Assessing the cost-effectiveness of interventions aimed at promoting and offering hepatitis C testing to injecting drug users: An economic modelling report

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Abbreviations hepatitis C virus (HCV), hepatitis B virus (HBV), injecting drug users (IDUs), quality adjusted life-year (QALY), dried blood spot (DBS), sustained viral response (SVR), incremental cost-effectiveness ratio (ICER), analysis of covariance (ANCOVA), antibody (Ab), ribonucleic acid (RNA), hepatocellular carcinoma (HCC), enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), general practitioner (GP), Health Protection Agency (HPA), Unlinked Anonymous (UA), peginterferon-alfa (PegIFN), ribavirin (RBV), United Kingdom (UK), British Pounds (GBP), National Health Service (NHS), National Institute for Clinical Excellence (NICE), Liverpool John Moores University (LJMU), Hospital and Community Health Services (HCHS)

Executive Summary

Background

This report was commissioned by the National Institute for Clinical Excellence (NICE) public health programme, which forms one part of an economic evaluation of interventions to promote and offer HCV and hepatitis B virus (HBV) testing to high risk groups. The aim of this report was to describe the results of cost-effectiveness analyses of interventions to promote and offer hepatitis C virus (HCV) testing to injecting drug users (IDUs). An accompanying report examines interventions to promote HCV and HBV testing among ethnic migrants[4]. These interventions, if effective, should lead to an increase in testing among the risk groups examined.

The starting point for this evaluation was the associated qualitative review[5], mapping[6], effectiveness and cost-effectiveness[7] reports completed by researchers at the Centre for Public Health, Liverpool John Moores University (LJMU). The mapping report sought to determine the current interventions taking place in England, whilst the qualitative, effectiveness and cost-effectiveness reports consisted of systematic reviews of the literature. The following questions were considered in the reports:

1. Which interventions are effective and cost effective in getting people from high risk groups to use services that currently (or potentially could) offer hepatitis testing?

2. What prevents people in high-risk groups from having a hepatitis B and hepatitis C test – and what factors increase the likelihood that they will seek and accept a test?

3. Which interventions are cost-effective at overcoming the barriers to hepatitis testing faced by high-risk groups and professionals?

4. How can practitioners ensure people who have tested positive continue to seek support from the appropriate services?

Setting the objectives

These questions were used as terms of reference for the cost-effectiveness analysis. However, as the questions were not focused on specific interventions, part of the analysis included determining which interventions to evaluate. This decision was taken after consideration of the evidence presented in the LJMU reports, and in conjunction with the PDG. The decision problems were determined by considering whether the interventions would represent useful additions to current UK policies, and whether suitable evidence on effectiveness was available. As current and former injecting drug users were deemed a high risk group for hepatitis C infection, this economic evaluation focused on interventions to target this risk group in particular.

Intervention decision problem 1: Is introducing dried blood spot testing in specialist addiction services, as described in Hickman et al.[1] and Craine et al.[2], cost-effective at increasing HCV testing amongst IDUs, compared with not offering this sampling method?

Intervention decision problem 2: Is introducing dried blood spot testing in prisons, as described in Hickman et al.[1] and Craine et al.[2], cost-effective at increasing HCV testing amongst IDUs and ex-IDUs, compared with not offering this sampling method?

Intervention decision problem 3: Is GP education and paid-testing of former IDUs in the age range of 30-54, as described in Cullen et al.[3], cost-effective at increasing HCV testing amongst former IDUs, compared with no intervention?

Intervention decision problem 1: The cluster randomized controlled trial by Hickman *et al*.[1] was used to assess whether introducing dried blood spot (DBS) testing in specialist addiction services could increase HCV testing. The intervention was compared to not offering DBS testing (most provide venepuncture sampling). The primary outcome was the proportional difference in the number of individuals tested for HCV in the 6 months after the intervention at the intervention addiction centres as compared to the paired addiction centres where no intervention took place (and DBS was not offered).

Intervention decision problem 2. The cluster randomised controlled trial by Hickman et al.[1] was used to assess whether introducing dried blood spot (DBS) testing in prisons services could increase HCV testing. The intervention was compared to not offering DBS testing. The primary outcome was the proportional difference in number of individuals tested for HCV in the 6 months after the intervention at the intervention prisons as compared to the numbers tested at the paired prisons where no intervention took place (and DBS was not offered).

Intervention decision problem 3. The non-randomized controlled trial by Cullen et al.[3] assessed whether providing general practitioner (GP) education and paid-testing of former IDUs aged 30-54 could increase HCV testing. The primary outcomes were the proportional difference in the numbers tested and case yield in the intervention GP practices as compared to paired GP practices with no intervention.

Methods

A previously developed[8 9] dynamic, deterministic compartmental model of HCV transmission, diagnosis, antiviral treatment, and disease progression among current and former IDUs was extended. In order to properly model incarceration (and fit to available prison data), the model was modified to include never-IDUs, and also expanded to

include never-in-prison, in prison, and formerly in prison compartments for all three groups. For IDUs, the model was modified to include flow in and out of addiction services (when not in prison). In this way, we aimed to realistically capture the dynamic contact with different testing services. The model states were divided into 7 age compartments so that interventions targeting particular ages could be examined and to allow age specific utilities and death rates.

Data used to parameterise the model was obtained from published literature, Health Protection Agency (HPA) sentinel surveillance of hepatitis testing, HPA Unlinked Anonymous Monitoring Survey of People Who Inject Drugs, IDU survey data collected from several UK sites[10], and personal communication with experts. Because of the uncertainty in many parameters, a fitting algorithm was used to obtain multiple fits of the model to incarceration data and baseline HCV prevalence among IDU with independent multivariately sampled epidemiological parameters. The model was then used to estimate the impact of interventions to increase testing on HCV treatment and transmission.

The analysis was performed from a UK National Health Service (NHS) cost perspective. Health outcomes were expressed in terms of quality-adjusted life-years (QALYs). Future costs and health outcomes were discounted at 3.5% per annum in the baseline analysis, and a time horizon of 100 years was used. The model was fitted to an average UK setting with average HCV chronic prevalence and genotype distribution among IDUs.

Cost-effectiveness evidence summary

1. Question 1: Which interventions are effective and cost effective in getting people from high risk groups to use services that currently (or potentially could) offer hepatitis testing?

Results from the decision problem 1 indicated that interventions to introduce dried blood spot testing in specialist addiction services were likely to be cost-effective (with an incremental cost-effectiveness ratio (ICER) estimated to be £14,600 per QALY gained), despite low estimated treatment and referral rates for current IDUs. There was considerable uncertainty surrounding this estimate, due to uncertainty in intervention effect and treatment rates of current IDUs. Hence, further research should focus on collecting information to reduce the uncertainty surrounding these parameters. Increasing referral and treatment for current IDUs served to both reduce HCV prevalence among IDU and increase the cost-effectiveness of this intervention. Additionally, ensuring continuity of care (treatment and referral) for injectors entering prison increased the cost-effectiveness of improving testing and care outside prison.

Results from decision problem 2 suggested that introducing dried blood spot testing in prisons was unlikely to be cost-effective (with an estimated ICER of £59,400 per QALY gained when treatment was not continued when a person entered or left prison). However, if continuity of treatment and referral could be ensured when individuals move in/out/between prisons, the situation changes. If at least 40% of continuity of care was maintained, introducing DBS was likely to be a cost-effective intervention (with an estimated ICER of £20,000 per QALY gained). Insufficient evidence exists surrounding continuity rates, as well as treatment completion, sustained viral response (SVR), and treatment initiation rates for those diagnosed in prisons, and future research should focus on collecting these data as a priority. Furthermore, considerable uncertainty surrounded the intervention

impact, and additional studies determining how introducing DBS testing in prisons alters both testing rates and yield would help inform this decision.

2. Question 2: What prevents people in high-risk groups from having a hepatitis B and hepatitis C test – and what factors increase the likelihood that they will seek and accept a test?

This question lies outside of the scope of the economic evaluation, and was covered by the LJMU reports[5-7].

3. Question 3: Which interventions are cost-effective at overcoming the barriers to hepatitis testing faced by high-risk groups and professionals?

Results from decision problem 3 indicated that GP education and testing of former IDUs in the age range 30-54 with GP remuneration was likely to be cost-effective (with an estimated ICER of £13,900 per QALY gained). This type of educational intervention could reduce barriers to offering testing in the GP setting, such as a lack of education on the part of the GP.

The qualitative and mapping reports found that dried blood spot testing (evaluated in decision problems 1 and 2) was associated with increased acceptability among service users than venepuncture[5 6]. As stated above, the economic evaluation indicated that introducing dried blood spot testing in addiction services was likely to be cost-effective, and introducing it in prisons was only cost-effective if at least 40% continuity of treatment/referral could be ensured.

4. Question 4: How can practitioners ensure people who have tested positive continue to seek support from the appropriate services?

This question lies outside of the scope of the economic evaluation, and was covered by the LJMU reports[5-7].

Summary

Injecting drug users are at high risk for HCV infection, and interventions to increase diagnoses in this risk group should target both current and former IDUs. The introduction of dried blood spot testing is more acceptable to service users, is associated with increased testing, and likely to be cost-effective in specialist addiction services. Ensuring continuity of care and referral to/from/between prison will increase the cost-effectiveness of all testing interventions, and is key to ensuring any prison intervention is cost-effective. Introducing dried blood spots in prison will only be cost-effective if at least 40% of those in treatment or referral remain in care on entry or exit from prison. GP education and paid targeted case finding of ex-IDUs between 30 and 54 years old is likely to be cost-effective, and even more cost-effective if current IDUs are also inadvertently tested as part of the strategy (as it is possible those classified as 'former' IDUs by their GP may still be injecting, or could relapse in the future). Considerable uncertainty surrounds continuity of treatment/care in the prison setting, current IDU treatment rates, and intervention effect; more data should be collected on these aspects.

1 Introduction and Objectives

The aim of this report was to undertake economic analyses of interventions to promote and offer HCV testing among injecting drug users (IDUs), with a view to increasing testing and antiviral treatment, subsequently reducing the burden of disease, liver-related death, and transmission of HCV (if treatment is provided to those with a risk of transmitting to others). The analysis presented was developed alongside the qualitative[5], mapping[6], effectiveness and cost-effectiveness[7] reports produced by Liverpool John Moores University (LJMU), as well as the economic evaluation on promoting HCV and HBV testing among ethnic migrants by Miners et al.[4], and should be viewed as a complement to those documents.

Four broad questions were included in the scope for the literature review and economic evaluation, as set out by NICE and reported in the effectiveness report:

1. Which interventions are effective and cost effective in getting people from high risk groups to use services that currently (or potentially could) offer hepatitis testing?

2. What prevents people in high-risk groups from having a hepatitis B and hepatitis C test – and what factors increase the likelihood that they will seek and accept a test?

3. Which interventions and cost-effective at overcoming the barriers to hepatitis testing faced by high-risk groups and professionals?

4. How can practitioners ensure people who have tested positive continue to seek support from the appropriate services?

1.1 Determining the relevant HCV and IDU-related testing interventions to be evaluated

The LJMU mapping survey[6] highlighted several areas of interest surrounding HCV testing among IDUs, in particular provision of dried blood spot testing, increasing testing in prisons, introducing testing in pharmacies, and educational interventions. The effectiveness report[7] found a range of studies examining interventions aimed at raising awareness or engaging with IDUs at risk of HCV infection, such as offering dried blood spot (DBS) testing in drugs services and prisons, case-finding and education in primary care, integration of testing and treatment in community settings, and a variety of interventions to increase knowledge such as peer outreach worker education, national awareness campaigns, and GP educational sessions. The cost-effectiveness report[7] found moderate evidence that case finding for hepatitis C may be cost-effective in settings such as drugs services and general practice, but the report noted that 'all studies were hampered by a lack of robust evidence for the effectiveness of screening and treatment approaches'. In particular, it was noted that more research was needed to establish the cost-effectiveness of prison interventions.

Unfortunately, few of the effectiveness studies reported data which could be used to model an intervention impact on testing rates (the focus of our economic evaluation), as many reported changes in knowledge or treatment rates only. Furthermore, many were low quality studies and/or from other countries which may not be applicable to the UK. Therefore, the decision on which interventions to model was made from a combination of assessment of study quality and UK applicability (determined by the effectiveness review), determination of themes of current interest in the UK (determined by the qualitative and mapping reviews), and in consultation with the PDG. A list of the

candidate studies and reasons for inclusion/exclusion can be found in **Appendix 1**.

1.2 Identified decision problems

Based on the best available data and the questions 1 and 3 in the scope document (relating to cost-effectiveness), and in consultation with the NICE PDG, the following three decision problems were identified:

Decision problem 1: Is introducing dried blood spot testing in addiction services, as described in Hickman et al.[1] and Craine et al.[3], cost-effective at increasing HCV testing amongst IDUs, compared with not offering this sampling method?

Decision problem 2: Is introducing dried blood spot testing in prisons, as described in Hickman et al.[1] and Craine et al.[2], cost-effective at increasing HCV testing amongst IDUs, compared with not offering this sampling method?

Decision problem 3: Is GP education and paid-testing of former IDUs in the age range of 30-54, as described in Cullen et al.[3], cost-effective at increasing HCV testing amongst former IDUs, compared with no intervention?

Decision problems 1 and 2 attempted to address question 1 in the scope (increased access of services), whereas all three decision problems addressed issues surrounding barriers to testing faced by high risk groups and professionals (question 3).

2 Methods

2.1 Summary of the cost-effectiveness evaluation process

Once the three interventions to increase HCV testing amongst current and former IDU (DBS in specialist addiction services, DBS in prison, and GP education and paid-testing for former IDU) had been identified, a multi-step process of parameter estimation, model building, model fitting, model simulation, incremental cost-effectiveness calculation, and uncertainty analysis was performed.

First, the effectiveness and cost-effectiveness evidence provided by the LJMU literature review[7] was reviewed, and relevant information was extracted for the specific decision problems. Where important model parameters (such as epidemiological or incarceration parameters) could not be found in the provided literature, a wider search was performed. To determine the intervention effect on increased testing, a meta-analysis of the primary data from the intervention studies was performed.

Second, a previously developed model of HCV transmission, disease progression, and treatment among injecting drug users[8 9] was modified to include HCV testing, 7 age groups, and incarceration dynamics. The model tracked transitions between populations of non-IDUs, current IDUs, and former IDUs, and also flows in and out of prison. From hereafter, any reference to 'IDUs' will mean current IDUs (unless the prefix 'former', 'ex', or 'non' is noted).

Third, whenever possible, parameters that had to be determined through fitting processes were obtained using simplified model structures to reduce computation time and also to verify the full model projections. A simplified prison model (neglecting HCV transmission) was used to determine age-specific incarceration and re-incarceration

rates and the injecting initiation rate by fitting to incarceration data (for IDUs and the general population), as well as data on the general population prevalence of current injecting drug use. Similarly, simplified models were used to determine the recruitment rate onto addiction services (fit to estimates of the proportion of IDUs in contact with addiction services) and the annual testing rate (fit to the proportion IDUs diagnosed[11]). Using the full model, the infection rate was fitted to estimates of HCV prevalence among IDUs[12] and rate of entry of never-IDUs in the youngest age group was fitted to a total population size with 1000 current IDUs.

Fourth, 1000 parameter sets were randomly and independently sampled multivariately from distributions, and the model was run with each baseline parameter set (but with no HCV testing) until steady state. We utilised the steady-state numbers of people in each disease state along with estimates of the proportions of IDUs and ex-IDUs currently diagnosed in order to determine the initial conditions of the model. These initial conditions were used with overall population testing rates (estimated from data on proportion IDUs diagnosed[11]) and distribution of tests among IDUs (HPA 2010 data, Mary Ramsay and Sarah Collins, *personal communication*) to calculate the setting-specific testing rates based on population size in each setting.

Fifth, the model was run for the baseline and intervention scenarios using the same 1000 parameter sets, producing matched runs. The interventions were modelled as permanent with recurring costs. The output of these simulations is the number of people in each health state/compartment per time step.

Sixth, costs and utilities were attached to each simulation through the cost and utilities associated with each compartment or health state, along with the costs associated with diagnosis and intervention.

Expected discounted costs and discounted QALYs were reported for each of the strategies and the mean incremental cost-effectiveness ratio (ICER) reported.

Seventh, uncertainty and sensitivity analyses were undertaken on the projections. An analysis of covariance (ANCOVA) was performed on the incremental costs and incremental QALYs to determine which parameter uncertainty contributed most to the variability in incremental outcomes. Finally, a univariate sensitivity analysis was performed on various parameter and model structure assumptions.

The base case analysis was performed from a UK National Health Service (NHS) cost perspective. Societal costs (such as crime associated with injecting drug use) were not considered. All costs were reported in 2011 UK GBP (£), and inflated to 2011 prices where necessary using the Hospital and Community Health Services (HCHS) pay and prices index[13]. All health utilities were reported in quality-adjusted life-years (QALYs). Future costs and benefits were discounted at 3.5% per annum, over a time horizon of 100 years.

2.2 Model description

A model of injecting drug use and HCV transmission and diagnosis amongst IDUs was developed, to project the impact of interventions to increase HCV testing of IDUs. The HCV transmission, antiviral treatment, and disease progression model was based on a model previously published by the authors[8]. This model assumes a proportion of acutely infected IDUs progress to chronic infection, with the remainder resolving their acute infection after a number of months and developing an antibody (Ab) response, thus becoming Ab+/RNA-. Those that develop chronic infection (Ab+/RNA+) remain infected and, unless successfully treated, progress through the various HCV disease stages (mild, moderate, compensated cirrhosis, decompensated

cirrhosis, hepatocellular carcinoma (HCC), liver transplant, and post transplant). Death occurs from all stages, but elevated mortality rates were used from the decompensated cirrhosis, HCC, liver transplant, and post-transplant stages. If treated, infected IDUs can achieve sustained viral response (SVR) whereby they are cured and are not at risk of progressing to a more advanced disease state, but remain at their current stage of liver progression (mild, moderate, or compensated cirrhosis), and are susceptible to reinfection. If reinfected after achieving SVR, the IDU re-enters the infected compartment of their associated HCV disease stage. If an IDU fails treatment (nonSVR), they remain infected and can progress to more severe disease stages. Successfully treated IDUs can be reinfected and retreated, but those who do not achieve SVR are ineligible for retreatment. Current injectors are at risk of infection, but after permanent cessation of injecting do not have any infection risk. For simplicity, the model does not assume any behavioural heterogeneity among the IDU population (such as high/low risk) as preliminary modelling indicated introducing heterogeneity in risk does not have an undue influence on treatment effectiveness as long as individuals circulate between high risk and intervention states[14].

For this analysis, the model was adapted in the following ways. First, the model compartments were subdivided to allow for a distinction between naïve uninfected (Ab-/RNA-) or spontaneously cleared individuals (Ab+/RNA-), as well as the following diagnosis stages for chronic infection: undiagnosed, diagnosed but lost to follow-up and not in referral, diagnosed and in the first 2 years of referral, and diagnosed and in referral after 2 years. For former IDUs, an additional compartment was added to represent those who were uninfected and tested (hence who would not be re-tested as they do not have a continuing infection risk). A model schematic for the HCV disease progression, testing, and treatment stages can be found in **figure 1**.

In order to appropriately model incarceration, the model structure was replicated to track the flow of IDUs and ex-IDUs between never incarcerated, currently incarcerated, and formerly incarcerated states. In addition, compartments for never-IDUs were added (never incarcerated, currently incarcerated, formerly incarcerated) in order to fit incarceration and reincarceration rates to general population data. A schematic of the incarceration flow can be found in **figure 2**. In particular, it was necessary to model separate compartments for never incarcerated and formerly incarcerated because the reincarceration rates are higher than primary incarceration rates. This model structure was based on previously published mathematical models of IDU incarceration[15 16], and it was assumed that incarceration and re-incarceration rates of ex-IDUs were equal to that of never-IDUs. We assumed that while in prison, IDUs only inject or share with other prisoners, and thus can only acquire HCV from other prisoners.

Importantly, there is considerable uncertainty surrounding continuity of care to, from, and between prisons. Many experts described substantial difficulty in ensuring patients remain in treatment or referral pathways, due to prison transfers or release (Peter Bramley, Eamonn O'Moore, Iain Brew, *personal communication*). Indeed, no data exist as to the proportion of prisoners who successfully complete treatment (either within the prison or after release). Due to the current difficulty in ensuring continuity of HCV treatment and care of IDUs entering/leaving prison, we conservatively assumed that those who are in treatment or referral become lost to follow-up upon entering or leaving prison for the baseline scenario. Those lost to follow-up can subsequently be re-tested and re-treated at a future date. We relaxed this assumption in the sensitivity analysis.

Additionally, for current IDUs who are not in prison (never imprisoned and formerly imprisoned) we further stratified the movement between those in contact with addiction services and those not in contact with addiction services **(figure 2)**. We assumed that only those in contact with addiction services could be tested in addiction services. We also assumed that on release from prison, IDUs were not immediately in contact with addiction services.

Finally, the model was split into 7 age compartments ([15-19],[20-24],[25-29],[30-54],[55-64],[65-74],[75+]). We assumed that an individual enters the model at age 15-19 as a never-IDU. In total, the model consists of 222 states and 7 age stratifications, leading to 222 x 7=1,554 compartments.

In the model, testing of IDUs and ex-IDUs occurs in GP settings (for current or ex-IDUs who are not in prison), prison (for incarcerated current or ex-IDUs), in addiction services (for current IDUs in contact with addiction services). Additionally, a background rate of testing occurs for all current and ex-IDUs who are not imprisoned, such as would occur through hospital or other settings. The model incorporated the possible effect of different interventions by alterations in these setting-specific testing rates. Additionally, the GP education intervention was found to alter the HCV yield (proportion of tests returning antibody positive). HCV yield varies substantially between settings (higher in prisons and addiction services who test more of the at-risk population), and was parameterised based on HPA 2010 sentinel surveillance data (Mary Ramsay and Sarah Collins, *personal communication*).

Transmission

All current injectors can potentially acquire and transmit HCV in the dynamic model. We assumed that those who are imprisoned only

inject with other prisoners, and hence sharing only occurs within the prison. Outside of the prison setting, we did not assume any difference in sharing behaviour between those who are never imprisoned or previously imprisoned, and these individuals share between each other. An individual's risk of acquiring HCV is related to the infection rate and the HCV prevalence in a given sharing setting (such as in or out of prison). Therefore, as the prevalence goes down (with HCV testing and treatment of current IDU), an individual's risk of acquiring HCV also decreases. We assumed that ex-IDU and never-IDU are not at risk of acquiring or transmitting HCV. Finally, due to the reduced viral loads during antiviral treatment (even for those who ultimately relapse and do not achieve SVR), our model is in line with previous HCV transmission models which assume that IDUs are not infectious during antiviral treatment[9 17 18].

2.3 Parameters

HCV disease progression parameters

Transition rates between the HCV disease stages (mild, moderate, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post transplant) were taken from previous UK hepatitis C health technology assessments[19-21] and are shown in **table 1**. Although previous estimates were not IDU specific, a published meta-analysis indicates the relative risk of progressing to cirrhosis was not statistically different between those who did and did not have IDU as a risk factor[22]. All transition probabilities were converted to instantaneous rates for use in the differential equation model.

Health state utilities

Baseline (uninfected) utility values for non-IDUs were taken from the UK population norms derived from EQ-5D[23], which included a disutility

with age (**table 2**). We assumed the utility values for ex-IDUs are equal to those of non-IDUs, in line with a previous publication[24]. Health state utility values for the HCV disease stages (mild, moderate, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post transplant) and treatment stages (on treatment, SVR, non-SVR) were taken from previous UK hepatitis C health technology assessments[19-21] and used for the ex-IDU population (**table 2**).

Some cross-sectional studies indicate there may be a disutility associated with HCV diagnosis among injecting drug users[25]. However, the weakness of a cross-sectional design to properly study this question, along with potential confounding, limits the usefulness of these data. Therefore, at baseline we assumed no disutility on diagnosis (diagnosed and undiagnosed HCV utility values are equal). However, we explored the implications of a disutility in the sensitivity analysis.

For the current IDU population, data from a large cross-sectional study of injectors in Scotland was used to estimate the uninfected baseline utility value for the 15-19 age group (Scott McDonald and Sharon Hutchinson, academic confidential). The same disutility by age for IDUs was assumed as for the non- or ex-IDU population.

HCV health state utility values for current IDUs are unknown. Due to the large uncertainty surrounding the estimates for the uninfected current IDU utility values, some of the simulations sampled a lower uninfected utility for current IDUs than for the mild HCV state for ex-IDUs. Therefore, it was not deemed reasonable to use the same HCV utility values for current and ex-IDUs. To circumvent this problem, all IDU HCV utility values were reduced by a fixed proportion, which was

calculated by dividing the uninfected IDU utility value for age 19-25 by the uninfected ex-IDU utility value for the same age range.

Health state costs

Health care costs for the HCV disease stages (mild, moderate, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post transplant) as well as antiviral treatment delivery and monitoring costs (excluding the drug costs) were taken from previous UK hepatitis C health technology assessments[19 20] and inflated to 2011 values using the HCHS pay and prices index[13] (**tables 3 and 4)**. Antiviral drug costs for pegylated interferon-alfa and ribavirin were taken from the British National Formulary[26]. In line with previous economic evaluations, we assumed that those in the mild undiagnosed, moderate undiagnosed, and compensated cirrhosis undiagnosed states do not incur any HCV related costs to the health system[16]. This was a conservative assumption as it reflects the fact that diagnosis may be associated with increased health care costs due to disease monitoring, with no associated utility benefit (if untreated).

Testing rates

The HPA collects comprehensive yearly data of HCV testing in their sentinel surveillance, which includes a question on IDU as a risk factor. However, only a very small proportion of tests are coded with IDU status as a risk factor, and even among these the current or former IDU status is not provided. Therefore, we were unable to use the HPA data to estimate the yearly testing rates of current and ex-IDUs.

To circumvent this problem, we fitted an overall current IDU annual testing rate to the estimated proportion of current IDUs who are diagnosed (approximately 50%[11]). This annual testing rate ensured the

proportion of diagnosed current IDU remained stable (at equilibrium) without any intervention.

As testing of IDUs takes place in different locations (GP, prison, addiction services, other settings) and the proportion of IDUs in contact with these settings varies, it was necessary to calculate setting-specific testing rates from the overall testing rate. This was done using three pieces of information: 1) the overall testing rate, 2) the fraction of tests attributable to each location, and 3) the proportion of the population found in each location. We obtained the fraction of tests attributable to each location from the HPA sentinel surveillance of hepatitis testing data, using the tests coded with an IDU risk only (**table 5**, Mary Ramsay and Sara Collins, *personal communication*). Although these data underestimate the number of tests given to IDUs, it is reasonable to assume that the HPA distribution between sites would be representative of the testing administered to IDUs as a whole. Finally, we ran the model to obtain steady state values of the proportion of population found in each testing location based on the input parameters (some of which were previously fitted, such as the proportion of IDUs in contact with addiction services and in prison). These three components were then combined to obtain setting specific testing rates for each parameter set simulation. The setting specific testing rates for IDUs and ex-IDUs were assumed equal, with the exception that the model assumes ex-IDUs are not in contact with addiction services, so no testing occurs from this scenario for this group.

We assumed that all tests which are determined to be antibody positive (Ab+) using an enzyme-linked immunosorbent assay (ELISA) are sent for a polymerase chain reaction (PCR) test for ribonucleic acid (RNA) to determine the presence or absence of chronic disease. As in Miners et al.[4], we assumed all diagnostic tests are 100% accurate due

to the high specificity and sensitivity of the tests (98-100% sensitivity and 100% specificity using dried blood spot or venepuncture[27 28]) as well as the fact that those who receive an initial positive test will receive a more detailed set of tests before treatment is initiated.

Testing costs

Time associated with HCV testing at baseline was estimated from previous economic evaluations [1 minute assessment, 25 minutes pre-test and sampling, 30 minutes post-test[29]], and adjusted to 2011 £ by using the 2011 Unit Costs of Health and Social Care estimates for consultant and nurse costs per patient contact hour[13]. Estimates for the costs of ELISA and PCR RNA tests were used from previous economic evaluations [29] and inflated using the HCHS pay and prices index[13]. The baseline testing costs can be found in **table 6.**

In the simulations, costs associated with testing were calculated as follows. The numbers tested in each setting were calculated, and associated with setting specific test costs as in **table 6.** Two additional costs were added: costs associated with RNA testing (only added for those tests which are antibody positive), and costs associated with testing non-IDUs. The number of non-IDUs who would need to be tested in order to test one IDU was calculated from the setting-specific test yield (proportion of tests antibody-positive). In settings with a high yield (closer to the HCV prevalence among IDUs), the high yield indicates that fewer non-IDUs are tested (for example, in addiction services and prison). In settings with a low yield, this indicates that more non-IDUs are tested for every IDU. Hence, the yield in a given setting, along with the baseline prevalence in the setting, was used to determine the number of non-IDU tests required for every IDU test. The costs of the additional non-IDU tests were then added to the test costs for each setting.

Referral and treatment transition rates

The referral rate from testing service to secondary care was estimated from a UK study[30] and can be found in **table 5**. Those who were not referred or who did not attend their referral appointments were considered 'lost to follow-up' and had to be re-tested in order to be re-referred and treated. Although the study found different referral rates to secondary care from the varying services (such as between addiction services and GP) in the study, it was more appropriate to use a single referral rate (35%) from all sources as referral practices have changed in recent years, with addiction services referring directly to secondary care instead of to GP (Will Irving, *personal communication*).

The model includes two referral compartments, 'early' referral (within 2 years of diagnosis) and 'late' referral (over 2 years from diagnosis). This stratification was made to properly account for the fact that the majority of ex- or non-IDUs are treated within the first two years, but that people do obtain treatment at later stages (Graham Foster, *personal communication*). This differs from previous models which assume a specific proportion (50%) of people are treated on diagnosis, and the remainder never engage with treatment[24]. We assumed 50% of ex-IDUs who are diagnosed and in referral are treated within the first 2 years[30-32] but that of the remainder, 10% of those not previously treated per year initiate treatment. The treatment rates for current-IDUs are unknown, but it is estimated to be extremely low, with less than 1% of the total infected population treated per year (Graham Foster, *personal communication*). Hence, we estimated that of those who attend referral (35%), between 1% and 10% (mean 5.5%) initiate treatment within the first 2 years, and of the remainder 1% of those not previously treated are treated every year thereafter. Within the prison system treatment rates are lower than in the community[30], and an internal audit at HMP Leeds in 2009 found 24% of those diagnosed were treated (Iain Brew, *personal communication*). Therefore we

estimated that treatment initiation rates are halved in prison as compared to out of prison rates.

Sustained viral response (SVR) rates were sampled by genotype, with mean values in the mild/moderate HCV disease stages of 45% for genotype 1 and 80% for genotype 2/3[33]. Patients with compensated cirrhosis exhibit proportional reductions in SVR values by about 45% and 25% for genotypes 1 and 2/3, respectively[34]. Preliminary studies suggest that SVR rates are equal between IDUs and ex/non-IDUs[35], so we assumed this in our base case. All treatment and SVR rates are reported in **table 5**.

Intervention effect

The effect of the intervention was modelled as a proportional change in the rate of testing in each intervention setting (addiction services, prison, or in GPs within the 35-54 age group of ex-IDUs). The effect was determined by comparing the number of tests performed in the 6 months after the intervention compared between the intervention and control sites. For the dried blood spot interventions the data covered 11 paired addiction services and 3 paired prisons[1]. For the GP intervention, the data covered 8 paired GP practices[3]. The overall effect was estimated using a random-effects meta-analysis of the primary intervention data. For the GP intervention, an increase in yield (proportion of tests HCV Ab+) was seen, probably due to the testing of a greater proportion of former IDUs (compared to non-IDUs). This additional impact on yield was similarly estimated using a random-effects meta-analysis and included in the impact estimates. The meta-analysis results can be found in **figures 3-6**.

The results from the meta-analysis (**table 7)** showed that the introduction of dried blood spot testing in addiction services resulted in a 3.61-fold increase in testing (95% confidence interval 2.26-5.77). The

meta-analysis indicated that there was heterogeneity among the intervention sites. Similarly, the introduction of dried blood spot testing among prison services resulted in a 2.63-fold increase in testing in prisons, but the confidence interval was wide (95% CI 0.20-34.88) and heterogeneity as found between sites. Finally, the GP intervention resulted in a 3.4-fold increase in testing rate (95% CI 1.57-7.37), and 2.05-fold increase in testing yield (95% CI 1.14-2.68). Again, the meta-analysis on testing rate in GP settings indicated heterogeneity between sites, though the intervention effect on test yield did not. All these intervention effects were sampled from lognormal distributions (appropriate for ratios) for each parameter set (**table 7**).

Intervention costs

Detailed costs for each intervention were determined from the study methods[1 3] and in consultation with the study authors or participants (Noel Craine and Beth Cullen, *personal communication*). Unit Costs of Health and Social Care[13] estimates for consultant and nurse staff time costs per hour were used (not per patient hour as the interventions involved educational sessions taking place outside of patient hours). The detailed costs can be found in **Tables 8-10.**

Epidemiological and model fitting parameters

As stated in section 2.1, wherever possible a simplified model was used to fit the transition rates between model stages to available data. This provided two benefits: reducing computational time and providing a way to verify the accuracy of the full model predictions by comparing the outputs of the full and simplified models with fitted parameters. For the prison dynamics, the parameters which needed fitting from data were age-specific incarceration and re-incarceration rates for never IDUs, current IDUs, and ex-IDUs, as well as the IDU initiation rate. These rates were determined using a simple age-stratified model of transitions between never, current, and ex-IDUs, and never, currently,

or formerly imprisoned. Hence, HCV transmission was neglected entirely in this model. The parameters were fitted to age-structured data on the proportion of the general population with a custodial sentence[36], proportion of current IDU population previously imprisoned (Unpublished data from the Health Protection Agencies, Unlinked Anonymous Monitoring Survey of People Who Inject Drugs, Vivian Hope and Fortune Ncube, Health Protection Agency, London, personal *communication*), age distribution of current prisoners[37], proportion of prisoners ever IDU (academic confidential) , and a general (not age-structured) estimate of the proportion of the population currently imprisoned[38 39] and the prevalence of current IDUs in the general population[12]. The epidemiological and prison parameters which were sampled for the fitting scenarios can be found in **table 11**, and the parameters to which the model was fitted can be found in **table 12.**

The HCV chronic prevalence among current IDUs was fitted to estimates of IDU antibody prevalence among current IDUs in England (45% [41-49% CI][12]), along with the estimation that about one-quarter of those acutely infected spontaneously clear the disease[40]. Hence, we estimated that about 35% of current IDUs are chronically infected with HCV. We did not fit the prevalence of HCV among former IDUs in the simulations, but both the model and data predict a slightly lower prevalence among ex-IDUs as compared to current IDUs, with the model estimate of 28% chronic prevalence among ex-IDUs falling in line with the upper uncertainty estimate for prevalence (antibody prevalence 30% [25-35% CI]) from the aforementioned study[12].

The proportion of IDUs in contact with addiction services at any given time was difficult to estimate. 92% of IDUs report ever accessing a needle exchange in the HPA Unlinked Anonymous Survey, though the proportion currently accessing services is not asked[41]. However, it is estimated that 50% of IDUs are currently on opiate substitution

therapy[10 42], and we therefore estimated that the same proportion is currently in contact with addiction services. Similarly, the average duration of time in contact with addiction services was estimated from data of average time IDUs are on OST[43].

2.4 Model fitting

All parameters were fitted using nonlinear least-squares methods using the MATLAB solver *lsqnonlin*. The fitting process involved a number of steps as parameters were fitted, wherever possible, to simplified versions of the full model. This allowed for a shorter computation time and also model verification (such that the predictions of the simplified models were compared against the full model to assure no mistakes were made in coding). For each separate fitting process, **table 11** details the models used, input parameters, fitting parameters, and output parameters from each fitting.

For fit #1, the incarceration dynamics and injecting initiation rate were fitted using a simple age-stratified model of imprisonment (never in prison, currently imprisoned, formerly imprisoned) for never, current, and ex-IDUs. This simple model ('Simplified model 1') neglected HCV transmission, testing, and treatment, and a schematic diagram of the simplified model can be found in **figure 7**. Simplified model 1 only required parameter inputs related to injecting duration, current IDU overdose rates, and current IDU incarceration durations. These epidemiological parameter sets were sampled from the range of values of shown in **table 12**, and fitted to the data in **table 13**. Due to the heavy computational burden of fitting the many incarceration parameters, the model was fitted to 45 different combinations of the three input parameters. In the full multivariate sampling used for the evaluation, one of these 45 'epidemic scenarios' was chosen for each of the 1000 runs.

As the prison data varied over several orders of magnitude (for example, the proportion of IDUs previously incarcerated was around 60%, while the proportion of the England population currently imprisoned between the ages of 15-59 is 0.2%), a log-transformation was used in order to minimize relative error in the least-squares regression[44]. Furthermore, the error measure was re-weighted with more weight given to the error from the non-age structured parameters to provide a better fit to those parameters. **Figure 8** provides an example of the model data and fit with the median values chosen for each parameter; all other fits were similar to this. The model fitted well to the parameters, with the notable exception of the proportion of IDUs previously incarcerated in the 15-19 age group, which the model consistently underestimates. This was due to the low proportion of prisoners who admit ever-IDU use in this age group, along with the low general rates of ever incarceration in this age group. It was decided *a posteriori* that this deviation was acceptable given the goodness of the rest of the fit and also because it is unlikely that the data sources are consistent.

For fit #2, a simplified model of incarceration and movement in/out of addiction services was used to determine the rate of recruitment into addiction services was fitted to the proportion of IDUs in contact with addiction services ('Simplified model #2', as in **figure 2** without HCV disease transmission states).

For fit #3, a simple model of HCV transmission and testing among IDUs was used to fit the overall IDU testing rate to the proportion of IDU who report being diagnosed for HCV. This model, 'Simplified model #3' is shown in **figure 9**, including only uninfected, chronically infected undiagnosed, and chronically infected diagnosed compartments, and neglected incarceration or addiction services dynamics.

At this point, 1000 parameter sets were sampled from the full range of disease progression, intervention, cost, and utility parameters (**Tables 1-10**). For fit #4, each of the 1000 parameter sets for the full analysis were then input into the full HCV transmission and testing model (without ex-IDU compartments) in order to fit the infection rate to the HCV chronic prevalence among IDUs. Finally, in fit #5, using the full model, the inflow rate of never-IDUs in the youngest age group [15-19] was fitted to the total population size (we use a current IDU population of 1000 for the analysis). Hence, the results presented are not for the entire population of England – instead the model tracks 1000 IDUs and the resulting number of never and former-IDUs estimated for this number of current IDUs (based on the model estimates of current IDU prevalence and sampled injecting duration/overdose parameters). This allows for the economic analysis of the total or incremental cost data at a local level, which could be scaled-up to national-level estimates. For this fitting process, no treatment of current IDUs at baseline was assumed because treatment of IDUs is currently extremely low and no reliable estimates were available. Using the full model to fit HCV chronic prevalence and total population size was necessary because the rates of disease progression/death related to HCV would impact both parameters.

All the above mentioned fitted parameter sets were then used as inputs for the full model. The full model outputs at steady-state were verified against the outputs of the simplified model to ensure the validity of the full model and ensure goodness of fit.

2.5 Initial conditions

As recent testing initiatives have mainly targeted current IDUs (and it is estimated that the proportion of diagnosed current IDUs is higher than diagnosed ex-IDUs (50% and 30%, respectively)) it was not realistic to

initialize the model with steady state population values of diagnosed/undiagnosed. Hence, the full model without any testing and treatment was run, and the number of people in all compartments was stored after the system reached steady-state. This vector of initial condition values was then edited to account for the current proportion of diagnoses estimated in the IDU and ex-IDU populations. As it is unknown what proportion of previously diagnosed IDUs are currently in referral for treatment, we made the conservative assumption that all previously-diagnosed are lost-to-follow-up at the beginning of the model if they have not been treated, and hence need retesting in order to enter the referral and treatment pathway. We assume that none of the current IDU population has been treated at baseline, and sample the proportion of ex-IDUs previously treated from the range found in **table 5**. Ex-IDUs who have been treated are not eligible for retesting and retreatment, and hence were removed from the model as they did not change the cost-effectiveness of testing strategies.

Hence, half of the chronically infected IDU population were placed in the ‘diagnosed and lost-to-follow-up’ compartment of their relative disease state. For the ex-IDU population, a proportion will have been treated, and of the remaining untreated proportion, 30% were considered diagnosed and were placed in the ‘diagnosed and lost to follow-up’ compartment. As a result of this initialisation procedure, the proportion of diagnosed ex-IDUs was not at steady state at the start of the simulation. As stated earlier, this was deemed appropriate, as recent testing initiatives have mainly targeted current IDUs, and therefore it is assumed that diagnosis rates among former IDUs are low. However, over time those who are IDUs will become former IDUs, and therefore the proportion of diagnosed former IDUs will increase naturally without an additional intervention.

2.6 Baseline and intervention impact analysis

For each parameter set, the model was run with and without the intervention ('intervention' and 'baseline', respectively). The equations were solved in MATLAB using the standard nonstiff solver for ordinary differential equations, *ode45*, a variable time-step solver based on the Runge-Kutta method. Costs and health utilities (measured in quality-adjusted life years, QALYs) were attached to each model compartment. In addition, costs related to baseline or intervention testing were added to the state costs.

Costs and QALYs were discounted 3.5% per annum. Using the results from the 1000 runs, mean discounted costs and mean discounted QALYs for a 100 year time horizon were calculated. From this, the incremental cost-effectiveness ratio (ICER) was calculated between the intervention and baseline scenarios:

For each intervention, incremental costs and incremental QALYs for each run were plotted on a cost-effectiveness plane. Additionally, cost-effectiveness acceptability curves were constructed. In addition to the economic outputs, the HCV IDU chronic prevalence changes with the interventions were recorded.

2.7 Uncertainty analysis

Analysis of covariance (ANCOVA) methods were used to summarize the proportion of the variability in the incremental costs and incremental QALYs associated with a given intervention explained by the uncertainty in the input parameters[45]. In this analysis, an ANCOVA analysis was used to determine the proportion of sum of squares for the incremental costs or QALYs explained by the input parameters. The ANCOVA analysis was performed in MATLAB using the function *anovan.* This analysis assumed a linear relationship between inputs

and outputs, and therefore was only an approximation of a more complex nonlinear relationship.

2.8 Sensitivity analyses

A one-way sensitivity analysis was performed on various model assumptions by changing one parameter and, where necessary, re-running the 1000 parameter sets (both baseline and intervention runs) to determine the resulting impact on the ICER. In this way, we examined the impact of decreasing (50 years) or increasing (200 years) the time horizon. We also examined alternative discounting scenarios such as 3.5% costs/1.5% QALYs, and 0% costs and 0% QALYs.

The baseline analysis did not incorporate variation in the baseline distribution of testing in the different settings (GP, addiction services, prisons, other). In order to examine how variations in the distribution of testing could impact the results, we examined simulations where the distribution of testing was 50% higher or 50% lower in the particular interventions setting examined. To balance the overall level of testing, we subsequently decrease/increase the level of testing in the other three testing areas, each by an equal amount in order to sum to the total amount added or subtracted from the intervention setting. For example, at baseline, 29.4% of all yearly tests for IDUs are given in addiction services (Health Protection Agency unpublished data, Mary Ramsay and Sarah Collins, *personal communications*). As a sensitivity analysis, we examined the impact of having 14.7% or 44.1% of tests arising in addiction services, with each of the other three areas (GP, prison, other) increasing/decreasing their fraction of tests accordingly.

In all interventions, we examined the impact of doubling the proportion of those referred to specialist care in all settings. Furthermore, for the interventions targeting current IDUs (dried blood spot introduction in

addiction services and prison), an additional sensitivity analysis examined the impact of increasing the proportion of IDUs treated within the first two years from referral to 50% (from a mean value of 5.5% out of prison, and 2.25% within prison). As the evidence surrounding IDU SVR is weak, we also examined the implications of a reduced SVR rates in IDU (by 30%) as compared to ex-IDU, either as a result of lower adherence or completion rates.

Due to the likely introduction of new antiviral treatments for genotype 1 patients such as telaprevir and boceprevir, we examined how the cost-effectiveness changed with the higher sustained viral response rates associated with the new drugs (a proportional increase in SVR of 68% for each genotype[46 47]) but also increased associated costs. The parameters associated with this simulation can be found in **table 14**.

To determine the impact of implementing the interventions in different prevalence scenarios, we refitted the model to a lower (20%) and higher (50%) baseline IDU chronic prevalence by varying the infection rate. In calculating the costs of testing in these scenarios, we assumed the equivalent non-IDU test factor (number of non-IDUs tested for every IDU) as in the baseline 35% chronic prevalence case.

Some weak cross-sectional data indicate that IDUs may experience a disutility associated with HCV diagnosis[25]. However, the magnitude and duration of this disutility is unknown, and it was felt there was insufficient evidence to support the inclusion of this disutility at baseline. Nevertheless, we explored the impact of a disutility by assuming that only those diagnosed with HCV were associated with the health utilities reported for the HCV disease states. Those who were undiagnosed in the mild stage were given the uninfected IDU utility value of their age group. Those who were undiagnosed in the moderate stages were assumed to have the same magnitude disutility

as a progressing (mild to moderate) diagnosed IDU (similar for uninfected compensated cirrhosis)

We explored the impact of the use of a dynamic model by performing simulations where there was no prevention benefit, which was achieved by fixing the force of infection throughout the simulation. Therefore, reductions in prevalence did not have any impact on incidence of infection. This sensitivity analysis was performed on the interventions which target current IDUs, and as such had a dynamic prevention impact (addiction services and prison interventions).

Finally, in all cases we explored a series of sensitivity analyses where we examined the impact of relaxing the assumption that all those in treatment or referral fall-out of care on entry or exit to prison. In these analyses, we varied the proportion of those continuing in treatment or referral on entry or exit from prison from 0% (baseline analysis) to 100%.

3 Results

3.1 Cost-effectiveness of introducing dried blood spot in specialist addiction services

The main cost-effectiveness results are shown in **Table 15**. Introducing dried blood spot testing in specialist addiction services was associated with an estimated ICER of £14,600 per QALY gained in the base case scenario. The intervention incremental costs and incremental QALYs were plotted on the cost-effectiveness plane in **figure 10**. The cost-effectiveness acceptability curve indicated that at £20,000 and £30,000 per QALY gained willingness-to-pay thresholds, the intervention was estimated to be 69% and 93% likely to be cost-effective, respectively (**figure 11**).

The ANCOVA uncertainty analysis (**figure 12**) indicated that uncertainty in the intervention effect contributed to 86% of the variation in incremental costs, and 58% of the variation in incremental QALYs. The remainder of the variation in incremental QALYs was due to uncertainty surrounding antiviral treatment rates (22%) and health utility values (about 17%).

A number of sensitivity analyses (**figure 13, table 16)** were performed to test how robust the results were to structural and parameter changes. Reducing the time horizon to 50 years reduced cost-effectiveness (increased the estimated ICER to £22,900 per QALY gained) as not all prevention benefits were accrued. Conversely, increasing the time horizon to 200 years increased cost-effectiveness slightly (estimated ICER £13,400 per QALY gained). Reducing the discount rates to 3.5% costs and 1.5% QALYs, or 0% costs and QALYs, decreased the estimated ICER to £5,100 and £6,700 per QALY gained, respectively.

We varied the baseline testing rate in addiction services as some tests attributed to GPs in the HPA data may in fact originate from addiction services (Will Irving, personal communication). Increasing the baseline testing rate in addiction services by 50% increased the cost effectiveness (estimated ICER £11,800 per QALY gained). Conversely, halving the baseline testing rate reduced the cost-effectiveness (estimated ICER £23,000 per QALY gained).

Increasing the numbers of current IDU on treatment increased the cost-effectiveness of the intervention. If 50% of IDUs were initiated on treatment within 2 years of referral, the estimated ICER reduced by nearly 2/3 (£4,500 per QALY gained). Similarly, if referral rates were doubled from baseline, the intervention became more cost-effective (estimated ICER £11,300 per QALY gained). If all SVR rates were reduced by 20% for IDUs as compared to ex-IDUs, the intervention became slightly less cost effective with an estimated ICER of £16,700 per QALY gained. The use of new antiviral treatments (telaprevir and boceprevir) for genotype 1 patients did not substantially alter the cost-effectiveness (estimated ICER £14,400 per QALY gained).

Variation in baseline IDU HCV chronic prevalence did not substantially alter the cost-effectiveness ratio. At lower (20%) and higher (50%) baseline HCV chronic prevalences, the incremental cost-effectiveness ratios were slightly higher than in the baseline 35% chronic prevalence scenario (at £16,000 and £15,700 per QALY gained, respectively). This was because at lower prevalence the cost of identifying infected cases was higher, but the prevention impact of treating current IDUs was also greater due to lower risk of reinfection at low prevalences. At high prevalences, the cost of identifying infected cases was lower, but this was balanced by a reduced prevention impact due to the higher rates of reinfection at this prevalence.

If no prevention benefit was modelled (and hence the force of infection was fixed), the incremental cost-effectiveness ratio doubled, to £29,900 per QALY gained.

If a disutility of diagnosis was assumed, the intervention was associated with negative incremental QALYs (due to low treatment rates), and the intervention was dominated (more expensive and with less health benefit). Hence, in this scenario, the baseline scenario was the preferable option.

If we assumed no fall-out of treatment/referral on entry or exit to prison, the cost-effectiveness of the baseline addiction services intervention increased, with the estimated ICER falling to £9,800 per QALY gained (**figure 13, table 16)**.

3.2 Cost-effectiveness of introducing dried blood spot in prison services

The main cost-effectiveness results are shown in **table 15**. Introducing dried blood spot testing in prison services was associated with an estimated ICER of £59,400 per QALY gained in the base case scenario. The intervention incremental costs and incremental QALYs were plotted on the cost-effectiveness plane in **figure 14.** The cost-effectiveness acceptability curve indicated that at £20,000 and £30,000 per QALY gained willingness-to-pay thresholds, the intervention was estimated to be 1% and 21% likely to be cost-effective, respectively (**figure 15**).

The ANCOVA uncertainty analysis (**figure 16, table 17**) indicated that uncertainty in the intervention effect contributed to 96% of the variation in incremental costs, and 87% of the variation in incremental QALYs. The remainder of the variation in incremental QALYs was mainly due

to uncertainty surrounding health utilities (5%), prison/epidemic dynamics (3%).

The results from the sensitivity analyses can be found in **figure 17**. Changing the time horizon to 50 or 200 years did not substantially change the cost-effectiveness, resulting in estimated ICERs of £71,800 or £57,300 per QALY gained, respectively. Reducing the discount rates to 3.5% costs and 1.5% QALYs, or 0% costs and QALYs, decreased the estimated ICER to £38,700 and £24,700 per QALY gained, respectively. Increasing the baseline testing rate in prison services by 50% increased the cost effectiveness slightly (estimated ICER £54,000 per QALY gained). Conversely, halving the baseline testing rate reduced the cost-effectiveness (estimated ICER £76,900 per QALY gained).

Increasing the numbers of current IDUs initiated on treatment increased the cost-effectiveness of the intervention. If 50% of IDU were initiated on treatment within 2 years, the estimated ICER was nearly halved (£30,000 per QALY gained). Similarly, if referral rates were doubled from baseline, the intervention became more cost-effective (estimated ICER £58,800 per QALY gained), although not as much as expected because most treatments were interrupted before completion or initiation due to fall-out. As in the previous addiction services intervention, the use of new antiviral treatments (telaprevir and boceprevir) for genotype 1 patients did not substantially alter the cost-effectiveness (estimated ICER £57,000 per QALY gained).

Variation in baseline IDU HCV chronic prevalence had more of an impact than in the addiction services intervention, with lower (20%) chronic prevalences associated with a substantially higher estimated ICER (£94,400 per QALY gained) and higher (50%) prevalences associated with a lower estimated ICER (£44,900 per QALY gained).

This was because as most treatments were interrupted on release from prison there was very little prevention benefit from the prison intervention. Thus, the ICER was dominated by the costs associated with finding an infected individual, which was more expensive at lower prevalence, and less expensive at higher prevalence. Hence, the model approached more of a 'static' model where very little prevention benefit was seen. This was supported by the sensitivity analysis which assumed no prevention benefit (a static-type model), where the resulting estimated ICER was very close to that predicted by the dynamic model (£61,300 as compared to £59,400 per QALY gained for the dynamic model).

As before, if a disutility of diagnosis was assumed, the intervention was associated with negative incremental QALYs (due to low treatment rates), and the intervention was dominated (more expensive and with less health benefit). Hence, in this scenario, the baseline scenario was the preferable option.

A sensitivity analysis was performed to relax the assumption that there was no continuity of treatment/care when moving in or out of prison (**table 18, figure 18**). Hence, in a set of simulations we varied the proportion of continuity of services from 0% (baseline scenario) to 100%. Increasing the continuity of care (and hence, decreasing the fall-out rate) increased the cost effectiveness, from an estimated ICER of £59,400 per QALY gained with 0% continuity to £10,400 per QALY gained with 100% continuity (no fall-out). With increasing continuity of care, the estimated ICER falls quickly (to £23,700 per QALY gained with 30% continuity). However, the estimated ICER did not fall below £20,000 until 50% continuity of care was ensured (an estimated ICER of £17,300 per QALY gained). With 50% continuity, the intervention was an estimated 69% and 87% likely to be cost-effective at the £20,000 and £30,000 per QALY gained willingness-to-pay thresholds,

respectively. Hence, the model was extremely sensitive to this assumption, and at least 40% continuity of care was necessary to ensure the intervention was cost-effective.

3.3 Cost-effectiveness of GP education and paid targeted testing of former IDU 30-54 years old

The main cost-effectiveness results are shown in **table 15**, with an estimated ICER of £13,900 per QALY gained in the base case scenario. The intervention incremental costs and incremental QALYs were plotted on the cost-effectiveness plane in **figure 19**. The cost-effectiveness acceptability curve indicated that at £20,000 and £30,000 per QALY gained willingness-to-pay thresholds, the intervention was estimated to be 79% and 93% likely to be cost-effective, respectively (**figure 20**).

The ANCOVA uncertainty analysis (**figure 21**) indicated that uncertainty in the intervention testing effect contributed to 47% of the variation in incremental costs, and 69% of the variation in incremental QALYs. Uncertainty in the intervention effect contributed to 30% of the variability in incremental costs, and uncertainty in the total intervention effect (on testing and yield) contributed to over 75% of the variability in incremental costs. The remainder of the variation in incremental costs and QALYs was mainly due to intervention cost (13%) and health utilities (27%), respectively.

The results from the sensitivity analyses can be found in **figure 22** and **table 19**. Changes in time horizon did not substantially alter the results, with time horizons of 50 or 200 years resulting in estimated ICERs of £18,900 or £13,200 per QALY gained, respectively. Reducing the discount rates to 3.5% costs and 1.5% QALYs, or 0% costs and QALYs, decreased the estimated ICER to £5,500 and £6,200 per QALY gained, respectively.

Increasing the baseline testing rate in GP services by 50% increased the cost effectiveness (estimated ICER £10,500 per QALY gained). Conversely, halving the baseline testing rate reduced the cost-effectiveness (estimated ICER £25,100 per QALY gained).

As this intervention targeted ex-IDUs only (and therefore had no impact on transmission), the intervention was less cost-effective at lower prevalences (estimated ICER of £18,000 per QALY gained at 20% IDU chronic prevalence) due to the increased costs related to finding infected cases. Conversely, the intervention was more cost-effective at higher prevalences (estimated ICER of £12,100 per QALY gained at 50% IDU chronic prevalence). Due to this, and because higher treatment rates among ex-IDUs resulted in more substantial reductions in prevalence among ex-IDUs than seen for IDUs, increasing the number of successful treatments through doubling of referral rates or the use of new antiviral therapies (telaprevir/boceprevir) for genotype 1 marginally increased the estimated ICER (to £15,200 and £14,900 per QALY gained, respectively, as compared to no testing intervention). This was because the high treatment initiation rates for ex-IDUs (50% of those who attend referral in the first 2 years) resulted in high numbers of successful treatments. The subsequent drop in prevalence among ex-IDUs over 100 years (a 35% relative reduction) resulted in an increase in the costs relating to diagnosis due to the lower prevalence, and therefore a marginally higher ICER with increased treatment over this timeframe.

As in the previous analyses, if a disutility of diagnosis was assumed, the intervention was associated with negative incremental QALYs (due to low treatment rates), and the intervention was dominated (more

expensive and with less health benefit). Hence, in this scenario, the baseline scenario was the preferable option.

Assuming no fall-out of care from treatment/referral when entering/exiting prison marginally decreased the cost-effectiveness to an estimated ICER of £15,400 per QALY gained, again because, counterintuitively, as the intervention was more effective at reducing prevalence, the cost of diagnosing infections because slightly more expensive over the 100 year timespan.

3.4 Epidemiological impact of interventions

Interventions to increase diagnosis of current IDUs will likely have an impact on the HCV prevalence among the IDU population, as successful antiviral treatment will reduce the background prevalence of the disease and therefore reduce an individual's risk of acquiring HCV. We utilised the model to investigate the magnitude of prevalence reductions expected with the interventions in a short (10-20 year) timeframe.

As we assumed no treatment of current IDUs prior to the start of the simulations, and very low treatment at baseline (50% diagnosed, 35% referred, and 5.5% of those who are referred are treated within the first 2 years, resulting in a yearly treatment initiation rate of <1% of the chronically infected IDU population), only small reductions in prevalence were seen in the baseline and intervention scenarios (**figure 23**). In particular, with fall-out of treatment and referral, even a smaller fraction of the IDUs were successfully treated than the <1% initiated. Hence, the baseline and addiction services intervention scenario resulted in a relative HCV chronic prevalence reduction at 10 years among current IDUs of 1% or 2%, respectively. This reduction was increased to just under 2% and 3% for the baseline and addiction services intervention, respectively, at 20 years. Assuming continuity of

treatment/referral, the relative prevalence reductions at 10 and 20 years became 3% and 5%, respectively. If continuity of care was ensured and IDU treatment rates were doubled, the intervention may reduce prevalence by just under 7% at 20 years. Clearly, higher treatment rates of IDU are necessary to result in substantial reductions in prevalence. However, despite this, even very low treatment rates had a substantial impact on cost-effectiveness (as seen with the 'no prevalence benefit (static-type)' sensitivity analysis).

In the baseline prison scenario (assuming loss to treatment/referral on entry/exit from prison) there was a negligible impact on prevalence as so few current IDU are successfully treated in the prison setting. Nevertheless, if no fall-out is assumed, some small prevalence reductions are seen (2% at 10 years), although less than in the addiction services intervention as the prison treatments are divided between both current and former-IDUs (while only treatment of current IDU will have an onward prevention impact). Similarly, no impact on HCV transmission and IDU prevalence was seen with the GP intervention as it targeted former-IDUs only, which we assumed did not contribute to HCV transmission.

4 Discussion

The aim of this evaluation was to assess the cost-effectiveness of interventions to promote and offer HCV testing to current and former injecting drug user populations. This analysis was based on a sequence of reports from LJMU (qualitative review, UK mapping review, effectiveness and cost-effectiveness review) surrounding interventions to promote HCV and HBV testing in high risk populations. From these reports and in consultation with the PDG, three interventions were chosen for the economic evaluation based on the strength of the study data, applicability to the UK setting, and current interest expressed in the mapping review. Our economic evaluation examined three interventions: 1) introducing dried blood spot testing in specialist addiction services, 2) introducing dried blood spot testing in prison services, and 3) GP education and paid-targeted testing of ex-IDUs 30-54 years old.

A dynamic, compartmental age-stratified model of HCV transmission, testing, disease progression, referral, and treatment among IDUs and ex-IDUs was created, including movement in/out of prison (all populations) and in/out of addiction services (IDUs only). The model was fitted to available incarceration, HCV prevalence, and injecting-related data. The intervention effect was determined by a meta-analysis of primary data and modelled as a proportional change in testing rate in a given setting/age group (and a proportional change in test yield where applicable). Parameters were sampled multivariately, and the results for 1000 runs were used to determine the mean incremental cost-effectiveness ratio for each intervention as compared to baseline (no testing intervention).

Main findings

Our results indicate that the introduction of dried blood spot testing is likely to be cost-effective in specialist addiction services, but may not be cost-effective in prison settings unless at least 40% continuity of treatment/referral can be ensured. Ensuring continuity of care and referral to/from/between prison will increase the cost-effectiveness of all testing interventions, and is the key to ensuring any prison intervention is cost-effective. GP education and paid targeted case finding of ex-IDUs between 30 and 54 years old is likely to be cost effective, and even more cost-effective if current IDUs are inadvertently tested as part of the strategy(as it is possible those classified as 'former' IDUs by their GP may still be injecting, or could relapse in the future).

Comparison with other cost-effectiveness studies of similar interventions

Several other economic evaluations have examined the cost-effectiveness of HCV testing or screening in current or former IDUs and in settings such as prison, GP, and drugs services. However, direct comparisons between results are difficult as none examined the specific interventions studied in this evaluation, and none used dynamic models. Castelnuovo et al.[24 48] evaluated the cost-effectiveness of HCV case-finding of former IDUs in GP settings, either targeting former IDUs or all patients between the ages of 30 and 54 years old, finding an estimated ICER of between £15,500-£16,500 per QALY gained depending on target group. This is comparable to our finding of an estimated ICER of £13,900 per QALY gained for a GP case finding intervention targeting former IDUs 30-54 years old. There are several notable differences between the analysis: 1) our analysis included the cost of GP remuneration and an educational session, 2) different discount rates 3) different baseline testing rates and 4) the intervention effect was modelled differently (we modelled a permanent proportional change in baseline testing, they modelled a static cohort

who all present for the intervention). Nevertheless, these results indicate that GP targeted case-finding among former IDUs is likely to be cost effective.

More recently, Helsper et al.[49] evaluated a GP education intervention alongside a national HCV publicity campaign in The Netherlands, finding an estimated ICER of 11,400 Euros per QALY gained. This is comparable to our estimate, however it is important to note their intervention/costs were different as they included a national publicity campaign which we did not evaluate. Interestingly, however, their intervention impact of the GP education (about a 3-fold increase in testing) is similar to our estimated effect (3.4-fold increase in testing). Differences in costs, referral rates, treatment rates, SVR, and model structure are likely contributors to differences in the results.

Two publications have evaluated the cost-effectiveness of testing former IDUs in prison, with differing results. Castelnuovo et al.[24] found case-finding in prison likely to be cost-effective, with an estimated ICER of £16,500-20,000 per QALY gained depending on prison scenario. By contrast, Sutton et al.[16] found testing of current and former IDUs in prison unlikely to be cost effective (estimated ICER £54,800 per QALY gained). Sutton et al. attributed the discrepancy to the use of different discount rates (Sutton et al. used 3.5% for cost/QALYs, Castelnuovo et al. used 6.5% costs/1.5% QALYs). Our results for a HCV testing intervention in prison (estimated ICER £59,400 per QALY gained) fall in line with those found by Sutton et al.[16].However it is important to note that the actual intervention evaluated in our study as compared to that examined in the Sutton/Castelnuovo papers[16 24] is very different. The intervention evaluated in Sutton/Castelnuovo[16 24] examined the introduction of a testing service in prison, with a seminar given to all new prisoners and testing offered. However, given that a recent HPA survey among

prisons found that 99% of prisons surveyed offer HCV testing[50], we evaluated the cost-effectiveness of offering dried blood spot testing in this (already existing) service. Hence, the intervention, costs, and intervention effect would differ in our evaluation. Most importantly, we included the possible prevention impact of testing and treatment, and addressed the issue of continuity of treatment/care on exit from prison. Our results showed that if at least 40% continuity of care is ensured for those who are in treatment or referral, introducing dried blood spot testing (and testing in general) in prisons is likely to be cost-effective.

Finally, several papers[24 29 48] evaluated testing of former IDUs in drug services. Differences in baseline assumptions (presence of background testing at baseline, impact of intervention on background testing, proportion of the population ex-IDUs (and therefore eligible for testing in their intervention)) led to estimated ICERs from £28,100 per QALY gained[29] to £17,500 per QALY gained[24 48]. Our results for DBS testing in addiction services (estimated ICER £13,900 per QALY gained) support those found in the latter studies[24 48]. However, again we caution a straight comparison between the studies as the intervention, costs, and impact were different between the studies. The intervention examined in previous studies[24 29 48] was a one-off offer of testing to ex-IDUs in addiction services using a cohort model, while we examined the dynamic impact of permanently offering dried blood spot testing in drugs services to both current and former IDUs. Again, our estimate included the potential prevention benefit of testing and treating current IDUs.

Strengths and Limitations

The model is complex. The key strengths are that it is dynamic – therefore capturing the impact of case-finding on prevention of future infections – and that the interventions and model assumptions are empirically based. Nonetheless there are several important limitations,

concerned both with uncertainty over key parameters and lack of heterogeneity.

Information on the interventions themselves was based only a few relatively small studies, and therefore generates wide confidence intervals for the size of the effect. Further studies strengthening the evidence on hepatitis case-finding interventions would substantially reduce model uncertainty. This should be possible as testing strategies are being rolled out and introduced in specialist drug agencies and prisons. Furthermore, it is unclear if introducing these services will have a permanent intervention effect, as the studies only examined an impact for 6 months. Additionally, in our model intervention effect is measured by a change in current testing rates. However, this had to be estimated based on the proportion of IDUs reported as diagnosed. Therefore, better reporting of testing data (in particular, more reliable coding of IDU status on tests) would strengthen the analysis.

The model assumed comparatively low treatment rates for IDUs in part because available information on current uptake is poor. HCV treatment has expanded recently in some areas, and more HCV treatment in the community is being developed. However, up to date information on numbers being treated was not available. This information is critical to cost-effectiveness, as higher treatment rates will reduce the ICER, and therefore increase the cost-effectiveness. This is especially so for prisons where information on SVRs and numbers entering and completing treatment after referral was unavailable – yet determines largely whether case finding in prison is cost effective. Additionally, even if treatment with peginterferon-alfa and ribivirin is interrupted, some of those may have benefited from the shortened treatment, which we did not explore in our model. However, rapid development of resistance observed with new treatments[51]

(telaprevir and boceprevir) means that continuity of care will become an increasingly crucial issue.

Also lacking was information on health utilities of people who inject, loss of utility following HCV infection for IDUs, and especially whether there is any loss of utility on diagnosis of HCV. If there is disutility following diagnosis then higher treatment rates than modelled in the baseline case would be required for case-finding to be cost effective. Additionally, a more sophisticated understanding of how health utilities change between the model stages (for example, from mild asymptomatic to mild symptomatic or on cessation of injecting drug use) would allow for more accurate cost-effectiveness estimates.

The model also did not incorporate fully other interventions that may have an impact on HCV risk (such as opiate substitution therapy (OST) and needle and syringe programmes (NSP)) or heterogeneities in behaviour and treatment uptake that may influence HCV risk and effectiveness of case-finding. For example, a recent meta-analysis of UK data indicates being on OST reduces an individual's risk of acquiring HCV by half[10], and also reduces crime and imprisonment[52]. Additionally, treatment of IDUs tends to be targeted towards those on opiate substitution therapy[35], and these lower risk IDU may contribute less to the HCV epidemic. Conversely, more chaotic IDUs may be less likely to be treated, contribute more to the HCV epidemic, but may have lower SVR than those recruited from OST programmes.

However, there is currently insufficient information to parameterise these heterogeneities. In previous models it has been shown that introducing heterogeneity in risk does not have an undue influence on treatment effectiveness as long as individuals circulate between high risk and intervention states[14], so that opportunities do arise during the injecting period for case finding and treatment (e.g. while individuals

are on OST or in prison). Expanding HCV treatment may lead to a loss of SVR as more complicated cases are included. There will be a trade-off between increasing HCV treatment and cure rate, but there is insufficient information on what the proportion achieving SVR may be for different groups of patients. Moreover, the baseline model assumes such a low treatment rate that it is unlikely that those treated would exhibit lower SVR.

Future work/research recommendations

Considerable uncertainty surrounds continuity of treatment/care in the prison setting, and the proper economic evaluation of any testing or treatment intervention in prison would benefit from enhanced monitoring and reporting of data surrounding treatment rates, SVR rates, and proportion of those tested who remain in referral and are treated later in the community.

Testing and treatment rates for current or former IDUs in the community are also uncertain. Enhanced reporting of IDU status on HCV tests would strengthen the data. Furthermore, the designation of 'current' or 'former' IDU on the test reporting would give greater insight as to the populations being tested. Improved collection of IDU treatment rates would allow for a better estimation of potential treatment impact on prevalence.

More studies should examine utility values of current and ex-IDUs, both uninfected and HCV infected. Longitudinal studies should examine any potential disutility on diagnosis (magnitude and duration).

Finally, more data on the intervention effect for the three interventions examined would reduce the model uncertainty. As there are a number of proposed research areas, an expected value of information analysis would aid in determining the priority areas of data collection.

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Transition probabilities (all probabilities converted to rates in the simulations)	Mean value	Distribution	Units	Ref.
Mild to moderate	0.025	Beta(38.0859,1485.3516)	Per year	[19]
Moderate to cirrhosis	0.037	Beta(26.905,700.2582)	Per year	[19]
Cirrhosis to decompensated cirrhosis	0.039	Beta(14.6168,360.1732)	Per year	[19]
Cirrhosis/decompensated cirrhosis to HCC	0.014	Beta(1.9326,136.1074)	Per year	[19]
Decompensated cirrhosis/HCC to LT	0.03	Beta(6.5256,210.9945)	Per year	[19]
Decompensated cirrhosis to death	0.13	Beta(147.03,983.97)	Per year	[19]
HCC to death	0.43	Beta(117.1033,155.23)	Per year	[19]
LT to death	0.21	Beta(16.2762,61.2294)	Per year	[19]
Post transplant to death	0.057	Beta(22.9017,378.8825)	Per year	[19]

Table 1. HCV disease progression parameters.

Health state utilities	Mean value	Distribution	Units	Ref.
Ex-IDUs				
Uninfected				
15-24 utility	0.94		Per year	[23]
25-29 disutility	0.005		Per year	[23]
30-54 disutility	0.049		Per year	[23]
55-64 disutility	0.14		Per year	[23]
65-74 disutility	0.16		Per year	[23]
75+ disutility	0.21		Per year	[23]
Mild [15-24] utility	0.77	Beta(521.2375,155.6943)	Per year	[19 20]
Moderate utility	0.66	Beta(168.2461,86.6723)	Per year	[19 20]
Cirrhosis utility	0.55	Beta(47.1021,38.5381)	Per year	[19 20]
Decompensated cirrhosis utility	0.45	Beta(123.75, 151.25)	Per year	[19 20]
Hepatocellular carcinoma utility	0.45	Beta(123.75, 151.25)	Per year	[19 20]
Liver transplant utility	0.45	Beta(123.75, 151.25)	Per year	[19 20]
Post transplant utility	0.67	Beta(59.2548,29.1852)	Per year	[20 21]
Mild utility - on treatment	0.66	Beta(115.706, 59.6063)	Per year	[19 20]
Moderate utility - on treat	0.55	Beta(47.1021, 38.5381)	Per year	[16 19 20]
Cirrhosis utility -on treat	0.46	Beta(3953, 4641)	Per year	[16]
Mild SVR utility	0.82	Beta(65.8678,14.4588)	Per year	[19 20]
Moderate SVR utility	0.72	Beta(58.0608, 22.5792)	Per year	[16 19 20]
Cirrhosis SVR utility	0.61	Beta(58.0476, 37.1124)		[21]
IDUs				
Uninfected				
15-24 utility	[redacted]	Uniform[redacted]	Per year	(Scott McDonald academic confidential)
Other ages		Reduced by same disutility as ex-IDUs.		Assumed
HCV disease states		As in ex-IDU, but reduced by PropIDU[a]		Assumed

Table 2. Health state utilities. [a] PropIDU=(Uninfected IDU utility value age 15-24/ Uninfected ex-IDU utility value age 15-24).

HCV state costs	Mean value (in 2011 £)	Distribution (2011 costs inflated from 2003/2004 cost distributions using the HCHS pay and prices index[13], PPI=1.228)	Units	Ref.
Mild diagnosed	169	PPI* Gamma(25.6995,5.3698)	Per year	19 20
Moderate diagnosed	880	PPI* Gamma (88.8502,8.0698)	Per year	19 20
Cirrhosis diagnosed	1,397	PPI* Gamma (24.2342,46.9584)	Per year	19 20
Decompensated cirrhosis	11,199	PPI* Gamma (36.0249,253.1582)	Per year	19 20
Hepatocellular carcinoma	9,980	PPI* Gamma (18.1081,448.8045)	Per year	19
Liver transplant	33,561	PPI* Gamma (89.7536,304.5004)	Per transplant	19
Cost of care in year of liver transplant	11,614	PPI* Gamma(13.7788,686.4168)	Per year	19
Post transplant	1,701	PPI* Gamma (15.2189,91.0053)	Per year	19
Mild SVR	318	PPI* Gamma (28.8141,8.9887)	Per year	19
Moderate SVR	880	PPI* Gamma (88.8502,8.0698)	Per year	19
Cirrhosis SVR	1,397	PPI* Gamma (24.2342,46.9584)	Per year	19
Undiagnosed states	0		Per year	

Table 3. HCV disease state costs.

HCV antiviral treatment costs	Mean value (in 2011 £)	Distribution	Ref.
PegIFN+RBV drug only			
12 weeks	2,660[a]	Halved from sampled cost at 24 wks	26
24 weeks	5,320[a]	Uniform (4788, 5852)	26
48 weeks	10,640[a]	Doubled from sampled cost at 24 wks	26
Treatment delivery			
12 weeks			
Staff	307	Varied by staff cost variation[b]	19
Tests	1,605	Varied by test cost variation[c]	19
24 weeks			
Staff	374	Varied by staff cost variation[b]	19
Tests	1,683	Varied by test cost variation[c]	19
48 weeks			
Staff	504	Varied by staff cost variation[b]	19
Tests	1,822	Varied by test cost variation[c]	19
Additional treatment delivery for IDUs		Varied by staff cost variation[b] and IDU staff time variation[d]	
IDU extra nurse time			
12 weeks	129		8
24 weeks	159		8
48 weeks	220		8
IDU extra basic assessments		Varied by test cost variation[c], staff cost variation[b] and IDU staff time variation[d]	
12 weeks			
Staff	58		8
Tests	43		8
24 weeks			
Staff	97		8
Tests	71		8
48 weeks			
Staff	174		8
Tests	129		8
IDU psychiatric visits	51	Varied by staff cost variation[b] and IDU staff time variation[d]	8

Table 4. HCV antiviral treatment costs. [a]Average peginterferon cost between alfa-2a (Pegasys) and alfa-2b(ViraferonPeg), and average ribavirin cost between Copegus and Rebetol. [b]Test value calculated by multiplying mean test cost with a test cost variation parameter, uniformly sampled between 0.8 and 1.2. [c]Staff value calculated by multiplying mean staff cost by a staff cost variation parameter, uniformly sampled between 0.8 and 1.2. [d]IDU staff cost calculated by multiplying mean staff cost by a staff cost variation parameter and an extra IDU staff time variation parameter (both uniformly sampled between 0.8 and 1.2)

HCV testing and treatment parameters	Value	Distribution	Units	Ref.
Proportion IDUs diagnosed (initial)	50%		-	[11]
Proportion IDUs treated (initial)	0%		-	Assumption
Proportion ex-IDUs diagnosed (initial)	30%	Uniform (24%,36%)	-	Assumption, less than proportion IDUs diagnosed
Proportion ex-IDUs treated (initial)	10%	Uniform (5%, 15%)	-	Estimated that less than 10% of those chronically infected have been treated [11]
Proportion HCV genotype 1	50%		-	[11 33]
Sustained viral response(SVR)				
Genotype 1 mild/moderate	0.45	Uniform (0.4, 0.5)	-	[33 54 55]
Genotype 2/3 mild/mod	0.8	Uniform (0.75, 0.85)	-	[33 56]
Genotype 1 cirrhosis	0.25	55% reduction from mild/mod SVR	-	[34]
Genotype 2/3 cirrhosis	0.6	75% reduction from mild/mod SVR	-	[34]
Antiviral treatment duration				
Genotype 1 SVR	48		weeks	[33]
Genotype 1 non-SVR	12		weeks	[33]
Genotype 2/3	24		weeks	[33]
Distribution of IDU HCV tests				
GP	38.4%		-	(Health Protection Agency unpublished data from the 2010 Sentinel Surveillance)
Prison	11.5%		-	HPA, as above
Addiction services	29.4%		-	HPA, as above
Other	20.7%		-	HPA, as above
Proportion who are referred and attend referral	35%	Uniform (25%, 45%)	-	[24 30]
Proportion in referral who initiate treatment within first 2 years (excl. prison)				
Ex-IDUs	50%	Uniform(40%, 50%)	-	[24 30-32]
IDUs	6%	Uniform(1%, 10%)	-	Assumption
Treatment initiation rate after 2 years in referral (excl. prison)				
Ex-IDUs	10%	Uniform(5%, 15%)	Per year	Assumption
IDUs	3%	Uniform(1%, 5%)	Per year	Assumption
Treatment rates in prison	Half out-of-prison rates			(HMP Leeds unpublished audit 2009, Iain Brew, personal communication)
Yield				
GP	2.7%		-	(Health Protection Agency unpublished data from the 2010 Sentinel Surveillance)
Prison	14.7%		-	HPA, as above
Addiction services	17.7%		-	HPA, as above
Other	1.7%		-	HPA, as above

Table 5. Testing and treatment parameters

HCV testing costs- baseline	Mean value (in 2011 £)	Distribution /notes	Units	Ref.
Assessment	1.78	1 minute (average nurse and consultant doctor cost[a])	Per test	[29]
Pre-test discussion and test	53.50	30 minutes (average nurse and consultant doctor cost[a])	Per test	[29]
Post-test results	44.58	25 minutes (average nurse and consultant doctor cost[a])	Per test	[29]
ELISA test	15.35		Per test	[29]
Additional assessment time (prison only)	29	Assuming 20 min. with nurse[a]	Per test	Estimated from timings in [29]
Total test costs in all settings except prison	115.21	Uniform +/- 50%	Per test	
Total test costs in prison setting	144.21	Uniform +/- 60%	Per test	
PCR RNA test (if antibody positive)	73.67		Per year	[29]

Table 6. Baseline HCV testing costs. [a]Assuming a consultant cost per hour of £127, and a staff-nurse cost per patient contact hour of £87 (median estimate for band 5 GP nurse, used as higher than estimate of £84 per hour for same band hospital day ward nurse) as found in the Unit Costs of Health and Social Care 2011[13].

HCV intervention effect	Mean proportional change [95% CI]	Distribution	Units	Ref.
Addiction services testing rate	3.614 [2.263-5.771]	Lognormal(1.285, 0.239)	-	[1]
Prison services testing rate	2.632 [0.199-34.883]	Lognormal(0.968, 1.317)	-	[1]
GP testing rate	3.399 [1.566-7.375]	Lognormal(1.223, 0.395)	-	[3]
GP yield	2.047 [1.138-3.684]	Lognormal(0.716 0.300)	-	[3]

Table 7. Intervention effect meta-analysis results.

HCV intervention costs- Addiction services	Mean value (in 2011 £)	Distribution /notes	Units	Ref.
Organisation/coordination of training per health board	2,005.71	1 nurse 2 days/week for 6 months for 7 health boards[a]. One training session per health board.	per health board	(Noel Craine, *personal communication*)
Training session	135	1 nurse half day[a]	per training session	(Noel Craine, *personal communication*)
Attendees time	1,620	12 nurses, half day [a]	per training session	(Noel Craine, *personal communication*)
Travel reimbursement for training leader per health board	90.86	1200 miles (53p per mile) for travel to 7 health boards	per training session	(Noel Craine, *personal communication*)
Total cost per addiction services training	3851.57		per training session	
Mean number tested per health board	40.3	Assumed 1 addiction service per health board	per addiction service	[1]
Total intervention cost per test	**95.57**	**Uniform +/- 50%**	per test	

Table 8. Intervention costs for the DBS in addiction services intervention. [a]Assuming a staff-nurse cost per hour of £36 (median estimate for band 5 GP nurse)[13]. Note that this estimate is lower than the cost per patient contact hour estimated for the actual testing process.

HCV intervention costs- Prison services	Mean value (in 2011 £)	Distribution /notes	Units	Ref.
Organisation/coordination of training per prison	7020	1 nurse full time for 5 prisons [a] (1 training session per prison)	per prison	(Noel Craine, *personal communication*)
Training session	135	1 nurse half day[a]	Per prison	(Noel Craine, *personal communication*)
Attendees time	405	3 nurses per prison, half day[a]	Per prison	(Noel Craine, *personal communication*)
Travel reimbursement for training leader	127.20	1200 miles (53p per mile) for 5 prisons	per prison	(Noel Craine, *personal communication*)
Total cost per prison training	7687.20		Per prison	
Mean number tested per prison	116		per prison	[1]
Total intervention cost per test	**66.27**	**Uniform +/- 50%**	Per test	

Table 9. Intervention costs for the DBS in prison services intervention. [a]Assuming a staff-nurse cost per hour of £36 (median estimate for band 5 GP nurse)[13]. Note that this estimate is lower than the cost per patient contact hour estimated for the actual testing process.

HCV intervention costs- GP education and targeted paid testing	Mean value (in 2011 £)	Distribution /notes	Units	Ref.
GPASS screening	36	1 hour by nurse[a]	Per GP practice	(Beth Cullen, *personal communication*)
Informing eligible patients	83	1 hour by GP[a]	Per GP practice	(Beth Cullen, *personal communication*)
Seminar organization	89	1 hour each 1 clinical nurse specialist and 1 BBV counselor (costed at 2 nurses[a])	Per GP practice	(Beth Cullen, *personal communication*)
Development of educational materials	234.38	4 half-day sessions 1 nurse and 2 BBV counselors (costed at 3 nurses[a])	Per GP practice	(Beth Cullen, *personal communication*)
Half day seminar- leader time	333.75	1 clinical nurse specialist and 1 BBV counselor (costed at 2 nurses[a])	Per GP practice	(Beth Cullen, *personal communication*)
Half day seminar attendance	446.25	1 GP and 1 nurse[a]	Per GP practice	(Beth Cullen, *personal communication*)
Total cost per GP practice	1222.38		Per GP practice	
Mean number tested per GP practice	13.13		Per GP practice	[3]
Reimbursement cost per test	100		per test	[3]
Total intervention cost per test	**193.13**	**Uniform +/- 50%**	Per test	

Table 10. Intervention costs for the GP intervention. [a]Assuming a GP cost per hour of £83, and a GP nurse cost per hour of £36 (median estimate for band 5 GP nurse) as found in the Unit Costs of Health and Social Care 2011[13].

	Model	Input parameters	Fitting parameters	Output parameters from fitting
Fit #1	Simplified model 1 (figure 7)	• Sampled cessation rate • Sampled overdose rate • Sampled IDU prison release rate • Death rates by age • Prison release rate for never-IDUs or ex-IDUs by age • Injecting initiation age distribution • (Estimated) entry rate of never-IDUs aged 15-19.	• Proportion general population with a custodial sentence by age • Proportion of current IDU population previously imprisoned by age • Age distribution of current prisoners • Proportion of prisoners ever-IDUs by age • Proportion of the population currently imprisoned • Prevalence of current IDUs in general population	• Incarceration rates by age • Re-incarceration rates by age • IDU incarceration rates by age • IDU re-incarceration rates by age • Injecting initiation rate
Fit #2	Simplified model 2 (figure 2 without HCV disease states)	• Input and output parameters from Fit #1 • Sampled addiction services duration • (Estimated) entry rate of never-IDUs aged 15-19.	• Proportion current IDU in contact with addiction services	• Recruitment rate into addiction services
Fit #3	Simplified model 3 (figure 8)	• Sampled injecting duration • Sampled overdose rate • Death rates by age • Injecting initiation age distribution • Fit injecting initiation rate (Fit #1) • (Estimated) entry rate of never-IDUs aged 15-19.	• Proportion current IDU diagnosed	• Overall (not setting-specific) IDU testing rate
Fit #4	Full model (figures 1 and 2) without ex-IDUs	• All model parameters from Fits #1-3 and sampled sets. • (Estimated) entry rate of never-IDUs aged 15-19.	• HCV IDU chronic prevalence	• Infection rate
Fit #5	Full model	• All model parameters from Fits #1-4 and sampled sets.	• Total population size (fit to 1000 current IDUs)	• Entry rate of never-IDUs in the 15-19 age group

Table 11. Model fitting procedure summary.

	Mean value	Sampled values	Units	Ref.
Average duration of injecting until cessation	11	6.2, 8.6, 11, 13.4, 15.8	years	[57 58]
IDU overdose rate	0.01	0.007, 0.01, 0.13	Per year	[43]
Duration in addiction services	9	7, 9, 11	months	Estimated equal to duration on OST[43]
Proportion infections leading to spontaneous clearance	0.26	Uniform (0.22, 0.29)	-	[40]
Incarceration duration				
IDUs				
All ages	4	2.67, 4, 5.33	Months	[15]
Ex-IDUs				
15-19	2.75		Months	[15]
20-24	6.26		Months	[15]
25-29	8.42		Months	[15]
30-54	9.76		Months	[15]
55-64	11.92		Months	[15]
65+	12.49		Months	[15]
Injecting initiation distribution by age				
15-19	41%		-	Combined UK dataset from [10]
20-24	30%		-	Combined UK dataset from [10]
25-29	16%		-	Combined UK dataset from [10]
30-54	13%		-	Combined UK dataset from [10]
55+	0%		-	Combined UK dataset from [10]
Death rate				
15-19	0.0003		Per year	[59]
20-24	0.0005		Per year	[59]
25-29	0.0006		Per year	[59]
30-54	0.0019		Per year	[59]
55-64	0.0073		Per year	[59]
65-74	0.0200		Per year	[59]
75+	0.165		Per year	[59]

Table 12. Epidemiological/prison input parameters for model fitting

	Age distribution					Reference
	15-19	20-24	25-29	30-54	55+	
Proportion general population with a custodial sentence	1.3%	2.5%	3%	4%	-	[36]
Age distribution of prisoners	8%	20%	18%	47%	7%	[38]
Proportion IDUs ever in prison	48%	46%	67%	73%	-	Unpublished data, Unlinked Anonymous Monitoring Survey of People Who Inject Drugs, Health Protection Agency, London
Proportion of prisoners with IDU history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Scotland data (academic confidential)
	Overall value					
Proportion of England population currently imprisoned aged 15-59	0.2%					[38 39]
Proportion of population who are current IDUs aged 15-59	0.65%					[60]
Proportion current IDUs in contact with addiction services	50%					[10 42]
Proportion current IDUs diagnosed with HCV	50%					[11]

Table 13. Prison/HCV data used for model fitting.

Telaprevir/boceprevir scenario parameters	Value	Units	Notes	Ref.
Proportional increase in SVR for genotype 1 patients	68%	-		[46 47 61 62]
Average duration of treatment for genotype 1	37	weeks	Assume 50% have a rapid viral response (RVR) and only require 26 weeks treatment (24 weeks telaprevir, 28 weeks boceprevir). The remaining 50% require 48 weeks. In trials, 58-65% achieve RVR.	[46 47 61 62]
Telaprevir or boceprevir drug cost only (pegIFN+RBV cost additional)	£19,600	per treatment	Mean cost between telaprevir (12 weeks, £22,398) and boceprevir (24 weeks, £16,800). Cost in addition to 37 weeks pegIFN+RBV (sampled as in **table 4**)	[63 64]

Table 14. Telaprevir/boceprevir sensitivity analysis parameters

Intervention	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
DBS in addiction services					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,099,060 [20,140,578–68,378,488]	5,354,393 [4,867,206–5,960,853]	917,478 [481,174–1,664,430]	63 [19–153]	14,632
DBS in prison					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,245,293 [19,852,634–68,601,970]	5,354,349 [4,867,184–5,960,823]	1,063,710 [-225,101 – 6,060,267]	18 [-12 – 75]	59,418
GP education and paid targeted testing of ex-IDUs 35-54 years old					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	40,547,027 [20,944,330–75,172,430]	5,354,573 [4,867,293–5,961,241]	3,365,444 [489,795–12,000,645]	243 [33–691]	13,877

Table 15. Cost-effectiveness results from the baseline intervention analyses.

Addiction services intervention sensitivity analysis scenario	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
Baseline scenario					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,099,060 [20,140,578–68,378,488]	5,354,393 [4,867,206–5,960,853]	917,478 [481,174–1,664,430]	63 [19–153]	14,632
50 year time horizon					
Baseline	31,624,821 [16,311,919–57,491,887]	4,541,002 [4,127,934–5,055,123]	-	-	-
Intervention	32,422,413 [16,953,489–58,573,580]	4,541,037 [4,127,954–5,055,172]	797,592 [407,366–1,467,765]	35 [9–90]	22,890
100 year time horizon					
Baseline	38,352,090 [20,032,722–69,289,456]	5,526,048 [5,023,237–6,151,983]	-	-	-
Intervention	39,291,780 [20,800,215–70,394,400]	5,526,118 [5,023,279–6,152,080]	939,690 [495,858–1,695,840]	70 [49–170]	13,356
0% cost and QALY discounting					
Baseline	131,269,304 [70,344,106–232,091,657]	19,032,003 [17,299,165–21,189,859]	-	-	-
Intervention	134,338,889 [72,735,442–235,520,507]	19,032,461 [17,299,454–21,189,613]	917,478 [481,174–1,664,430]	63 [19–153]	6,702
3.5% cost/1.5% QALY discounting					
Baseline	37,181,582 [19,384,816–67,271,249]	9,898,109 [899,719–11,019,882]	-	-	-
Intervention	38,099,060 [20,140,578–68,378,488]	9,898,288 [899,730–11,020,129]	917,478 [481,174–1,664,430]	179 [56–425]	5,118
Addiction baseline testing rate -50%					
Baseline	37,248,293 [19,505,898–67,102,295]	5,354,363 [4,867,182–5,960,829]	-	-	-
Intervention	38,004,191 [20,078,096–68,172,641]	5,354,397 [4,867,202–5,960,875]	755,898 [370,952–1,484,875]	33 [10–81]	23,023
Addiction baseline testing rate +50%			-		
Baseline	37,107,001 [19,232,524–67,329,066]	5,354,295 [4,867,153–5,960,696]		-	-
Intervention	38,169,290 [20,174,072–68,617,254]	5,354,385 [4,867,207–5,960,923]	1,062,289 [594,867–1,836,757]	90 [28–216]	11,758
Initiate 50% IDU on treatment within 2 years					
Baseline	36,990,149 [19,367,964–66,622,539]	5,354,541 [4,867,270–5,961,056]	-	-	-
Intervention	37,786,134 [20,119,144–67,406,636]	5,354,716 [4,867,371–5,961,255]	795,984 [432,134–1,387,210]	175 [59–402]	4,546

Double referral proportion					
Baseline	37,712,072 [19,807,378–67,857,408]	5,354,673 [4,867,328–5,961,410]	-	-	-
Intervention	38,610,147 [20,540,453–68,934,734]	5,354,752 [4,867,380–5,961,516]	898,075 [476,217–1,599,098]	79 [26–176]	11,340
IDU SVR reduced by 20%					
Baseline	37,206,317 [19,397,185–67,324,708]	5,354,317 [4,867,160–5,960.741]	-	-	-
Intervention	38,136,634 [20,151,642–68,468,730]	5,354,373 [4,867,193–5,960,818]	930,317 [486,719–1,848,114]	56 [16–138]	16,710
Telaprevir/boceprevir					
Baseline	37,267,861 [19,518,085–67,256,446]	5,354,499 [4,867,239–5,961,127]	-	-	-
Intervention	38,182,264 [20,222,666–68,380,891]	5,354,575 [4,867,285–5,961,232]	914,403 [481,388–1,656,281]	76 [23–185]	12,026
20% IDU chronic prevalence					
Baseline	24,539,960 [12,548,516–45,775,871]	5,354,807 [4,859,588–5,968,193]	-	-	-
Intervention	25,313,337 [13,249,653–46,876,977]	5,354,856 [4,859,603–5,968,289]	773,378 [389,399–1,500,763]	48 [14–120]	16,023
50% IDU chronic prevalence					
Baseline	50,615,429 [26,464,503–90,151,348]	5,353,717 [4,873,626–5,952,848]	-	-	-
Intervention	51,696,936 [27,485,884–91, 719,318]	5,353,785 [4,873,674–5,952,941]	1,081,507 [580,261–1,881,737]	69 [20–170]	15,691
Disutility on diagnosis					
Baseline	37,181,582 [19,384,816–67,271,249]	5,356,436 [4,868,848–5,963,166]	-	-	-
Intervention	38,099,060 [20,140,578–68,378,488]	5,356,256 [4,868,667–5,963,005]	917,478 [481,174–596,300]	-181 [-295 – -96]	Dominated
No fall-out from prison					
Baseline	37,271,151 [19,501,405–67,253,280]	5,354,506 [4,867,296–5,961,008]	-	-	-
Intervention	38,188,467 [20,272,330–68,355,900]	5,354,599 [4,867,371–5,961,123]	917,305 [486,942–1,656,382]	94 [32–202]	9,806
No prevention benefit (static)					
Baseline	37,301,092 [19,454,718–67,498,289]	5,354,272 [4,867,133–5,960,654]	-	-	-
Intervention	38,286,796 [20,211,866–68,459,080]	5,354,058 [4,867,150–5,960,700]	985,704 [502,569–1,799,615]	33 [7–90]	29,862

Table 16. Results from the sensitivity analyses for the DBS in addiction services intervention.

Prison intervention sensitivity analysis scenario	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
Baseline scenario					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	38,245,293 [19,852,634–68,601,970]	5,354,349 [4,867,184–5,960,823]	1,063,710 [-225,101 – 6,060,267]	18 [-12 – 75]	59,420
50 year time horizon					
Baseline	31,624,821 [16,311,919–57,491,887]	4,541,002 [4,127,934–5,055,123]	-	-	-
Intervention	32,524,311 [16,753,110–58,719,192]	4,541,015 [4,127,945–5,055,164]	899,490 [-188,659 – 5,129,371]	13 [-8 – 52]	71,812
200 year time horizon					
Baseline	38,352,090 [20,032,722–69,289,456]	5,526,048 [5,023,237–6,151,983]	-	-	-
Intervention	39,450,534 [20,504,678–70,688,539]	5,526,067 [5,023,253–6,152,045]	1,098,444 [-232,844 – 6,257,492]	19 [-13 – 80]	57,339
0% cost and QALY discounting					
Baseline	131,269,304 [70,344,106–232,091,657]	19,032,003 [17,299,165–21,189,859]	-	-	-
Intervention	135,084,581 [72,110,572–238,335,323]	19,032,102 [17,299,256–21,190,104	1,063,710 [-224,102 – 6,060,267]	18 [-12 – 75]	38,660
3.5% cost/1.5% QALY discounting					
Baseline	37,181,582 [19,384,816–67,271,249]	9,898,109 [8,997,192–11,019,882]	-	-	-
Intervention	38,245,293 [19,852,634–68,601,970]	9,898,152 [8,997,233–11,019,975]	1,063,710 [-225,101 – 6,060,267]	43 [-28 – 177]	24,730
Prison baseline testing rate -50%				-	
Baseline	37,204,722 [19,430,192–67,193,641]	5,354,351 [4,867,178–5,961,808]	-		-
Intervention	38,301,334 [19,812,198–68,894,466]	5,354,365 [4,867,189–5,960,856]	1,096,612 [-182,958 – 6,408,127]	14 [-7 – 68]	76,920
Prison baseline testing rate +50%					
Baseline	37,151,656 [19,331,024–67,336,749]	5,354,309 [4,867,158–5,960,720]	-	-	-
Intervention	38,201,217 [19,869,522–68,535,554]	5,354,328 [4,867,178–5,960,782]	1,049,561 [-282,046 – 5,920,724]	19 [-16 – 74]	53,940
Initiate 50% IDU on treatment within 2 years					
Baseline	37,181,175 [19,385,999–67,267,778]	5,354,337 [4,867,170–5,960,776]	-	-	-
Intervention	38,256,079 [19,856,146–68,697,483]	5,354,373 [4,867,197–5,960,890]	1,074,904 [-224,323 – 6,167,784]	36 [-17 – 157]	29,986

Double referral proportion					
Baseline	37,712,072 [19,807,378–67,857,408]	5,354,673 [4,867,328–5,961,410]	-	-	-
Intervention	38,803,757 [20,284,850–69,810,363]	5,354,692 [4,867,346–5,961,468]	1,091,685 [-226,827 – 6,284,914]	19 [-13 – 70]	58,750
Telaprevir/boceprevir					
Baseline	37,267,861 [19,518,085–67,256,446]	5,354,399 [4,867,239–5,961,127]	-	-	-
Intervention	38,345,149 [19,961,876–69,084,621]	5,354,518 [4,867,256–5,961,190]	1,077,288 [-225,364 – 6,176,985]	19 [-12 – 82]	55,640
20% IDU chronic prevalence					
Baseline	24,539,960 [12,548,516–45,775,871]	5,354,807 [4,859,588–5,968,193]	-	-	-
Intervention	25,529,615 [12,984,235–47,320,975]	5,354,818 [4,859,949–5,968,185]	980,656 [-137,975 – 6,116,728]	10 [-7 – 43]	94,393
50% IDU chronic prevalence					-
Baseline	50,615,429 [26,464,503–90,151,348]	5,353,717 [4,873,626–5,952,848]	-	-	
Intervention	51,762,624 [27,088,409–92,221,381]	5,252,742 [4,873,653–5,952,930]	1,147,195 [-338,515 – 5,936,328]	26 [-17 – 105]	44,861
Disutility on diagnosis					
Baseline	37,181,582 [19,384,816–67,271,249]	5,356,436 [4,868,848–5,963,166]	-	-	-
Intervention	38,245,293 [19,852,636–68,601,970]	5,356,288 [4,868,582–5,962,946]	1,063,710 [-225,102 – 6,060,267]	-148 [-480 – 85]	Dominated
No fall-out from treatment/referral					
Baseline	37,271,151 [19,501,405–67,253,280]	5,354,506 [4,867,296–5,961,008]	-	-	-
Intervention	38,446,836 [20,035,103–69,253,105]	5,354,619 [4,867,423–5,961,292]	1,175,684 [-259,158 – 6,640,839]	113 [-48 – 498]	10,402
No prevention benefit (static)					
Baseline	37,301,092 [19,454,718–67,498,289]	5,354,272 [4,867,133–5,960,654]	-	-	-
Intervention	38,366,893 [19,923,841–68,843,749]	5,354,290 [4,867,150–5,960,700]	1,065,802 [-227,958 – 6,059,407]	17 [-12 – 72]	61,289

Table 17. Results from the sensitivity analyses for the DBS in prison intervention.

Prison services intervention sensitivity scenario	ICER (£ per QALY gained)	Probability cost-effective at £20,000 WTP	Probability cost-effective at £30,000 WTP
No continuity (baseline)	59,418	10%	21%
10% continuity	38,955	18%	41%
20% continuity	29,342	31%	61%
30% continuity	23,718	44%	75%
40% continuity	20,001	57%	83%
50% continuity	17,338	69%	87%
60% continuity	15,320	76%	90%
70% continuity	13,722	82%	92%
80% continuity	12,414	86%	94%
90% continuity	11,318	90%	95%
100% continuity	10,402	91%	95%

Table 18. Cost-effectiveness results from the prison intervention sensitivity analysis: implication of varying fall-out from treatment/referral to and from prison.

GP intervention sensitivity analysis scenario	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
Baseline scenario					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	40,547,027 [20,944,330–75,172,430]	5,354,573 [4,867,293–5,961,241]	3,365,444 [489,795–12,000,645]	243 [33–691]	13,877
50 year time horizon					
Baseline	31,624,821 [16,311,919–57,491,887]	4,541,002 [4,127,934–5,055,123]	-	-	-
Intervention	34,673,561 [17,790,452–64,651,001]	4,451,116 [4,128,015–5,055,451]	3,048,740 [486,003–10,546,635]	161 [19–481]	18,911
200 year time horizon					
Baseline	38,352,090 [20,032,722–69,289,456]	5,526,048 [5,023,237–6,151,983]	-	-	-
Intervention	41,786,295 [21,618,339–77,384,153]	5,526,308 [5,023,372–6,152,490]	3,434,206 [490,147–12,303,263]	261 [37–739]	13,178
0% cost and QALY discounting					
Baseline	131,269,304 [70,344,106–232,091,657]	19,032,003 [17,299,165–21,189,859]	-	-	-
Intervention	140,196,904 [74,029,189–254,381,854]	19,033,447 [17,299,940–21,192,071]	3,365,444 [489,795–1,200,065]	243 [33–691]	6,184
3.5% cost/1.5% QALY discounting					
Baseline	37,181,582 [19,384,816–67,271,249]	9,898,109 [8,997,192–11,019,882]	-	-	-
Intervention	40,547,027 [20,944,330–75,172,430]	9,898,723 [8,997,193–11,020,872]	3,365,444 [489,795–12,000,645]	614 [94–164]	5,479
GP baseline testing rate -50%					
Baseline	37,063,336 [19,159,883–67,306,013]	5,354,259 [4,867,138–5,960,620]	-	-	-
Intervention	41,077,236 [20,920,272–77,404,976]	5,354,419 [4,867,220–5,960,947]	4,013,900 [469,195–14,353,918]	160 [19–490]	25,060
GP baseline testing rate +50%					
Baseline	37,282,946 [19,560,856–67,018,994]	5,354,394 [4,867,196–5,960,892]	-	-	-
Intervention	40,326,710 [21,006,718–73,874,151]	5,354,682 [4,867,346–5,961,438]	3,043,764 [450,564–10,798,949]	289 [44–757]	10,542
Double referral proportion					
Baseline	37,712,072 [19,807,377–67,857,408]	5,354,673 [4,867,328–5,961,410]	-	-	-
Intervention	41,320,256	5,354,911	3,608,183	238	15,172

	[21,407,764–76,331,108]	[4,867,460–5,961,822]	[516,616–12,835,031]	[40–580]	
Telaprevir/boceprevir					
Baseline	37,267,861 [19,518,085–67,256,446]	5,354,499 [4,867,239–5,961,127]	-	-	-
Intervention	40,864,377 [21,108,668–75,883,067]	5,354,807 [4,867,400–5,961,732]	3,596,516 [464,428–13,257,863]	308 [43–891]	11,675
20% IDU chronic prevalence					
Baseline	24,539,960 [12,548,516–45,775,871]	5,354,807 [4,859,588–5,968,193]	-	-	-
Intervention	27,027,350 [13,711,128–51,083,782]	5,354,945 [4,859604–5,968,376]	2,487,391 [190,928–8,811,111]	138 [19–393]	18,082
50% IDU chronic prevalence					
Baseline	50,615,429 [26,464,503–90,151,348]	5,353,717 [4,873,626–5,952,848]	-	-	-
Intervention	53,537,160 [48,736,258–59,528,484]	5,354,070 [4,873,835–5,953,538]	4,299,427 [703,232–1,508,680]	354 [49–1,001]	12,141
Disutility on diagnosis					
Baseline	37,181,582 [19,384,816–67,271,249]	5,356,436 [4,868,848–5,963,166]	-	-	-
Intervention	40,548,027 [20,944,330–75,172,431]	5,356,329 [4,868,754–5,963,136]	3,365,444 [489,795–12,000,645]	-107 [-297 – 69]	Dominated
No fall-out to prison					
Baseline	37,271,151 [19,501,405–67,253,280]	5,354,506 [4,867,296–5,961,008]	-	-	-
Intervention	40,709,773 [21,037,839–75,400,789]	5,354,729 [4,867,413–5,961,446]	3,438,622 [496,468–12,165,395]	223 [32–616]	15,412

Table 19. Results from the sensitivity analyses for the GP intervention.

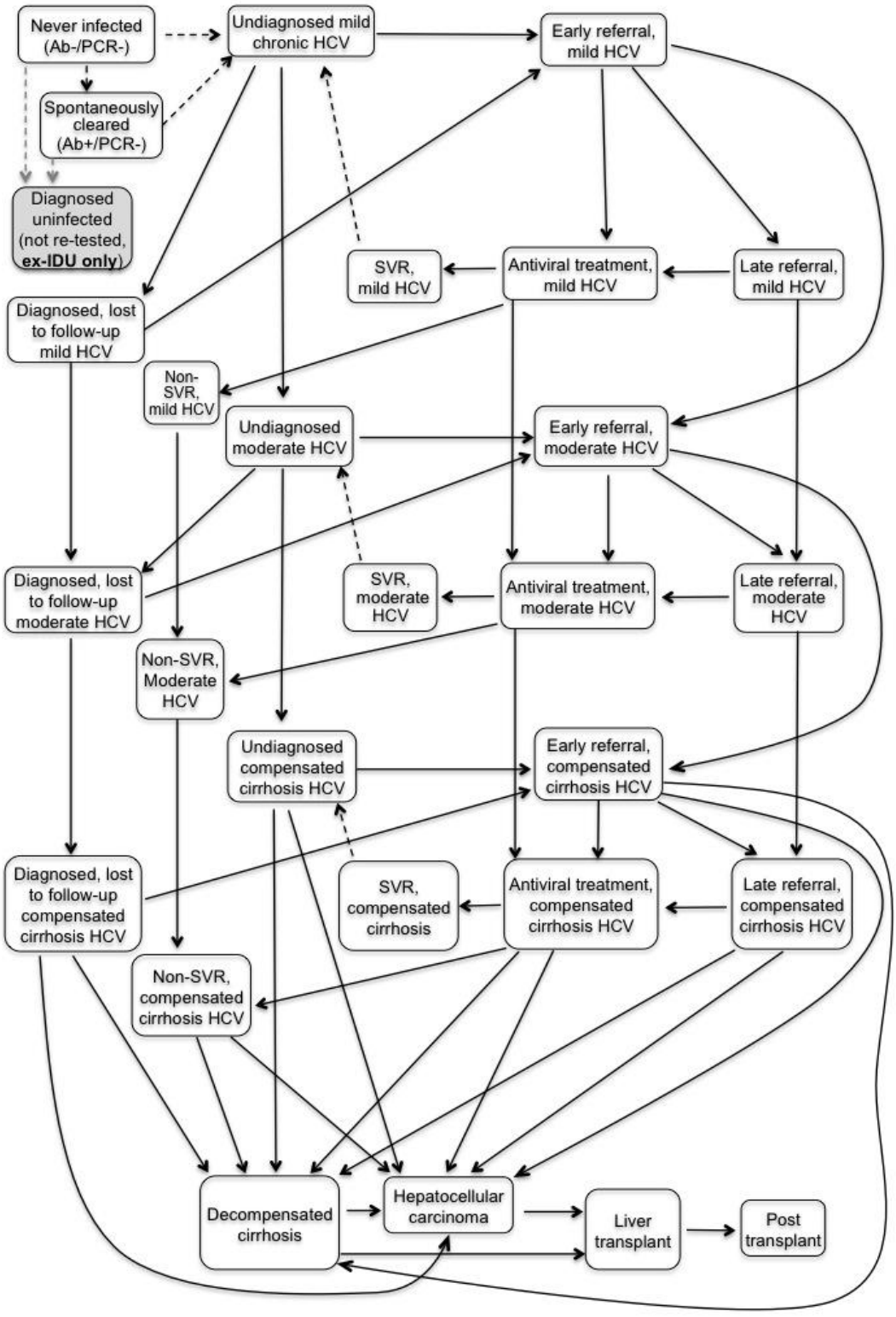
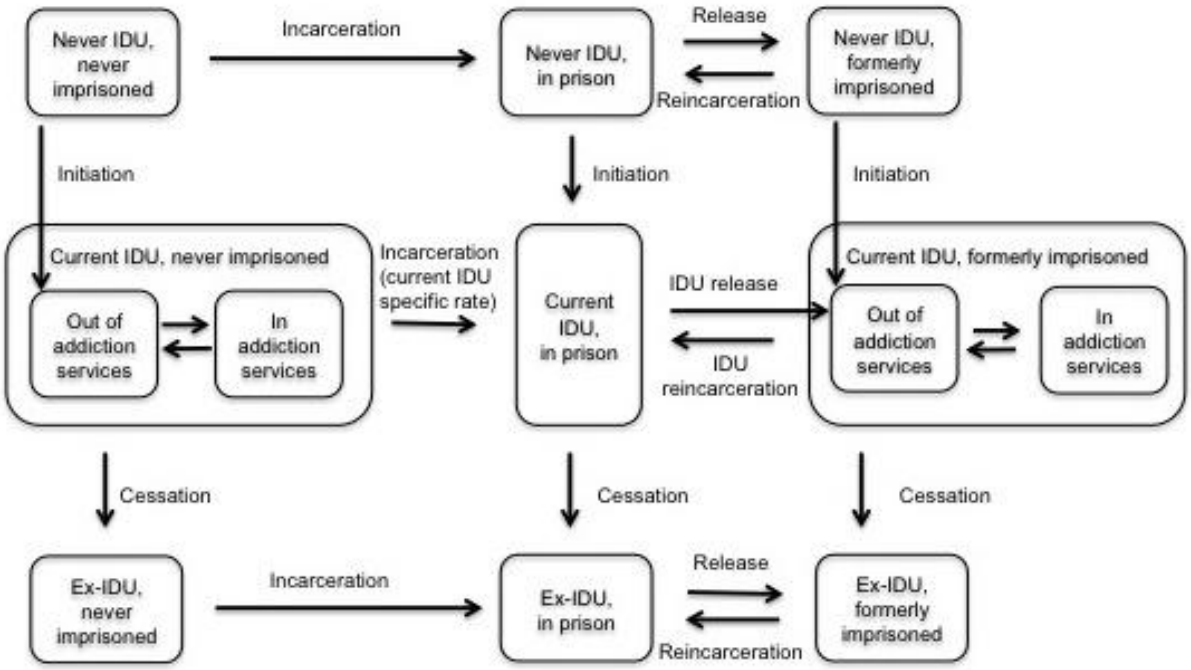


Figure 1. HCV disease progression, treatment, and diagnosis model schematic. Solid black lines indicate transitions for both IDUs and ex-IDUs. Dashed black lines indicate IDU transitions only. Dashed grey lines (and grey boxes) indicate ex-IDU transitions/compartments only.



Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from IDU compartments, and inflow to the youngest 'Never IDU, never imprisoned' compartment.

Figure 2. General model flow schematic (each IDU and ex-IDU compartment includes HCV infection sub-compartments).

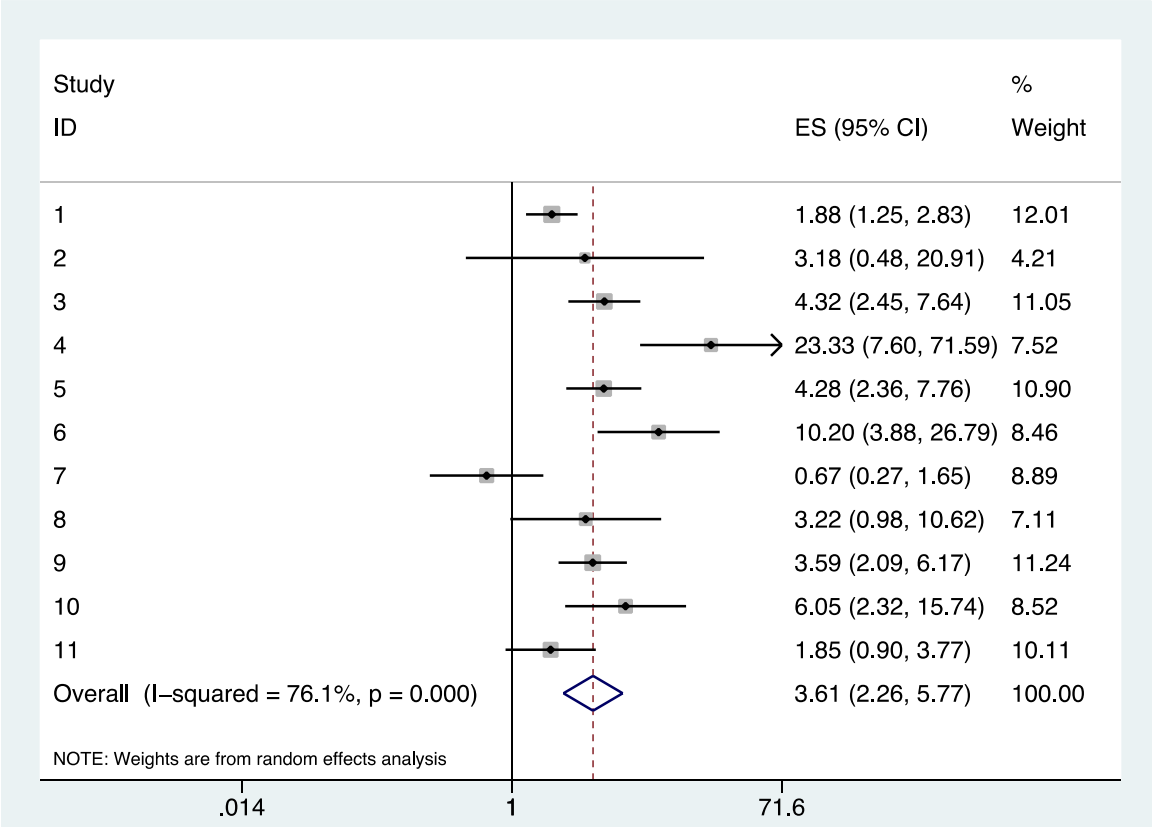


Figure 3. Meta-analysis results for the dried blood spot in addiction services intervention effect on testing rate.

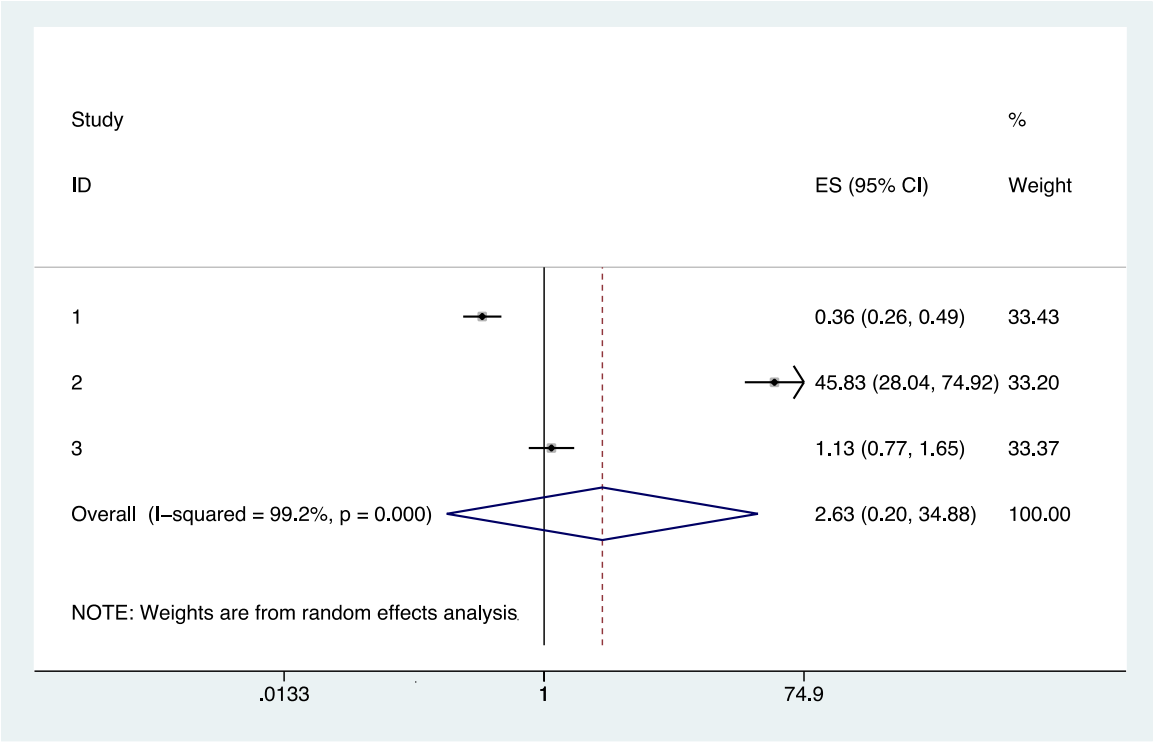


Figure 4. Meta-analysis results for the dried blood spot in prison services intervention effect on testing rate.

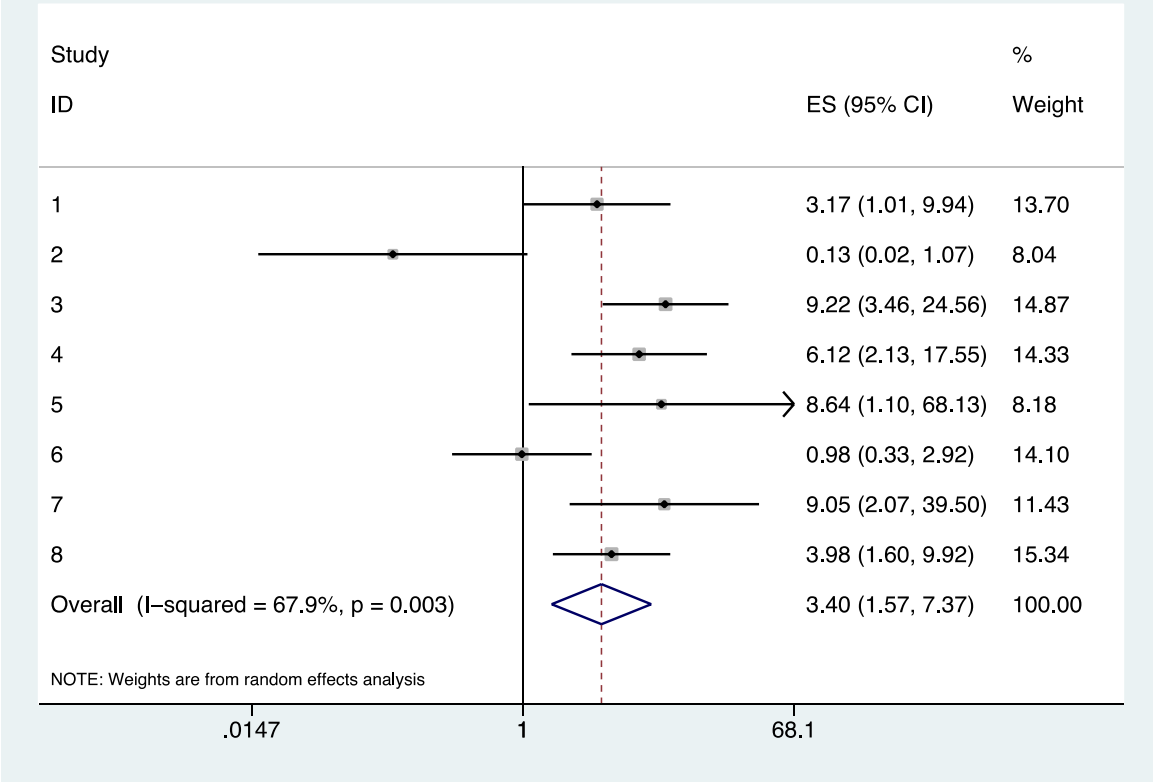


Figure 5. Meta-analysis results for the GP intervention on testing rate.

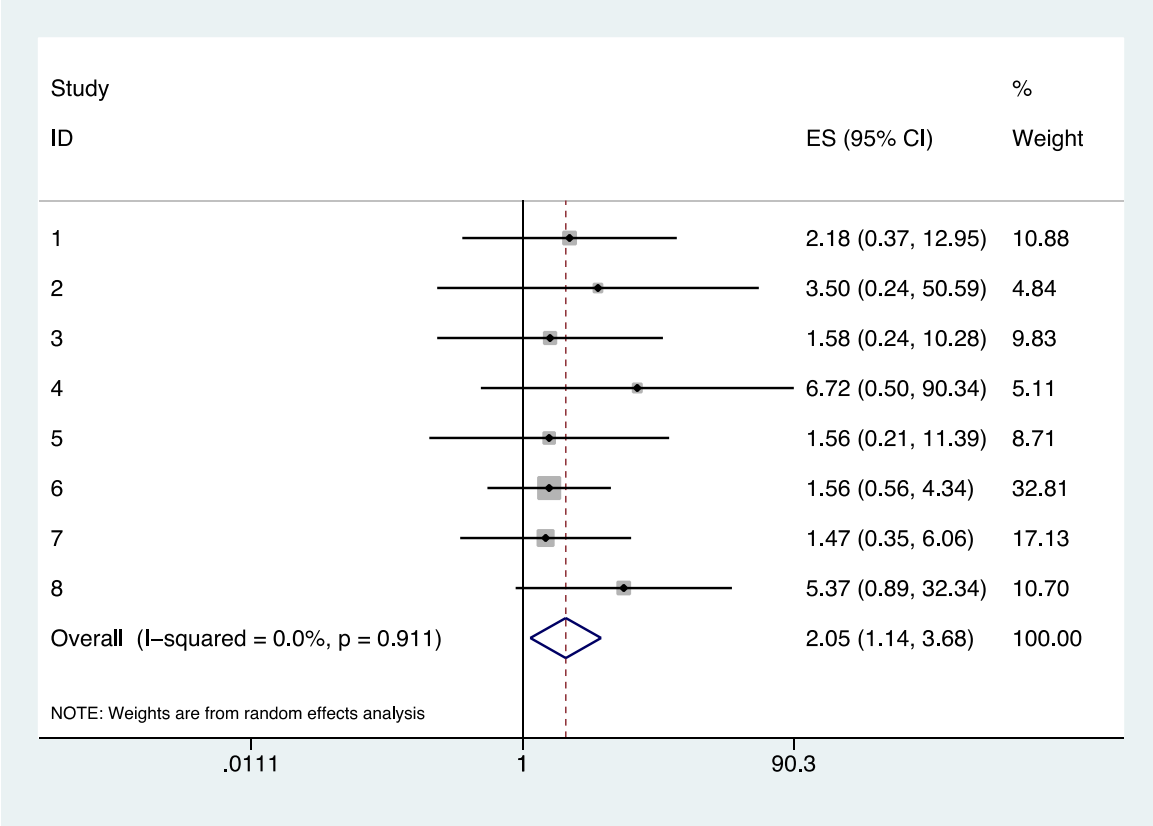
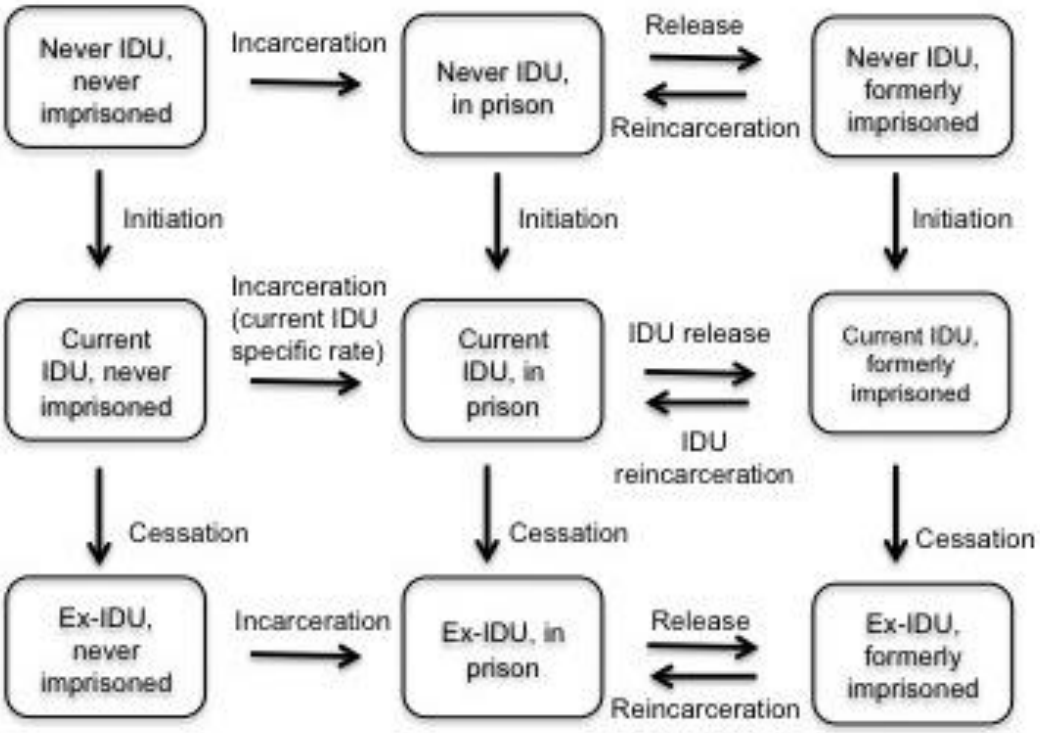


Figure 6. Meta-analysis results for the GP intervention on test yield (proportion tests antibody positive).



Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from IDU compartments, and inflow to the youngest 'Never IDU, never imprisoned' compartment.

Figure 7. Simplified model #1 schematic for fitting procedure #1.

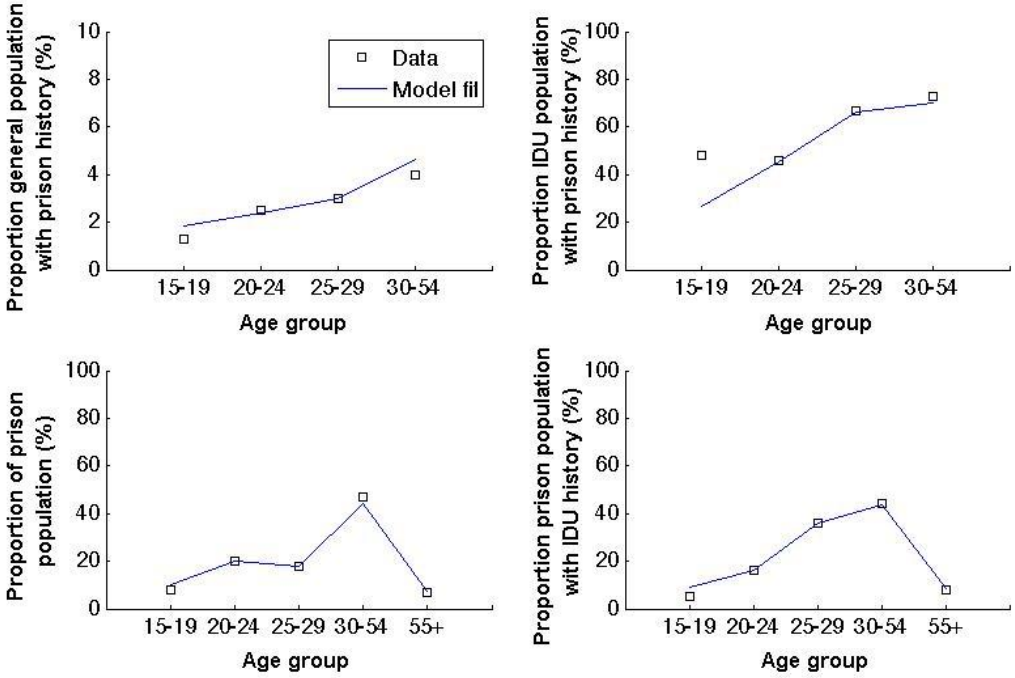
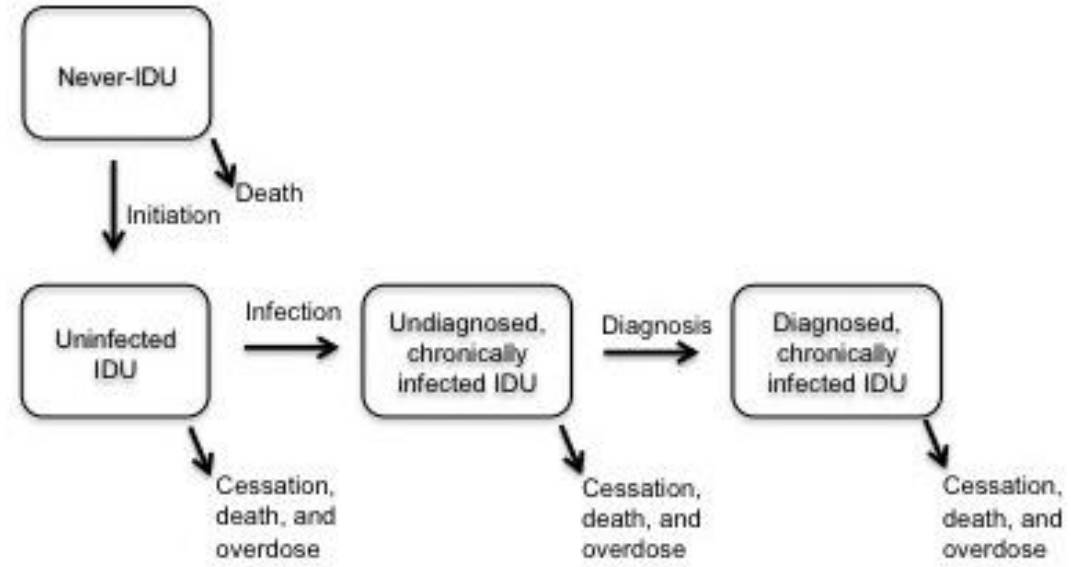


Figure 8. Example of one characteristic model fit to the prison data (injecting duration 11 years, IDU incarceration duration 4 months, IDU overdose rate 1% per year). The top left shows the age-distributed proportion of general population with a custodial sentence. The bottom left shows the age-distribution within the prison population. The top right shows the proportion of IDUs who have previously been incarcerated. The bottom right shows the proportion of prisoners who report ever IDU. Additionally, the model was fit to proportion of the general population imprisoned (simulated 0.21% as compared to 0.2%[38 39]) and the proportion of population current IDUs (simulated 0.58% as compared to 0.65%[12])



Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]) and includes inflow to the youngest [15-19] 'Never IDU' compartment.

Figure 9. Simplified model #3 schematic for fitting procedure #3.

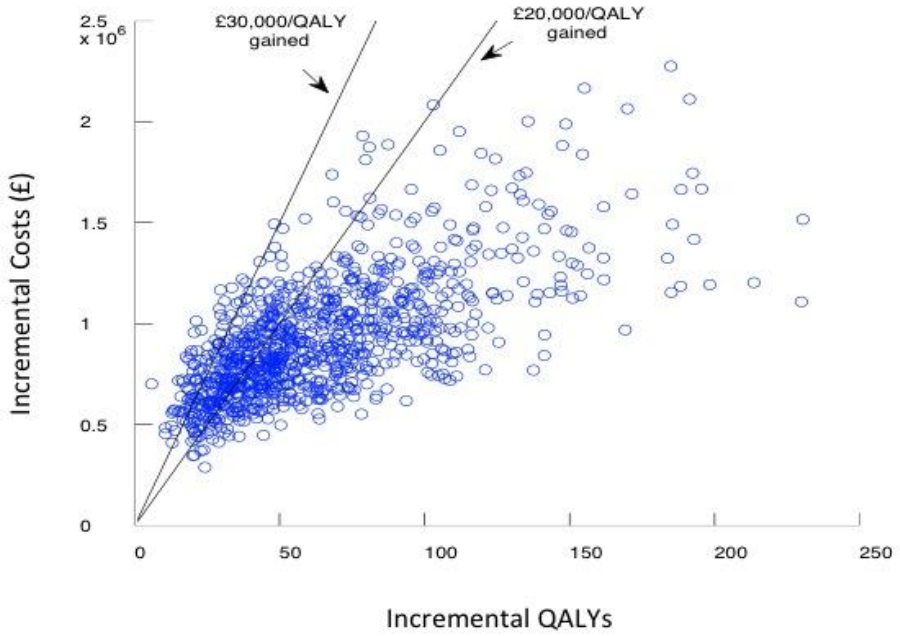


Figure 10. Results for the dried blood spot in addiction services intervention, showing the incremental costs and incremental QALYs for each of the 1000 simulation runs.

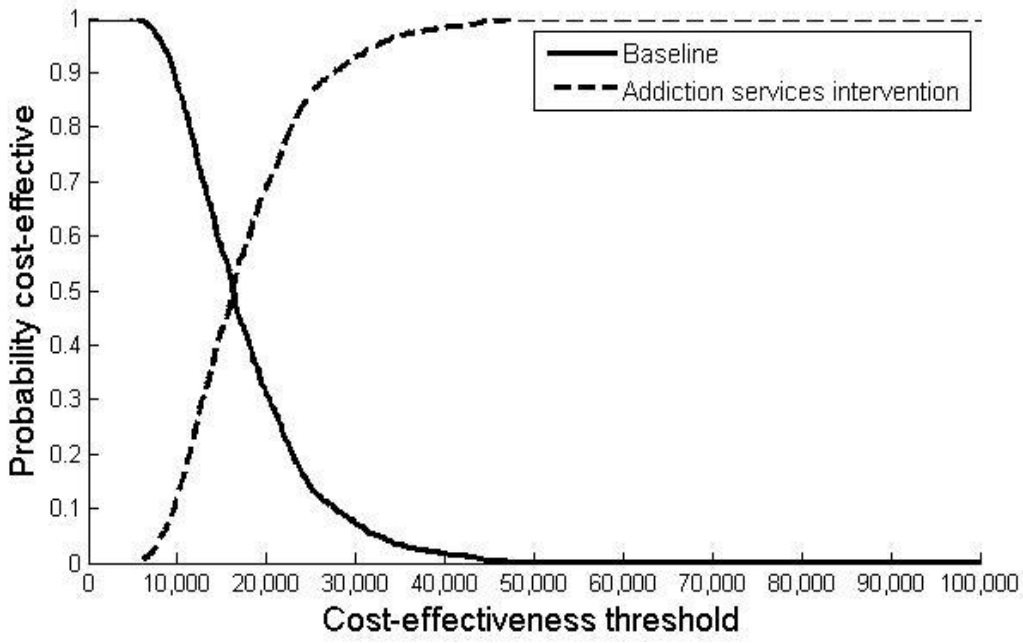


Figure 11. Cost-effectiveness acceptability curves for the dried blood spot in addiction services intervention. The cost-effectiveness threshold is given in £ per QALY gained.

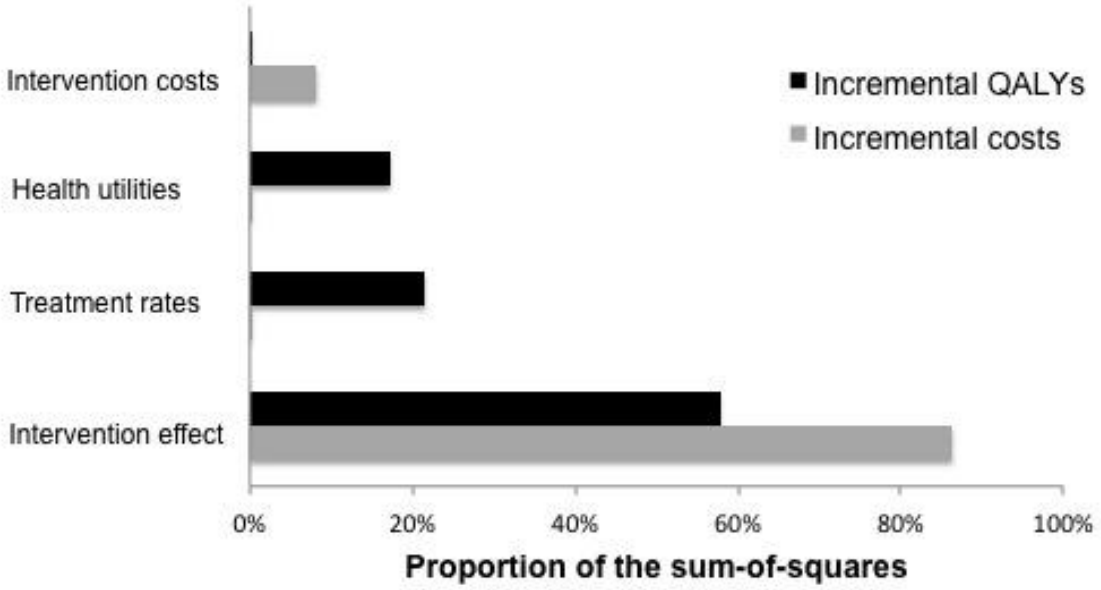


Figure 12. ANCOVA results of the proportion of the sum-of-squares of the incremental QALYs (black) and incremental costs(gray) explained by the model parameters (only most important ones shown) for the dried blood spot in addiction services intervention.

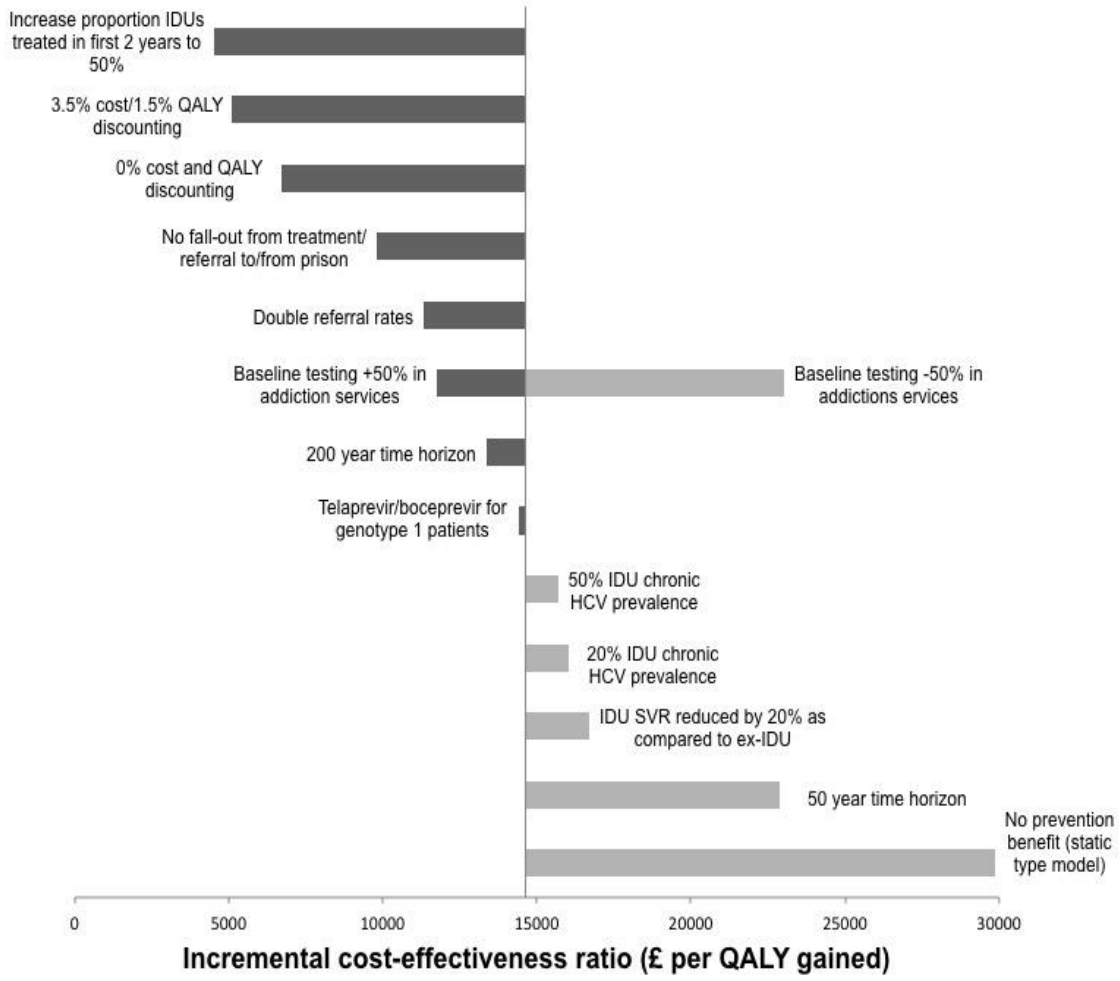


Figure 13. Sensitivity analyses results for the addiction services intervention. The vertical line indicates the incremental cost-effectiveness ratio) for the baseline scenario.

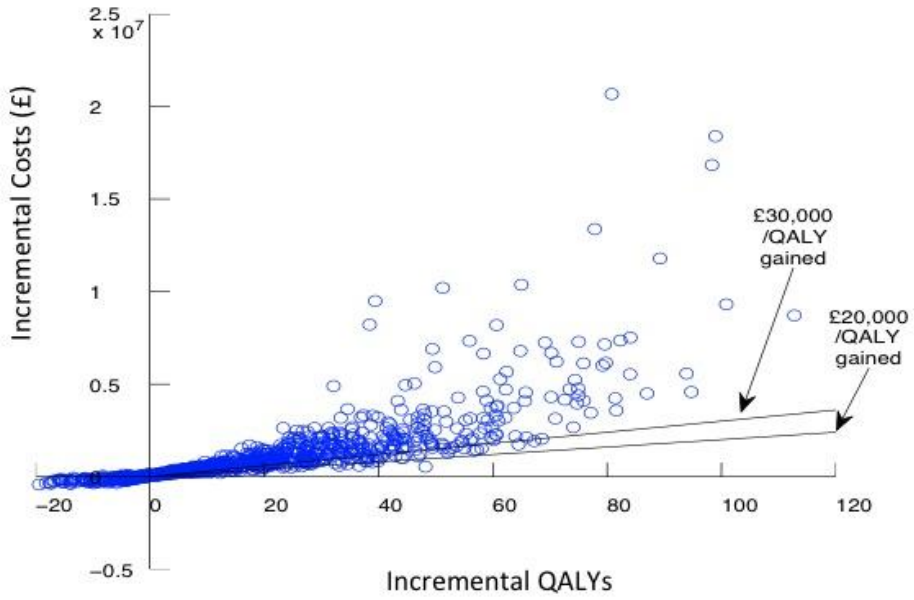


Figure 14. Results for the dried blood spot in prison services intervention, showing the incremental costs and incremental QALYs for each of the 1000 simulation runs.

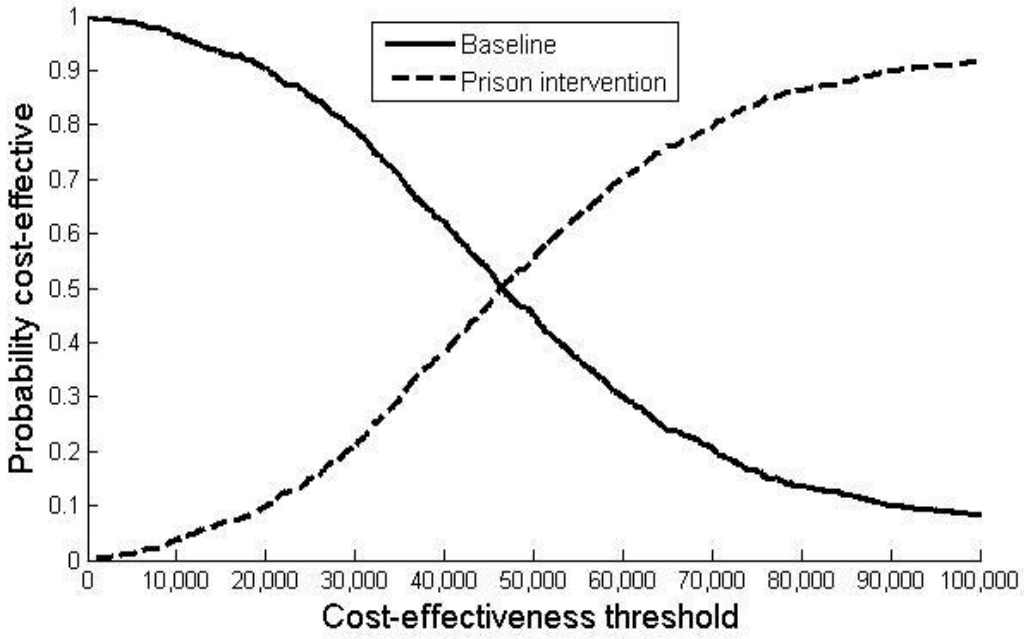


Figure 15. Cost-effectiveness acceptability curves for the dried blood spot in prison services intervention. The cost-effectiveness threshold is given in £ per QALY gained.

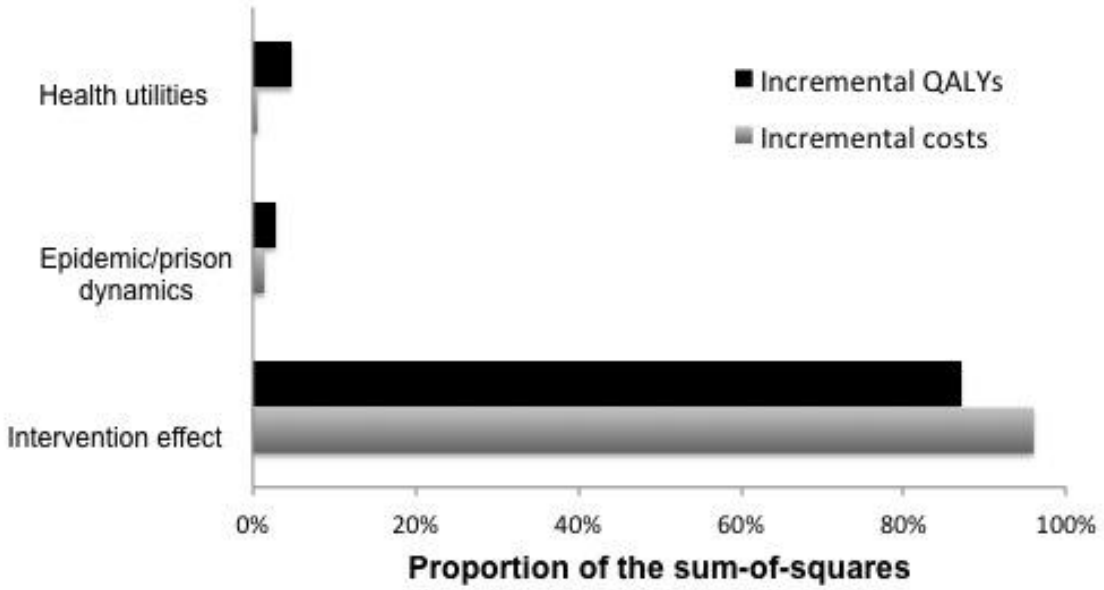


Figure 16. ANCOVA results of the proportion of the sum-of-squares of the incremental QALYs (black) and incremental costs (gray) explained by the model parameters (only most important ones shown) for the dried blood spot in prison services intervention.

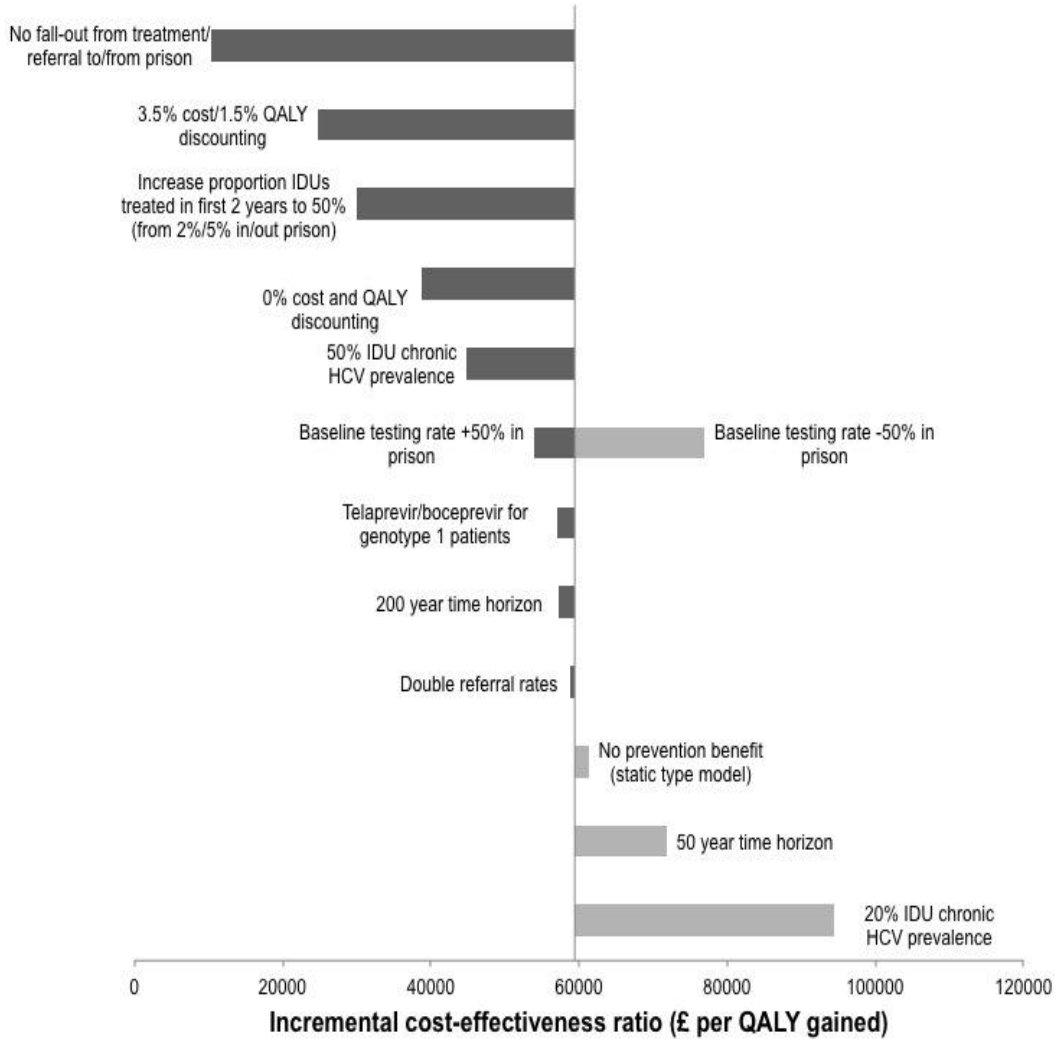


Figure 17. Sensitivity analyses results for the prison intervention. The vertical line indicates the incremental cost-effectiveness ratio (£ per QALY gained) for the baseline scenario.

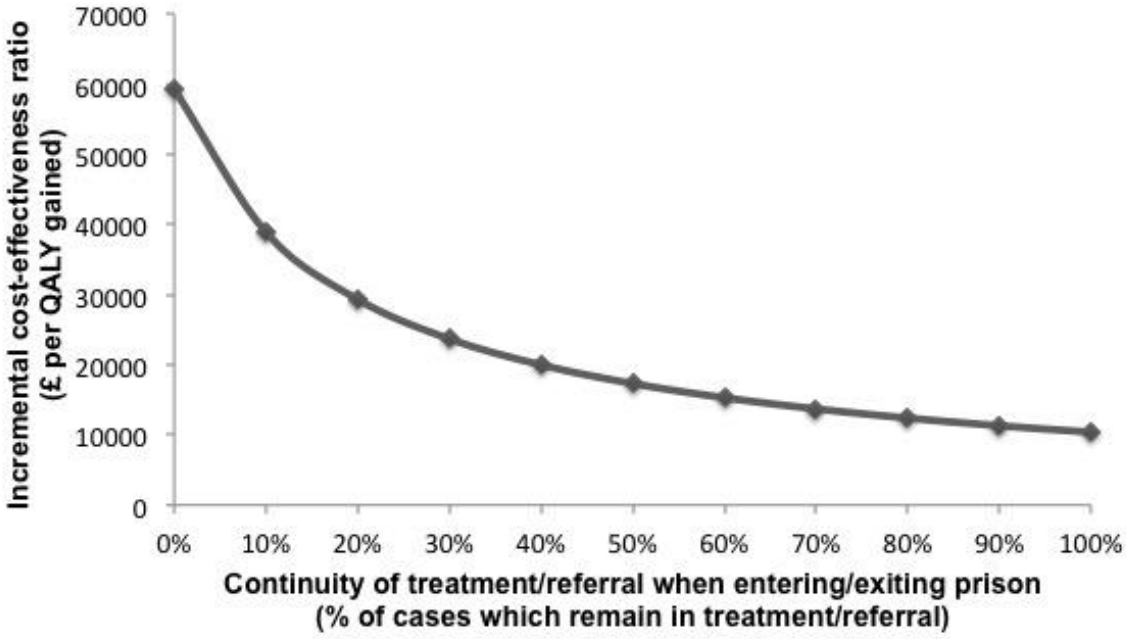


Figure 18. Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions.

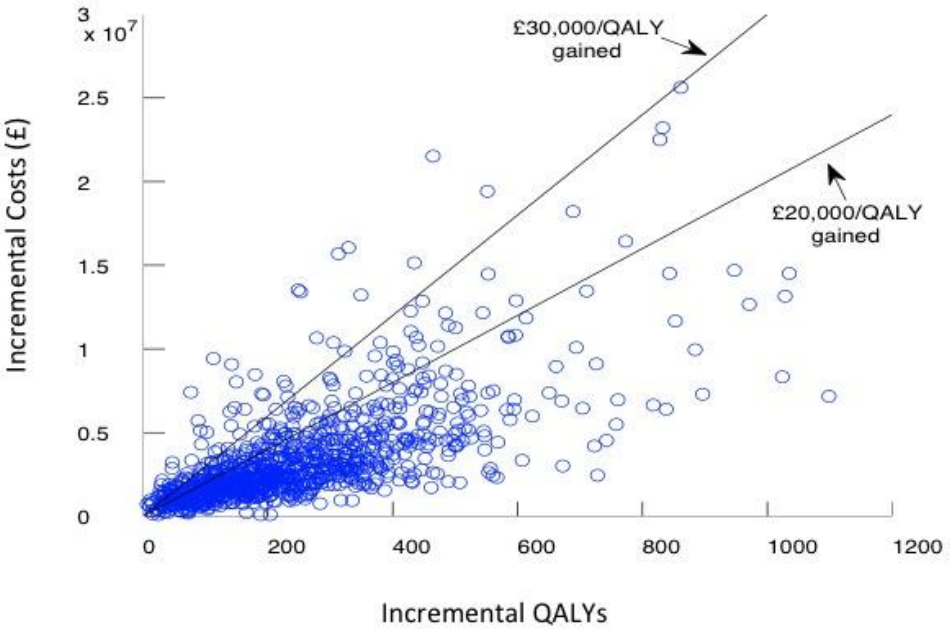


Figure 19. Results for the GP intervention, showing the incremental costs and incremental QALYs for each of the 1000 simulation runs.

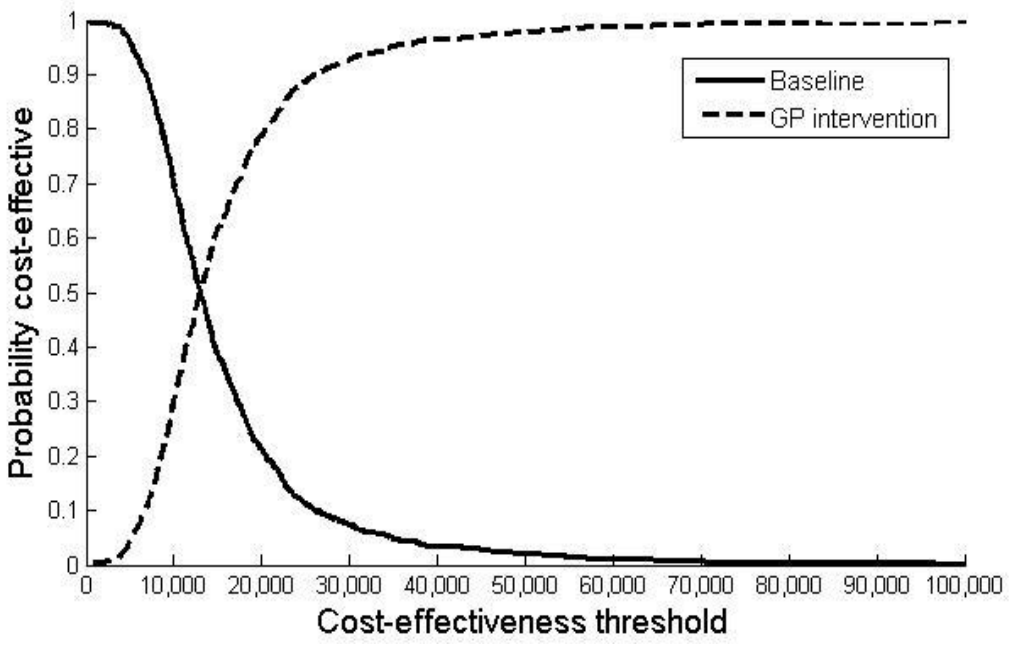


Figure 20. Cost-effectiveness acceptability curves for the GP intervention. The cost-effectiveness threshold is given in £ per QALY gained.

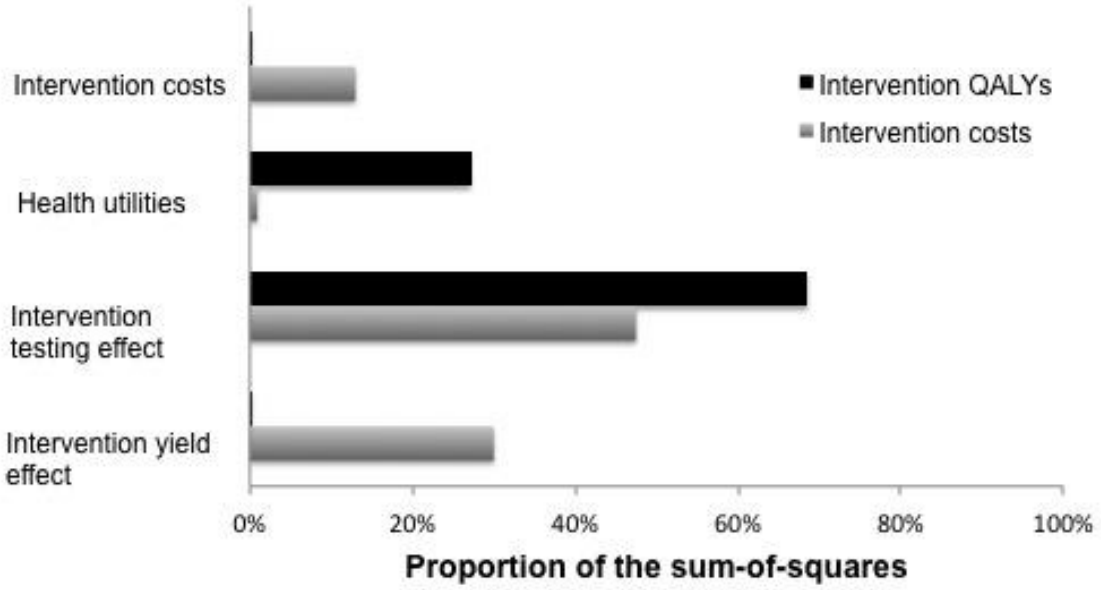


Figure 21. ANCOVA results of the proportion of the sum-of-squares of the incremental QALYs (black) and incremental costs(gray) explained by the model parameters (only most important ones shown) for the GP intervention.

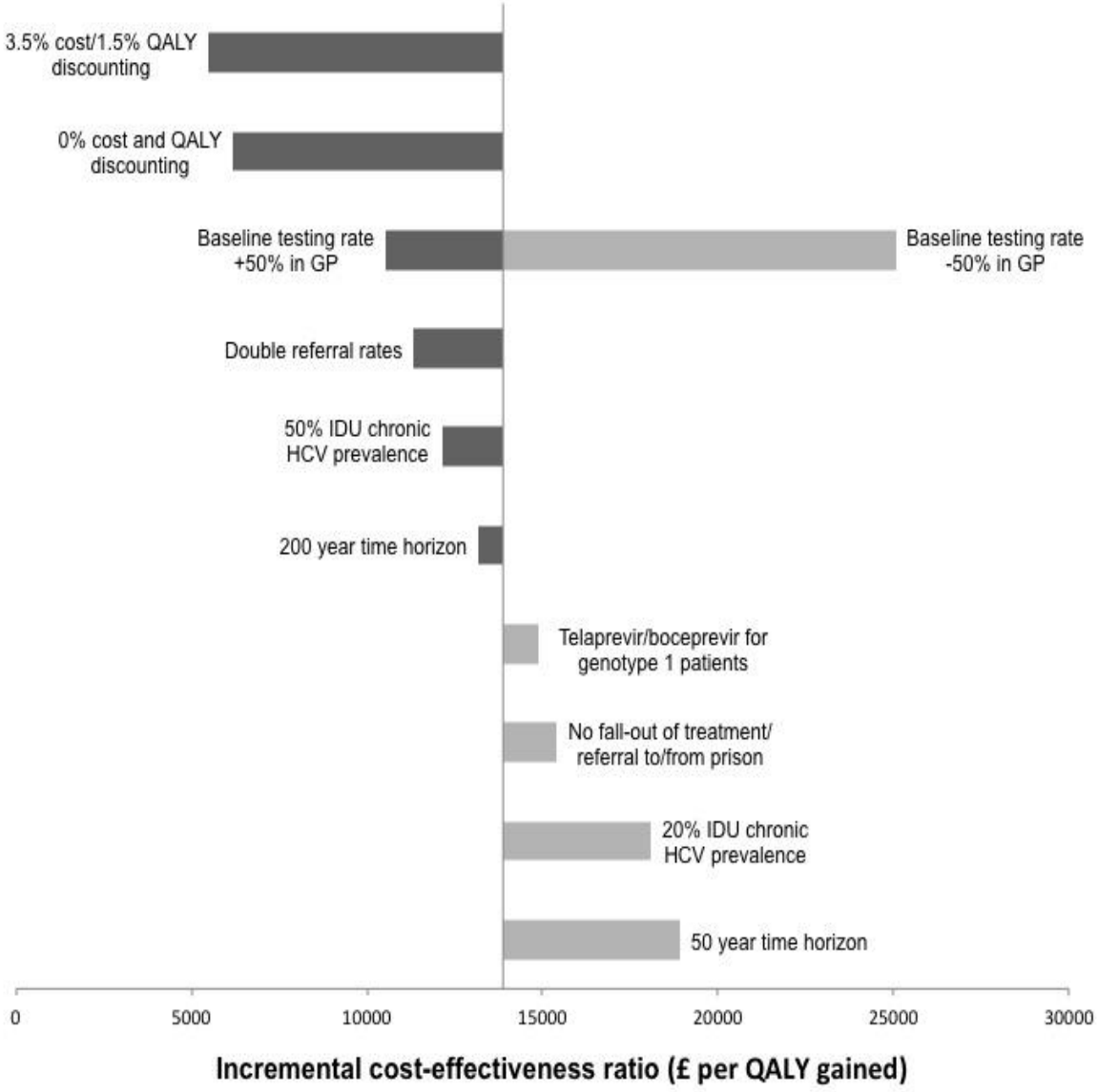


Figure 22. Sensitivity analyses results for the GP intervention. The vertical line indicates the incremental cost-effectiveness ratio for the baseline scenario.

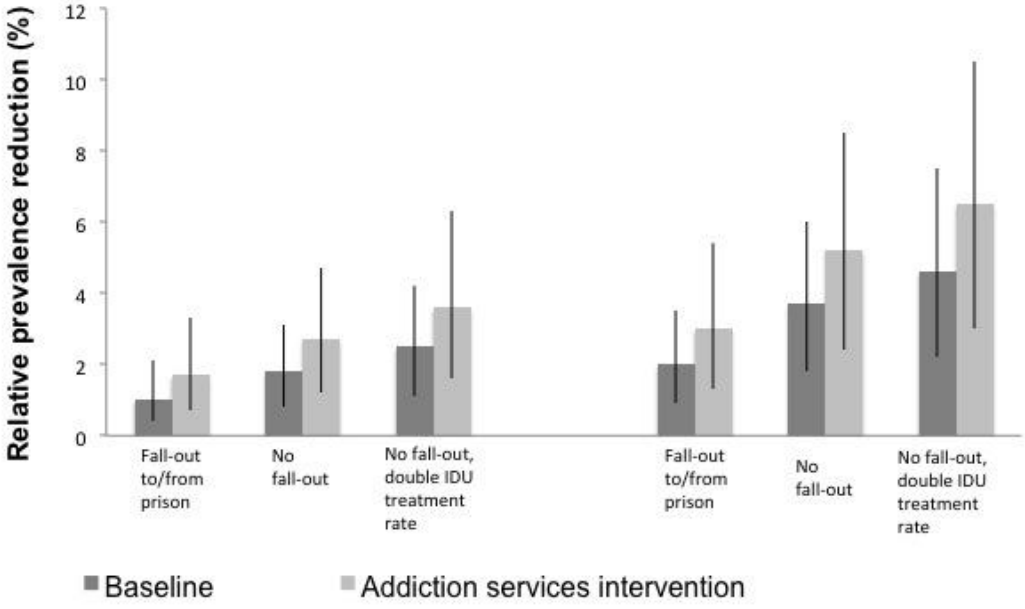


Figure 23. Epidemiological impact (relative prevalence reduction) on the IDU HCV chronic prevalence at 10 and 20 years with the dried blood spot in addiction services intervention.

1. Hickman M, McDonald T, Ali J, Nichols T, Hope V, Skidmore S, et al. Increasing the uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment and prison settings by using dried blood spots for diagnostic testing: a cluster randomized controlled trial. *Journal of Viral Hepatitis* 2008;15(4):250-254.
2. Craine N, Parry J, O'Toole J, D'Arcy S, Lyons M. Improving blood-borne viral diagnosis; clinical audit of the uptake of dried blood spot testing offered by a substance misuse service. *Journal of Viral Hepatitis* 2009;16:219-222.
3. Cullen BL, Hutchinson SJ, Cameron SO, Anderson E, Ahmed S, Spence E, et al. Identifying former injecting drug users infected with hepatitis C: an evaluation of a general practice-based case-finding intervention. *J Public Health (Oxf)* 2011;Epub ahead of print.
4. Miners A, Ghosh A, Martin NK, Vickerman P. An economic evaluation of finding cases of hepatitis B and C infection in UK migrant populations, 2012.
5. Jones L, Bates G, McCoy E, Beynon C, McVeigh J, Bellis M. A systematic review of qualitative research on the views, perspectives and experiences of hepatitis B and C testing among practitioners and people at greatest risk of infection., 2011.
6. Jones L, Bates G, McCoy E, Luxton A, Beynon C, McVeigh J, et al. A practice survey of activities and interventions that aim to raise awareness among, and/or engage with, groups who are at an increased risk of hepatitis B and C infection, 2012.
7. Jones L, Bates G, McCoy E, Beynon C, McVeigh J, Bellis M. A systematic review of the effectiveness & cost-effectiveness of interventions aimed at raising awareness and engaging with groups who are at an increased risk of hepatitis B and C infection, 2012.
8. Martin NK, Miners A, Vickerman P, Foster G, Hutchinson S, Goldberg D, et al. The cost-effectiveness of HCV antiviral treatment for injecting drug user populations. *Hepatology* 2012;55(1):49-57.
9. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modelling analysis of its prevention utility. *Journal of Hepatology* 2011;54:1137-1144.
10. Turner K, Hutchinson S, Craine N, Hope V, Palmateer N, Vickerman P, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of Hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction* 2011;106(11):1978-88.
11. Health Protection Agency Colindale. Hepatitis C in the UK 2011, July 2011.
12. Harris RJ, Ramsay M, Hope VD, Brant L, Hickman M, Foster GR, et al. Hepatitis C prevalence in England remains low and varies by ethnicity: an updated evidence synthesis. *European Journal of Public Health* 2011;Epub ahead of print.
13. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2011: University of Kent, 2011.

14. Martin NK. Can HCV antiviral treatment play a role in prevention? Modelling impact, cost-effectiveness, and heterogeneity. *International Network on Hepatitis in Substance Users (INHSU) 2nd International Symposium*. Brussels, Belgium, 2011.
15. Sutton AJ, Gay NJ, Edmunds WJ, Andrews NJ, Hope VD, Gilbert RL, et al. Modelling the hepatitis B vaccination programme in prisons. *Epidemiol Infect* 2006;134:231 - 242.
16. Sutton AJ, Edmunds WJ, Sweeting MJ, Gill ON. The cost-effectiveness of screening and treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis. *Journal of Viral Hepatitis* 2008;15(11):797-808.
17. Martin NK, Vickerman P, Hickman M. Mathematical modelling of Hepatitis C Treatment for Injecting Drug Users. *Journal of Theoretical Biology* 2011;274:58-66.
18. Zeiler I, Langlands T, Murray JM, Ritter A. Optimal targeting of Hepatitis C virus treatment among injecting drug users to those not enrolled in methadone maintenance programs. *Drug and Alcohol Dependence* 2010;In Press, Corrected Proof.
19. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaulation. *Health Technology Assessment* 2007;11(11):1-224.
20. Wright M, Grieve R, Roberts J, Main J, HC T. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006;10(21).
21. Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment, or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(17):1-210.
22. John-Baptiste A, Krahn MD, Heathcote J, Laporte A, Tomlinson G. The natural history of hepatitis C infection acquired through injection dru guse: Meta-analysis and meta-regression. *Journal of Hepatology* 2010;53(2):245-251.
23. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D: University of York, 2008.
24. Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, et al. The cost-effectiveness of testing for hepatitis C in former injecting drug users. *Health Technology Assessment* 2006;2006(10):32.
25. Dalgard O, Egeland A, Skaug K, Vilimas K, Steen T. Health-related Quality of Life in Active Injecting Drug Users With and WIthout Chronic Hepatitis C Virus Infection. *Hepatology* 2004;39(1):74-80.
26. British Medical Association. *British National Formulary, number 62*: BMJ Publishing Group, 2011.
27. Judd A, Parry J, Hickman M, McDonald T, Jordan L, Lewis K, et al. Evaluation of a modified commercial assay in detecting antibody to hepatitis C virus in oral fluids and dried blood spots. *J Med Virol* 2003;71:49 - 55.

28. Colin C, Lanoir D, Touzet S, Meyaud-Kraemer L, Bailly F, Trepo C. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. *J Viral Hepat* 2001;8(2):87-95.
29. Stein K, Dalziel K, Walker A, Jenkins B, Round A, Royle P. Screening for Hepatitis C in injecting drug users: A cost utility analysis. *Journal of Public Health* 2004;26(1):61-71.
30. Irving WL, Smith S, Cater R, Pugh S, Neal KR, Coupland CAC, et al. Clinical pathways for patients with newly diagnosed hepatitis C - What actually happens. *Journal of Viral Hepatitis* 2006;13(4):264-271.
31. Jowett SL, Agarwal K, Smith BC, Craig W, Hewett M, Bassendine DR, et al. Managing chronic hepatitis C acquired through intravenous drug use. *Q J Med* 2001;94:153-158.
32. Foster G, Goldin RD, Main J, Murray-Lyon I, Hargreaves S, Thomas HC. Management of chronic hepatitis C: clinical audit of bipsy based management algorithm. *BMJ* 1997;315:453-8.
33. NICE. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. *Technology appraisal guidance 106*: National Institute for Health and Clinical Excellence, 2006.
34. Bruno S, Shiffman M, Roberts SK, Gane EJ, Messinger D, Hadziyannis SJ, et al. Efficacy and Safety of Peginterferon Alfa-2D (40KD) Plus Ribavirin in Hepatitis C Patients with Advanced Fibrosis and Cirrhosis. *Hepatology* 2010;51(2):388-397.
35. Hellard M, Sacks-Davis R, Gold J. Hepatitis C Treatment for Injection Drug Users: A Review of the Available Evidence. *Clinical Infectious Diseases* 2009;49(4):561-573.
36. Prime J, White S, Liriano S, K P. Criminal careers of those born between 1953 and 1978, England and Wales: Home Office, Statistical Bulletin, 2001.
37. Ministry of Justice. Offender Management Statistics Quarterly Bulletin, April to June 2011, England and Wales, 2011.
38. Ministry of Justice. Population in Custody Tables August 2010, 2010.
39. Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2010, 2010.
40. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following hepatitis C infection: a systematic review of longitudinal studies. *Journal of Viral Hepatitis* 2006;13:34-41.
41. Health Protection Agency. Data tables of the Unlinked Anonymous Monitoring Survey of HIV and Hepatitis in Injecting Drug Users Surveillance Update: July 2011, 2011.
42. Hickman M, Hope V, Brady T, Madden P, Jones S, Honor S, et al. Hepatitis C virus (HCV) prevalence, and injecting risk behaviour in multiple sites in England in 2004. *Journal of Viral Hepatitis* 2007;14(9):645-652.
43. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *BMJ* 2010;341.

44. Carroll RJ, Ruppert D. *Transformation and Weighting in Regression*: Chapman and Hall, 1988.
45. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press, 2006.
46. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *New England Journal of Medicine* 2011;364(25):2405-2416.
47. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. *New England Journal of Medicine* 2011;364(13):1195-1206.
48. Thompson Coon J, Castelnuovo E, Pitt M, Cramp M, Siebert U, Stein K. Case finding for hepatitis C in primary care: a cost utility analysis. *Family Practice* 2006;23(4):393-406.
49. Helsper CW, Borkent-Raven BA, De Wit NJ, Van Essen GA, Bonten MJM, Hoepelman AIM, et al. Cost-effectiveness of targeted screening for hepatitis C in The Netherlands. *Epidemiol Infec* 2012;140:58-69.
50. Department of Health, HPA Prison Infection Prevention Team, Liver Strategy Team. National Survey of hepatitis C services in prisons (Draft report). 2011.
51. Halfon P, Locarnini S. Hepatitis C virus resistance to protease inhibitors. *Journal of Hepatology* 2011;55(1):192-206.
52. Jones A, Weston S, Moody A, Millar T, Dollin L, Anderson T, et al. The drug treatment outcomes research study (DTORS): baseline report, 2007.
53. Judd A, Hutchinson S, Wadd S, Hickman M, Taylor A, Jones S, et al. Prevalence of, and risk factors for, hepatitis C virus infection among recent initiates to injecting in London and Glasgow: cross sectional analysis. *Journal of Viral Hepatitis* 2005;12(6):655-662.
54. Hadziyannis SJ, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-Î±2a and Ribavirin Combination Therapy in Chronic Hepatitis C. *Annals of Internal Medicine* 2004;140(5):346-355.
55. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon Alfa-2b or Alfa-2a with Ribavirin for Treatment of Hepatitis C Infection. *New England Journal of Medicine* 2009;361(6):580-593.
56. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, et al. Peginterferon Alfa-2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3. *N Engl J Med* 2007;357(2):124-134.
57. Sweeting MJ, De Angelis D, Ades AE, Hickman M. Estimating the prevalence of ex-injecting drug use in the population. *Statistical Methods in Medical Research* 2009;18(4):381-395.
58. Vickerman P, Miners A, Williams J. Assessing the cost-effectiveness of interventions linked to needle and syringe programmes for injecting drug users. In: NICE, editor. London, 2008.
59. Government Actuary's Department. Interim life tables 1980-82 to 2004-06: Office for National Statistics.
60. Hay G, Gannon M, MacDougall J, Eastwood C, Williams K, Millar T. Capture-recapture and anchored preavlence estimation of injecting drug users in

England: national and regional estimates. *Statistical Methods in Medical Research* 2009;18(4):323-339.
61. Schering Corporation. VICTRELIS (boceprevir) prescribing information. 2011.
62. Vertex Pharmaceuticals Incorporated. INCIVEK (telaprevir) prescribing information. 2011.
63. NELM.NHS.UK Press Release. Janssen Cilag launches telaprevir (Incivo) 375mg tablets for the treatment of genotype 1 chronic hepatitis c, 2011.
64. NELM.NHS.UK Press Release. MD launches boceprevir (Victrelis) for the treatment of chronic hepatitis C in the UK, 2011.
65. Lindenburg C, Lambers F, Urbanus A, Schinkel J, Jansen P, Krol A, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. *European Journal of Gastroenterology and Hepatology* 2011;23(1):23-31.
66. Rosenberg S, Goldberg R, Dixon L, Wolford G, Slade E, Himelboch S, et al. Assessing the STIRR Model of Best Practices for Blood-Borne Infections of Clients With Severe Mental Illness. *Psychiatric Services* 2010;61(9):885-891.
67. Anderson EM, Mandeville R, Hutchinson SJ, Cameron S, Mills PR, Fox R, et al. Evaluation of a General Practice Based Hepatitis C Virus Screening Intervention. *Scottish Medical Journal* 2009;54(3):3-7.
68. Hagedorn H, Dieperink E, Dingmann D, Durfee J, Ho S, Isenhart C, et al. Integrating hepatitis prevention services into a substance use disorder clinic. . *Journal of Substance Abuse Treatment* 2007;32(4):391-398.
69. Hennessy R, Weisfuse I, Schlanger K. Does integrating viral hepatitis services into a public STD clinic attract injection drug users for care? . *Public Health Reports* 2007;122:31-35.
70. Roudot-Thoraval F, Monnet E, Marcet P, Bastie A, Dhumeaux D, Miguet J. Strategies of hepatitis C virus screening in general practice. A two-centre randomized trial. . *Gasterenterologie Clinique et Biologique* 2000;24(11):1037-1041.
71. Perrett S. Prisoner health: assessing a nurse-led hepatitis C testing clinic. *British Journal of Nursing* 2011;20(10):611-4.
72. Sahajian F, Bailly F, Vanhems P, Fantino B, Vannier-Nitenberg C, Fabry J, et al. A randomized trial of viral hepatitis prevention among underprivileged people in the Lyon area of France. *Journal of Public Health* 2011;33(2):182-192.
73. Hagedorn H, Leighton T, Heim L. Assessment of a hepatitis educational group for veterans with substance use disorders. *American Journal of Drug and Alcohol Abuse* 2010;36(1):57-60.
74. Defossez G, Verneau A, Ingrand I, Silvain C, Ingrand P, Beauchant M. Evaluation of the French national plan to promote screening and early management of viral hepatitis C, between 1997 and 2003: a comparative cross-sectional study in Poitou-Charentes region. . *European Journal of Gastroenterology and Hepatology* 2008;20(5):367-372.
75. Skipper C, Guy JM, Parkes J, Roderick P, Rosenberg WM. Evaluation of a prison outreach clinic for the diagnosis and prevention of hepatitis C: implications for the national strategy. *Gut* 2003;52:1500 - 1504.

76. Helsper C, van Essen G, Bonten M, de Wit N. A support programme for primary care leads to substantial improvements in the effectiveness of a public hepatitis C campaign. . *Family Practice* 2010;27(3):328-332.
77. Garrard J, Choudary V, Groom H, Dieperink E, Willenbring M, Durfee J, et al. Organizational change in management of hepatitis C: evaluation of a CME program. . *Journal of Continuing Education in the Health Professions* 2006;26(2):145-60.
78. Cullen W, Stanley J, Langton D, Kelly Y, Bury G. Management of hepatitis C among drug users attending general practice in Ireland: Baseline data from the Dublin Area Hepatitis C in General Practice Initiative. *European Journal of General Practice* 2007;13(1):5-12.
79. Sahajian F, Excler G, Bailly F, Caillat-Vallet E, Trepo C, Sepetjan M, et al. Hepatitis C screening practices among private practitioners: Impact of an information campaign. . *Gastroenterologie Clinique et Biologique* 2004;28(8-9):714-719.
80. D'Souza R, Glynn M, Alstead E, Foster G, Osonayo C. Improving general practitioners' knowledge of chronic hepatitis C infection. *Quarterly Journal of Medicine* 2004;97(8):549-50.
81. Zdanuk S, Gimpel J, Uhanova J, Kaita K, Minuk G. The impact of medical informatics on the confidence of rural physicians caring for patients with chronic hepatitis C viral infections. *Family Practice* 2001;18(6):602-604.
82. Fischer L, Conboy K, Tope D, Shewmake D. Educating health professionals: a hepatitis C educational program in a health maintenance organization. *American Journal of Managed Care* 2000;6(9):1029-36.
83. Foucher J, Reiller B, Jullien V, Leal F, di Cesare E, Merrouche W, et al. FibroScan used in street-based outreach for drug users is useful for hepatitis C virus screening and management: a prospective study. *Journal of Viral Hepatitis* 2009;16(2):121-31.
84. Aitken C, Kerger M, Crofts N. Peer-delivered hepatitis c testing and counselling: A means of improving the health of injecting drug users. . *Drug and Alcohol Review* 2002;21(1):33-37.
85. Surjadi M, Torruellas C, Ayala C, Yee H, Khalili Jr. M. Formal patient education improves patient knowledge of hepatitis C in vulnerable populations. . *Digestive Diseases & Sciences* 2011;56(1):213-9.
86. Harris K, Arnsten J, Litwin A. Successful integration of hepatitis C evaluation and treatment services with methadone maintenance. *Journal of Addiction Medicine* 2010;4(1):20-26.
87. Moussalli J, Delaquaize H, Boubilley D, Lhomme J, Merleau Ponty J, Sabot D, et al. Factors to improve the management of hepatitis C in drug users: An observational study in an addiction centre. . *Gastroenterology Research and Practice* 2010;doi:10.1155/2010/261472.
88. Grebely J, Knight E, Genoway K, Viljoen M, Khara M, Elliott D, et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. . *European Journal of Gastroenterology and Hepatology* 2010;22(3):270-7.
89. Grebely J, Genoway K, Khara M, Duncan F, Viljoen M, Elliott D, et al. Treatment uptake and outcomes among current and former injection drug users

receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. *International Journal of Drug Policy* 2007;18(5):437-443.
90. Brewer D, Hagan H. Evaluation of a patient referral contact tracing programme for hepatitis B and C virus infection in drug injectors. *Euro Surveillance: European Communicable Disease Bulletin* 2009;14(14):5-9.

APPENDIX 1. List of candidate studies (from LJMU mapping and effectiveness reviews) and reasons for inclusion or exclusion in the economic evaluation.

Author	Year	Country	Intervention	LJMU rating	Modelling priority and reason
Dried blood spot testing					
Craine et al.[2]	2009	UK	Offering DBS in addiction services	poor	Medium: poor study, high UK priority, insufficient intervention data on testing
Hickman et al.[1]	2008	UK	Offering DBS in addiction services and prisons	+	High: good study, high UK priority/applicability
Increase number/types services testing					
Cullen et al.[3]	2011	UK	GP education and paid-testing of former IDU 30-54 years old	+	High: good study, high UK priority/applicability
Lindenburg et al.[65]	2011	Netherlands	Referral from methadone clinics	poor	Low: poor study, insufficient intervention data on testing
Rosenberg et al.[66]	2010	USA	Mental health treatment site testing	++	Low: narrow study population (mental health sites only)
Anderson et al.[67]	2009	UK	GP case finding in high IDU prevalences of clients 30-54 years old	+	Medium: good study, high UK priority/applicability, but newer data from Cullen et al. study.
Hagedorn et al.[68]	2007	USA	Veterans misuse clinic testing	poor	Low: poor study, narrow study population, UK applicability unclear
Hennessy et al.[69]	2007	USA	STD clinic testing	poor	Low: poor study, low UK priority, limited effectiveness
Stopka et al.	2007	USA	HIV services testing	poor	Low: poor study, narrow study population
Rainey et al.	2005	USA	Offering home test	poor	Low: poor study, insufficient intervention data on testing
Roudot-Thoraval et al.[70]	2000	France	GP screening, training, leaflets	+	Medium: high UK priority, insufficient intervention data (no control group)
HCV Trust	Unpublished	UK	Offering pharmacy testing	N/A	Medium: medium UK priority, insufficient intervention data
Client education					
Perrett SE.[71]	2011	UK	Prison education and nurse led clinic establishment	Not rated	Low: insufficient intervention data on testing
Sahajian et al.[72]	2011	France	Homeless shelter education	+	Low: narrow study population, UK applicability unclear due to study setting
Hagedorn et al.[73]	2010	USA	Veterans substance abuse clinic education	poor	Low: poor study, narrow study population, UK applicability unclear
Defossez et al.[74]	2008	France	National education campaign	+	Low: no reported interest in national campaign in mapping review, UK applicability unclear

Skipper et al.[75]	2003	UK	Prison education and nurse-led clinic establishment	poor	Low: poor study, cost-effectiveness previously evaluated, prison testing already occurring
Professional education					
Helsper et al.[76]	2010	Netherlands	National campaign and GP education	+	Low: no reported interest in national campaign in mapping review, UK applicability unclear
Garrard et al.[77]	2006	USA	Veterans centre staff education	poor	Low: poor study, UK applicability unclear, insufficient intervention data on testing
Cullen et al.[78]	2007	Ireland	Education of GPs in shared care centres who prescribe methadone,	++	High: good study, high UK priority. It was decided by a vote among the PDG to evaluate the Cullen et al. 2011 intervention instead in order to have one intervention which focuses on targeting former IDUs.
Sahajian et al[79]	2004	France	Public information campaign and GP education	poor	Low: poor study, no reported interest in public information campaign in mapping review
D'Souza et al.[80]	2004	UK	GP educational meeting	poor	Low: poor study, insufficient intervention data on testing
Zdanuk et al.[81]	2001	Canada	GP CD-based education	poor	Low: poor study, insufficient intervention data on testing
Fischer et al.[82]	2000	USA	Health care provider education	poor	Low: poor study, insufficient intervention data on testing
Other methods of enhancing access to testing					
Foucher et al.[83]	2009	France	Fibroscan	poor	Low: poor study, insufficient intervention data on testing
Aitken et al.[84]	2002	Australia	Peer outreach worker	poor	Low: poor study, insufficient intervention data on testing
Enhanced access to follow-up/treatment					
Surjadi et al.[85]	2011	US	Educational session by liver specialist	poor	Low: poor study, insufficient intervention data on testing
Harris et al.[86]	2010	US	Merging HCV and OST clinics	poor	Low: poor study, insufficient intervention data on testing
Moussalli et al.[87]	2010	France	Treatment in addiction centres	poor	Low: poor study, insufficient intervention data on testing
Grebely et al.[88]	2010	Canada	Refer diagnosed IDUs to weekly support group	poor	Low: poor study, insufficient intervention data on testing
Jack et al.	2008	UK	Onsite specialist nurse in shared care clinic	poor	Low: poor study, insufficient intervention data on testing
Wilkinson et al.	2009	UK	Specialist appointments in addiction services	poor	Low: poor study, insufficient intervention data on testing
Grebely et al.[89]	2007	Canada	Refer diagnosed IDUs to weekly support group	poor	Low: poor study, insufficient intervention data on testing
Contact tracing					
Brewer et al.[90]	2009	USA	Contact tracing in prisons	poor	Low: poor study, insufficient intervention data on testing