Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons

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Complete List of Authors:	Martin, Natasha; University of Bristol, Department of Social Medicine; London School of Hygiene and Tropical Medicine, Social and Mathematical Epidemiology Group Hickman, M; Bristol Miners, Alec; London School of Hygiene and Tropical Medicine, Department of Health Services Research and Policy Hutchinson, Sharon; Health Protection Scotland, ; Glasgow Caledonian University, School of Health and Life Sciences Taylor, Avril; University of the West of Scotland, Vickerman, Peter; London School of Hygiene & Tropical Medicine, Social and Mathematical Epidemiology Group
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Title: Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons

Authors: Natasha K. Martin[1,2], Matthew Hickman[1], Alec Miners[2], Sharon J. Hutchinson[3,4], Avril Taylor[5], Peter Vickerman[2,1]

Affiliations: [1]Department of Social and Community Medicine, University of Bristol, Bristol, UK. [2]Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine [3]Health Protection Scotland, UK. [4]School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK. [5]University of the West of Scotland, Glasgow, UK.

Corresponding author contact: Natasha.Martin@bristol.ac.uk. Department of Social and Community Medicine, 39 Whatley Road, Bristol, BS8 2PS.

Abbreviations: hepatitis C virus (HCV), people who inject drugs (PWID), dried blood spot (DBS), incremental cost-effectiveness ratio (ICER), quality-adjusted life-year (QALY), willingness-to-pay (WTP), hepatocellular carcinoma (HCC), liver transplant (LT), pegylated interferon (pegIFN), ribavirin (RBV), sustained viral response (SVR), 95% confidence interval (CI), antibody (Ab)

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ABSTRACT (265 words)

Objectives: People who inject drugs (PWID) are at high-risk for acquiring hepatitis C virus (HCV), but many are unaware of their infection. HCV dried blood spot (DBS) testing increases case-finding in addiction services and prisons. We determine the cost-effectiveness of increasing HCV case-finding among PWID by offering DBS testing in specialist addiction services or prisons as compared to using venepuncture.

Design: Cost-utility analysis using a dynamic HCV transmission model among PWID, including: disease progression, diagnosis, treatment, injecting status, incarceration, and addition services contact.

Setting: United Kingdom

Participants: N/A

Intervention: DBS testing in specialist addiction services or prisons. Intervention impact was determined by a meta-analysis of primary data

Primary and secondary outcome measures: Costs (in UK £, £1=$1.60 USD) and utilities (quality adjusted life years, QALYs) were attached to each state and the incremental cost effectiveness ratio (ICER) determined. Multivariate uncertainty and one-way sensitivity analyses were performed.

Results: For a £20,000 per QALY gained willingness-to-pay threshold, DBS testing in addiction services is cost-effective (ICER of £14,600 per QALY gained). Under the base-case assumption of no continuity of treatment/care when exiting/entering prison, DBS testing in prisons is not cost-effective (ICER of £59,400 per QALY gained). Results are robust to changes in HCV prevalence; increasing PWID treatment rates to those for ex-PWID considerably reduces the ICER (£4,500 and £30,000 per QALY gained for addiction services and prison, respectively). If

continuity of care is >40%, the prison DBS ICER falls below £20,000 per QALY gained.

Conclusions: Despite low PWID treatment rates, increasing case-finding can be cost-effective in specialist addiction services, and in prisons if continuity of treatment/care is ensured.

Trial Registration: N/A

ARTICLE SUMMARY

Article focus

- We perform a cost-utility analysis of increasing HCV case-finding among PWID by offering dried blood spot testing in specialist addiction services or prisons.

Key messages

- Despite low PWID treatment rates, increasing case-finding for PWID can be cost-effective in specialist addiction services.
- In prisons, the cost-effectiveness of HCV case-finding depends on adequate continuity of treatment/care between prison and the community, as many treatments are discontinued due to short incarceration times.

Strengths and limitations of this study

- We use a dynamic mathematical model of HCV transmission to capture the potential prevention benefits of treatment, which has been shown to increase cost-effectiveness of HCV treatment for PWID.
- Key limitations are the limited empirical data on PWID health utilities, treatment rates, and intervention impact.

INTRODUCTION

In developed countries, the hepatitis C virus (HCV) is spread primarily through injecting drug use, with over 90% of new infections among people who inject drugs (PWID) and approximately 10 million PWID infected worldwide[1 2]. However, diagnosis rates are low, with only half of infected PWID in the US and UK diagnosed[3 4], putting many at risk of cirrhosis, liver cancer, and death.

The majority of HCV testing performed in the US and UK is through venepuncture, which is available in virtually all prisons[5 6] and addiction services (structured programs providing pharmacological or nonpharmacological drug treatment in the community) either on site or by referral. However, testing opportunities among PWID still may be limited. This is because venous access can be poor and specialist staff (who may not be available at all potential testing sites) are required to take blood, which if only available in hospital phlebotomy services can increase stigma[7].

Dried blood spot (DBS) testing is non-invasive and can be performed by clinical and non-clinical staff. Two UK studies[8 9] showed offering DBS testing within specialist addiction services and prisons led to a 3 to 6-fold increase in HCV testing, and a recent systematic review identified DBS as the best available targeted intervention for increasing HCV case-finding amongst PWID[10]. Hence, DBS testing could be an important component of any strategy attempting to scale-up treatment provision for PWID, for both care and prevention[11].

We perform a cost-utility analysis of introducing DBS testing amongst current and former PWID in specialist addiction services and prisons in the UK[8]. Unlike

previous economic evaluations of HCV testing in these settings[12 13], we incorporate a dynamic mathematical model to capture the potential prevention benefits of treatment, which can substantially increase the cost-effectiveness of HCV treatment for PWID[14]. Our model is also the first to explore the importance of continuity of care between prison and the community.

METHODS

Mathematical model

An existing dynamic, deterministic model of HCV transmission, progression and HCV treatment was adapted to project the impact of introducing DBS testing in prisons and addiction services[14]. See **appendix** for details and model schematics. Briefly, the model stratifies by: injecting state (never PWID/PWID/ex-PWID); incarceration status (never/currently/formerly); contact with addiction services (in contact/not in contact); age ([15-19],[20-24],[25-29],[30-54],[55-64],[65-74],[75+]); HCV infection and disease progression (never infected, spontaneously cleared, mild HCV, moderate HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post-transplant). HCV disease stages are further subdivided into undiagnosed or diagnosed, where those who are diagnosed can either be lost to follow-up, in referral (early/late), on antiviral treatment, sustained viral response (SVR), or non-SVR.

All PWID can acquire and transmit HCV, but imprisoned PWID only transmit HCV to other prisoners. We define ex-PWID as those who have permanently ceased injecting, and assume no ongoing transmission from non/ex-PWID. An individual's risk of acquiring HCV is proportional to the setting-specific HCV prevalence

(prison/community). The model assumes a background rate of HCV testing for all PWID and ex-PWID in the community/prison, and in addiction services for PWID.

No UK data exist regarding continuity of care (treatment or referral) on prison entry/exit, but experts described difficulty in ensuring continuity on release (Eamonn O'Moore[Offender Health, UK Department of Health], Iain Brew[HMP Leeds] *personal communication*). Therefore, in our base-case we assume those in treatment or referral become lost to follow-up upon entering/exiting prison, but can be re-tested/re-treated.

Model fitting and base-case projections

For the probabilistic uncertainty analysis, 1000 parameter sets were sampled from each parameter uncertainty distribution in **tables 1-3**. For each of these parameter sets, the model was calibrated to UK epidemiological data on incarceration, injecting drug use, HCV prevalence, and diagnosis. This was achieved through a multi-step parameter sampling and model calibration process, utilizing simplified models where possible to reduce computational time and to verify the full model predictions against simplified models. For details on the model calibration (including schematics and equations) and initialization, see **appendix**.

After calibration, for each of the 1000 parameter sets, the model was run with and without the intervention ('intervention' and 'baseline', respectively). We model an intervention of offering DBS testing in prison, compared to a baseline of current testing with venepuncture only. Additionally, we evaluate an intervention of offering DBS in specialist addiction services, compared to a baseline of current testing with

venepuncture. The economic analysis was performed from a UK National Health Service perspective. Costs (in 2011 GBP, £1=$1.55 USD) and health utilities (in quality-adjusted life years, QALYs) were attached to each model compartment. Costs and QALYs were discounted 3.5% per annum as per NICE guidelines, with a 100 year time horizon (to accrue individual and population benefits). The mean incremental cost-effectiveness ratio (ICER) was calculated and cost-effectiveness determined using the UK willingness-to-pay (WTP) threshold, estimated between £20,000 and £30,000 per QALY gained[15]. Cost-effectiveness acceptability curves were constructed and univariate sensitivity analyses undertaken. Analysis of covariance (ANCOVA) methods were used to summarize the proportion of the variability in the incremental costs and QALYs explained by the uncertainty in input parameters[16].

Parameters

Health state utilities: Uninfected utility values were taken from UK population norms[17] for non-PWID, and a large cross-sectional study of injectors in Scotland[18] for current PWID. We assumed equal utilities for ex-PWID and non-PWID[13]. Utilities for HCV disease and treatment stages came from UK HCV trials and economic evaluations[19-21] and used for ex-PWID (**table 1**). To derive PWID HCV utilities, non-PWID HCV utilities were rescaled by multiplying by the ratio of the uninfected PWID utility to the uninfected ex-PWID utility for the youngest age group. All states included disutilities with age[17].

No disutility was associated with testing in the base-case. However, some evidence suggests PWID may experience a disutility after positive HCV diagnosis[18 22]. We

explored the impact of a disutility (0.09[18], see **appendix**) on diagnosis, which was fully regained with treatment SVR.

Health state and testing costs: Health care costs for HCV disease stages, antiviral treatment (pegylated interferon-alfa and ribavirin, pegIFN+RBV), and testing were taken from UK economic analyses[19 20 23 24](**table 1** and **appendix**). Data on the yield (proportion tests Ab+) and prevalence in each setting were used to calculate the number of non-PWID tested for each PWID/ex-PWID (see **appendix**). Costs were inflated to 2011 GBP using the Health and Community Hospital Service pay and prices index[25]. Additional PWID treatment delivery costs were applied[14]. We assumed undiagnosed individuals do not incur HCV-related health care costs unless progressing to decompensated disease[12].

HCV disease progression parameters: Transition rates between disease stages were taken from UK economic evaluations[19-21] (**table 1**). Although estimates were not PWID specific, a recent meta-analysis suggests little evidence for differences in progression between PWID and non-PWID[26].

HCV prevalence: PWID HCV chronic prevalence was estimated from HCV antibody prevalence among PWID in England (45% [41-49%, 95% confidence interval (CI)][27]), with spontaneous clearance of 26% of acute infections[28] resulting in 35% chronic infection.

Testing rates: The overall baseline PWID testing rate was estimated through fitting the model to the current proportion of diagnosed PWID (approximately 50%[4]), and

used to calculate setting-specific testing rates (prison, addiction services, other) (see **appendix**). We assume ex-PWID are tested at equal rates to PWID in prison and in general community settings. We assumed all diagnostic tests are 100% accurate due to the high sensitivity and specificity of DBS and venepuncture [29 30] and because those who receive an initial positive test will receive additional tests before treatment.

Referral and treatment transition rates: The referral rate from testing services to secondary care (35%) was estimated from a UK study[31]. Those not referred or not attending referral were considered 'lost to follow-up'.

Approximately 50% of diagnosed ex-PWID in referral are treated within 2 years[31-33]. Since many delay treatment, we assume that after 2 years, 10% of those in referral initiate treatment annually. Within prison, treatment rates are much lower than in the community[31 34], although a recent UK prison audit found 24% of those diagnosed were treated (Iain Brew[HMP Leeds], unpublished data). We therefore estimated half the treatment initiation rate in prison as compared to the community.

PWID treatment rates are unknown, but thought to be similarly low to other countries[35 36], with an estimated <1% of PWID treated annually (Graham Foster[Consultant Hepatologist], *personal communication*). Hence, if we assume 1% of infected PWID are treated within 2 years, this equates to treating approximately 5.5% of those who attend referral (35% of the 50% diagnosed) within 2 years. After 2 years, 1% of those in referral are treated annually thereafter. Testing and treatment rates are shown in **table 1**.

Intervention: The effect of introducing DBS was modelled by assuming a 3.6-fold increase in testing [2.2-5.8 CI] in addiction services, and 2.6-fold increase in testing [0.1-34.9 CI] in prison, based on two multicentre studies (**table 2** and **appendix**). Intervention costs were determined from the study methods[8] and in consultation with the authors (**table 2**).

Sensitivity analyses

We performed one-way sensitivity analyses on: time horizon (50/200 years), discount rates (3.5% costs/1.5% QALYs), PWID treatment rates (increased in each setting), PWID SVR rates (reduced by 20%), PWID HCV chronic prevalence (20%/50%), antiviral treatment (telaprevir/boceprevir for genotype 1 patients, see **appendix**), and continuity of care for treatment/referral on entry/exit from prison (varied from 0% to 100%). We also explored the effect of assuming no prevention benefit (but allowing for reinfectiopg n), by permanently fixing the force of infection.

RESULTS

Case finding in addiction services

The incremental cost effectiveness ratio (ICER) of increasing case-finding in addiction services, by introducing DBS testing, was an estimated £14,600 ($22,630 USD) per QALY gained in the base-case (**table 4**). At a £20,000 or £30,000 WTP threshold, the intervention is likely to be cost-effective in 69% or 93% of the simulations, respectively (**figure 1a**). Uncertainty in the intervention effect

contributed to 86% and 58% of the variation in incremental costs and QALYs, respectively. The remaining variation in incremental QALYs was mainly due to uncertainty in treatment rates (22%) and health utilities (17%).

For most sensitivity analyses, the ICER remained below a £30,000 WTP threshold (**figure 2a)**. Reducing the time horizon to 50 years increased the estimated ICER to £22,900 per QALY gained because fewer prevention benefits were accrued, whereas lengthening to 200 years increased cost-effectiveness. Changing the discount rates to 3.5% costs/1.5% QALYs or no discounting decreased the estimated ICER to £5,100 or £6,700 per QALY gained, respectively. Variations in baseline HCV chronic prevalence had little effect (<10%). At lower prevalence (20%), identifying cases was more expensive but prevention impact was greater due to reduced reinfection risk, whereas the opposite occurred at higher prevalence (50%).

Increasing treatment rates increased the intervention's cost-effectiveness. If 50% (compared to 5.5% for base-case) of PWID in referral initiated treatment within 2 years (a treatment rate achieved by one UK service[37]) the ICER fell to £4,500 per QALY gained. If SVR rates amongst PWID were 20% lower than in ex-PWID, the ICER increased by 14% (£16,700 per QALY gained). Using telaprevir/boceprevir for genotype 1 patients minimally altered the ICER. Ignoring any prevention benefit doubled the ICER to £29,900 per QALY gained.

Only one sensitivity analysis substantially altered the cost-effectiveness conclusion. If a disutility was attached to diagnosis, the intervention resulted in negative incremental QALYs (due to low treatment rates) and was dominated (more

expensive with fewer health benefits). However, even with this disutility, if treatment rates were increased to 50% of PWID in referral initiating treatment within 2 years, then the estimated ICER was £20,100 per QALY gained.

Case finding in prison

The ICER of increasing case-finding in prison, by introducing DBS testing, was estimated at £59,400 ($92,070 USD) per QALY gained (21% likely to be cost-effective at a £30,000 WTP threshold) in the base-case (**table 4** and **figure 1b**). Uncertainty in the intervention effect contributed to most (>85%) of the variation in incremental costs and QALYs.

The base-case conclusion was robust to most one-way sensitivity analyses (**figure 2b)** – including time horizon, discount rates, HCV prevalence, and use of new treatments. If 50% of PWID in referral initiated treatment within 2 years, the ICER halved to just below £30,000 per QALY gained.

Introducing continuity of care (which measures the proportion of initiated treatments/referrals that are continued when entering/exiting prison) led to an increase in cost-effectiveness: from an ICER of £59,400 per QALY gained with 0% continuity to £10,400 per QALY gained with 100% continuity **(figure 3)**. The ICER fell below £20,000 when >40% continuity of care was ensured; at 40% continuity the intervention was 57% and 83% likely to be cost-effective at the £20,000 and £30,000 WTP thresholds, respectively. The level of continuity required for prison case-finding to be cost-effective also depended on treatment rates. If prison treatment rates were increased to equal those in the community (50%/5.5% of ex-PWID/PWID treated

within 2 years of referral), then 35% continuity results in an ICER just below £20,000 per QALY gained. Increasing treatment rates further so 50% of all referred prisoners initiate treatment within 2 years lowers the required continuity to 20% for an ICER below £20,000.

DISCUSSION

Main findings

Our results indicate the introduction of dried blood spot testing for HCV case-finding is likely to be cost-effective under commonly used willingness-to-pay thresholds in the UK (£20,000-£30,000/QALY gained[15]) and US ($50,000/QALY gained[38]) in addiction services, but not in prison unless a minimum level of continuity of care in treatment or referral between prison and the community can be ensured. Ignoring the prevention benefit doubles the ICER of the intervention in addiction services. In the base-case, most PWID treatments initiated in prison were interrupted due to the lack of continuity of care and short PWID incarceration times (~4 months) in the UK. Consequently, little prevention benefit was achieved from the prison intervention, with the results approaching the 'static' model. With the low base-case PWID treatment rates, the continuity required for DBS to be cost-effective was approximately 35-40% of the estimated treatment/referral rates, but if treatment/referral rates increased then lower levels of continuity would be cost-effective. Crucially, not all treatments need to be initiated or completed in prison, as only maintaining treatment or referral contact is necessary. Finally, both interventions are most cost-effective at higher treatment rates.

Strengths and Limitations

The key strength of this analysis is that the model is dynamic, therefore capturing the prevention impact of case-finding and treatment. The main limitations are concerned with parameter uncertainty and lack of model heterogeneity. First, we based our increase in case-finding on the DBS intervention, which though empirically founded, was informed by relatively small UK studies, resulting in wide uncertainty around the effect estimates.

Second, the base-case assumed comparatively low treatment rates for PWID, partly because UK data on PWID treatment numbers are not available, although similar rates have been reported in the US[36] and Canada[35]. This information is critical, as higher treatment rates increase the intervention's cost-effectiveness. This is especially important for prisons where information on treatment completion was unavailable, yet these factors strongly influenced cost-effectiveness. Additionally, even if treatment is interrupted, some may benefit from shortened treatment, which we did not incorporate. However, the rapid development of resistance observed with new treatments[39] indicates treatment continuity will become an increasingly crucial issue.

Third, more data are needed to quantify PWID health utilities, which can be below the general population[40]. Especially important is whether any transient or permanent disutility on HCV diagnosis occurs, as current data are weak and not based on prospective studies. No consensus exists regarding diagnosis utilities in other diseases[41 42]. Our projections indicate if a disutility occurs then higher treatment rates are required for case-finding to be cost-effective.

Fourth, the model did not incorporate other interventions or behaviours that may influence HCV risk or treatment uptake. For example, case-finding and treatment of PWID is targeted towards those on opiate substitution therapy[43] who may contribute fewer secondary infections[44]. However, modelling work has shown introducing risk heterogeneity does not substantially reduce intervention impact if PWID circulate between risk states[45] which is likely to occur as individuals move in/out of drug treatment and prison.

Fifth, the model was parameterized to UK data, so our results are not necessarily applicable to other settings. However, our conclusions are robust to changes in HCV prevalence. Continuity of care could also be an issue in Australia, where PWID incarceration duration is similar to the UK[46]. However, sentences are longer in the US[47], so fewer treatments may be interrupted, and therefore case-finding in US prisons could be more cost-effective than our results indicate.

Our modelled UK treatment and HCV health care costs are within the range of those presented by recent US studies[48 49], with the exception of approximately 3-fold higher liver transplantation costs, which would increase the cost-effectiveness of case-finding in the US. Finally, the higher proportion of genotype 1 (75%) in the US would reduce the population average SVR by approximately 15%, but we show case-finding is still cost-effective in addiction services with a reduction in PWID SVR by 20%.

Comparison with other studies

Two publications evaluated the cost-effectiveness of testing ex-PWID in prison, with ICERs varying from about £20,000[13] to £55,000[12] per QALY gained. Our results are consistent with Sutton et al.[12], which used the same discount rates as our study. However, we included the possible prevention impact of treating PWID, and unlike the previous studies, show how continuity of care between prison and the community can make case-finding cost-effective.

Three papers evaluated testing PWID in drug services[13 24 50]. Differences in baseline assumptions led to varying ICERs from £28,100[24] to £17,500[13 50] per QALY gained. Our results for addiction services support those found in the latter studies[13 50]. However, the intervention examined in these studies[13 24 50] was one-off testing using a cohort model (with no evidence based intervention effect) and neglected any prevention benefit.

Several US studies examined birth cohort screening for all people born in 1945-1965[49 51] or 1946-1970[48] as compared to risk based screening, reporting ICERs of $38,000 per QALY gained with direct-acting antivirals[48 49] and $5,400-16,000 per QALY gained with pegIFN+RBV[49 51]. Critically, the cost-effectiveness varies substantially by HCV prevalence[51], and the estimated US prevalence is higher than many other developed countries. Additionally, the ICERs were generated given assumptions of higher treatment rates, as well as greater utility gains with SVR than we consider. Importantly, our intervention targets PWID with a risk of transmitting infection to others, whereas birth cohort screening is likely to identify infections among ex-injectors and non-injecting populations which will have little primary prevention impact.

Implications

Our cost-effectiveness work indicates increasing HCV case-finding in addiction services can be cost-effective. However, the cost-effectiveness of prison case-finding interventions depends on adequate continuity of care with the community. Few settings have developed comprehensive strategies to address this issue, though New York state recently initiated the Hepatitis C Continuity Program[52]. In all settings, treatment uptake is critical: higher treatment rates prevent more disease transmission and increase the cost-effectiveness of case-finding interventions. If a disutility on diagnosis occurs, higher treatment rates would be necessary to ensure cost-effectiveness. Further empirical data are required on treatment uptake and changes in utilities following diagnosis and treatment in order to compare targeted case-finding with cohort models.

AUTHOR CONTRIBUTIONS

NKM contributed to the study design, model development, analysis, manuscript drafting and editing. MH contributed to the study design, model development, analysis, and manuscript editing. AM contributed to the analysis and manuscript editing. SJH contributed to the model parameterization, analysis, and manuscript editing. AT contributed to the model parameterization and manuscript editing. PV contributed to the study design, model development, analysis, and manuscript editing.

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Competing Interests

NM has received an honorarium for speaking at a conference sponsored by Janssen. SH has received honoraria for speaking at conferences sponsored by MSD, Janssen, Gilead, and Roche. MH, AM, AT, PV have no competing interests.

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Figure Legends:

Figure 1. **Base-case cost-effectiveness acceptability curves for the dried blood spot intervention.** Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.

Figure 2. **Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER).** Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.

Figure 3. **Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions.** Base-case scenario assumed 0% continuity.

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	Mean value	Distribution	Reference
Transition probabilities per year (all probabilities converted to instantaneous rates)			
Mild to moderate	0.025	Beta(α=38.0859, β=1485.3516)	[19]
Moderate to cirrhosis	0.037	Beta(α=26.905, β=700.2582)	[19]
Cirrhosis to decompensated cirrhosis	0.039	Beta(α=14.6168, β=360.1732)	[19]
Cirrhosis/decomp. cirrhosis to HCC	0.014	Beta(α=1.9326, β=136.1074)	[19]
Decompensated cirrhosis/HCC to LT	0.03	Beta(α=6.5256, β=210.9945)	[19]
Decompensated cirrhosis to death	0.13	Beta(α=147.03, β=983.97)	[19]
HCC to death	0.43	Beta(α=117.1033, β=155.23)	[19]
LT to death	0.21	Beta(α=16.2762, β=61.2294)	[19]
Post transplant to death	0.057	Beta(α=22.9017, β=378.8825)	[19]
Health state utilities/disutilities per year			
Ex-PWID age 15-19			
Uninfected	0.94		[17]
Mild	0.77	Beta(α=521.2375, β=155.6943)	[19 20]
Moderate	0.66	Beta(α=168.2461, β=86.6723)	[19 20]
Cirrhosis	0.55	Beta(α=47.1021, β=38.5381)	[19 20]
Decompensated cirrhosis	0.45	Beta(α=123.75, β=151.25)	[19 20]
Hepatocellular carcinoma	0.45	Beta(α=123.75, β=151.25)	[19 20]
Liver transplant	0.45	Beta(α=123.75, β=151.25)	[19 20]
Post transplant	0.67	Beta(α=59.2548, β=29.1852)	[20 21]
Mild - on treatment	0.66	Beta(α=115.706, β=59.6063)	[19 20]
Moderate - on treatment	0.55	Beta(α=47.1021, β=38.5381)	[12 19 20]
Cirrhosis - on treatment	0.46	Beta(α=3953, β=4641)	[12]
Mild SVR	0.82	Beta(α=65.8678, β=14.4588)	[19 20]
Moderate SVR	0.72	Beta(α=58.0608, β=22.5792)	[12 19 20]
Cirrhosis SVR	0.61	Beta(α=58.0476, β=37.1124)	[21]
PWID age 15-19			
Uninfected	0.74	Uniform(0.67,0.8)	*[18]*
HCV disease states	As in ex-PWID, but reduced by PropPWID†		Assumed
Disutility with age			
20-24	0		[17]
25-29	0.005		[17]
30-54	0.049		[17]
55-64	0.14		[17]
65-74	0.16		[17]
75+	0.21		[17]
Costs (£ per year, except where noted)			
Mild diagnosed	169	PPI‡×Gamma(*k*=25.6995,θ=5.3698)	[19 20]
Moderate diagnosed	880	PPI‡×Gamma(*k*=88.8502, θ=8.0698)	[19 20]
Cirrhosis diagnosed	1,397	PPI‡×Gamma(*k*=24.2342, θ=46.9584)	[19 20]
Decompensated cirrhosis	11,199	PPI‡×Gamma(*k*=36.0249, θ=253.1582)	[19 20]
Hepatocellular carcinoma	9,980	PPI‡×Gamma(*k*=18.1081, θ=448.8045)	[19]
Liver transplant (per transplant)	33,561	PPI‡×Gamma(*k*=89.7536, θ=304.5004)	[19]
Cost of care in year of liver transplant	11,614	PPI‡×Gamma(*k*=13.7788, θ=686.4168)	[19]
Post transplant	1,701	PPI‡×Gamma(*k*=15.2189, θ=91.0053)	[19]
Mild SVR	318	PPI‡×Gamma(*k*=28.8141, θ=8.9887)	[19]
Moderate SVR	880	PPI‡×Gamma(*k*=88.8502, θ=8.0698)	[19]
Cirrhosis SVR	1,397	PPI‡×Gamma(*k*=24.2342, θ=46.9584)	[19]
Undiagnosed states	0		
PegIFN+RBV drug only			
24 weeks, halved/doubled for 12/48 wks	5,320	Uniform (4788, 5852)	[23]
Treatment delivery			
Ex-PWID, 12 weeks	1,912	Varied, see appendix	See appendix[19]

Ex-PWID, 24 weeks	2,057	Varied, see appendix	See appendix[19]
Ex-PWID, 48 weeks	2,326	Varied, see appendix	See appendix[19]
PWID, 12 weeks	2,193	Varied, see appendix	See appendix
PWID, 24 weeks	2,435	Varied, see appendix	See appendix
PWID, 48 weeks	2,900	Varied, see appendix	See appendix
Testing costs in all settings except prison	115.21	Uniform +/- 50%	See appendix
Testing costs in prison	144.21	Uniform +/- 60%	See appendix
PCR RNA test (if antibody positive)	73.67		[24]
Testing and treatment parameters			
Proportion PWID diagnosed (initial)	50%		[4]
Proportion PWID treated (initial)	0%		Assumption
Proportion ex-PWID diagnosed (initial)	30%	Uniform (24%, 36%)	Assumption [53]
Proportion of diagnosed ex-PWID treated (initial)	10%	Uniform (5%, 15%)	Estimated <10% diagnosed chronic infections treated [4]
Proportion HCV genotype 1	50%		[4 54]
Sustained viral response(SVR)			
Genotype 1 mild/moderate	0.45	Uniform (0.4, 0.5)	[54-56]
Genotype 2/3 mild/mod	0.8	Uniform (0.75, 0.85)	[54 57]
Genotype 1 cirrhosis	0.25	55% reduction from mild/mod	[58]
Genotype 2/3 cirrhosis	0.6	75% reduction from mild/mod	[58]
Antiviral treatment duration (weeks)			
Genotype 1 SVR	48		[54]
Genotype 1 non-SVR	12		[54]
Genotype 2/3	24		[54]
Distribution of PWID HCV tests			
GP	38.4%		§
Prison	11.5%		§
Addiction services	29.4%		§
Other	20.7%		§
Proportion who are referred and attend referral	35%	Uniform (25%, 45%)	[13 31]
Proportion in referral who initiate treatment within 2 years (excl. prison)			
Ex-PWID	50%	Uniform(40%, 60%)	[13 31-33]
PWID	5.5%	Uniform(1%, 10%)	Assumption
Treatment initiation rate after 2 years in referral (excl. prison) per year			
Ex-PWID	10%	Uniform(5%, 15%)	Assumption
PWID	3%	Uniform(1%, 5%)	Assumption
Treatment rates in prison	Half out-of- prison rates		Assumption"
Yield (proportion tests Ab+)			
GP	2.7%		§
Prison	14.7%		§
Addiction services	17.7%		§
Other	1.7%		§

Table 1. Model parameters. †PropPWID=(uninfected PWID utility value for age 15-19)/(uninfected ex-PWID utility for age 15-19). ‡PPI=Hospital and Community Health Services Pay and Prices Index inflation factor. §Health Protection Agency (HPA) unpublished data from the 2010 Sentinel Surveillance. "Iain Brew, HMP Leeds, unpublished data. HCC= hepatocellular carcinoma; LT=liver transplant; SVR=sustained viral response; pegIFN=pegylated interferon; RBV= ribavirin

	Mean value	Distribution	Units	Ref.
Intervention effect (proportional change in testing rate)				
Addiction services	3.6 [2.3-5.8]	Lognormal (μ=1.285, σ=0.239)	-	[8]
Prison	2.6 [0.2-34.9]	Lognormal (μ=0.968, σ=1.317)	-	[8]
Intervention costs (addiction services)				
Organization/coordination of training*	2,005.71		per health board	†
Training session‡	135		per training session	†
Attendees time§	1,620		per training session	†
Travel reimbursement for training leader‖	90.86		per training session	†
Total cost per addiction services training	3851.57		per training session	†
Mean number tested	40.3		per addiction service¶	[8]
Total intervention cost per test	**95.57**	**Uniform +/-50%**	per test	
Intervention costs (prison)				
Organization/coordination of training**	7020		per prison	†
Training session‡	135		per prison	†
Attendees time††	405		per prison	†
Travel reimbursement for training leader‡‡	127.20		per prison	†
Total cost per prison training	7687.20		per prison	†
Mean number tested per prison	116		per prison	**[8]**
Total intervention cost per test	**66.27**	**Uniform +/- 50%**	per test	

Table 2. Intervention parameters. All cost estimates assume a staff-nurse cost per hour of £36 (median estimate for band 5 general practice nurse[25]). *1 nurse 2 days/week for 6 months for 7 health boards. One training session per health board. †Noel Craine, *personal communication*. ‡1 nurse, half day. §12 nurses, half day. ‖1200 miles (£0.53 per mile) for travel to 7 health boards. ¶Assumed 1 addiction service per health board. **1 nurse full time for 3 prisons (1 training session per prison) ††3 nurses per prison, half day. ‡‡1200 miles (£0.53 per mile) for 5 prisons.

	Mean value	Sampled values	Units	Ref.
Average duration of injecting until cessation	11	6.2, 8.6, 11, 13.4, 15.8	years	[59 60]
PWID overdose rate	0.01	0.007, 0.01, 0.013	Per year	[61]
Duration in addiction services	9	7, 9, 11	months	Estimated from OST duration[61]
Incarceration duration				
PWID				
All ages	4	2.67, 4, 5.33	Months	[62]
Ex-PWID				
15-19	2.75		Months	[62]
20-24	6.26		Months	[62]
25-29	8.42		Months	[62]
30-54	9.76		Months	[62]
55-64	11.92		Months	[62]
65+	12.49		Months	[62]
Age of first injection distribution				
15-19	41%		-	Combined UK data from [44]
20-24	30%		-	Combined UK data from [44]
25-29	16%		-	Combined UK data from [44]
30-54	13%		-	Combined UK data from [44]
55+	0%		-	Combined UK data from [44]
Death rate by age				
15-19	0.0003		Per year	[63]
20-24	0.0005		Per year	[63]
25-29	0.0006		Per year	[63]
30-54	0.0019		Per year	[63]
55-64	0.0073		Per year	[63]
65-74	0.0200		Per year	[63]
75+	0.165		Per year	[63]
Proportion of England population currently imprisoned aged 15-59	0.2%			[64 65]
Proportion of population who are PWID aged 15-59	0.65%			[66]
Proportion PWID in contact with addiction services	50%			[44]
Proportion PWID diagnosed	50%			[4]
PWID HCV chronic prevalence	35%			[27]
Proportion infections leading to spontaneous clearance	0.26	Uniform (0.22, 0.29)	-	[28]

	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%	-	[67]
Age distribution of prisoners	8%	20%	18%	47%	7%	[64]
Proportion PWID ever in prison	48%	46%	67%	73%	-	*
Proportion prisoners ever PWID	5%	16%	36%	44%	8%	†

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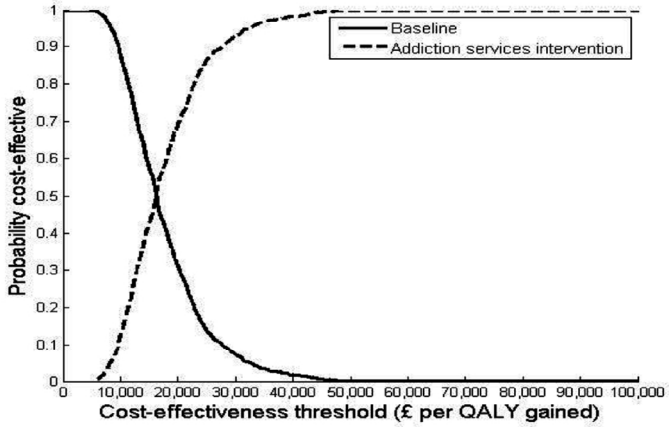
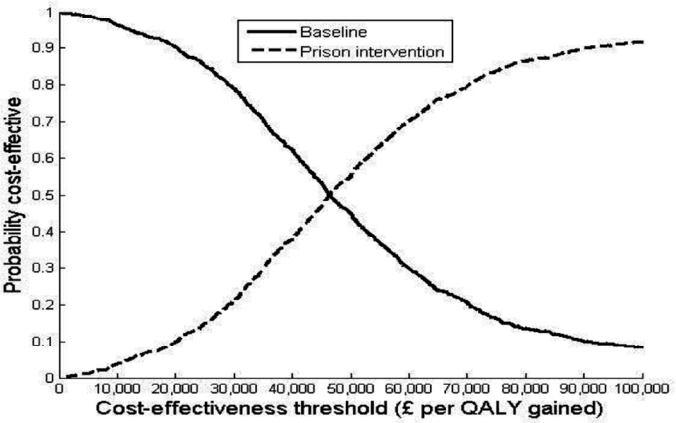
Table 3. Epidemiological/prison input parameters for model fitting *Unlinked Anonymous Monitoring Survey of PWID, Health Protection Agency, London, unpublished data. †Scottish prison data, Avril Taylor, unpublished data.

Intervention location	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
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
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

Table 4. Cost-effectiveness results from the base-case intervention analyses.



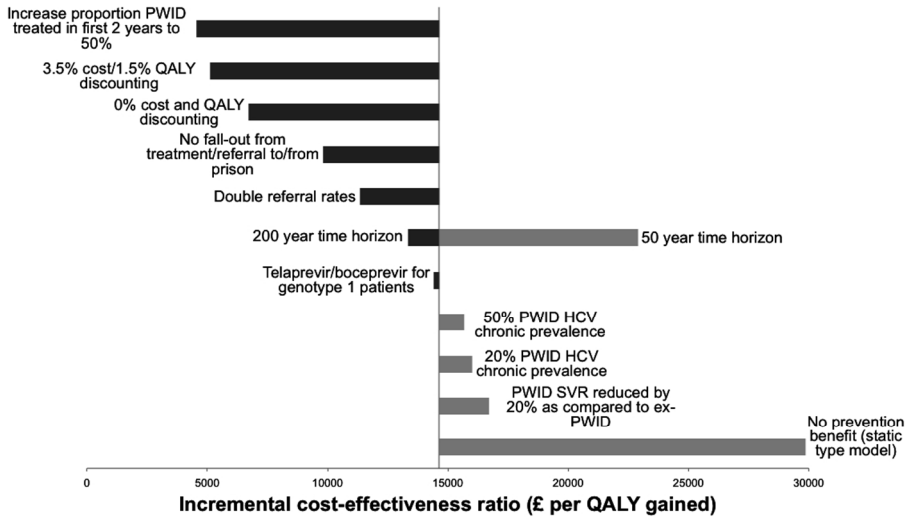
(a)



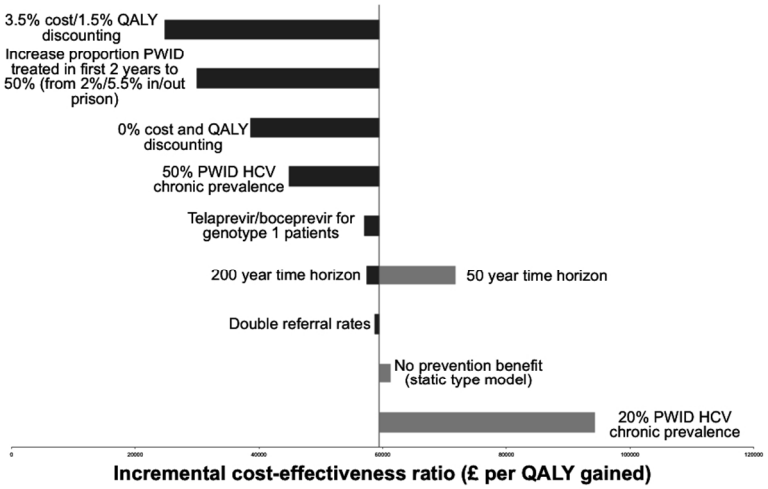
(b)

Figure 1

Base-case cost-effectiveness acceptability curves for the dried blood spot intervention. Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.
396x529mm (72 x 72 DPI)



(a)



(b)

Figure 2

Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER). Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.
396x529mm (72 x 72 DPI)

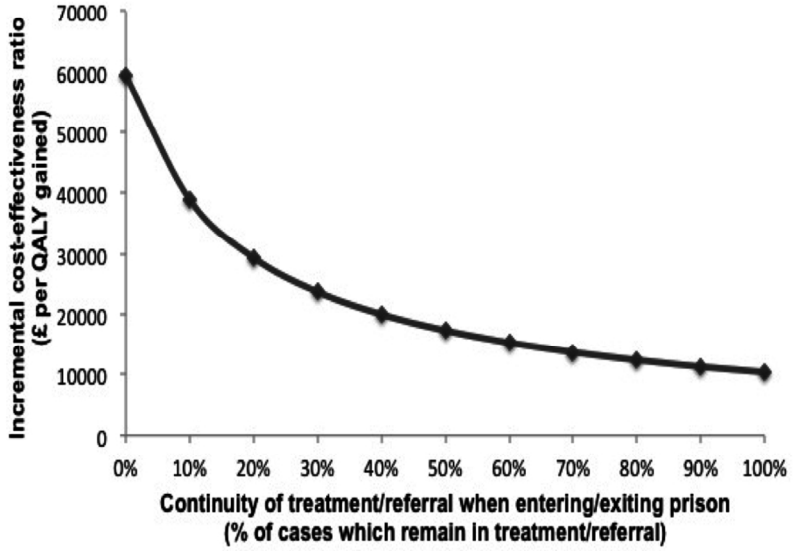


Figure 3

Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions. Base-case scenario assumed 0% continuity.
396x529mm (72 x 72 DPI)

APPENDIX

Mathematical model

A dynamic, deterministic compartmental model of injecting drug use, HCV transmission, progression, treatment, and diagnosis amongst PWID was developed, to project the impact of interventions to increase HCV testing of PWID. Schematics for the model components can be found in **appendix figures 1 and 2**. The HCV transmission, antiviral treatment, and disease progression model was based on a coupled system of ordinary differential equations previously published by the authors[1]. Susceptible PWID can become acutely infected with HCV by sharing injecting equipment with other infected PWID. We model a frequency dependent force of infection, such that an individual's risk of infection is proportional to the overall prevalence of infection. This model assumes a proportion (26%) of acutely infected PWID 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 PWID 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 PWID re-enters the infected compartment of their associated HCV disease stage. If a PWID fails treatment (non-SVR), they remain infected and can progress to more severe disease stages. Successfully treated PWID can be reinfected and retreated, but those who do not achieve SVR are ineligible for retreatment. Due to reduced viral loads during treatment (even amongst those who relapse and do not achieve SVR), we assume PWID are not infectious during treatment[2, 3]. 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 PWID population

(such as high/low risk), as modelling indicated introducing heterogeneity in risk does not have an undue influence on prevention intervention effectiveness as long as individuals circulate between high risk and intervention states[4].

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 ex-PWID, 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).

In order to appropriately model incarceration, the model structure was replicated to track the flow of PWID and ex-PWID between never incarcerated, currently incarcerated, and formerly incarcerated states. In addition, compartments for never-PWID were added (never incarcerated, currently incarcerated, formerly incarcerated) to enable model calibration to general population incarceration data. This model structure was based on previously published mathematical models of PWID incarceration[5, 6], and it was assumed that incarceration and re-incarceration rates of ex-PWID were equal to that of never-PWID.

Additionally, for PWID not imprisoned (never imprisoned and formerly imprisoned) we further stratified movement by contact with addiction services (in contact/not in contact). We assumed only those in contact with addiction services could be tested in addiction services. We also assumed that on release from prison, PWID 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+]), with individuals entering the model at age 15-19 as never-

PWID. In total, the model consists of 222 states and 7 age stratifications, leading to 222 x 7=1,554 compartments.

The model assumes that prisoners only share with other prisoners. Similarly, outside prison, 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.

The dynamic transmission aspect of the model is similar to our previously published mathematical models. Let $P^{n}_{m,a,I}$ represent the number of PWID, where the superscript *m* represents incarceration status (*m*=0,1,2 for never, currently, formerly incarcerated, respectively), the superscript n represents addiction services status (*n*=*out* for out of contact and *n*=*in* in contact, and noting that n=*out* for all incarcerated states when *m*=1), subscript *a* represents the age group, with *a*=1,2…7 for each age group. The subscript *I* represents the HCV state, where $I=x_i$ for susceptible where *i* represents the different susceptible stages (never infected, spontaneously cleared), $I=y_i$ for chronic infected undiagnosed (including mild, moderate, compensated cirrhosis), $I=z_i$ for chronic infected diagnosed (including mild, moderate, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant, post-transplant and in early referral, late referral, or lost to follow-up states), $I=v_i$ for on treatment (including mild, moderate, compensated cirrhosis), $I=s_i$ for SVR (mild, moderate, compensated cirrhosis) and $I=f_i$ for treatment failure/non-SVR (mild, moderate, compensated cirrhosis). For example, $P^{out}_{0,1,y_i}$ represents a PWID who has never been imprisoned and is not in contact with addiction services, is in age group 1 (15-19), and is undiagnosed mild chronically infected. We assume proportionate mixing by age. Using this notation, the force of infection for a PWID who is not imprisoned (*m*=0 or 2) is:

$$\pi \frac{\sum_{\text{all } a,n,y_i,z_i,f_i} (P^{n}_{0,a,y_i}+P^{n}_{0,a,z_i}+P^{n}_{0,a,f_i}+P^{n}_{2,a,y_i}+P^{n}_{2,a,z_i}+P^{n}_{2,a,f_i})}{\sum_{\text{all } a,n,x_i,y_i,z_i,v_i,s_i,f_i} (P^{n}_{0,a,x_i}+P^{n}_{0,a,y_i}+P^{n}_{0,a,z_i}+P^{n}_{0,a,v_i}+P^{n}_{0,a,s_i}+P^{n}_{0,a,f_i}+P^{n}_{2,a,x_i}+P^{n}_{2,a,y_i}+P^{n}_{2,a,z_i}+P^{n}_{2,a,v_i}+P^{n}_{0,a,s_i}+P^{n}_{2,a,f_i})}$$

where π represents the infection rate, which is fit to the HCV prevalence among PWID.

While incarcerated, PWID can only transmit to other incarcerated PWID, so the force of infection for a susceptible PWID in prison (*m*=1) is:

$$\pi \frac{\sum_{\text{all } a,y_i,z_i,f_i} (P_{1,a,y_i}+P_{1,a,z_i}+P_{1,a,f_i})}{\sum_{\text{all } a,x_i,y_i,z_i,v_i,s_i,f_i} (P_{1,a,x_i}+P_{1,a,y_i}+P_{1,a,z_i}+P_{1,a,v_i}+P_{1,a,s_i}+P_{1,a,f_i})}$$

As stated before, all PWID in never infected (Ab-/RNA-), spontaneously cleared (Ab+/RNA-), and SVR states are susceptible for infection as described above.

Model Parameters

Intervention impact

The intervention impact was modelled a proportional increase in setting-specific testing rates, determined by a random effects meta-analysis of the primary data[7] for each setting (addiction services and prisons) separately. The results of the meta-analysis can be found in **appendix figure 3**.

SVR rates

Sustained viral response (SVR) rates for pegIFN+RBV 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[8]. Patients with compensated cirrhosis exhibit proportional reductions in SVR values by about 45% and 25% for genotypes 1 and 2/3, respectively[9]. Preliminary studies indicate SVR rates are equal between PWID and ex/non-PWID[10], which we assumed in our base-case.

Calculation of testing rates

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

To circumvent this problem, we fitted an overall PWID annual testing rate to calibrate the model to the estimated proportion of PWID who are diagnosed (approximately 50%[11]). This rate varied for each sampled group of parameters, but the mean annual testing rate was 12% per year among undiagnosed PWID. This annual testing rate ensured the proportion of diagnosed PWID remained stable (at equilibrium) without any intervention.

As testing of PWID takes place in different locations (prison, addiction services, other settings) and the proportion of PWID 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 in contact with 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 PWID risk only (Mary Ramsay and Sara Collins[Health Protection Agency], *unpublished data.*). Although these data underestimate the number of tests given to PWID, it is reasonable to assume the HPA distribution between sites would be representative of the testing administered to PWID 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 PWID in contact with addiction services and in prison). We assume all ex-PWID are in contact with a GP. These three components were then combined to obtain setting specific testing rates for each parameter set simulation. The setting specific testing rates for PWID and ex-PWID were assumed equal, with the exception that the model assumes ex-PWID are not in contact with addiction services, so no testing occurs from this scenario for this group.

Testing costs

Costs associated with testing were calculated as follows. The numbers of PWID tested in each setting were calculated, and associated with setting specific test costs. Two additional costs were added: RNA testing (for all Ab+ tests) and non-PWID testing. The

number of non-PWID tested in order to test one PWID was calculated from the setting-specific test yield (proportion of tests Ab+) and 'true' baseline prevalence. A setting with a low yield indicates more non-PWID are tested for every PWID; if yield equals baseline prevalence, this indicates only PWID are tested.

Contact with addiction services rates

The proportion of PWID in contact with addiction services at any given time was difficult to estimate. 92% of PWID report ever accessing a needle exchange in the HPA Unlinked Anonymous Survey, though the proportion currently accessing services is not asked[12]. However, it is estimated that 50% of PWID are currently on opiate substitution therapy[13, 14], 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 PWID are on OST[15].

Model fitting

Overview of model fitting and baseline projections

A multi-step parameter sampling and model calibration/fitting method was used with simplified models to reduce computational time and allow for verification of full model predictions against the simplified models. For each fitting process (5 separate model fits in total), **appendix table 3** details the model used, input parameters, calibration data used to fit the model, and parameters estimated through model fitting. The seven-step sampling and calibration process is as follows:

1) Values were randomly sampled for four parameters (cessation rate, overdose rate, PWID prison release rate, and addiction services duration), yielding a total of 135 possible parameter combinations, or 'calibration scenarios'. Due to the heavy computational burden of fitting the many incarceration parameters, the model was fitted to a limited range of sampled 'calibration scenarios'.
2) **Fit #1:** Simplified model 1 (**appendix figure 4**) was run for each sampled calibration scenario, in order to calibrate the simplified model to the (not

sampled) incarceration data shown in **table 3**. Inputs included the sampled scenario parameters, and non-sampled input parameters estimated from literature/sources (age-specific death rates, prison release rates for never PWID, distribution of ages of first injection, and a preliminary estimate of the entry rate of never-PWID aged 15-19 which will be refit in Fit #5). The parameters which were estimated through model calibration were the age-dependent incarceration rate, reincarceration rates, PWID incarceration rates, PWID reincarceration rates, and injecting initiation rate. Simplified model 1 neglected HCV transmission, testing, and treatment. More details can be found in the section '**Details of fit #1**' and model equations can be found the section entitled "**Model Equations: Simplified Model 1**".

3) **Fit #2:** Simplified model 2 (**appendix figure 5**) was run for each sampled calibration scenario, in order to calibrate the model to addiction services data. For fit #2, a simplified model of incarceration and movement in/out of addiction services was used. The inputs for these simulations were the sampled calibration scenarios and inputs from Simplified model 1, as well as the estimated incarceration parameters from Simplified model 1. The model was calibrated to data on the proportion of PWID in contact with addiction services, and the estimated parameter obtained through model fitting was the recruitment rate into addiction services. Model equations can be found in the section entitled "**Model Equations: Simplified Model 2**".
4) **Fit #3:** Simplified model 3 (**appendix figure 6**) was run for each sampled calibration scenario, in order to calibrate the model to the diagnosis data. For fit #3, a simple model of HCV transmission and testing among PWID was used to estimate the overall PWID testing rate by calibrating the model to the proportion of PWID who report being diagnosed for HCV. The model inputs were the sampled calibration scenarios and non-sampled inputs of age-specific death rates, distribution of injecting initiation age, and preliminary estimate of the entry rate of never-PWID aged 15-19. The model also required an input of the estimated injecting initiation rate from simplified model 1. Model equations can be found in the appendix section entitled "**Model Equations: Simplified Model 3**".

5) 1000 parameter sets were sampled from each parameter uncertainty distribution in from the full range of disease progression, intervention, cost, and utility parameters (**Tables 1-3**). For each of the 1000 parameter sets, one of the 135 fitted 'calibration scenarios' was selected.
6) **Fit #4:** For each of the 1000 parameter sets, the full model was calibrated to three separate HCV PWID chronic prevalences (35%[16], used in the base-case, as well as 20% and 50% for the sensitivity analyses) to estimate the infection rate, pi, associated with each chronic prevalence.
7) **Fit #5:** For each of the 1000 parameter sets, the full model was calibrated to a total PWID population size (fit to 1000 PWID at baseline), to estimate the entry rate of never-PWID in the 15-19 age group.

Model fitting was performed by using nonlinear least-squares methods using the MATLAB solver *lsqnonlin*.

Model Equations

Simplified model 1

For Simplified Model 1, the mathematical model tracks injecting drug use state (never/current/former PWID) and incarceration state (never/currently/formerly incarcerated). $N^m_{a,t}$ represents never PWID, with superscript *m* representing incarceration status (*m*=0,1,2 for never, currently, formerly incarcerated, respectively) and subscript *a* representing age group, with *a*=1,2…7 for each age group. Using the same subscript notation, $P_{a,t}$ represents PWID and $E_{a,t}$ represents ex-PWID. The full system of equation is as follows:

$$
\begin{aligned}
\frac{dN_{0,a}}{dt} &= \theta_a - (\rho_{0,a} + \xi_a + \gamma_a)N_{0,a} \\
\frac{dN_{1,a}}{dt} &= \rho_{0,a}N_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \xi_a + \gamma_a)N_{1,a} \\
\frac{dN_{2,a}}{dt} &= \beta_{0,a}N_{1,a} - (\alpha_{0,a} + \xi_a + \gamma_a)N_{2,a} \\
\frac{dP_{0,a}}{dt} &= \xi_a N_{0,a} - (\rho_{1,a} + \zeta + \gamma_a + \eta)P_{0,a} \\
\frac{dP_{1,a}}{dt} &= \xi_a N_{1,a} + \rho_{1,a}P_{0,a} + \alpha_{1,a}P_{2,a} - (\beta_{1,a} + \zeta + \gamma_a + \eta)P_{1,a} \\
\frac{dP_{2,a}}{dt} &= \xi_a N_{2,a} + \beta_{1,a}P_{1,a} - (\alpha_{1,a} + \zeta + \gamma_a + \eta)P_{2,a} \\
\frac{dE_{0,a}}{dt} &= \zeta P_{0,a} - (\rho_{0,a} + \gamma_a)E_{0,a} \\
\frac{dE_{1,a}}{dt} &= \zeta P_{1,a} + \rho_{0,a}E_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \gamma_a)E_{1,a} \\
\frac{dE_{2,a}}{dt} &= \zeta P_{2,a} + \beta_{0,a}E_{1,a} - (\alpha_{0,a} + \gamma_a)E_{2,a}
\end{aligned}
$$

where time is represented by the variable *t*. All populations experience age-specific death rates specified by rate γ_a and PWID have an additional death rate due to overdose of η. New never-PWID enter the system into the youngest age compartment at rate θ_1 (θ_a=0 for $a \neq 1$). Never or former PWID are incarcerated at an age specific rate $\rho_{0,a}$, are released at a rate $\beta_{0,a}$, and are reincarcerated at a rate $\alpha_{0,a}$. Similarly, PWID are incarcerated at an age specific rate $\rho_{1,a}$, are released at a rate $\beta_{1,a}$, and are reincarcerated at a rate $\alpha_{1,a}$. Never PWID initiate injecting at an age-specific rate of ξ_a, and cessate from injecting at a rate ζ.

Simplified model 2

For Simplified Model 2, the mathematical model in Simplified Model 1 is extended to include flow in and out of addiction services for PWID who are not incarcerated. Using the same subscript notation as before, but adding a superscript with *n*= *in* if the PWID is in contact with addiction services, and *n*=*out* if they are not in contact, then $P_{i,a}^{n}$ represents PWID. The full system of equation is as follows:

$$
\begin{aligned}
\frac{dN_{0,a}}{dt} &= \theta_a - (\rho_{0,a} + \xi_a + \gamma_a)N_{0,a} \\
\frac{dN_{1,a}}{dt} &= \rho_{0,a}N_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \xi_a + \gamma_a)N_{1,a} \\
\frac{dN_{2,a}}{dt} &= \beta_{0,a}N_{1,a} - (\alpha_{0,a} + \xi_a + \gamma_a)N_{2,a} \\
\frac{dP^{out}_{0,a}}{dt} &= \xi_a N_{0,a} + \sigma P^{in}_{0,a} - (\rho_{1,a} + \zeta + \gamma_a + \eta + \nu)P^{out}_{0,a} \\
\frac{dP^{in}_{0,a}}{dt} &= \nu P^{out}_{0,a} - (\rho_{1,a} + \zeta + \gamma_a + \eta + \sigma)P^{in}_{0,a} \\
\frac{dP_{1,a}}{dt} &= \xi_a N_{1,a} + \rho_{1,a}(P^{out}_{0,a} + P^{in}_{0,a}) + \alpha_{1,a}(P^{out}_{2,a} + P^{in}_{2,a}) - (\beta_{1,a} + \zeta + \gamma_a + \eta)P_{1,a} \\
\frac{dP^{out}_{2,a}}{dt} &= \xi_a N_{2,a} + \beta_{1,a}P_{1,a} + \sigma N^{out}_{2,a} - (\alpha_{1,a} + \zeta + \gamma_a + \eta + \nu)P^{out}_{2,a} \\
\frac{dP^{in}_{2,a}}{dt} &= \nu N^{out}_{2,a} - (\alpha_{1,a} + \zeta + \gamma_a + \eta + \sigma)P^{in}_{2,a} \\
\frac{dE_{0,a}}{dt} &= \zeta(P^{out}_{0,a} + P^{in}_{0,a}) - (\rho_{0,a} + \gamma_a)E_{0,a} \\
\frac{dE_{1,a}}{dt} &= \zeta P_{1,a} + \rho_{0,a}E_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \gamma_a)E_{1,a} \\
\frac{dE_{2,a}}{dt} &= \zeta(P^{out}_{2,a} + P^{in}_{2,a}) + \beta_{0,a}E_{1,a} - (\alpha_{0,a} + \gamma_a)E_{2,a}
\end{aligned}
$$

where the variables are as in Simplified Model 1, with the addition that PWID enter addiction services at a rate *v*, and exit at a rate *σ*. The model assumes that when people initiate injecting, or are released from prison, they are not immediately in contact with addiction services (but can subsequently be recruited into contact at rate *v.*

Simplified model 3

Simplified model 3 is used to fit the PWID diagnosis rate to the overall proportion of PWID diagnosed at a given time. Hence, it includes never PWID, uninfected PWID, infected undiagnosed PWID, and infected diagnosed PWID. As in the other simplified models, $N_{a,}$ represents never PWID, with *a* representing age group, with *a*=1,2…7 for each age group. Here, $P_{1,a}$ represents susceptible PWID, $P_{1,a}$ represents infected but undiagnosed PWID, and $P_{1,a}$ represents infected and diagnosed PWID. The full system of equation is as follows:

$$\begin{aligned}
\frac{dN_a}{dt} &= \theta_a - (\xi_a + \gamma_a)N_a \\
\frac{dP_{a,x}}{dt} &= \xi_a N_a - \pi P_{a,x}\frac{P_{a,y}+P_{a,z}}{P_{a,x}+P_{a,y}+P_{a,z}} - (\zeta + \gamma_a + \eta)P_{a,x} \\
\frac{dP_{a,y}}{dt} &= \pi P_{a,x}\frac{P_{a,y}+P_{a,z}}{P_{a,x}+P_{a,y}+P_{a,z}} - (\kappa + \zeta + \gamma_a + \eta)P_{a,y} \\
\frac{dP_{a,z}}{dt} &= \kappa P_{a,y} - (\zeta + \gamma_a + \eta)P_{a,z}
\end{aligned}$$

where the parameters are as in Simplified Model 1 with the addition that κ represents the diagnosis rate, and π is the infection rate.

Details of fit #1

In fit #1, the simplified incarceration model was calibrated to age-structured data on the proportion of the general population with a custodial sentence[17], proportion of PWIDs previously imprisoned, age distribution of current prisoners[18], proportion of prisoners ever PWID, proportion of the population currently imprisoned[19, 20], and the prevalence of PWID in the general population[16]. The epidemiological and prison parameters sampled for this fitting algorithm can be found in **table 3.**

As the prison data varied over several orders of magnitude (for example, the proportion of PWID 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 of the calibration data was used in order to minimize relative error in the least-squares regression[21]. 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. Specifically, the error measure associated with each individual age-specific parameter of the 7 age-groups was weighted 1/7th as much as a non-age specific parameter. **Appendix figure 7** provides an example of the data and calibrated model projections with the median values chosen for each parameter; all other fits were similar to this. The model fitted well to the data, with the notable exception of the proportion of PWID 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-injecting 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 fit to the rest of the data and also because it is unlikely that the data sources are consistent.

Initial conditions

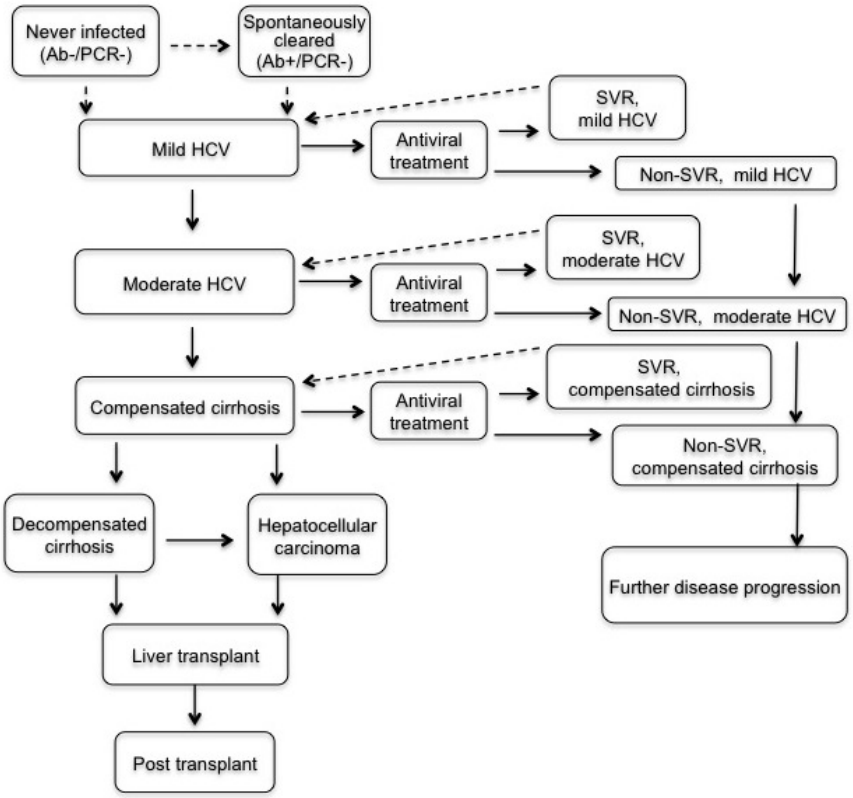
The steady-state values of the full model without testing and treatment were used as initial conditions for the baseline/intervention simulations, with the following alterations. At baseline, the proportion of diagnosed ex-PWID was not thought to be at steady-state. This was because recent testing initiatives have mainly targeted PWID; it is estimated the proportion of diagnosed PWID (50%[11]) is currently likely higher than that of ex-PWID (estimated at 30% based on proportion PWID diagnosed in 2000 who are likely to be ex-PWID[12]). Hence, the steady-state values for infected populations were divided between undiagnosed/diagnosed states for the initial conditions. As treatment rates of PWID are extremely low, we assume none of the PWID population have been treated at baseline, and sample the proportion of ex-PWID previously treated (mean sampled value 10%[11]) from the range found in **table 1**.

We calculate the initial conditions as follows. 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 as follows to account for the current proportion of diagnoses estimated in the PWID and ex-PWID populations, as well as the proportion of ex-PWID already treated. As it is unknown what proportion of previously diagnosed PWID 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 no PWID have been treated at baseline. Ex-PWID 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.

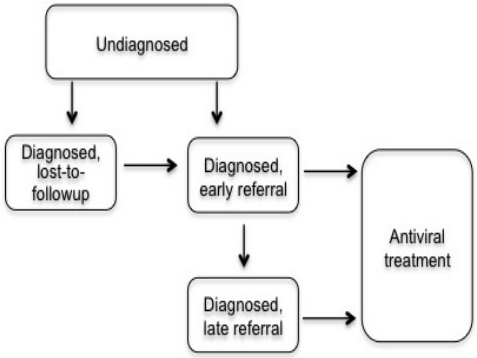
Hence, half of the chronically infected PWID population were placed in the diagnosed compartment of their relative disease state, with the remaining placed in the 'diagnosed and lost-to-follow-up' compartment of their relative disease state. For the ex-PWID population, a proportion will have been treated, 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-PWID was not at steady state at the start of the simulation. As stated in the main text of the paper, this was deemed appropriate, as recent testing initiatives have mainly targeted PWID, and therefore it is assumed that diagnosis rates among ex-PWID are low. However, over time those who are PWID will become ex-PWID, and therefore the proportion of diagnosed ex-PWID will increase over time.

Results

The incremental costs and incremental QALYs are shown on a cost-effectiveness plane in **appendix figure 8**.

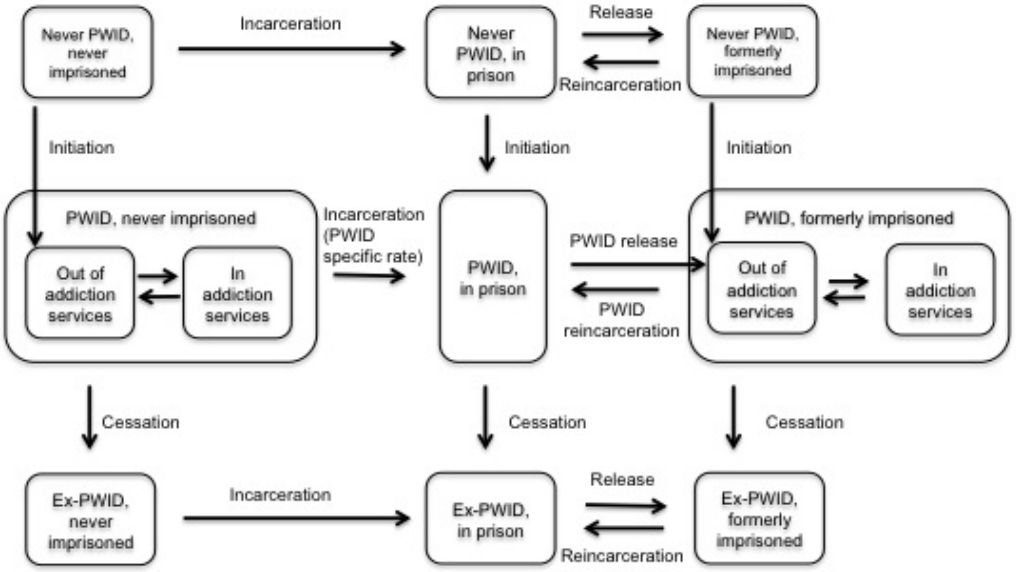


(a)



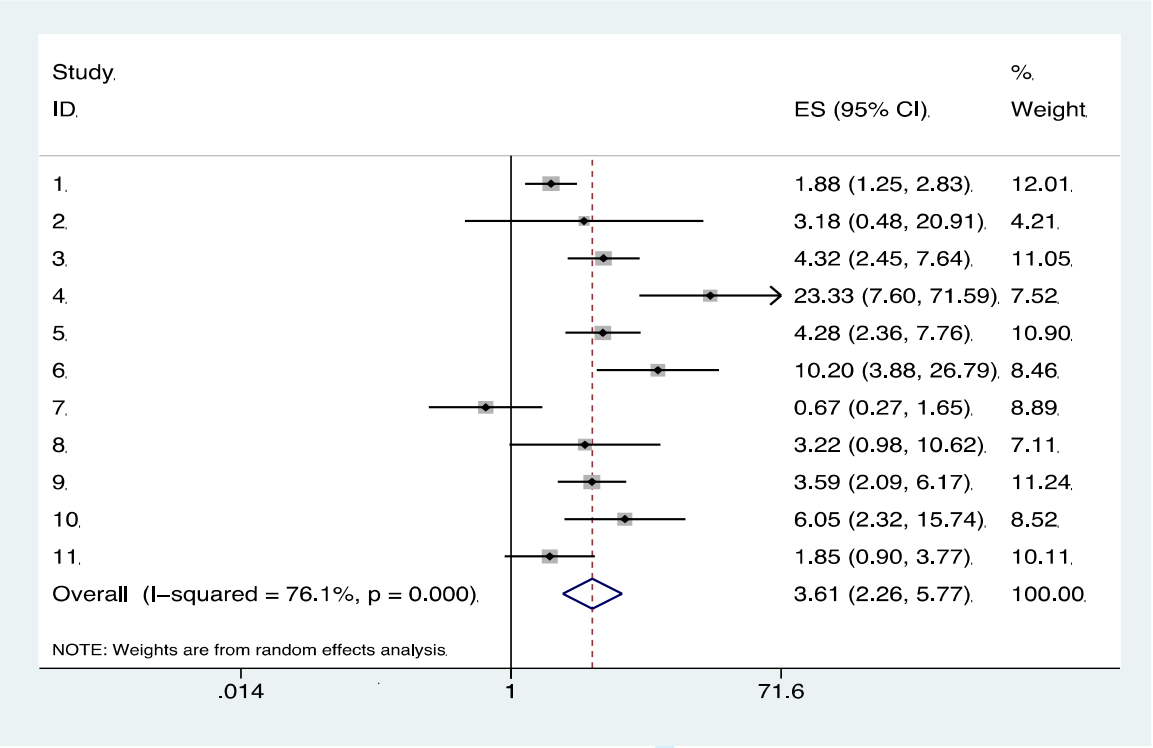
(b)

Appendix figure 1. HCV disease progression model schematics. Schematics show treatment (a) and diagnosis (b) model components. Solid black lines indicate transitions for both PWID and ex-PWID. Dashed black lines indicate PWID transitions only. For PWID, uninfecteds can be retested due to continuing risk behaviour; ex-PWID are not retested in the model.

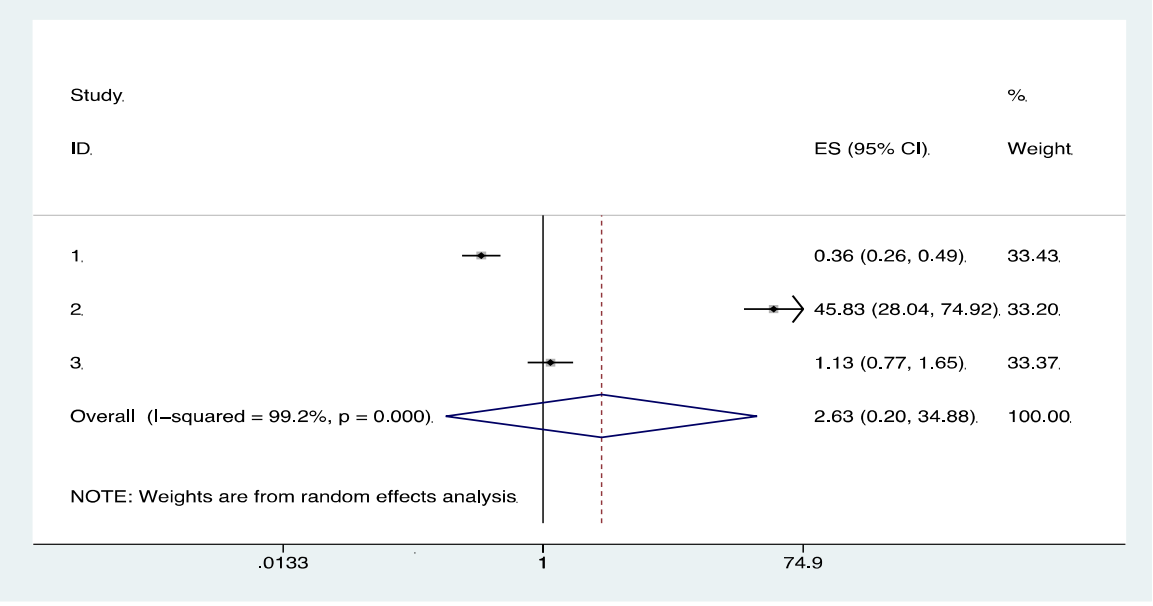


Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 2. General model flow schematic (each PWID and ex-PWID compartment includes HCV infection sub-compartments).

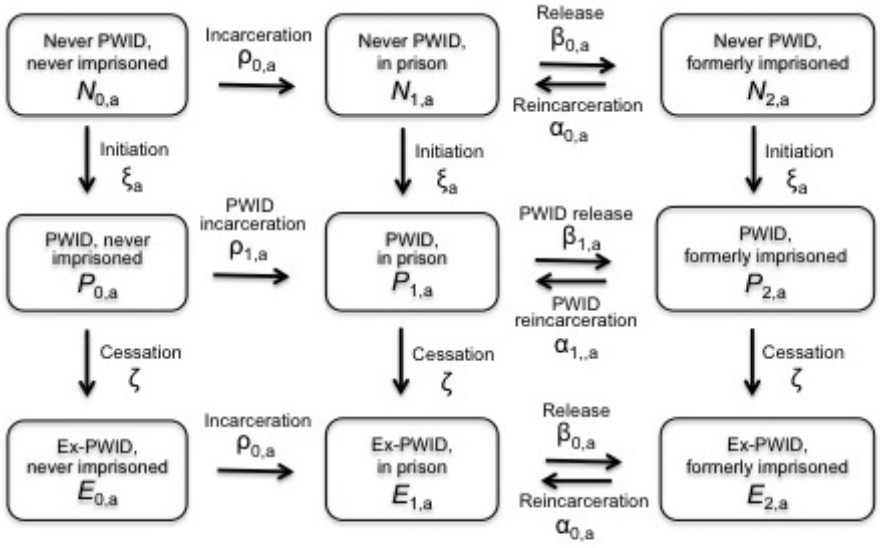


(a)



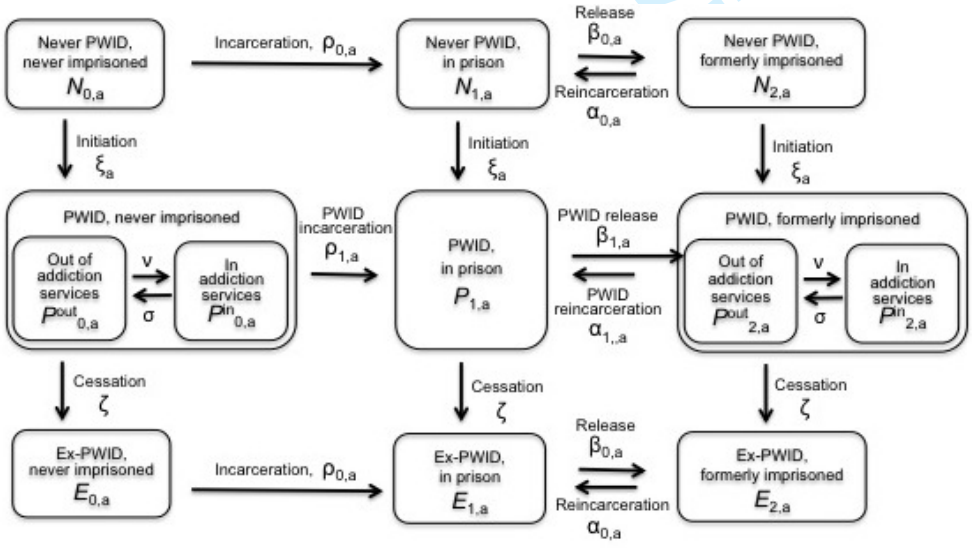
(b)

Appendix figure 3. Random effects meta-analysis results for the dried blood spot intervention effect on testing rate (proportional increase in testing rate). Results shown for (a) addiction services and (b) prison.



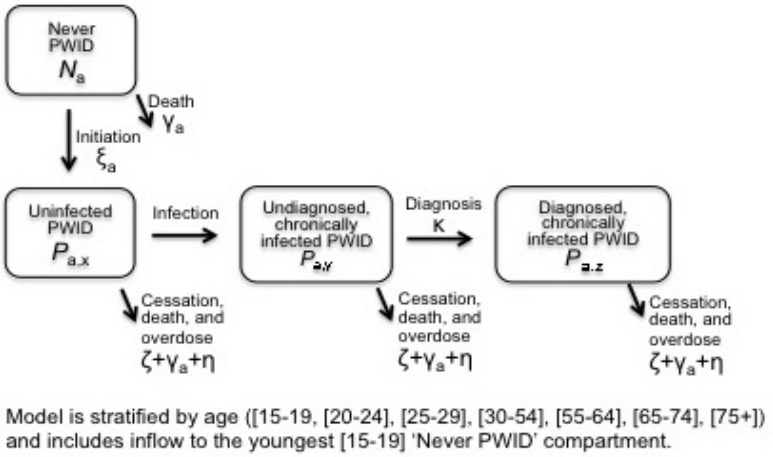
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 4. Simplified model #1 schematic.

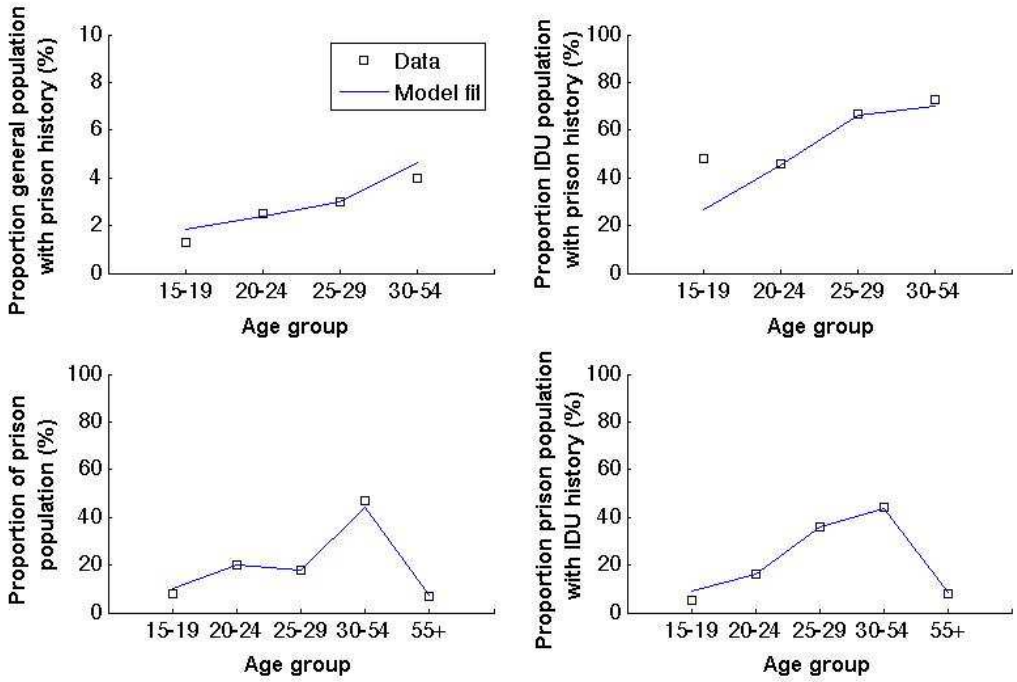


Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

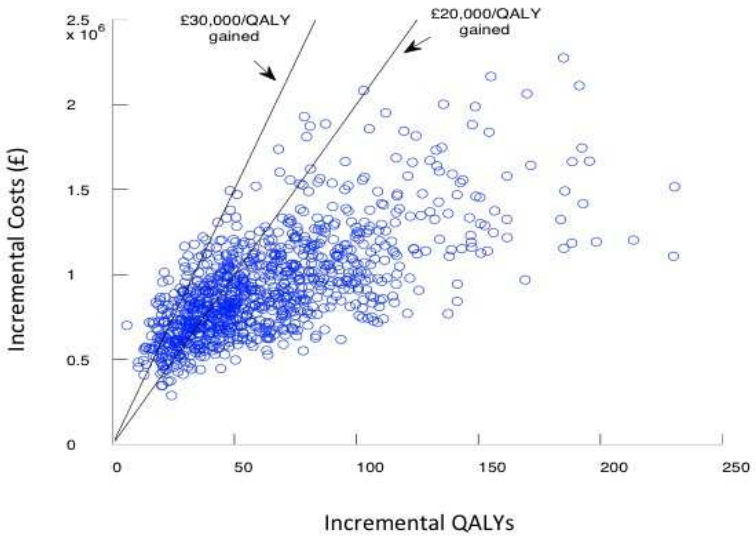
Appendix figure 5. Simplified model #2 schematic.



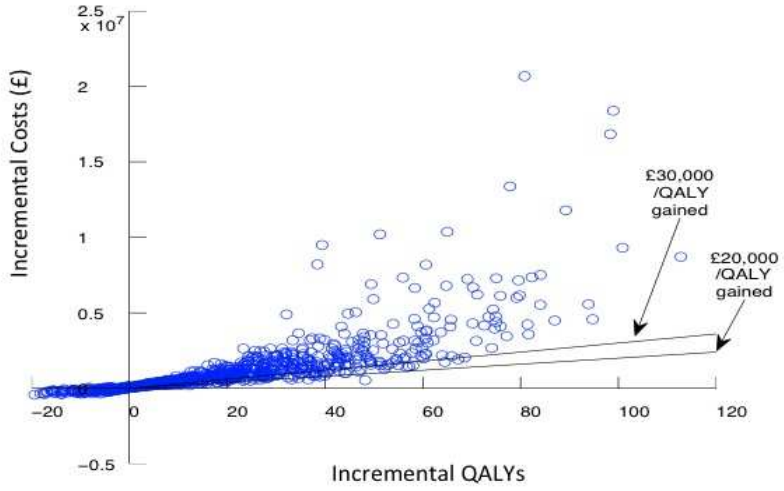
Appendix figure 6. Simplified model #3 schematic.



Appendix figure 7. Example of one characteristic model fit to the prison data (injecting duration 11 years, PWID incarceration duration 4 months, PWID 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 PWID who have previously been incarcerated. The bottom right shows the proportion of prisoners who report ever PWID. Additionally, the model was fit to proportion of the general population imprisoned (simulated 0.21% as compared to 0.2%[19, 20]) and the proportion of population PWID (simulated 0.58% as compared to 0.65%[16])



(a)



(b)

Appendix figure 8. Incremental costs and incremental QALYs for each of the 1000 simulation runs. Results shown for (a) addiction services and (b) prison interventions.

HCV testing costs- baseline	Mean value (in 2011 £)	Distribution /notes	Units	Ref.
Assessment	1.78	1 minute (average nurse and consultant doctor cost*)	Per test	[22]
Pre-test discussion and test	53.50	30 minutes (average nurse and consultant doctor cost*)	Per test	[22]
Post-test results	44.58	25 minutes (average nurse and consultant doctor cost*)	Per test	[22]
ELISA test	15.35		Per test	[22]
Additional assessment time (prison only)	29	Assuming 20 min. with nurse*	Per test	Estimated from timings in [22]
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	[22]

Appendix table 1. Baseline HCV testing costs. *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[23]. †Greater uncertainty surrounding costs of testing in prison is due to uncertainty surrounding method of test offer (on prison entry, BBV/sexual health screening, or during routine health check).

HCV antiviral treatment costs	Mean value (in 2011 £)	Distribution	Ref.
PegIFN+RBV drug only			
12 weeks	2,660*	Halved from sampled cost at 24 wks	[24]
24 weeks	5,320*	Uniform (4788, 5852)	[24]
48 weeks	10,640*	Doubled from sampled cost at 24 wks	[24]
Treatment delivery			
12 weeks			
Staff	307	Varied by staff cost variation†	[25]
Tests	1,605	Varied by test cost variation‡	[25]
24 weeks			
Staff	374	Varied by staff cost variation†	[25]
Tests	1,683	Varied by test cost variation‡	[25]
48 weeks			
Staff	504	Varied by staff cost variation†	[25]
Tests	1,822	Varied by test cost variation‡	[25]
Additional treatment delivery for PWID			
PWID extra nurse time		Varied by staff cost variation†	
12 weeks	129	and PWID staff time	[1] "
24 weeks	159	variation§	[1] "
48 weeks	220		[1] "
PWID extra basic assessments		Varied by test cost variation‡, staff cost variation†, and	
12 weeks			
Staff	58	PWID staff time variation§	[1] "
Tests	43		[1] "
24 weeks			
Staff	97		[1] "
Tests	71		[1] "
48 weeks			
Staff	174		[1] "
Tests	129		[1] "
PWID psychiatric visits	51	Varied by staff cost variation‡ and PWID staff time variation§	[1] "

Appendix table 2. HCV antiviral treatment costs. *Average peginterferon cost between alfa-2a (Pegasys) and alfa-2b(ViraferonPeg), and average ribavirin cost between Copegus and Rebetol. †Test value calculated by multiplying mean test cost with a test cost variation parameter, uniformly sampled between 0.8 and 1.2. ‡Staff value calculated by multiplying mean staff cost by a staff cost variation parameter, uniformly sampled between 0.8 and 1.2. §PWID staff cost calculated by multiplying mean staff cost by a staff cost variation parameter and an extra PWID staff time variation parameter (both uniformly sampled between 0.8 and 1.2). "Graham Foster, Consultant Hepatologist, *personal communication*. pegIFN=pegylated interferon; RBV=ribavirin.

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

Appendix table 3. Model fitting procedure summary

Telaprevir/boceprevir scenario parameters	Value	Units	Notes	Ref.
Proportional increase in SVR for genotype 1 patients	68%	-		[26, 27]
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.	[26, 27]
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 1 of main text**)	[28, 29]

Appendix table 4. Telaprevir/boceprevir sensitivity analysis parameters. pegIFN=pegylated interferon; RBV=ribavirin; RVR=rapid viral response; SVR=sustained viral response.

Health state utilities/disutilities per year	Mean	Distribution	Ref.
Ex-PWID			
Mild diagnosed [age 15-19]	0.77	Beta(α=521.2375, β=155.6943)	[25, 30]
Moderate diagnosed [age 15-19]	0.66	Beta(α=168.2461, β=86.6723)	[25, 30]
Compensated cirrhosis diagnosed [age 15-19]	0.55	Beta(α=47.1021, β=38.5381)	[25, 30]
Undiagnosed stages		Diagnosed state utility value + 0.09	[31]
Mild SVR [age 15-19]	0.82	Beta(α=65.8678, β=14.4588)	[25, 30]
Moderate SVR [age 15-19]	0.72	Beta(α=58.0608, β=22.5792)	[6, 25, 30]
Compensated cirrhosis SVR [age 15-19]	0.61	Beta(α=58.0476, β=37.1124)	[32]
PWID			
HCV disease states	As in ex-PWID, but reduced by PropPWID†		Assumed

Appendix table 5. Disutility on diagnosis sensitivity analysis parameters †PropPWID=(uninfected PWID utility value for age 15-19)/(uninfected ex-PWID utility for age 15-19). SVR=sustained viral response.

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The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals:

BJOG: An International Journal of Obstetrics and Gynaecology
BMC Medicine 2013; 11:80
BMJ 2013;346:f1049
Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003)
Cost Effectiveness and Resource Allocation 2013 11:6.
The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print]
International Journal of Technology Assessment in Health Care
Journal of Medical Economics 2013 Mar 25. [Epub ahead of print]
Pharmacoeconomics 2013 Mar 26. [Epub ahead of print]
Value in Health 2013 March - April;16(2):e1-e5

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1, line 1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	pg 2-3, line 47-74
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy o practice decisions.	pg 4, line 110-124
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	pg 4, line 96-100. pg 5 line 130-136, 140-143
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 5, 128-130
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	pg 7, lines 170-173
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	pg 6, line 165-170
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	pg 7, line 173-174
Discount rate	9	Report the choice of discount rate(s) used for costs and	pg 7, line 173

		outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	pg 7, line 172-173 and 184-196
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	pg 10, lines 246-250 and appendix
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	n/a
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	pg 8, line 198-206 pg 10, line 249-250 and appendix
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	pg 7, lines 171-172. pg 8, 202-204
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	pg 5, lines 120-123 and 128-130. figure in appendix
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	pg 5, lines 128-153 and appendix
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	pg 6, lines 155-181. pg10 lines 252-259, appendix
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Tables 1-3, appendix

Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 4
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Figure 2 and 3, pg 10-12, lines 267-297. pg 12-13, lines 303-323
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Figure 2
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pg 13-17, lines 326-431
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	pg 1, lines 22-36
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	pg 18, lines 445-448

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
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Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons

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Title: Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons

Authors: Natasha K. Martin[1,2], Matthew Hickman[1], Alec Miners[2], Sharon J. Hutchinson[3,4], Avril Taylor[5], Peter Vickerman[2,1]

Affiliations: [1]Department of Social and Community Medicine, University of Bristol, Bristol, UK. [2]Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine [3]Health Protection Scotland, UK. [4]School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK. [5]University of the West of Scotland, Glasgow, UK.

Corresponding author contact: Natasha.Martin@bristol.ac.uk. Department of Social and Community Medicine, 39 Whatley Road, Bristol, BS8 2PS.

Abbreviations: hepatitis C virus (HCV), people who inject drugs (PWID), dried blood spot (DBS), incremental cost-effectiveness ratio (ICER), quality-adjusted life-year (QALY), willingness-to-pay (WTP), hepatocellular carcinoma (HCC), liver transplant (LT), pegylated interferon (pegIFN), ribavirin (RBV), sustained viral response (SVR), 95% confidence interval (CI), antibody (Ab)

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ABSTRACT (265 words)

Objectives: People who inject drugs (PWID) are at high-risk for acquiring hepatitis C virus (HCV), but many are unaware of their infection. HCV dried blood spot (DBS) testing increases case-finding in addiction services and prisons. We determine the cost-effectiveness of increasing HCV case-finding among PWID by offering DBS testing in specialist addiction services or prisons as compared to using venepuncture.

Design: Cost-utility analysis using a dynamic HCV transmission model among PWID, including: disease progression, diagnosis, treatment, injecting status, incarceration, and addition services contact.

Setting: United Kingdom

Participants: N/A

Intervention: DBS testing in specialist addiction services or prisons. Intervention impact was determined by a meta-analysis of primary data

Primary and secondary outcome measures: Costs (in UK £, £1=$1.60 USD) and utilities (quality adjusted life years, QALYs) were attached to each state and the incremental cost effectiveness ratio (ICER) determined. Multivariate uncertainty and one-way sensitivity analyses were performed.

Results: For a £20,000 per QALY gained willingness-to-pay threshold, DBS testing in addiction services is cost-effective (ICER of £14,600 per QALY gained). Under the base-case assumption of no continuity of treatment/care when exiting/entering prison, DBS testing in prisons is not cost-effective (ICER of £59,400 per QALY gained). Results are robust to changes in HCV prevalence; increasing PWID treatment rates to those for ex-PWID considerably reduces the ICER (£4,500 and £30,000 per QALY gained for addiction services and prison, respectively). If

continuity of care is >40%, the prison DBS ICER falls below £20,000 per QALY gained.

Conclusions: Despite low PWID treatment rates, increasing case-finding can be cost-effective in specialist addiction services, and in prisons if continuity of treatment/care is ensured.

Trial Registration: N/A

ARTICLE SUMMARY

Article focus

- We perform a cost-utility analysis of increasing HCV case-finding among PWID by offering dried blood spot testing in specialist addiction services or prisons.

Key messages

- Despite low PWID treatment rates, increasing case-finding for PWID can be cost-effective in specialist addiction services.
- In prisons, the cost-effectiveness of HCV case-finding depends on adequate continuity of treatment/care between prison and the community, as many treatments are discontinued due to short incarceration times.

Strengths and limitations of this study

- We use a dynamic mathematical model of HCV transmission to capture the potential prevention benefits of treatment, which has been shown to increase cost-effectiveness of HCV treatment for PWID.
- Key limitations are the limited empirical data on PWID health utilities, treatment rates, and intervention impact.

INTRODUCTION

In developed countries, the hepatitis C virus (HCV) is spread primarily through injecting drug use, with over 90% of new infections among people who inject drugs (PWID) [1]. However, diagnosis rates are low, with only half of infected PWID in the US and UK diagnosed[2].

The majority of HCV testing performed in the US and UK is through venepuncture, which is available in virtually all prisons[3] and addiction services (structured programs providing pharmacological or nonpharmacological drug treatment in the community) either on site or by referral. However, testing opportunities among PWID still may be limited. This is because venous access can be poor and specialist staff (who may not be available at all potential testing sites) are required to take blood, which if only available in hospital phlebotomy services can increase stigma[4].

Dried blood spot (DBS) testing is non-invasive and can be performed by clinical and non-clinical staff. Two UK studies[5 6] showed offering DBS testing within specialist addiction services and prisons led to a 3 to 6-fold increase in HCV testing, and a recent systematic review identified DBS as the best available targeted intervention for increasing HCV case-finding amongst PWID[7]. Hence, DBS testing could be an important component of any strategy attempting to scale-up treatment provision for PWID, for both care and prevention[8].

We perform a cost-utility analysis of introducing DBS testing amongst current and former PWID in specialist addiction services and prisons in the UK[5]. Unlike

previous economic evaluations of HCV testing in these settings[9 10], we incorporate a dynamic mathematical model to capture the potential prevention benefits of treatment, which can substantially increase the cost-effectiveness of HCV treatment for PWID[11]. A dynamic model accounts for both individual and population benefits of treatment, as well as the dynamic nature of incarceration, especially among PWID. Our model is the first to explore the importance of continuity of care between prison and the community.

METHODS

Mathematical model

An existing dynamic, deterministic model of HCV transmission, progression and HCV treatment was adapted to project the impact of introducing DBS testing in prisons and addiction services[11]. See **appendix** for details and model schematics. Briefly, the model stratifies by: injecting state (never PWID/PWID/ex-PWID); incarceration status (never/currently/formerly); contact with addiction services (in contact/not in contact); age ([15-19],[20-24],[25-29],[30-54],[55-64],[65-74],[75+]); HCV infection and disease progression (never infected, spontaneously cleared, mild HCV, moderate HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post-transplant). HCV disease stages are further subdivided into undiagnosed or diagnosed, where those who are diagnosed can either be lost to follow-up, in referral (early/late), on antiviral treatment, sustained viral response (SVR), or non-SVR.

All PWID can acquire and transmit HCV, but imprisoned PWID only transmit HCV to other prisoners. We define ex-PWID as those who have permanently ceased

injecting, and assume no ongoing transmission from non/ex-PWID. An individual's risk of acquiring HCV is proportional to the setting-specific HCV prevalence (prison/community). The model assumes a background rate of HCV testing for all PWID and ex-PWID in the community/prison, and in addiction services for PWID.

No UK data exist regarding continuity of care (treatment or referral) on prison entry/exit, but experts described difficulty in ensuring continuity on release (Eamonn O'Moore[Offender Health, UK Department of Health], Iain Brew[HMP Leeds] *personal communication*). Therefore, in our base-case we assume those in treatment or referral become lost to follow-up upon entering/exiting prison, but can be re-tested/re-treated.

Model fitting and base-case projections

For the probabilistic uncertainty analysis, 1000 parameter sets were sampled from each parameter uncertainty distribution in **table 1 and appendix tables 1-2**. For parameter set, the model was calibrated to UK epidemiological data on incarceration, injecting drug use, HCV prevalence, and diagnosis. This was achieved through a multi-step parameter sampling and model calibration process, utilizing simplified models where possible to reduce computational time and to verify the full model predictions against simplified models. For details on the model calibration (including schematics and equations) and initialization, see **appendix**.

After calibration, for each of the 1000 parameter sets, the model was run with and without the intervention ('intervention' and 'baseline', respectively). We model an intervention of offering DBS testing in prison, compared to a baseline of current

testing with venepuncture only. Additionally, we evaluate an intervention of offering DBS in specialist addiction services, compared to a baseline of current testing with venepuncture. The economic analysis was performed from a UK National Health Service perspective. Costs (in 2011 GBP, £1=$1.55 USD) and health utilities (in quality-adjusted life years, QALYs) were attached to each model compartment. Costs and QALYs were discounted 3.5% per annum as per NICE guidelines, with a 100 year time horizon (to accrue individual and population benefits). The mean incremental cost-effectiveness ratio (ICER) was calculated and cost-effectiveness determined using the UK willingness-to-pay (WTP) threshold, estimated between £20,000 and £30,000 per QALY gained[12]. Cost-effectiveness acceptability curves were constructed and univariate sensitivity analyses undertaken. Analysis of covariance (ANCOVA) methods were used to summarize the proportion of the variability in the incremental costs and QALYs explained by the uncertainty in input parameters[13].

Parameters

All parameters can be found in table 1 and **appendix tables 1-4**.

Health state utilities: Uninfected utility values were taken from UK population norms for non-PWID, and a large cross-sectional study of injectors in Scotland[14] for current PWID. We assumed equal utilities for ex-PWID and non-PWID[10]. Utilities for HCV disease and treatment stages came from UK HCV trials and economic evaluations[15-17] and used for ex-PWID.To derive PWID HCV utilities, non-PWID HCV utilities were rescaled by multiplying by the ratio of the uninfected PWID utility to the uninfected ex-PWID utility for the youngest age group. All states included disutilities with age.

No disutility was associated with testing in the base-case. However, some evidence suggests PWID may experience a disutility after positive HCV diagnosis[14 18]. We explored the impact of a disutility (0.09[14], see **appendix**) on diagnosis, which was fully regained with treatment SVR.

Health state and testing costs: Health care costs for HCV disease stages, antiviral treatment (pegylated interferon-alfa and ribavirin, pegIFN+RBV), and testing were taken from UK economic analyses[15 16 19 20]**.** Data on the yield (proportion tests Ab+) and prevalence in each setting were used to calculate the number of non-PWID tested for each PWID/ex-PWID (see **appendix**). Costs were inflated to 2011 GBP using the Health and Community Hospital Service pay and prices index[21]. Additional PWID treatment delivery costs were applied[11]. We assumed undiagnosed individuals do not incur HCV-related health care costs unless progressing to decompensated disease[9].

HCV disease progression parameters: Transition rates between disease stages were taken from UK economic evaluations[15-17]. Although estimates were not PWID specific, a recent meta-analysis suggests little evidence for differences in progression between PWID and non-PWID[22].

HCV prevalence: PWID HCV chronic prevalence was estimated from HCV antibody prevalence among PWID in England (45% [41-49%, 95% confidence interval (CI)][23]). As one-quarter of acute infections spontaneously clear [24] we assume

three-quarters of those who are ever exposed (antibody positive) are chronically infected, resulting in 35% chronic infection among PWID.

Incarceration duration: Incarceration duration for non-PWID and ex-PWID was age-stratified, with a mean of 8 months[25]. However, PWID have shorter durations in custody than non-PWID[25-27]. We used a 4 month PWID incarceration duration, based on an estimate for England and Wales[25]. A recent study in Scotland reported a median sentence of 7.1 months in PWID[27] which given most prisoners serve approximately half their sentence[28] would also equate to a duration of 4 months.

Testing rates: The overall baseline PWID testing rate (mean 12% undiagnosed PWID per year) was estimated through fitting the model to the current proportion of diagnosed PWID (approximately 50%[2]). Data on the proportion of tests from each setting was used in combination with the model projected annual numbers of PWID in contact with each setting to calculate setting-specific testing rates (6% and 13% per year of undiagnosed PWID in contact with addiction services and prisons, respectively, see **appendix**). We assume ex-PWID are tested at equal rates to PWID in prison and in general community settings. We assumed all diagnostic tests are 100% accurate due to the high sensitivity and specificity of DBS (99.6% sensitivity, 100% specificity in a setting with 50% prevalence [29]) and venepuncture assays[30], and because those who receive an initial positive test will receive additional tests before treatment.

Referral and treatment transition rates: The referral rate from testing services to secondary care (35%) was estimated from a UK study[31]. Those not referred or not attending referral were considered 'lost to follow-up'.

Approximately 50% of diagnosed ex-PWID in referral are treated within 2 years[31-33]. Since many delay treatment, we assume that after 2 years, 10% of those in referral initiate treatment annually. Within prison, treatment rates are lower than in the community[31 34], although a recent UK prison audit found 24% of those diagnosed were treated (Iain Brew[HMP Leeds], unpublished data). We therefore estimated halved treatment initiation rates in prison as compared to the community.

PWID treatment rates are unknown, but thought to be similarly low to other countries[35 36], with an estimated <1% of PWID treated annually (Graham Foster[Consultant Hepatologist], *personal communication*). Hence, if we assume 1% of infected PWID are treated within 2 years, this equates to treating approximately 5.5% of those who attend referral (35% of the 50% diagnosed) within 2 years. After 2 years, 1% of those in referral are treated annually thereafter.

Intervention: The effect of introducing DBS was modelled by assuming a 3.6-fold increase in testing [2.2-5.8 CI] in addiction services, and 2.6-fold increase in testing [0.1-34.9 CI] in prison, based on two multicentre studies (**table 1** and **appendix**). Intervention costs were determined from the study methods[5] and in consultation with the authors (**table 1**).

Sensitivity analyses

We performed one-way sensitivity analyses on: time horizon (50/200 years), discount rates (3.5% costs/1.5% QALYs), PWID treatment rates (increased in each setting), PWID SVR rates (reduced by 20%), PWID HCV chronic prevalence (20%/50%), antiviral treatment (telaprevir/boceprevir for genotype 1 patients, see **appendix**), and continuity of care for treatment/referral on entry/exit from prison (varied from 0% to 100%). We also explored the effect of assuming no prevention benefit (but allowing for reinfection), by permanently fixing the force of infection.

RESULTS

Case finding in addiction services

The incremental cost effectiveness ratio (ICER) of increasing case-finding in addiction services, by introducing DBS testing, was an estimated £14,600 ($22,630 USD) per QALY gained in the base-case (**table 2**). At a £20,000 or £30,000 WTP threshold, the intervention is likely to be cost-effective in 69% or 93% of the simulations, respectively (**figure 1a**). Uncertainty in the intervention effect contributed to 86% and 58% of the variation in incremental costs and QALYs, respectively. The remaining variation in incremental QALYs was mainly due to uncertainty in treatment rates (22%) and health utilities (17%).

For most sensitivity analyses, the ICER remained below a £30,000 WTP threshold (**figure 2a)**. Reducing the time horizon to 50 years increased the estimated ICER to £22,900 per QALY gained because fewer prevention benefits were accrued, whereas lengthening to 200 years increased cost-effectiveness. Changing the

discount rates to 3.5% costs/1.5% QALYs or no discounting decreased the estimated ICER to £5,100 or £6,700 per QALY gained, respectively. Variations in baseline HCV chronic prevalence had little effect (<10%). At lower prevalence (20%), identifying cases was more expensive but prevention impact was greater due to reduced reinfection risk, whereas the opposite occurred at higher prevalence (50%).

Increasing treatment rates increased the intervention's cost-effectiveness. If 50% (compared to 5.5% for base-case) of PWID in referral initiated treatment within 2 years (a treatment rate achieved by one UK service[37]) the ICER fell to £4,500 per QALY gained. If SVR rates amongst PWID were 20% lower than in ex-PWID, the ICER increased by 14% (£16,700 per QALY gained). Using telaprevir/boceprevir for genotype 1 patients minimally altered the ICER. Ignoring any prevention benefit doubled the ICER to £29,900 per QALY gained.

Only one sensitivity analysis substantially altered the cost-effectiveness conclusion. If a disutility was attached to diagnosis, the intervention resulted in negative incremental QALYs (due to low treatment rates) and was dominated (more expensive with fewer health benefits). However, even with this disutility, if treatment rates were increased to 50% of PWID in referral initiating treatment within 2 years, then the estimated ICER was £20,100 per QALY gained.

Case finding in prison

The ICER of increasing case-finding in prison, by introducing DBS testing, was estimated at £59,400 ($92,070 USD) per QALY gained (21% likely to be cost-effective at a £30,000 WTP threshold) in the base-case (**table 2** and **figure 1b**).

Uncertainty in the intervention effect contributed to most (>85%) of the variation in incremental costs and QALYs.

The base-case conclusion was robust to most one-way sensitivity analyses (**figure 2b)** – including time horizon, discount rates, HCV prevalence, and use of new treatments. If 50% of PWID in referral initiated treatment within 2 years, the ICER halved to just below £30,000 per QALY gained.

Introducing continuity of care (which measures the proportion of initiated treatments/referrals that are continued when entering/exiting prison) led to an increase in cost-effectiveness: from an ICER of £59,400 per QALY gained with 0% continuity to £10,400 per QALY gained with 100% continuity **(figure 3)**. The ICER fell below £20,000 when >40% continuity of care was ensured; at 40% continuity the intervention was 57% and 83% likely to be cost-effective at the £20,000 and £30,000 WTP thresholds, respectively. The level of continuity required for prison case-finding to be cost-effective also depended on treatment rates. If prison treatment rates were increased to equal those in the community (50%/5.5% of ex-PWID/PWID treated within 2 years of referral), then 35% continuity results in an ICER just below £20,000 per QALY gained. Increasing treatment rates further so 50% of all referred prisoners initiate treatment within 2 years lowers the required continuity to 20% for an ICER below £20,000.

DISCUSSION

Main findings

Our results indicate the introduction of dried blood spot testing for HCV case-finding is likely to be cost-effective under commonly used willingness-to-pay thresholds in the UK (£20,000-£30,000/QALY gained[12]) and US ($50,000/QALY gained[38]) in addiction services, but not in prison unless a minimum level of continuity of care in treatment or referral between prison and the community can be ensured. Ignoring the prevention benefit doubles the ICER of the intervention in addiction services. In the base-case, most PWID treatments initiated in prison were interrupted due to the lack of continuity of care and short PWID incarceration times (~4 months) in the UK[25 27]. Consequently, little prevention benefit was achieved from the prison intervention, with the results approaching the 'static' model. With the low base-case PWID treatment rates, the continuity required for DBS to be cost-effective was approximately 35-40% of the estimated treatment/referral rates, but if treatment/referral rates increased then lower levels of continuity would be cost-effective. Crucially, not all treatments need to be initiated or completed in prison, as only maintaining treatment or referral contact is necessary. Finally, both interventions are most cost-effective at higher treatment rates.

Strengths and Limitations

The key strength of this analysis is that the model is dynamic, therefore capturing the prevention impact of case-finding and treatment. The main limitations are concerned with parameter uncertainty and lack of model heterogeneity. First, we based our increase in case-finding on the DBS intervention, which though empirically founded, was informed by relatively small UK studies, resulting in wide uncertainty around the effect estimates.

Second, the base-case assumed comparatively low treatment rates for PWID, partly because UK data on PWID treatment numbers are not available. This information is critical, as higher treatment rates increase cost-effectiveness. This is especially important for prisons where treatment completion information was unavailable, yet strongly influenced cost-effectiveness. Additionally, even if treatment is interrupted, some may benefit from shortened treatment, which we did not incorporate.

Third, more data are needed to quantify PWID health utilities, which can be below the general population[39]. Especially important is whether any transient or permanent disutility on HCV diagnosis occurs, as current data are weak and not based on prospective studies. Our projections indicate if a disutility occurs then higher treatment rates are required for case-finding to be cost-effective.

Fourth, the model did not incorporate other interventions or behaviours that may influence HCV risk or treatment uptake. However, modelling work has shown introducing risk heterogeneity does not substantially reduce intervention impact if PWID circulate between risk states[40] which is likely to occur as individuals move in/out of drug treatment and prison.

Fifth, the model was parameterized to UK data, so our results are not necessarily applicable to other settings. However, our conclusions are robust to changes in HCV prevalence. Continuity of care could also be an issue in Australia, where PWID incarceration duration is similar to the UK[41]. However, sentences are longer in the US[42], so fewer treatments may be interrupted, and therefore case-finding in US prisons could be more cost-effective than our results indicate.

Our modelled UK treatment and HCV health care costs are within the range of those presented by recent US studies[43 44], with the exception of approximately 3-fold higher liver transplantation costs, which would increase the cost-effectiveness of case-finding in the US. Testing costs were taken from UK economic evaluations, however it is possible a streamlined and experienced testing service could lower costs associated with staff time, thus increasing cost-effectiveness.

Sixth, we were unable to evaluate future interferon-free direct-acting antiviral therapies as information on treatment costs and health utilities are unavailable. These treatments will likely have increased SVR (90% for all genotypes), shorter treatment durations (12-24 weeks), lower toxicity, and simpler dosing regimes[45]. Therapies with shorter duration could increase the impact of testing and treatment in prison as more patients will be able to complete therapy prior to release, and could potentially be more cost-effective depending on the ratio of additional costs to incremental impact.

Comparison with other studies

Two publications evaluated the cost-effectiveness of testing ex-PWID in prison, with ICERs varying from about £20,000[10] to £55,000[9] per QALY gained. Our results are consistent with Sutton et al.[9], which used the same discount rates as our study. However, we included the possible prevention impact of treating PWID, and unlike the previous studies, show how continuity of care between prison and the community can make case-finding cost-effective.

Three papers evaluated testing PWID in drug services[10 20 46]. Differences in baseline assumptions led to varying ICERs from £28,100[20] to £17,500[10 46] per QALY gained. Our results for addiction services support those found in the latter studies[10 46]. However, the intervention examined in these studies[10 20 46] was one-off testing using a cohort model (with no evidence based intervention effect) and neglected any prevention benefit.

Several US studies examined birth cohort screening for all people born in 1945-1965[44 47] or 1946-1970[43] as compared to risk based screening, reporting ICERs of $38,000 per QALY gained with direct-acting antivirals[43 44] and $5,400-16,000 per QALY gained with pegIFN+RBV[44 47]. Critically, the cost-effectiveness varies substantially by HCV prevalence[47], and the estimated US prevalence is higher than many other developed countries. Additionally, the ICERs were generated given assumptions of higher treatment rates, as well as greater utility gains with SVR than we consider. Importantly, our intervention targets PWID with a risk of transmitting infection to others, whereas birth cohort screening is likely to identify infections among ex-injectors and non-injecting populations which will have little primary prevention impact.

Implications

Our cost-effectiveness work indicates increasing HCV case-finding in addiction services can be cost-effective. However, the cost-effectiveness of prison case-finding interventions depends on adequate continuity of care with the community. Few settings have developed comprehensive strategies to address this issue, though New York recently initiated the Hepatitis C Continuity Program[48]. In all

settings, treatment uptake is critical: higher treatment rates prevent more disease transmission and increase the cost-effectiveness of case-finding interventions. If a disutility on diagnosis occurs, higher treatment rates would be necessary to ensure cost-effectiveness. Further empirical data are required on treatment uptake and changes in utilities following diagnosis and treatment in order to compare targeted case-finding with cohort models.

AUTHOR CONTRIBUTIONS

NKM contributed to the study design, model development, analysis, manuscript drafting and editing. MH contributed to the study design, model development, analysis, and manuscript editing. AM contributed to the analysis and manuscript editing. SJH contributed to the model parameterization, analysis, and manuscript editing. AT contributed to the model parameterization and manuscript editing. PV contributed to the study design, model development, analysis, and manuscript editing.

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Competing Interests

NM has received an honorarium for speaking at a conference sponsored by Janssen. SH has received honoraria for speaking at conferences sponsored by MSD, Janssen, Gilead, and Roche. MH, AM, AT, PV have no competing interests.

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Figure Legends:

Figure 1. **Base-case cost-effectiveness acceptability curves for the dried blood spot intervention.** Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.

Figure 2. **Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER).** Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.

Figure 3. **Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions.** Base-case scenario assumed 0% continuity.

	Mean value	Distribution	Units	Ref.
Intervention effect (proportional change in testing rate)				
Addiction services	3.6 [2.3-5.8]	Lognormal (μ=1.285, σ=0.239)	-	[5]
Prison	2.6 [0.2-34.9]	Lognormal (μ=0.968, σ=1.317)	-	[5]
Intervention costs (addiction services)				
Organization/coordination of training*	2,005.71		per health board	†
Training session‡	135		per training session	†
Attendees time§	1,620		per training session	†
Travel reimbursement for training leader‖	90.86		per training session	†
Total cost per addiction services training	3851.57		per training session	†
Mean number tested	40.3		per addiction service¶	[5]
Total intervention cost per test	**95.57**	**Uniform +/-50%**	per test	
Intervention costs (prison)				
Organization/coordination of training**	7020		per prison	†
Training session‡	135		per prison	†
Attendees time††	405		per prison	†
Travel reimbursement for training leader‡‡	127.20		per prison	†
Total cost per prison training	7687.20		per prison	†
Mean number tested per prison	116		per prison	**[5]**
Total intervention cost per test	**66.27**	**Uniform +/- 50%**	per test	

Table 1. Intervention parameters. All cost estimates assume a staff-nurse cost per hour of £36.25 (median estimate for band 5 general practice nurse[21]). *1 nurse 2 days/week for 6 months for 7 health boards. One training session per health board. †Noel Craine, *personal communication*. ‡1 nurse, half day. §12 nurses, half day. ‖1200 miles (£0.53 per mile) for travel to 7 health boards. ¶Assumed 1 addiction service per health board. **1 nurse full time for 5 prisons (1 training session per prison) ††3 nurses per prison, half day. ‡‡1200 miles (£0.53 per mile) for 5 prisons.

Intervention location	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
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
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

Table 2. Cost-effectiveness results from the base-case intervention analyses.

Title: Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons

Authors: Natasha K. Martin[1,2], Matthew Hickman[1], Alec Miners[2], Sharon J. Hutchinson[3,4], Avril Taylor[5], Peter Vickerman[2,1]

Affiliations: [1]Department of Social and Community Medicine, University of Bristol, Bristol, UK. [2]Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine [3]Health Protection Scotland, UK. [4]School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK. [5]University of the West of Scotland, Glasgow, UK.

Corresponding author contact: Natasha.Martin@bristol.ac.uk. Department of Social and Community Medicine, 39 Whatley Road, Bristol, BS8 2PS.

Abbreviations: hepatitis C virus (HCV), people who inject drugs (PWID), dried blood spot (DBS), incremental cost-effectiveness ratio (ICER), quality-adjusted life-year (QALY), willingness-to-pay (WTP), hepatocellular carcinoma (HCC), liver transplant (LT), pegylated interferon (pegIFN), ribavirin (RBV), sustained viral response (SVR), 95% confidence interval (CI), antibody (Ab)

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ABSTRACT (265 words)

Objectives: People who inject drugs (PWID) are at high-risk for acquiring hepatitis C virus (HCV), but many are unaware of their infection. HCV dried blood spot (DBS) testing increases case-finding in addiction services and prisons. We determine the cost-effectiveness of increasing HCV case-finding among PWID by offering DBS testing in specialist addiction services or prisons as compared to using venepuncture.

Design: Cost-utility analysis using a dynamic HCV transmission model among PWID, including: disease progression, diagnosis, treatment, injecting status, incarceration, and addition services contact.

Setting: United Kingdom

Participants: N/A

Intervention: DBS testing in specialist addiction services or prisons. Intervention impact was determined by a meta-analysis of primary data

Primary and secondary outcome measures: Costs (in UK £, £1=$1.60 USD) and utilities (quality adjusted life years, QALYs) were attached to each state and the incremental cost effectiveness ratio (ICER) determined. Multivariate uncertainty and one-way sensitivity analyses were performed.

Results: For a £20,000 per QALY gained willingness-to-pay threshold, DBS testing in addiction services is cost-effective (ICER of £14,600 per QALY gained). Under the base-case assumption of no continuity of treatment/care when exiting/entering prison, DBS testing in prisons is not cost-effective (ICER of £59,400 per QALY gained). Results are robust to changes in HCV prevalence; increasing PWID treatment rates to those for ex-PWID considerably reduces the ICER (£4,500 and £30,000 per QALY gained for addiction services and prison, respectively). If

continuity of care is >40%, the prison DBS ICER falls below £20,000 per QALY gained.

Conclusions: Despite low PWID treatment rates, increasing case-finding can be cost-effective in specialist addiction services, and in prisons if continuity of treatment/care is ensured.

Trial Registration: N/A

ARTICLE SUMMARY

Article focus

- We perform a cost-utility analysis of increasing HCV case-finding among PWID by offering dried blood spot testing in specialist addiction services or prisons.

Key messages

- Despite low PWID treatment rates, increasing case-finding for PWID can be cost-effective in specialist addiction services.
- In prisons, the cost-effectiveness of HCV case-finding depends on adequate continuity of treatment/care between prison and the community, as many treatments are discontinued due to short incarceration times.

Strengths and limitations of this study

- We use a dynamic mathematical model of HCV transmission to capture the potential prevention benefits of treatment, which has been shown to increase cost-effectiveness of HCV treatment for PWID.
- Key limitations are the limited empirical data on PWID health utilities, treatment rates, and intervention impact.

INTRODUCTION

In developed countries, the hepatitis C virus (HCV) is spread primarily through injecting drug use, with over 90% of new infections among people who inject drugs (PWID) ~~and approximately 10 million PWID infected worldwide~~[1]. However, diagnosis rates are low, with only half of infected PWID in the US and UK diagnosed[2]~~, putting many at risk of cirrhosis, liver cancer, and death~~.

The majority of HCV testing performed in the US and UK is through venepuncture, which is available in virtually all prisons[3] and addiction services (structured programs providing pharmacological or nonpharmacological drug treatment in the community) either on site or by referral. However, testing opportunities among PWID still may be limited. This is because venous access can be poor and specialist staff (who may not be available at all potential testing sites) are required to take blood, which if only available in hospital phlebotomy services can increase stigma[4].

Dried blood spot (DBS) testing is non-invasive and can be performed by clinical and non-clinical staff. Two UK studies[5 6] showed offering DBS testing within specialist addiction services and prisons led to a 3 to 6-fold increase in HCV testing, and a recent systematic review identified DBS as the best available targeted intervention for increasing HCV case-finding amongst PWID[7]. Hence, DBS testing could be an important component of any strategy attempting to scale-up treatment provision for PWID, for both care and prevention[8].

We perform a cost-utility analysis of introducing DBS testing amongst current and former PWID in specialist addiction services and prisons in the UK[5]. Unlike previous economic evaluations of HCV testing in these settings[9 10], we incorporate a dynamic mathematical model to capture the potential prevention benefits of treatment, which can substantially increase the cost-effectiveness of HCV treatment for PWID[11]. A dynamic model accounts for both individual and population benefits of treatment, as well as the dynamic nature of incarceration, especially among PWID. Our model is ~~also~~ the first to explore the importance of continuity of care between prison and the community.

METHODS

Mathematical model

An existing dynamic, deterministic model of HCV transmission, progression and HCV treatment was adapted to project the impact of introducing DBS testing in prisons and addiction services[11]. See **appendix** for details and model schematics. Briefly, the model stratifies by: injecting state (never PWID/PWID/ex-PWID); incarceration status (never/currently/formerly); contact with addiction services (in contact/not in contact); age ([15-19],[20-24],[25-29],[30-54],[55-64],[65-74],[75+]); HCV infection and disease progression (never infected, spontaneously cleared, mild HCV, moderate HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post-transplant). HCV disease stages are further subdivided into undiagnosed or diagnosed, where those who are diagnosed can either be lost to follow-up, in referral (early/late), on antiviral treatment, sustained viral response (SVR), or non-SVR.

All PWID can acquire and transmit HCV, but imprisoned PWID only transmit HCV to other prisoners. We define ex-PWID as those who have permanently ceased injecting, and assume no ongoing transmission from non/ex-PWID. An individual's risk of acquiring HCV is proportional to the setting-specific HCV prevalence (prison/community). The model assumes a background rate of HCV testing for all PWID and ex-PWID in the community/prison, and in addiction services for PWID.

No UK data exist regarding continuity of care (treatment or referral) on prison entry/exit, but experts described difficulty in ensuring continuity on release (Eamonn O'Moore[Offender Health, UK Department of Health], Iain Brew[HMP Leeds] *personal communication*). Therefore, in our base-case we assume those in treatment or referral become lost to follow-up upon entering/exiting prison, but can be re-tested/re-treated.

Model fitting and base-case projections

For the probabilistic uncertainty analysis, 1000 parameter sets were sampled from each parameter uncertainty distribution in **table~~s~~ 1 and appendix tables 1–~~23~~**. For ~~each of these~~ parameter set~~s~~, the model was calibrated to UK epidemiological data on incarceration, injecting drug use, HCV prevalence, and diagnosis. This was achieved through a multi-step parameter sampling and model calibration process, utilizing simplified models where possible to reduce computational time and to verify the full model predictions against simplified models. For details on the model calibration (including schematics and equations) and initialization, see **appendix**.

After calibration, for each of the 1000 parameter sets, the model was run with and without the intervention ('intervention' and 'baseline', respectively). We model an intervention of offering DBS testing in prison, compared to a baseline of current testing with venepuncture only. Additionally, we evaluate an intervention of offering DBS in specialist addiction services, compared to a baseline of current testing with venepuncture. The economic analysis was performed from a UK National Health Service perspective. Costs (in 2011 GBP, £1=$1.55 USD) and health utilities (in quality-adjusted life years, QALYs) were attached to each model compartment. Costs and QALYs were discounted 3.5% per annum as per NICE guidelines, with a 100 year time horizon (to accrue individual and population benefits). The mean incremental cost-effectiveness ratio (ICER) was calculated and cost-effectiveness determined using the UK willingness-to-pay (WTP) threshold, estimated between £20,000 and £30,000 per QALY gained[12]. Cost-effectiveness acceptability curves were constructed and univariate sensitivity analyses undertaken. Analysis of covariance (ANCOVA) methods were used to summarize the proportion of the variability in the incremental costs and QALYs explained by the uncertainty in input parameters[13].

Parameters

All parameters can be found in table 1 and **appendix tables 1-4**.

Health state utilities: Uninfected utility values were taken from UK population norms for non-PWID, and a large cross-sectional study of injectors in Scotland[14] for current PWID. We assumed equal utilities for ex-PWID and non-PWID[10]. Utilities for HCV disease and treatment stages came from UK HCV trials and economic evaluations[15-17] and used for ex-PWID ~~**(table 1).**~~ To derive PWID HCV

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utilities, non-PWID HCV utilities were rescaled by multiplying by the ratio of the uninfected PWID utility to the uninfected ex-PWID utility for the youngest age group. All states included disutilities with age.

No disutility was associated with testing in the base-case. However, some evidence suggests PWID may experience a disutility after positive HCV diagnosis[14 18]. We explored the impact of a disutility (0.09[14], see **appendix**) on diagnosis, which was fully regained with treatment SVR.

Health state and testing costs: Health care costs for HCV disease stages, antiviral treatment (pegylated interferon-alfa and ribavirin, pegIFN+RBV), and testing were taken from UK economic analyses[15 16 19 20]. ~~(table 1 and appendix).~~ Data on the yield (proportion tests Ab+) and prevalence in each setting were used to calculate the number of non-PWID tested for each PWID/ex-PWID (see **appendix**). Costs were inflated to 2011 GBP using the Health and Community Hospital Service pay and prices index[21]. Additional PWID treatment delivery costs were applied[11]. We assumed undiagnosed individuals do not incur HCV-related health care costs unless progressing to decompensated disease[9].

HCV disease progression parameters: Transition rates between disease stages were taken from UK economic evaluations[15-17]. ~~(table 1).~~ Although estimates were not PWID specific, a recent meta-analysis suggests little evidence for differences in progression between PWID and non-PWID[22].

HCV prevalence: PWID HCV chronic prevalence was estimated from HCV antibody prevalence among PWID in England (45% [41-49%, 95% confidence interval (CI)][23]). As one-quarter of acute infections spontaneously clear, ~~with spontaneous clearance of 26% of acute infections~~[24] we assume three-quarters of those who are ever exposed (antibody positive) are chronically infected, resulting in 35% chronic infection among PWID.

Incarceration duration: Incarceration duration for non-PWID and ex-PWID was age-stratified, with a mean of 8 months[25]. However, PWID have shorter durations in custody than non-PWID[25-27]. We used a 4 month PWID incarceration duration, based on an estimate for England and Wales[25]. A recent study in Scotland reported a median sentence of 7.1 months in PWID[27] which given most prisoners serve approximately half their sentence[28] would also equate to a duration of 4 months.

Testing rates: The overall baseline PWID testing rate (mean 12% undiagnosed PWID per year) was estimated through fitting the model to the current proportion of diagnosed PWID (approximately 50%[2]). , ~~and used~~ Data on the proportion of tests from each setting was used in combination with the model projected annual numbers of PWID in contact with each setting to calculate setting-specific testing rates (6% and 13% per year of undiagnosed PWID in contact with addiction services and prisons, respectively ~~(prison, addiction services, other),~~ (see **appendix**). We assume ex-PWID are tested at equal rates to PWID in prison and in general community settings. We assumed all diagnostic tests are 100% accurate due to the high sensitivity and specificity of DBS (99.6% sensitivity, 100% specificity in a setting

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with 50% prevalence [29]) and venepuncture assays[30], ~~[29 30]~~ and because those who receive an initial positive test will receive additional tests before treatment.

Referral and treatment transition rates: The referral rate from testing services to secondary care (35%) was estimated from a UK study[31]. Those not referred or not attending referral were considered 'lost to follow-up'.

Approximately 50% of diagnosed ex-PWID in referral are treated within 2 years[31-33]. Since many delay treatment, we assume that after 2 years, 10% of those in referral initiate treatment annually. Within prison, treatment rates are ~~much~~ lower than in the community[31 34], although a recent UK prison audit found 24% of those diagnosed were treated (Iain Brew[HMP Leeds], unpublished data). We therefore estimated ~~half the~~halved treatment initiation rates in prison as compared to the community.

PWID treatment rates are unknown, but thought to be similarly low to other countries[35 36], with an estimated <1% of PWID treated annually (Graham Foster[Consultant Hepatologist], *personal communication*). Hence, if we assume 1% of infected PWID are treated within 2 years, this equates to treating approximately 5.5% of those who attend referral (35% of the 50% diagnosed) within 2 years. After 2 years, 1% of those in referral are treated annually thereafter. ~~Testing and treatment rates are shown in **table 1**.~~

Intervention: The effect of introducing DBS was modelled by assuming a 3.6-fold increase in testing [2.2-5.8 CI] in addiction services, and 2.6-fold increase in testing

[0.1-34.9 CI] in prison, based on two multicentre studies (**table 1~~2~~** and **appendix**). Intervention costs were determined from the study methods[5] and in consultation with the authors (**table 1~~2~~**).

Sensitivity analyses

We performed one-way sensitivity analyses on: time horizon (50/200 years), discount rates (3.5% costs/1.5% QALYs), PWID treatment rates (increased in each setting), PWID SVR rates (reduced by 20%), PWID HCV chronic prevalence (20%/50%), antiviral treatment (telaprevir/boceprevir for genotype 1 patients, see **appendix**), and continuity of care for treatment/referral on entry/exit from prison (varied from 0% to 100%). We also explored the effect of assuming no prevention benefit (but allowing for reinfectio~~pg~~n), by permanently fixing the force of infection.

RESULTS

Case finding in addiction services

The incremental cost effectiveness ratio (ICER) of increasing case-finding in addiction services, by introducing DBS testing, was an estimated £14,600 ($22,630 USD) per QALY gained in the base-case (**table 2~~4~~**). At a £20,000 or £30,000 WTP threshold, the intervention is likely to be cost-effective in 69% or 93% of the simulations, respectively (**figure 1a**). Uncertainty in the intervention effect contributed to 86% and 58% of the variation in incremental costs and QALYs, respectively. The remaining variation in incremental QALYs was mainly due to uncertainty in treatment rates (22%) and health utilities (17%).

For most sensitivity analyses, the ICER remained below a £30,000 WTP threshold (**figure 2a)**. Reducing the time horizon to 50 years increased the estimated ICER to £22,900 per QALY gained because fewer prevention benefits were accrued, whereas lengthening to 200 years increased cost-effectiveness. Changing the discount rates to 3.5% costs/1.5% QALYs or no discounting decreased the estimated ICER to £5,100 or £6,700 per QALY gained, respectively. Variations in baseline HCV chronic prevalence had little effect (<10%). At lower prevalence (20%), identifying cases was more expensive but prevention impact was greater due to reduced reinfection risk, whereas the opposite occurred at higher prevalence (50%).

Increasing treatment rates increased the intervention's cost-effectiveness. If 50% (compared to 5.5% for base-case) of PWID in referral initiated treatment within 2 years (a treatment rate achieved by one UK service[37]) the ICER fell to £4,500 per QALY gained. If SVR rates amongst PWID were 20% lower than in ex-PWID, the ICER increased by 14% (£16,700 per QALY gained). Using telaprevir/boceprevir for genotype 1 patients minimally altered the ICER. Ignoring any prevention benefit doubled the ICER to £29,900 per QALY gained.

Only one sensitivity analysis substantially altered the cost-effectiveness conclusion. If a disutility was attached to diagnosis, the intervention resulted in negative incremental QALYs (due to low treatment rates) and was dominated (more expensive with fewer health benefits). However, even with this disutility, if treatment rates were increased to 50% of PWID in referral initiating treatment within 2 years, then the estimated ICER was £20,100 per QALY gained.

Case finding in prison

The ICER of increasing case-finding in prison, by introducing DBS testing, was estimated at £59,400 ($92,070 USD) per QALY gained (21% likely to be cost-effective at a £30,000 WTP threshold) in the base-case (**table 24** and **figure 1b**). Uncertainty in the intervention effect contributed to most (>85%) of the variation in incremental costs and QALYs.

The base-case conclusion was robust to most one-way sensitivity analyses (**figure 2b)** – including time horizon, discount rates, HCV prevalence, and use of new treatments. If 50% of PWID in referral initiated treatment within 2 years, the ICER halved to just below £30,000 per QALY gained.

Introducing continuity of care (which measures the proportion of initiated treatments/referrals that are continued when entering/exiting prison) led to an increase in cost-effectiveness: from an ICER of £59,400 per QALY gained with 0% continuity to £10,400 per QALY gained with 100% continuity **(figure 3)**. The ICER fell below £20,000 when >40% continuity of care was ensured; at 40% continuity the intervention was 57% and 83% likely to be cost-effective at the £20,000 and £30,000 WTP thresholds, respectively. The level of continuity required for prison case-finding to be cost-effective also depended on treatment rates. If prison treatment rates were increased to equal those in the community (50%/5.5% of ex-PWID/PWID treated within 2 years of referral), then 35% continuity results in an ICER just below £20,000 per QALY gained. Increasing treatment rates further so 50% of all referred prisoners

initiate treatment within 2 years lowers the required continuity to 20% for an ICER below £20,000.

DISCUSSION

Main findings

Our results indicate the introduction of dried blood spot testing for HCV case-finding is likely to be cost-effective under commonly used willingness-to-pay thresholds in the UK (£20,000-£30,000/QALY gained[12]) and US ($50,000/QALY gained[38]) in addiction services, but not in prison unless a minimum level of continuity of care in treatment or referral between prison and the community can be ensured. Ignoring the prevention benefit doubles the ICER of the intervention in addiction services. In the base-case, most PWID treatments initiated in prison were interrupted due to the lack of continuity of care and short PWID incarceration times (~4 months) in the UK[25 27]. Consequently, little prevention benefit was achieved from the prison intervention, with the results approaching the 'static' model. With the low base-case PWID treatment rates, the continuity required for DBS to be cost-effective was approximately 35-40% of the estimated treatment/referral rates, but if treatment/referral rates increased then lower levels of continuity would be cost-effective. Crucially, not all treatments need to be initiated or completed in prison, as only maintaining treatment or referral contact is necessary. Finally, both interventions are most cost-effective at higher treatment rates.

Strengths and Limitations

The key strength of this analysis is that the model is dynamic, therefore capturing the prevention impact of case-finding and treatment. The main limitations are concerned

with parameter uncertainty and lack of model heterogeneity. First, we based our increase in case-finding on the DBS intervention, which though empirically founded, was informed by relatively small UK studies, resulting in wide uncertainty around the effect estimates.

Second, the base-case assumed comparatively low treatment rates for PWID, partly because UK data on PWID treatment numbers are not available~~., although similar rates have been reported in the US[36] and Canada[35].~~ This information is critical, as higher treatment rates increase ~~the intervention's~~ cost-effectiveness. This is especially important for prisons where ~~information on~~ treatment completion information was unavailable, yet ~~these factors~~ strongly influenced cost-effectiveness. Additionally, even if treatment is interrupted, some may benefit from shortened treatment, which we did not incorporate. ~~However, the rapid development of resistance observed with new treatments[39] indicates treatment continuity will become an increasingly crucial issue.~~

Third, more data are needed to quantify PWID health utilities, which can be below the general population[39]. Especially important is whether any transient or permanent disutility on HCV diagnosis occurs, as current data are weak and not based on prospective studies. ~~No consensus exists regarding diagnosis utilities in other diseases[41-42].~~ Our projections indicate if a disutility occurs then higher treatment rates are required for case-finding to be cost-effective.

Fourth, the model did not incorporate other interventions or behaviours that may influence HCV risk or treatment uptake. ~~For example, case-finding and treatment of~~

~~PWID is targeted towards those on opiate substitution therapy[43] who may contribute fewer secondary infections[44].~~ However, modelling work has shown introducing risk heterogeneity does not substantially reduce intervention impact if PWID circulate between risk states[40] which is likely to occur as individuals move in/out of drug treatment and prison.

Fifth, the model was parameterized to UK data, so our results are not necessarily applicable to other settings. However, our conclusions are robust to changes in HCV prevalence. Continuity of care could also be an issue in Australia, where PWID incarceration duration is similar to the UK[41]. However, sentences are longer in the US[42], so fewer treatments may be interrupted, and therefore case-finding in US prisons could be more cost-effective than our results indicate.

Our modelled UK treatment and HCV health care costs are within the range of those presented by recent US studies[43 44], with the exception of approximately 3-fold higher liver transplantation costs, which would increase the cost-effectiveness of case-finding in the US. Testing costs were taken from UK economic evaluations, however it is possible a streamlined and experienced testing service could lower costs associated with staff time, thus increasing cost-effectiveness.

Sixth, we were unable to evaluate future interferon-free direct-acting antiviral therapies as information on treatment costs and health utilities are unavailable. These treatments will likely have increased SVR (90% for all genotypes), shorter treatment durations (12-24 weeks), lower toxicity, and simpler dosing regimes[45]. Therapies with shorter duration could increase the impact of testing and treatment in

prison as more patients will be able to complete therapy prior to release, and could potentially be more cost-effective depending on the ratio of additional costs to incremental impact.

Comparison with other studies

Two publications evaluated the cost-effectiveness of testing ex-PWID in prison, with ICERs varying from about £20,000[10] to £55,000[9] per QALY gained. Our results are consistent with Sutton et al.[9], which used the same discount rates as our study. However, we included the possible prevention impact of treating PWID, and unlike the previous studies, show how continuity of care between prison and the community can make case-finding cost-effective.

Three papers evaluated testing PWID in drug services[10 20 46]. Differences in baseline assumptions led to varying ICERs from £28,100[20] to £17,500[10 46] per QALY gained. Our results for addiction services support those found in the latter studies[10 46]. However, the intervention examined in these studies[10 20 46] was one-off testing using a cohort model (with no evidence based intervention effect) and neglected any prevention benefit.

Several US studies examined birth cohort screening for all people born in 1945-1965[44 47] or 1946-1970[43] as compared to risk based screening, reporting ICERs of $38,000 per QALY gained with direct-acting antivirals[43 44] and $5,400-16,000 per QALY gained with pegIFN+RBV[44 47]. Critically, the cost-effectiveness varies substantially by HCV prevalence[47], and the estimated US prevalence is higher

than many other developed countries. Additionally, the ICERs were generated given assumptions of higher treatment rates, as well as greater utility gains with SVR than we consider. Importantly, our intervention targets PWID with a risk of transmitting infection to others, whereas birth cohort screening is likely to identify infections among ex-injectors and non-injecting populations which will have little primary prevention impact.

Implications

Our cost-effectiveness work indicates increasing HCV case-finding in addiction services can be cost-effective. However, the cost-effectiveness of prison case-finding interventions depends on adequate continuity of care with the community. Few settings have developed comprehensive strategies to address this issue, though New York ~~state~~ recently initiated the Hepatitis C Continuity Program[48]. In all settings, treatment uptake is critical: higher treatment rates prevent more disease transmission and increase the cost-effectiveness of case-finding interventions. If a disutility on diagnosis occurs, higher treatment rates would be necessary to ensure cost-effectiveness. Further empirical data are required on treatment uptake and changes in utilities following diagnosis and treatment in order to compare targeted case-finding with cohort models.

AUTHOR CONTRIBUTIONS

NKM contributed to the study design, model development, analysis, manuscript drafting and editing. MH contributed to the study design, model development, analysis, and manuscript editing. AM contributed to the analysis and manuscript editing. SJH contributed to the model parameterization, analysis, and manuscript

editing. AT contributed to the model parameterization and manuscript editing. PV contributed to the study design, model development, analysis, and manuscript editing.

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Competing Interests

NM has received an honorarium for speaking at a conference sponsored by Janssen. SH has received honoraria for speaking at conferences sponsored by MSD, Janssen, Gilead, and Roche. MH, AM, AT, PV have no competing interests.

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Figure Legends:

Figure 1. **Base-case cost-effectiveness acceptability curves for the dried blood spot intervention.** Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.

Figure 2. **Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER).** Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.

Figure 3. **Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions.** Base-case scenario assumed 0% continuity.

	Mean value	Distribution	Reference
Transition probabilities per year (all probabilities converted to instantaneous rates)			
Mild to moderate	0.025	Beta(α=38.0859, β=1485.3516)	[19]
Moderate to cirrhosis	0.037	Beta(α=26.905, β=700.2582)	[19]
Cirrhosis to decompensated cirrhosis	0.039	Beta(α=14.6168, β=360.1732)	[19]
Cirrhosis/decomp. cirrhosis to HCC	0.014	Beta(α=1.9326, β=136.1074)	[19]
Decompensated cirrhosis/HCC to LT	0.03	Beta(α=6.5256, β=210.9945)	[19]
Decompensated cirrhosis to death	0.13	Beta(α=147.03, β=983.97)	[19]
HCC to death	0.43	Beta(α=117.1033, β=155.23)	[19]
LT to death	0.21	Beta(α=16.2762, β=61.2294)	[19]
Post transplant to death	0.057	Beta(α=22.9017, β=378.8825)	[19]
Health state utilities/disutilities per year			
Ex-PWID age 15-19			
Uninfected	0.94		[17]
Mild	0.77	Beta(α=521.2375, β=155.6943)	[19 20]
Moderate	0.66	Beta(α=168.2461, β=86.6723)	[19 20]
Cirrhosis	0.55	Beta(α=47.1021, β=38.5381)	[19 20]
Decompensated cirrhosis	0.45	Beta(α=123.75, β=151.25)	[19 20]
Hepatocellular carcinoma	0.45	Beta(α=123.75, β=151.25)	[19 20]
Liver transplant	0.45	Beta(α=123.75, β=151.25)	[19 20]
Post transplant	0.67	Beta(α=59.2548, β=29.1852)	[20 21]
Mild - on treatment	0.66	Beta(α=115.706, β=59.6063)	[19 20]
Moderate - on treatment	0.55	Beta(α=47.1021, β=38.5381)	[12 19 20]
Cirrhosis - on treatment	0.46	Beta(α=3953, β=4641)	[12]
Mild SVR	0.82	Beta(α=65.8678, β=14.4588)	[19 20]
Moderate SVR	0.72	Beta(α=58.0608, β=22.5792)	[12 19 20]
Cirrhosis SVR	0.61	Beta(α=58.0476, β=37.1124)	[21]
PWID age 15-19			
Uninfected	0.74	Uniform(0.67,0.8)	*[18]*
HCV disease states	As in ex-PWID, but reduced by PropPWID‡		Assumed
Disutility with age			
20-24	0		[17]
25-29	0.005		[17]
30-54	0.049		[17]
55-64	0.14		[17]
65-74	0.16		[17]
75+	0.21		[17]
Costs (£ per year, except where noted)			
Mild diagnosed	169	PPI‡×Gamma(*k*=25.6995,θ=5.3698)	[19 20]
Moderate diagnosed	880	PPI‡×Gamma(*k*=88.8502, θ=8.0698)	[19 20]
Cirrhosis diagnosed	1,397	PPI‡×Gamma(*k*=24.2342, θ=46.9584)	[19 20]
Decompensated cirrhosis	11,199	PPI‡×Gamma(*k*=36.0249, θ=253.1582)	[19 20]
Hepatocellular carcinoma	9,980	PPI‡×Gamma(*k*=18.1081, θ=448.8045)	[19]
Liver transplant (per transplant)	33,561	PPI‡×Gamma(*k*=89.7536, θ=304.5004)	[19]
Cost of care in year of liver transplant	11,614	PPI‡×Gamma(*k*=13.7788, θ=686.4168)	[19]
Post transplant	1,701	PPI‡×Gamma(*k*=15.2189, θ=91.0053)	[19]
Mild SVR	318	PPI‡×Gamma(*k*=28.8141, θ=8.9887)	[19]
Moderate SVR	880	PPI‡×Gamma(*k*=88.8502, θ=8.0698)	[19]
Cirrhosis SVR	1,397	PPI‡×Gamma(*k*=24.2342, θ=46.9584)	[19]
Undiagnosed states	0		
PegIFN+RBV drug only			
24 weeks, halved/doubled for 12/48 wks	5,320	Uniform (4788, 5852)	[23]
Treatment delivery			

Ex-PWID, 12 weeks	1,912	Varied, see appendix	See appendix[19]
Ex-PWID, 24 weeks	2,057	Varied, see appendix	See appendix[19]
Ex-PWID, 48 weeks	2,326	Varied, see appendix	See appendix[19]
PWID, 12 weeks	2,193	Varied, see appendix	See appendix
PWID, 24 weeks	2,435	Varied, see appendix	See appendix
PWID, 48 weeks	2,900	Varied, see appendix	See appendix
Testing costs in all settings except prison	115.21	Uniform +/- 50%	See appendix
Testing costs in prison	144.21	Uniform +/- 60%	See appendix
PCR RNA test (if antibody positive)	73.67		[24]
Testing and treatment parameters			
Proportion PWID diagnosed (initial)	50%		[4]
Proportion PWID treated (initial)	0%		Assumption
Proportion ex-PWID diagnosed (initial)	30%	Uniform (24%, 36%)	Assumption [58]
Proportion of diagnosed ex-PWID treated (initial)	10%	Uniform (5%, 15%)	Estimated <10% diagnosed chronic infections [4]
Proportion HCV genotype 1	50%		[4 59]
Sustained viral response(SVR)			
Genotype 1 mild/moderate	0.45	Uniform (0.4, 0.5)	[59 62]
Genotype 2/3 mild/mod	0.8	Uniform (0.75, 0.85)	[59 62 63]
Genotype 1 cirrhosis	0.25	55% reduction from mild/mod	[64]
Genotype 2/3 cirrhosis	0.6	75% reduction from mild/mod	[64]
Antiviral treatment duration (weeks)			
Genotype 1 SVR	48		[59]
Genotype 1 non-SVR	12		[59]
Genotype 2/3	24		[59]
Distribution of PWID HCV tests			
GP	38.4%		§
Prison	11.5%		§
Addiction services	29.4%		§
Other	20.7%		§
Proportion who are referred and attend referral	35%	Uniform (25%, 45%)	[13 35]
Proportion in referral who initiate treatment within 2 years (excl. prison)			
Ex-PWID	50%	Uniform(40%, 60%)	[13 35 37]
PWID	5.5%	Uniform(1%, 10%)	Assumption
Treatment initiation rate after 2 years in referral (excl. prison) per year			
Ex-PWID	10%	Uniform(5%, 15%)	Assumption
PWID	3%	Uniform(1%, 5%)	Assumption
Treatment rates in prison	Half out-of- prison rates		Assumption¶
Yield (proportion tests Ab+)			
GP	2.7%		§
Prison	14.7%		§
Addiction services	17.7%		§
Other	1.7%		§

Table 1. Model parameters. ‡PropPWID=(uninfected PWID utility value for age 15-19)/(uninfected ex-PWID utility for age 15-19). ‡PPI=Hospital and Community Health Services Pay and Prices Index inflation factor. §Health Protection Agency (HPA) unpublished data from the 2010 Sentinel Surveillance. ¶Iain Brew, HMP Leeds, unpublished data. HCC= hepatocellular carcinoma; LT=liver transplant; SVR=sustained viral response; pegIFN=pegylated interferon; RBV= ribavirin

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	Mean value	Distribution	Units	Ref.
Intervention effect (proportional change in testing rate)				
Addiction services	3.6 [2.3-5.8]	Lognormal (μ=1.285, σ=0.239)	-	[5]
Prison	2.6 [0.2-34.9]	Lognormal (μ=0.968, σ=1.317)	-	[5]
Intervention costs (addiction services)				
Organization/coordination of training*	2,005.71		per health board	†
Training session‡	135		per training session	†
Attendees time§	1,620		per training session	†
Travel reimbursement for training leader‖	90.86		per training session	†
Total cost per addiction services training	3851.57		per training session	†
Mean number tested	40.3		per addiction service¶	[5]
Total intervention cost per test	**95.57**	**Uniform +/-50%**	per test	
Intervention costs (prison)				
Organization/coordination of training**	7020		per prison	†
Training session‡	135		per prison	†
Attendees time††	405		per prison	†
Travel reimbursement for training leader‡‡	127.20		per prison	†
Total cost per prison training	7687.20		per prison	†
Mean number tested per prison	116		per prison	**[5]**
Total intervention cost per test	**66.27**	**Uniform +/- 50%**	per test	

Table 12. Intervention parameters. All cost estimates assume a staff-nurse cost per hour of £36 (median estimate for band 5 general practice nurse[21]). *1 nurse 2 days/week for 6 months for 7 health boards. One training session per health board. †Noel Craine, *personal communication*. ‡1 nurse, half day. §12 nurses, half day. ‖1200 miles (£0.53 per mile) for travel to 7 health boards. ¶Assumed 1 addiction service per health board. **1 nurse full time for 5 prisons (1 training session per prison) ††3 nurses per prison, half day. ‡‡1200 miles (£0.53 per mile) for 5 prisons.

	Mean value	Sampled values	Units	Ref.
Average duration of injecting until cessation	11	6.2, 8.6, 11, 13.4, 15.8	years	[65 66]
PWID overdose rate	0.01	0.007, 0.01, 0.013	Per year	[67]
Duration in addiction services	9	7, 9, 11	months	Estimated from OST duration[67]
Incarceration duration				
PWID				
All ages	4	2.67, 4, 5.33	Months	[29 31]
Ex-PWID				
15-19	2.75		Months	[29]
20-24	6.26		Months	[29]
25-29	8.42		Months	[29]
30-54	9.76		Months	[29]
55-64	11.92		Months	[29]
65+	12.49		Months	[29]
Age of first injection distribution				
15-19	41%		-	Combined UK data from [48]
20-24	30%		-	Combined UK data from [48]
25-29	16%		-	Combined UK data from [48]
30-54	13%		-	Combined UK data from [48]
55+	0%		-	Combined UK data from [48]
Death rate by age				
15-19	0.0003		Per year	[68]
20-24	0.0005		Per year	[68]
25-29	0.0006		Per year	[68]
30-54	0.0019		Per year	[68]
55-64	0.0073		Per year	[68]
65-74	0.0200		Per year	[68]
75+	0.165		Per year	[68]
Proportion of England population currently imprisoned aged 15-59	0.2%			[69 70]
Proportion of population who are PWID aged 15-59	0.65%			[71]
Proportion PWID in contact with addiction services	50%			[48]
Proportion PWID diagnosed	50%			[4]
PWID HCV chronic prevalence	35%			[27]
Proportion infections leading to spontaneous clearance	0.26	Uniform (0.22, 0.29)	-	[28]

	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%	-	[72]
Age distribution of prisoners	8%	20%	18%	47%	7%	[69]
Proportion PWID ever in prison	48%	46%	67%	73%	-	*
Proportion prisoners ever PWID	5%	16%	36%	44%	8%	[31]‡

Table 3. Epidemiological/prison input parameters for model fitting *Unlinked Anonymous Monitoring Survey of PWID, Health Protection Agency, London, unpublished data. ‡Scottish prison data, Avril Taylor, unpublished data.

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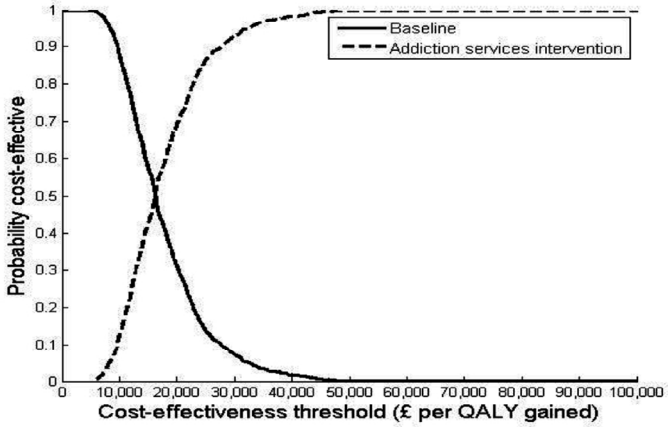
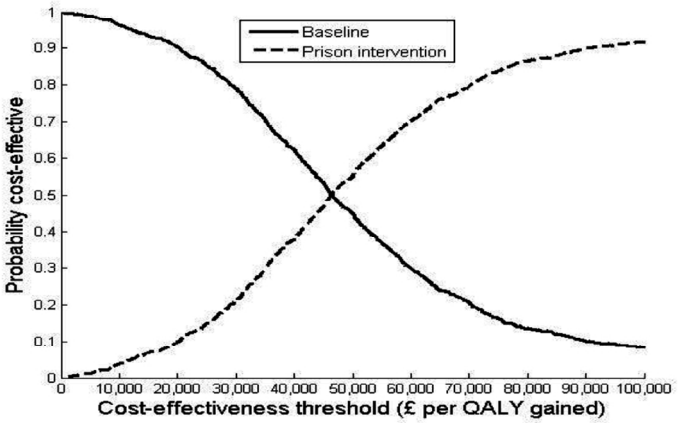
Intervention location	Discounted Costs (2011 £) [95% interval]	Discounted QALYs [95% interval]	Incremental costs [95% interval]	Incremental QALYs [95% interval]	ICER (£ per QALY gained)
Addiction services					
Baseline	37,181,582 [19,384,816–67,271,249]	5,354,331 [4,867,168–5,960,766]	-	-	-
Intervention	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
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

Table 24. Cost-effectiveness results from the base-case intervention analyses.



(a)



(b)

Figure 1

Base-case cost-effectiveness acceptability curves for the dried blood spot intervention. Results shown for the (a) addiction services and (b) prison interventions for various willingness-to-pay thresholds.
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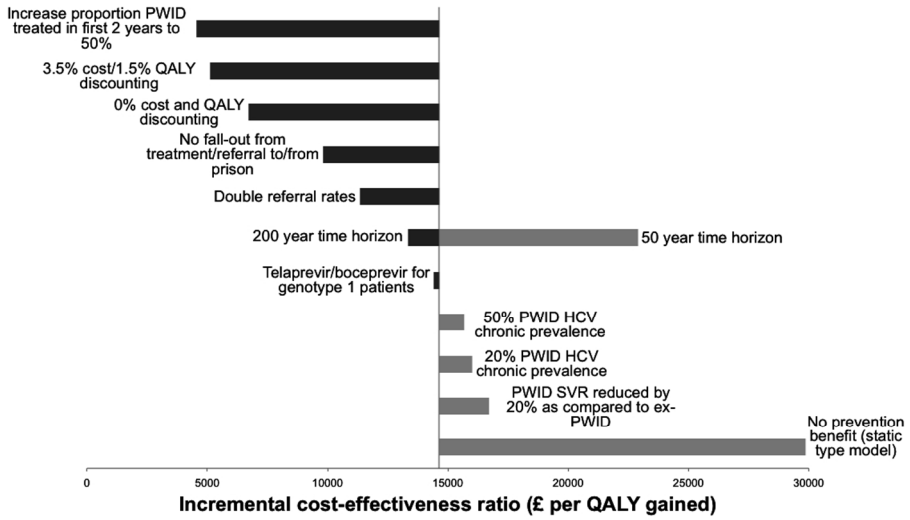
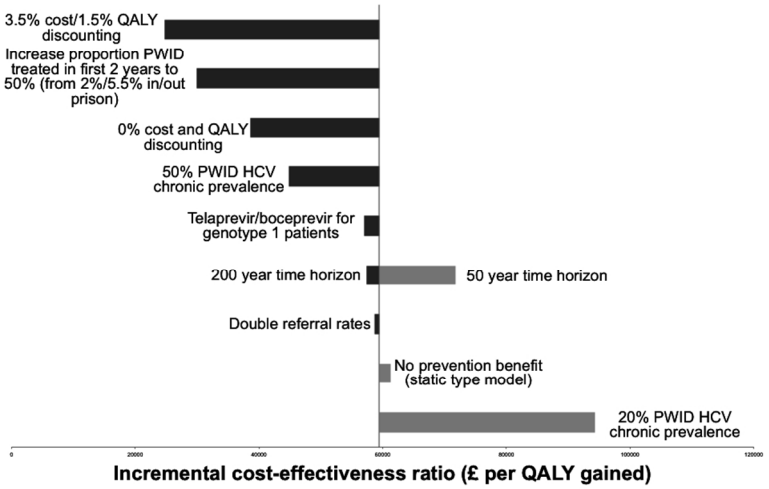


(a)



(b)

Figure 2

Univariate sensitivity analyses on the mean incremental cost-effectiveness ratio (ICER). Results shown for the dried blood spot intervention in (a) addiction services and (b) prison. Vertical line represents the base-case ICER, estimated at (a) £14,600 per QALY gained and (b) £59,400 per QALY gained.
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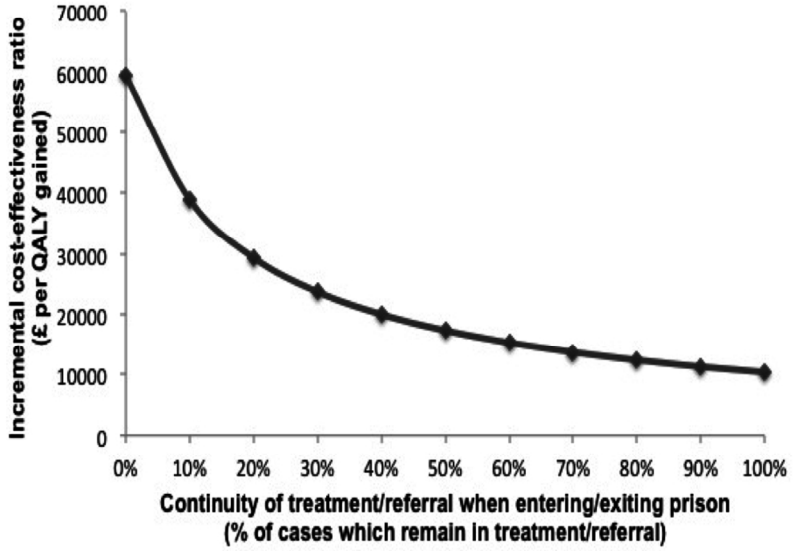

Figure 3

Incremental cost-effectiveness ratios for the prison intervention with varying continuity of care assumptions. Base-case scenario assumed 0% continuity.
396x529mm (72 x 72 DPI)

APPENDIX

Mathematical model

A dynamic, deterministic compartmental model of injecting drug use, HCV transmission, progression, treatment, and diagnosis amongst PWID was developed, to project the impact of interventions to increase HCV testing of PWID. Schematics for the model components can be found in **appendix figures 1 and 2**. The HCV transmission, antiviral treatment, and disease progression model was based on a coupled system of ordinary differential equations previously published by the authors[1]. Susceptible PWID can become acutely infected with HCV by sharing injecting equipment with other infected PWID. We model a frequency dependent force of infection, such that an individual's risk of infection is proportional to the overall prevalence of infection. This model assumes a proportion (~~26~~74%) of acutely infected PWID progress to chronic infection, with the remainder (26%, [2]) 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[3]. If treated, infected PWID 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 PWID re-enters the infected compartment of their associated HCV disease stage. If a PWID fails treatment (non-SVR), they remain infected and can progress to more severe disease stages. Successfully treated PWID can be reinfected and retreated, but those who do not achieve SVR are ineligible for retreatment. Due to reduced viral loads during treatment (even amongst those who relapse and do not achieve SVR), we assume PWID are not infectious during treatment[4, 5]. 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 PWID population (such as high/low risk), as modelling indicated introducing heterogeneity in risk does not have an undue influence on prevention intervention effectiveness as long as individuals circulate between high risk and intervention states[6].

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 ex-PWID, 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).

In order to appropriately model incarceration, the model structure was replicated to track the flow of PWID and ex-PWID between never incarcerated, currently incarcerated, and formerly incarcerated states. In addition, compartments for never-PWID were added (never incarcerated, currently incarcerated, formerly incarcerated) to enable model calibration to general population incarceration data. This model structure was based on previously published mathematical models of PWID incarceration[7, 8], and it was assumed that incarceration and re-incarceration rates of ex-PWID were equal to that of never-PWID.

Additionally, for PWID not imprisoned (never imprisoned and formerly imprisoned) we further stratified movement by contact with addiction services (in contact/not in contact). We assumed only those in contact with addiction services could be tested in addiction services. We also assumed that on release from prison, PWID 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+]), with individuals entering the model at age 15-19 as never-

PWID. In total, the model consists of 222 states and 7 age stratifications, leading to 222 x 7=1,554 compartments.

The model assumes that prisoners only share with other prisoners. Similarly, outside prison, 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.

The dynamic transmission aspect of the model is similar to our previously published mathematical models. Let $P^{m}_{n,a,I}$ represent the number of PWID, where the superscript *m* represents incarceration status (*m*=0,1,2 for never, currently, formerly incarcerated, respectively), the superscript n represents addiction services status (*n*=*out* for out of contact and *n*=*in* in contact, and noting that n=*out* for all incarcerated states when *m*=1), subscript *a* represents the age group, with *a*=1,2…7 for each age group. The subscript *I* represents the HCV state, where $I=x_i$ for susceptible where *i* represents the different susceptible stages (never infected, spontaneously cleared), $I=y_i$ for chronic infected undiagnosed (including mild, moderate, compensated cirrhosis), $I=z_i$ for chronic infected diagnosed (including mild, moderate, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant, post-transplant and in early referral, late referral, or lost to follow-up states), $I=v_i$ for on treatment (including mild, moderate, compensated cirrhosis), $I=s_i$ for SVR (mild, moderate, compensated cirrhosis) and $I=f_i$ for treatment failure/non-SVR (mild, moderate, compensated cirrhosis). For example, $P^{out,1,y_i}_{0,a,z_i}$ represents a PWID who has never been imprisoned and is not in contact with addiction services, is in age group 1 (15-19), and is undiagnosed mild chronically infected. We assume proportionate mixing by age. Using this notation, the force of infection for a PWID who is not imprisoned (*m*=0 or 2) is:

$$\pi \frac{\sum_{\text{all } a,n,y_i,z_i,f_i} (P^n_{0,a,y_i}+P^n_{0,a,z_i}+P^n_{0,a,f_i}+P^n_{2,a,y_i}+P^n_{2,a,z_i}+P^n_{2,a,f_i})}{\sum_{\text{all } a,n,x_i,y_i,z_i,v_i,s_i,f_i} (P^n_{0,a,x_i}+P^n_{0,a,y_i}+P^n_{0,a,z_i}+P^n_{0,a,v_i}+P^n_{0,a,s_i}+P^n_{0,a,f_i}+P^n_{2,a,x_i}+P^n_{2,a,y_i}+P^n_{2,a,z_i}+P^n_{2,a,v_i}+P^n_{0,a,s_i}+P^n_{2,a,f_i})}$$

where π represents the infection rate, which is fit to the HCV prevalence among PWID.

While incarcerated, PWID can only transmit to other incarcerated PWID, so the force of infection for a susceptible PWID in prison (*m*=1) is:

$$\pi \frac{\sum_{\text{all } a,y_i,z_i,f_i} (P_{1,a,y_i}+P_{1,a,z_i}+P_{1,a,f_i})}{\sum_{\text{all } a,x_i,y_i,z_i,v_i,s_i,f_i} (P_{1,a,x_i}+P_{1,a,y_i}+P_{1,a,z_i}+P_{1,a,v_i}+P_{1,a,s_i}+P_{1,a,f_i})}$$

As stated before, all PWID in never infected (Ab-/RNA-), spontaneously cleared (Ab+/RNA-), and SVR states are susceptible for infection as described above.

Model Parameters

Intervention impact

The intervention impact was modelled a proportional increase in setting-specific testing rates, determined by a random effects meta-analysis of the primary data[9] for each setting (addiction services and prisons) separately. The results of the meta-analysis can be found in **appendix figure 3**.

SVR rates

Sustained viral response (SVR) rates for pegIFN+RBV 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[10]. Patients with compensated cirrhosis exhibit proportional reductions in SVR values by about 45% and 25% for genotypes 1 and 2/3, respectively[11]. Preliminary studies indicate SVR rates are equal between PWID and ex/non-PWID[12, 13], which we assumed in our base-case.

Calculation of testing rates

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

To circumvent this problem, we fitted an overall PWID annual testing rate to calibrate the model to the estimated proportion of PWID who are diagnosed (approximately 50%[14]). This rate varied for each sampled group of parameters, but the mean annual testing rate was 12% per year among undiagnosed PWID. This annual testing rate ensured the proportion of diagnosed PWID remained stable (at equilibrium) without any intervention.

As testing of PWID takes place in different locations (prison, addiction services, other settings) and the proportion of PWID 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 in contact with 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 PWID risk only (Mary Ramsay and Sara Collins[Health Protection Agency], *unpublished data.*). Although these data underestimate the number of tests given to PWID, it is reasonable to assume the HPA distribution between sites would be representative of the testing administered to PWID 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 PWID in contact with addiction services and in prison). We assume all ex-PWID are in contact with a GP. These three components were then combined to obtain setting specific testing rates for each parameter set simulation. The setting specific testing rates for PWID and ex-PWID were assumed equal, with the exception that the model assumes ex-PWID are not in contact with addiction services, so no testing occurs from this scenario for this group.

Testing costs

Costs associated with testing were calculated as follows. The numbers of PWID tested in each setting were calculated, and associated with setting specific test costs. Two additional costs were added: RNA testing (for all Ab+ tests) and non-PWID testing. The

number of non-PWID tested in order to test one PWID was calculated from the setting-specific test yield (proportion of tests Ab+) and 'true' baseline prevalence. A setting with a low yield indicates more non-PWID are tested for every PWID; if yield equals baseline prevalence, this indicates only PWID are tested.

Contact with addiction services rates

The proportion of PWID in contact with addiction services at any given time was difficult to estimate. 92% of PWID report ever accessing a needle exchange in the HPA Unlinked Anonymous Survey, though the proportion currently accessing services is not asked[15]. However, it is estimated that 50% of PWID are currently on opiate substitution therapy[16, 17], 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 PWID are on OST[18].

Model fitting

Overview of model fitting and baseline projections

A multi-step parameter sampling and model calibration/fitting method was used with simplified models to reduce computational time and allow for verification of full model predictions against the simplified models. For each fitting process (5 separate model fits in total), **appendix table ~~3~~ 5** details the model used, input parameters, calibration data used to fit the model, and parameters estimated through model fitting. The seven-step sampling and calibration process is as follows:

1) Values were randomly sampled for four parameters (cessation rate, overdose rate, PWID prison release rate, and addiction services duration), yielding a total of 135 possible parameter combinations, or 'calibration scenarios'. Due to the heavy computational burden of fitting the many incarceration parameters, the model was fitted to a limited range of sampled 'calibration scenarios'.
2) **Fit #1:** Simplified model 1 (**appendix figure 4**) was run for each sampled calibration scenario, in order to calibrate the simplified model to the (not

sampled) incarceration data shown in **appendix table 23**. Inputs included the sampled scenario parameters, and non-sampled input parameters estimated from literature/sources (age-specific death rates, prison release rates for never PWID, distribution of ages of first injection, and a preliminary estimate of the entry rate of never-PWID aged 15-19 which will be refit in Fit #5). The parameters which were estimated through model calibration were the age-dependent incarceration rate, reincarceration rates, PWID incarceration rates, PWID reincarceration rates, and injecting initiation rate. Simplified model 1 neglected HCV transmission, testing, and treatment. More details can be found in the section '**Details of fit #1**' and model equations can be found the section entitled "**Model Equations: Simplified Model 1**".

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3) **Fit #2:** Simplified model 2 (**appendix figure 5**) was run for each sampled calibration scenario, in order to calibrate the model to addiction services data. For fit #2, a simplified model of incarceration and movement in/out of addiction services was used. The inputs for these simulations were the sampled calibration scenarios and inputs from Simplified model 1, as well as the estimated incarceration parameters from Simplified model 1. The model was calibrated to data on the proportion of PWID in contact with addiction services, and the estimated parameter obtained through model fitting was the recruitment rate into addiction services. Model equations can be found in the section entitled "**Model Equations: Simplified Model 2**".
4) **Fit #3:** Simplified model 3 (**appendix figure 6**) was run for each sampled calibration scenario, in order to calibrate the model to the diagnosis data. For fit #3, a simple model of HCV transmission and testing among PWID was used to estimate the overall PWID testing rate by calibrating the model to the proportion of PWID who report being diagnosed for HCV. The model inputs were the sampled calibration scenarios and non-sampled inputs of age-specific death rates, distribution of injecting initiation age, and preliminary estimate of the entry rate of never-PWID aged 15-19. The model also required an input of the estimated injecting initiation rate from simplified model 1. Model equations can be found in the appendix section entitled "**Model Equations: Simplified Model 3**".

5) 1000 parameter sets were sampled from each parameter uncertainty distribution in from the full range of disease progression, intervention, cost, and utility parameters (**Table~~s~~ 1, Appendix tables 1-~~43~~**). For each of the 1000 parameter sets, one of the 135 fitted 'calibration scenarios' was selected.
6) **Fit #4:** For each of the 1000 parameter sets, the full model was calibrated to three separate HCV PWID chronic prevalences (35%[19], used in the base-case, as well as 20% and 50% for the sensitivity analyses) to estimate the infection rate, pi, associated with each chronic prevalence.
7) **Fit #5:** For each of the 1000 parameter sets, the full model was calibrated to a total PWID population size (fit to 1000 PWID at baseline), to estimate the entry rate of never-PWID in the 15-19 age group.

Model fitting was performed by using nonlinear least-squares methods using the MATLAB solver *lsqnonlin*.

Model Equations

Simplified model 1

For Simplified Model 1, the mathematical model tracks injecting drug use state (never/current/former PWID) and incarceration state (never/currently/formerly incarcerated). $N_{n,a}$ represents never PWID, with superscript *m* representing incarceration status (*m*=0,1,2 for never, currently, formerly incarcerated, respectively) and subscript *a* representing age group, with *a*=1,2…7 for each age group. Using the same subscript notation, $P_{n,c}$ represents PWID and $E_{n,a}$ represents ex-PWID. The full system of equation is as follows:

$$
\begin{aligned}
\frac{dN_{0,a}}{dt} &= \theta_a - (\rho_{0,a} + \xi_a + \gamma_a)N_{0,a} \\
\frac{dN_{1,a}}{dt} &= \rho_{0,a}N_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \xi_a + \gamma_a)N_{1,a} \\
\frac{dN_{2,a}}{dt} &= \beta_{0,a}N_{1,a} - (\alpha_{0,a} + \xi_a + \gamma_a)N_{2,a} \\
\frac{dP_{0,a}}{dt} &= \xi_a N_{0,a} - (\rho_{1,a} + \zeta + \gamma_a + \eta)P_{0,a} \\
\frac{dP_{1,a}}{dt} &= \xi_a N_{1,a} + \rho_{1,a}P_{0,a} + \alpha_{1,a}P_{2,a} - (\beta_{1,a} + \zeta + \gamma_a + \eta)P_{1,a} \\
\frac{dP_{2,a}}{dt} &= \xi_a N_{2,a} + \beta_{1,a}P_{1,a} - (\alpha_{1,a} + \zeta + \gamma_a + \eta)P_{2,a} \\
\frac{dE_{0,a}}{dt} &= \zeta P_{0,a} - (\rho_{0,a} + \gamma_a)E_{0,a} \\
\frac{dE_{1,a}}{dt} &= \zeta P_{1,a} + \rho_{0,a}E_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \gamma_a)E_{1,a} \\
\frac{dE_{2,a}}{dt} &= \zeta P_{2,a} + \beta_{0,a}E_{1,a} - (\alpha_{0,a} + \gamma_a)E_{2,a}
\end{aligned}
$$

where time is represented by the variable *t*. All populations experience age-specific death rates specified by rate γ_a and PWID have an additional death rate due to overdose of η. New never-PWID enter the system into the youngest age compartment at rate θ_1 (θ_a =0 for $a \neq 1$). Never or former PWID are incarcerated at an age specific rate $\rho_{0,a}$, are released at a rate $\beta_{0,a}$, and are reincarcerated at a rate $\alpha_{0,a}$. Similarly, PWID are incarcerated at an age specific rate $\rho_{1,a}$, are released at a rate $\beta_{1,a}$, and are reincarcerated at a rate $\alpha_{1,a}$. Never PWID initiate injecting at an age-specific rate of ξ_a, and cessate from injecting at a rate ζ.

Simplified model 2

For Simplified Model 2, the mathematical model in Simplified Model 1 is extended to include flow in and out of addiction services for PWID who are not incarcerated. Using the same subscript notation as before, but adding a superscript with *n= in* if the PWID is in contact with addiction services, and *n=out* if they are not in contact, then $P_{i,a}^{in}$ represents PWID. The full system of equation is as follows:

$$
\begin{aligned}
\frac{dN_{0,a}}{dt} &= \theta_a - (\rho_{0,a} + \xi_a + \gamma_a)N_{0,a} \\
\frac{dN_{1,a}}{dt} &= \rho_{0,a}N_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \xi_a + \gamma_a)N_{1,a} \\
\frac{dN_{2,a}}{dt} &= \beta_{0,a}N_{1,a} - (\alpha_{0,a} + \xi_a + \gamma_a)N_{2,a} \\
\frac{dP^{out}_{0,a}}{dt} &= \xi_a N_{0,a} + \sigma P^{in}_{0,a} - (\rho_{1,a} + \zeta + \gamma_a + \eta + \nu)P^{out}_{0,a} \\
\frac{dP^{in}_{0,a}}{dt} &= \nu P^{out}_{0,a} - (\rho_{1,a} + \zeta + \gamma_a + \eta + \sigma)P^{in}_{0,a} \\
\frac{dP_{1,a}}{dt} &= \xi_a N_{1,a} + \rho_{1,a}(P^{out}_{0,a} + P^{in}_{0,a}) + \alpha_{1,a}(P^{out}_{2,a} + P^{in}_{2,a}) - (\beta_{1,a} + \zeta + \gamma_a + \eta)P_{1,a} \\
\frac{dP^{out}_{2,a}}{dt} &= \xi_a N_{2,a} + \beta_{1,a}P_{1,a} + \sigma N^{out}_{2,a} - (\alpha_{1,a} + \zeta + \gamma_a + \eta + \nu)P^{out}_{2,a} \\
\frac{dP^{in}_{2,a}}{dt} &= \nu N^{out}_{2,a} - (\alpha_{1,a} + \zeta + \gamma_a + \eta + \sigma)P^{in}_{2,a} \\
\frac{dE_{0,a}}{dt} &= \zeta(P^{out}_{0,a} + P^{in}_{0,a}) - (\rho_{0,a} + \gamma_a)E_{0,a} \\
\frac{dE_{1,a}}{dt} &= \zeta P_{1,a} + \rho_{0,a}E_{0,a} + \alpha_{0,a}N_{2,a} - (\beta_{0,a} + \gamma_a)E_{1,a} \\
\frac{dE_{2,a}}{dt} &= \zeta(P^{out}_{2,a} + P^{in}_{2,a}) + \beta_{0,a}E_{1,a} - (\alpha_{0,a} + \gamma_a)E_{2,a}
\end{aligned}
$$

where the variables are as in Simplified Model 1, with the addition that PWID enter addiction services at a rate *v*, and exit at a rate *σ*. The model assumes that when people initiate injecting, or are released from prison, they are not immediately in contact with addiction services (but can subsequently be recruited into contact at rate *v*.

Simplified model 3

Simplified model 3 is used to fit the PWID diagnosis rate to the overall proportion of PWID diagnosed at a given time. Hence, it includes never PWID, uninfected PWID, infected undiagnosed PWID, and infected diagnosed PWID. As in the other simplified models, N_{a} represents never PWID, with *a* representing age group, with *a*=1,2…7 for each age group. Here, $P_{a,s}$ represents susceptible PWID, $P_{a,u}$ represents infected but undiagnosed PWID, and $P_{a,d}$ represents infected and diagnosed PWID. The full system of equation is as follows:

$$
\begin{aligned}
\frac{dN_a}{dt} &= \theta_a - (\xi_a + \gamma_a)N_a \\
\frac{dP_{a,x}}{dt} &= \xi_a N_a - \pi P_{a,x}\frac{P_{a,y}+P_{a,z}}{P_{a,x}+P_{a,y}+P_{a,z}} - (\zeta + \gamma_a + \eta)P_{a,x} \\
\frac{dP_{a,y}}{dt} &= \pi P_{a,x}\frac{P_{a,y}+P_{a,z}}{P_{a,x}+P_{a,y}+P_{a,z}} - (\kappa + \zeta + \gamma_a + \eta)P_{a,y} \\
\frac{dP_{a,z}}{dt} &= \kappa P_{a,y} - (\zeta + \gamma_a + \eta)P_{a,z}
\end{aligned}
$$

where the parameters are as in Simplified Model 1 with the addition that κ represents the diagnosis rate, and π is the infection rate.

Details of fit #1

In fit #1, the simplified incarceration model was calibrated to age-structured data on the proportion of the general population with a custodial sentence[20], proportion of PWIDs previously imprisoned, age distribution of current prisoners[21], proportion of prisoners ever PWID, proportion of the population currently imprisoned[22, 23], and the prevalence of PWID in the general population[19]. The epidemiological and prison parameters sampled for this fitting algorithm can be found in **appendix table 23**.

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As the prison data varied over several orders of magnitude (for example, the proportion of PWID 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 of the calibration data was used in order to minimize relative error in the least-squares regression[24]. 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. Specifically, the error measure associated with each individual age-specific parameter of the 7 age-groups was weighted $1/7^{th}$ as much as a non-age specific parameter. **Appendix figure 7** provides an example of the data and calibrated model projections with the median values chosen for each parameter; all other fits were similar to this. The model fitted well to the data, with the notable exception of the proportion of PWID 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-injecting 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 fit to the rest of the data and also because it is unlikely that the data sources are consistent.

Initial conditions

The steady-state values of the full model without testing and treatment were used as initial conditions for the baseline/intervention simulations, with the following alterations. At baseline, the proportion of diagnosed ex-PWID was not thought to be at steady-state. This was because recent testing initiatives have mainly targeted PWID; it is estimated the proportion of diagnosed PWID (50%[14]) is currently likely higher than that of ex-PWID (estimated at 30% based on proportion PWID diagnosed in 2000 who are likely to be ex-PWID[15]). Hence, the steady-state values for infected populations were divided between undiagnosed/diagnosed states for the initial conditions. As treatment rates of PWID are extremely low, we assume none of the PWID population have been treated at baseline, and sample the proportion of ex-PWID previously treated (mean sampled value 10%[14]) from the range found in **appendix table 1**.

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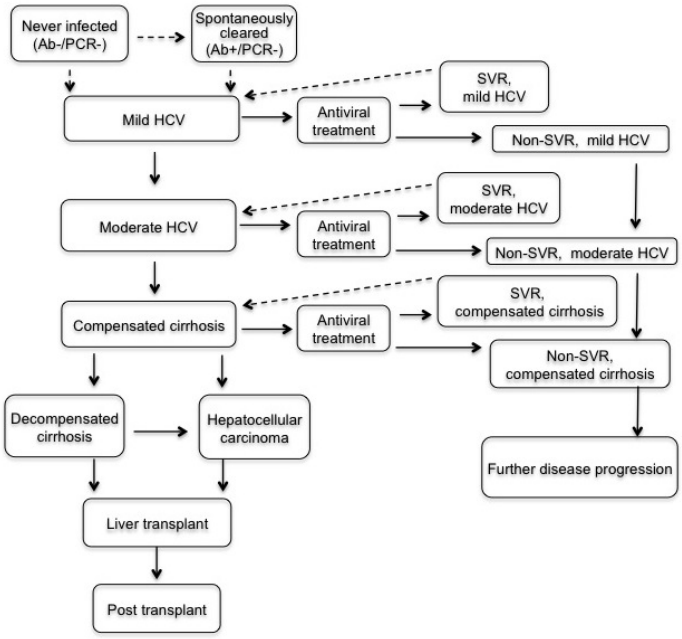
We calculate the initial conditions as follows. The full model without any testing and treatment was run, and the number of people in all compartments was stored after the system reached steady-state. This vector of initial condition values was then edited as follows to account for the current proportion of diagnoses estimated in the PWID and ex-PWID populations, as well as the proportion of ex-PWID already treated. As it is unknown what proportion of previously diagnosed PWID 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 no PWID have been treated at baseline. Ex-PWID 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.

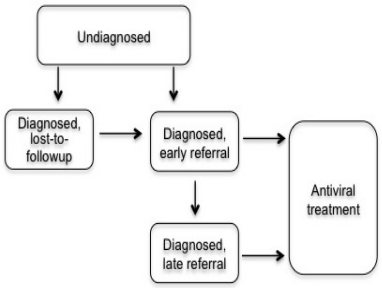
Hence, half of the chronically infected PWID population were placed in the diagnosed compartment of their relative disease state, with the remaining placed in the 'diagnosed and lost-to-follow-up' compartment of their relative disease state. For the ex-PWID population, a proportion will have been treated, 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-PWID was not at steady state at the start of the simulation. As stated in the main text of the paper, this was deemed appropriate, as recent testing initiatives have mainly targeted PWID, and therefore it is assumed that diagnosis rates among ex-PWID are low. However, over time those who are PWID will become ex-PWID, and therefore the proportion of diagnosed ex-PWID will increase over time.

Results

The incremental costs and incremental QALYs are shown on a cost-effectiveness plane in **appendix figure 8**.

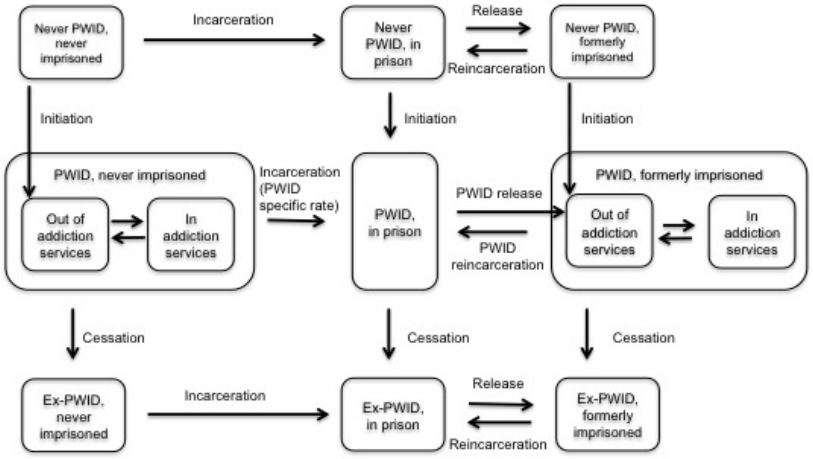


(a)



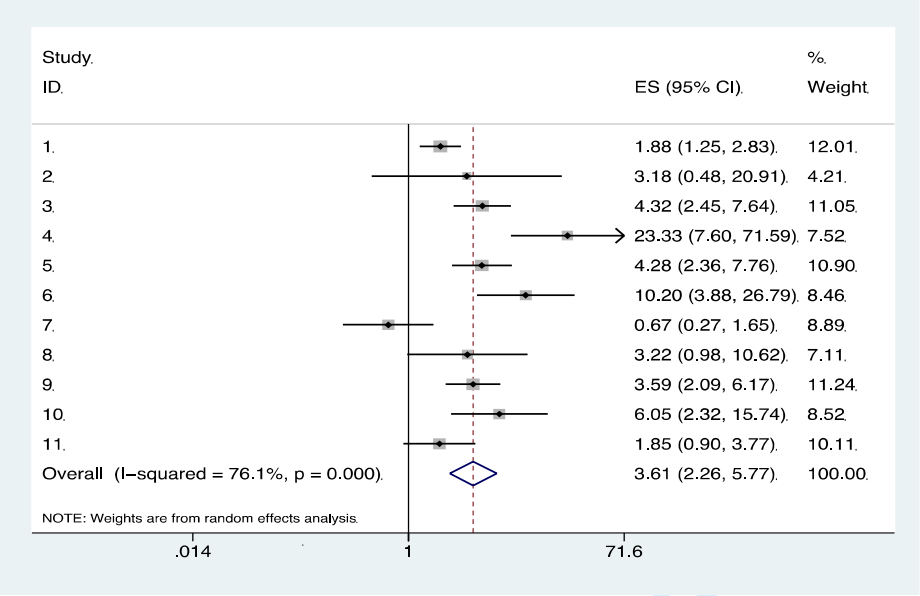
(b)

Appendix figure 1. HCV disease progression model schematics. Schematics show treatment (a) and diagnosis (b) model components. Solid black lines indicate transitions for both PWID and ex-PWID. Dashed black lines indicate PWID transitions only. For PWID, uninfecteds can be retested due to continuing risk behaviour; ex-PWID are not retested in the model.

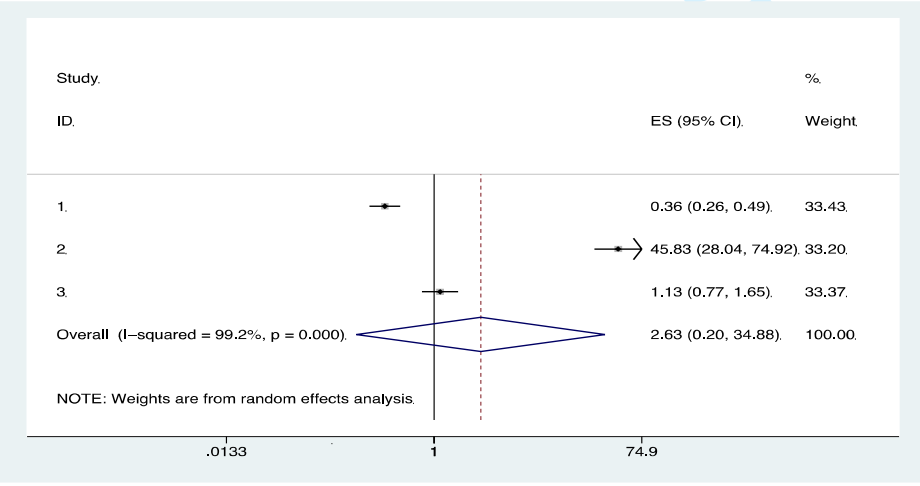


Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 2. General model flow schematic (each PWID and ex-PWID compartment includes HCV infection sub-compartments).

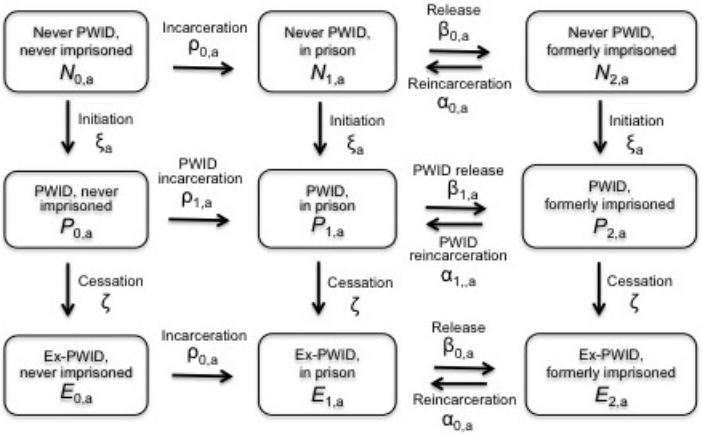


(a)



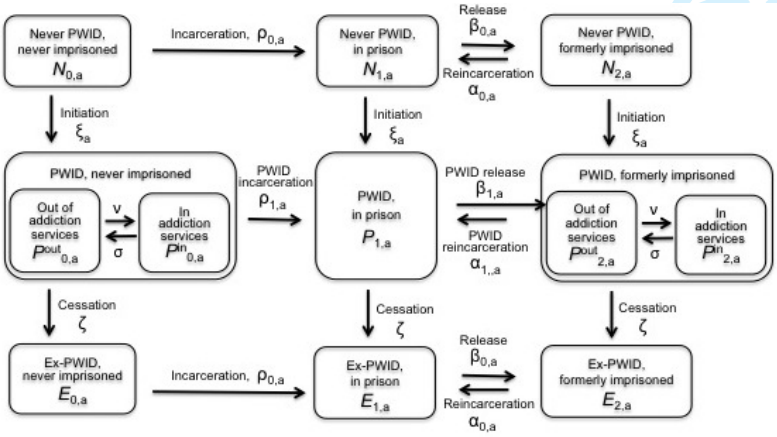
(b)

Appendix figure 3. Random effects meta-analysis results for the dried blood spot intervention effect on testing rate (proportional increase in testing rate). Results shown for (a) addiction services and (b) prison.



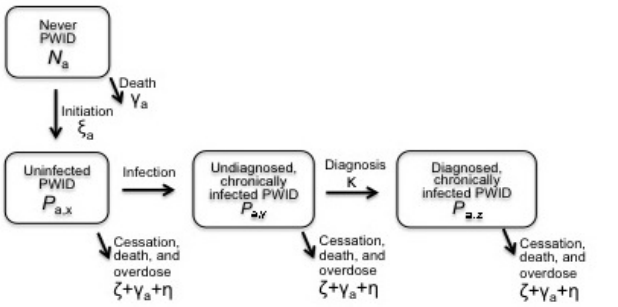
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 4. Simplified model #1 schematic.



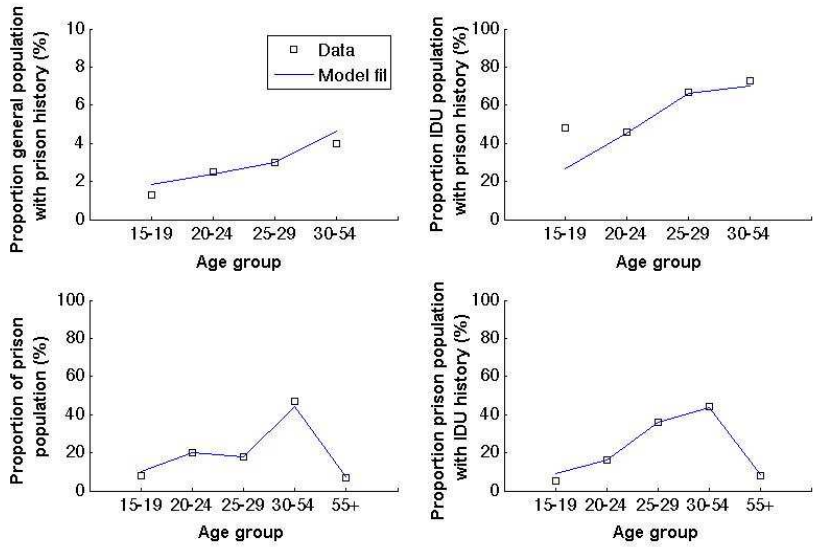
Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]), includes death from all compartments, overdose death from PWID compartments, and inflow to the youngest 'Never PWID, never imprisoned' compartment.

Appendix figure 5. Simplified model #2 schematic.

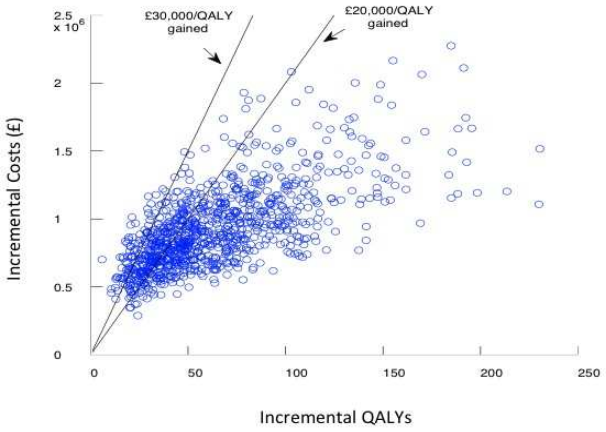


Model is stratified by age ([15-19, [20-24], [25-29], [30-54], [55-64], [65-74], [75+]) and includes inflow to the youngest [15-19] 'Never PWID' compartment.

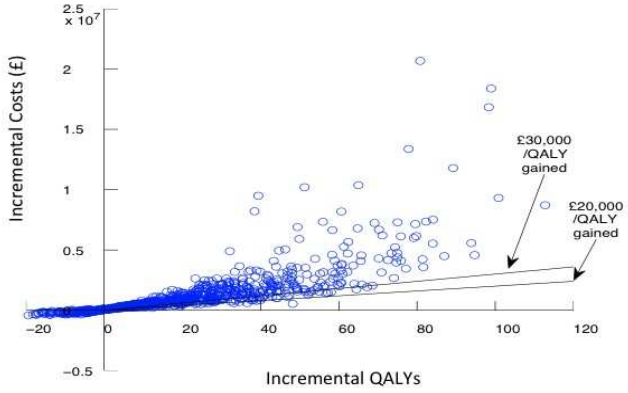
Appendix figure 6. Simplified model #3 schematic.



Appendix figure 7. Example of one characteristic model fit to the prison data (injecting duration 11 years, PWID incarceration duration 4 months, PWID 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 PWID who have previously been incarcerated. The bottom right shows the proportion of prisoners who report ever PWID. Additionally, the model was fit to proportion of the general population imprisoned (simulated 0.21% as compared to 0.2%[22, 23]) and the proportion of population PWID (simulated 0.58% as compared to 0.65%[19])



(a)



(b)

Appendix figure 8. Incremental costs and incremental QALYs for each of the 1000 simulation runs. Results shown for (a) addiction services and (b) prison interventions.

		Mean value	Distribution	Reference
Transition probabilities per year (all probabilities converted to instantaneous rates)				
Mild to moderate		0.025	Beta(α=38.0859, β=1485.3516)	[3]
Moderate to cirrhosis		0.037	Beta(α=26.905, β=700.2582)	[3]
Cirrhosis to decompensated cirrhosis		0.039	Beta(α=14.6168, β=360.1732)	[3]
Cirrhosis/decomp. cirrhosis to HCC		0.014	Beta(α=1.9326, β=136.1074)	[3]
Decompensated cirrhosis/HCC to LT		0.03	Beta(α=6.5256, β=210.9945)	[3]
Decompensated cirrhosis to death		0.13	Beta(α=147.03, β=983.97)	[3]
HCC to death		0.43	Beta(α=117.1033, β=155.23)	[3]
LT to death		0.21	Beta(α=16.2762, β=61.2294)	[3]
Post transplant to death		0.057	Beta(α=22.9017, β=378.8825)	[3]
Health state utilities/disutilities per year				
Ex-PWID age 15-19				
	Uninfected	0.94		[25]
	Mild	0.77	Beta(α=521.2375, β=155.6943)	[3, 26]
	Moderate	0.66	Beta(α=168.2461, β=86.6723)	[3, 26]
	Cirrhosis	0.55	Beta(α=47.1021, β=38.5381)	[3, 26]
	Decompensated cirrhosis	0.45	Beta(α=123.75, β=151.25)	[3, 26]
	Hepatocellular carcinoma	0.45	Beta(α=123.75, β=151.25)	[3, 26]
	Liver transplant	0.45	Beta(α=123.75, β=151.25)	[3, 26]
	Post transplant	0.67	Beta(α=59.2548, β=29.1852)	[26, 27]
	Mild - on treatment	0.66	Beta(α=115.706, β=59.6063)	[3, 26]
	Moderate - on treatment	0.55	Beta(α=47.1021, β=38.5381)	[3, 8, 26]
	Cirrhosis - on treatment	0.46	Beta(α=3953, β=4641)	[8]
	Mild SVR	0.82	Beta(α=65.8678, β=14.4588)	[3, 26]
	Moderate SVR	0.72	Beta(α=58.0608, β=22.5792)	[3, 8, 26]
	Cirrhosis SVR	0.61	Beta(α=58.0476, β=37.1124)	[27]
PWID age 15-19				
	Uninfected	0.74	Uniform(0.67,0.8)	*[28]*
	HCV disease states	As in ex-PWID, but reduced by PropPWID†		Assumed
Disutility with age				
	20-24	0		[25]
	25-29	0.005		[25]
	30-54	0.049		[25]
	55-64	0.14		[25]
	65-74	0.16		[25]
	75+	0.21		[25]
Costs (£ per year, except where noted)				
Mild diagnosed		169	PPI‡×Gamma(*k*=25.6995,θ=5.3698)	[3, 26]
Moderate diagnosed		880	PPI‡×Gamma(*k*=88.8502, θ=8.0698)	[3, 26]
Cirrhosis diagnosed		1,397	PPI‡×Gamma(*k*=24.2342, θ=46.9584)	[3, 26]
Decompensated cirrhosis		11,199	PPI‡×Gamma(*k*=36.0249, θ=253.1582)	[3, 26]
Hepatocellular carcinoma		9,980	PPI‡×Gamma(*k*=18.1081, θ=448.8045)	[3]
Liver transplant (per transplant)		33,561	PPI‡×Gamma(*k*=89.7536, θ=304.5004)	[3]
Cost of care in year of liver transplant		11,614	PPI‡×Gamma(*k*=13.7788, θ=686.4168)	[3]
Post transplant		1,701	PPI‡×Gamma(*k*=15.2189, θ=91.0053)	[3]
Mild SVR		318	PPI‡×Gamma(*k*=28.8141, θ=8.9887)	[3]
Moderate SVR		880	PPI‡×Gamma(*k*=88.8502, θ=8.0698)	[3]
Cirrhosis SVR		1,397	PPI‡×Gamma(*k*=24.2342, θ=46.9584)	[3]
Undiagnosed states		0		
PegIFN+RBV drug only				
	24 weeks, halved/doubled for 12/48 wks	5,320	Uniform (4788, 5852)	[29]
Treatment delivery				

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Ex-PWID, 12 weeks	1,912	Varied, see appendix	See appendix[3]
Ex-PWID, 24 weeks	2,057	Varied, see appendix	See appendix[3]
Ex-PWID, 48 weeks	2,326	Varied, see appendix	See appendix[3]
PWID, 12 weeks	2,193	Varied, see appendix	See appendix
PWID, 24 weeks	2,435	Varied, see appendix	See appendix
PWID, 48 weeks	2,900	Varied, see appendix	See appendix
Testing costs in all settings except prison	115.21	Uniform +/- 50%	See appendix
Testing costs in prison	144.21	Uniform +/- 60%	See appendix
PCR RNA test (if antibody positive)	73.67		[30]
Testing and treatment parameters			
Proportion PWID diagnosed (initial)	50%		[14]
Proportion PWID treated (initial)	0%		Assumption
Proportion ex-PWID diagnosed (initial)	30%	Uniform (24%, 36%)	Assumption [15]
Proportion of diagnosed ex-PWID treated (initial)	10%	Uniform (5%, 15%)	Estimated <10% diagnosed chronic infections [14]
Proportion HCV genotype 1	50%		[10, 14]
Sustained viral response(SVR) with pegIFN+RBV			
Genotype 1 mild/moderate	0.45	Uniform (0.4, 0.5)	[10, 13, 31, 32]
Genotype 2/3 mild/mod	0.8	Uniform (0.75, 0.85)	[10, 13, 33]
Genotype 1 cirrhosis	0.25	55% reduction from mild/mod	[11]
Genotype 2/3 cirrhosis	0.6	75% reduction from mild/mod	[11]
Antiviral treatment duration with pegIFN+RBV (weeks)			
Genotype 1 SVR	48		[10]
Genotype 1 non-SVR	12		[10]
Genotype 2/3	24		[10]
Distribution of PWID HCV tests			
GP	38.4%		§
Prison	11.5%		§
Addiction services	29.4%		§
Other	20.7%		§
Proportion who are referred and attend referral	35%	Uniform (25%, 45%)	[34, 35]
Proportion in referral who initiate treatment within 2 years (excl. prison)			
Ex-PWID	50%	Uniform(40%, 60%)	[34-37]
PWID	5.5%	Uniform(1%, 10%)	Assumption
Treatment initiation rate after 2 years in referral (excl. prison) per year			
Ex-PWID	10%	Uniform(5%, 15%)	Assumption
PWID	3%	Uniform(1%, 5%)	Assumption
Treatment rates in prison	Half out-of- prison rates		Assumption[¶]
Yield (proportion tests Ab+)			
GP	2.7%		§
Prison	14.7%		§
Addiction services	17.7%		§
Other	1.7%		§

Appendix table 1. Model parameters. †PropPWID=(uninfected PWID utility value for age 15-99)/(uninfected ex-PWID utility for age 15-19). ‡PPI=Hospital and Community Health Services Pay and Prices Index inflation factor. §Health Protection Agency (HPA) unpublished data from the 2010 Sentinel Surveillance. ¶Iain Brew, HMP Leeds, unpublished data. HCC= hepatocellular carcinoma; LT=liver transplant; SVR=sustained viral response; pegIFN=pegylated interferon; RBV= ribavirin

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	Mean value	Sampled values	Units	Ref.
Average duration of injecting until cessation	11	6.2, 8.6, 11, 13.4, 15.8	years	[38, 39]
PWID overdose rate	0.01	0.007, 0.01, 0.013	Per year	[18]
Duration in addiction services	9	7, 9, 11	months	Estimated from OST duration[18]
Incarceration duration				
PWID				
All ages	4	2.67, 4, 5.33	Months	[7, 40]
Ex-PWID				
15-19	2.75		Months	[7]
20-24	6.26		Months	[7]
25-29	8.42		Months	[7]
30-54	9.76		Months	[7]
55-64	11.92		Months	[7]
65+	12.49		Months	[7]
Age of first injection distribution				
15-19	41%		-	Combined UK data from [16]
20-24	30%		-	Combined UK data from [16]
25-29	16%		-	Combined UK data from [16]
30-54	13%		-	Combined UK data from [16]
55+	0%		-	Combined UK data from [16]
Death rate by age				
15-19	0.0003		Per year	[41]
20-24	0.0005		Per year	[41]
25-29	0.0006		Per year	[41]
30-54	0.0019		Per year	[41]
55-64	0.0073		Per year	[41]
65-74	0.0200		Per year	[41]
75+	0.165		Per year	[41]
Proportion of England population currently imprisoned aged 15-59	0.2%			[22, 23]
Proportion of population who are PWID aged 15-59	0.65%			[42]
Proportion PWID in contact with addiction services	50%			[16]
Proportion PWID diagnosed	50%			[14]
PWID HCV chronic prevalence	35%			[19]
Proportion infections leading to spontaneous clearance	0.26	Uniform (0.22, 0.29)	-	[2]

	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%	-	[20]
Age distribution of prisoners	8%	20%	18%	47%	7%	[22]
Proportion PWID ever in prison	48%	46%	67%	73%	-	*
Proportion prisoners ever PWID	5%	16%	36%	44%	8%	[40]

Appendix table 2. Epidemiological/prison input parameters for model fitting *Unlinked Anonymous Monitoring Survey of PWID, Health Protection Agency, London, unpublished data.

HCV testing costs- baseline	Mean value (in 2011 £)	Distribution /notes	Units	Ref.
Assessment	1.78	1 minute (average nurse and consultant doctor cost*)	Per test	[30]
Pre-test discussion and test	53.50	30 minutes (average nurse and consultant doctor cost*)	Per test	[30]
Post-test results	44.58	25 minutes (average nurse and consultant doctor cost*)	Per test	[30]
ELISA test	15.35		Per test	[30]
Additional assessment time (prison only)	29	Assuming 20 min. with nurse*	Per test	Estimated from timings in [30]
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	[30]

Appendix table 34. Baseline HCV testing costs. *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[43]. †Greater uncertainty surrounding costs of testing in prison is due to uncertainty surrounding method of test offer (on prison entry, BBV/sexual health screening, or during routine health check).

HCV antiviral treatment costs	Mean value (in 2011 £)	Distribution	Ref.
PegIFN+RBV drug only			
12 weeks	2,660*	Halved from sampled cost at 24 wks	[29]
24 weeks	5,320*	Uniform (4788, 5852)	[29]
48 weeks	10,640*	Doubled from sampled cost at 24 wks	[29]
Treatment delivery			
12 weeks			
Staff	307	Varied by staff cost variation†	[3]
Tests	1,605	Varied by test cost variation‡	[3]
24 weeks			
Staff	374	Varied by staff cost variation†	[3]
Tests	1,683	Varied by test cost variation‡	[3]
48 weeks			
Staff	504	Varied by staff cost variation†	[3]
Tests	1,822	Varied by test cost variation‡	[3]
Additional treatment delivery for PWID			
PWID extra nurse time		Varied by staff cost variation†	
12 weeks	129	and PWID staff time	[1] "
24 weeks	159	variation§	[1] "
48 weeks	220		[1] "
PWID extra basic assessments		Varied by test cost variation‡,	
12 weeks		staff cost variation†, and	
Staff	58	PWID staff time variation§	[1] "
Tests	43		[1] "
24 weeks			
Staff	97		[1] "
Tests	71		[1] "
48 weeks			
Staff	174		[1] "
Tests	129		[1] "
PWID psychiatric visits	51	Varied by staff cost variation‡ and PWID staff time variation§	[1] "

Appendix table 42. HCV antiviral treatment costs. *Average peginterferon cost between alfa-2a (Pegasys) and alfa-2b(ViraferonPeg), and average ribavirin cost between Copegus and Rebetol. †Test value calculated by multiplying mean test cost with a test cost variation parameter, uniformly sampled between 0.8 and 1.2. ‡Staff value calculated by multiplying mean staff cost by a staff cost variation parameter, uniformly sampled between 0.8 and 1.2. §PWID staff cost calculated by multiplying mean staff cost by a staff cost variation parameter and an extra PWID staff time variation parameter (both uniformly sampled between 0.8 and 1.2). "Graham Foster, Consultant Hepatologist, *personal communication*. pegIFN=pegylated interferon; RBV=ribavirin.

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

Appendix table 53. Model fitting procedure summary

Telaprevir/boceprevir scenario parameters	Value	Units	Notes	Ref.
Proportional increase in SVR for genotype 1 patients	68%	-		[44, 45]
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.	[44, 45]
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 1 of main text**)	[46, 47]

Appendix table 64. Telaprevir/boceprevir sensitivity analysis parameters. pegIFN=pegylated interferon; RBV=ribavirin; RVR=rapid viral response; SVR=sustained viral response.

Health state utilities/disutilities per year	Mean	Distribution	Ref.
Ex-PWID			
Mild diagnosed [age 15-19]	0.77	Beta(α=521.2375, β=155.6943)	[3, 26]
Moderate diagnosed [age 15-19]	0.66	Beta(α=168.2461, β=86.6723)	[3, 26]
Compensated cirrhosis diagnosed [age 15-19]	0.55	Beta(α=47.1021, β=38.5381)	[3, 26]
Undiagnosed stages		Diagnosed state utility value + 0.09	[28]
Mild SVR [age 15-19]	0.82	Beta(α=65.8678, β=14.4588)	[3, 26]
Moderate SVR [age 15-19]	0.72	Beta(α=58.0608, β=22.5792)	[3, 8, 26]
Compensated cirrhosis SVR [age 15-19]	0.61	Beta(α=58.0476, β=37.1124)	[27]
PWID			
HCV disease states	As in ex-PWID, but reduced by PropPWID†		Assumed

Appendix table 75. Disutility on diagnosis sensitivity analysis parameters
PropPWID=(uninfected PWID utility value for age 15-19)/(uninfected ex-PWID utility for age 15-19).
SVR=sustained viral response.

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