Title: Impact of current and scaled up levels of Hepatitis C (HCV) prevention and treatment interventions for people who inject drugs in three UK settings – what is required to achieve the WHO's HCV elimination targets?

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Abstract

Aims: We estimate the impact of existing high coverage needle and syringe provision (HCNSP, defined as obtaining more than one sterile needle and syringe per injection reported) and opioid substitution therapy (OST) on hepatitis C virus (HCV) transmission among people who inject drugs (PWID) in three United Kingdom (UK) settings. We determine required scale-up of interventions, including HCV treatment, needed to reach the World Health Organisation (WHO) target of reducing HCV incidence by 90% by 2030.

Design HCV transmission modelling utilising UK empirical estimates for effect of OST and/or HCNSP on individual risk of HCV acquisition

Setting Three UK cities with varying HCV antibody prevalence (Bristol 60%, Dundee 46%, Walsall 32%), OST (72-81%), and HCNSP coverage (28-56%).

Measurements Relative change in new HCV infections over 2016-2030 if current interventions were stopped. Scale-up of HCNSP, OST and HCV treatment required to achieve the WHO elimination target.

Findings Removing HCNSP or OST would increase the number of new HCV infections over 2016-2030 by 23-64% and 92-483%, respectively. Conversely, scaling-up these interventions to 80% coverage could achieve a 29% or 49% reduction in Bristol and Walsall, respectively, whereas Dundee achieves a 90% decrease in incidence with current levels of intervention because of existing high levels of HCV treatment (47-58 treatments per 1000 PWID). If OST and HCNSP are scaled-up, Walsall and Bristol can achieve the same impact by treating 14 or 40 per 1000 PWID annually, respectively (currently 1-3 and 6-12 treatments per 1000 PWID), while 18 and 43 treatments per 1000 PWID would be required if OST and HCNSP are not scaled-up.

Conclusions Current opioid substitution therapy and high coverage needle and syringe provision coverage is averting substantial Hepatitis C transmission in the United Kingdom. Maintaining this coverage while initiating current injectors on treatment can reduce incidence by 90% by 2030.

Introduction

Hepatitis C virus (HCV) is a major cause of morbidity worldwide(1). Approximately 85% of HCV infections in the UK are acquired through injection drug use(2, 3), therefore prevention of HCV transmission among people who inject drugs (PWID) is crucial for reducing the HCV disease burden.

Primary prevention interventions for HCV are opioid substitution therapy (OST) and needle and syringe programmes amongst PWID(4). OST and high coverage needle and syringe provision (HCNSP, defined as obtaining more than one sterile needle and syringe per injection) can reduce the risk of HCV acquisition by 40-80%(5-10). Although low in many settings(11, 12), UK coverage levels for OST (70%) and HCNSP (48%) are high(2). Further, the emergence of highly efficacious antiviral HCV drugs(13) has raised the possibility of scaling-up HCV treatment as a prevention strategy amongst PWID(14, 15). Consequently, the World Health Organisation (WHO) recently produced a global strategy for eliminating HCV(1).

Modelling has suggested that OST and HCNSP has reduced HCV prevalence in the UK, but further scale-up will have limited impact(16), with HCV treatment being needed to markedly reduce HCV prevalence(15, 17, 18). However, no analyses have considered how the impact of OST or HCNSP may vary between regional settings, or what combined scale-up of HCV treatment with OST and HCNSP are required to achieve the WHO HCV-elimination targets.

In this paper, a HCV transmission model incorporating improved empirical evidence for the effectiveness of harm reduction interventions is used to evaluate the impact of current levels of OST and HCNSP on cumulative number of incident HCV infections in three UK settings (Bristol, Dundee and Walsall), and the required scale-up of these interventions with HCV treatment to reach WHO's targets of reducing HCV incidence by 90% by 2030(1).

Methods

Model Description and assumptions

We developed a dynamic deterministic model of HCV transmission and disease progression among PWID, similar to other HCV transmission models(16, 17) using principles outlined by recent guidelines for HIV or economic infectious disease models(19, 20). The model simulates the movement of current PWID through different stages of injecting duration, intervention coverage, risk and HCV infection states, as shown in Figure 1. Further model details are in the supplementary materials.

Stratifications by injecting duration are included to incorporate increased injecting cessation and HCV-acquisition risk among people recently initiated into injecting(5, 21, 22), with the chosen category in line with reporting from the unlinked anonymous monitoring (UAM) survey of PWID (23). PWID are also stratified into different intervention states that influence HCV transmission risk: no intervention, OST only, HCNSP only, or both. PWID enter the model as recent initiates with no intervention coverage. They transition through successive injecting duration categories with rates of injecting cessation and non-HCV related death. Due to a lack of data, we assumed recruitment and leaving rates onto and off OST and HCNSP were independent of the current intervention state; previous modelling suggests this should not affect our model projections(16). The model is further stratified by high and low HCV transmission risk, with a proportion starting injecting in the high-risk category(24) and PWID transitioning between these categories. PWID were defined as high-risk if they had been homeless in the last year

and/or injected crack in last 4 weeks (low-risk otherwise), which was associated with increased HCV transmission risk(25).

New initiates into injecting are initially susceptible to HCV, and become infected at a per-capita rate depending on their intervention state, injecting duration category, risk category, and prevalence of HCV infection in the population. Previous analyses suggest incorporating like-with-like mixing (individuals with the same risk behaviour or characteristics being more likely to form injecting contacts with each other than with other individuals) will have little effect on our model projections(16), with data suggesting it only occurs weakly in Bristol(26), and so random mixing was assumed between all sub-groups.

Once infected, some PWID spontaneously clear infection(27), with the remainder becoming chronically infected, which is life-long unless treated. Chronically infected PWID progress through disease states (Figure 1c*)* with HCV disease-related death occurring from the decompensated cirrhosis, hepatocellular carcinoma, liver transplant and post-liver transplant stages.

HCV treatment is only allowed in the F0-F3 and compensated cirrhosis states as it was contraindicated for more severe liver disease for interferon-based therapy (28) and evidence is only now emerging of its benefits with new DAA therapies(29). An annual number of PWID are treated, with a proportion achieving a sustained virological response (SVR-effective cure) and the remainder returning to their prior infection category. Following successful treatment, no further disease progression occurs in the F0-F3 states(30, 31), but continued slower progression occurs among those with compensated cirrhosis(31, 32). We allow re-infection of those who have attained SVR, and re-treatment of those who fail treatment or become re-infected in line with current recommendations(13).

[Figure 1 here]

Model Parameterisation

The model was parameterised for three UK settings: Bristol, Dundee and Walsall. These sites were chosen because of the availability of survey data and to give a range of epidemic settings. The model parameters and uncertainty ranges are given in Table 1 and Table S1. Effect estimates for how HCV transmission risk is modified by OST and/or HCNSP, or injecting duration were taken from a pooled analysis of UK and Australian data(25) and a Cochrane systematic review(10). Estimated leaving rates from the high-risk category (1.16 per year), OST (1.65 per year) or HCNSP (0.52 per year) came from two UK studies(24, 33).

HCV treatment was initiated in 2009 at rates determined by local data, except for Walsall where Bristol treatment rates were used. Before 2015, UK-specific PWID SVR rates(34) for pegylated interferon (pegIFN) and ribavirin (RBV) were assumed, whereas post-2015 a weighted average of SVRs for genotypes 1 and 2/3(35, 36) for direct acting antiviral drugs was assumed.

HCV disease progression rates were calculated from two meta-analyses(28, 37) (Table S1). Non-HCV related death rates were derived from two UK studies(21, 38).

[Table 1 here]

Model Calibration and uncertainty

The model was calibrated to temporal data on HCV prevalence, recent estimates of coverage of OST and HCNSP, proportion of PWID with high-risk attributes, population size estimates of PWID, and their distribution by injecting duration (Table 2 and S2)(23, 26, 39-46). Data on HCV incidence for Dundee and Bristol, and HCV prevalence after 2006 for Bristol and Walsall were used for model validation, with both extracted from routine surveys of PWID (Needle exchange surveillance initiative in Scotland (NESI)(46), Unlinked anonymous monitoring survey (UAM) in England and Wales(23), and two additional community surveys using respondent driven sampling from Bristol(26), see supplementary information for details of the surveys).

[Table 2 here]

A sequential Bayesian method was used to calibrate the model, each to get 1,000 model fits. Firstly, a demographic sub-model was fitted to data on the population size of PWID for each setting and their distribution by injecting duration, which was assumed to be stable in Dundee(46), but decreasing(39-41, 47) and aging(26, 43-45, 48) in Bristol and Walsall. Secondly, an intervention sub-model was fitted to changing trends in the coverage of OST and HCNSP from each setting(26, 43, 46, 48), with OST coverage increasing in each setting over recent years from 40 to 70-81%, and the proportion with HCNSP remaining stable in Bristol (ranging between 38-82%) and Walsall (ranging between 21-42%), but increasing in Dundee (up to 34-79%, see Table S2). Thirdly, a high/low-risk sub-model was fitted to setting-specific data on the trends in crack injecting and/or homelessness(46, 48), which has remained stable in Dundee (33% high-risk) and Walsall (52% high-risk) but increased in Bristol over recent years (88% high-risk in 2014).

Lastly, the full model was calibrated to HCV prevalence data from each setting. For each of the 1,000 combined parameter sets from the previous calibration steps, the model's infection rate was calibrated to an initial sampled prevalence estimate for each city (Bristol 2004, Walsall 2006 and Dundee 2008; Table S2 and Figure S1), assuming a stable epidemic at that time. For Walsall and Bristol, this infection rate accurately captured the subsequent epidemic dynamics (Figure S1), whereas for Dundee a second infection rate (median 2.0-fold (95% credibility interval (95%CrI) 1.8-2.7-fold) greater than initial infection rate) was used to capture the HCV prevalence in 2014. Table S2 summarises the model parameters obtained through model-fitting and the supplementary materials includes further detail.

Model Analyses

The model estimated the impact of current coverage levels of OST, HCNSP and HCV treatment over 2016-30, by comparing the baseline model with a counterfactual where the effect of these interventions was removed from 2016. Impact was assessed in terms of the relative change in the cumulative number of incident infections over 2016-2030. Results were obtained for each parameter set and given in terms of 95% Credible Intervals (supplementary information for details).

We then estimated the impact to 2030 of scaling up both OST and HCNSP to 80% coverage. This maximum coverage was partially based on the fact that 85% of PWID inject opioids(48), and so would derive a benefit from OST, and that higher intervention coverage levels are likely unsustainable(16). Additionally, the HCNSP target of 80% coverage is a current target of needle and syringe providers (personal communication Rachel Ayres). Following this, we estimated what additional HCV treatment scale-up is needed to reduce HCV incidence by 90% by 2030. We also considered how these projections were modified if the heightened transmission risk associated with our high-risk categories were halved.

Uncertainty Analysis
A linear regression analysis of covariance (ANCOVA) (49) was undertaken to determine which parameter uncertainties (exposure variables in the linear regression analysis) contributed most to variability in the percentage reduction in incident HCV infections over 15 years due to current levels of HCNSP or OST (outcome variable). The proportion of each model outcome's sum-of-squares contributed by each parameter was calculated to estimate the importance of individual parameters to the overall uncertainty.

Results

Baseline epidemic projections

The chronic HCV prevalence pre-2016 was projected to be stable in all three settings (Figure 2). Over 2016-30, HCV prevalence will decrease slightly in Bristol (by 5%) and Walsall (by 0.4%), but reduce markedly in Dundee (by 99%). These decreases are due to the current scale-up of new treatments from 2015, with heightened impact in Dundee due to treatment already being scaled up (47-58 per 1000 PWID). The projected HCV incidence in 2014 varied between settings. The highest incidence was in Dundee (7.7 per 100py, 95% Credible Interval (CrI) 4.0-12.6) and Bristol (6.9 per 100py, 95%CrI 3.9-11.5), both lower but comparable to recent empirical estimates from these settings (Dundee: 14.3 per 100py, 95% Confidence Interval (CI) 4.9-25.9 (46) and Bristol: 10.0 per 100py, 95%CI 9.7-14.0(26)). Incidence was 3.4 per 100py in Walsall (95%CrI 1.7-6.6), corresponding to the low prevalence in that setting. Incidence is expected to decrease slightly in Walsall (by 1%) and Bristol (by 11%) over 2016-2030, but will decrease by over 90% in Dundee (99.97%, 95% CrI 99.0-99.99).

[Figure 2 here]

Impact of existing interventions

Figures 2 and 3 (and Table S3) show that, regardless of setting, removing HCNSP and/or OST would lead to a large increase in the number of incident infections and increased HCV prevalence and incidence by 2030. Removing OST has greater impact than removing HCNSP with less impact being achieved from removing HCV treatment. This differential impact is due both to the differing coverage of these interventions and their relative effectiveness. For example, in Walsall the number of incident infections over 2016-2030 would increase by 23%, 129% or 176% if HCNSP, OST or both interventions were removed, respectively, compared with 3% if HCV treatment were removed. In Dundee, a greater increase (380%) would result from removing treatment because of the higher treatment rate in that setting.

[Figure 3 here]

Impact of combined OST/NSP interventions and treatment scale-up on HCV incidence

Through scaling-up HCNSP and OST to 80% coverage from the current levels, it is possible to reduce HCV incidence by 29%(95%CrI 4.7-58%) in Bristol, 100%(95%CrI 99-100%) in Dundee and 49%(95%CrI 1.2-77%) in Walsall by 2030 compared to 2015 levels (Figure S2). Greater impact is achieved in Dundee due to recent HCV treatment scale-up. In all settings, most impact (>80%) is achieved from scaling-up HCNSP due to its lower baseline coverage (28-56% depending on setting).

With current levels of HCNSP and OST, the annual number of HCV treatments needed to reduce incidence by 90% by 2030 (WHO elimination target) is 43(95%CrI 26-61), 29(95%CrI 14-45) and 18(95%CrI 8-36) per 1000 PWID for Bristol, Dundee and Walsall, respectively (Figure 4). This would require considerable scale-up of treatment in Bristol (5-fold from 9 annual treatments per 1000 PWID) and Walsall (9-fold from 2 annual treatments per 1000 PWID), while treatment numbers could be reduced by 45%(95%CrI 11-63%) in Dundee and still achieve this target.

Concurrent scale-up of HCNSP and OST to 80% coverage decreases the yearly treatments required to reach the WHO target (Figure 4); from 43 to 40 per 1000 PWID for Bristol, 29 to 22 for Dundee, and 18 to 14 for Walsall. If, additionally, the transmission risk associated with high-risk injecting (homelessness and crack injecting) was also halved then the required number of treatments would reduce further by one-fifth (19-22% - see Figure 4) in each setting. In all scenarios, fewer treatments are always needed in Dundee than the current number of treatments (47-58 per 1000 PWID).

[Figure 4 here]

Uncertainty analysis

Analyses of covariance (Figure S3) suggest that most of the variability in the effect of removing HCNSP on increasing the number of infections between 2016-2030 is due to uncertainty in the efficacy of HCNSP (accounting for 41%, 4% and 49% of variability in Bristol, Dundee and Walsall, respectively), the coverage of HCNSP in 2014 (32% of variation in Bristol, 39% in Walsall and <1% in Dundee), and HCV prevalence in 2014 (77% in Dundee, 0.1% in Bristol, 3% in Walsall). Increasing effectiveness and coverage of HCNSP increases the impact of removing the intervention (Bristol and Walsall) and in Dundee the lower the 2014 HCV prevalence the greater the increase in infections (Figure S4). All other parameters and inputs had little effect. For the impact of removing OST (Figure S5), most variability is due to uncertainty in the efficacy of OST (45% in Bristol, 44% in Dundee and 38% in Walsall).

Discussion

Main Findings

Current levels of HCNSP and OST in the UK are averting considerable HCV transmission, with their removal likely to double the number of new HCV infections occurring over the next 15 years. If HCNSP and OST levels are maintained, only moderate rates of HCV treatment (18-43 per 1000 PWID annually) are needed to reduce HCV incidence by 90% by 2030, so achieving the WHO elimination target. This scale up has already been achieved in Dundee. Although scaling up HCNSP and OST further (to 80% coverage) will reduce these treatment targets (by a fifth), their existing moderate coverage in the UK limits the additional impact they can have.

Strengths and limitations

Our detailed modelling of three contrasting settings provides insights into how the impact of existing interventions varies across the UK, with our projections being strengthened by using detailed local data and utilising new synthesised estimates for the efficacy of OST and HCNSP. Additionally, calibrating our model to temporal trends in injecting duration and PWID population size allowed us to incorporate possible changes in injecting over recent years, increasing the potential realism of our model projections.

However, limitations exist, primarily relating to the data used to inform our model. First, despite synthesising the best available international evidence(10), there remains substantial uncertainty in the intervention effectiveness of HCNSP, which our uncertainty analyses show was the most important contributor to uncertainty in our model projections. Further data collection of individual injecting frequency, real-life syringe provision and blood borne virus status could improve these estimates.

Second, self-reported data on NSP coverage derived from surveys recruiting from needle and syringe providers are likely to overestimate coverage in the population as a whole(46, 50), so instead we estimated the HCNSP coverage in each city as the ratio of the number of syringes distributed to the estimated total number of injections undertaken by PWID in that city. Unfortunately, this measure utilised three uncertain pieces of information (PWID population size, yearly injecting frequency and the number of new needles distributed), with the resulting uncertainty in HCNSP coverage contributing considerably to the variability in our projections. Less biased estimates of syringe coverage could only come from better monitoring of service users.

Third, our use of homelessness or crack use as a marker of high transmission risk is incomplete because it does not explicitly incorporate differences in injecting risk. This was done because of the inherent difficulty in using data on specific injecting behaviours to reliably estimate the variability in transmission risk between different PWID, and so we used proxy markers that have been found to be related to increased transmission risk. Importantly, previous analyses(15, 16) suggest risk heterogeneity rarely plays an important role in determining the impact of HCV interventions and so this simplification should not have affected our projections.

Fourth, we assumed all PWID were eligible for OST despite a growing proportion (3.9% in 2004 and 12% in 2014) are injecting non-opioids(2), for which OST is not an appropriate treatment. Although this was partially accounted for by assuming the coverage of OST could not be greater than 80%, future analyses could improve on this by explicitly modelling non-opioid injecting PWID as a separate group where HCNSP would be the only harm reduction strategy available. This could mean that existing interventions would have less prevention benefit.

Fifthly, we assumed that HCV treatment was not allowed for individuals with severe liver disease (decompensated cirrhosis and beyond) despite recent treatment guidelines allowing it (13). This assumption is unlikely to affect our impact projections because fewer than 7% of all chronically infected PWID have this level of liver disease.

Lastly, we assumed that Walsall had the same low treatment rate among PWID as Bristol due to lack of data. This will have had little impact on our results which show that treatment needs to be scaled-up substantially to have a large impact on HCV incidence. In contrast, current treatment numbers in Dundee are very high (25% of infected per year from 2015), with our modelling suggesting they will achieve HCV elimination by 2030 if maintained at this high level. To determine if this may have affected our impact projections for OST and HCNSP, we undertook a scenario analysis (not shown) which halved treatment rates from 2016 and showed similar impacts for the same levels of HCNSP and OST coverage.

Comparison with other studies

Few model analyses have estimated the impact of HCNSP or OST on HCV transmission, with previous analyses either not using empirical intervention effect estimates(51) and/or not using detailed context-specific data to evaluate how impact may vary across settings(16, 17). This

analysis is consistent with previous findings that HCNSP and OST can have substantial impact(16), with our analysis also highlighting how impact can vary depending on local-levels of intervention coverage and epidemic trends. Additionally, our analysis is the first to estimate the required scale-up of OST, HCNSP and HCV treatment needed to achieve WHO's HCV-elimination targets amongst PWID in a European setting, with previous analyses either considering their required scale-up in a rural U.S. setting(52), or just the treatment scale-up requirements in Australia(53). Without scale-up of OST and HCNSP, our analyses suggest similar treatment rates (43/1000 PWID annually) are needed in Bristol as for Australia (59/1000 PWID annually), which has a similar chronic prevalence of HCV, but much lower than in the rural U.S. setting (89/1000 PWID annually) due to the increasing HCV epidemic occurring there. However, further scale-up of OST and HCNSP results in lower treatment rates being needed in the UK (14-44/1000 PWID annually) than in Australia, although the reduction is smaller (20% decrease in treatment requirements) than for the rural U.S. (halves treatment requirements) due to the negligible current coverage of these interventions in the U.S. setting.

Conclusions and Implications

Our projections highlight the considerable impact that existing harm reduction interventions are having in high coverage settings, such as Europe and Australia, emphasising the need to maintain current coverage levels of these interventions, avoid reductions in prevention funding, or changes in drug treatment policy away from harm reduction towards abstinence. There is also an urgent imperative to continue funding for NSPs, since changes in drug use favouring non-opioid use may reduce the impact of OST.

Our projections suggest benefits could be achieved from scaling-up OST and HCNSP further, especially in lower coverage settings such as Walsall. This highlights the need to initiate strategies for increasing the coverage of OST and HCNSP in these and similar settings, which should be done in close consultation with service users. Evidence shows the benefits of extending opening hours(54), and promotion of secondary distribution via peers(55, 56) or vending machines for increasing coverage(57). Additionally, better monitoring at the local district level is needed to identify lower coverage settings.

Although our analyses emphasised the importance of OST and HCNSP for reducing HCV transmission, a combined approach utilising HCV treatment is needed to reduce HCV incidence to low-levels, as advocated by WHO. This scale-up will require policy driven expansion of case-finding interventions in settings such as drug treatment centres and NSPs, as already undertaken in Dundee; emphasising their crucial role for any scaled-up HCV prevention response. Strategies also need to be developed to reduce the harms associated with structural factors, such as homelessness and incarceration, which modelling suggests could be heightening HCV transmission amongst PWID(25, 58, 59). Such a multi-pronged approach must be prioritised to achieve the HCV-elimination targets set by WHO(1).

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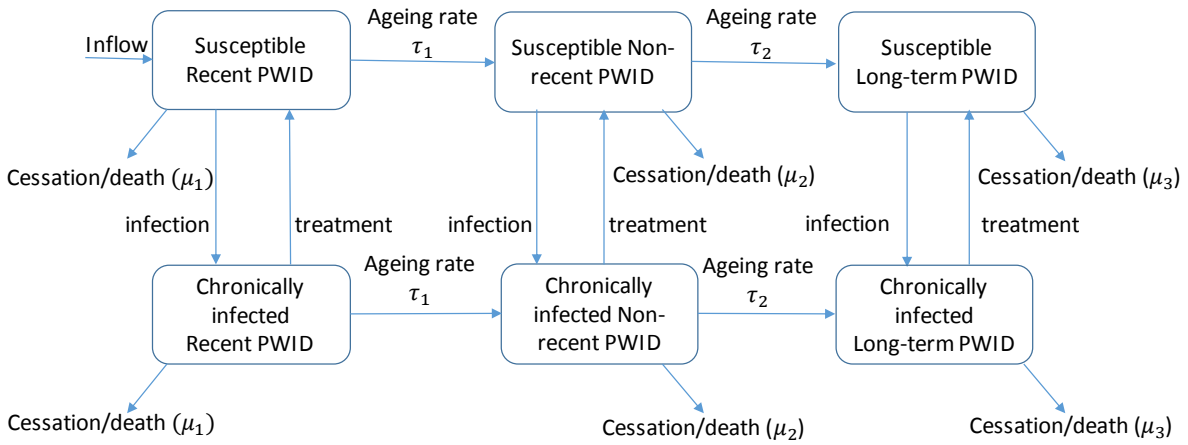
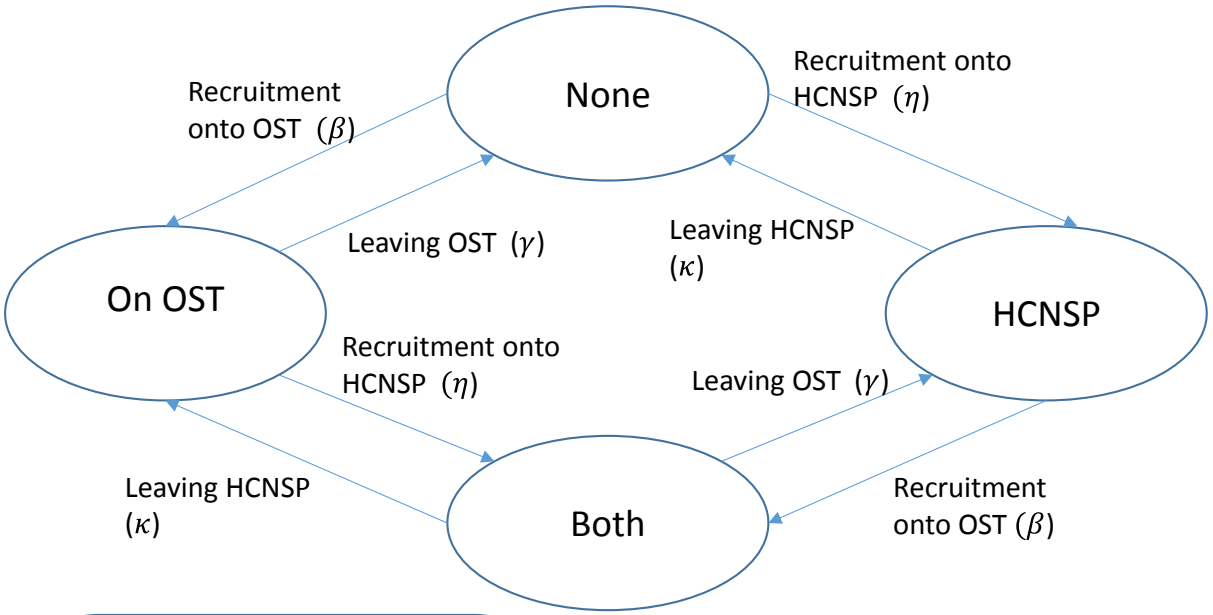
Figure 1: Schematics of different model components.
1a: Schematic of injecting duration and infection components of model.
Susceptible individuals are free from disease and upon infection move to the chronically infected category. Successfully treated individuals move back into the susceptible category. Injecting duration is modelled as three categories; recently initiated PWID (denoted Recent PWID, <3 years), non-recent PWID (>=3 and <10 years) and long term PWID (>=10 years), with PWID transitioning through these categories at rates τ_i, where $i = 1,2$ for recent and non-recent injectors respectively. Injectors cease injecting (cessation or death) at rate μ_i where $i = 1,2,3$ for recent (<3 years of injecting), non-recent (>=3 years and <10 years) and long-term injectors (>=10 years) respectively.
1b: Schematic of intervention component of model. It is assumed the recruitment rates β and η are independent of the current intervention state. OST, opioid substitution therapy; HCNSP, high coverage needle and syringe provision (defined as at least one clean needle for every injection).
1c: Schematic of disease progression component of the model. Each of the disease states is stratified by injecting duration n, risk category m, OST category i and NSP category j. Progression through the disease states occurs at a rate determined by the current disease state, as are the disease related death rates. Metavir states F0, F1 (mild HCV disease), F2, F3 (moderate HCV disease), compensated cirrhosis (also denoted as metavir state F4), decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplant and post-liver transplant. All states have a cessation rate from injecting and a non-disease related background death rate. Infection can occur between all disease states but not shown for clarity.




None
On OST
HCNSP
Both
Recruitment onto OST (β)
Recruitment onto HCNSP (η)
Leaving OST (γ)
Leaving HCNSP (κ)
Recruitment onto HCNSP (η)
Leaving HCNSP (κ)
Leaving OST (γ)
Recruitment onto OST (β)

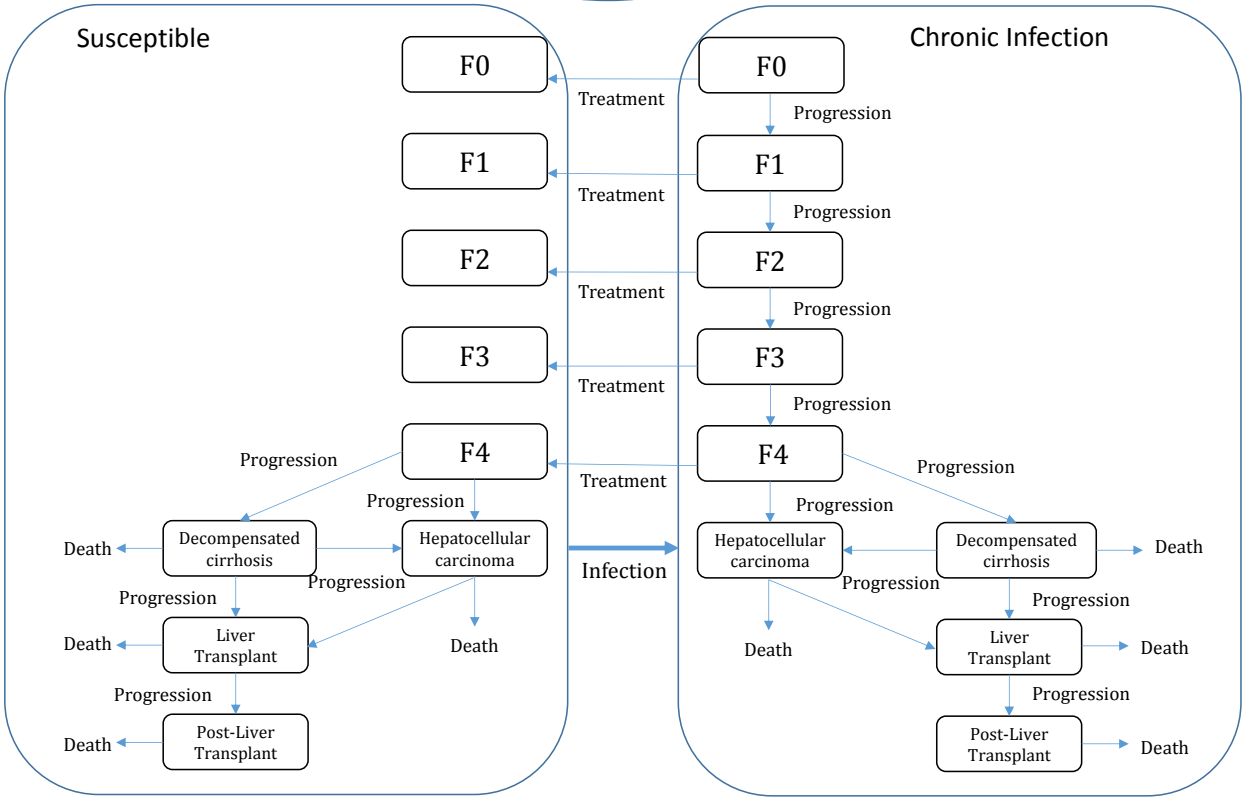
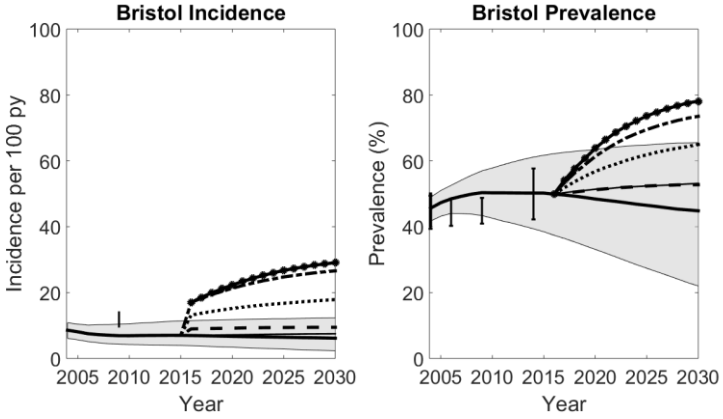
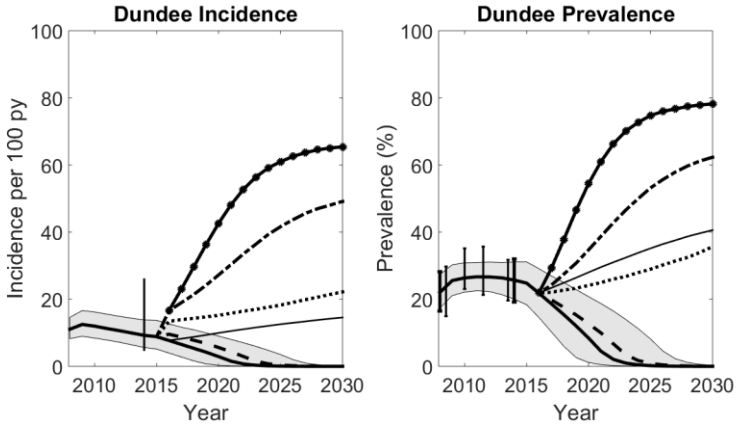

Susceptible
Chronic Infection
F0
F1
F2
F3
F4
Treatment
Progression
Infection
Decompensated cirrhosis
Hepatocellular carcinoma
Liver Transplant
Post-Liver Transplant
Death

Figure 2 Impact of each intervention scenario on HCV incidence and prevalence in Bristol (2a and 2b), Walsall (2c and 2d) and Dundee (2e and 2f). Thick solid line is median baseline scenario, with shaded region the 95% credible intervals. The black points with thin whiskers are the data points (with 95% CrI) that were not fit to, whereas the black points with thick whiskers are the data points used for model calibration.

2a and 2b: Bristol Incidence and prevalence



2c and 2d: Dundee Incidence and prevalence



2e and 2f: Walsall Incidence and prevalence

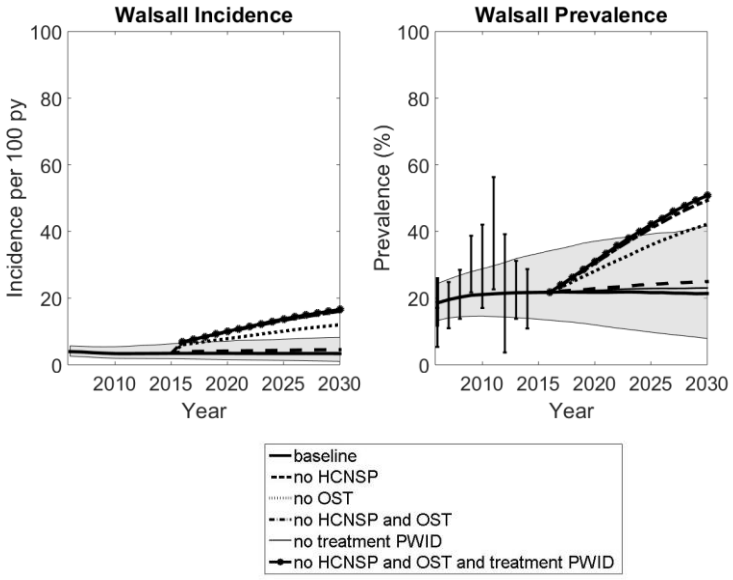


Figure 3: Relative increase in new HCV infections (2016-2030) resulting from removing existing coverage levels of NSP, OST, both NSP and OST, HCV treatment of PWID or all interventions in each city. The box-plots signify the uncertainty (middle line is the median, the limits of the box are 25% and 75% percentiles and the whiskers 2.5% and 97.5% percentiles).

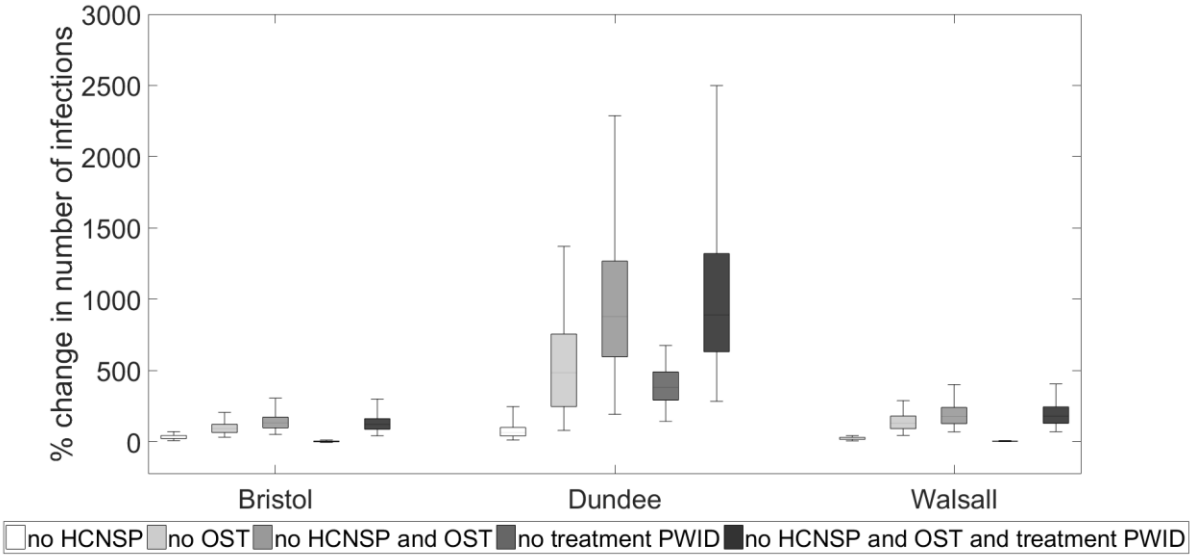


Figure 4: Required annual number of HCV treatments per 1000 PWID needed to reduce incidence by 90%, with or without HCNSP and OST scaling up to 80% coverage. The box-plots signify the uncertainty in the model projections (middle line is the median, the limits of the box are 25% and 75% percentiles and the whiskers 2.5% and 97.5% percentiles). The dashed boxes show the uncertainty range in the current treatment rate per 1000 PWID in each setting.

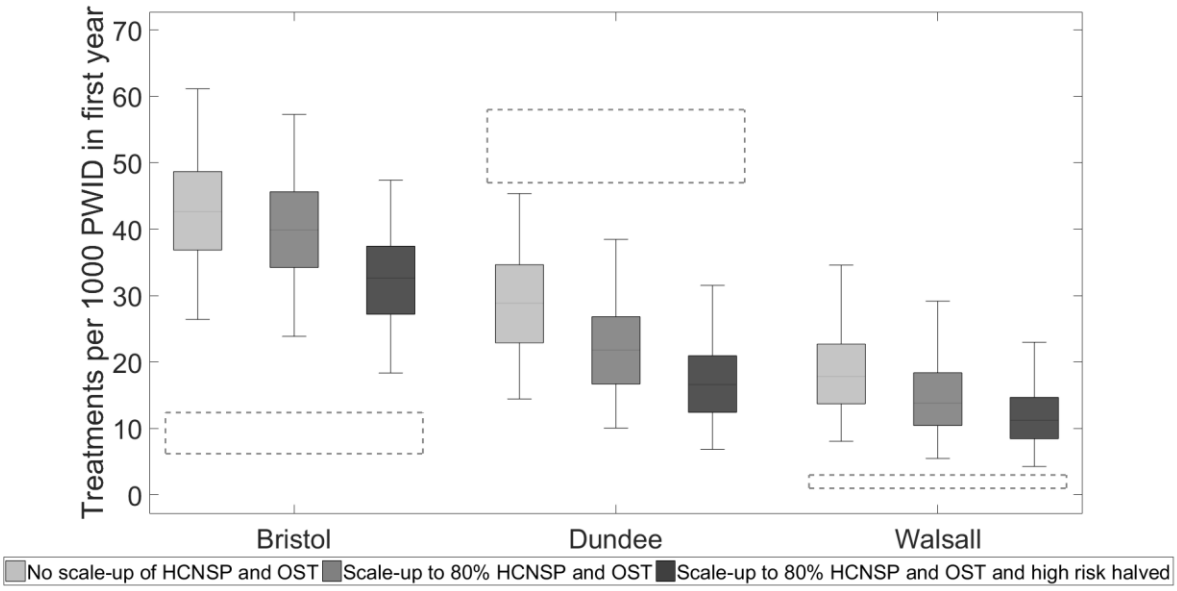


Table 1 Model Parameters

Parameters	Symbol	Value/Range	Reference
Epidemiological and Demographic parameters			
Number of new injectors per year	θ	Fitted to obtain population sizes	Bristol (39, 41), Walsall (41) and unpublished estimates, Dundee (42). See Table S2 and supporting information
Combined mortality and injecting cessation rates per year	μ_i	Fitted to obtain injecting duration profiles for each setting	Lower bounds of 0.004 and 0.008 chosen to ensure leaving rate greater than the death rate (38, 60). See Table S2 and supporting information
Infection rate per year	π	Fitted to obtain HCV prevalence for each setting	See Table S2 and supporting information
Proportion of new infections which spontaneously clear	δ	Sampled from uniform distribution (0.22-0.29)	(27)
Annual leaving rate from high to low risk behaviour	ζ	Sampled range (0.6761-1.617)	Data from cohort study (24) found 78/145 injectors no longer homeless after 8 months. Transition probability sampled from beta distribution ($\alpha = 78$, $\beta = 67$) and converted to yearly rate
Annual recruitment rate from low risk to high risk behaviour	σ	Fitted to obtain required high risk proportions in each setting	See Table S2 and supporting information
Intervention Related parameters			
Annual OST leaving rate	γ	1-3	Duration on OST was 8 months (4-12 months) in cohort of PWID in UK (60)
Annual HCNSP leaving rate	κ	0.37-0.77	Welsh cohort study 61% PWID still HCNSP after 1 year, so estimated duration on HCNSP as 1.3-2.7 years. (61)
Annual recruitment rate into OST	β	Fitted to obtain required OST coverage proportions in each setting	See Table S2 and supporting information
Annual recruitment rate onto HCNSP	η	Fitted to obtain required high NSP coverage proportions in each setting	See Table S2 and supporting information
Proportion of treatments achieving SVR prior to 2015	α	Sampled from uniform distribution (0.40-0.67)	Weighted mean of pooled intention to treat SVR for genotypes 1 and 2/3 taken from UK treatment data for PWID (34)
Proportion of treatments achieving SVR post 2015	α	Sampled from uniform distribution (0.86-0.92)	(36) - Weighted mean of SVR for genotype 1 (90%) and genotypes 2/3 (82-93%) from (35).
Number of PWID treated per year	Φ	Bristol – 18 (2009 onwards) Dundee – 34 (2009 to 2015), and then 40 (2015 onwards) Walsall – 2 (2009 onwards)	Number of HCV treatments in 2011. Assumed treatment of PWID commenced in 2009(34). More recent estimate for Dundee (personal communication John Dillon). Walsall assumed same rate as Bristol.
Relative Transmission Risk parameters			
Risk associated with being on OST only	Γ	0.41(0.22-0.75) sampled from Lognormal distribution	Odds ratio and 95% CI from pooled analysis (25)
Risk associated with being on HCNSP only	Π	0.59(0.36-0.96) sampled from Lognormal distribution	Odds ratio and 95% CI from pooled analysis (25)

Risk associated with being on both OST and HCNSP	$\Gamma \times \Pi$	0.26 (0.09-0.64)	Calculated as product of risk associated with being solely on OST or NSP. Compares well to estimate from systematic review 0.29 (0.13-0.65)(25)
Risk associated with being a recent injector compared to a long-term injector	X_1	1.53(0.93-2.52) sampled from Lognormal distribution	Odds ratio from pooled analysis (25)
Risk associated with being in the high-risk category	Ξ	Scotland: 2.13(1.40-3.24) Bristol and Walsall: 2.75(1.97-4.22). Both sampled from lognormal distribution	Odds ratio from pooled analysis (25). For Scotland, the OR is just for homelessness because there is little crack injection, whereas it is for crack injection or homelessness for Bristol and Walsall

OST=Opioid Substitution Therapy, HCNSP=High Coverage Needle Syringe Provision, SVR= sustained virological response, high-risk defined as crack injecting in last 4 weeks or homeless in the last year.

Table 2 Summary of baseline characteristics of people who inject drugs for each setting (minimum-maximum values)

Baseline Characteristics (2014 unless stated)	**Setting**		
	Bristol	**Dundee**	**Walsall**
Chonic HCV Prevalence	40-50% +	19-32% #	11-26% +
HCV Incidence	10.0 per 100py, 95%CI 9.7-14.0(26) in 2009	14.3 per 100py, 95% CI 4.9-25.9(46)	Not available
Population size (2011)	2025-2564 (62)	675-825 (42)	1296-1623 unpublished estimates
Proportion High risk	80-95%+	26-42% #	50-65% +
Proportion on OST	77-86% (26)	65-79% #	61-82% +
Proportion with HCNSP	38-82% +(39)	34-79% #	21-42% +
Treatments per year	18 (34)	40 (from 2015) (personal communication John Dillon)	2 (assumed similar rate per infected PWID as Bristol)

+ Data extracted from unlinked anonymous monitoring survey (50), # data extracted from Needle Exchange Surveillance Initiative (46). OST=Opioid Substitution Therapy, HCNSP=High Coverage Needle Syringe Provision, high-risk defined as crack injecting in last 4 weeks or homeless in the last year, CI=confidence interval.