, the Centers for Disease Control (CDC) recommended all persons, regardless of risk factors, born between 1945-1965 should undergo one-time testing for identification of the presence of chronic HCV. The basis of the recommendation for this strategy were [81]:

- Anti-HCV antibody prevalence was highest amongst persons born between 1945-1965
- Lack of efficacy of risk based screening
- Accuracy of serological testing
- Untreated HCV was associated with significant health risks placing economic and health burden

- Therapies were available with increasing efficacies and effective treatment could reduce risk of HCV related complications
- Harms of screening were limited

Subsequently the United States Preventative Services Task Force (USPSTF), despite initial concerns about the lack of direct evidence that the strategy reduced mortality or morbidity, upgraded Birth Cohort Screening to a grade B recommendation [269].

The cost of birth cohort screening in the USA has been estimated at $2 billion to test 66 million people, with a further $26 billion to treat 551,000 over a 10 year period. Three seminal analyses helped promote the cost effectiveness benefits of this screening strategy. Rein et al reports cost-effectiveness when compared to a traditional risk based screening which is largely contingent on both linkage to care and high efficacy rates of newer HCV antiviral regimens. Monte Carlo simulation modelling assumed 86% of undiagnosed cases would be identified at a cost of $2,874 per case. It assumed that 40% of positively diagnosed patients initiated treatment. It was estimated that antiviral therapy would generate 532,000 QALYs at a cost of $19 billion thereby resulting an incremental cost effective ratio of $35,700 per QALY compared to risk based testing (USA threshold for cost effectiveness $50,000 per QALY) [80]. McEwan et al. used the MONARCH model, a Markov simulation also comparing birth cohort screening with risk based screening. The most cost effective strategy would likely be gained in focussing treatment in those with more advanced disease, i.e. those at highest risk of complication. It was estimated that treating those with advanced fibrosis decreased hepatitis C complications by 60,000 with a relative cost reduction by $7.5billion. Again this study emphasised the importance of linkage to care on realise the potential gains of screening [78]. Finally, McGarry et al. also used Markov simulation to examine the cost effectiveness of screening all USA residents born between 1946

and 1970 over 5 years with treatment with interferon based therapies. Compared to high-risk screening it was estimated that this strategy would lead to 46,000 fewer HCCs, 10,000 fewer liver transplants and 78,000 liver related deaths at an incremental cost of $37,700 per QALY [79].

It is estimated that the background prevalence in the UK of HCV is below 1% [19]. In more targeted age groups it is possible that prevalences rates are higher in keeping with that postulated within the US cohort [276]. We aim to investigate whether and age dependent effect may occur in prevalence rates of HCV which may offer a comparable screening strategy to the US birth cohort analysis. Further we explore whether such a strategy could be envisaged to be cost effective as a national screening strategy in the UK.

8.1.1 Hypotheses

Distribution of HCV Ab-positive patients will follow a Gaussian distribution. As a result an age cohort encompassing 75% of the population with hepatitis C can be ascertained to calculate the amount that could be spent to achieve a screening programme within a threshold of £20,000 per QALY.

8.1.2 Aims:

- A preliminary study to evaluate whether birth cohort testing within this UK population can identify an age cohort encompassing 75% of HCV Ab-positive patients, which could inform further studies on cost-effectiveness.
- To ascertain the distribution of HCV Ab-positive patients according to 5-year birth cohort in a UK population and analyse which birth cohort 75% falls within.
- To evaluate the age distribution of persons with HCV viraemia.
- To calculate the amount that could be spent on a UK birth cohort screening programme maintaining a cost per QALY of £20,000.

8.2 Methods

All positive HCV antibody results from Imperial College NHS Trust Virology Laboratories between 1st January 2007 and 14th May 2015 were included for analysis. Herewith this cohort will be referred to as the Northwest London Cohort. The laboratories provide results from other secondary care and regional primary care sites:

Secondary care

- St Mary's Hospital
- Hammersmith Hospital
- Charing Cross Hospital
- Chelsea and Westminster Hospital

Primary Care

- Hammersmith and Fulham
- Kensington and Chelsea
- Westminster
- Ealing
- Hounslow
- Brent and Harrow
- Richmond

All individuals were identified using a unique identifier used by the laboratory that was linked to NHS number. All duplicate samples were excluded and where one patient had multiple records

the first result was used for analysis and all others excluded. An Excel spreadsheet was used to label gender, date of birth and date of diagnosis. Current age and age at diagnosis were calculated. Age was determined as current age, as of 15th March 2015, when the data collection was undertaken and patient information was only extracted if year of birth was from 1900 onwards. Where data on gender, date of birth or date of diagnosis were missing, the record was not included. Data was also collected on first viral load and genotype for secondary analysis of birth cohort of viraemic patients.

Inclusion criteria:

- HCV antibody positive results from Imperial College NHS database
- Date of birth after 1900

Exclusion criteria:

- Patient date of birth unavailable
- Patient date of diagnosis unavailable
- Patient gender unavailable

8.2.1 Data Analysis

8.2.1.1 Testing for normality

In order to assess reference intervals to identify 75% of the patients it is essential to first understand the underlying distribution. It is assumed that this birth cohort distribution should follow a normal (Gaussian) distribution. For confirmation both visualisation and also significance tests can be used [277]. The frequency distribution of a histogram and Q-Q (quantile-quantile) plot, whilst at times unreliable, are validated for assessing distribution. The Q-Q plot splits the analysed cohort data into equal portions (quantiles) which is useful in large data sets. The cumulative probability of each variable is plotted against the cumulative probability of a normal distribution. After the data is ranked and sorted the z-score is calculated and plotted against expected z-scores and if the data is normally distributed then the Q-Q plot will demonstrate a straight diagonal line. Further validation can be provided from a kurtosis test which assesses deviation of a distribution from normal [277]. Further, z-scores express distributions in standard deviation units relative to the mean. The z scale is based on an underlying normal distribution and therefore allows to assess for interval values from the mean in order to capture a particular population [278]. In this case 12.5^{th} and 87.5^{th} centiles to represent 75% of the population within our presumed Normal distribution.

Frequency tables were used to collect data, grouping outcomes for 5-yearly cohorts. Distribution curves were assessed comparing age cohorts to HCV antibody, HCV viraemia, genotype and gender. Assessment for Gaussian distribution was made based on histograms and Q-Q plots. A kurtosis value <1 was considered confirmatory for fitting a Gaussian distribution. Where a

normal distribution could be confirmed z-values could be used to calculate where 75% of the distribution lies using the equation Z=(X- mean)/standard deviation

(Z=(x-μ)/sd)

Calculations utilising known values of mean age, standard deviation and percentiles (12.5th percentile and 87.5th percentile) determined upper and lower values for the middle 75% of the standard normal curve (Figure 8.1).

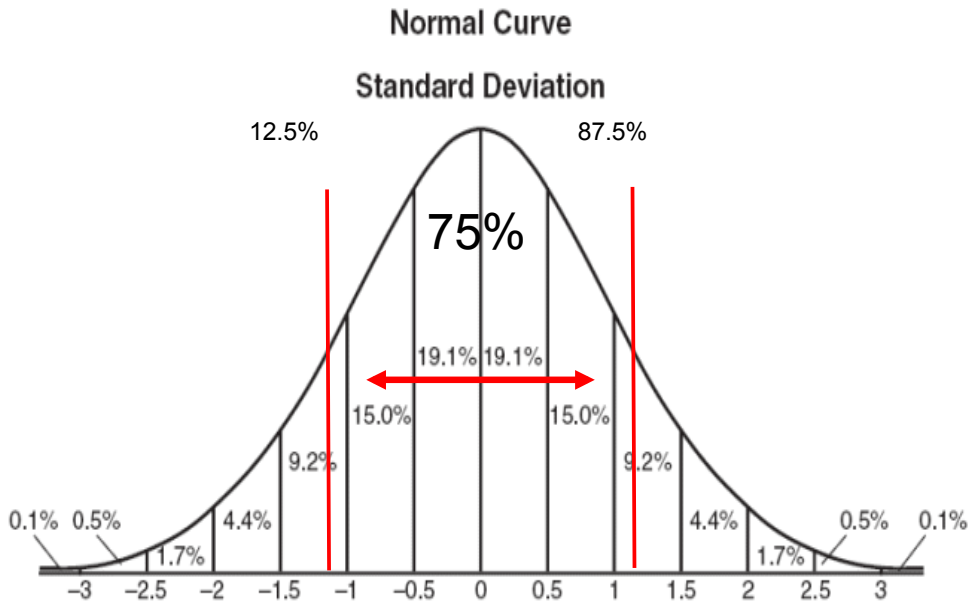
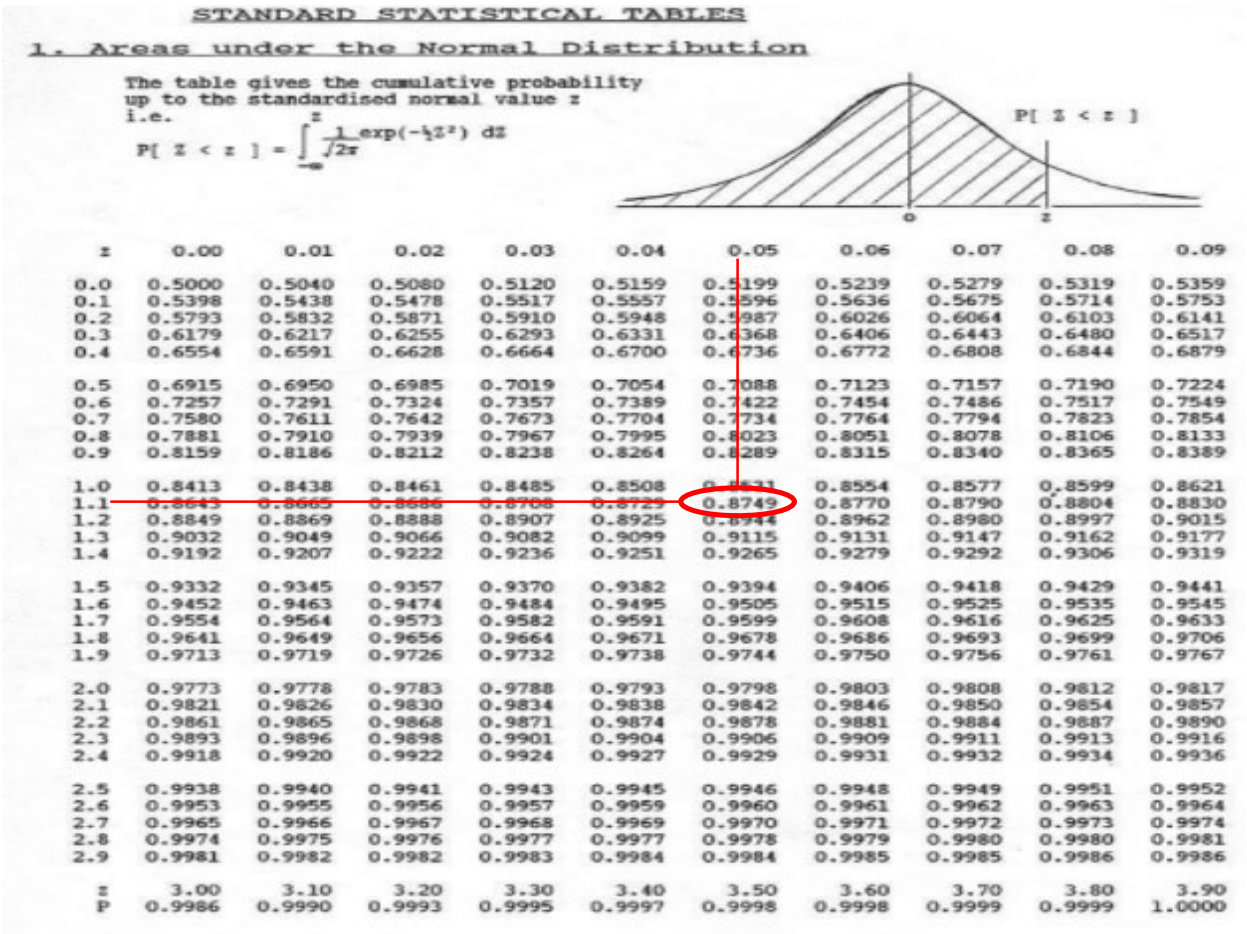


Figure 8.1 Normal distribution curve with demarcation of where 75% lies (Courtesy of www.google.co.uk)



STANDARD STATISTICAL TABLES

1. Areas under the Normal Distribution

The table gives the cumulative probability up to the standardised normal value z

i.e. $P[\,Z < z\,] = \int_{-\infty}^{z} \frac{1}{\sqrt{2\pi}} \exp(-\frac{1}{2}Z^2)\, dZ$

z	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
0.0	0.5000	0.5040	0.5080	0.5120	0.5159	0.5199	0.5239	0.5279	0.5319	0.5359
0.1	0.5398	0.5438	0.5478	0.5517	0.5557	0.5596	0.5636	0.5675	0.5714	0.5753
0.2	0.5793	0.5832	0.5871	0.5910	0.5948	0.5987	0.6026	0.6064	0.6103	0.6141
0.3	0.6179	0.6217	0.6255	0.6293	0.6331	0.6368	0.6406	0.6443	0.6480	0.6517
0.4	0.6554	0.6591	0.6628	0.6664	0.6700	0.6736	0.6772	0.6808	0.6844	0.6879
0.5	0.6915	0.6950	0.6985	0.7019	0.7054	0.7088	0.7123	0.7157	0.7190	0.7224
0.6	0.7257	0.7291	0.7324	0.7357	0.7389	0.7422	0.7454	0.7486	0.7517	0.7549
0.7	0.7580	0.7611	0.7642	0.7673	0.7704	0.7734	0.7764	0.7794	0.7823	0.7854
0.8	0.7881	0.7910	0.7939	0.7967	0.7995	0.8023	0.8051	0.8078	0.8106	0.8133
0.9	0.8159	0.8186	0.8212	0.8238	0.8264	0.8289	0.8315	0.8340	0.8365	0.8389
1.0	0.8413	0.8438	0.8461	0.8485	0.8508	0.8531	0.8554	0.8577	0.8599	0.8621
1.1	0.8643	0.8665	0.8686	0.8708	0.8729	0.8749	0.8770	0.8790	0.8804	0.8830
1.2	0.8849	0.8869	0.8888	0.8907	0.8925	0.8944	0.8962	0.8980	0.8997	0.9015
1.3	0.9032	0.9049	0.9066	0.9082	0.9099	0.9115	0.9131	0.9147	0.9162	0.9177
1.4	0.9192	0.9207	0.9222	0.9236	0.9251	0.9265	0.9279	0.9292	0.9306	0.9319
1.5	0.9332	0.9345	0.9357	0.9370	0.9382	0.9394	0.9406	0.9418	0.9429	0.9441
1.6	0.9452	0.9463	0.9474	0.9484	0.9495	0.9505	0.9515	0.9525	0.9535	0.9545
1.7	0.9554	0.9564	0.9573	0.9582	0.9591	0.9599	0.9608	0.9616	0.9625	0.9633
1.8	0.9641	0.9649	0.9656	0.9664	0.9671	0.9678	0.9686	0.9693	0.9699	0.9706
1.9	0.9713	0.9719	0.9726	0.9732	0.9738	0.9744	0.9750	0.9756	0.9761	0.9767
2.0	0.9773	0.9778	0.9783	0.9788	0.9793	0.9798	0.9803	0.9808	0.9812	0.9817
2.1	0.9821	0.9826	0.9830	0.9834	0.9838	0.9842	0.9846	0.9850	0.9854	0.9857
2.2	0.9861	0.9865	0.9868	0.9871	0.9874	0.9878	0.9881	0.9884	0.9887	0.9890
2.3	0.9893	0.9896	0.9898	0.9901	0.9904	0.9906	0.9909	0.9911	0.9913	0.9916
2.4	0.9918	0.9920	0.9922	0.9924	0.9927	0.9929	0.9931	0.9932	0.9934	0.9936
2.5	0.9938	0.9940	0.9941	0.9943	0.9945	0.9946	0.9948	0.9949	0.9951	0.9952
2.6	0.9953	0.9955	0.9956	0.9957	0.9959	0.9960	0.9961	0.9962	0.9963	0.9964
2.7	0.9965	0.9966	0.9967	0.9968	0.9969	0.9970	0.9971	0.9972	0.9973	0.9974
2.8	0.9974	0.9975	0.9976	0.9977	0.9977	0.9978	0.9979	0.9980	0.9980	0.9981
2.9	0.9981	0.9982	0.9982	0.9983	0.9984	0.9984	0.9985	0.9985	0.9986	0.9986
z	3.00	3.10	3.20	3.30	3.40	3.50	3.60	3.70	3.80	3.90
P	0.9986	0.9990	0.9993	0.9995	0.9997	0.9998	0.9998	0.9999	0.9999	1.0000

Figure 8.2 Calculating z-scores using standard statistical tables depicting areas under the curve (Courtesy of www.google.co.uk)

Associated z-values for these percentiles were looked up in a z-value table for standard normal curves (Figure 8.2) and re-entered into the Z=(X-μ)/sd equation, to calculate age values (X) incorporating 75% of the population. The same methodology was undertaken for calculating 75% of viraemic patients. All statistical analysis was performed using IBM SPSS software.

Validation of the cohort made comparing to separate published UK cohort study from the Trent region and laboratory data from Public Health England [19, 279]. The data from these evaluations would then help to inform a potential population for age targetted screening. Using

established data a cost-effective analysis could be used to explore whether such a strategy should be considered.

8.2.2 Cost effectivness

The MONARCH model was utilised to predict the maximum expenditure that could be atttributable to a screening programme and it remain cost effective at £20,000/QALY threshold. Assumptions on screening and treatment uptake where kept consistent with US birth cohort publications to maintain uniformity [78, 79]. Whilst published data on actual uptakes is limited, it is appreciated that it may not have mirrored initial expectations. It was assumed that 91% of patients would be screened and that over a 10 year period 52% of HCV positive patients would subsequently be scheduled for treatment over a 10 year period (24% treated in year 1 and the remaining patients treated in equal proportions over the remaining years (Figure 8.3). Upon model initiation, patients were distributed across METAVIR fibrosis stages, based on UK studies reported in a published meta-regression analysis: F0: 22%; F1: 31%; F2: 22%; F3: 16%; F4: 10% based on the UK studies reported in the Thein transition rate paper [104]. The mean age of the cohort was taken as the midpoint of the birth cohort and published UK-specific data informed all other patient characteristics [104]. All patients are assumed to undergo 12 weeks of DAA therapy with 95% SVR (Table 8.1).

Transition	Rate	Health state	Cost	Utility
Fibrosis	Equation	**F0/F1**	177.47	0.77
F4 to DC	0.039	**F2/F3**	922.08	0.66
F4 to HCC	0.014	**F4**	1,463.50	0.55
DC to HCC	0.014	**DC**	11,728.61	0.45
DC to LT	0.030	**HCC**	10,451.58	0.45
DC to Death	0.130	**LT (Yr 1)**	47,310.55	0.45
HCC to LT	0.030	**LT (Yr 2+)**	1,781.15	0.67
HCC to Death	0.430	**SVR from F0/F1**	333.08	0.82
LT (Yr 1) to Death	0.210	**SVR from F2/F3**	922.08	0.82
LT (Yr 2+) to Death	0.057	**SVR from F4**	1,463.50	0.82

Treatment	Weekly cost [280]	Duration (weeks)		SVR (%)
		Genotype 1	Genotype 3	
DAA	2,500	12	12	F0-F4:95%

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; IFN, pegylated interferon-alpha; LT, liver transplant; RBV, ribavirin; SVR, sustained virologic response; TVR, telaprevir; Yr, year.

Table 8.1 Health state transition rates, yearly costs and treatment costs

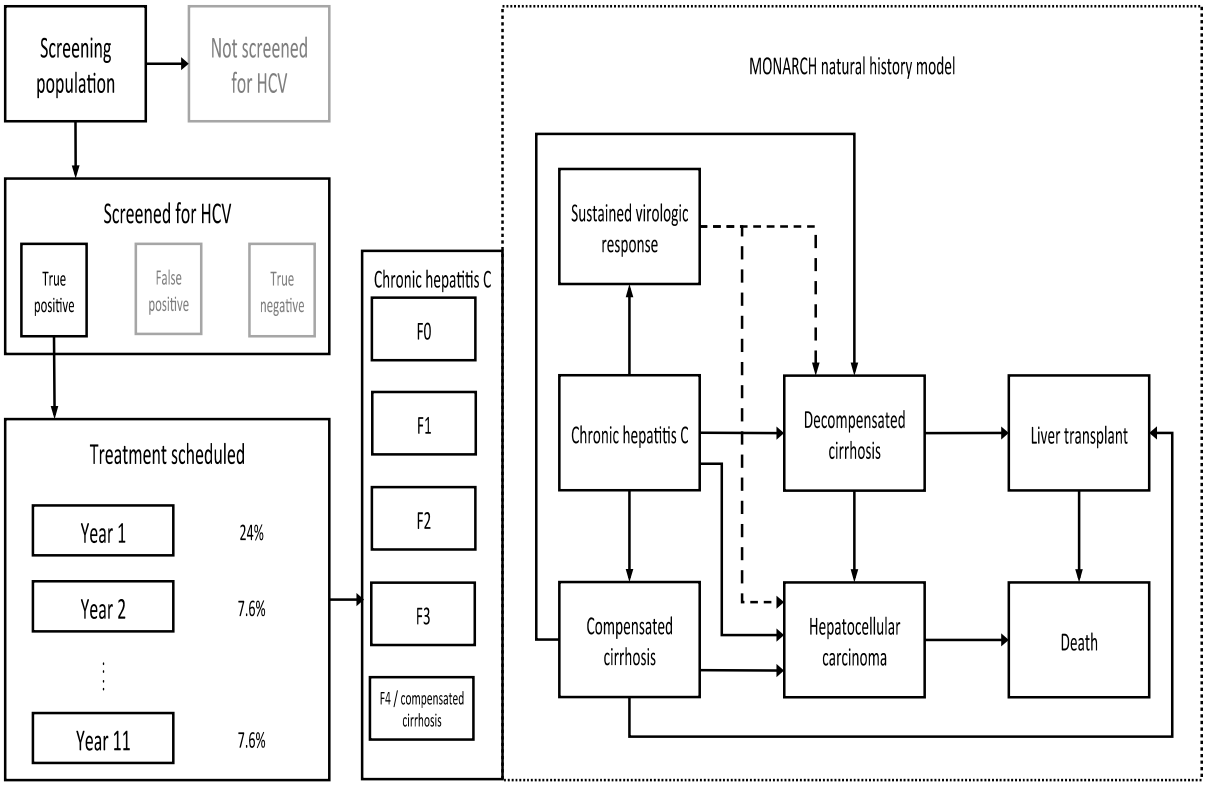


Figure 8.3 Flow diagram demonstrating the screening strategy with subsequent treatment strategy over a 10 year horizon.

The screening and treatment programme was compared to a scenario of no screening in which no additional HCV diagnoses were made. A UK HCV prevalence estimate of 0.33%, was combined with an estimate of current diagnoses (58%) to inform the population eligible for screening [19]. Importantly, in the absence of robust data for age specific HCV prevalences in the general UK population, the birth cohort assumed a conservative estimate that prevalence reflected the national prevalence within birth cohort analysis. In UK Accident and Emergency setting anti-HCV prevalence of 4.76% was reported in males aged between 35-44 [276]. Sensitivity analyses

were then performed varying both the prevalence of newly diagnosed HCV and the treatment uptake rates to assess impact on outcome. The effect of varying undiagnosed HCV prevalence and treatment uptake was investigated assuming treatment with a hypothetical direct-acting antiviral (DAA) regimen. Treatment assumptions were that all patients were treated for 12 weeks, with weekly treatment costs of £2,500 and SVR rates of 95% irrespective of fibrosis stage. Published disease transition rates, costs, health utility values and sustained virologic response (SVR) rates were utilised (Table 8.1). Outcomes were discounted at an annual rate of 3.5%.

8.2.3 Sensitivity analysis

Univariate sensitivity analysis was undertaken in order to investigate the affect of alternative parameter assumptions upon results:

a) Age +/- 10 years
b) Sex (all female and all male)
c) Fibrosis distribution (All F0/F1 and all F3/F4)
d) Health State utility (+/- 20%)
e) Health state cost (+/- 20%)
f) Transition rate (+/- 20%)
g) Treatment timing (1 year/ 5years)
h) Therapy cost (+/- 20%)

8.3 Results

8.3.1 Primary outcomes

A total of 25,213 blood tests pertaining to hepatitis C positive samples were collected during the study time period from the Northwest London cohort. Of these, 9,938 individuals were identified to be HCV antibody positive during this time period and with data fields that satisfied the inclusion and exclusion criteria of this study. The results have been demonstrated in Table 8.2, in 5 year age cohorts for evidence of HCV Ab. Table 8.3 reports according to gender, evidence of viraemia and genotype.

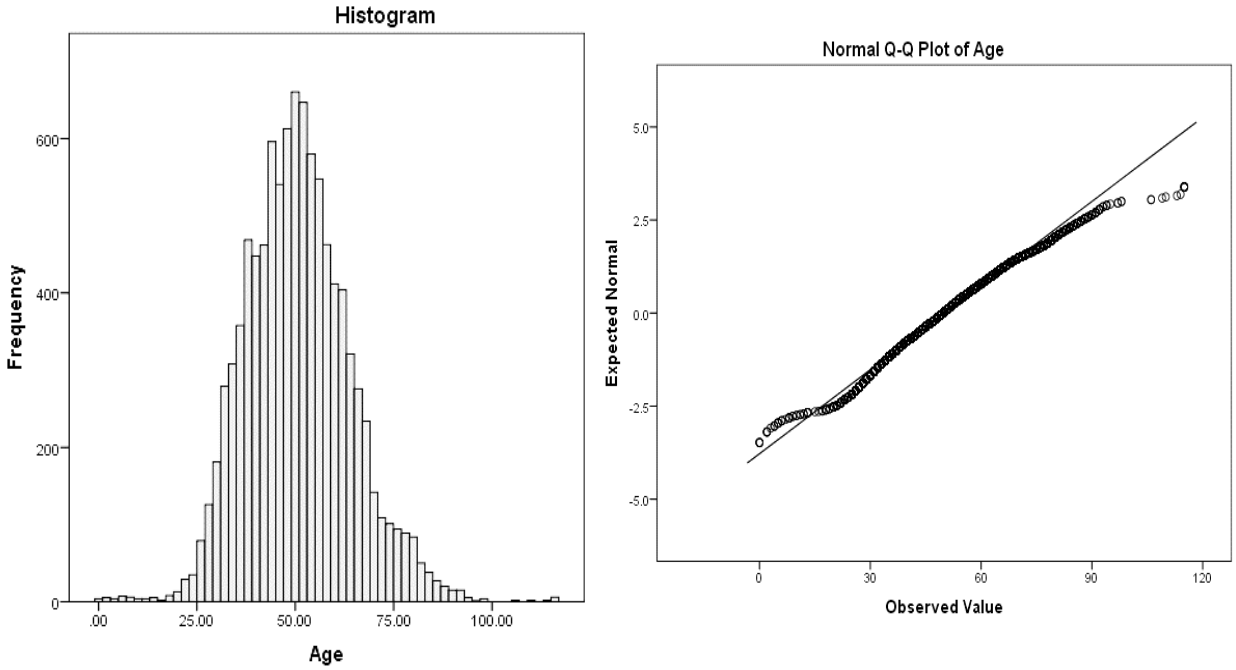


Figure 8.4 Histogram and Q-Q plot demonstrating likeliness of fit to Gaussian distribution for HCV antibody distribution according to age

Overall distribution of age within those who had evidence of HCV antibody demonstrated a normal distribution when considering histogram plot and Q-Q distribution (Figure 8.4). Skewness and kurtosis values were 0.34 and 0.76 respectively i.e. <1 threshold.

Following this, ages of the 12.5th percentile and 87.5th percentile could be calculated using Z-values from standard normal curve tables in order to assess the age range for 75% (Figure 8.2). the 85.5th percentile corresponds to a Z-score of 1.15 and 12.5th percentile -1.15. Values for mean age (50.19) and standard deviation (13.28), were entered into the rearranged equation $Z=(x-\mu)/sd$ to work out X-values of age:

Lower limit (X)=(-1.15 x 13.28)+ 50.19= 34.92= 34 years (rounded down to nearest integer for age)

Upper Limit (X)=(1.15 x 13.28) + 50.19= 65.46= 65 years (rounded down to nearest integer for age)

Therefore it can be concluded that 75% of HCV Ab-positive patients were found to be between 34 and 65 years old.

Age	Total HCV Ab pos n=9938	Male	Female	Total Viraemic (confirmed PCR+/Genotype +ve)	% of Total Viraemic in each age cohort
		n=7047	n=2891	n=5184	
0-4	13	9	4	4	0.08
5-9	15	8	7	8	0.15
10-14	11	9	2	2	0.04
15-19	13	6	7	3	0.06
20-24	74	43	31	29	0.56
25-29	292	184	108	121	2.33
30-34	680	469	211	332	6.40
35-39	1055	765	290	522	10.07
40-44	1282	975	307	660	12.73
45-49	1493	1140	353	776	14.97
50-54	1558	1131	427	816	15.74
55-59	1210	874	336	679	13.10
60-64	937	655	282	530	10.22
65-69	584	401	183	312	6.02
70-74	279	169	110	148	2.85
75-79	226	120	106	121	2.33
80-84	129	55	74	76	1.47
85-89	55	19	36	30	0.58
90-94	27	13	14	12	0.23
95-99	5	2	3	3	0.06
100-104	0	0	0	0	0.00

Table 8.2 HCV antibody distribution per 5 year age cohorts

Age	Viraemic Male n=3819	% of total viraemic population	Viraemic Female n=1365	% of total viraemic population	G1 n=1243	G2 n=132	G3 n=583	G4 n=202	G6 n=3
0-4	2	0.04	2	0.04	0	0	0	0	0
5-9	4	0.08	4	0.08	0	0	2	0	0
10-14	2	0.04	0	0.00	0	0	0	0	0
15-19	2	0.04	1	0.02	1	0	0	0	0
20-24	20	0.39	9	0.17	15	0	2	1	0
25-29	84	1.62	37	0.71	34	1	13	6	0
30-34	249	4.80	83	1.60	93	4	42	9	0
35-39	399	7.70	123	2.37	140	5	70	17	1
40-44	528	10.19	132	2.55	171	16	79	32	0
45-49	614	11.84	162	3.13	200	18	86	36	0
50-54	615	11.86	201	3.88	209	13	111	34	0
55-59	495	9.55	184	3.55	149	22	78	13	0
60-64	379	7.31	151	2.91	113	17	53	21	1
65-69	212	4.09	100	1.93	53	12	22	16	1
70-74	91	1.76	57	1.10	33	5	14	5	0
75-79	72	1.39	49	0.95	17	11	6	10	0
80-84	32	0.62	44	0.85	10	5	2	2	0
85-89	11	0.21	19	0.37	4	1	3	0	0
90-94	7	0.14	5	0.10	1	1	0	0	0
95-99	1	0.02	2	0.04	0	1	0	0	0
100-104	0	0.00	0	0.00	0	0	0	0	0

Table 8.3 Distribution of HCV viraemic patients and representative genotypes

8.3.2 Comparison to historic data

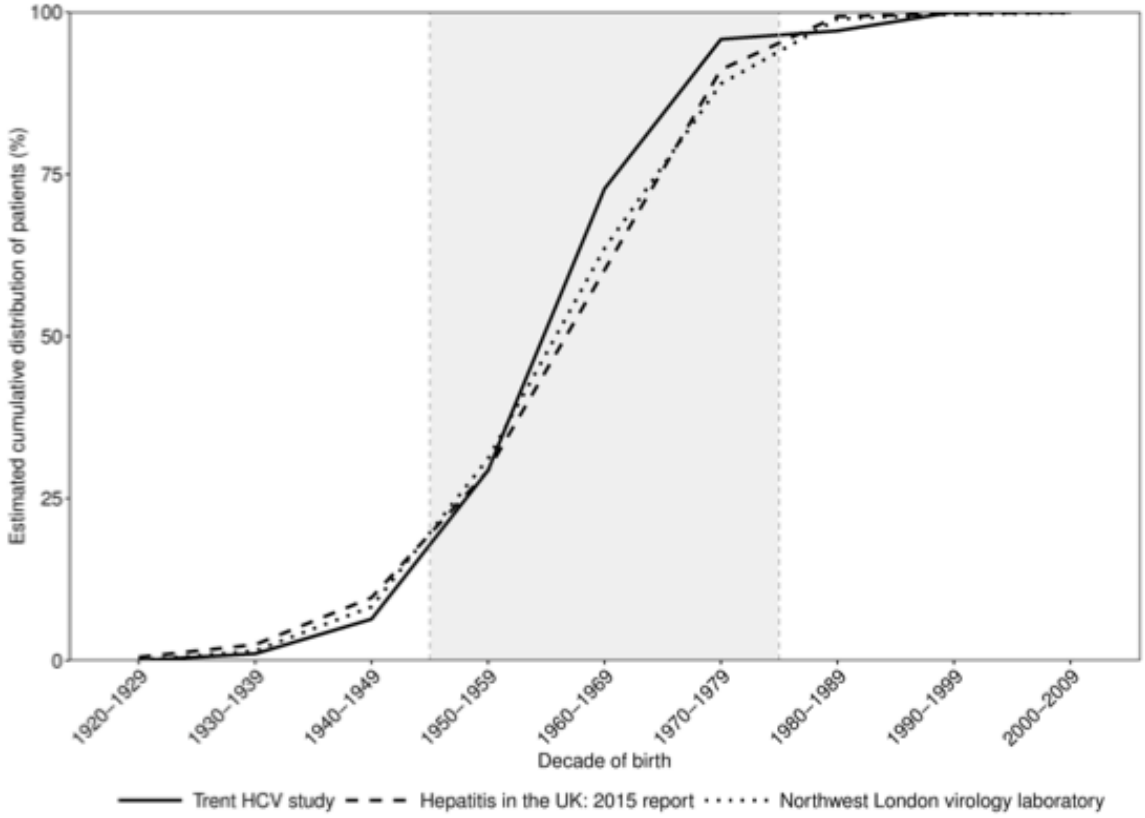


Figure 8.5 Comparison of age distributions demonstrated within this study cohort (Northwest London) compared to Trent and Public Health England reports, demonstrating good concordance

The data from our Northwest London cohort is plotted against data from Public Health England and a historical cohort from the Trent region of the UK between 1991 and 1998. Reasonable concordance is noted between the three datasets suggesting the age distribution demonstrated within the Northwest London cohort appears to correlate with other UK specific findings.

8.3.3 Secondary Outcomes

8.3.3.1 Gender-specific birth distributions

Within this cohort presence of hepatitis C was more common in males compared to females. Overall 7047 out of 9938 (70.9%) were male. Figure 8.6 demonstrates that between 20-74 there is a marked disparity between genders. The peak incidence of males were within the 45-49 years age cohort whereas in females it was the 50-54 years age cohort. When only considering proven evidence of viraemia there is a significantly higher proportion of males than females in the 35-64 years age cohort described (p=0.037).

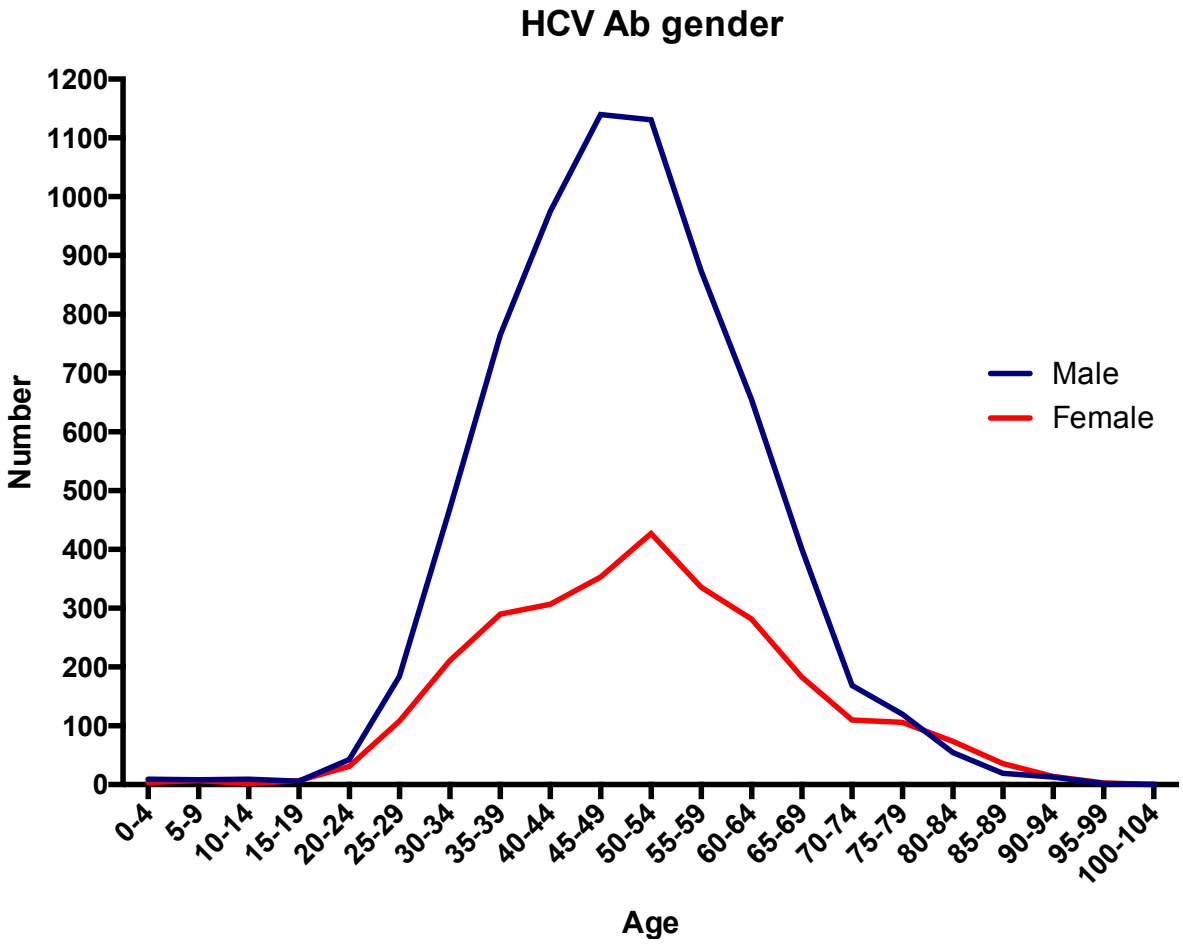


Figure 8.6 Gender specific distributions of HCV antibody prevalence and age

8.3.4 HCV viraemia birth distributions

The overall concordance between age distributions in HCV Ab positive and viraemic patients was strong. Figure 8.7. demonstrates the normal distribution of age in HCV viraemic patients.

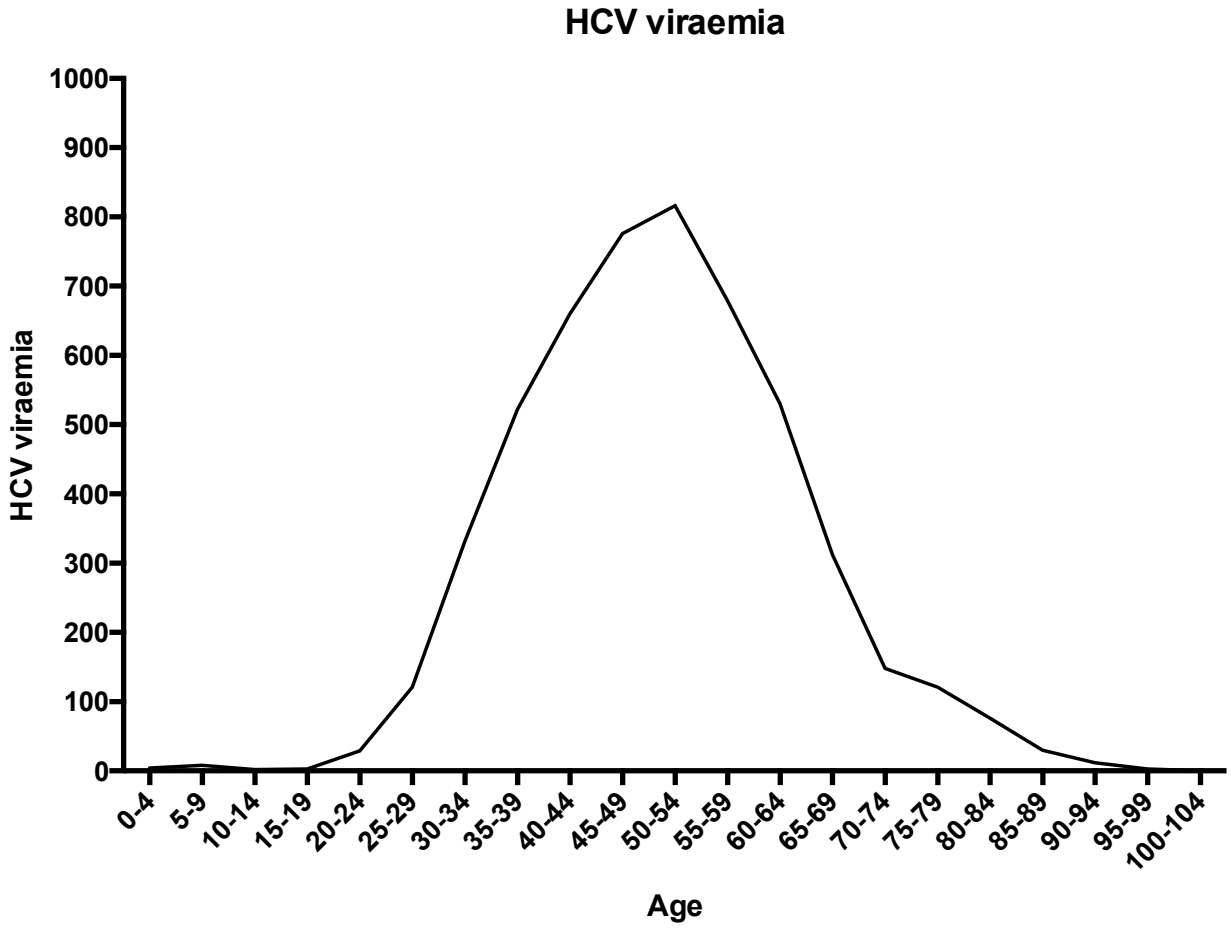


Figure 8.7 HCV viraemia distribution per age

Skewness (0.036) and kurtosis (0.072) of the distribution curve of viraemic patients are <1, which indicate a normal distribution. As described above, Z-values were used to calculate a cohort encompassing 75%:

Mean age (50.70) and standard deviation (13.16) were entered into the equation

Lower limit (X)=(-1.15 x 13.16)+ 50.70= 35.57= 35 years (rounded down to nearest integer for age)

Upper Limit (X)=(1.15 x 13.16) + 50.70= 65.84= 65 years (rounded down to nearest integer for age)

Therefore 75% of HCV viraemic patients were found to be between 35 and 65 years old.

8.3.5 Genotype specific age Distribution

Of 5184 persons with confirmed viraemia, genotype was recorded in 2163. In this cohort genotype 1 was the most common accounting for 57% (n=1243) followed by genotype 3 accounting for 27%. In both genotype 1 and 3 the peak age group cohort was 50-54. Genotype 4 accounted for 9% and 6% were genotype 2. In genotype 2 and 4 the peak cohorts were 45-49. Figure 8.8 demonstrates the age cohorts per genotype but owing to the limited number of genotype 6 it was not included for diagrammatic representation.

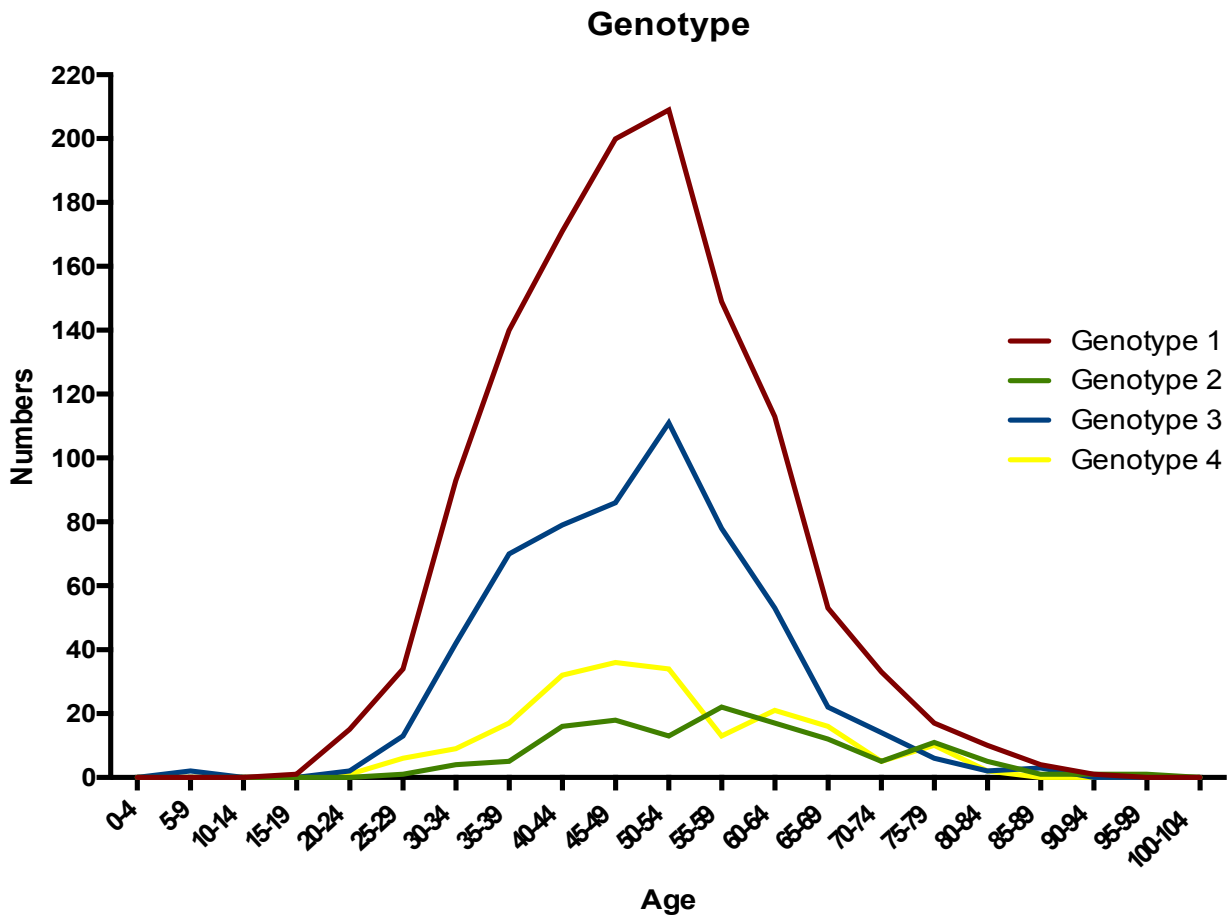


Figure 8.8 Distribution of HCV genotypes by age

8.3.6 Cost effectiveness

Under base case assumptions, it was estimated that £26.96 per person screened could be spent on identifying HCV infections maintain cost effectiveness at a willingness to pay threshold of £20,000 per QALY. UK census data estimates that between the age of 35-65 (age cohort of 1950-1980 in 2015) there are 20,816,600 persons [281]. Using the assumption of a 91% screening uptake rate this would require screening of 18,943,106 persons incurring an approximate cost of £511million. This strategy would identify 189,431 new diagnoses would be identified and 18,753,675 negative or already diagnosed cases. Sensitivity analysis suggests a conservative scenario where the undiagnosed prevalence of 1% with a 50% treatment uptake rate the amount spent person screened could be £152.86 and if all were treated £414.76. In these scenarios the cost incurred would be £2.9 billion and £7.9 billion respectively.

UK NHS tariffs of HCV antibody testing is estimated to cost £5.91. In contrast, a positive diagnosis, consisting of antibody testing, polymerase chain reaction testing, genotype identification, viral load testing and liver screening, is estimated to cost approximately £384.91–467.07 [282]. Therefore with these assumption the screening costs would cost £189,402,620 ([189,431 x £414.76] + [18,753,675 x £5.91]), not including infrastructure costs and costs independent of serological screening and work-up for positive diagnoses.

	Treatment uptake										
		10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
HCV prevalence	0.10%	-5.67	-0.43	4.81	10.05	15.29	20.52	25.76	31.00	36.24	41.48
	0.20%	-11.33	-0.86	9.62	20.10	30.57	41.05	51.52	62.00	72.48	82.95
	0.30%	-17.00	-1.28	14.43	30.14	45.86	61.57	77.29	93.00	108.71	124.43
	0.40%	-22.66	-1.71	19.24	40.19	61.14	82.10	103.05	124.00	144.95	165.90
	0.50%	-28.33	-2.14	24.05	50.24	76.43	102.62	128.81	155.00	181.19	207.38
	0.60%	-34.00	-2.57	28.86	60.29	91.72	123.14	154.57	186.00	217.43	248.86
	0.70%	-39.66	-3.00	33.67	70.34	107.00	143.67	180.33	217.00	253.67	290.33
	0.80%	-45.33	-3.42	38.48	80.38	122.29	164.19	206.10	248.00	289.90	331.81
	0.90%	-50.99	-3.85	43.29	90.43	137.57	184.72	231.86	279.00	326.14	373.28
	1.00%	-56.66	-4.28	48.10	100.48	152.86	205.24	257.62	310.00	362.38	414.76

Table 8.4 Amount that can be spent (£) per person screened when comparing background HCV prevalence within the 1950-1980 cohort with treatment uptake rates

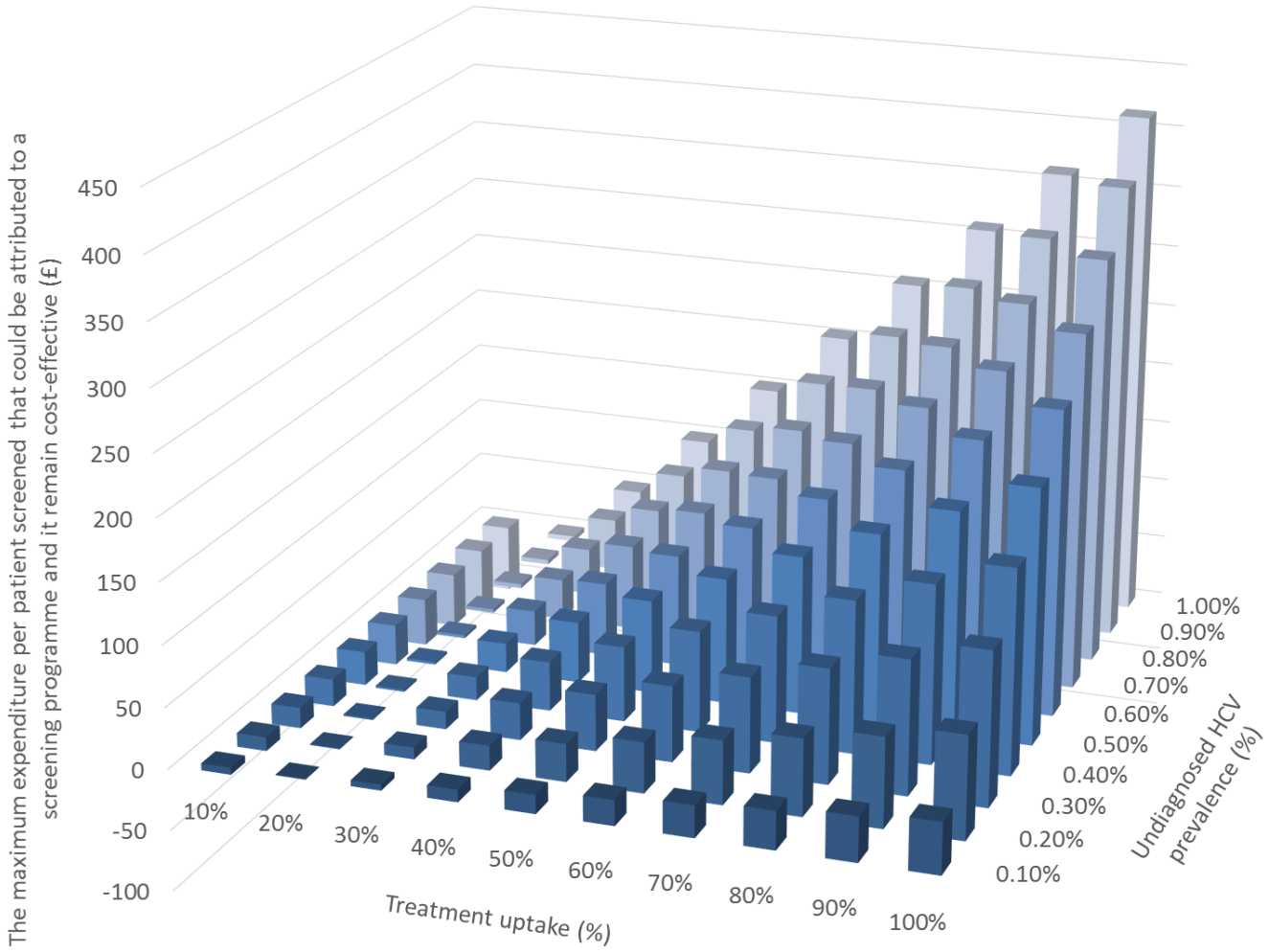


Table 8.5 The maximum expenditure per patient screened that could be attributed to a screening programme and it remain cost effective

Results of the univariate sensitivity analysis demonstrate that there is a reasonable degree of uncertainty surrounding the use of alternative parameter values. Figure 8.9 demonstrates the range of variation from the base case depending on the individual univariate analysis assessed. The light grey area reflects the spread of outputs when assessing the individual affect of age, alternative fibrosis stage distributions, transition rates, health state utility and therapy timing. These appear to have most significant impact on results. The dark grey area reflects outputs on health utility costs, sex, therapy costs and transition rates which have less impact on cost outputs.

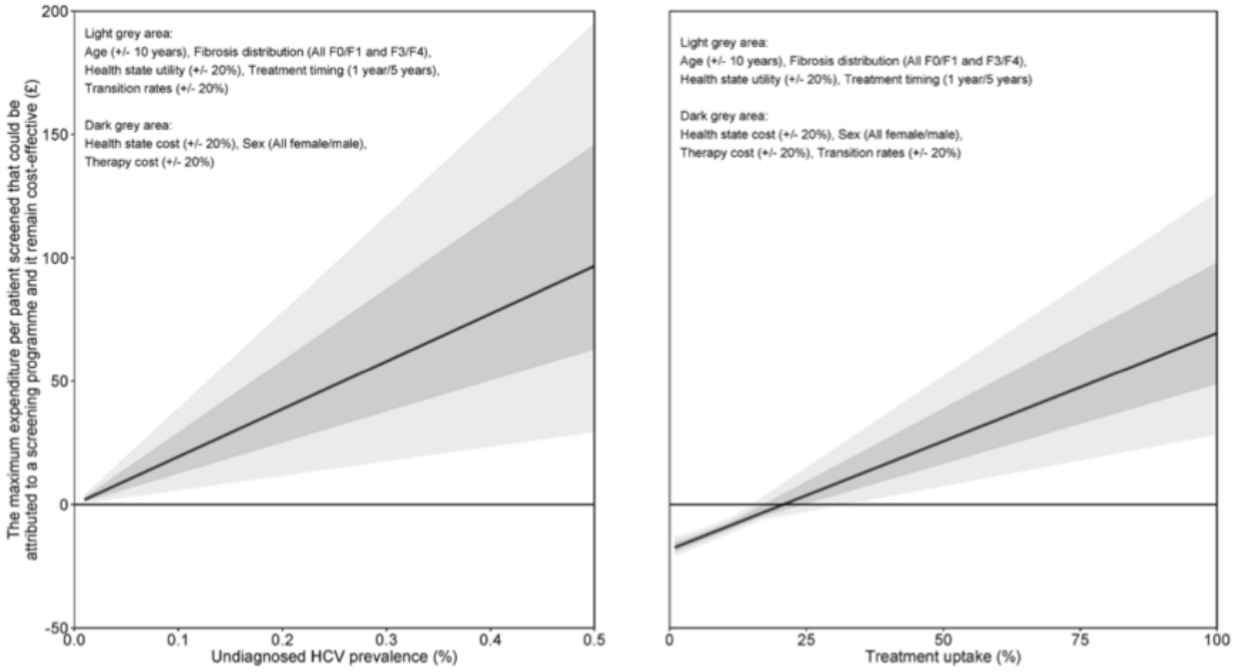


Figure 8.9 The effect of alternative parameter assumptions on the maximum expenditure per patient screened attributable to a screening programme whilst remaining cost-effective. Light Grey areas: (Age +/- 10 years); Fibrosis distribution (All F0/F1 and F3/F4); Health State Utility (+/-20%); Treatment timing (1 year/5years). Dark Grey areas: Health state cost (+/- 20%); Sex (All female/male); Therapy cost (+/-20%); Transition Rates (+/-20%).

8.4 Discussion

This study demonstrates that 75% of persons with HCV viraemia that were tested within the reference laboratory were aged born between 1950-1981 within this Northwest London cohort. This therefore encapsulates a wider and younger population than that defined in the USA, where a similar proportion of HCV antibody positive persons are believed to be born between 1945-1965. This study assesses the impact of testing people in the UK born between 1950-1980. Whilst this represents a broader age range, an thus more people, we assess if this is off-set by inclusion of a younger population of HCV infected persons that may be at higher risk of development of complications of HCV and end stage liver disease.

Results of the birth cohort assessment support the case for investigating a birth cohort screening scenario. Sensitivity analyses demonstrate the reliance on reliable HCV prevalence rates and clear characterisation of the cohort with particular regard age, fibrosis distribution and treatment timing. It is estimated when evaluating the maximum cost that could be spent on a birth cohort programme where national screening was instituted and treatment was taken up by 91% over a 10 year time horizon that £511 million could be spent. It should not be underestimated that the costs of setting up a national screening programme can be prohibitively expensive. In the USA the birth cohort testing initiated is estimated incur an extra cost of $12 -17.4 billion compared to risk-based screening [283]. The Centers for Disease Control and Prevention anticipate that of this initial implementation costs would be $664 million [81]. Within this population it is however anticipated that 1,070,840 new cases would be identified, with 552,000 patients treated and 229 000 patients achieving an SVR [80]. Furthermore treatment costs in the UK for HCV vary from approximately £12,000 to £34,000 depending on patient characteristics and treatment regimen. Treatment costs alone, if treating at the lower bound cost for 100,000 persons is likely

to exceed the amount that could be spend to maintain the willingness to pay thresholds set by policymakers in the UK. Infrastructure, screening and healthcare costs factored in would certainly reduce the chances of such a screening measure being within a cost effective threshold.

It is observed within this cohort that 71% of HCV Ab positive and 74% of HCV viraemic patients are male. Whilst no conclusions can be drawn from this data set as to causal factors, this is consistent with previous findings [264, 276, 284]. It is suggested that women have increased chance of spontaneous clearance of HCV due to protective hormonal and immune responses [285]. It is also reported that injecting drug use behaviours are approximately three times more likely in males than females [284]. Increasingly, in the UK, there is an emerging trend of HCV transmission amongst HIV positive men who have sex with men (MSM) populations. High risk behaviours including injecting drug use, and high risk sexual practices do increase exposure risk and resultant prevalences [286-288]. Nonetheless, given the economic constraints of policy makers it could potentially be investigated as to whether focussing resources on men within certain age groups (depending on undiagnosed prevalence) may help further increase the probability of cost-effectiveness.

In the UK of those with HCV viraemia, it is estimated that 44% have genotype 1, 5% genotype 2, 47% genotype 3 and 4% genotype 4 [264]. Within our study cohort 57% were genotype 1, 6% genotype 2, 27% genotype 3 and 9% genotype 4. Some local variations include a high Sub-Saharan and Egyptian local population to explain a relatively high genotype 4 population as previously described [289]. A higher genotype 1 proportion may be explained in part by a large local population of “baby boomer” generation that may have experimented with illicit drug behaviours in the 1960’s and 1970’s as well as large relative population of Eastern Europeans

where in particular genotype 1b is common. With regards, birth cohort curves between genotypes, similar trends to overall population was observed.

Whilst the samples were anonymously unlinked to individuals, and therefore patient characteristics, risk factors and other demographics can not be deciphered, some interesting observations can be made which may support further evaluation for more targeted screening strategies. In the USA, the cost effectiveness of the 1945-1965 birth cohort screening strategy is based on estimates that the cohort has an overall 2% HCV prevalence. In a separate study based in another London Accident and Emergency department, anonymous unlinked HCV sampling of 997 patients demonstrated overall 2.65% had evidence of HCV Ab and 1.2% were viraemic [276]. Within their cohort males aged 35-45 the prevalence of HCV RNA positive patients was 4.76%. In our study cohort approximately 74% of viraemic patients were male. Amongst females in our cohort the peak age group with HCV viraemia was those aged 50-54 which accounted for 3.88% of the total number that were viraemic. Amongst males in the same age group, the peak prevalence was also amongst those aged 50-54 which accounts for 11.86% of persons tested positive of HCV RNA within the overall cohort. When grouping males aged between 40-54 (i.e. born between 1960 and 1974), this would identify approximately 34% of the total viraemic population within this study cohort.

The dataset used within this exploratory study is subject to unavoidable bias. Firstly, the age cohort was based on the age of diagnosed persons with hepatitis C and which may not necessarily mirror "undetected" HCV, which of course is more relevant. As described by Orkin and colleagues above, it is likely that rates in various age groups may be sensitive to variances in gender, immigration status, PWID proportions and possibly socioeconomic backgrounds which

are unaccounted for within our dataset. Finally, assumptions were made based on population data to define characteristics of our group for the purpose of health economic analysis including fibrosis staging which is central to progression rates and subsequent cost impacts of treatment. It is inconceivable that these biases could be avoided without complete census data collected at population level to identify background undiagnosed HCV rates and characteristics. This in itself would be expensive and resource intense.

Whilst a limitation of this study is that the reference laboratory defines a population of a specific area of the country, namely the Northwest region of Inner and Greater London. In addition, a major limitation is that the background population prevalence can not be defined as we do not have accurate age and sex specific population numbers for this cohort. However, the findings of this study appear consistent with previous work from other UK groups. Between 1991 and 1998 a group from Trent, which accounted for approximately 5.12 million persons in the UK assessed HCV infections diagnosed in secondary care clinics [279]. The estimated prevalence of HCV antibody in this cohort was 0.05%. Within this study group those born between 1950-1980 accounted for 73.4% of the total that were identified with HCV Ab, 68% were males overall. Health Protection Agency (HPA in the UK appears to concur that birth cohort estimates from this study, with very similar national birth cohort curves in both males and females [264, 284]. Based on 2005 Office for National Statistics data it is reported relatively high prevalence rates in those aged 15-59 that were either current or ex-IDU's and less than 1% in white and South Asian non-injectors in the same age cohort, except South Asian non-injectors aged 35-44 who represented 1.14% of HCV infected persons [284]. In the absence of supporting evidence for a national birth cohort screening programme, it could be further considered whether screening of a defined gender and age population may or may not be cost effective.

The other limitation of this study relates to the assumptions made for an exploratory study of this nature. Firstly undiagnosed prevalence rates are based on conservative estimates in the absence of accurate age specific data. Furthermore, treatment costs which are integral to cost outputs are constantly changing in rapid market and laboratory costs would likely be discounted in such a theoretical national screening programme and therefore costs are probably overstated. Whilst it is estimated that within the 1950-1980 UK cohort 49,022 are currently diagnosed [19] which would unlikely require repeat testing, this study estimates that 91% uptake screening. Following this treatment of this cohort takes place over a 10 year horizon. This strategy was essential, as in a hypothetical cohort like this it would place extra assumptions to produce a dynamic model that would incorporate screening in unison with treatment over the 10 year horizon. Whilst it is unlikely all 91% could be screened in one year it was essential to model this way in order to maintain a reasonable ratio of fibrosis stages. In a model that split the screening over a longer time horizon, significant assumptions would need to be made for the cohort fibrosis progression beyond year 1.

To date, this is the first published cost effectiveness analysis of a UK birth cohort screening programme. In the absence of accurate costings for setting up such a programme, an alternative analysis was performed to explore whether this strategy could be economically viable. The calculation of the total cost that could be spent to meet the £20,000 per QALY threshold requires assumptions to be made with regards to modes of acquisition, fibrosis staging and alcohol consumption which are prerequisites for modelling within the MONARCH Markov model to establish transition rates of the population studied. Therefore assumptions for these parameters had to be made based on population data. Whilst in many other aspects the cohort characteristics

appear similar to the Trent cohort and Health Protection Agency published so far, these aspects may not necessarily reflect this particular cohort population. It would however seem very unlikely that these assumptions would have significantly altered the overall outcome given the magnitude of the result outputs and the effects of the sensitivity analyses.

The results of this study demonstrates that in the UK, it appears that the age distribution of hepatitis C is different compared to the birth cohort distribution used in the USA that identifies about 75% of hepatitis C infected persons. This exploratory analysis supports the need for further research to gauge the estimated prevalence of hepatitis C in the UK for persons born between 1950-1980 to determine if this could be a cost effective strategy.

9 Concluding Discussion

Within this thesis we studied both the burden of hepatitis C cirrhosis and various screening and treatment strategies within a constant study setting provided by the Liver and Antiviral Unit at St Mary's Hospital, London. Using a "difficult to treat" population of genotype 4 patients we established that treatment outcomes were in keeping with best practice and registration trials. This supports comparison with broader health economic analyses that use outcome data from Phase 3 Clinical Trials within their assumptions. When comparing the outcomes from this study centre it appears appropriate to assume that these maybe applicable and comparable to other published settings.

We subsequently tested our hypotheses by evaluating different screening and treatment strategies with direct linkage to care. We compared current recommended guidelines of "high risk" settings with prevalence likely greater than 20% to novel lower prevalence settings. Having established a significant burden of disease attributable to hepatitis C, it appears important to address novel methods to increase diagnosis and treatment. We aimed to challenge the established benchmarks that only in high prevalence settings is screening appropriate, by investigating whether improved linkage to care can widen the scope for cost effective screening strategies in lower prevalence settings.

We evaluated a drug treatment unit as a "gold standard" comparison arm. It provided the setting for a "high risk" group with high HCV prevalence as per NICE guidelines. This was then

compared to three scenarios which currently do not fulfil UK screening guidelines: (1) antenatal screening (2) homeless screening (3) birth cohort screening. Within the scenarios, except the birth cohort screening scenario, real life data was used to inform the cost effectiveness analysis. Further, the primary strategic difference to current screening practices was the use of measures to facilitate direct linkage into care, i.e. involvement of specialist services without the need for intermediary primary care referrals.

When considering the importance of linkage to care, we evaluated the effectiveness of utilisation of the hepatocellular carcinoma surveillance programme within the study centre and compliance with the recommendations for 6 monthly surveillance with ultrasound or other cross sectional imaging. Disappointingly only 65% of patients that could have been screened did so within the permitted timeframe. Whilst patient non-attendance was an important reason for this, hospital related factors were attributable in 42% of cases. This demonstrates the critical difficulties when relying on long-term retention of patients within healthcare services. When comparing two possible strategies: Strategy 1 is treating a condition that means the patient can be discharged from care and Strategy 2 to watch and wait and treat later, from a health economic point of view Strategy 2 appears more beneficial as there is less disutility in early years. However from a practical point of view Strategy 2 is more likely to fail as patients who need treatment at a later date may for various reasons may become lost to follow-up.

With regards HCC surveillance aetiology for cirrhosis did not appear to predict failure to comply with surveillance. This further refutes classical stereotypes for demographics of patients that are likely not to be linked into care. However, data on alcohol consumption, injecting drug use and socio-economic status were not collected for the cohort which may have had an influence on the

42% of patient related factors for non attendance. This study was not powered to look at impact on HCC outcomes as result of pick up on surveillance, however in keeping with established literature earlier cancers were picked up on surveillance numerically trended towards more curative outcomes. Importantly within this 6 month cycle the conservative cost for this screening programme, excluding overheads, was approximately £233,560 for patients with HCV. In comparison to screening costs described within this thesis, this reflects a sizeable economic impact.

Of greater economic impact and of importance in terms of patient quality of life, is the impact of cirrhosis resulting in hospital admissions. Importantly we demonstrate that early treatment and achievement of SVR is associated with reduced admissions and liver related complications. This is still relevant years after treatment and not just a short term effect. From the analysis performed it cannot be deciphered exactly if the beneficial effects related directly to the elimination of virus or simply stabilisation and improvement of liver cirrhosis. However the data does provide compelling evidence for the benefits of early treatment. Short-term analysis of decompensated liver disease patients who had significant burdens of hospitalisation appear to be ameliorated by the introduction of treatment with direct acting antiviral therapy. However, longer follow-up is required to establish if this is a sustainable phenomena.

Screening and treatment in a drug treatment unit (DTU), was demonstrably feasible. Within a 2 year horizon there was a 41% HCV Ab prevalence and overall 31% had proven viraemia. Whilst 8% were never linked to care 44% of viraemic patients underwent treatment. It should be pointed out that others may have been keen on treatment but may either have been ineligible or opted to await newer DAA therapies which at the time of the study were not available on the NHS. In a

setting where patients are appropriately selected, counselled and supported an overall SVR rate of 72% was achieved, mainly on interferon based regimes. From a public health view point this strategy is highly effective and imperative to reduce onward transmission and thus future prevalences. However lending further support to such a programme, it is estimated that this programme on average gained £2,498 over a lifetime per patient treated and gained 4.1 QALYS. i.e. in the long term such programmes are cost saving to the healthcare system. Further, in a hypothetical scenario where all patients are treated with DAAs (prices quoted as per 2014/15) a modest incremental cost of £1,029 per QALY would be incurred. It is likely on-going changes to DAA tariffs will have huge positive impacts on this.

As previously demonstrated, the DTU setting with high prevalence rates is a cost effective strategy. We analysed 3 novel settings with presumed prevalence rates much lower than 20%. First we considered the cost effectiveness of adding hepatitis C to antenatal screening. The advantages of such a strategy are the relatively low set up costs as blood borne virus screening is already established within this population. This study demonstrated that prevalence rates were probably lower than originally expected. When considering 10 years of screening of more than 35,000 women the prevalence of newly diagnosed viraemic women was 0.16%. That said, many women identified would unlikely have been identified through conventional screening and 3 vertical transmissions were identified in newly diagnosed HCV mothers. This screening strategy demonstrated excellent linkage to care. This should be expected given the patient demographic and presence of an established blood borne virus network in situ. A combination of low screening costs, good treatment uptake and response at early stages of disease yielded a very cost effective strategy. The actual screening programme itself was estimated to cost £2,400 per QALY and treatment with DAA therapies would incur a cost of £9,139 per QALY. Both these

strategies fall well below the £20-30,000 per QALY threshold recommended by NICE. It should be noted that the major obstacle, at this stage is the lack of intervention that can be offered during pregnancy to reduced transmission and the relatively low background vertical transmission rates without intervention. In the future, it is conceivable that DAAs could be used in pregnancy and during such time the argument for universal antenatal HCV screening may become more compelling.

Another novel strategy was using OraQuick saliva testing as a point of care screening mechanism in homeless shelters. Homeless communities are under-represented in the literature with regards HCV screening and treatment. Given the transient nature of such populations, reliance on repeat appointments and attendance to specialist care clinics in hospitals is a realistic barrier to linkage to care. This study evaluates whether providing a diagnosis and counselling with a rapid, relatively minimally invasive and acceptable test may improve linkage to care. This study demonstrated that this strategy was acceptable with a prevalence rate of 5%. Whilst lower than previously reported in the literature, this is significantly higher than the general population or the antenatal population we studied. Whilst this screening strategy could subjectively be considered successful with good linkage to care for assessment and work up and discussion regarding treatment, the small numbers and lack of treatment outcome data meant it was not possible to perform a meaningful cost effectiveness analysis. Further work on larger numbers and over a longer time horizon however appear merit worthy based on this pilot data.

Finally, we explored the potential impact of a UK national birth cohort screening programme akin to the model used in the United States where one time testing is offered to all persons born between 1945-1965. The results of which provide interesting findings. In the UK the equivalent

birth cohort would require screening of persons aged between 1950-1980, both a younger and wider age group than the US. Using conservative assumptions it is estimated that £26.96 could be spent per person screened (approximately £511 million total) to remain within a willingness to pay threshold of £20,000 per QALY. However, unlike in the cost effectiveness analyses within the drug treatment unit and antenatal settings, the findings were very reliant and sensitive to changes in base case assumption parameters. This necessitates more reliable data with regards background prevalence rates in persons born between 1950-1980 in the UK. Further a more detailed understanding of infrastructure costs to set up such a strategy is vital in understanding if such a strategy could be truly deemed cost effective.

This thesis uses study data based on retrospective analysis of a single centre cohort. Whilst this facilitates a uniform analysis with potentially less variation in clinical practice and resources available it is also subject to limitations. Firstly, the use of retrospective data is prone to bias as there is no provision for control groups or alternative comparison of no screening strategies. Data collection in this manner is also subject to measurement bias. However, the novel strategies studied are in essence a comparison to no screening. At that given point in time when the patients were screened they would not have otherwise been opportunistically screened for HCV. As demonstrated in Chapter 3, the impact of late diagnosis when patients are symptomatic or have complications of HCV can have important negative health and economic implications.

Further, the study centre itself is a Central London teaching hospital. Given the urban setting it is plausible that HCV prevalence rates are higher than other parts of the country or globally. Further, being a specialist liver centre resources and infrastructure are already in place to cope with the increased work load of increasing diagnoses. However in each study, sensitivity

analyses have been performed to demonstrate the impact of differing prevalences and also provided estimations of the monies that could be spent to maintain cost effectiveness. In particular antenatal screening and outreach Drug Treatment Unit screening are highly likely to remain cost effective even if extra cost is required to set up new services. Cost effective analyses were performed using a validated Hepatitis C natural history Markov model and where appropriate real life parameters were used to inform cost effectiveness analyses. Where these couldn't be applied assumptions were made based on UK specific data available. Modelling studies such as these are undoubtedly subject to assumptions made both within the model design and input parameters. Whilst a limitation of this study is the relatively small number of patients used to inform analyses when compared to technical population based analyses, the strength of this study compared to such analyses is that assumptions made are generally fewer due to the ability to provide accurate baseline characteristics that inform more accurate transition rates. Also many costs of screening and treatment provided are study centre specific. This may have less applicability to other health economic systems, such as the United States, where health costs are generally significantly higher. To address these limitations sensitivity analyses have been provided adjusting disease and intervention costs, transition rates and health state utilities.

In the interest of maintaining consistency and comparability of the Cost Effectiveness analyses performed in this thesis with current published literature, QALY was used as the main outcome measure. This is consistent with the bulk of published literature in HCV screening. However, increasingly in Lower and Middle Income Countries (LMIC) alternative measures are being considered for measuring affordability. The World Health Organisation (WHO) and Health Action International (HAI) have looked at measuring affordability of an intervention in relation to an actual proportion of a healthcare payers budget as opposed to arbitrary cut off's such as that

currently used by policymakers such as NICE. For example the WHO consider affordability based on the wage of the lowest paid unskilled government worker (LPGW) to calculate the affordability of medicines [290]. Such affordability has been expressed in terms of the number of days the LPGW has to work to be able to pay for a course of treatment with a particular drug. Increasingly such surrogates for affordability, are being considered but at the time of study design of this thesis they were not the standard practice within health economic literature. It would have questionable applicability in understanding how novel screening strategies compared to current practice given that to date most comparable studies use QALY as outcome measure.

The current strategy of only screening HCV in "high risk" persons is a demonstrably cost effective strategy. However, we propose that current screening practices should be considered to have failed given the burden of HCV cirrhosis demonstrated. It can be argued that in the context of a public health intervention, economic values should be of less importance. However, given the emphasis placed on economic viability, novel strategies in low prevalence scenarios have proven cost effective when linkage to care allows for good treatment uptake. Previous health economic modelling suggests that early treatment may result in higher costs due to disutility in a disease process that is largely asymptomatic for years. But the results within this thesis demonstrates that early treatment can be cost effective and has the added benefit of potentiating a reduced burden of disease related to HCC surveillance and hospital admissions.

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11 Appendix

11.1 Manuscripts arising from this thesis

ARTICLE IN PRESS

Research Article

EASL JOURNAL OF HEPATOLOGY

Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre

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Background & Aims: This study aims to assess the cost-effectiveness of a routine universal antenatal hepatitis C virus (HCV) screening programme at a London centre.

Methods: Ten years' retrospective antenatal screening and outcome data informed a cost-effectiveness analysis using the previously validated MONARCH model. The cost and quality of life outcomes associated with the screening and treatment of newly identified hepatitis C cases were used to generate cost-effectiveness estimates for the screening programme.

Results: A total of 35,355 women were screened between 1st November 2003 and 1st March 2013; 136 women (0.38%) were found to be HCV antibody positive. Of 78 (0.22%) viraemic cases, 44 (0.12%) were newly diagnosed. In addition, the screening programme identified three (6.8%) vertical transmissions in children of newly diagnosed mothers. Of 16 newly diagnosed mothers biopsied, all were in the F0-F2 METAVIR disease stages, and 50% had HCV genotype 1. Postnatal treatment with pegylated interferon and ribavirin was initiated in 19 women, with 14 (74%) achieving sustained virologic response. The total cost of screening and confirmation of diagnoses was estimated to be £240,641. This translates to £5469 per newly diagnosed individual. The incremental cost-effectiveness ratio of this screening and treatment strategy was £2400 per QALY gained. Treatment with newer direct-acting antiviral regimens would have a projected cost of £9139 per QALY gained, well below the £20,000-30,000/QALY gained willingness-to-pay threshold applied by policy advisory bodies.

Conclusions: This study demonstrates that an antenatal screening and treatment programme is feasible and effective, at a cost considered acceptable.

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Keywords: Antenatal; Pregnancy; Screening; Hepatitis C; Cost-effectiveness; MONARCH.

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Abbreviations: HCV, hepatitis C virus; ESLD, end stage liver disease; HCC, hepatocellular carcinoma; DAA, direct acting antiviral; HBV, hepatitis B virus; REDCAP, research electronic data capture; MONARCH, modelling the natural history and cost-effectiveness of hepatitis C; QALY, quality adjusted life year; SVR, sustained virologic response; eRVR, extended rapid virologic response; SA, sensitivity analysis; BC, base case; ICER, incremental cost-effectiveness ratio.

Introduction

Hepatitis C virus (HCV) is a blood borne virus with a chronic course in most infected individuals. It is usually asymptomatic in the early years, but persistent infection can lead to end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) [1]. In the UK, both hospital admissions and deaths from HCV-related ESLD and HCC are continuing to rise, and the number of transplants indicated due to HCV-related cirrhosis has more than quadrupled between 1996 and 2013 [2]. Previously published European antenatal data suggest an HCV prevalence of up to 0.6% in this population [3,4].

It is estimated that at least 40% of cases remain undiagnosed in the UK [2]. In 2012, birth cohort screening for HCV was recommended by the Centers for Disease Control and Prevention (CDC) [5]; however, outside the US, screening for HCV is generally only undertaken in high risk populations. Risk based screening may not be effective for three main reasons: firstly, in the primary care setting, HCV risk factors are often not fully explored [6,7]; secondly, patients do not always report transient behaviours (e.g. injecting drug use) that occurred years or decades ago; thirdly, many acquire infection iatrogenically in their country of origin and are unaware of exposure risk. Other strategies for HCV case finding are therefore becoming increasingly pertinent, especially given the recent advances in treatments with the introduction of new generation direct-acting antivirals (DAAs). Antenatal screening for several infectious diseases, including HIV and hepatitis B virus (HBV), is performed routinely in many countries including the UK [8]. This is commonly motivated by the risk of perinatal transmission; this is estimated at 6% amongst HCV patients [9,10]. However, in the absence of interventions available to prevent HCV transmission, routine screening for HCV in pregnancy has not been recommended in most countries [11]. Successful

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Hepatocellular Carcinoma Surveillance
Are We Utilizing It?

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Background and Goals: International guidelines recommend 6-monthly ultrasound scan surveillance in cirrhotic patients for hepatocellular carcinoma (HCC) screening. The aim of this study was to evaluate HCC surveillance and to provide the outcomes for the largest reported cirrhosis cohort in the United Kingdom.

Study: We retrospectively reviewed all cirrhotic patients during the 6 months before April 1, 2014 at 3 teaching hospitals within the Imperial College Healthcare NHS Trust. All patients with cirrhosis eligible for HCC screening in the cohort were reviewed for evidence of screening and were characterized as either "routine" or "overdue." Reasons for failure to meet guidelines were identified in overdue patients. Univariate analyses were conducted to determine clinical and sociodemographic predictors of surveillance with a view to performing multivariate analysis.

Results: Of the 898 patients eligible for inclusion, 65% patients had HCC surveillance performed in the past 6 months. During the observation period, 61 (6.8%) cases of HCC were detected. Thirty-eight were picked up on surveillance, 9 incidentally and in 14 cases it could not be determined from the notes. Within this cohort HCCs diagnosed on surveillance did not demonstrate significantly superior outcomes compared with those picked up incidentally.

Conclusions: Surveillance of patients with cirrhosis within this cohort is suboptimal. Although disappointing at a local level, this is likely to be reflective of practice elsewhere.

Key Words: hepatocellular carcinoma, HCC, surveillance, screening, utilization

(J Clin Gastroenterol 2016;50:e8–e12)

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third commonest cause of cancer mortality.[1,2] Although most of the burden of disease is in developing countries due to hepatitis B virus, it is fast developing into an increasing problem in western Countries due to rising trends of hepatitis C virus, alcoholic liver disease, and nonalcoholic steatohepatitis (NASH).[1,3] In the United States approximately 20,000 new cases of HCC are reported per year and in the United Kingdom HCC is responsible for roughly 1500 deaths per year.[1,4] Cirrhosis is associated with 80% to 90% of HCC.[1]

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The authors declare that they have nothing to disclose.
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Regular surveillance increases the likelihood of detecting HCC at an early stage where it is more likely to be amenable to curative treatment.[5] This strategy has been demonstrated to be cost-effective.[6] The average 5-year survival rate for advanced tumors remains low at approximately 12%.[1] Yet 5-year survival rates as high as 70% have been demonstrated in tumors picked-up at an early stage that are suitable for curative therapies.[7] In a United States retrospective cohort of 4482 patients with HCC listed for liver transplantation the overall 5-year survival was 62%, however, in those with more advanced cancers 5-year survival was 38%.[8] International guidelines have been introduced to guide clinicians in the practice of HCC surveillance. The European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases currently recommend screening of high-risk individuals using abdominal ultrasound scan (USS), at 6-monthly intervals.[9,10]

A recent meta-analysis of 47 studies with 15,158 patients suggested only 41% of HCCs are detected by surveillance. Outcomes of patients detected on surveillance were twice as likely to have curative therapy and live longer.[7] Thus far, the small number of studies looking directly at HCC surveillance adherence suggest low utilization rates for HCC surveillance in high-risk individuals.[11] Extremes of age, male sex, and etiology have been implicated in negative likelihood for adherence to HCC screening.[11]

To date, there have been relatively few large studies assessing surveillance practice in Europe. This study aims to provide the largest cohort analysis into surveillance utilization, from a UK perspective, with the aim of providing the international community more insight into the factors affecting surveillance utilization.

MATERIALS AND METHODS

Data Collection

The electronic clinic letter database at Imperial College Healthcare NHS Trust was interrogated to retrospectively screen all hepatology patients seen at St Mary's, Hammersmith and Charing Cross hospitals to identify patients diagnosed with cirrhosis before October 1, 2013. The search term (CIRRHO) was used to detect all clinic letters containing the descriptors "cirrhosis" and "cirrhotic." Only letters from after January 2012 were inspected.

Each clinic letter was examined individually to confirm a diagnosis of cirrhosis. Hospital radiology reporting software was used to identify whether these patients had a screening scan between October 1, 2013 and April 1, 2014. Scans performed within this time frame were categorized as "routine" and if not "overdue."

We attempted to identify possible explanations for patients falling into the "overdue" category from hospital

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A European Single Centre Experience of Management of Hepatitis C Virus Genotype 4 Infection With Pegylated-Interferon and Ribavirin

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New direct acting antiviral agents are revolutionising hepatitis C virus (HCV) treatment. However, to date limited clinical trial data exists for outcomes in genotype 4 (GT4) HCV patients. GT4 HCV is more common in Africa, the Middle East, and Asia, and limited data exists to date for outcomes in Europe. We report the first "real-life" sustained virological response (SVR) outcomes using pegylated interferon and ribavirin for HCV GT4 in the UK, and the largest European single centre cohort. HCV GT4 patients treated at a London, UK centre between 2002 and 2014 were assessed for SVR outcomes. Patient age, sex, region of origin, co-infection with HIV, pre-treatment liver biopsy histological assessment, genotype subtyping, treatment duration, and dose reductions were compared against SVR outcomes on univariate analysis. Multivariate analysis was performed on results with $P < 0.1$. A total of 118 patients were treated with HCV GT4 during the study period, 57 achieved SVR (48%). On univariate analysis age ≥ 45 ($P < 0.0001$), high viral load ($P < 0.0001$), Ishak staging 5–6 ($P < 0.0001$), and non-Egyptian Africans ($P = 0.0059$) were all negatively associated with SVR. Eastern Europeans appeared to have higher SVR ($P < 0.0001$). Using multivariate correlation viral load ($P = 0.0005$); Ishak staging ($P = 0.0031$) and age ($P = 0.0003$) were associated with SVR but not country of origin ($P = 0.0645$). Outcomes with pegylated interferon and ribavirin for HCV GT4 in this "real-life" setting were sub-optimal especially in the context of newer regimens. Patients with older age, high viral loads, and advanced disease need prioritisation for alternative treatments. ***J. Med. Virol.*** © 2015 Wiley Periodicals, Inc.

KEY WORDS: Hepatitis C Virus; Genotype 4; Interferon; ribavirin

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INTRODUCTION

Hepatitis C virus (HCV) results in chronic infection in the majority of infected people. Persistent infection can lead to end stage liver disease (ESLD) and hepatocellular carcinoma (HCC) [Alberti et al., 1999]. Hospital admissions and deaths from HCV related ESLD and HCC are continuing to rise, with the number of transplant listings due to HCV cirrhosis more than doubling between 1996 and 2011 [Health protection agency, 2012].

Among the six major genotypes of HCV, 90% infected people in western countries have genotypes 1–4. Hepatitis C virus genotype 4 (HCV GT4) is more prevalent in Egypt, the Middle East, and Sub-Saharan Africa [Legrand-Abravanel et al., 2005; Kamal, 2011]. In Europe, due to immigration and spread through injecting drug use HCV GT4 infection is becoming more prevalent [Legrand-Abravanel et al., 2005]. The Journalrecently reported the phylogenetic variations of UK based HCV GT4 contingent on regions of origin of infected patients. Over a 4-year period 242 HCV GT4 patients were identified from 23 centres [Ngui et al., 2015]. However, unlike other countries, no published data exists for UK GT4 HCV treatment outcomes. To date the standard treatment options include pegylated interferon and ribavirin, usually for 48 weeks. Patients that achieve a rapid virological response (RVR) have been demonstrated to have improved chances of sustained virological response (SVR) allowing for reduction in treatment durations [Fried et al., 2011; Kamal, 2011].

New direct acting antiviral agents (DAAs) have demonstrated SVR rates of 89–100% in recent phase

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LETTERS

Early diagnosis and treatment: the goal of hepatitis C screening

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Koretz and colleagues correctly highlight the need for robust evidence for hepatitis C screening, but a few points warrant a more balanced discussion.[1]

The impact of hepatitis C should not be underestimated. Deaths associated with hepatitis C trebled in the UK between 1996 and 2010. By 2020, an estimated 15 480 infected people in the UK will have associated cirrhosis or hepatocellular carcinoma.[2]

The US birth cohort screening programme the authors described has shown cost effectiveness.[3] Newer regimens will ultimately improve pricing competition and sustained virological response (SVR) rates compared with interferon based treatments. The authors question the benefit of achieving SVR, despite a meta-analysis of 34 563 treated patients showing a 62% reduction in all cause mortality.[4]

The article focuses on whether risks of treatment outweigh benefits. Previous reports suggest achieving SVR is associated with improved quality of life.[5] Traditional interferon based treatments have serious side effects. However, newer direct acting antiviral regimens have greater tolerability. One study that the authors cited used a sofosbuvir and ledipasvir regimen.[1] Of 647 treated patients only three (0.5%) discontinued treatment early because of side effects. Ten (1.5%) experienced serious adverse events. However, it is unclear how many of these events were genuinely attributable to these drugs.

Patients successfully treated with mild to moderate disease may be alarmed to read the authors' interpretation of SVR. These patients should be reassured that ongoing hepatitis C mediated liver damage is unlikely. Reactivation after SVR is exceedingly rare. Conversely, patients with cirrhosis are at risk of disease progression after SVR. This emphasises the importance of early diagnosis and treatment, which is the ultimate goal of screening.

Competing interests: NS has received support to attend international conferences by BMS and honorariums for educational talks by Gilead and BMS. AB has acted in an advisory capacity and/or received speaker honorariums for AbbVie, BMS, Gilead, Janssen, and Merck. MT is involved with the Gilead speaker bureau and is on the advisory board and received speaker fees for Gilead, BMS, Abbott, AbbVie, and Janssen.

Full response at: www.bmj.com/content/350/bmj.g7809/rr-1.

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