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Title: Modelling the impact of a national scale-up of interventions on hepatitis C virus transmission among people who inject drugs in Scotland

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Contributions: PV, SH, NKM, DG and MH conceived the study. PV, HF and MH provided overall leadership for the study design, analysis and interpretation of the findings with input from the other co-authors. HF developed the model and performed all final model analyses, with earlier model development and projections undertaken by CM. NP, AM, AT, SH and MH collated and contributed data for the analysis. HF wrote the first draft with PV and MH. All authors have contributed to interpreting the results, and to writing the manuscript.

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Abstract

Background and Aims: To reduce hepatitis C virus (HCV) transmission among people who inject drugs (PWID), Scottish Government-funded national strategies, launched in 2008, promoted scaling-up opioid substitution therapy (OST) and needle and syringe provision (NSP), with some increases in HCV treatment. We test whether observed decreases in HCV incidence post-2008 can be attributed to this intervention scale-up.

Design: A dynamic HCV transmission model amongst PWID incorporating intervention scale-up and observed decreases in behavioural risk, calibrated to Scottish HCV prevalence and incidence data for 2008/09.

Setting: Scotland, UK

Participants: PWID

Measurements: Model projections from 2008-2015 were compared with data to test whether they were consistent with observed decreases in HCV incidence amongst PWID while incorporating the observed intervention scale-up, and to determine the impact of scaling-up interventions on incidence.

Findings: Without fitting to epidemiological data post-2008/09, the model incorporating observed intervention scale-up agreed with observed decreases in HCV incidence amongst PWID between 2008-2015, suggesting HCV incidence decreased by 61.3% (95% credibility interval 45.1-75.3%) from 14.2/100pyrs (9.0-20.7) to 5.5/100pyrs (2.9-9.2). On average, each model fit lay within 84% (10.1/12) of the confidence bounds for the 12 incidence data points which the model was compared against. We estimate that scale-up of interventions (OST+NSP+HCV treatment) and decreases in high-risk behaviour from 2008-2015 resulted in a 33.9% (23.8-44.6%) decrease in incidence, with the remainder (27.4% (17.6-37.0%)) explained by historical changes in OST+NSP coverage and risk pre-2008. Projections suggest scaling-up of all interventions post-2008 averted 1,492 (657-2,646) infections over 7-years, with 1,016 (308-1,996), 404 (150-836) and 72 (27-137) due to scale-up of OST+NSP, decreases in high-risk behaviour, and HCV treatment, respectively.

Conclusions: Most of the decline in hepatitis C virus (HCV) incidence in Scotland between 2008-2015 appears to be attributable to intervention scale-up (opioid substitution therapy and needle and syringe provision) due to government strategies on HCV and drugs.

Keywords: Hepatitis C, people who inject drugs, injecting drug users, opioid substitution therapy, needle and syringe programmes, Scotland

Introduction

Hepatitis C virus (HCV) is a blood-borne disease with high global burden(1), and a leading cause of death and morbidity(2,3). It is estimated that 90% of HCV infections in Scotland are acquired through injecting drug use(4), with people who inject drugs (PWID) harbouring a high burden of infection (54% sero-prevalence in 2008/09(5,6)).

Evidence suggests that needle and syringe provision (NSP) and opioid substitution therapy (OST) can reduce an individual's risk of HCV acquisition(7), but little evidence exists of their impact at the population-level(8-11). Modelling has estimated the impact of these interventions on HCV transmission at the population-level(12,13), as well as the impact of HCV treatment as prevention(14,15), however no analyses have validated their projections against epidemiological data.

In Scotland, NSP and OST were introduced in the 1980s, increasing incrementally since then, with their scale-up credited to decreasing HCV prevalence amongst PWID in the 1990s(16,17). However, HCV prevalence has remained high since then and new presentations for HCV-related liver failure/cancer have been increasing(4,5). Therefore, in 2008, the Scottish government launched a national action plan for HCV, aiming to reduce HCV transmission amongst PWID alongside reducing HCV-related morbidity. The strategy was underpinned by additional investment above existing HCV funding (~100 million during 2008-15) and focussed on scaling-up harm reduction interventions (particularly providing needle/syringes and other injecting equipment) and HCV testing/treatment services(4,18). Contemporaneously, the Scottish Government published a new drug and alcohol strategy, setting out a programme to tackle Scotland's drug problem and reduce waiting times for drug treatment; thus having the potential to impact the delivery of OST(19). Over the first 3 years of these strategies (2008/09 to 2011/12), the scale-up of high coverage needle and syringe provision (high coverage NSP – defined as exchanging at least one sterile needle/syringe per injection) increased by 40%(5), OST coverage increased by 30%(5), and annual numbers of HCV treatments doubled to 1,000(4), with almost half amongst current or temporarily ceased PWIDs (mostly on OST). Concurrently, a halving in HCV incidence occurred(5). However, there was no control comparison for this nationwide programme; and so it is difficult to determine whether this decrease in HCV incidence occurred due to the intervention scale-up, or would have occurred anyway. Similar issues have been addressed in the HIV-field by using modelling to determine whether observed changes in disease transmission are consistent with the scale-up of specific interventions(11,20-24).

We model the transmission of HCV among PWID in Scotland using data from national cross-sectional surveys carried out between 2008 and 2014. A dynamic, deterministic model is implemented to capture all intervention components and behavioural changes, enabling us to quantify how they may have affected transmission. Using synthesised evidence on the efficacy of NSP and OST(7), the model is used to test whether observed decreases in HCV incidence and prevalence amongst PWID from 2008–2015 are consistent with the scale-up of interventions over this period, and then quantify the impact of the national HCV and drug strategies that resulted in this scale-up. This dynamic transmission process is something that could not be tested with a statistical model.

Methods

Model description

A dynamic, deterministic mathematical model of HCV transmission amongst PWID was developed. The PWID population was stratified into current (had injected in the previous year) and temporarily ceased (had not injected in the previous year) PWID. These groups were divided into short-term (<1 year since onset), mid-term (1–9 years since onset) and long-term (≥ 10 years since onset) PWID,

stratified into those on OST and high coverage NSP, as well as whether they were high-risk (defined as either currently homeless or injecting stimulants) or not (Supplementary Figure S1a).

PWID enter the model through initiating injecting into the current, short-term injecting group, and leave through permanently ceasing injecting (from the temporarily ceased groups) or through drug-related or non-drug related mortality (all groups). All PWID enter the model with no coverage of OST or high coverage NSP, with a time-varying proportion being high- or low-risk (see Model Parameterisation). PWID transition between different injecting, intervention and risk states at specified rates. All transitions are bi-directional except for those between injecting durations. All current PWID can temporarily cease injecting (more likely if on OST), with these PWID then either leaving the model due to permanently ceasing injecting or returning to currently injecting status.

The model is also stratified by HCV infection status (Supplementary Figure S1b), with all new PWID being susceptible to infection. The model simulates transmission of HCV amongst currently injecting PWID, with transmission occurring at a per-capita rate dependent on the injecting risk (high-risk or not), intervention status (OST and/or high coverage NSP), and duration of injecting (Supplementary Materials for further details). Once infected, PWID either transition to the chronically infected group, or spontaneously clear infection, transitioning to the previously infected group. Due to uncertainty in the evidence(25-29), we assume that previously infected PWID are re-infected with the same risk as for primary infections of susceptible PWID. Chronically infected individuals can be treated, whereupon they either attain a sustained viral response (SVR) and move to the previously infected group, or transition to the treatment failure group. In the baseline model, treatment failures are not retreated. The model assumes that PWID mix to form transmission contacts, with a user defined proportion of these contacts being formed randomly proportional to the overall transmission risk of PWID in different sub-groups, and the remainder being formed assortatively (like-with-like) with PWID of the same duration of injecting (short-term, mid-term or long-term) or risk level (high- or low-risk).

Model parameterisation

The model was primarily parameterised and calibrated using data from four large surveys (n=2194-3315 for each survey) undertaken amongst people who had ever injected drugs (~80% had injected in the previous 6 months), recruited from ~100 (50% of all) sites providing injecting equipment across Scotland between 2008-2014: the Needle Exchange Surveillance Initiative (NESI) surveys(5,6,30). Data analyses were undertaken using Stata Version 14.2. Historical survey data, intervention output, and PWID size estimation data were also incorporated as described below, with the data sources described in the Supplementary Materials.

Risk-status parameters

Risk Status: Post-2005, data from the NESI surveys and two other cross-sectional surveys conducted in Glasgow (2005 and 2007)(31) were used to estimate the proportion of PWID that were high-risk (defined by either being homeless in the past six months or currently injecting stimulants – both associated with increased HCV risk in the NESI datasets) for different durations of injecting. The prevalence of high-risk behaviours was greater in those with shorter rather than longer injecting durations, and so this was incorporated into the model.

Intervention parameters

OST Coverage: We assumed OST started in 1985, in response to the spread of HIV infection among PWID. Estimates of OST coverage amongst PWID in Scotland between 1995-2014 were derived from data on methadone prescriptions dispensed across Scotland(32-34), and self-reported survey data

on OST uptake from Glasgow (2005)(31) and the NESI surveys. NESI data suggested higher OST coverage amongst those injecting for longer, which was incorporated into the model (Table S2).

NSP Coverage: NSP coverage was estimated from the number of syringes distributed in Glasgow or nationally from 1988/89 to 2012/13(5,35-37), estimates of the number of PWID in Scotland(38), and the average injecting frequency while accounting for differences by OST status (from NESI) and the changing coverage of OST. Due to high NSP coverage across all injecting durations, we assumed the same coverage for all PWID.

HCV Risk: Data from a UK pooled analysis were used to parameterise the degree to which being on OST, high coverage NSP, or both reduces the risk of acquiring HCV(7,39). Using NESI, risk ratios were calculated for the increased risk of HCV acquisition associated with being homeless or injecting stimulants (denoted as high-risk), and for different durations of injection. These increases in risk status were not found to differ if adjusted for OST and high coverage NSP status.

HCV Treatment: Pre-2002, PWID were not recommended for HCV treatment in the UK(40). Post-2002, data on the number of treatments in Scotland were used to estimate the number occurring amongst PWID(41). We calculated a weighted SVR rate and treatment duration based on the genotype distribution(42-44), and assumed that only PWID on OST are treated based on current HCV treatment/care pathways in Scotland(45).

PWID related parameters

Injecting Duration: Data on injecting cessation (1/duration) and relapse were based on the Edinburgh Addiction cohort(46,47).

Probability distributions were attached to all uncertain model parameters and calibration data thought to affect the decrease in HCV prevalence and incidence. Parameter values and distributions used in the model are shown in Table 1, while calibration data from NESI are given in supplementary Table S2. More details on the model parameterisation is included in the Supplementary Materials.

[Table 1 here]

Model calibration

A Bayesian model-fitting algorithm was used for model calibration. Five-thousand model parameter sets were randomly sampled from the parameter uncertainty distributions in Table 1, and 5,000 HCV sero-prevalence estimates for current PWID in 2008/09.

Other parameters were not sampled, but estimated for each parameter set. Through fitting reduced sub-models to specific data quantities, estimates were generated for the: (1) rate PWID initiate injecting by fitting to the sampled PWID population size; (2 and 3) time varying recruitment rates onto OST and NSP by fitting to the sampled OST and high coverage NSP coverage for specified years (1985, 2005, 2008 and 2013/14 for OST; and 1990, 2008 and 2011/12 for NSP); and (4) proportion high-risk when initiating injecting and transition rates from low to high-risk by fitting to the sampled proportion high-risk for specified years (1990, 2005, 2008 and 2013/14). See Supplementary Materials for more detail.

These fitted parameters, along with the initially sampled parameters, were used to calibrate the full model to the sampled HCV sero-prevalence amongst current PWID for 2008/09 by varying the overall transmission rate amongst PWID. These preliminary model fits to the overall HCV sero-prevalence in 2008/09 were compared against the HCV sero-prevalence amongst short-term PWID and incidence in current PWID, both from NESI in 2008/09. Any run that lay within the 95%

confidence bounds for both quantities was accepted as a **baseline model fit**. From 5,000 sampled parameter sets, **581 baseline model fits** were obtained, which were used for all subsequent analyses. It is noteworthy that the baseline model fits were not calibrated to any HCV epidemiological data from later surveys, or mid-term or long-term PWID. All model fitting used the lsqnonlin algorithm in MATLAB 2016a.

Model analyses

Projections from **all baseline model fits** were compared against all available NESI HCV incidence estimates (2008/09, 2010, 2011/12 and 2013/14) for short-term, mid-term and long-term PWID – in total 12 data points. This was done to assess whether the model replicated the observed decreases in these epidemiological measures while incorporating the observed scale-up of interventions and decrease in high-risk status over time. Specifically, we estimated the percentage of the 95% confidence intervals for these 12 data points that each baseline model fit lay within, and estimated the average of this across all baseline model fits.

We also generated model projections using **all baseline model fits** for a full counterfactual of no increase in intervention coverage (OST, NSP and HCV treatment) or decrease in high-risk behaviour post-2008, and partial counterfactuals assuming one or more of the intervention components were at constant coverage post-2008. The full and partial counterfactuals were used to estimate the number of HCV infections averted due to each intervention component, and the relative change in HCV incidence that would have occurred without any changes in intervention coverage or high-risk behaviour post-2008. 95% credibility intervals (95%CrI) were produced using the 2.5 to 97.5 percentile range in the projections across the model fits.

Lastly, an analysis of co-variance (ANCOVA) was performed on the relative decrease in incidence between 2008–2015 when all interventions were scaled up, and on the number of HCV infections averted over this period compared to the full counterfactual. This determined the importance of uncertainty in different parameters to the variability in these outcomes by calculating the proportion of the sum of squares contributed by each parameter(48).

Results

Model comparison with available data

The baseline ‘intervention’ model accurately captures the overall (Figure 1, and by injecting duration—Figure S3) increasing trend in OST and NSP coverage, and decreasing trend in ‘high-risk’ PWID between 2008/09–2013/14. Although not calibrated to HCV incidence data post-2008/09, Figures 2 and S4 show the model reproduces observed trends in HCV incidence from NESI between 2008–2014, overall and by different injecting duration categories. Indeed, on average, each baseline model fit lies within 84% (10.1/12) of the confidence bounds (95% confidence intervals) for the 12 incidence data points that the model was compared against – none of which were fit to. The model also, though to a lesser extent, reproduces the trends in HCV prevalence (Figure 2 and Figure S4).

[Figure 1 and 2 here]

Impact of intervention

The model projects a mean baseline incidence of 14.2 per 100pyrs (95%CrI 9.0–20.7) amongst current PWID in 2008. When incorporating all changes in intervention coverage and high-risk status, the baseline ‘intervention’ model projects that between 2008–2015, HCV incidence amongst current PWID decreased by 61.3% (95%CrI 45.1–75.3%) to 5.5 per 100pyrs (95%CrI 2.9–9.2) (Table 2). However, the counterfactual model suggests without this intervention scale-up or change in high-risk status since 2008, HCV incidence could still have decreased (Table 2 and Figures 3/S4) by a

quarter (27.4%, 95%CrI 17.6-37.0%) to 10.3 per 100pyrs (95%CrI 6.1-15.7) by 2015. Therefore, we estimate that increases in intervention coverage and decreases in high-risk status post-2008 resulted in an additional 33.9% decrease (95%CrI 23.8-44.6%) in HCV incidence. This translates to 1,492 (95%CrI 657-2,646) HCV infections averted between 2008–2015 or 31.3% (95%CrI 16.1-50.7%) of all HCV infections (Table 2) occurring over that period compared to the counterfactual model. Most of the HCV infections averted (66.8%, 95%CrI 39.9-83.7%) were due to scale-up in OST and NSP post-2008, which averted 1,016 (95%CrI 308-1,996) HCV infections, whereas HCV treatment averted 72 (95%CrI 27-137) infections (Table 2) with the remainder (404, 95%CrI 150-836) due to decreases in high-risk PWID.

[Table 2 and figure 3 here]

ANCOVA analysis

ANCOVA analysis indicates that the largest contributor to the variability in the impact projections for HCV incidence came from uncertainty in the efficacy of being on both OST and NSP for reducing HCV acquisition risk (36% of the variation), and uncertainty in the efficacy of NSP alone (31% of variation). Uncertainty in the increased risk of transmission amongst short-term and mid-term PWID contributed 7% and 3% of the variation, respectively, whereas all other parameters contributed less than 3% (Supplementary Figure S5).

Variability in the number of infections averted was mainly due to uncertainty in the turnover and size of the PWID population. Approximately 30% of the variation was due to uncertainty in the temporary cessation rate amongst mid-term and long-term PWID, whilst uncertainty in the permanent cessation rate, injecting relapse rate and PWID population size contributed a further 16%, 10% and 10% to the variation, respectively (Supplementary Figure S5).

Discussion

Our model projections suggest that historical changes in intervention coverage and injecting risk pre-2008 would themselves have resulted in HCV incidence decreasing among PWID in Scotland, from approximately 14 per 100pyrs in 2008 to 10 per 100pyrs in 2015. Additionally, scaling-up opioid substitution therapy (OST) and needle and syringe provision (NSP) post-2008 contributed a further reduction in HCV incidence to 5 per 100pyrs by 2015, and an estimated 1,400 HCV infections averted over 7-years. HCV treatment scale-up, however, has only had modest impact to date, averting an estimated 72 infections by 2015. This small impact of HCV treatment is both due to few (<5%) infected PWID being treated per year between 2008-2015, and HCV treatment only averting infections indirectly, first through reducing prevalence and as a by-product reducing the risk that someone becomes infected from an infected PWID.

Strengths and limitations

The strengths of our modelling are that it was developed and parameterised using detailed data on the local epidemic and intervention coverage in Scotland, and was validated through its ability to mimic the changing epidemic patterns amongst PWID in Scotland between 2008-2015, despite only being fitted to epidemiological data for 2008/09. However, limitations still exist.

First, the model did not simulate precisely all epidemiological trends from the NESI surveys. Model projections of HCV antibody-prevalence post-2008 tended to be lower than observed trends in Scotland. This may be due to more injectors continuing to inject than the model projected, thereby not fully capturing the long-term dynamics of injecting. Alternatively, the NESI survey may not be representative of all PWID, possibly through over sampling older PWID. Both factors could reduce the resulting observed impact of decreases in HCV incidence on reducing HCV prevalence overall,

which is largely a product of population turnover. However, this would not affect the impact of intervention scale-up on more recently initiated PWID (which were simulated more accurately) where most new HCV infections occur.

Second, the counterfactual model also projected a decrease in HCV incidence. Figure S4 shows that it agrees equally well with observed trends in HCV incidence as the intervention model, mainly due to the upturn in HCV incidence between 2011/12-2013/14 (NESI). This emphasises that without strong evidence for intervention scale-up over this period, it would have been impossible to decide whether the observed decreases in HCV incidence were due to improvements in intervention coverage or other historical changes.

Third, several model parameters were uncertain – including intervention effect estimates for OST and NSP, historical OST and NSP coverage, dynamics of high-risk behaviours, cessation and relapse rates, and the PWID prevalence in Scotland over time. Our projections incorporated uncertainty in all these parameters, and although they were robust despite this it did result in a low hit rate during the model calibration (581 of 5,000 model runs were a baseline model fit). Importantly, most imprecision resulted from uncertainty in the efficacy of NSP (alongside OST or not) and factors related to PWID population turnover and size, highlighting the need for better data on these quantities.

Finally, we assume that the decrease in high-risk behaviours in PWID is independent of the scale-up in harm reduction measures and treatment. Whilst evidence from Scotland and a recent Cochrane review shows that OST decreases the risk of HCV acquisition through reducing the frequency of injecting, independent of this, homelessness and stimulant injecting still increase the risk of HCV transmission in Scotland, as shown in a recent pooled analysis(49). It is possible that the increase in OST and or NSP coverage may have decreased the prevalence of high-risk behaviours, but due to a lack of data to support this it was not included as a model assumption.

Comparison with other studies

Previous modelling studies have estimated the impact of OST, NSP (8,11-13) and HCV treatment(14,15,50,51) on HCV transmission at the population-level, but none have validated whether their projections are consistent with observed epidemiological data. In contrast, our model projections evaluate the evidence that increases in intervention coverage impacted on observed population-level HCV incidence trends. Evidence from Scotland shows that these interventions are associated with decreases in HCV acquisition risk at the individual-level, and that HCV incidence decreased at the population-level concurrently with their scale-up(5). However, these epidemiological analyses did not determine whether the observed decrease in incidence was consistent with the scale-up in intervention coverage; nor did they account for possible decreases in HCV transmission due to historical changes in intervention coverage and evolving epidemic dynamics. These are issues that modelling can address, as done in this analysis. Only one previous analysis has considered a similar question for HCV; modelling from Amsterdam showed that historical changes in risk behaviour prior to intervention scale-up contributed most to observed reductions in HCV incidence in Amsterdam(11).

Implications and Conclusions

Our model projections provide good evidence that the observed decline in HCV incidence in Scotland post-2008 was largely due to increased OST and NSP coverage, made possible through strategies implemented by the Scottish Government. These strategies provided dedicated funding for prevention(52), and set targets for improvements in services relating to injection equipment provision, HCV treatment, and treatment for addiction.

Our model projections also highlight uncertainty in the evidence base. Further data collection is needed to better evaluate the role of NSP in decreasing HCV transmission risk, preferably from

multiple studies using comparable measures of coverage or intervention intensity(7,39). Additionally, more linkage studies are needed to better capture the natural history and transitions between injecting risk states for PWID populations(46,53,54). Both these factors contributed considerable uncertainty to our projections.

This study illustrates how a country-level HCV action plan incorporating scale-up of a range of HCV prevention interventions can markedly reduce HCV incidence. This contrasts sharply with most countries where restrictions in these interventions, due to funding limitations or legal constraints(55), severely limit their impact on HCV incidence(56-61). However, even with high OST and NSP coverage, the impact achieved in Scotland still falls short of the World Health Organisation's strategy for reducing HCV incidence by 90%(62), highlighting that additional interventions are required to eliminate HCV. This could include scaling-up HCV treatment, which modelling has suggested could have substantial impact(12,50), and the scale-up of other interventions to reduce HCV transmission, such as: safe injecting facilities(63); expanding the use of low dead space syringes(64,65); or interventions such as prison-based OST to reduce the heightened risk associated with incarceration(66,67). This model could be an invaluable tool for determining which of these interventions are now needed to reduce HCV transmission to elimination levels in Scotland.

Tables

Table 1: Model parameters with 95% confidence intervals in brackets. Ranges and sampling distributions for parameters varied in the model fitting are shown in bold.

Parameter	Symbol	Value	Reference	Sampled range	Distribution
Risk status parameters:					
Duration stay high-risk in years	$1/\sigma$	1.2	(68)		
Relative risk (compared to low-risk) for acquiring HCV if high-risk for different durations of injecting					
for short-term high-risk PWID	ψ_0	4.7 (1.7 – 17.5)	Calculated using NESI (30)	4.7 (1.7 – 17.5)	Log normal
mid-term high-risk PWID	ψ_1	3.0 (1.5 – 6.1)		3.0 (1.5 – 6.1)	Log normal
Intervention parameters:					
<u>OST and high coverage NSP</u>					
Duration on OST in years	$1/\gamma$	2/3	(69)		
Duration on high coverage NSP in years	$1/\kappa$	2/3	Assume same as OST		
Relative risk (compared to no intervention state) for acquiring HCV for different intervention states					
while on OST and not on high coverage NSP	Γ	0.48 (0.17 – 1.33)	(7)	0.48 (0.17 – 1.33)	Log normal
while on high coverage NSP and not on OST	Π	0.5 (0.22 – 1.12)	(7)	0.5 (0.22 – 1.12)	Log normal
while on OST and high coverage NSP	B	0.21 (0.08 – 0.52)	(7)	0.21 (0.08 – 0.52)	Log normal
<u>Treatment parameters:</u>					
Annual treatment rate from 2009 to 2015 amongst					
Currently injecting PWID	Φ_0	150 per year (75 – 225) ^b	HCV register/link (41,43)	150 (75 – 225)	Normal
Temporarily ceased PWID	Φ_1	300 per year (150–450) ^b		300 (150 – 450)	Normal
Percentage of infections genotype 1 (G1)		47.8% (46.9 – 48.6%)	(42)	47.8% (46.9 – 48.6%)	Normal
SVR: PEG-INF-RBV (G1)		39.0% (33.6 – 44.7%)	(70)	39.0% (33.6 – 44.7%)	Normal
SVR: PEG-INF-RBV (G2/3)	α^a	69.7% (65.8 – 73.4%)	(70)	69.7% (65.8 – 73.4%)	Normal
Average treatment duration (G1 SVR)	$1/\omega^a$	48/52 years	(44)		
Average treatment duration (G1 no SVR)		12/52 years			
Average treatment duration (G2/3)		24/52 years			
PWID-related parameters					
Current PWID population size	Vary θ to fit	16000 (11500 – 19400)	(38)	16000 (12050 – 19950)^c	Normal
PWID mortality rate per year	μ	1%	(71)	0.01	Poisson
Proportion temporarily ceased amongst short-term PWID	p_0	0.46 (0.41 – 0.50)	(46)	0.23 – 0.69^d	Uniform

Increased temporary cessation rate if on OST	τ	1.71 (1.40 – 2.09)	(46)	1.36 – 2.07^d	Uniform
Probability of relapsing within 1 year	Used to find	0.37 (0.32 – 0.42)	(46)	0.185 – 0.555^d	Uniform
Probability of relapsing after 5 years	relapse and	0.59 (0.54 – 0.64)	(46)	0.295 – 0.885^d	Uniform
Probability of sustaining cessation at 30 years from first cessation	permanent cessation rates (q_1, \bar{q}_1)	~0.25	Estimated from Kaplan-Meier curve (46)	0.125 – 0.375^d	Uniform
Probability of temporary cessation of injecting at 5yrs among current injectors.	Used to find temporary cessation rate (p_1) of current injectors	0.72 (0.67 – 0.76)	(46)	0.36 – 1^d	Uniform
Probability of assortative (like-with-like) mixing					
High with low-risk PWID	ρ	0 – 0.5	Little data (from Bristol)	0 – 0.5	Uniform
Between short-term, mid-term and long-term PWID	q	0 – 0.5	suggests probability should be 0.3 or less – wide range used because data is uncertain (72)	0 – 0.5	Uniform
Proportion spontaneously clear infection	δ	0.26	(73)		

^aAs SVR varies by genotype, the average SVR was calculated using a weighted estimate based on population genotype distribution and SVR. ^bFor treatment numbers, we used uncertainty range of +/- 50%. ^cWe averaged the distance from mean so we could use a normal distribution for uncertainty range.

^dDoubled range of confidence interval due to uncertainty in this data. Abbreviations: PWID people who inject drugs; OST opioid substitution therapy; HCNSP high coverage needle and syringe programmes; G1 genotype 1; G2/3 genotypes 2 or 3; SVR sustained viral response; PEG-INF-RBV pegylated interferon and ribavirin.

Table 2: Infections averted amongst people who inject drugs and the relative decrease in incidence between 2008 and 2015 for the different scenarios of interventions being scaled-up from 2008. Ranges in brackets are 95% credibility intervals.

Change from 2008 to 2015 compared to counterfactual	Mean number of infections	Mean infections averted (95% CrI)	Mean relative decrease in incidence
No change (i.e. no intervention scale-up or decrease in proportion high-risk)	6353 (3450-9728)	N/A	27.4% (17.6-37.0%)
Scale-up of OST and high coverage NSP only	5337 (3035-8329)	1016 (308-1996)	47.3% (30.0-62.7%)
Scale-up of OST and high coverage NSP plus decrease in high-risk status	4933 (2714-7767)	1420 (613-2544)	57.9% (41.1-72.3%)
Scale-up of OST and high coverage NSP plus decrease in high risk status plus increase in HCV treatment	4861 (2646-7681)	1492 (657-2646)	61.3% (45.1-75.3%)

Projections are means of model fits, with 95% credibility intervals in brackets

Figures

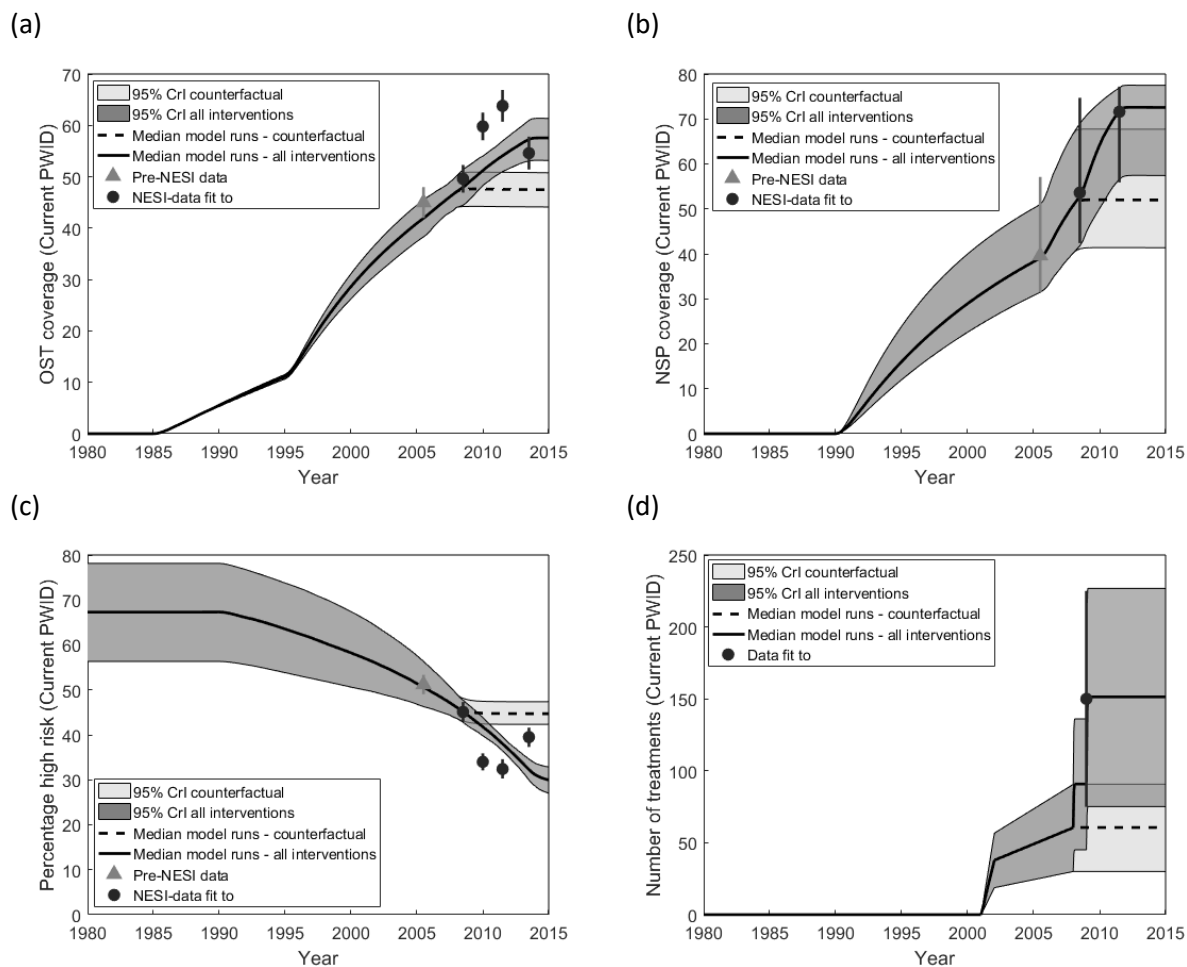


Figure 1: Comparison of model projections with data on the scale-up of (a) OST coverage; (b) NSP coverage; (c) percentage of PWID that are high-risk; and (d) number of HCV treatments over time. In all graphs, black solid and dashed lines indicate the median projections for the 581 baseline ‘intervention’ and counterfactual model runs, respectively, whereas light grey triangles indicate the mean (whiskers are 95% confidence intervals) estimates for the pre-NESI data and dark grey circles indicate the mean (whiskers are 95% confidence intervals) estimates from different rounds of NESI or estimates from the period covered by NESI. Note that for NSP coverage, the upper intervals are bounded by the mean self-reported NSP coverage from NESI.

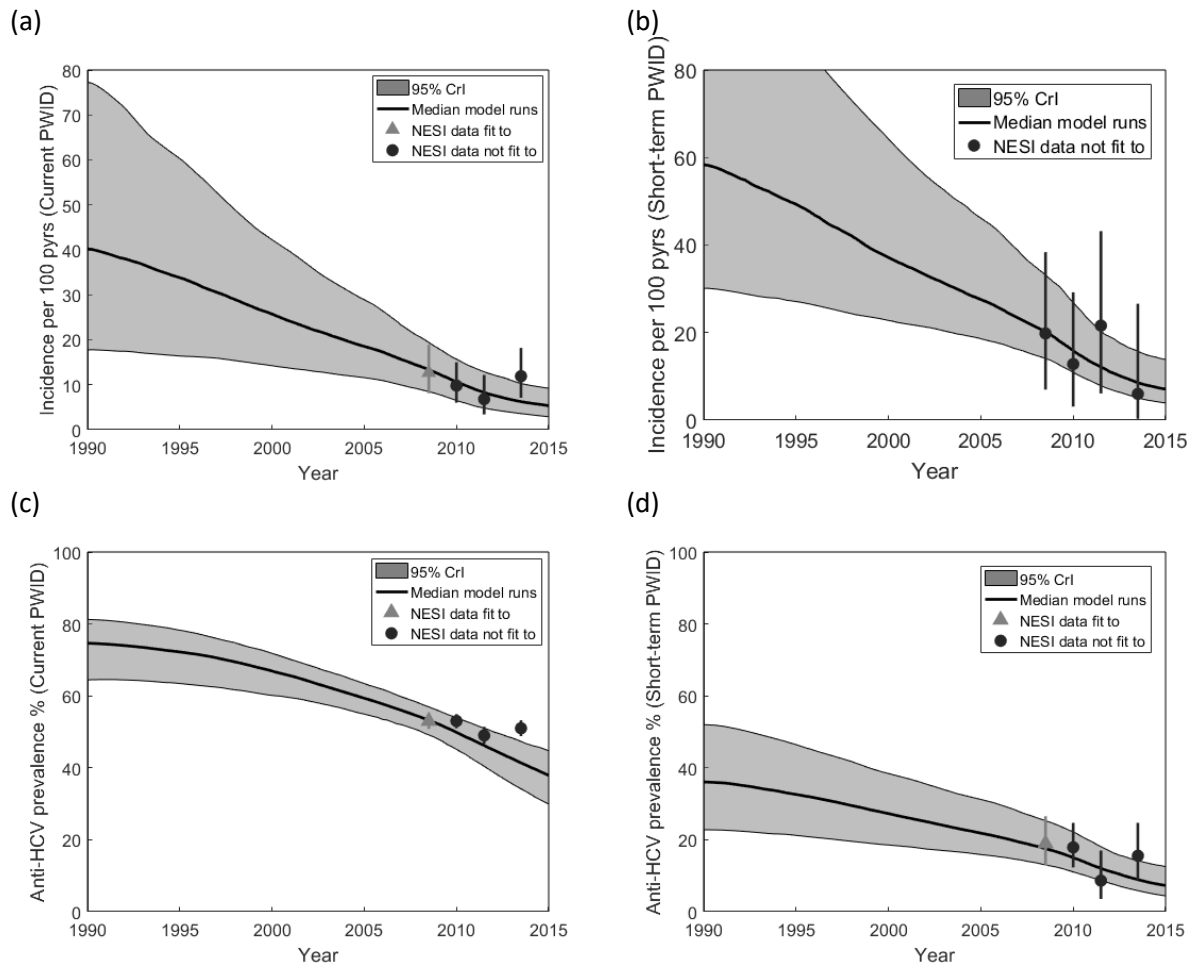


Figure 2: Model and NESI estimated HCV incidence (figures (a) and (b)) and anti-HCV prevalence (figures (c) and (d)) amongst PWID. (a) HCV incidence amongst all current injectors (b) HCV incidence amongst short-term current injectors (injecting <1yrs), (c) Anti-HCV prevalence amongst all current injectors, and (d) Anti-HCV prevalence amongst short-term current injectors (injecting <1 yrs). In all graphs, black solid lines indicate the median projections for the 581 baseline ‘intervention’ model runs. The light grey triangles indicate the mean (whiskers are 95% CI) data estimates from NESI which were fit too and the dark grey circles indicate the mean (whiskers are 95% CI) data estimates from NESI that were not fit to. Note: Anti-HCV prevalence was fit to a wider range of 49-57%.

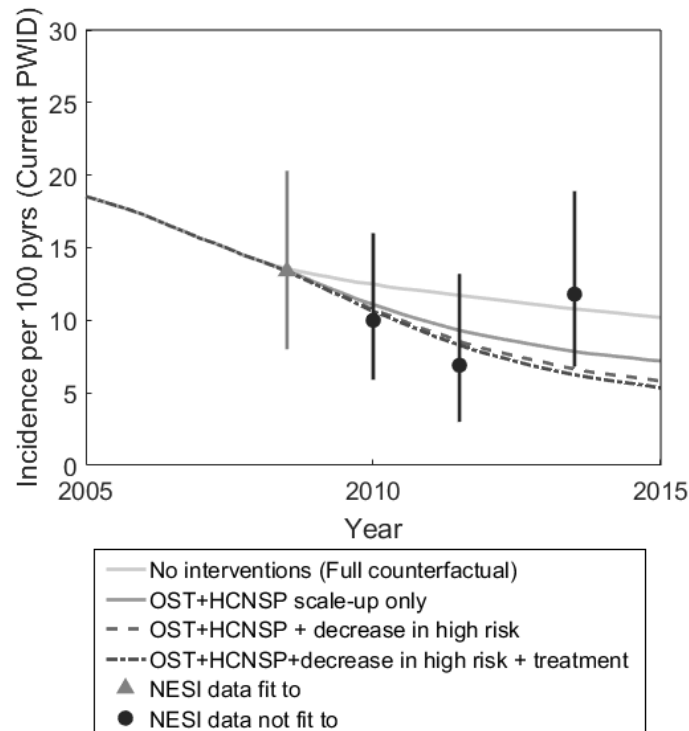


Figure 3: A comparison of NESI HCV incidence estimates for different years (grey and black points) with the model projected HCV incidence amongst all PWID (median across all full model fits) for different intervention scenarios: no intervention scale-up or decrease in high-risk behaviour from 2008 onwards (light grey line – full counterfactual); Scale up of OST and high coverage NSP only from 2008 onwards (dark grey line); Scale up of OST and high coverage NSP plus decrease in high risk behaviour from 2008 onwards (single dashed line); Scale up of all interventions from 2008 onwards (dash and dotted line – baseline intervention runs). Whiskers denote the 95% CI for each NESI HCV incidence estimate.

References

1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *Journal of hepatology*. 2014;61(1 Suppl):S45-57.
2. Cooke GS, Lemoine M, Thursz M, Gore C, Swan T, Kamarulzaman A, et al. Viral hepatitis and the Global Burden of Disease: a need to regroup. *Journal of viral hepatitis*. 2013;20(9):600-1.
3. Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, et al. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385(9963):117-71.
4. Hutchinson SJ, Dillon JF, Fox R, McDonald SA, Innes HA, Weir A, et al. Expansion of HCV treatment access to people who have injected drugs through effective translation of research into public health policy: Scotland's experience. *International Journal of Drug Policy*. 2015;26(11):1041-9.
5. Palmateer NE, Taylor A, Goldberg DJ, Munro A, Aitken C, Shepherd SJ, et al. Rapid decline in HCV incidence among people who inject drugs associated with national scale-up in coverage of a combination of harm reduction interventions. *PloS one*. 2014;9(8):e104515.
6. University of the West of Scotland, Health Protection Scotland, Glasgow Caledonian University, Centre WoSSV. Needle Exchange Surveillance Initiative (NESI): Prevalence of HCV and injecting risk behaviours among people who inject drugs (PWID) attending injecting equipment provision services (IEPs) in Scotland, 2008/2009-2013/2014.; 2015.
7. Turner KME, Hutchinson S, Vickerman P, Hope V, Craine N, Palmateer N, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction*. 2011;106(11):1978-88.
8. Vickerman P, Martin N, Turner K, Hickman M. Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings. *Addiction*. 2012;107(11):1984-95.
9. Sweeting MJ, Hope VD, Hickman M, Parry JV, Ncube F, Ramsay ME, et al. Hepatitis C Infection Among Injecting Drug Users in England and Wales (1992-2006): There and Back Again? *American Journal of Epidemiology*. 2009;170(3):352-60.
10. Mehta SH, Astemborski J, Kirk GD, Strathdee SA, Nelson KE, Vlahov D, et al. Changes in Blood-borne Infection Risk Among Injection Drug Users. *Journal of Infectious Diseases*. 2011;203(5):587-94.
11. de Vos AS, van der Helm JJ, Matser A, Prins M, Kretzschmar MEE. Decline in incidence of HIV and hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction? *Addiction*. 2013;108(6):1070-81.
12. Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination Interventions to Prevent HCV Transmission Among People Who Inject Drugs: Modeling the Impact of Antiviral Treatment, Needle and Syringe Programs, and Opiate Substitution Therapy. *Clinical Infectious Diseases*. 2013;57:S39-S45.
13. Kwon JA, Iversen J, Maher L, Law MG, Wilson DP. The impact of needle and syringe programs on HIV and HCV transmissions in injecting drug users in Australia: a model-based analysis. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2009;51(4):462-9.
14. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *J Hepatol*. 2011;54(6):1137-44.
15. Cousien A, Tran VC, Deuffic-Burban S, Jauffret-Roustide M, Dhersin JS, Yazdanpanah Y. Hepatitis C Treatment as Prevention of Viral Transmission and Liver-Related Morbidity in Persons Who Inject Drugs. *Hepatology*. 2016;63(4):1090-101.
16. Goldberg D, Burns S, Taylor A, Cameron S, Hargreaves D, Hutchinson S. Trends in HCV prevalence among injecting drug users in Glasgow and Edinburgh during the era of needle/syringe exchange. *Scandinavian journal of infectious diseases*. 2001;33(6):457-61.
17. Hutchinson S, McIntyre P, Molyneaux P, Cameron S, Burns S, Taylor A, et al. Prevalence of hepatitis C among injectors in Scotland 1989–2000: declining trends among young injectors halt in the late 1990s. *Epidemiology and Infection*. 2002;128(03):473-7.
18. Scottish Government. The Scottish Government Hepatitis C Action Plan for Scotland: Phase II (May 2008 - March 2011). 2008.
19. Government SS. The road to recovery: A new approach to tackling Scotland's drug problem: Scottish Government; 2008.
20. Pickles M, Boily M-C, Vickerman P, Lowndes CM, Moses S, Blanchard JF, et al. Assessment of the population-level effectiveness of the Avahan HIV-prevention programme in South India: a preplanned, causal-pathway-based modelling analysis. *Lancet Global Health*. 2013;1(5):E289-E99.
21. Boily MC, Masse B, Alsallaq R, Padian NS, Eaton JW, Vesga JF, et al. HIV Treatment as Prevention: Considerations in the Design, Conduct, and Analysis of Cluster Randomized Controlled Trials of Combination HIV Prevention. *Plos Medicine*. 2012;9(7):10.
22. Boily M-C, Pickles M, Lowndes CM, Ramesh BM, Washington R, Moses S, et al. Positive impact of a large-scale HIV prevention programme among female sex workers and clients in South India. *Aids*. 2013;27(9):1449-60.

23. Hallett TB, Gregson S, Mugurungi O, Gonese E, Garnett GP. Assessing evidence for behaviour change affecting the course of HIV epidemics: A new mathematical modelling approach and application to data from Zimbabwe. *Epidemics*. 2009;1(2):108-17.
24. Fraser H, Mukandavire C, Martin NK, Hickman M, Cohen MS, Miller WC, et al. HIV treatment as prevention among people who inject drugs—a re-evaluation of the evidence. *International Journal of Epidemiology*. 2016:dyw180.
25. Mehta SH, Cox A, Hoover DR, Wang X-H, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. *The Lancet*. 2002;359(9316):1478-83.
26. Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, Lauer G, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *The Lancet Infectious Diseases*. 2012;12(5):408-14.
27. Micallef J, Macdonald V, Jauncey M, Amin J, Rawlinson W, Van Beek I, et al. High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. *Journal of viral hepatitis*. 2007;14(6):413-8.
28. Aitken CK, Lewis J, Tracy SL, Spelman T, Bowden DS, Bharadwaj M, et al. High incidence of hepatitis C virus reinfection in a cohort of injecting drug users. *Hepatology*. 2008;48(6):1746-52.
29. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. *Clinical Infectious Diseases*. 2016:civ948.
30. University of the West of Scotland, Health Protection Scotland, West of Scotland Specialist Virology Centre. The Needle Exchange Surveillance Initiative (NESI): Prevalence of HCV and injecting risk behaviours among injecting drug users attending needle exchanges in Scotland, 2008/2009. . Paisley: University of the West of Scotland.; 2010.
31. O'Leary MC, Hutchinson SJ, Allen E, Palmateer N, Cameron S, Taylor A, et al. The association between alcohol use and hepatitis C status among injecting drug users in Glasgow. *Drug and Alcohol Dependence*. 2012;123(1-3):180-9.
32. Information Services Division. Drug Misuse Statistics Scotland 2004. . Edinburgh: Common Services Agency.; 2005.
33. Information Services Division. Drug Misuse Statistics Scotland 1998. Edinburgh: Common Services Agency; ; 1999.
34. Information Services Division. Drug Prescribing Scotland 2014/15. .
35. Gruer L, Cameron J, Elliott L. BUILDING A CITY WIDE SERVICE FOR EXCHANGING NEEDLES AND SYRINGES. *British Medical Journal*. 1993;306(6889):1394-7.
36. Greater Glasgow Health Board AIDS Control act reports.
37. Injecting Equipment Provision in Scotland Survey 2011/12. 2013.
38. Overstall AM, King R, Bird SM, Hutchinson SJ, Hay G. Incomplete contingency tables with censored cells with application to estimating the number of people who inject drugs in Scotland. *Statistics in Medicine*. 2014;33(9):1564-79.
39. Platt L, Reed J, Minozzi S, Vickerman P, Hagan H, French C, et al. Effectiveness of needle/syringe programmes and opiate substitution therapy in preventing HCV transmission among people who inject drugs. *The Cochrane Library*. 2016.
40. Booth JC, O'Grady J, Neuberger J. Clinical guidelines on the management of hepatitis C. *Gut*. 2001;49(suppl 1):11-121.
41. Public Health England. Hepatitis C in the UK: 2014 report. 2014.
42. McLeod A, Hutchinson S, Goldberg D. Surveillance of known hepatitis C antibody positive cases in Scotland: Results to 31 December 2013. 2014.
43. Innes H, Goldberg D, Dillon J, Hutchinson SJ. Strategies for the treatment of Hepatitis C in an era of interferon-free therapies: what public health outcomes do we value most? *Gut*. 2015;64(11):1800-9.
44. NICE. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. 2006.
45. Tait J, McIntyre P, McLeod S, Nathwani D, Dillon J. The impact of a managed care network on attendance, follow-up and treatment at a hepatitis C specialist centre. *Journal of viral hepatitis*. 2010;17(10):698-704.
46. Xia Y, Seaman S, Hickman M, Macleod J, Robertson R, Copeland L, et al. Factors affecting repeated cessations of injecting drug use and relapses during the entire injecting career among the Edinburgh Addiction Cohort. *Drug and Alcohol Dependence*. 2015;151:76-83.
47. Kimber J, Copeland L, Hickman M, Macleod J, McKenzie J, De Angelis D, et al. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. *BMJ*. 2010;341:c3172.
48. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation United States*: Oxford University Press; 2006.
49. Platt L, Sweeney S, Ward Z, Guinness L, Hickman M, Hope V, et al. Assessing the impact and cost-effectiveness of needle and syringe provision and opioid substitution therapy on hepatitis C transmission among people who inject drugs in the UK: an analysis of pooled data sets and economic modelling. 2017.
50. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*. 2013;58(5):1598-609.
51. Durham DP, Skrip LA, Bruce RD, Vilarinho S, Elbasha EH, Galvani AP, et al. The impact of enhanced screening and treatment on hepatitis C in the United States. *Clinical Infectious Diseases*. 2016;62(3):298-304.
52. Goldberg D, Brown G, Hutchinson S, Dillon J, Taylor A, Howie G, et al. Hepatitis C action plan for Scotland: phase II (May 2008-March 2011). *Eurosurveillance*. 2008;13(4-6):1-2.

53. White SR, Bird SM, Merrall EL, Hutchinson SJ. Drugs-Related Death Soon after Hospital-Discharge among Drug Treatment Clients in Scotland: Record Linkage, Validation, and Investigation of Risk-Factors. *PloS one*. 2015;10(11):e0141073.
54. McDonald S, Hutchinson S, Bird S, Robertson C, Mills P, Dillon J, et al. A record-linkage study of the development of hepatocellular carcinoma in persons with hepatitis C infection in Scotland. *British journal of cancer*. 2008;99(5):805-10.
55. Latypov A, Bidordinova A, Khachatryan A. Opioid substitution therapy in Eurasia: How to increase the access and improve the quality. IDPC briefing series on drug dependence treatment no 1. 2012.
56. Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans JL, et al. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. *The Journal of infectious diseases*. 2002;186(11):1558-64.
57. Page K, Morris MD, Hahn JA, Maher L, Prins M. Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. *Clinical infectious diseases*. 2013;57(suppl 2):S32-S8.
58. Hagan H, Pouget ER, Williams IT, Garfein RL, Strathdee SA, Hudson SM, et al. Attribution of hepatitis C virus seroconversion risk in young injection drug users in 5 US cities. *The Journal of infectious diseases*. 2010;201(3):378-85.
59. Jordan AE, Des Jarlais DC, Arasteh K, McKnight C, Nash D, Perlman DC. Incidence and prevalence of hepatitis c virus infection among persons who inject drugs in New York City: 2006–2013. *Drug and alcohol dependence*. 2015;152:194-200.
60. Wiessing L, Ferri M, Grady B, Kantzanou M, Sperle I, Cullen KJ, et al. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a systematic review of data for scaling up treatment and prevention. *PloS one*. 2014;9(7):e103345.
61. Sypsa V., Vickerman P., M. M, A. H. HCV infection and HIV-HCV coinfection among “new” injectors during an HIV outbreak in Athens, Greece: Results from the ARISTOTLE programme. *International Symposium on Hepatitis C in Substance Users; Oslo, Norway 2016*.
62. World Health Organization. Draft global health sector strategies. *Viral hepatitis, 2016-2021*. 2016.
63. Bayoumi AM, Zaric GS. The cost-effectiveness of Vancouver's supervised injection facility. *Canadian Medical Association Journal*. 2008;179(11):1143-51.
64. Vickerman P, Martin N, Hickman M. Could low dead-space syringes really reduce HIV transmission to low levels? *International Journal of Drug Policy*. 2013;24(1):8-14.
65. Zule WA, Cross HE, Stover J, Pretorius C. Are major reductions in new HIV infections possible with people who inject drugs? The case for low dead-space syringes in highly affected countries. *International Journal of Drug Policy*. 2013;24(1):1-7.
66. Altice FL, Azbel L, Stone J, Brooks-Pollock E, Smyrnov P, Dvoriak S, et al. The perfect storm: incarceration and the high-risk environment perpetuating transmission of HIV, hepatitis C virus, and tuberculosis in Eastern Europe and Central Asia. *The Lancet*. 2016;388(10050):1228-48.
67. Stone J, Martin NK, Hickman M, Hutchinson SJ, Aspinall E, Taylor A, et al. Modelling the impact of incarceration and prison-based hepatitis C virus (HCV) treatment on HCV transmission among people who inject drugs in Scotland. *Addiction*. 2017.
68. Kemp PA, Neale J, Robertson M. Homelessness among problem drug users: prevalence, risk factors and trigger events. *Health & Social Care in the Community*. 2006;14(4):319-28.
69. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *British Medical Journal*. 2010;341.
70. Innes HA, Hutchinson SJ, Allen S, Bhattacharyya D, Bramley P, Carman B, et al. Ranking predictors of a sustained viral response for patients with chronic hepatitis C treated with pegylated interferon and ribavirin in Scotland. *European Journal of Gastroenterology & Hepatology*. 2012;24(6):646-55.
71. Merrall EL, Bird SM, Hutchinson SJ. Mortality of those who attended drug services in Scotland 1996–2006: record-linkage study. *Int J Drug Policy*. 2012;23(1):24-32.
72. Mills H, Colijn C, Vickerman P, Leslie D, Hope V, Hickman M. Respondent driven sampling and community structure in a population of injecting drug users, Bristol, UK. *Drug and alcohol dependence*. 2012;126(3):324-32.
73. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *Journal of Viral Hepatitis*. 2006;13(1):34-41.