Ward, Z; Platt, L; Sweeney, S; Hope, VD; Maher, L; Hutchinson, S; Palmateer, N; Smith, J; Craine, N; Taylor, A; +5 more... Martin, N; Ayres, R; Dillon, J; Hickman, M; Vickerman, P; (2018) Impact of current and scaled-up levels of hepatitis C prevention and treatment interventions for people who inject drugs in three UK settings-what is required to achieve the WHO’s HCV elimination targets? Addiction (Abingdon, England). ISSN 0965-2140 DOI: https://doi.org/10.1111/add.14217

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Supplementary Material

Model equations

\[ S_{i,j,k}^{n,m} \] and \[ C_{i,j,k}^{n,m} \] are the number of susceptible and chronically infected individuals in the model, where \( i = 0,1 \) for off OST and on OST respectively, \( j = 0,1 \) for No HCNSP and HCNSP respectively, \( n = 1,2,3,4 \) for recent (injecting 0-3 years), non-recent (injecting >3 years to 10 years), long-term injectors (>10 years), or ex injector respectively, \( m = 0,1 \) for low and high risk respectively and \( k = 1,2 \ldots 9 \) for the disease progression states chronic infected (F0, F1, F2, F3), compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and post liver transplant, respectively.

The ordinary differential equation model is made up of 450 equations which are described below in sections for different aspects of the model.

Inflow of injectors

The number of new injectors per year is \( \theta \) and the proportion of injectors that are high risk initially is \( \phi \). There are only two compartments in the model (\( S_{0,0,0}^{0,0} \) and \( S_{0,0,0}^{0,1} \)) which allow an inflow of new injectors. These are low and high risk susceptible individuals in the first disease progression category with no intervention: the number of new low risk individuals per year is \( \theta (1 - \phi) \) and the number of new high risk individuals per year is \( \theta \phi \).

Injecting duration progression

These terms in the equations are concerned with movement from one injecting duration category to another as well as PWID related and background mortality. \( ID_{i,j,k}^{n,m} \) denotes the terms in an ordinary differential equation of injecting duration category \( n \). It occurs for all values of \( m, i, j, k \). \( Y_{i,j,k}^{n,m} \) is used to describe one of the compartments in the model, where \( Y = S \) or \( C \) and the subscripts and superscripts are as described previously. The leaving rate, \( \mu_i = \omega_i + \nu_i \), where \( \omega_i \) is the cessation rate and \( \nu_i \) is the death rate for injecting duration \( i \). The progression rates from recent to non-recent injector and non-recent injector to long term injector are \( \tau_1 \) and \( \tau_2 \) respectively.

\[
\begin{pmatrix}
ID_{1,m}^{i,j,k} \\
ID_{2,m}^{i,j,k} \\
ID_{3,m}^{i,j,k}
\end{pmatrix} =
\begin{pmatrix}
-\tau_1 - \mu_1 & 0 & 0 \\
\tau_1 & -\tau_2 - \mu_2 & 0 \\
0 & \tau_2 & -\mu_3
\end{pmatrix}
\begin{pmatrix}
Y_{i,j,k}^{1,m} \\
Y_{i,j,k}^{2,m} \\
Y_{i,j,k}^{3,m}
\end{pmatrix}
\]

When \( n = 4 \) (exinjectors) the terms have a different form:

\[
ID_k^4 = \sum_{i,j,m} \omega_1 Y_{i,j,k}^{1,m} + \sum_{i,j,m} \omega_2 Y_{i,j,k}^{2,m} + \sum_{i,j,k,m} \omega_3 Y_{i,j,k}^{3,m} - \nu_4 Y_k^4
\]

Interventions: OST and HCNSP

These terms in the equations are concerned with movement of injectors from one intervention category to another. \( IT_{i,j,k}^{n,m} \) denotes the terms in the ordinary differential equation of OST intervention category \( i \) and HCNSP intervention category \( j \) For all values of \( m, k, n = 1,2,3 \), for \( n = 4 \) (ex-injectors), these interventions don’t apply. The rate of starting on OST is \( \beta \) and leaving OST is \( \gamma \). The rate of starting on HCNSP is \( \eta \) and leaving HCNSP is \( \kappa \).
\[
\begin{pmatrix}
\gamma^n_m & 0 & 0 \\
\beta - \gamma & 0 & \kappa \\
0 & -\kappa & \gamma - \kappa \\
\end{pmatrix}
\]

High and Low risk

These terms in the equations are concerned with movement of current injectors between low and high risk. \(HR^n_m\) denotes the terms in the ordinary differential equation of risk category \(m\). These terms can be found in the equations for all values of \(i, j, k\) and \(n = 1,2,3\). The rate of entering the high risk category is \(\sigma\) and leaving the high risk category is \(\zeta\).

\[
\begin{pmatrix}
HR^{n,0}_{i,j,k} \\
HR^{n,1}_{i,j,k}
\end{pmatrix}
= \begin{pmatrix} -\sigma & \zeta \\ \sigma & -\zeta \end{pmatrix} 
\begin{pmatrix}
\gamma^n_m & 0 & 0 \\
\beta - \gamma & 0 & \kappa \\
0 & -\kappa & \gamma - \kappa \\
\end{pmatrix}
\]

Disease progression

These terms in the equations are concerned with movement through the disease states. Infection and treatment are described separately. \(D^n_{i,j,k}\) denotes the terms in the ordinary differential equation of disease category \(k\) for susceptible individuals and \(D^n_{i,j,k}\) for infected individuals. These terms can be found in the equations for all values of \(i, j, n\) and \(m\). See Table S1 for the description of these parameters.
Define the matrix
\[
\begin{pmatrix}
C_{i,j,1}^{n,m} \\
C_{i,j,2}^{n,m} \\
C_{i,j,3}^{n,m} \\
C_{i,j,4}^{n,m} \\
C_{i,j,5}^{n,m} \\
C_{i,j,6}^{n,m} \\
C_{i,j,7}^{n,m} \\
C_{i,j,8}^{n,m} \\
C_{i,j,9}^{n,m}
\end{pmatrix}
\]

Infection terms

The forces of infection below are concerned with acquiring infection. The terms are of the form

\[FOI_{i,j,k}^{n,m} = \lambda_{i,j,k}^{n,m} C_{i,j,k}^{n,m}\]

When the ordinary differential equation is for susceptible the FOI term is subtracted and the same term is added to the matching infectious category.

\[
\begin{align*}
\lambda_{0,0,k}^{1,0} &= \pi X_1 (1 - \delta) Y \\
\lambda_{0,0,k}^{2,0} &= \pi X_2 (1 - \delta) Y \\
\lambda_{0,0,k}^{3,0} &= \pi (1 - \delta) Y \\
\lambda_{0,0,k}^{1,1} &= \pi X_1 \Xi (1 - \delta) Y \\
\lambda_{0,0,k}^{2,1} &= \pi X_2 \Xi (1 - \delta) Y \\
\lambda_{9,0,k}^{3,1} &= \pi \Xi (1 - \delta) Y \\
\lambda_{0,1,k}^{n,m} &= \Gamma \lambda_{0,0,k}^{n,m} \\
\lambda_{1,0,k}^{n,m} &= \Pi \lambda_{0,0,k}^{n,m} \\
\lambda_{1,1,k}^{n,m} &= B \lambda_{0,0,k}^{n,m}
\end{align*}
\]

Define the vector

\[C^{n,m} = \sum_{k=1}^{9} (C_{0,0,k}^{n,m} \ C_{0,1,k}^{n,m} \ C_{1,0,k}^{n,m} \ C_{1,1,k}^{n,m})\]
\[ S^{n,m} = \sum_{k=1}^{9} (S_{0,0,k}^{n,m} S_{0,1,k}^{n,m} S_{1,0,k}^{n,m} S_{1,1,k}^{n,m}), \]

\[ I = \begin{pmatrix} 1 \\ \Gamma \\ \Pi \\ B \end{pmatrix}, \]

to give a scalar

\[ \Upsilon = \frac{(X_1(C^{1,0} + \Xi C^{1,1}) + X_2(C^{2,0} + \Xi C^{2,1}) + (C^{3,0} + \Xi C^{3,1}))I}{(X_1(C^{1,0} + S^{1,0} + \Xi(C^{1,1} + S^{1,1})) + X_2(C^{2,0} + S^{2,0} + \Xi(C^{2,1} + S^{2,1})) + (C^{3,0} + S^{3,0} + \Xi(C^{3,1} + S^{3,1}))I} \]

**Treatments**

There are a fixed number of treatments per year, given by \( \Phi \). When the total number of eligible infected individuals \( (C^{treat}) \) in the model is greater than this number, the treatments are allocated proportionately. When the total number of eligible infected individuals is less than the number of possible treatments per year, all are treated. Only the first five disease progression categories are eligible for treatment and will have treatment terms. Therefore, the treatment term, \( T_{i,j,k}^{n,m} \), is a function which depends on the number of people in these categories who are infected. The SVR rate is denoting successful treatment is \( \alpha \). If the ordinary differential equation is for an infected category the treatment term will be subtracted and for a susceptible category the term will be added.

If

\[ \Phi < \sum_{k=1}^{5} \sum_{n=0}^{3} \sum_{m,i,j} C_{i,j,k}^{n,m} = C^{treat}, \]

\[ T_{i,j,k}^{n,m}(C_{i,j,k}^{n,m}) = \frac{\alpha C_{i,j,k}^{n,m}}{C^{treat}}, \]

for \( k = 1,2 \ldots 5, n = 1,2,3 \).

Otherwise

\[ T_{i,j,k}^{n,m}(C_{i,j,k}^{n,m}) = \alpha C_{i,j,k}^{n,m}, \]

for \( k = 1,2 \ldots 5, n = 1,2,3 \).

For ex-injectors treatment is more straightforward with a proportion, \( r \) of the chronically infected and compensated cirrhosis individuals being treated each year.

\[ T_{k}^{4}(C_{k}^{4}) = a r C_{k}^{4}, \]

for \( k = 1,2 \ldots 5 \).

As an example, here is the ordinary differential equation for the susceptible category for the first disease progression category, no interventions, recent injector (0-3 years) and low risk. On the right-hand side in order from left to right there is an inflow term, injecting duration terms, intervention terms, high/low risk terms, disease progression terms, infection term and treatment term.
\[\frac{dS_{0,1}^{1.0}}{dt} = \theta(1 - \phi) + ID_{0,0,1}^{1.0} + JT_{0,0,1}^{1.0} + HR_{0,0,1}^{1.0} + DS_{0,0,1}^{1.0} - \lambda_{0,0,1}^{1.0}S_{0,0,1}^{1.0} + T_{0,0,1}^{1.0}\]

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>symbol</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yearly progression rate from f0 to f1</td>
<td>(\rho_1)</td>
<td>0.0529-0.2095 sampled from normal distribution</td>
<td>PWID specific instantaneous rates from (1)</td>
</tr>
<tr>
<td>Yearly progression rate from f1 to f2</td>
<td>(\rho_2)</td>
<td>0.0216-0.1013 sampled from normal distribution</td>
<td></td>
</tr>
<tr>
<td>Yearly progression rate from f2 to f3</td>
<td>(\rho_3)</td>
<td>0.0450-0.1145 sampled from normal distribution</td>
<td></td>
</tr>
<tr>
<td>Yearly progression rate from f3 to compensated cirrhosis</td>
<td>(\rho_4)</td>
<td>0.0513-0.1838 sampled from normal distribution</td>
<td></td>
</tr>
<tr>
<td>Yearly progression rate from compensated cirrhosis to</td>
<td>(\rho_5)</td>
<td>0.0166-0.0921</td>
<td>Instantaneous rates calculated from sampled beta distributions in (2)</td>
</tr>
<tr>
<td>decompensated cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yearly progression rate from compensated cirrhosis or</td>
<td>(\rho_6)</td>
<td>0.0003-0.0684</td>
<td></td>
</tr>
<tr>
<td>decompensated cirrhosis to hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yearly progression rate from decompensated cirrhosis or</td>
<td>(\rho_7)</td>
<td>0.0062-0.0962</td>
<td></td>
</tr>
<tr>
<td>HCC to liver transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yearly progression rate from liver transplant to post liver</td>
<td>(\rho_8)</td>
<td>1.0423-2.4412</td>
<td></td>
</tr>
<tr>
<td>transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decompensated cirrhosis related death rate per year</td>
<td>(d_6)</td>
<td>0.1063-0.1842</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma related death rate per year</td>
<td>(d_7)</td>
<td>0.3904-0.7697</td>
<td></td>
</tr>
<tr>
<td>Liver transplant related death rate per year</td>
<td>(d_8)</td>
<td>0.0911-0.4348</td>
<td></td>
</tr>
<tr>
<td>Post liver transplant related death rate per year</td>
<td>(d_9)</td>
<td>0.0280-0.1016</td>
<td></td>
</tr>
<tr>
<td>Relative risk for progression rate from compensated</td>
<td>(e_5)</td>
<td>0.07 (95%CI 0.03,0.2)</td>
<td>Sampled from transformed lognormal distribution (3)</td>
</tr>
<tr>
<td>cirrhosis (\rho_5) following SVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk for progression rate from compensated</td>
<td>(e_6)</td>
<td>0.23 (95%CI 0.16,0.35)</td>
<td>Sampled from transformed lognormal distribution (4)</td>
</tr>
<tr>
<td>cirrhosis (\rho_6) following SVR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Model Calibration

The Needle Exchange Surveillance Initiative (NESI) is a voluntary anonymous survey conducted in 2008-2009 (n=83), 2010 (n=143), 2011-2012 (n=99) and 2013-2014 (n=146), with numbers of respondents in the Dundee area in brackets. It is a cross-sectional survey of PWID across Scotland, whereby PWID are recruited at sites providing sterile injecting equipment (and sometimes methadone as well). Individuals provided a blood spot for blood borne virus testing (Antibody and RNA) and undertake a questionnaire on injecting risk behaviours and intervention contact (5). The Unlinked Anonymous Monitoring survey is conducted annually in drug treatment centres and needle and syringe provision sites in England, Wales and Northern Ireland and also collects a blood spot for blood borne virus Antibody testing as well as each PWID undertaking a questionnaire similar to the NESI survey (6). UAM survey numbers in Bristol ranged from 11 in 2010 to 120 in 2004, and in Walsall from 14 in 2012 to 82 in 2007. In Bristol two community surveys were carried out in 2006 (n=299) and 2009 (n=336) using respondent driven sampling aiming to recruit PWID and blood spot samples to detect HCV RNA and antibodies (7).

Model calibration was carried out in three steps with 1000 parameter sets obtained at each step:

1. Population size and injecting duration fitting using a PWID demographic sub-model without infection.
2. HCNSP and OST coverage fitting using a sub-model that includes HCV transmission but no disease progression.
3. HCV prevalence fitting using the full model with disease progression.

Step 1

In Dundee, survey data (6) suggested that the proportion of the PWID population in each injecting duration category was stable from 2008 to 2014, and so we assumed a constant population size estimated from unpublished data from Scotland. In Bristol and Walsall, size estimation data suggests that the PWID population has decreased by between 10% and 30% from 2009 and 2011 (8-11). Concurrently, survey data (6, 7, 12-14) suggests the proportion of PWID injecting for longer than 10 years has increased whilst the proportion injecting for between 3 and 10 years decreased as shown in black error bars on Figure S1 for Bristol and Walsall. There has been little change in the proportion injecting for less than 3 years. It was assumed that these changes were partly due to a decrease in the initiation rate of new injectors and a change in the cessation rates of non-recent and long-term injectors. We allowed for uncertainty around these parameters and estimated them by fitting the model to the population size and injecting duration profile (proportion of PWID in each
injecting duration category) at two points in time for Walsall and Bristol and one time point for Dundee. This fitting was done with a demographic sub-model, which only had three injecting duration categories and no other stratification. We assumed that the PWID population size was at equilibrium initially (before 2004, 2006 and 2008 for Bristol, Walsall and Dundee, respectively). We sampled 1000 values for this ‘stable’ initial population size and the cessation rate from the recent injector category for each setting. For each of these 1000 parameter sets, the wide prior distributions for the cessation rates from non-recent and long-term injectors (see Supplementary Table 2) were then sampled, and for each sample the model was fit to the initial population size by calculating a suitable PWID recruitment rate using the steady state equations for the demographic sub-mode. Parameter sets were retained if the resulting injecting duration profile lay within the ranges suggested from data, otherwise the cessation rates were resampled. We then sampled 1000 estimates for the later population size in 2011 for Bristol and Walsall, as well as new cessation rates for non-recent and long-term injectors, and the PWID recruitment rate was re-calibrated to fit to this new sampled population size for the 2011 data (only Bristol and Walsall). This refitting of the demographic sub-model was done using the Matlab algorithm fzero applied to the analytic solution of the model with initial conditions from the first step of fitting. Parameter sets were retained if the resulting injecting duration profile lay within ranges suggested from data for years 2004 and 2011 for Bristol and 2008 and 2011 for Walsall, otherwise the new cessation rates for this second step were resampled to obtain a fit to each of the first step parameter sets (1000 each for Bristol and Walsall).

**Step 2**

Coverage levels for PWID currently on OST have increased over the last 12 years. In Bristol, the proportion of PWID currently on OST increased from 40% in 2004 (12) up to 81% in 2009 (7). In Walsall, OST coverage increased from 40% in 2006 to 70% in 2009 (6), and in Dundee it increased from 43% in 2008 to 72% in 2014 (5). Conversely, over this same time period, the proportion of PWID with HCNSP coverage remained stable in both Bristol (55%) (6, 7, 12) and Walsall (38%) (6), while it increased over time in Dundee from 41% in 2008 to 60% in 2014 (5). Modelled OST coverage levels for each city were calibrated to this coverage data by varying the recruitment rate onto each intervention. A service provision estimate of HCNSP coverage was calculated for each setting using data on needles distributed from the costings analysis (2014 data), population size (calculated from the model in 2014) and injecting frequency from survey data. Bootstrap samples of the mean injecting frequency were calculated for each setting using UAM (Bristol and Walsall) and NESI (Dundee) data. In addition the mean injecting frequency in Dundee has decreased from 717 injections per year in 2008 to 388 injections per year in 2014. Therefore an estimate of HCNSP coverage was calculated for each time point. The average service provision estimates of HCNSP coverage were 56% and 28% in Bristol and Walsall respectively in 2014 and 27% and 49% in 2008 and 2014 respectively for Dundee (see Supplementary Table 2 for more details). The recruitment rates were estimated using an intervention sub-model that incorporated no onward disease progression as these mechanisms have little effect on the coverage levels obtained. Using the Matlab fitting algorithm lsqnonlin, recruitment rates were found to fit the sub-model to the initial and endpoint coverage of each intervention as shown in Supplementary Table 2, while assuming coverage levels were quasi stable. In the full model, the recruitment
rates for the initial coverage level was first used to obtain initial conditions for the first time point for each city, and then the recruitment rate was gradually varied linearly between the two values to obtain the required increase in coverage for that city.

Survey data suggests that the prevalence of crack injecting and/or homelessness, our markers of high HCV transmission risk, have remained stable in Dundee (33% homeless) and Walsall (52% homeless or crack injection), whereas it has increased in Bristol from 75% in 2004 to 87% in 2014 (homeless or crack injection). We assumed that a proportion of injectors are high-risk when they initiate injecting, which is consistent with available data(15). The leaving rate from these high-risk categories was estimated from a cohort study on homelessness which found that approximately two thirds of homeless PWID are no longer homeless after one year(15). This agrees with unpublished findings from a Welsh cohort study for both crack and homelessness(9, 16). The leaving rate was sampled 1000 times and used for all three setting. The proportion of PWID that are high-risk was also sampled 1000 times for each setting. The recruitment rates were then calculated for each parameter set using the steady state solution of the high/low risk sub-model (two variables).

In Bristol, where the proportion of PWID that are high-risk has increased, we calculated a second recruitment rate for the second time point (2014) using the same method. For Bristol, the recruitment rate was gradually varied linearly to obtain the increase in the proportion of PWID that are high-risk.

Step 3
The last step of the model calibration involved fitting the full model to the HCV prevalence data from each setting (sampled 1000 times from the ranges given in Supplementary Table 2). This incorporated the 1000 parameter sets from the previous model calibration steps, and involved calibrating the model's infection rate using the lsqnonlin function in Matlab. The model was first fit to the initial prevalence estimate (sampled from the ranges given in Supplementary Table 2) in 2004, 2006 and 2008 for Bristol, Walsall and Dundee, respectively (Supplementary Figure 1 and Supplementary Table 2), while assuming the epidemic was in a stable state at that time. For Walsall and Bristol, this one infection rate well captured the subsequent baseline epidemic dynamics (slightly increasing in Bristol and Walsall) and so no change in the infection rate was assumed after that point. The baseline transmission rates in Bristol and Walsall were comparable (0.07-0.21 and 0.09-0.22 respectively), whereas Dundee had a slightly higher baseline transmission risk (0.16-0.39). However, for Dundee we needed to fit a second increased infection rate (0.36-0.94) to capture the increase in HCV prevalence from 2008 to 2014 (using the parameters from the first prevalence fitting step as the initial conditions). This either suggests the epidemic was not stable in 2008 or that there has been a change in the risk profile of PWID in Dundee that is not fully captured by changes in intervention coverage or the prevalence of high-risk behaviours. Supplementary Table 2 and Supplementary Figure 1 show the model parameters that were fitted in the model.

Table S2  Summary of data collated for each setting for model calibration
<table>
<thead>
<tr>
<th>Relevant parameter</th>
<th>Bristol</th>
<th>Dundee</th>
<th>Walsall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current PWID population size</td>
<td>2004: sampled 111-125% (11) of 2011 value (8).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2011: 2025-2564 adjusted from (6) to include only 60% of people on OST not in contact with other services (6). Sampled Uniformly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant level 675-825 local estimate adjusted from (17) Sampled uniformly</td>
<td></td>
<td>2006: 125%(11) of 2011 value 2011: 1296-1623 estimated from local number on OST and unpublished PWID prevalence estimates for West Midlands. Sampled uniformly</td>
</tr>
<tr>
<td>Injecting duration profile: Proportion of PWID that are recent (R), non-recent (NR), or long-term injectors (LT)</td>
<td>2004: R: 0.04-0.2 NR: 0.25-0.45 LT: 0.4-0.65 (UAM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2014: R: 0.075-0.2 NR: 0.05-0.22 LT: 0.55-0.85 (UAM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant level R: 0.15-0.35 NR: 0.36-0.65 LT: 0.12-0.35 (NESI)</td>
<td></td>
<td>2006: R: 0.1-0.3 NR: 0.45-0.65 LT: 0.2-0.3 2014: R:0.1-0.3 NR: 0.15-0.4 LT: 0.4-0.6 (UAM)</td>
</tr>
<tr>
<td>Chronic HCV Prevalence (75% of HCV Ab prevalence)</td>
<td>Constant level 40-50% (community surveys, UAM) Sampled from truncated Beta(305.25,364.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008: 15-30% (NESI) Sampled from truncated Beta(18.75,64.25) 2014: 19-32% adjusted from (NESI) Sampled from truncated Beta(43.45,125.55)*</td>
<td></td>
<td>2006: 11-26% (UAM) Sampled from truncated Beta(30.75,132.25) 2014: 15-39% (no fitting required)</td>
</tr>
</tbody>
</table>

\( \hat{\theta} \), Number of new injectors per year

Value of \( \hat{\theta} \) found using steady state equations of population sub-model for the first time point in all 3 settings. In Bristol and Walsall a second value of \( \hat{\theta} \) is found using Matlab fzero and analytical solution to population sub-model that gives population size required with sampled cessation rates

Death and cessation rates (\( \mu_i \)) per year. Prior distribution for \( \mu_1 \) (0.0351 – 0.1702) calculated from assumption that between 10% and 40% of recent initiates cease injecting within 3 years (18). A large upper bound of 0.4 was assumed for the prior distributions of \( \mu_2 \) and \( \mu_3 \) due to lack of information. Lower bounds of 0.004 and 0.008 were chosen to ensure the leaving rate was greater than the likely death rate (19)

Parameter sets accepted if PWID demographic sub-model fits were within the ranges for each injecting duration

\( \pi \), infection rate used to fit the HCV prevalence estimates

\( \phi \), proportion of injectors initially high risk assumed same as sampled proportion high risk

\( \alpha \), recruitment rate per year from low to high risk behaviour, calculated from sampled leaving rate \( \zeta \) and proportion high risk \( \phi \).
<table>
<thead>
<tr>
<th>Year</th>
<th>Proportion on OST</th>
<th>HCNSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>80-95% (UAM). Sampled uniformly.</td>
<td>—</td>
</tr>
<tr>
<td>2008</td>
<td>76.5-86.3% (community survey, 2009) sampled from truncated Beta(241,55)</td>
<td>—</td>
</tr>
<tr>
<td>2007</td>
<td>76-79% (NESI) sampled from truncted Beta(36,47)</td>
<td>—</td>
</tr>
<tr>
<td>2006</td>
<td>75-80% (UAM) sampled from truncated Beta(32,48)</td>
<td>—</td>
</tr>
<tr>
<td>2005</td>
<td>61-82% (UAM) sampled from truncated Beta(47,18)</td>
<td>—</td>
</tr>
<tr>
<td>2004</td>
<td>33.3-46.7% (9) sampled from truncated Beta(81,121)</td>
<td>—</td>
</tr>
<tr>
<td>2003</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Proportion on OST</th>
<th>HCNSP</th>
</tr>
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<tr>
<td>2014</td>
<td>—</td>
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<td>2006</td>
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<td>2005</td>
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<tr>
<td>2004</td>
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</tbody>
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- *Chronic prevalence was available from the NESI survey for 2014*
Sub-Models used in the fitting procedure

Injecting duration model

A model with 3 injecting duration categories was used to fit the population data and the injecting duration profiles from survey data. Here $S^i$ is the number of susceptible injectors in the $i$ category. The categories are: $r$, recent injector (0-3 years), $n$, non-recent injector (>3-10 years) and $l$, long-term injector (>10 years). The $\mu_i$ and $\tau_i$ are the same as the full model.

\[
\frac{dS^r}{dt} = \theta - (\mu_1 + \tau_1)S^r \\
\frac{dS^n}{dt} = \mu_1 S^r - (\mu_2 + \tau_2)S^n \\
\frac{dS^l}{dt} = \mu_2 S^n - \mu_3 S^l
\]

The steady state solution of this model is given below:

\[
S^r = \frac{\theta}{\mu_1 + \tau_1}, \quad S^n = \frac{\theta \tau_1}{(\mu_1 + \tau_1) (\mu_2 + \tau_2)}, \quad S^l = \frac{\theta \tau_1 \tau_2}{(\mu_3 (\mu_1 + \tau_1) (\mu_2 + \tau_2))}
\]

with total population $N = S^r + S^n + S^l$. 
The analytical solution of this system is

\[
S^r(t) = S^r(0)e^{-(\mu_1+\tau_1)t} + \frac{\theta}{\mu_1+\tau_1} \left(1 - e^{-(\mu_1+\tau_1)t}\right),
\]

\[
S^\nu(t) = \frac{\tau_1 \theta}{(\mu_1+\tau_1)(\mu_2+\tau_2)} + S^\nu(0)e^{-(\mu_2+\tau_2)t} + \frac{\tau_1}{\mu_1+\tau_1-\mu_2-\tau_2} S^r(0)(e^{-(\mu_2+\tau_2)t} - e^{-(\mu_1+\tau_1)t})
\]

\[
+ \frac{\tau_1 \theta}{\mu_1+\tau_1-\mu_2-\tau_2} \frac{e^{-(\mu_1+\tau_1)t}}{\mu_1+\tau_1-\mu_2-\tau_2} / (\mu_1+\tau_1) - e^{-(\mu_2+\tau_2)t} / (\mu_2+\tau_2),
\]

\[
S^i(t) = e^{-\mu_3 t} \left(S^i(0) + \frac{\tau_2}{\mu_2+\tau_2-\mu_3} \left(\frac{\tau_1 S^r(0)}{\mu_1+\tau_1-\mu_3} - \frac{\tau_1 \theta}{\mu_2+\tau_2} + S^\nu(0)\right) + \frac{\tau_1 \theta}{\mu_2+\tau_2-\mu_3} \right)
\]

\[
+ \frac{e^{-(\mu_2+\tau_2)t} \tau_2}{(\mu_2+\tau_2)(\mu_2+\tau_2)} \frac{e^{-(\mu_1+\tau_1)t} \tau_1 \tau_2 \theta}{\mu_3(\mu_4+\tau_1)(\mu_1+\tau_2)} + S^\nu(0)\right).
\]

High risk model
A model with a high risk and low risk only was used to calculate parameter values in the calibration process. The variable \(S^h\) denotes high risk and \(S^l\) denotes low risk.

\[
\frac{dS^h}{dt} = -\zeta S^h + \sigma S^l \\
\frac{dS^l}{dt} = \zeta S^h - \sigma S^l
\]

As this is a closed system we have: \(N - S^h = S^l\), which gives

\[
\frac{dS^h}{dt} = -\zeta S^h + \sigma (N - S^h)
\]

Setting the left hand side to zero and solving gives to obtain the proportion of the total population that are high risk

\[
\Phi = \frac{\sigma}{\sigma + \zeta}
\]

This expression was used to calculate the required value of the recruitment rate \(\sigma\), from the sampled values of the proportion of high risk individuals and the leaving rate \(\zeta\).

Credible Intervals
All impact scenarios were carried out for each of the 1000 parameter sets. Output measures were calculated for each run and the 95% credible interval reported using the 2.5 percentile and 97.5 percentiles of the results.
Figure S1 Graphs showing fitting of the baseline scenarios in each setting. Error bars in black are data points from surveys, error bars in red are the ranges used for model calibration.

Bristol

Dundee

Walsall
**Table S3** Impact of interventions on prevalence, incidence and the number of new infections. Median projections with 95% credibility intervals in brackets.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Prevalence in 2030</th>
<th>Incidence in 2030</th>
<th>Relative increase in number of new infections between 2016 and 2030</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bristol Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No NSP</td>
<td>53% (27-73%)</td>
<td>9 (3-19) per 100py</td>
<td>+32% (7-71%)</td>
</tr>
<tr>
<td>No OST</td>
<td>65% (41-79%)</td>
<td>18 (9-27) per 100py</td>
<td>+92% (31-205%)</td>
</tr>
<tr>
<td>No HCV treatment</td>
<td>74% (52-86%)</td>
<td>27 (13-43) per 100py</td>
<td>+132% (51-306%)</td>
</tr>
<tr>
<td>No HCV treatments + NSP + OST</td>
<td>78% (59-89%)</td>
<td>29 (15-47) per 100py</td>
<td>+121% (42-300%)</td>
</tr>
<tr>
<td><strong>Dundee baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No NSP</td>
<td>0.03% (0-29%)</td>
<td>0.01 (0.003-60) per 100py</td>
<td>+64% (12-247%)</td>
</tr>
<tr>
<td>No OST</td>
<td>35% (0-69%)</td>
<td>22 (0.003-60) per 100py</td>
<td>+483% (79-1371%)</td>
</tr>
<tr>
<td>No HCV treatment</td>
<td>62% (0-76%)</td>
<td>49 (0.02-84) per 100py</td>
<td>+878% (192-2288%)</td>
</tr>
<tr>
<td>No treatments</td>
<td>41% (21-57%)</td>
<td>15 (6-26) per 100py</td>
<td>+381% (143-675%)</td>
</tr>
<tr>
<td>No treatments + NSP + OST</td>
<td>78% (65-86%)</td>
<td>65 (35-103) per 100py</td>
<td>+889% (283-2499%)</td>
</tr>
<tr>
<td><strong>Walsall baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No NSP</td>
<td>25% (9-47%)</td>
<td>5 (1-11) per 100py</td>
<td>+23% (6-43%)</td>
</tr>
<tr>
<td>No OST</td>
<td>42% (20-64%)</td>
<td>12 (5-22) per 100py</td>
<td>+129% (44-288)</td>
</tr>
<tr>
<td>No HCV treatment</td>
<td>49% (25-70%)</td>
<td>16 (6-27) per 100py</td>
<td>+176% (69-401%)</td>
</tr>
<tr>
<td>No treatments</td>
<td>23% (9-43%)</td>
<td>4 (1-9) per 100py</td>
<td>+3% (1-8%)</td>
</tr>
<tr>
<td>No treatments + NSP + OST</td>
<td>51% (27-71%)</td>
<td>17 (7-28) per 100py</td>
<td>+179% (7-405%)</td>
</tr>
</tbody>
</table>
Figure S2 Reduction in incidence by 2030 compared with 2016 through scaling up HCNSP and OST to 80% coverage. 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 S3:** ANCOVA results of the contribution of each model parameter or input to the overall variation in the relative change in number of infections when HCNSP is removed (only those aspects with greater than 3% contribution for any setting are shown).

3a. Bristol

![Graph showing contribution of each model parameter or input to the overall variation in the relative change in number of infections when HCNSP is removed for Bristol.]

3b. Dundee

![Graph showing contribution of each model parameter or input to the overall variation in the relative change in number of infections when HCNSP is removed for Dundee.]

3c. Walsall

![Graph showing contribution of each model parameter or input to the overall variation in the relative change in number of infections when HCNSP is removed for Walsall.]
Figure S4 Impact of important parameters on the percentage increase in infections when NSP is removed in each setting.

a1 Bristol HCNSP Effectiveness

![Bristol HCNSP Effectiveness](image1)

a2 Bristol HCNSP Coverage

![Bristol HCNSP Coverage](image2)

b1 Dundee HCV Prevalence

![Dundee HCV Prevalence](image3)

c1 Walsall HCNSP Effectiveness

![Walsall HCNSP Effectiveness](image4)
Figure S5: ANCOVA results of the contribution of each model parameter or input to the overall variation in the relative change in number of infections when OST is removed (only those aspects with greater than 3% contribution for any setting are shown).

5a Bristol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Proportion of Sum of Squares</th>
</tr>
</thead>
<tbody>
<tr>
<td>OST effectiveness</td>
<td>45.1%</td>
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<tr>
<td>OST leaving rate</td>
<td>21.0%</td>
</tr>
<tr>
<td>HR transmission risk</td>
<td>7.6%</td>
</tr>
<tr>
<td>OST coverage</td>
<td>7.2%</td>
</tr>
<tr>
<td>Population parameters</td>
<td>5.6%</td>
</tr>
<tr>
<td>HCV prevalence</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

5b Dundee
5c Walsall
References
