An Economic Evaluation of Finding Cases of Hepatitis B and C Infection in UK Migrant Populations

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Table of Contents

1 Foreword 4

2 Executive summary 5

2.1 Objectives 5

2.2 Methods 5

2.3 Results 6

2.4 Summary 6

2.5 Suggested areas for further research 7

3 Project scope 8

4 Literature review 8

5 A prerequisite to establishing the cost-effectiveness of case finding 9

6 Methods 9

6.1 General Framework 9

6.2 The Decision Problem 11

6.3 Model Structures and how they work 12

6.3.1 The HBV model 12

6.3.2 The HCV model 14

6.4 Test accuracy 15

6.5 Infection prevalence 15

6.6 Cohort demographics 15

6.7 The background probability of testing 16

6.8 Intervention effects and treatment uptake 17

6.9 Utilities and costs 18

6.10 Transition probabilities 19

6.10.1 Initial probabilities 19

6.10.2 All cause mortality 20

6.10.3 Disease progression and treatment effects 20

7 Results 21

7.1 HCV 21

7.2 HBV 21

8 Summary 22

9 Suggested areas for further research 25

10 Acknowledgments 25
11 Tables 26
12 Figures 34
13 References 42

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1 Foreword

The work contained in this document has been commissioned by the National Institute for Health and Clinical Excellence's (NICE) Public Health programme. It represents part of a wide body of work aimed at assessing the effectiveness and cost-effectiveness of methods 'to promote and offer testing to people at risk of hepatitis B / C infection'. This section reports economic evaluations of case finding interventions for hepatitis B / C infection in people who are migrants to the UK. Two separate models are reported, one relating to testing for hepatitis B (HBV) infection and the other for hepatitis C (HCV) infection; the cost-effectiveness of simultaneously testing for both infections is not modelled at any point. A model relating to interventions for intravenous drug users (IDUs) is available in a separate report.

2 Executive summary

2.1 Objectives

The specific aim of this report was to assess the cost-effectiveness of interventions to increase hepatitis C (HCV)/hepatitis B (HBV) testing and/or treatment uptake in migrant populations to the UK. However, the accompanying systematic review and call for evidence produced few useful studies on intervention effectiveness on which to base the cost-effectiveness modelling. Therefore, with the agreement of the PDG, particular efforts were made to also highlight the parameters/areas of greatest uncertainty in terms of determining cost-effectiveness, in order to inform the further research recommendations.

2.2 Methods

To achieve these objectives, two decision models were built one relating to HCV testing and treatment, the other to HBV. Both models evaluated the cost-effectiveness of a hypothetical 'one off' intervention aimed at increasing testing, although it is loosely based on a recent UK study available as a conference abstract[1]. The comparator intervention consisted of a background rate of testing only (i.e. no intervention). The majority of evidence required to populate the model was taken from UK health technology assessment (HTA) reports, Health Protection Agency (HPA) publications and the IDU model also commissioned as part of this project. Both case finding models used a Markov approach, cycled 6 monthly and were analysed using cohort techniques. Uncertainty was assessed using probabilistic- and one way-sensitivity analysis. Analysis of covariance (ANCOVA) was also undertaken. Health outcomes were expressed in terms of Quality-Adjusted Life-Years (QALYs). Costs were assessed from a UK National Health Services (NHS) perspective and expressed in £2010/11 prices.

2.3 Results

The results from the HCV/HBV models produced estimated incremental cost-effectiveness ratios (ICERs) of approximately £10,200 and £20,900 per additional QALY respectively, when the assumptions were made that the HCV/HBV prevalence was 2%, the mean cost of the intervention was £20 per person invited for a test and a 17.5% chance of testing for a period of 6 months as a result of the intervention. The one way sensitivity analysis and ANCOVA suggested that both model results were highly sensitive to a number of parameters including the rate at which future QALYs are discounted, the infection prevalence, assumptions regarding treatment uptake, the costs and effectiveness of the intervention. The results from the HBV model were also particularly sensitive to assumptions regarding the proportion of tested individuals who required treatment and the likelihood of household contacts requiring treatment for CHB.

2.4 Summary

The results from these analyses suggest that HCV case finding is likely to be cost-effective at a 2% prevalence level and at a willingness to pay per additional QALY of £20,000 if it increases testing to 17% and costs £50-75 per person tested. This conclusion was robust to most alternative assumptions except those related to treatment uptake. The base case ICER for HBV case finding at the same 2% prevalence level, intervention effect and cost was about £21,000. Thus it is on the cusp of the £20,000 per additional QALY cost-effectiveness threshold. However, this result is highly sensitive to a number of assumptions, particularly those relating to treatment uptake, contact tracing and the proportion of identified cases that require treatment. Thus, there is a large amount of uncertainty around the base case ICER. All are areas where evidence is lacking, and further research is required if more robust estimates of cost-effectiveness are to be produced in the future.

2.5 Suggested areas for further research

Research on the following would particularly help to produce more robust estimates of cost-effectiveness in the future:

- Intervention effectiveness
- Intervention costs
- The likelihood that identified cases of HBV require treatment
- The effectiveness of case finding
- The prevalence of both HBV and HCV infections, but particularly HBV
- Treatment uptake rates

3 Project scope

The project scoping (briefing) document was clear that the interventions to be evaluated should focus on identifying cases of HBV / HCV in migrant populations to the UK and / or encouraging uptake of treatment. The original intention was to use the results from the systematic review by Liverpool John Moores University (LJMU)[2] and information available via PDG members, and a later call for evidence, to define a set of interventions to evaluate. However, very few studies assessing intervention effectiveness were identified meaning that producing robust estimates of cost-effectiveness would be difficult. Therefore, in the absence of this evidence, the decision was made by the PDG to also focus the cost-effectiveness analyses on establishing potential research priorities from an economic perspective. That is, to undertake the evaluation but also to identify the parameters that are particularly important in determining the cost-effectiveness of case finding as well as highlighting those that are not.

4 Literature review

The systematic literature search undertaken by LJMU[2] for this NICE Public Health Project suggests that a only small number of economic evaluations relating to the identification of cases of HBV/HCV infections in migrants to the UK have been published to date. Perhaps the strongest from a methodological stance is the study by Veldhuijzen et al [3]. However, the main criticism of this study from a policy perspective is that the impact of increased testing was based on participation rates in breast cancer screening studies, presumably because of a lack of basic evidence on intervention effect. A more detailed critique of the Veldhuijzen study is provided in the LJMU[2] report. No additional reviewing has been attempted here but it and other

studies have been used as a source of evidence to estimate a number of the model parameters and to inform their design.

5 A prerequisite to establishing the cost-effectiveness of case finding

By definition, for HBV/HCV case finding to be cost-effective, it is essential that subsequent treatment also represents value for money. This is because the overall incremental cost per Quality-Adjusted Life-Year (QALY) equals the sum of case finding, testing and the cost of treating, all divided by the number of QALYs gained. Since no QALYs are gained from finding and testing without treatment, then the overall cost per QALY will be greater than the cost per QALY for treatment. If the cost per QALY for treatment is higher than the threshold at which an intervention is deemed cost-effective, then the overall cost per QALY (which is higher again) will exceed the cost effectiveness threshold.

A brief examination of NICE-related [4-6] and other relevant literature [7, 8] suggests that most if not all reported ICERs of recommended HBV/HCV treatments are below a cost-effectiveness threshold value of £20,000; indeed they were often substantially less than this. Thus this basic prerequisite for case finding to be cost-effective has been fulfilled.

6 Methods

6.1 General Framework

Two de novo economic decision models were built to assess the objectives, one for increasing the likelihood of finding cases of HBV and the other for finding cases of HCV infection, both in migrant populations to the UK. No attempt has been made to

assess the cost-effectiveness of finding HCV and HBV in a single model, because of the complexities involved of modelling co-infection.

Both models are based on discrete-time (Markov) approaches. Discrete-time models are convenient/appropriate to use when it is important to consider the costs and benefits of treatment options over relatively long periods of time, as is the case with the natural history of both HBV and HCV infection [9-12]. In all instances, the models were evaluated using 1,000 probabilistic sensitivity analysis (PSA) runs.

Analysis of covariance analyses (ANCOVA) and a number of one way sensitivity analyses have also been reported, in order to highlight the parameters that were most important in terms of driving the results. The models were built using TreeAge Pro 2009 and 2011[13], whereas the ANCOVA was undertaken using STATA version 12[14].

A model structure was created to represent HBV disease progression and current understanding of policies regarding disease management, using PDG members to provide necessary clinical advice where necessary. The natural history element of the model was based on Shepherd et al. [5, 7]. The majority of model parameters were estimated using previous HTA reports [4, 5, 7, 15], Health Protection Agency (HPA) publications [16, 17], data provided on request by the HPA and other literature sources. Where necessary data were missing, assumptions were made also using expert opinion where possible. It was assumed that infection transmission could not occur in either model, as it is understood that the majority of infections that happen in these populations occur outside of the UK.

The HCV model structure is very similar to the HCV IDU[18] analysis that was also constructed for this NICE Public Health project. The main changes relate to the

parameter estimates, such as intervention effects and treatment uptake, and that the migration models do not consider infection transmission. The latter was assumed because it is believed that relatively few infections occur in the UK as a result of transmission within the country, with around 90% of HBV infections being acquired outside of the UK.

All costs are displayed in £ using 2010/11 prices. Where necessary, costs were inflated using the Hospital and Community Health Services Index[19]. Both models cycled 6-monthly, used a lifetime horizon and were carried out from a UK National Health Service (NHS) cost perspective. Outcomes were expressed in terms of QALYs and all future base case costs. QALYs and costs were discounted at 3.5% per annum according to current NICE recommendations[20].

6.2 The Decision Problem

Given the paucity of effectiveness evidence, the decision was made to evaluate a hypothetical intervention for both HCV and HBV models, although it is broadly based on the 'opt out' case finding approach described in a recent conference abstract by Lewis et al [1]. In this study, Pakistani/British Pakistani people registered at GPs were written to and invited to opt out of HCV/HBV case finding. Those who did not opt out were telephoned and asked to attend testing clinics.

The basic logic underlying each model was that increased testing leads to an increase in the number of people who are diagnosed with chronic HBV/HCV and treated and/or reduces the time it takes for a person to start treatment. Each model run was assumed to include a cohort of individuals who were all eligible for HCV or HBV testing, a proportion of whom were infected. The 'intervention' was designed to increase the likelihood of testing for each infection, over the initial model cycle (6 months). After this time, the intervention effect was assumed to be zero, with the

probability of testing reverting to background levels. The comparator technology was defined as the background chance of testing; i.e. a 'no intervention' option.

6.3 Model Structures and how they work

6.3.1 The HBV model

The HBV model is much more detailed than its HCV counterpart, largely because of greater complexities in terms of modelling the disease progression process, but also because it includes contact tracing. The model starts by creating a cohort of 'index' cases, a proportion of whom are HBsAg+ according to the prevalence parameter. Known HBsAg- individuals remained in the model with a general population level of mortality but incurring no further HBV-related costs. On the other hand, known HBsAg+ people were assumed to undergo a full viral profile to establish their infection stage and suitability for treatment. Individuals with known acute infection were assumed to be offered a repeat test in 6 months time (i.e. the next model cycle). Whether infection status was known or unknown, individuals with acute infection either cleared the infection in the following cycle or developed chronic hepatitis B (CHB). All individuals with known CHB were offered treatment or monitoring strategies, depending on their stage of infection, alanine transaminase (ALT) and HBV RNA levels, broadly according to recent European Association for the Study for the Liver (EASL) guidelines (Figure 1)[21]. Mutually exclusive stages of CHB that were modelled included: HBeAg seroconverted (where ALT levels and HBV RNA are both low), hepatitis B e antigen negative (HBeAg-) and hepatitis B e antigen positive (HBeAg+) disease. The infection status of all individuals with CHB was assumed to become known if/as soon as they developed decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) or required a liver transplant (Figure 2).

Individuals with CHB whose infection status was unknown and individuals that tested HBsAg+, but who declined or were not offered treatment, were assumed to develop progressive disease according to a set of defined transition probabilities (Table 2). A different set of transition probabilities was used to define CHB disease progression for those who accepted treatment (Table 2).

Current UK NHS HBV-testing policy is to contact household members once a case has been identified. This possibility was therefore included in the model by assuming that each index case who was HBsAg+ (whether known or unknown) was associated with a household of individuals and that a proportion of these people had CHB at the start of the model (Table 2). Contacts that were indentified and tested HBsAg+ were assumed to be managed as per index cases, and were assumed to be 'known' if they developed symptoms related to CHB such as decompensated cirrhosis.

Efforts were made via the HPA to gather evidence on the size of households, the probability that contacts were HBsAg+ and the likelihood that contacts could be traced in the first instance. However, this proved difficult as the information was not routinely recorded and most infections often did not appear to relate to the populations of interest (i.e. migrant populations). Instead, the mean household size was estimated using evidence from the Office for National Statistics along with an assumed discrete distribution and probability of infection (Table 1 and Table 2). Household contacts of HBsAg- index cases were not modelled, as they would not be traced, meaning by definition their inclusion or exclusion from the analysis cannot affect the incremental results.

6.3.2 The HCV model

The structure of the HCV model is very similar to the model built for the IDU cost-effectiveness analysis[18] (Figure 2). It is also similar to other cost-effectiveness models that have incorporated HCV disease progression [4, 15]). It consists of nine main health states: HCV negative (uninfected), mild disease, moderate disease, compensated cirrhosis (CC), decompensated cirrhosis (DC), hepatocelluar carcinoma (HCC), liver transplant, post liver transplant and dead. The first four of these health states were further subdivided into whether or not individuals: 1) were undiagnosed, 2) have been diagnosed, 3) were receiving treatment, 4) had responded to treatment (sustained virological response [SVR]), 5) had failed treatment or 6) had not been referred or declined treatment. As per the HBV model, in each cycle, individuals could be tested for HCV, according to the intervention effects and the background rate of testing. Individuals who tested positive would be offered treatment at a given rate. Individuals who accepted treatment received it for 6 months at which time they were considered to be SVRs or not. Individuals who tested HCV-antibody-negative were assumed to incur no further costs. Individuals with SVR were assumed to have utility levels above those related to non-SVRs and a general population level of mortality and not to experience any further disease progression. As with the HBV model, those who were not tested were assumed to have 'known' infection only if and when they developed decompensated cirrhosis or hepatocellular carcinoma.

Neither model includes possible adverse events associated with anti-HBV or anti-HCV treatments, treatment resistance or the possibility of treatment switching.

6.4 Test accuracy

In all simulation runs, the diagnostic tests were assumed to be 100% accurate. However, it should be noted that all individuals who tested HBsAg+ received a full viral profile before treatment, meaning that individuals who are genuinely HBsAg- are unlikely to mistakenly receive treatment.

6.5 Infection prevalence

The proportion of people with a given infection/disease is an important consideration within any economic evaluation that assesses the cost-effectiveness of case finding interventions. Data are available from the HPA on the number of people who are tested for HCV and HBV each year in specific UK surveillance sites (thought to cover about 30% of the population), although there appears to be some question as to how well it approximates 'true' underlying levels of HBV infection. The data are also broken down by a number of ethnic groupings, the most useful in the context of this report being South Asians (HBV/HCV prevalence of approximately 2% each). However, evidence suggests that the infection prevalence varies by migrant/community group. For example, the prevalence of CHB in UK Chinese migrants is thought to be between 7%[22, 23] and 20% (Personal communication Eddie Chan), implying that there is a large degree of heterogeneity within and across communities. Thus, rather than sampling the infection prevalence for each model run, it was fixed in an attempt to mimic intervention costs and effects in specific communities. In the base case, the prevalence was fixed at 2% for both HCV and HBV infection but increased to 5% (as an assumed upper limit) and 20% in the one way sensitivity analyses respectively.

6.6 Cohort demographics

HPA data suggests that the average age at HBV/HCV diagnosis in South Asian populations is approximately 35 years of age[16]. Although this was used as the

starting age in the model, it is an imprecise estimate of the age at diagnosis when used in the context of this modelling exercise (as individuals enter the model at this age, but not all will be tested immediately). For this reason, the age at entry to the model was varied in the sensitivity analysis. For the sake of simplicity the same age was assumed for all household contacts in the HBV model.

Evidence available from the HPA also suggests that migrant people with HCV are one third as likely to be infected with genotype 1 as with genotype 2/3. As treatment response is affected by genotype, this evidence was included in the model. However, the sample size for this evidence was not available, meaning that the distribution had to be assumed (Table 2).

Neither models distinguished between males and females, or make any attempt to differentiate between first- or later-generation migrants either in terms of demographics or testing/treatment behaviour. Moreover, all migration was assumed to be permanent insofar as the NHS was liable for all costs and consequences associated with HBV/HCV infection.

6.7 The background probability of testing

Primary cases infected with HBV/HCV were assumed to be identified either as the result of the intervention, because they developed symptoms related to chronic hepatitis (decompensated cirrhosis or hepatocellular carcinoma) or because of a 'background' probability of testing, which was estimated as follows. First, the total population of the UK is estimated to be 62.3 million of which 3.2% are estimated to be of South Asian origin. Second, HPA data suggests that in 2010 17,226 HBV tests were undertaken in the UK in South Asian people, excluding all ante-natal tests; data thought to cover about a third of all tests. Thus, the annual background probability of testing was estimated to be ([[1/0.333]*17,226]/[62.3 million*0.032]) = 2.6%. This

probability was used in both HBV and HCV models, although it was varied using one way sensitivity analysis.

6.8 Intervention effects and treatment uptake

The base case rate of testing in the first 6 months in the intervention arm (i. e. the intervention effect) was broadly based on the abstract by Lewis et al, for the described opt out option. In this study approximately 20% (223/1,134) of individuals invited for a HBsAg test received it. However, this estimate was not directly incorporated into the evaluation using a beta distribution, as is traditionally the case for the following reasons. First, the sample size was large, so very little uncertainty was generated when the corresponding beta distribution was sampled. Given one of the project aims was to assess the potential importance of each parameter in terms of determining cost-effectiveness, this wasn't considered to be helpful. Second, there are other issues with the design of the study which would suggest that the (relative) treatment effects are more uncertain than they might appear at face value. For example, the study was not randomised or controlled. Lastly, other interventions, including two also reported by Lewis et al[1], were much less successful in terms of the numbers of people who were tested. For these reasons, the assumption was made to specify the intervention effect as a uniform distribution with a mean (probability) of testing in the initial 6 month intervention period of 0.175 U~(minimum 0.05, maximum 0.3). In other words, in the base case it was assumed that the intervention effect led to an average of 17.5% of targeted individuals being tested within the initial 6 months. After this time, the intervention effect was assumed to be zero, but with a remaining background level of testing.

No useful quantitative evidence could be found on the probability of treatment uptake specifically in migrant populations, following a positive diagnosis for HCV or HBV.

Moreover following conversations with experts, it remained very unclear whether the value was indeed likely to be 'high' or 'low', although there was some suggestion that it might vary by community. The assumption of 80% uptake per 6 months was used in the base case. In addition to being sampled in the PSA, both the intervention effects and treatment uptakes were subject to further one way sensitivity analysis.

6.9 Utilities and costs

Utility values are combined with estimates of survival in order to calculate QALYs. All utility values for the HBV model were sourced from a recent HTA monograph by Shepherd et al[5], including age specific adjustments (Table 3), as were most of the required costs (Table 4). The initial test for HBV infection was a surface antigen test (HBsAg), costing £10 per test. Clinical advice suggested that when treatment is indicated for HBsAg+ people, it typically consists of pegylated interferon for 12 months, or entecavir or tenofovir for a minimum of 3-5 years but of an unknown maximum duration. Rather than evaluate the cost-effectiveness of each treatment option, the base case assumed that all individuals who required and accepted treatment received either entecavir or tenofovir until they achieved low ALT and HBV RNA levels (or HBeAg serocoverted). For the HCV model, individuals were assumed to be initially tested for hepatitis C antibodies costing £10 with a confirmatory PCR test costing £70.

The utility values (other than the intervention cost) used for the remaining HCV model parameters were the same as those used in the IDU cost-effectiveness analysis (see Tables 1 and 2 in the IDU report[18]). The costs associated with compensated cirrhosis, decompensated cirrhosis, hepatocelluar carcinoma, liver transplantation and post-liver transplantation were the same as those used for the HBV model[5], in order to be consistent with it. Other remaining costs, such as those

associated with the mild-SVR, moderate-SVR and compensated cirrhosis-SVR health states, were broadly the same as those used in the IDU analysis.

No useful quantitative evidence could be found on the likely cost of providing an intervention for HBV or HCV case finding. Therefore, the assumption was made in the base case that it cost £20 per person eligible for a test (excluding household contacts in the HBV model), with a standard error of a third of this amount. Therefore, if each model run had contained 100 people, the total mean intervention cost would have been £2,000. Despite this assumption, it is acknowledged that 'true' intervention costs are likely to vary widely according to intervention design. For example, a one-off sweep of GP records to indentify people to invite for testing, if possible electronically, might have far lower upfront costs than interventions to increase 'awareness and testing' amongst relevant health care professionals; even if the latter has a longer duration of effect.

6.10 Transition probabilities

6.10.1 Initial probabilities

Initial probabilities are required in discrete time models, as they indicate where individuals enter it. For the HBV model, individuals were either HBsAg- or HBsAg+, although all were assumed to be unaware of their infection status. Data from the HPA, both published [16] and via personal communication, were then used to subdivide infected individuals by stage of disease (Table 2). For the HCV model, the initial distributions were based on the values calculated by calibration techniques for the IDU model.

6.10.2 All cause mortality

Individuals without HCV / HBV infection, those who cleared acute HBV infection and HCV individuals with a sustained virological response were assumed to have a life expectancy equivalent to that of the general UK population [24].

6.10.3 Disease progression and treatment effects

The majority of the information required to parameterise the HBV disease progression model was taken from Shepherd et al[5], with two notable exceptions. First, in Shepherd et al, the parameters were specified as beta distributions, with calculated residuals, so that PSA could be undertaken. In this analysis however, the way the HBV model was built meant that multivariate alternatives to beta distributions were required, namely Dirichlet distributions, to prevent sampling probability values that sum to greater than one[12]. To do this, the mean values presented by Shepherd were converted to Dirichlet distributions by assuming a sample size of 200; taken to represent a reasonably sized RCT. For example, if Shepherd et al. specified mean beta distributed values of 0.2, 0.3 and 0.5 (1-0.2-0.3), then the corresponding Dirichlet distribution was calculated to be α(40,60,100). Second, newer drugs have been recommended by NICE for the treatment of HBV since the Shepherd monograph was published, specifically entecavir and tenofovir. Similarly to Shepherd et al[5], treatment effects for people in the HBV model for HBeAg+ and HBeAg- individuals were specified as the probability of HBeAg seroconversion and normalisation of ALT levels respectively. The absolute treatment effects (or probabilities of response) were both taken from a recent systematic review and meta-analysis by Woo et al[25], which at 1-year, were 23% and 73% respectively. The same disease progression parameters, treatment effects and distributions specified for the HCV IDU model were used in this migrant version.

7 Results

7.1 HCV

The base case incremental cost-effectiveness ratios (ICERs) assuming prevalence's of 2% and 5%, were estimated to be £10,200 and £7,500 respectively (Table 5). The cost-effectiveness acceptability frontiers (CEAFs) suggested that the uncertainty around the intervention being the most cost-effective option was low in both prevalence settings, at a willingness to pay for an additional QALY of between £20,000-30,000 (Figure 3 and Figure 4). However, results from the one-way sensitivity analysis (Table 6) showed that the ICERs were sensitive to assumptions regarding the probability of treatment uptake, the analysis time horizon and particularly the cost and effectiveness of the intervention. The ANCOVA results support this finding, as it clearly shows that most of the uncertainty in the incremental costs and QALYs was explained by the intervention effect and the intervention cost (Figure 6).

7.2 HBV

The results from the analysis estimated that the intervention cost an additional £20,900 and £12,200 per additional QALY at prevalences of 2% and 20% respectively compared with 'no intervention' (Table 7 and Figure 7). However, similar to the HCV results, the base case ICER was particularly sensitive to assumptions regarding the treatment effect and cost. It was also particularly sensitive to assumptions regarding the prevalence, the likelihood of requiring treatment when identified, assumptions regarding contact tracing, the rate at which future QALYs are discounted and the time horizon (Table 8)

8 Summary

Two economic evaluations of a hypothetical case finding intervention in migrant populations to the UK have been presented in this report, one relating to cases of HBV, the other to HCV. The results suggest that a 'one-off' HCV case finding intervention in prevalence areas of 2% or more, that achieves levels of testing of at least 17.5%, is likely to be cost effective at a willingness to pay for an additional QALY of £20,000 if it costs between £50-75 per person invited for a test. This finding was generally robust to alternative assumptions, except those relating to treatment uptake. For example, if it was assumed that only 25% of indentified HCV cases ever take up treatment, then the ICER increased to well over £30,000 per additional QALY.

The base case ICER for HBV case finding was estimated to be approximately £21,000 when similar assumptions were made (intervention effect of 17.5%, £20 per person invited for a test and a 2% prevalence level). Thus it is on the cusp of the £20,000 per additional QALY cost-effectiveness threshold. However, it is important to note that this base case result was highly sensitive to a number of assumptions, including the prevalence, treatment uptake rate, the effectiveness of contact tracing and the proportion of identified HBsAg+ individuals who required treatment. Indeed, the latter point almost exclusively explains the difference in the HBV and HCV case finding results - based on HPA data, the base case assumed that only 20% of identified CHB cases required treatment. No such consideration is included in the HCV model, where all identified cases are considered eligible for treatment. However, the HBV case finding ICER decreased to approximately £12,000 per additional QALY if the prevalence was assumed to be 20%, which is thought to be representative of the infection prevalence in some UK-Chinese communities.

Irrespective of the results and whether or not they are above or below a threshold QALY value, it should be noted that the supporting systematic review[2] reported a very limited amount of effectiveness evidence on case finding interventions and that our base case testing up take rate of 17.5% over 6 months was based on a single intervention reported in a recent conference abstract[1]. Indeed, the effectiveness of two other interventions reported in the same abstract were much lower than 17.5%. Similarly, no useful evidence could be found on the costs of delivering case finding interventions in the target groups of interest. These considerations are important as the sensitivity analysis clearly indicates the reliance of the ICER on the intervention costs and effects.

In addition to the intervention costs and effects, the sensitivity analysis showed that the models' results were dependent on assumptions regarding treatment uptake (for which there is very little evidence in migrant populations), the prevalence, the time horizon and the rate at which future QALYs are discounted. For the HBV model, the assumptions regarding the likelihood of finding further cases of infection via household contact tracing was also particularly important. Thus, the scope and importance of further research in these areas is likely to be considerable.

The base case 2% HBV prevalence results is higher than the incremental cost per QALY of €8,966 reported by Veldhuijzen et al [3]. However, possible reasons for the difference include their use of a HBsAg+ prevalence nearer 3.5%. Further comparison between with this study is difficult not least because the evaluation by Veldhuijzen appears to be assessing the cost-effectiveness of more than one intervention, increasing the likelihood of testing and subsequent referral to a specialist physician, but the (combined) intervention effects are unclear.

Both the HBV and HCV decision models contain a number of limitations. First, the cost-effectiveness of simultaneously testing for HBV and HCV was not considered because of the difficulties of modelling co-infection. While at some level it would appear intuitive to believe that simultaneously testing could only increase cost-effectiveness, this rests on the assumption that prevalence rates are similar, or are at least positively correlated in a given community. For example, HBV prevalence rates of 20% in UK Chinese communities have been recorded, but it appears that HCV is much less of a concern in these communities. Thus, testing for HCV in UK Chinese communities might not make economic sense in the first instance. However, for UK Bangladeshi / Pakistani communities, HBV and HCV prevalence's of around 1 to 2% have been recorded thus, if active case finding does happen, it would make sense to test for both infections simultaneously.

The approach taken to modelling treatment uptake was a particular limitation. In the models it was assumed that there was a recurring probability of receiving treatment, and in this sense, the parameter reflected a time to treatment rather than a probability of ever accepting treatment. This approach was taken as it was simple to implement in the model, and a lack of detailed relevant evidence meant that more sophisticated attempts were unwarranted. While the results from the ANCOVA suggested that treatment uptake was not a particular issue in terms of driving the cost-effectiveness results, further investigations involving structural changes to the HCV model suggested that different assumptions lead to very different results, and that it is indeed an important area in terms of future research.

9 Suggested areas for further research

Research on the following would particularly help to provide more robust estimates of cost-effectiveness in the future:

- Intervention effects
- Intervention costs
- The likelihood that identified cases of HBV require treatment
- The relative effectiveness of case finding
- The prevalence of both infections, but particularly HBV
- Treatment uptake rates

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11 Tables

Table 1: Household size

Size of household	Probability
0	0.10
1	0.13
2	0.18
3	0.22
4	0.18
5	0.19

The mean household size of 2.82 was taken from Office for National Statistics information, but the discrete distribution was assumed

Table 2: HBV probability parameters, initial- and other-distributions.

Parameter	Mean value	PSA parameter^	Source
Intervention effect*for 6 months	0.175	Uniform, (0.05;0.3)	Lewis [1] and assumption
Annual background rate of testing**	0.026	Beta, n = 1993600, r = 52200	HPA [16] and assumptions
Referral / treatment uptake per 6 months	0.80	Beta, n = 100, r = 80	Assumption
Size of household	2.82	Table distribution, see Table 4 below	ONS and assumptions
Each household contact infected with CHB	0.05	Beta, n = 1000, r = 50	Assumption
Initial distributions			
Acute infection	0.08	Beta, n = 2697, r = 214	HPA
% of those with CHB who had normal ALT and HBV RNA levels	0.8	Beta, n = 10024, r = 8068	HPA, personal communication
% of those with raised ALT or HBV RNA levels that were HBeAg+	0.57	Beta, n = 1956, r = 1108	HPA, personal communication
6 monthly transition probabilities			
HBeAg seroconverted to HCC	0.00005	Beta, α = 0.9187, β = 18373	Shepherd [5]
Cleared acute infection	-	Dirichlet α(199.995,0,0,0,0,0,0.005,0,0)	Shepherd [5] and assumptions
HBeAg seroconverted	-	Dirichlet α(2.01,193.46,3.02,0,1,0,0.5,0,0)	Shepherd [5] and assumptions
CHB HBeAg+ (treated)	-	Dirichlet α(1.76,21.11,171.21,0,5.06,0,0.5,0,0.35)	Shepherd [5], Woo [25] and assumptions
CHB HBeAg+ (untreated)	-	Dirichlet α(1.76,9.22,183.12,0,5.06,0,0.5,0,0.35)	Shepherd [5] and assumptions
CHB HBeAg- (treated)	-	Dirichlet α (0.5;96.08;0;97.51;5.06;0;0.5;0;0.35)	Shepherd [5], Woo [25] and assumptions
CHB HBeAg- (untreated)	-	Dirichlet α(0.5;14.52;0;179.06;5.06;0;0.5;0;0.35)	Shepherd [5] and assumptions
CHB HBeAg+ compensated cirrhosis	-	Dirichlet α(0;9.2;0;0;178.04;5.06;2.52;0;5.17)	Shepherd [5] and assumptions
CHB HBeAg- compensated cirrhosis	-	Dirichlet α(0;0;0;0;187.25;5.06;2.52;0;5.17)	Shepherd [5] and assumptions
Decompensated cirrhosis	-	Dirichlet α(0;0;0;0;0;150.7;2.52;3.02;43.8)	Shepherd [5] and assumptions
Hepatocelluar carcinoma	-	Dirichlet α(0;0;0;0;0;0;132.7;0;67.34)	Shepherd [5] and assumptions
Liver transplant	-	Dirichlet α(0;0;0;0;0;0;0;177.7;22.24)	Shepherd [5] and assumptions
Post Liver transplant to dead	-	Beta(α = 22.9; β=378.9)	Shepherd [5]

^PSA, probabilistic sensitivity analysis; *Initial 6 months only; **Annual, converted to 6 monthly in the program; Where Dirichlet distributions are specified they represent movements from the named health state to the following, in order: 1) cleared infection, 2) HBeAg seroconverted, 3) CHB HBeAg+, 4) CHB HBeAg-, 5) compensated cirrhosis, 6) decompensated cirrhosis, 7) hepatocelluar carcinoma, 8) Liver transplant and 9) dead from HBV infection

Table 3: Annual utility values and associated parameters used in the HBV model, taken from Shepherd et al [5].

Age group / *health state*	Utility	Utility decrement	PSA parameters^,**
0-45	0.91	-	-
46-55	0.85	-	-
56-65	0.8	-	-
66-75	0.78	-	-
HBsAg negative	-	*0*	-
Acute HBV infection	-	*0*	-
CHB – HBeAg seroconversion	-	*0*	-
CHB – HBeAg-	-	*0.04*	*α=14.7512, β=354.028*
CHB – HBeAg+	-	*0.04*	*α=14.7512, β=354.028*
Compensated cirrhosis	-	*0.44*	*α=37.5142, β=47.7543*
Decompensated cirrhosis	-	*0.54*	*α=46.4138, β=39.5377*
Hepatocelluar carcinoma	-	*0.54*	*α=46.4138, β=39.5377*
Liver transplant (first year)	-	*0.54*	*α=46.4138, β=39.5377*
Liver transplant (subsequent years)	-	*0.32*	*α=29.0491, β=51.2*

***Note all utility values were divided by 2 in the programming to account for 6 monthly cycles**

^PSA, probabilistic sensitivity analysis

****All specified as beta distributions**

CHB, chronic hepatitis B

Table 4: 6-Monthly costs and associated parameters used in the HBV model, in 2010 UK prices

Event / *health state*	Mean cost (£)	PSA parameters^	Source
Intervention cost	20	Gamma (α = (20^2)/(10^2), λ = 20/(10^2))	Assumption
HBsAg test (laboratory)	10	Gamma, α = (10^2)/(2^2), λ = 10/(2^2) -	http://www.uclh.org/aboutus/wwd/Pages/ProvidertoProviderTariffs.aspx and assumptions
Anti-HBV drug	1,926		BNF [26]
Cost of identifying each household contact	25	Gamma, α = (25^2)/((25/3)^2), λ = 25/((25/3)^2)	Assumption
ALT and ultrasound	69	-	Assumption
Biopsy	717	-	Assumption
Full viral profile	388	-	Assumption
HBsAg negative	0	-	
Acute HBV infection	0	-	
CHB – HBeAg seroconversion	150	Gamma, α = 25.04313, λ = 0.166446	Shepherd [5]
CHB – HBeAg-	303	Gamma, α = 24.74132, λ = 0.081761	Shepherd [5]
CHB – BeAg+	303	Gamma, α = 24.74132, λ = 0.081761	Shepherd [5]
Compensated cirrhosis	641	Gamma, α = 3538.776, λ = 5.518	Shepherd [5]
Decompensated cirrhosis	5,139	Gamma, α = 1830.328, λ = 0.356148	Shepherd [5]
Hepatocelluar carcinoma	4,580	Gamma, α = 460.012, λ = 0.100447	Shepherd [5]
Liver transplant (first 6 months)	36,788	Gamma, α = 10895.99, λ = 0.296183	Shepherd [5]
Liver transplant (subsequent 6 months)	780	Gamma, α = 1295.349, λ = 1.659717	Shepherd [5]
Monitoring cost HBeAg seroconverters (annual)	301	Gamma, α = (301^2)/((301/3)^2), λ = 301/((301/3)^2)	Shepherd [5] and assumptions

^PSA, probabilistic sensitivity analysis

Table 5: HCV model cost-effectiveness results

	Total Cost (£)	Total QALYs	ICER (£)*
Prevalence 2%			
No intervention	244	17.79113	
Intervention	289	17.9539	10,237
Prevalence 5%			
No intervention	604	17.6025	
Intervention	683	17.6129	7,494

***ICER, incremental cost-effectiveness ratio**

Results are per person

Table 6: HCV cost-effectiveness analysis, sensitivity analysis based on 2% prevalence. Results are based on one-way sensitivity analysis unless otherwise stated

Parameter	ICER (£)
Base Case	**10,273**
£50 per person invited to attend (instead of £20)	17,877
£75 per person invited to attend (instead of £20)	23,211
£100 per person invited to attend (instead of £20)	29,904
80% intervention effect (instead of 17.5%)	6,726
5% intervention effect (instead of 17.5%)	26,624
50% initial treatment uptake then 0% thereafter*	20,588
25% initial treatment uptake then 0% thereafter*	42,005
Drug cost £10,000 for 6 months (instead of £5,612)	12,763
Double background testing rate (5.2% instead of 2.6% per year)	11,978
Utility for SVR health states 95% of base case values	13,809
QALYs discounted at 1.5% per annum (instead of 3.5%)	6,561
Costs discounted at 1.5% per annum (instead of 3.5%)	10,345
Antibody test £30 (instead of £10)	10,993
Prevalence 1% (instead of 2%)	15,328
Prevalence 1% (instead of 2%) and £50 per person invited to attend (instead of £20)	29,377
Time horizon 25 years (instead of lifetime)	17,761

ICER, incremental cost-effectiveness ratio; SVR, sustained virological response; *individuals who do not take up treatment when indicated are assumed to be equivalent to treatment failures (i.e non-SVRs)

Table 7: HBV model cost-effectiveness results

	Total Cost (£)	Total QALYs	ICER (£)*
Prevalence 2%			
No intervention	130,474	18,202.986	
Intervention	176,643	18,205.190	20,907
Prevalence 20%			
No intervention	1,268,738	17,960.578	
Intervention	1,537,626	17,982.660	12,176

***ICER, incremental cost-effectiveness ratio**

Results are based on 1,000 PSA runs and index cohorts consisting of 1,000 individuals

Table 8: HBV cost-effectiveness analysis, one way sensitivity analysis based on a 2% prevalence

Parameter	ICER (£)
Base case	**20,907**
£50 per person invited to attend for a test (instead of £20)	34,319
5% intervention effect (instead of 17.5%)	90,048
No contact tracing	45,933
Doubling the drug cost (instead of £1,926)	27,101
No HBeAg seroconversions on initial test / ALT and HBV RNA both low (instead of 80%)	12,773
Doubled background rate of testing	21,558
6 household contacts (instead of a mean of 2.82)	17,712
1% prevalence	30,608
Time horizon 25 years (instead of lifetime)	71,320

ICER, incremental cost-effectiveness ratio

12 Figures

Figure 1: Hepatitis B model schematic

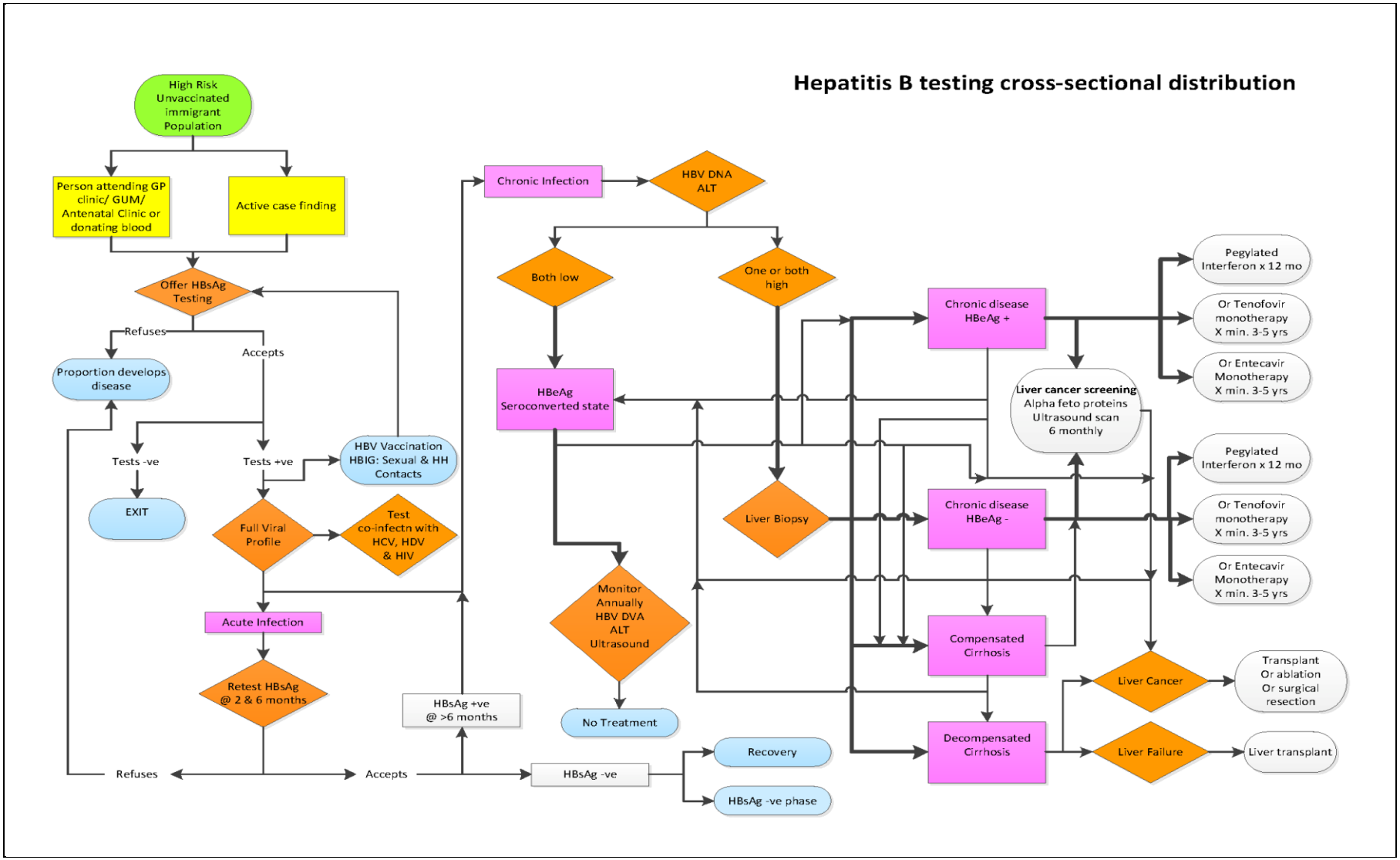
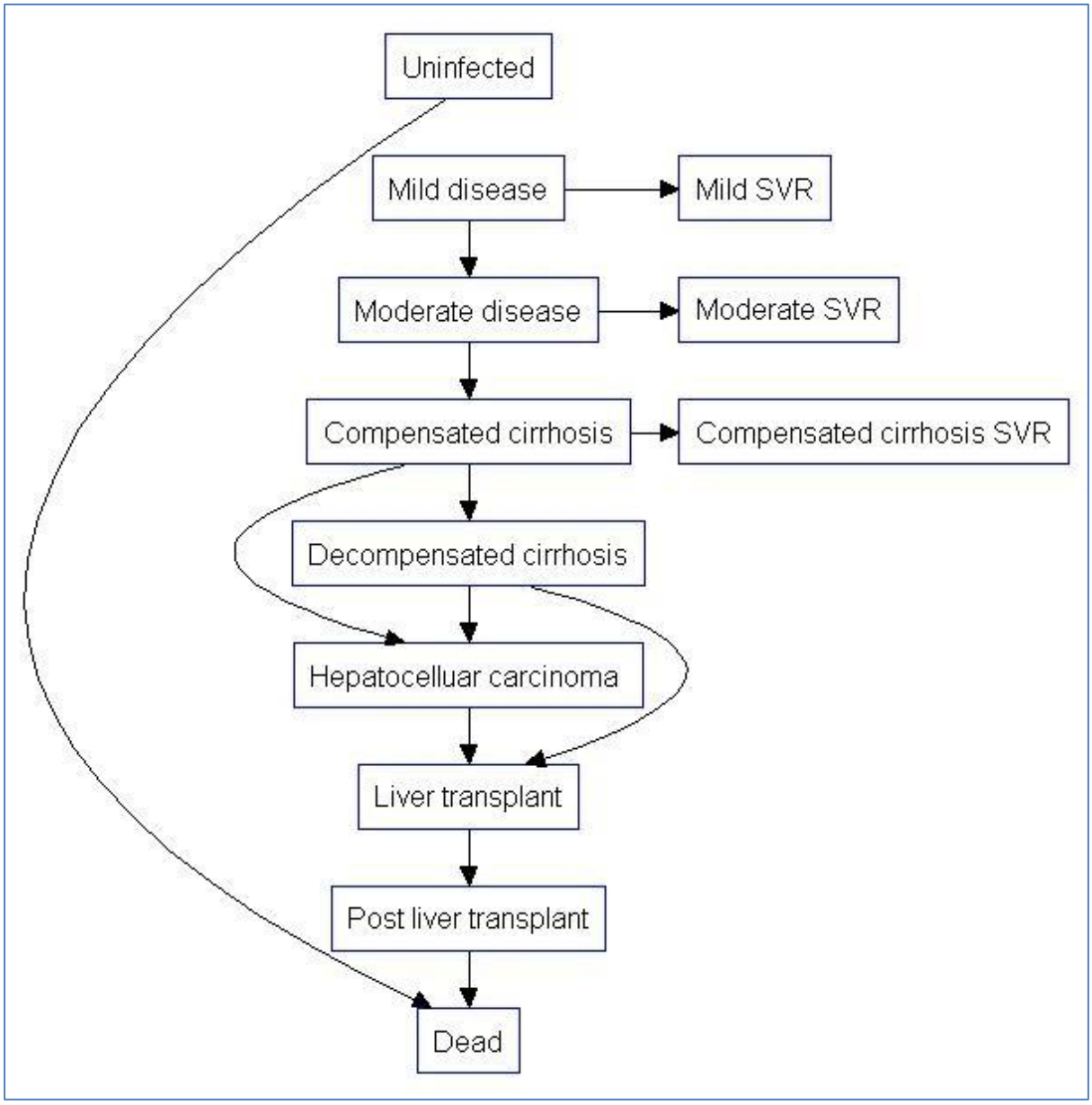


Figure 2: Hepatitis C model schematic



All health states are associated with a probability of death. Other subdivisions include whether or not an individuals infection is known, and whether or not they are receiving treating.

Figure 3: Cost-effectiveness acceptability frontier for the HCV model for a 2% prevalence

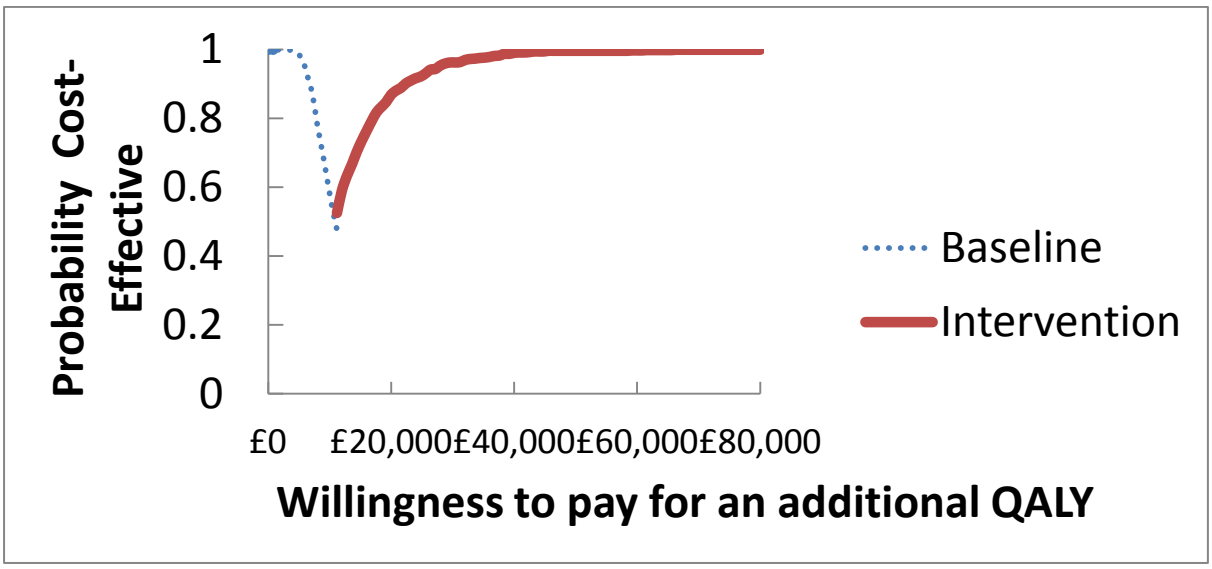


Figure 4: Cost-effectiveness acceptability frontier for the HCV model for a 5% prevalence

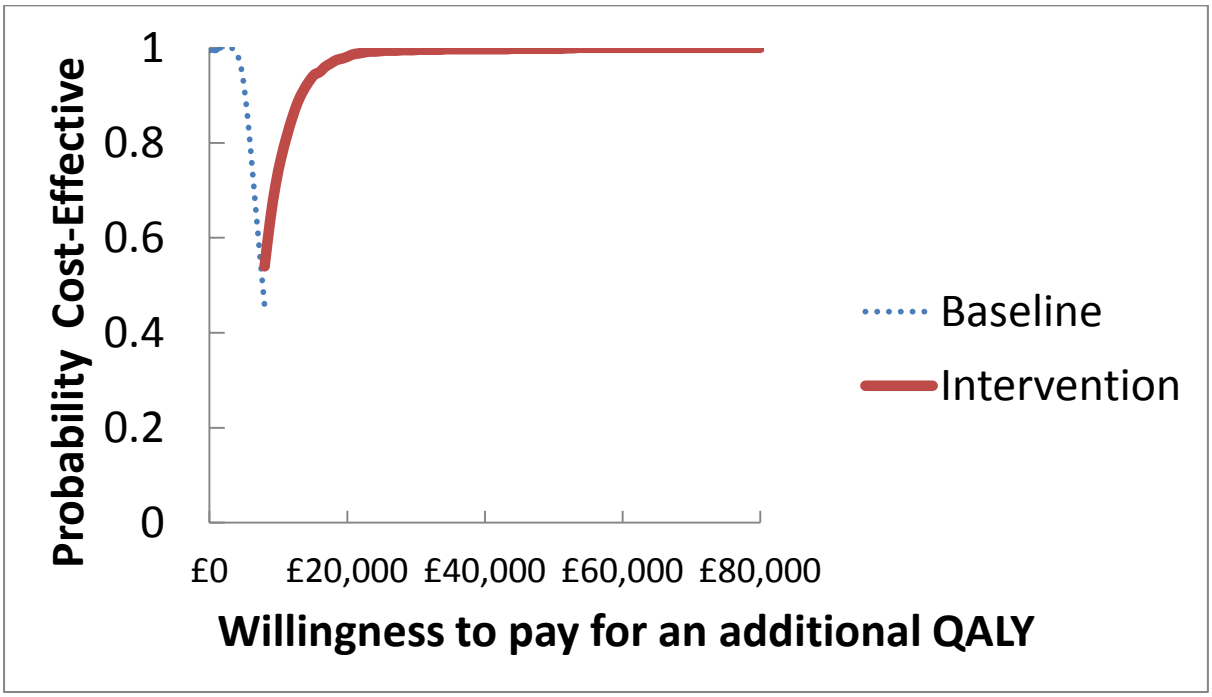


Figure 5: Cost-effectiveness acceptability frontier for the HCV model for a 2% prevalence assuming that 25% of people start treatment as soon as indicated, with the remaining 75% never starting treatment

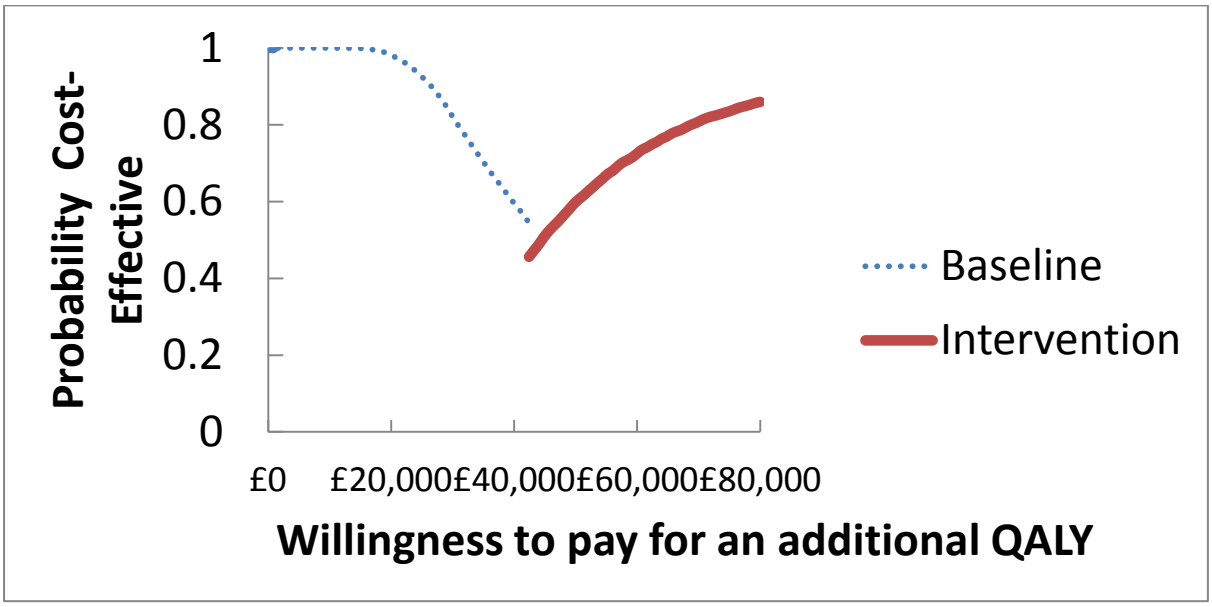
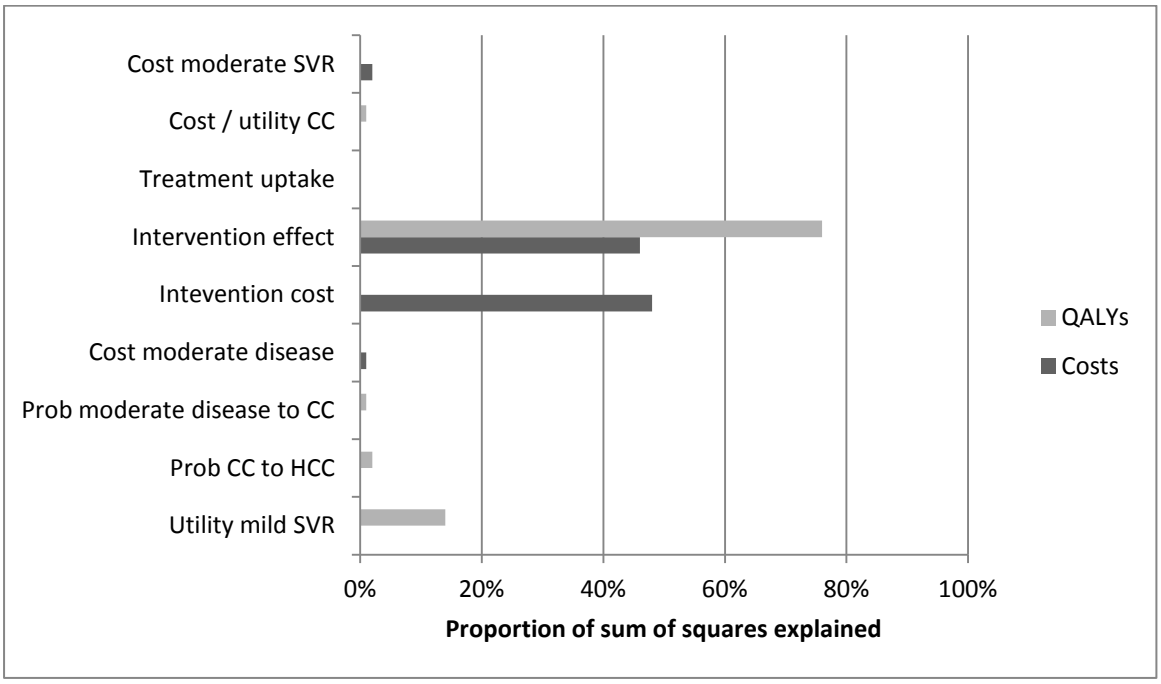
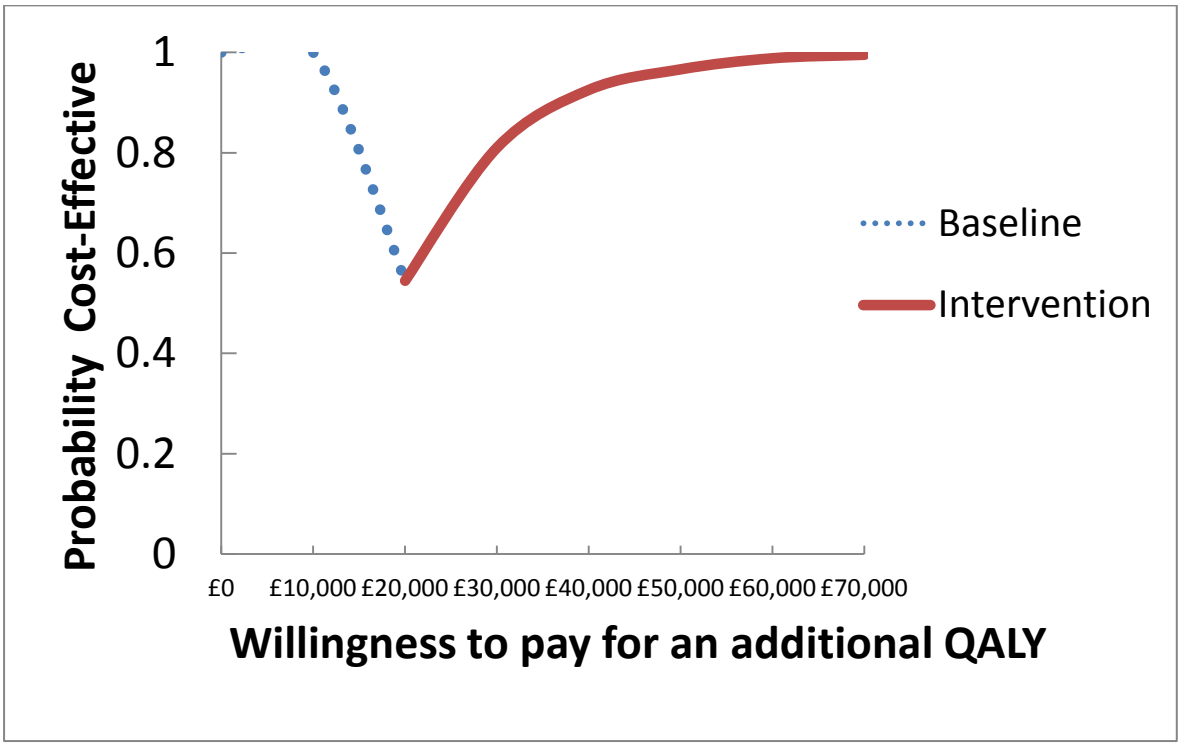


Figure 6: HCV model analysis of covariance (ANCOVA) results for incremental costs and QALYs assuming a 2% prevalence level



CC, compenstated cirrhosis; HCC, Hepatocelluar carcinoma; SVR, sustained virological response

Figure 7: Cost-effectiveness acceptability frontier for the HBV model for a 2% prevalence



13 References

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