# Curbing the Hepatitis C Virus Epidemic in Pakistan: The Impact of Scaling Up Treatment and Prevention for Achieving Elimination

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## Supplementary Materials

## 1 Model Structure and Model Equations

Here we describe the model equations shown schematically in Figure S1, which is equivalent to the full model schematic as illustrated in Figure 1. Figure S1 separates out the different strata of the model structure into components, representing separately the baseline epidemic detailing the transmission dynamics of HCV infection (Figure S1(a)), the demographic and behavioural aspects of the model, namely stratification by gender, age, injecting drug use (Figure S1(b)), medical/community risk (Figure S1(c)), and the progression stages of HCV-associated disease (Figure S1(d)).

The full model is a system of 384 non-linear ordinary differential equations. However, it is foundationally based on the baseline epidemic structure described above, which can be represented by a more basic Susceptible-Infected-Treated (S-I-T) model comprised of three non-linear equations, corresponding to respective compartments of individuals who are susceptible, chronically infected, and undergoing treatment. The full model is then obtained by iteration accordingly to incorporate the aforementioned demographic and behavioural characteristics (gender, age structure, and injecting drug use), epidemic characteristics (disease progression stages from no pathology to cirrhosis, decompensation, and HCC), as well as risk characteristics (low or high medical and community risk factors).

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We denote the variables for the general (non-PWID) population in the full model by

$$\begin{aligned} S^{m,c}_{ij,g}(t) &= \text{Susceptible Individuals} \\ I^{m,c}_{iI,g}(t) &= \text{Infected Individuals, Chronic No Disease} \\ C^{m,c}_{iC,g}(t) &= \text{Infected Individuals, Cirrhotic} \\ D^{m,c}_{iD,g}(t) &= \text{Infected Individuals, Decompensated} \\ H^{m,c}_{iH,g}(t) &= \text{Infected Individuals, HCC} \\ T^{m,c}_{ij,g}(t) &= \text{Treatment Individuals} \end{aligned}$$

The variables for the PWID compartments are denoted by

$$\begin{aligned} X^{m,c}_{j,g}(t) &= \text{Susceptible PWID} \\ Y^{m,c}_{I,g}(t) &= \text{Infected PWID, Chronic No Disease} \\ U^{m,c}_{C,g}(t) &= \text{Infected PWID, Cirrhotic} \\ V^{m,c}_{D,g}(t) &= \text{Infected PWID, Decompensated} \\ W^{m,c}_{H,g}(t) &= \text{Infected PWID, HCC} \\ Z^{m,c}_{j,g}(t) &= \text{Treatment PWID} \end{aligned}$$

where the subscripts and superscripts specify the more detailed demographic, epidemic, and risk structures extending from the baseline epidemic model structure as defined in Supplementary Table S1. Note that the infected compartments can be written in more compact notation as

$$\begin{aligned} J^{m,c}_{ij,g}(t) &= \text{Infected Individuals, and} \\ K^{m,c}_{j,g}(t) &= \text{Infected PWID,} \end{aligned}$$

where the progression state variables are denoted accordingly by $J = I, C, D, H$ and $K = Y, U, V, W$ for each disease progression index $j = I, C, D, H$.

Table S1: Definition of indices that characterise the full set of model equations.

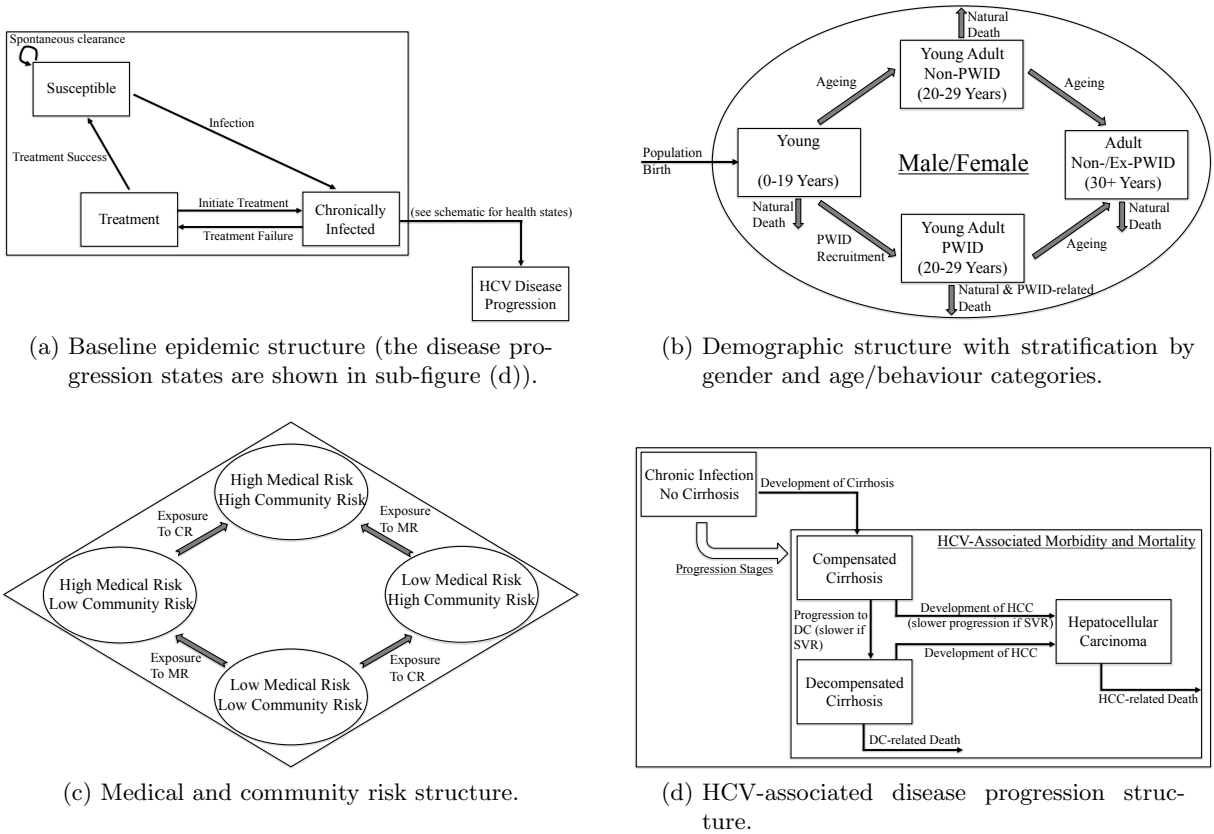
| Indexed Structure | Index | Index Values | Meaning |
|---|---|---|---|
| Gender | $g$ | $1, 2$ | Male ($g = 1$) |
| | | | Female ($g = 2$) |
| Age/Behaviour | $i$ | $1, 2, 3$, PWID | Young ($i = 1$) |
| | | | Young Adult Non-PWID ($i = 2$) |
| | | | Young Adult PWID ($i = \text{PWID}$) |
| | | | Adult Ex-/Non-PWID ($i = 3$) |
| Epidemic/Progression | $j$ | $I, C, D, H$ | Chronic No Disease ($j = I, Y$) |
| | | PWID: $Y, U, V, W$ | Cirrhotic ($j = C, U$) |
| | | | Decompensated ($j = D, V$) |
| | | | Hepatocellular Carcinoma ($j = H, W$) |
| Medical Risk | $m$ | $0, 1$ | Low Medical Risk ($m = 0$) |
| | | | High Medical Risk ($m = 1$) |
| Community Risk | $c$ | $0, 1$ | Low Community Risk ($c = 0$) |
| | | | High Community Risk ($c = 1$) |

Note: The subscripts $i = 1, 2, 3$ for the age structure refer to the Young, Young Adult, and Adult populations, whereas the subscripts $j = I, C, D, H$ refer to the progression states, namely, non-cirrhotic, cirrhotic, decompensated, and HCC, respectively, for the general non-PWID compartments. The corresponding compartments in the Young Adult PWID population are denoted using a different notation as described above, namely, $i = \text{PWID}$ and $j = Y, U, V, W$.

Define each sub-population according to gender and medical/community risk for each age/behaviour category as follows:

$$\mathcal{N}_{i,g}^{m,c} = \begin{cases} \sum\limits_{j,J\in\{I,C,D,H\}} \left(S_{ij,g}^{m,c} + J_{ij,g}^{m,c} + T_{ij,g}^{m,c}\right), & \text{for } i = 1,2,3 \\ \sum\limits_{\substack{j\in\{I,C,D,H\} \\ K\in\{Y,U,V,W\}}} \left(X_{j,g}^{m,c} + K_{j,g}^{m,c} + Z_{j,g}^{m,c}\right), & \text{for } i = \text{PWID} \end{cases}$$

A detailed description of the model structure and formulation of the model equations is presented below with respect to the different structural characteristics (shown graphically in Figure S1), specifically, (i) baseline epidemic structure, (ii) demographic structure, (iii) risk structure, and (iv) disease progression structure. For clarity, we then list the equations explicitly for each age/behaviour class and epidemic/progression stage at the end of this section. These equations are then iterated over the four medical/community risk stages, $m, c \in \{0, 1\}$, as well as for each gender.




(a) Baseline epidemic structure (the disease progression states are shown in sub-figure (d)).

(b) Demographic structure with stratification by gender and age/behaviour categories.

(c) Medical and community risk structure.

(d) HCV-associated disease progression structure.

Figure S1: HCV model structure components. The model is stratified by infection state including progression, age/behaviour, medical and community risk, and gender.

## 1.1 Baseline Epidemic Structure

The baseline epidemic structure of the model distinguishes individuals that are susceptible to HCV infection, chronically infected, or undergoing treatment, resulting in a Susceptible-Infected-Treated ($S - I - T$) model, which is then iterated over the various demographic, risk, and disease progression strata (detailed in the subsequent sections). The equations for the

baseline epidemic structure are as follows (refer to Figure S1(a)):

$$\begin{aligned}
\frac{\mathrm{d}S^{m,c}_{ij,g}}{\mathrm{d}t} &= -(1-\delta)\lambda^{m,c}_{i,g}S^{m,c}_{ij,g} + \alpha_j\omega_j T^{m,c}_{ij,g} \\
\frac{\mathrm{d}I^{m,c}_{ij,g}}{\mathrm{d}t} &= (1-\delta)\lambda^{m,c}_{i,g}S^{m,c}_{ij,g} + (1-\alpha_j)\omega_j T^{m,c}_{i,g} - \tau_j I^{m,c}_{i,g} \\
\frac{\mathrm{d}T^{m,c}_{ij,g}}{\mathrm{d}t} &= \tau_j I^{m,c}_{i,g} - \omega_j T^{m,c}_{i,g},
\end{aligned}$$

where the force of infection, $\lambda^{m,c}_{i,g}$, is described in detail in Subsection 1.5.

## 1.2 Demographic Structure

To describe the demographic structure, we stratify the population by gender and age/behaviour categories. Specifically, for each gender, we divide the general population into three broad age classes: Young (0-19 years of age), Young Adult Non-PWID (20-29 years of age), and Adult Non-/Ex-PWID (30+ years of age, sometimes simply called Adult), with an additional category to represent the pool of PWID. Because the majority of PWID are young adults and the average duration of injecting is in the order of one decade, we assume that all PWID coincide with the Young Adult age range, which we refer to as Young Adult PWID, or simply as PWID. Each of these age/behaviour compartments can be further stratified into categories according to different levels of medical and community transmission risk, namely, those with both low medical and community risk, high medical risk only, high community risk only, or both high medical and community risk.

With respect to the formulation of the mathematical model, we distinguish gender by the subscript $g$, where $g = g_1, g_2$ refer to male and female gender, respectively. Meanwhile, the three broad age classes are distinguished by the subscript $i$, where $i = 1, 2, 3$, refer to the Young, Young Adult Non-PWID, and Adult Non-/Ex-PWID age categories, respectively. The PWID category is considered separately and denoted using different notation.

Newborn individuals enter the model in the Young male or female category according to the birth rate, $\Lambda_g$, and are assumed to be initially susceptible to HCV infection and not have high medical or community risk. Individuals in the Young category transition to the Young Adult category after an average duration of $(1/\eta_1)$ years, with a small proportion, $\phi_g$, initiating injecting drug use at this point (i.e. enter the Young Adult PWID category) and the remainder, $(1-\phi_g)$, entering the Young Adult Non-PWID category. Regardless of injecting drug use status, individuals in the Young Adult strata transition to the Adult category after an average duration of $(1/\eta_2)$ years. We assume cessation of injecting drug use (for those in the PWID compartment) upon entering the Adult age category. Individuals in each age category experience age-specific mortality rates ($\mu_{1,g}$, $\mu_{2,g}$, and $\mu_{3,g}$), with PWID experiencing an additional mortality rate $\mu$ due to drug-related factors such as overdose. Because the demographics of Pakistan indicate an increasing population size, the birth rate $\Lambda_g$ is non-constant such that it replaces all natural deaths and also incorporates an additional population growth rate, as detailed below.

The expression for the population birth rate $\Lambda_g$ takes the following form:

$$\Lambda_g = \Lambda_{1,g} + \Lambda_{2,g},$$

where $\Lambda_{1,g}$ replaces all natural deaths and $\Lambda_{2,g}$ is the growth rate, given below.

$$\begin{aligned}\Lambda_{1,g} &= \mu_{1,g} * \Big(\text{Young}\Big)_g + \mu_{2,g} * \Big(\text{Young Adult Non-PWID}\Big)_g \\ &\quad + (\mu_{2,g} + \mu) * \Big(\text{Young Adult PWID}\Big)_g + \mu_{3,g} * \Big(\text{Adult}\Big)_g \\ \Lambda_{2,g} &= b_g * \Big(\text{Total Population}\Big)_g,\end{aligned}$$

the latter of which results in exponential growth of the total population at a constant rate, $b_g$.

Define the population in each age/behaviour group by gender as:

$$\mathcal{A}_{i,g} = \sum_{m,c\in\{0,1\}} \mathcal{N}_{i,g}^{m,c}, \qquad \text{for each } i \in \{1,2,3\} \cup \{\text{PWID}\}.$$

Denote each $\mathcal{A}_{i,g}$ for $i = 1, 2, \text{PWID}, 3$ to be the Young, Young Adult Non-PWID (denoted by Young Adult in the equations below), Young Adult PWID, and Adult sub-populations, respectively. Then, these age/behaviour categories satisfy the set of equations (refer to Figure S1(b)):

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Young}\Big) &= \Lambda_g - (\eta_1 + \mu_{i,g})\Big(\text{Young}\Big) \\ \frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Young Adult}\Big) &= (1-\phi_g)\eta_1\Big(\text{Young}\Big) - (\eta_2 + \mu_{2,g})\Big(\text{Young Adult}\Big) \\ \frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Young Adult PWID}\Big) &= \phi_g\eta_1\Big(\text{Young}\Big) - (\eta_2 + \mu_{2,g} + \mu)\Big(\text{Young Adult PWID}\Big) \\ \frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Adult}\Big) &= \eta_2\Big[\Big(\text{Young Adult}\Big) + \Big(\text{Young Adult PWID}\Big)\Big] - \mu_{3,g}\Big(\text{Adult}\Big).\end{aligned}$$

### 1.3 Risk Structure

The population is further stratified with respect to low and high medical/community risk categories. Risk structure is distinguished by the superscripts $m$ and $c$ for medical and community risk, respectively, where $m, c = 0$ correspond to low medical/community risk and $m, c = 1$ correspond to high medical/community risk. Individuals in a low medical risk stage enter a high medical risk stage at a gender- and age-related rate $\nu_{i,g}$; meanwhile, those in a low community risk stage enter a high community risk stage at a gender- and age-related rate $\kappa_{i,g}$. Thus, at any given time, an individual can be found in one of the following four risk categories: low medical risk & low community risk $\big(\{m,c\} = \{0,0\}\big)$, low medical risk & high community risk $\big(\{m,c\} = \{0,1\}\big)$, high medical risk & low community risk $\big(\{m,c\} = \{1,0\}\big)$, and high medical risk & high community risk $\big(\{m,c\} = \{1,1\}\big)$.

Individuals in any age category can also transition at age and gender specific rates from the low medical and community risk category to either the high medical risk only or high community risk only categories, from which they can then transition to the combined high medical and community risk category (see Figure S1(c)). We assume that the transition rates of acquiring high medical risk and high community risk are independent and are denoted, respectively, for each age group by $\nu_{i,g}$ and $\kappa_{i,g}$, where $i = 1, 2, 3$, or PWID. These states are associated with elevated transmission risk, namely, $\psi_g$ and $\chi_g$ for the respective relative risks of HCV infection

associated with high medical risk and high community risk factors, with the transitions to these states being one way because the risk factor data used to parameterise the model only considering ever exposure to risk factors. There is an additional relative risk adjustment factor $\rho_g$ when medical and community risks are combined.

Define the populations in each risk category by gender as

$$\mathcal{R}_g^{m,c} = \sum_{i\in\{1,2,3\}\cup\{\text{PWID}\}} \mathcal{N}_{i,g}^{m,c}, \qquad \text{for each } m,c \in \{0,1\}.$$

Denote each $\mathcal{R}_g^{m,c}$ for each pair of $m, c \in \{0,1\}$ using the lexicographical ordering mentioned above so that the risk categories are: (Low MR, Low CR) for $\{m,c\} = \{0,0\}$, (Low MR, High CR) for $\{m,c\} = \{0,1\}$, (High MR, Low CR) for $\{m,c\} = \{1,0\}$, and (High MR, High CR) for $\{m,c\} = \{1,1\}$. Then, the various medical and community risk groups satisfy the set of equations as below (refer to Figure S1(c)):

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Low MR, Low CR}\Big) &= -\sum_{i\in\{1,2,3\}\cup\{\text{PWID}\}} \big(\kappa_{i,g}+\nu_{i,g}\big)\Big(\text{Low MR, Low CR}\Big)\\
\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Low MR, High CR}\Big) &= \sum_{i\in\{1,2,3\}\cup\{\text{PWID}\}} \Big[\kappa_{i,g}\Big(\text{Low MR, Low CR}\Big) - \nu_{i,g}\Big(\text{Low MR, High CR}\Big)\Big]\\
\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{High MR, Low CR}\Big) &= \sum_{i\in\{1,2,3\}\cup\{\text{PWID}\}} \Big[\nu_{i,g}\Big(\text{Low MR, Low CR}\Big) - \kappa_{i,g}\Big(\text{High MR, Low CR}\Big)\Big]\\
\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{High MR, High CR}\Big) &= \sum_{i\in\{1,2,3\}\cup\{\text{PWID}\}} \Big[\nu_{i,g}\Big(\text{Low MR, High CR}\Big) + \kappa_{i,g}\Big(\text{High MR, Low CR}\Big)\Big].
\end{aligned}$$

### 1.4 Modelling Disease Progression Due to Long-Term HCV

To estimate the burden of HCV-related morbidity and mortality, we further expand the epidemic structure of the basic age-structured model to incorporate a progression through four health states, namely, chronic infection without disease, cirrhosis, decompensation, and hepatocellular carcinoma (HCC) (see Figure S1(d)). Each of the health states is stratified using the same $S-I-T$ structure as described in the baseline epidemic structure. We assume that disease progression is uni-directional; that is, there is forward movement, but no backward movement, from an earlier health state into a later one. Moreover, infected individuals who have progressed to a particular disease state (i.e. cirrhotic, decompensated, or HCC) and achieve SVR, either spontaneously or through successful HCV treatment, return to being susceptible, but remain at their present disease state.

Chronic HCV infection leading to the development of cirrhosis occurs at a rate represented in the model by the parameter, $\sigma$. Cirrhosis can then progress to decompensation at a rate, $\gamma$, and to HCC at a rate, $\xi$. Resolution of HCV infection at the cirrhotic stage (i.e. SVR) is associated with slower progression either to decompensation or HCC, with a decreased relative risk of $\epsilon_{CD}$ for the former and $\epsilon_{CH}$ for the latter. Meanwhile, decompensation can also progress to HCC; however, at this disease state, SVR is not assumed to slow down progression to HCC, i.e. $\epsilon_{DH} = 1$. Clinical evidence presented in a systematic review of the natural history of HCV indicates a link between advanced disease progression and increased mortality.[43] To account for

this in the model, we assume additional mortality due to decompensation at a rate, $\mu_4$, and due to HCC at a rate, $\mu_5$.

For each $j \in \{I, C, D, H\}$, define the sub-population in each HCV disease progression state as

$$\mathcal{P}_j = \sum_{\substack{m,c\in\{0,1\}\\ g\in\{g_1,g_2\}}} \left[ \left[ \sum_{i\in\{1,2,3\}} \left( S_{ij,g}^{m,c} + J_{ij,g}^{m,c} + T_{ij,g}^{m,c} \right) \right] + \left( X_{j,g}^{m,c} + K_{j,g}^{m,c} + Z_{j,g}^{m,c} \right) \right],$$

where $J \in \{I, C, D, H\}$ and $K \in \{Y, U, V, W\}$.

Denote $P_j$ for $j \in \{I, C, D, H\}$ to be individuals with no cirrhosis, compensated cirrhosis, decompensation, and HCC, respectively. Then, disease progression follows the set of equations below (refer to Figure S1(d)):

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Non-Cirrhotic}\Big) &= -\sigma\Big(\text{Non-Cirrhotic Infected}\Big) \\
\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Cirrhotic}\Big) &= \sigma\Big(\text{Non-Cirrhotic Infected}\Big) - \Big[\hat{\epsilon}_{CD}\gamma + \hat{\epsilon}_{CH}\xi_{CH}\Big]\Big(\text{Cirrhotic}\Big) \\
\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{Decompensated}\Big) &= \hat{\epsilon}_{CD}\gamma\Big(\text{Cirrhotic}\Big) - \Big[\hat{\epsilon}_{DH}\xi_{DH} + \mu_4\Big]\Big(\text{Decompensated}\Big) \\
\frac{\mathrm{d}}{\mathrm{d}t}\Big(\text{HCC}\Big) &= \Big[\hat{\epsilon}_{CH}\xi_{CH}\Big(\text{Cirrhotic}\Big) + \hat{\epsilon}_{DH}\xi_{DH}\Big(\text{Decompensated}\Big)\Big] - \mu_5\Big(\text{HCC}\Big),
\end{aligned}$$

where for $k \in \{CD, CH, DH\}$,

$$\hat{\epsilon}_k = \begin{cases} \epsilon_k, & \text{if SVR,} \\ 1, & \text{if infected.} \end{cases}$$

### 1.5 The Force of Infection and Incorporating High Transmission Risk Factors

The force of infection (FOI), $\lambda_{i,g}^{m,c}$, describes the rate of HCV transmission and is weighted accordingly to account for factors that can influence this transmission rate, such as age/behaviour as well as differential degrees of medical and community risk exposures. The force of infection specifically associated with HCV transmission due to injecting drug use among PWID is denoted by $\pi_{Y,g}^{i,j}$.

We represent the following details in the force of infection:

(i) First, there is a baseline force of infection affecting each age group, which is characterised by an age-specific HCV transmission coefficient $\beta_i$;

(ii) Second, PWID are assumed to have an additional force of infection with HCV transmission coefficient $\theta$ associated with injecting drug use;

(iii) Third, within each gender, the total and infected populations are weighted by relative risk ratios arising from high medical risk factors ($\psi_g$) and those associated with high community risk factors ($\chi_g$). There is an additional scaling for the section of the population exposed to combined high medical and community risk factors ($\rho_g$);

(iv) Fourth, mixing between the two genders differs from mixing within each gender in that only high medical risk is assumed to affect the force of infection across both genders, whereas high community risk in one gender is assumed not to influence the force of infection of the opposite gender. In other words, medical risk factors that have an increased relative risk of HCV transmission are shared between genders, but community risk factors are not. This is a plausible assumption based on the results of a multivariate statistical analysis that we have performed on the 2007 national survey data,[46] which suggests that high medical risk factors did not differ by gender, for instance, history of blood transfusions, surgery, or haemodialysis, whereas high community risk factors tended to be gender-specific behaviours such as barbering for males and ear/nose piercings for females (refer to Subsection 3.6 below for further details).

(v) Fifth, we assume that chronically infected individuals who are undergoing treatment do not transmit infection. This assumption is plausible because of the way that DAAs target key points in the HCV life cycle, which can disrupt viral replication and viral assembly.[12] In other words, patients on treatment are assumed to be infected, but not infectious.

Define the various populations weighted by high medical and community risks as follows.

Non-weighted for each gender

$$\text{Tot}_g^{m,c} = \mathcal{R}_g^{m,c},$$

$$\text{Tot Inf}_g^{m,c} = \sum_{\substack{j,J\in\{I,C,D,H\}\\ K\in\{Y,U,V,W\}}} \left[ \left( \sum_{i\in\{1,2,3\}} J_{ij,g}^{m,c} \right) + K_{j,g}^{m,c} \right],$$

$$\text{Tot PWID}_g^{m,c} = \mathcal{N}_{\text{PWID},g}^{m,c},$$

$$\text{PWID Inf}_g^{m,c} = \sum_{\substack{j\in\{I,C,D,H\}\\ K\in\{Y,U,V,W\}}} K_{j,g}^{m,c}.$$

Weighted by medical/community risks within each gender

$$\text{Tot}_{\text{wtd,g}} = \mathcal{R}_g^{0,0} + \chi_g \mathcal{R}_g^{0,1} + \psi_g \mathcal{R}_g^{1,0} + \rho_g \mathcal{R}_g^{1,1},$$

$$\text{Tot Inf}_{\text{wtd,g}} = \left[\text{Tot Inf}_g^{0,0}\right] + \chi_g \left[\text{Tot Inf}_g^{0,1}\right] + \psi_g \left[\text{Tot Inf}_g^{1,0}\right] + \rho_g \left[\text{Tot Inf}_g^{1,1}\right],$$

$$\text{Tot PWID}_{\text{wtd,g}} = \left[\text{Tot PWID}_g^{0,0}\right] + \chi_g \left[\text{Tot PWID}_g^{0,1}\right] + \psi_g \left[\text{Tot PWID}_g^{1,0}\right] + \rho_g \left[\text{Tot PWID}_g^{1,1}\right],$$

$$\text{PWID Inf}_{\text{wtd,g}} = \left[\text{PWID Inf}_g^{0,0}\right] + \chi_g \left[\text{PWID Inf}_g^{0,1}\right] + \psi_g \left[\text{PWID Inf}_g^{1,0}\right] + \rho_g \left[\text{PWID Inf}_g^{1,1}\right].$$

Weighted by medical/community risks between genders

$$\text{Tot}_{\text{mx wtd,g}} = \mathcal{R}_g^{0,0} + \mathcal{R}_g^{0,1} + \psi_g \mathcal{R}_g^{1,0} + \psi_g \mathcal{R}_g^{1,1},$$

$$\text{Tot Inf}_{\text{mx wtd,g}} = \Big[\text{Tot Inf}_g^{0,0}\Big] + \Big[\text{Tot Inf}_g^{0,1}\Big] + \psi_g\Big[\text{Tot Inf}_g^{1,0}\Big] + \psi_g\Big[\text{Tot Inf}_g^{1,1}\Big],$$

$$\text{Tot PWID}_{\text{mx wtd,g}} = \Big[\text{Tot PWID}_g^{0,0}\Big] + \Big[\text{Tot PWID}_g^{0,1}\Big] + \psi_g\Big[\text{Tot PWID}_g^{1,0}\Big] + \psi_g\Big[\text{Tot PWID}_g^{1,1}\Big],$$

$$\text{PWID Inf}_{\text{mx wtd,g}} = \Big[\text{PWID Inf}_g^{0,0}\Big] + \Big[\text{PWID Inf}_g^{0,1}\Big] + \psi_g\Big[\text{PWID Inf}_g^{1,0}\Big] + \psi_g\Big[\text{PWID Inf}_g^{1,1}\Big].$$

The forces of infection at baseline are of the following general form:

$$\lambda_{i,g}^{0,0} = \beta_i\left(\frac{\text{Weighted Total Infectious}}{\text{Weighted Total}}\right), \quad \pi_{Y,g}^{0,0} = \theta_Y\left(\frac{\text{Weighted PWID Infectious}}{\text{Weighted Total PWID}}\right).$$

Specifically, for each age/behaviour category, the force of infection at baseline for males and females, respective, is

MALE

$$\lambda_{i,g1}^{0,0} = \beta_i\left(\frac{\text{Tot Inf}_{\text{wtd,g1}} + \text{Tot Inf}_{\text{mx wtd,g2}}}{\text{Tot}_{\text{wtd,g1}} + \text{Tot}_{\text{mx wtd,g2}}}\right), \quad \pi_{Y,g1}^{0,0} = \theta_Y\left(\frac{\text{PWID Inf}_{\text{wtd,g1}} + \text{PWID Inf}_{\text{mx wtd,g2}}}{\text{Tot PWID}_{\text{wtd,g1}} + \text{Tot PWID}_{\text{mx wtd,g2}}}\right).$$

FEMALE

$$\lambda_{i,g2}^{0,0} = \beta_i\left(\frac{\text{Tot Inf}_{\text{mx wtd,g1}} + \text{Tot Inf}_{\text{wtd,g2}}}{\text{Tot}_{\text{mx wtd,g1}} + \text{Tot}_{\text{wtd,g2}}}\right), \quad \pi_{Y,g2}^{0,0} = \theta_Y\left(\frac{\text{PWID Inf}_{\text{mx wtd,g1}} + \text{PWID Inf}_{\text{wtd,g2}}}{\text{Tot PWID}_{\text{mx wtd,g1}} + \text{Tot PWID}_{\text{wtd,g2}}}\right).$$

Note that we have assumed proportional mixing within each gender according to both medical and community risk factors, whereas assortative mixing with respect to community risk factors only is used to describe the transmission risk between genders (medical risk between genders remains proportional).

It is also assumed that relative risks associated with medical and community factors are independent, and there is an additional relative risk associated with having combined high medical and high community risk.

Lastly, the force of infection in each high-risk category is multiplied by its corresponding relative risk. This represents the additional risk of acquiring infection if susceptible within that particular risk category.

$$\begin{aligned}
\lambda_{i,g}^{0,1} &= \chi_g \lambda_{i,g}^{0,0}, & \pi_{Y,g}^{0,1} &= \chi_g \pi_{Y,g}^{0,0} \\
\lambda_{i,g}^{1,0} &= \psi_g \lambda_{i,g}^{0,0}, & \pi_{Y,g}^{1,0} &= \psi_g \pi_{Y,g}^{0,0} \\
\lambda_{i,g}^{1,1} &= \rho_g \lambda_{i,g}^{0,0}, & \pi_{Y,g}^{1,1} &= \rho_g \pi_{Y,g}^{0,0}.
\end{aligned}$$

Note that individuals undergoing treatment are still considered infected; however, they are assumed to not be infectious as the anti-viral drugs significantly lower the viral burden within an individual and its potential to transmit between people.

### 1.6 Calculating HCV Infected Incidence

The HCV infected incidence $\text{Inc}_{\mathcal{G}}$ for a particular subgroup $\mathcal{G}$ of all compartments can be calculated from the force of infection, $\text{FOI}_{\mathcal{G}}$, using the general formula

$$\text{Inc}_{\mathcal{G}} = \frac{\sum_{s\in\mathcal{G}}\Big(\text{FOI}_s \times \text{Susceptible}_s\Big)}{\sum_{s\in\mathcal{G}}\text{Susceptible}_s}.$$

We observe that the numerator is a weighted sum of the FOI and the susceptible individuals in each compartment with the weights depending on the FOI for the particular compartment. Meanwhile, the denominator is the total number of susceptible individuals across all compartments of the subgroup of interest.

For instance, to calculate the HCV incidence for non-PWID versus PWID, denote the two subgroups to be $\mathcal{G}_1$ for Non-PWID and $\mathcal{G}_2$ for PWID, respectively. Then,

$$\text{Inc}_{(\text{Non}-\text{PWID})} = \sum_{\substack{i\in\{1,2,3\}\\ j\in\{I,C,D,H\}\\ m,c\in\{0,1\}\\ g\in\{g_1,g_2\}}} \lambda_{i,g}^{m,c} S_{ij,g}^{m,c} \Bigg/ \sum_{\substack{i\in\{1,2,3\}\\ j\in\{I,C,D,H\}\\ m,c\in\{0,1\}\\ g\in\{g_1,g_2\}}} S_{ij,g}^{m,c}$$

and

$$\text{Inc}_{(\text{PWID})} = \sum_{\substack{j\in\{I,C,D,H\}\\ m,c\in\{0,1\}\\ g\in\{g_1,g_2\}}} \Big(\lambda_{2,g}^{m,c} + \pi_{Y,g}^{m,c}\Big) X_{j,g}^{m,c} \Bigg/ \sum_{\substack{j\in\{I,C,D,H\}\\ m,c\in\{0,1\}\\ g\in\{g_1,g_2\}}} X_{j,g}^{m,c}.$$

The total or overall HCV incidence is calculated by considering $\mathcal{G}$ to emcompass all population subgroups.

$$\text{Total Inc} = \sum_{\substack{j\in\{I,C,D,H\}\\ m,c\in\{0,1\}\\ g\in\{g_1,g_2\}}} \left[\left(\sum_{i\in\{1,2,3\}} \lambda_{i,g}^{m,c} S_{ij,g}^{m,c}\right) + \Big(\lambda_{2,g}^{m,c} + \pi_{Y,g}^{m,c}\Big) X_{j,g}^{m,c}\right] \Bigg/ \sum_{\substack{j\in\{I,C,D,H\}\\ m,c\in\{0,1\}\\ g\in\{g_1,g_2\}}} \left[\left(\sum_{i\in\{1,2,3\}} S_{ij,g}^{m,c}\right) + X_{j,g}^{m,c}\right].$$

# Model Equations for Epidemic and Disease Progression Stages by Age/Behaviour

In the following, we present the model equations describing the epidemic and disease progression aspects according to age/behaviour. These equations are then iterated over each medical/community risk category for each gender. For each of the four age/behaviour categories, the set of equations shown below is an equivalent representation of the combined epidemic and progression aspects of the full model as shown in Figure 1(c) in the main text.

### Young Population:

$$
\begin{aligned}
\frac{\mathrm{d}S^{m,c}_{1I,g}}{\mathrm{d}t} &= \Lambda_g - (1-\delta)\lambda^{m,c}_{1,g} S^{m,c}_{1I,g} + \alpha_1\omega_1 T^{m,c}_{1I,g} - (\eta_1 + \mu_{1,g}) S^{m,c}_{1I,g} \\
\frac{\mathrm{d}I^{m,c}_{1I,g}}{\mathrm{d}t} &= (1-\delta)\lambda^{m,c}_{1,g} S^{m,c}_{1I,g} + (1-\alpha_1)\omega_1 T^{m,c}_{1I,g} - (\sigma_1 + \tau^{m,c}_{1I,g} + \eta_1 + \mu_{1,g}) I^{m,c}_{1I,g} \\
\frac{\mathrm{d}T^{m,c}_{1I,g}}{\mathrm{d}t} &= \tau^{m,c}_{1I,g} I^{m,c}_{1I,g} - (\omega_1 + \eta_1 + \mu_{1,g}) T^{m,c}_{1I,g} \\
\frac{\mathrm{d}S^{m,c}_{1C,g}}{\mathrm{d}t} &= -(1-\delta)\lambda^{m,c}_{1,g} S^{m,c}_{1C,g} + \alpha_1\omega_1 T^{m,c}_{1C,g} - (\epsilon_{CD}\gamma_1 + \epsilon_{CH}\xi + \eta_1 + \mu_{1,g}) S^{m,c}_{1C,g} \\
\frac{\mathrm{d}C^{m,c}_{1C,g}}{\mathrm{d}t} &= \sigma_1 I^{m,c}_{1I,g} + (1-\delta)\lambda^{m,c}_{1,g} S^{m,c}_{1C,g} + (1-\alpha_1)\omega_1 T^{m,c}_{1C,g} - (\gamma_1 + \xi + \tau^{m,c}_{1C,g} + \eta_1 + \mu_{1,g}) C^{m,c}_{1C,g} \\
\frac{\mathrm{d}T^{m,c}_{1C,g}}{\mathrm{d}t} &= \tau^{m,c}_{1C,g} C^{m,c}_{1C,g} - (\gamma_1 + \xi + \omega_1 + \eta_1 + \mu_{1,g}) T^{m,c}_{1C,g} \\
\frac{\mathrm{d}S^{m,c}_{1D,g}}{\mathrm{d}t} &= \epsilon_{CD}\gamma_1 S^{m,c}_{1C,g} - (1-\delta)\lambda^{m,c}_{1,g} S^{m,c}_{1D,g} + \alpha_1\omega_1 T^{m,c}_{1D,g} - (\epsilon_{DH}\xi + \eta_1 + \mu_{1,g} + \mu_4) S^{m,c}_{1D,g} \\
\frac{\mathrm{d}D^{m,c}_{1D,g}}{\mathrm{d}t} &= \gamma_1 C^{m,c}_{1C,g} + (1-\delta)\lambda^{m,c}_{1,g} S^{m,c}_{1D,g} + (1-\alpha_1)\omega_1 T^{m,c}_{1D,g} - (\xi + \tau^{m,c}_{1D,g} + \eta_1 + \mu_{1,g} + \mu_4) D^{m,c}_{1D,g} \\
\frac{\mathrm{d}T^{m,c}_{1D,g}}{\mathrm{d}t} &= \gamma_1 T^{m,c}_{1C,g} + \tau^{m,c}_{1D,g} D^{m,c}_{1D,g} - (\xi + \omega_1 + \eta_1 + \mu_{1,g} + \mu_4) T^{m,c}_{1D,g} \\
\frac{\mathrm{d}S^{m,c}_{1H,g}}{\mathrm{d}t} &= \xi\big(\epsilon_{CH} S^{m,c}_{1C,g} + \epsilon_{DH} S^{m,c}_{1D,g}\big) - (1-\delta)\lambda^{m,c}_{1,g} S^{m,c}_{1H,g} + \alpha_1\omega_1 T^{m,c}_{1H,g} - (\eta_1 + \mu_{1,g} + \mu_5) S^{m,c}_{1H,g} \\
\frac{\mathrm{d}H^{m,c}_{1H,g}}{\mathrm{d}t} &= \xi\big(C^{m,c}_{1C,g} + D^{m,c}_{1D,g}\big) + (1-\delta)\lambda^{m,c}_{1,g} S^{m,c}_{1H,g} + (1-\alpha_1)\omega_1 T^{m,c}_{1H,g} - (\tau^{m,c}_{1H,g} + \eta_1 + \mu_{1,g} + \mu_5) H^{m,c}_{1H,g} \\
\frac{\mathrm{d}T^{m,c}_{1H,g}}{\mathrm{d}t} &= \xi\big(T^{m,c}_{1C,g} + T^{m,c}_{1D,g}\big) + \tau^{m,c}_{1H,g} H^{m,c}_{1H,g} - (\omega_1 + \eta_1 + \mu_{1,g} + \mu_5) T^{m,c}_{1H,g}
\end{aligned}
$$

**Young Adult Non-PWID Population:**

$$
\begin{aligned}
\frac{\mathrm{d}S^{m,c}_{2I,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 S^{m,c}_{1I,g} - (1-\delta)\lambda^{m,c}_{2,g} S^{m,c}_{2I,g} + \alpha_2\omega_2 T^{m,c}_{2I,g} - (\eta_2+\mu_{2,g})S^{m,c}_{2I,g} \\
\frac{\mathrm{d}I^{m,c}_{2I,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 I^{m,c}_{1I,g} + (1-\delta)\lambda^{m,c}_{2,g} S^{m,c}_{2I,g} + (1-\alpha_2)\omega_2 T^{m,c}_{2I,g} - (\sigma_2+\tau^{m,c}_{2I,g}+\eta_2+\mu_{2,g})I^{m,c}_{2I,g} \\
\frac{\mathrm{d}T^{m,c}_{2I,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 T^{m,c}_{1I,g} + \tau^{m,c}_{2I,g} I^{m,c}_{2I,g} - (\omega_2+\eta_2+\mu_{2,g})T^{m,c}_{2I,g} \\
\frac{\mathrm{d}S^{m,c}_{2C,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 S^{m,c}_{1C,g} - (1-\delta)\lambda^{m,c}_{2,g} S^{m,c}_{2C,g} + \alpha_2\omega_2 T^{m,c}_{2C,g} - (\epsilon_{CD}\gamma_2+\epsilon_{CH}\xi+\eta_2+\mu_{2,g})S^{m,c}_{2C,g} \\
\frac{\mathrm{d}C^{m,c}_{2C,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 C^{m,c}_{1C,g} + \sigma_1 I^{m,c}_{2I,g} + (1-\delta)\lambda^{m,c}_{2,g} S^{m,c}_{2C,g} + (1-\alpha_2)\omega_2 T^{m,c}_{2C,g} \\
&\quad -(\gamma_2+\xi+\tau^{m,c}_{2C,g}+\eta_2+\mu_{2,g})C^{m,c}_{2C,g} \\
\frac{\mathrm{d}T^{m,c}_{2C,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 T^{m,c}_{1C,g} + \tau^{m,c}_{2C,g} C^{m,c}_{2C,g} - (\gamma_2+\xi+\omega_2+\eta_2+\mu_{2,g})T^{m,c}_{2C,g} \\
\frac{\mathrm{d}S^{m,c}_{2D,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 S^{m,c}_{1D,g} + \epsilon_{CD}\gamma_2 S^{m,c}_{2C,g} - (1-\delta)\lambda^{m,c}_{2,g} S^{m,c}_{2D,g} + \alpha_2\omega_2 T^{m,c}_{2D,g} \\
&\quad -(\epsilon_{DH}\xi+\eta_2+\mu_{2,g}+\mu_4)S^{m,c}_{2D,g} \\
\frac{\mathrm{d}D^{m,c}_{2D,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 D^{m,c}_{1D,g} + \gamma_2 C^{m,c}_{2C,g} + (1-\delta)\lambda^{m,c}_{2,g} S^{m,c}_{2D,g} + (1-\alpha_2)\omega_2 T^{m,c}_{2D,g} \\
&\quad -(\xi+\tau^{m,c}_{2D,g}+\eta_2+\mu_{2,g}+\mu_4)D^{m,c}_{2D,g} \\
\frac{\mathrm{d}T^{m,c}_{2D,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 T^{m,c}_{1D,g} + \gamma_2 T^{m,c}_{2C,g} + \tau^{m,c}_{2D,g} D^{m,c}_{2D,g} - (\xi+\omega_2+\eta_2+\mu_{2,g}+\mu_4)T^{m,c}_{2D,g} \\
\frac{\mathrm{d}S^{m,c}_{2H,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 S^{m,c}_{1H,g} + \xi\big(\epsilon_{CH}S^{m,c}_{2C,g} + \epsilon_{DH}S^{m,c}_{2D,g}\big) - (1-\delta)\lambda^{m,c}_{2,g} S^{m,c}_{2H,g} + \alpha_2\omega_2 T^{m,c}_{2H,g} \\
&\quad -(\eta_2+\mu_{2,g}+\mu_5)S^{m,c}_{2H,g} \\
\frac{\mathrm{d}H^{m,c}_{2H,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 H^{m,c}_{1H,g} + \xi\big(C^{m,c}_{2C,g} + D^{m,c}_{2D,g}\big) + (1-\delta)\lambda^{m,c}_{2,g} S^{m,c}_{2H,g} + (1-\alpha_2)\omega_2 T^{m,c}_{2H,g} \\
&\quad -(\tau^{m,c}_{2H,g}+\eta_2+\mu_{2,g}+\mu_5)H^{m,c}_{2H,g} \\
\frac{\mathrm{d}T^{m,c}_{2H,g}}{\mathrm{d}t} &= (1-\phi_g)\eta_1 T^{m,c}_{1H,g} + \xi\big(T^{m,c}_{2C,g} + T^{m,c}_{2D,g}\big) + \tau^{m,c}_{2H,g} H^{m,c}_{2H,g} - (\omega_2+\eta_2+\mu_{2,g}+\mu_5)T^{m,c}_{2H,g}
\end{aligned}
$$

**Young Adult PWID Population:**

$$
\begin{aligned}
\frac{\mathrm{d}X_{I,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 S_{1I,g}^{m,c} - (1-\delta)\big(\lambda_{2,g}^{m,c}+\pi_{Y,g}^{m,c}\big)X_{I,g}^{m,c} + \alpha_2\omega_2 Z_{I,g}^{m,c} - (\eta_2+\mu_{2,g}+\mu)X_{I,g}^{m,c}\\
\frac{\mathrm{d}Y_{I,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 I_{1I,g}^{m,c} + (1-\delta)\big(\lambda_{2,g}^{m,c}+\pi_{Y,g}^{m,c}\big)X_{I,g}^{m,c} + (1-\alpha_2)\omega_2 Z_{I,g}^{m,c} - (\sigma_2+\tau_{2I,g}^{m,c}+\eta_2+\mu_{2,g}+\mu)Y_{I,g}^{m,c}\\
\frac{\mathrm{d}Z_{I,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 T_{1I,g}^{m,c} + \tau_{2I,g}^{m,c}Y_{I,g}^{m,c} - (\omega_2+\eta_2+\mu_{2,g}+\mu)Z_{I,g}^{m,c}\\
\frac{\mathrm{d}X_{C,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 S_{1C,g}^{m,c} - (1-\delta)\big(\lambda_{2,g}^{m,c}+\pi_{Y,g}^{m,c}\big)X_{C,g}^{m,c} + \alpha_2\omega_2 Z_{C,g}^{m,c} - (\epsilon_{CD}\gamma_2+\epsilon_{CH}\xi+\eta_2+\mu_{2,g}+\mu)X_{C,g}^{m,c}\\
\frac{\mathrm{d}U_{C,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 C_{1C,g}^{m,c} + \sigma_2 Y_{I,g}^{m,c} + (1-\delta)\big(\lambda_{2,g}^{m,c}+\pi_{Y,g}^{m,c}\big)X_{C,g}^{m,c} + (1-\alpha_2)\omega_2 Z_{C,g}^{m,c}\\
&\quad -(\gamma_2+\xi+\tau_{2C,g}^{m,c}+\eta_2+\mu_{2,g}+\mu)U_{C,g}^{m,c}\\
\frac{\mathrm{d}Z_{C,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 T_{1C,g}^{m,c} + \tau_{2C,g}^{m,c}U_{C,g}^{m,c} - (\gamma_2+\xi+\omega_2+\eta_2+\mu_{2,g}+\mu)Z_{C,g}^{m,c}\\
\frac{\mathrm{d}X_{D,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 S_{1D,g}^{m,c} + \epsilon_{CD}\gamma_2 X_{C,g}^{m,c} - (1-\delta)\big(\lambda_{2,g}^{m,c}+\pi_{Y,g}^{m,c}\big)X_{D,g}^{m,c} + \alpha_2\omega_2 Z_{D,g}^{m,c}\\
&\quad -(\epsilon_{DH}\xi+\eta_2+\mu_{2,g}+\mu+\mu_4)X_{D,g}^{m,c}\\
\frac{\mathrm{d}V_{D,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 D_{1D,g}^{m,c} + \gamma_2 U_{C,g}^{m,c} + (1-\delta)\big(\lambda_{2,g}^{m,c}+\pi_{Y,g}^{m,c}\big)X_{D,g}^{m,c} + (1-\alpha_2)\omega_2 Z_{D,g}^{m,c}\\
&\quad -(\xi+\tau_{2D,g}^{m,c}+\eta_2+\mu_{2,g}+\mu+\mu_4)V_{D,g}^{m,c}\\
\frac{\mathrm{d}Z_{D,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 T_{1D,g}^{m,c} + \gamma_2 Z_{C,g}^{m,c} + \tau_{2D,g}^{m,c}V_{D,g}^{m,c} - (\xi+\omega_2+\eta_2+\mu_{2,g}+\mu+\mu_4)Z_{D,g}^{m,c}\\
\frac{\mathrm{d}X_{H,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 S_{1H,g}^{m,c} + \xi\big(\epsilon_{CH}X_{C,g}^{m,c}+\epsilon_{DH}X_{D,g}^{m,c}\big) - (1-\delta)\big(\lambda_{2,g}^{m,c}+\pi_{Y,g}^{m,c}\big)X_{H,g}^{m,c} + \alpha_2\omega_2 Z_{H,g}^{m,c}\\
&\quad -(\eta_2+\mu_{2,g}+\mu+\mu_5)X_{H,g}^{m,c}\\
\frac{\mathrm{d}W_{H,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 H_{1H,g}^{m,c} + \xi\big(U_{C,g}^{m,c}+V_{D,g}^{m,c}\big) + (1-\delta)\big(\lambda_{2,g}^{m,c}+\pi_{Y,g}^{m,c}\big)X_{H,g}^{m,c} + (1-\alpha_2)\omega_2 Z_{H,g}^{m,c}\\
&\quad -(\tau_{2H,g}^{m,c}+\eta_2+\mu_{2,g}+\mu+\mu_5)W_{H,g}^{m,c}\\
\frac{\mathrm{d}Z_{H,g}^{m,c}}{\mathrm{d}t} &= \phi_g\eta_1 T_{1H,g}^{m,c} + \xi\big(Z_{C,g}^{m,c}+Z_{D,g}^{m,c}\big) + \tau_{2H,g}^{m,c}W_{H,g}^{m,c} - (\omega_2+\eta_2+\mu_{2,g}+\mu+\mu_5)Z_{H,g}^{m,c}
\end{aligned}
$$

**Adult Non-/Ex-IDU Population:**

$$
\begin{aligned}
\frac{\mathrm{d}S^{m,c}_{3I,g}}{\mathrm{d}t} &= \eta_2\big(S^{m,c}_{2I,g}+X^{m,c}_{I,g}\big)-(1-\delta)\lambda^{m,c}_{3,g}S^{m,c}_{3I,g}+\alpha_3\omega_3T^{m,c}_{3I,g}-(\mu_{3,g})S^{m,c}_{3I,g}\\
\frac{\mathrm{d}I^{m,c}_{3I,g}}{\mathrm{d}t} &= \eta_2\big(I^{m,c}_{2I,g}+Y^{m,c}_{I,g}\big)+(1-\delta)\lambda^{m,c}_{3,g}S^{m,c}_{3I,g}+(1-\alpha_3)\omega_3T^{m,c}_{3I,g}-(\sigma_3+\tau^{m,c}_{3I,g}+\mu_{3,g})I^{m,c}_{3I,g}\\
\frac{\mathrm{d}T^{m,c}_{3I,g}}{\mathrm{d}t} &= \eta_2\big(T^{m,c}_{2I,g}+Z^{m,c}_{I,g}\big)+\tau^{m,c}_{3I,g}I^{m,c}_{3I,g}-(\omega_3+\mu_{3,g})T^{m,c}_{3I,g}\\
\frac{\mathrm{d}S^{m,c}_{3C,g}}{\mathrm{d}t} &= \eta_2\big(S^{m,c}_{2C,g}+X^{m,c}_{C,g}\big)-(1-\delta)\lambda^{m,c}_{3,g}S^{m,c}_{3C,g}+\alpha_3\omega_3T^{m,c}_{3C,g}-(\epsilon_{CD}\gamma_3+\epsilon_{CH}\xi+\mu_{3,g})S^{m,c}_{3C,g}\\
\frac{\mathrm{d}C^{m,c}_{3C,g}}{\mathrm{d}t} &= \eta_2\big(C^{m,c}_{2C,g}+U^{m,c}_{C,g}\big)+\sigma_1I^{m,c}_{3I,g}+(1-\delta)\lambda^{m,c}_{3,g}S^{m,c}_{3C,g}+(1-\alpha_3)\omega_3T^{m,c}_{3C,g}\\
&\quad -(\gamma_3+\xi+\tau^{m,c}_{3C,g}+\mu_{3,g})C^{m,c}_{3C,g}\\
\frac{\mathrm{d}T^{m,c}_{3C,g}}{\mathrm{d}t} &= \eta_2\big(T^{m,c}_{2C,g}+Z^{m,c}_{C,g}\big)+\tau^{m,c}_{3C,g}C^{m,c}_{3C,g}-(\gamma_3+\xi+\omega_3+\mu_{3,g})T^{m,c}_{3C,g}\\
\frac{\mathrm{d}S^{m,c}_{3D,g}}{\mathrm{d}t} &= \eta_2\big(S^{m,c}_{2D,g}+X^{m,c}_{D,g}\big)+\epsilon_{CD}\gamma_3S^{m,c}_{3C,g}-(1-\delta)\lambda^{m,c}_{3,g}S^{m,c}_{3D,g}+\alpha_3\omega_3T^{m,c}_{3D,g}-(\epsilon_{DH}\xi+\mu_{3,g}+\mu_4)S^{m,c}_{3D,g}\\
\frac{\mathrm{d}D^{m,c}_{3D,g}}{\mathrm{d}t} &= \eta_2\big(D^{m,c}_{2D,g}+V^{m,c}_{D,g}\big)+\gamma_3C^{m,c}_{3C,g}+(1-\delta)\lambda^{m,c}_{3,g}S^{m,c}_{3D,g}+(1-\alpha_3)\omega_3T^{m,c}_{3D,g}\\
&\quad -(\xi+\tau^{m,c}_{3D,g}+\mu_{3,g}+\mu_4)D^{m,c}_{3D,g}\\
\frac{\mathrm{d}T^{m,c}_{3D,g}}{\mathrm{d}t} &= \eta_2\big(T^{m,c}_{2D,g}+Z^{m,c}_{D,g}\big)+\gamma_3T^{m,c}_{3C,g}+\tau^{m,c}_{3D,g}D^{m,c}_{3D,g}-(\xi+\omega_3+\mu_{3,g}+\mu_4)T^{m,c}_{3D,g}\\
\frac{\mathrm{d}S^{m,c}_{3H,g}}{\mathrm{d}t} &= \eta_2\big(S^{m,c}_{2H,g}+X^{m,c}_{H,g}\big)+\xi\big(\epsilon_{CH}S^{m,c}_{3C,g}+\epsilon_{DH}S^{m,c}_{3D,g}\big)-(1-\delta)\lambda^{m,c}_{3,g}S^{m,c}_{3H,g}+\alpha_3\omega_3T^{m,c}_{3H,g}\\
&\quad -(\mu_{3,g}+\mu_5)S^{m,c}_{3H,g}\\
\frac{\mathrm{d}H^{m,c}_{3H,g}}{\mathrm{d}t} &= \eta_2\big(H^{m,c}_{2H,g}+W^{m,c}_{H,g}\big)+\xi\big(C^{m,c}_{3C,g}+D^{m,c}_{3D,g}\big)+(1-\delta)\lambda^{m,c}_{3,g}S^{m,c}_{3H,g}+(1-\alpha_3)\omega_3T^{m,c}_{3H,g}\\
&\quad -(\tau^{m,c}_{3H,g}+\mu_{3,g}+\mu_5)H^{m,c}_{3H,g}\\
\frac{\mathrm{d}T^{m,c}_{3H,g}}{\mathrm{d}t} &= \eta_2\big(T^{m,c}_{2H,g}+Z^{m,c}_{H,g}\big)+\xi\big(T^{m,c}_{3C,g}+T^{m,c}_{3D,g}\big)+\tau^{m,c}_{3H,g}H^{m,c}_{3H,g}-(\omega_3+\mu_{3,g}+\mu_5)T^{m,c}_{3H,g}
\end{aligned}
$$

# 2 HCV Prevalence Trends in Non-PWID Risk Groups in Pakistan

A review was undertaken to collate data on HCV prevalence trends amongst non-PWID populations in Pakistan. Firstly, a review of all available non-PWID data was undertaken and a call to collaborators for HCV prevalence trends (in antenatal women and blood donors) was made. Secondly, collated data was grouped by geographical location and population sub-group. Only those cities and population sub-groups that had 5 or more HCV prevalence estimates were then grouped and graphed to explore whether there was evidence for any trends in HCV prevalence over the years. These trend analyses were then used in the model analyses to parameterise the degree to which the Pakistan HCV epidemic is increasing or decreasing.

## 2.1 Methods

### Search Strategy

Our review included a broad literature search of published papers relating to Pakistan HCV studies in order to synthesise available HCV prevalence data within non-high risk populations within Pakistan. Searches were carried out using the Pubmed electronic database. We used a combination of focused computerized retrieval and hand searching, where articles deemed relevant were hand searched for additional publications to identify further references of primary studies that may not have been captured by the computerized search.

Searches were performed using a combination of the following keywords "Pakistan and (hcv or hepatitis c)" and a MeSH term search using the following keywords: ("Hepatitis C"[Mesh]) OR "Hepacivirus"[Mesh]) OR "Hepatitis C, Chronic"[Mesh]) OR "Hepatitis C Antibodies"[Mesh]) OR "Hepatitis C Antigens"[Mesh]) AND ( "Pakistan/epidemiology"[Mesh] OR "Pakistan/statistics and numerical data"[Mesh] ).

In addition a combination of the above keywords and Mesh term searches were run :hcv[tiab] OR "hepatitis c"[tiab] OR "Hepatitis C"[Mesh] OR "Hepacivirus"[Mesh] OR "Hepatitis C, Chronic"[Mesh] OR "Hepatitis C Antibodies"[Mesh] OR "Hepatitis C Antigens"[Mesh]) AND (Pakistan[tiab] OR "Pakistan/epidemiology"[Mesh] OR "Pakistan/statistics and numerical data"[Mesh] ) . The last search was performed on the 17th June 2015.

### Selected Studies

Papers included in the review had to meet the following inclusion criteria: studies conducted in Pakistan or using data from Pakistan studies on the prevalence of hepatitis C in non-high risk populations. Articles that were not accessible through the University Of Bristol institutional library service were requested from the Pakistan research group.

## 2.2 Results

170 studies were identified that provided over 253 HCV prevalence estimates, spanning 7 population types in 39 different Pakistan settings. Prevalence data was available for 1994 to 2014 with most data coming from major cities, including Lahore (53 estimates), Karachi (51 estimates) and Islamabad (25 estimates). For each study the following information was recorded: Pakistan province, Pakistan region, study/place site, population type, how populations were sampled, where sampling took place, author/reference, year published, method used (for Ab Hep C test), the type of test sample, population size, average age, antibody HCV prevalence (%) and whether the study had information on HCV risk factors.

### Characteristics of the Studies

Location of included studies by Pakistan province were as follows: Punjab (n=78), Sindh (n=48), North West Frontier province (n=4), Kyber Pakhtunkhwa (n=21), Balochistan (n=6), Gilgit-Baltistan (n=2), Azad Kashmir (n=1) and studies conducted across Pakistan (n=10).

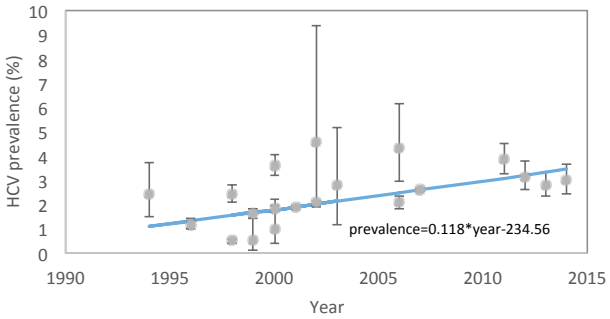
HCV prevalence data was collected on the following population groups: general population (n=44), paediatric populations (n=9), recruitment for employment (n=23), pregnant women (n=21), blood donors (n=64), patients seeking hospital care (not related to HCV) (n=8), and students (n=1). Studies used a number of different methods to test individuals for HCV antibodies and/or HCV RNA. These included rapid immunochromatographic test (ICT), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassays (EIAs), Polymerase chain reaction (PCR), chemiluminescence immunoassay (CIA), gelatin hemagglutination assay (GHA), partcle hemagglutination assay (PHA), recombinant immumoblot assay (RIA) and micro particle immunoabsorbent assay (MEIA).

For documenting prevalence trends over time, sufficient prevalence estimates were only available for blood donors and antenatal women from 5 cities and 1 city, respectively. These included Lahore, Karachi, Peshawar, Islamabad and Rawalpindi for blood donors and Lahore for antenatal women.

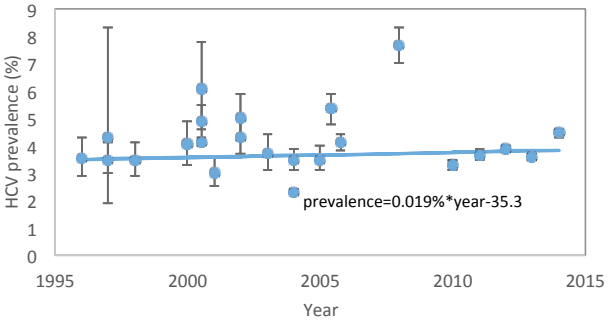
The HCV prevalence trends for blood donors in different cities, with associated 95% confidence intervals, are presented in Figures S2(a)–(e). Although the trends in most cities suggest considerable variation, they consistently suggest a stable or slow upward trend over the last 10 to 20 years with greater consistency generally present in the samples with smaller uncertainty (larger sample sizes). When regression lines were fit to these data for each city (shown in each figure), with each prevalence estimate being weighted by its sample size, they all suggest an upward trend over the last 10 or 20 years, although $p$-values vary. These regression lines suggest that HCV seroprevalence has been increasing by 0.2 to 1.2% every 10 years over this time period. The largest increase was documented in Karachi, which started with one of the lowest HCV seroprevalences at baseline (1% in 1996), and the smallest increase was documented in Lahore and Rawalpindi, which both had a high HCV prevalence at baseline (3–3.5% in 1996).

The HCV seroprevalence trends for antenatal women in Lahore are presented in Figure S2(f). This data also suggests a fairly stable HCV seroprevalence since 2000 with a possible decline in

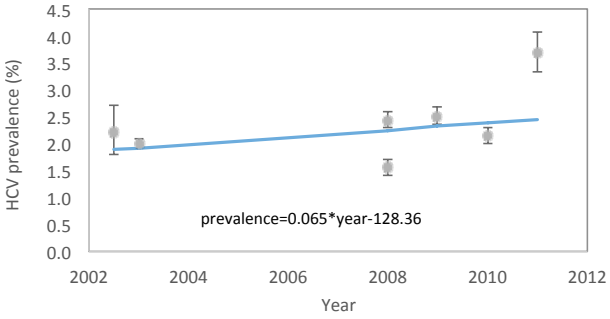
the last 5 years, which results in our regression line suggesting an overall decline over the whole period. However, it is unlikely that the recent decline is real because the change seems too large (from 8.5 to 5% antibody prevalence over 3 years) for the short time period over which it occurred. For this reason, we have focussed on the blood donor data for determining the likely trends in HCV seroprevalence over the recent past.



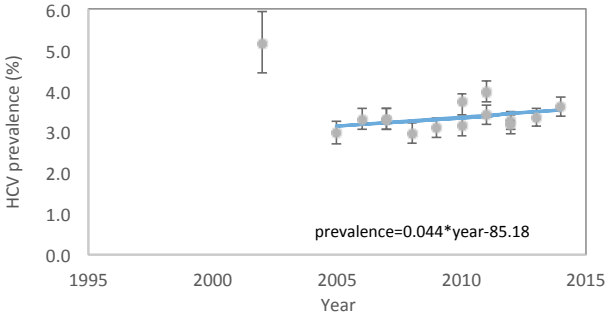

(a) HCV seroprevalence trends for blood donors in Karachi ($p < 0.01$ for regression trend).



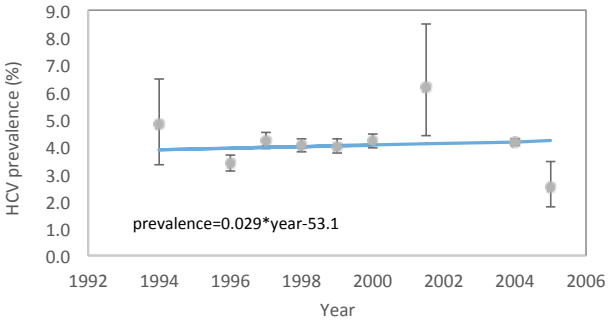

(b) HCV seroprevalence trends for blood donors in Lahore ($p = 0.66$ for regression trend).



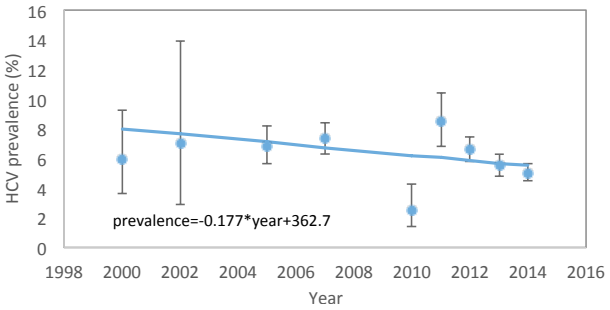

(c) HCV seroprevalence trends for blood donors in Peshawar ($p = 0.18$ for regression trend).




(d) HCV seroprevalence trends for blood donors in Islamabad (*$p = 0.03$ for regression trend).




(e) HCV seroprevalence trends for blood donors in Rawalpindi ($p < 0.32$ for regression trend).




(f) HCV seroprevalence trends for antenatal women in Lahore ($p < 0.01$ for regression trend).

*The first outlier data point was not included in the regression analysis for Islamabad.

Figure S2: HCV antibody prevalence trends for non-PWID high-risk groups, namely, blood donors and antenatal women, across five cities in Pakistan from 1994 to 2014. (a)–(e) Blood donor data. (f) Antenatal data. The uncertainty bounds are the 95% confidence intervals for each estimate, and the regression line weights each prevalence estimate by its respective sample size.

# 3 Methods for Model Uncertainty Analysis: Model Parameterisation and Calibration to Data

The model was parameterised using demographic and HCV prevalence data from a range of sources and calibrated within a probabilistic uncertainty analysis framework to assess the likely uncertainty in our model projections. Estimates for specific model parameters with their uncertainty ranges are shown in Supplementary Table S2, whereas baseline values and uncertainty ranges for the demographic and epidemiological data used to calibrate the model is shown in Supplementary Table S3.

## 3.1 Population Demographics

The total population in 2015 has been estimated to be in the range of 188,925,000 and 199,085,847 (Male: [97,052,000-102,231,058]; Female: [91,873,000-96,854,789])[8,13,49], with respective proportions in each of the following age categories, as reported by the UN Department of Economic and Social Affairs, Population Division: 43.7% (0-19 years of age), 19.3% (20-29 years of age), and 37.0% (30+ years of age).[49] The parameters, $\eta_1$ and $\eta_2$, which describe the ageing rates of the 0-19 and 20-29 age categories, are given values of 1/20 and 1/10, respectively, based on the average duration of individuals within each of these age categories. Baseline values for the mortality rates in the three age categories, represented by the model parameters, $\mu_1$, $\mu_2$, and $\mu_3$ are initially set to $1/(66-10)$ per year, $1/(66-25)$ per year, and $1/(66-48)$ per year, respectively, which are based on a life expectancy at birth estimate of 66 years in Pakistan in the year 2015.[8,49]

The average annual growth rate reflects the rapid growth rate of the Pakistan population and is represented by the parameter $b_g$ in our age-structured mathematical model. Historical demographic data reported from 1960 suggest that the population was growing faster in the past and slowed down around the year 2000.[8,13,49] Current estimates from various sources also appear to indicate that the population growth rate is continuing to decrease.[8,13,44,49,52,53] For instance, demographic data from the UN Department of Economic and Social Affairs, Population Division, suggest the average growth rate between 1960 and 2000 is estimated to be 2.81%, in contrast to the lower estimate of 2.08% between 2000 and 2015.[49] Moreover, the US Census Bureau projects the average growth rate to fall to 1.33% by the year 2030.[52] To better represent this shift in the demographics of the population, for each gender, we calibrate the parameter $b_g$ describing the population growth rate to three different values, one for pre-2000, one for the interim 2000-2015 time period, and one post-2015. To do this, we sample the uncertainty ranges for the total population reported from the demographic data in 1960 and the year 2000. We then calibrate the pre-2000 estimate for the average annual growth rate to the sampled total population in 1960 and 2000. Similarly, the interim 2000-2015 growth rate is calibrated to capture the change in the sampled total population from 2000 to 2015. All total population samples are drawn from their respective uncertainty ranges using a uniform distribution. The post-2015 growth rate is obtained by sampling uniformly from an uncertainty range whose bounds are determined by the minimum and maximum estimated values derived from demographic data for the current growth rate and the projected growth rate up to the year 2030. For each set of demographic data, we back-project the initial population by calibrating it to the sampled

total population and growth rates pre-2000. Lastly, we fit the mortality rates accordingly to the proportions in each age category. We assume that there is negligible uncertainty in these proportions representing the age distribution due to the considerable sample sizes.

### 3.2 Injecting Drug Use

There is a great deal of uncertainty in the proportion of the general population that are PWID. Mathers et al. estimated the prevalence of PWID in 2006 to be 0.14% of persons 15-64 years of age, with low and high estimates of 0.13% and 0.16%.[25] This equates to 0.09% [0.08–0.1%] of the whole population. The HASP IV 2011 report, which mapped PWID in 19 Pakistan cities, reported an overall estimated PWID prevalence of 3.7 per 1000 adult males.[30] Considering that adult males (aged 20 and above) constitute 32.1% of the total population, this yields an estimated PWID prevalence of roughly 0.12% of the total population. Regional PWID estimates display a wide variation between 0.074% of the total population in Rawalpindi to 3.44% of the total population in Faisalabad.[10] The most recent estimate is from the UN Office on Drugs and Crime (UNODC) report on Drug Use in Pakistan 2013, which examined patterns of drug use collated from the National Health Behaviour Survey in 2012 involving 51,453 participants as well as a 23 district study on Problem Drug Users involving 4,533 participants.[51] These results reported a PWID prevalence in 2012 of 0.4% of people aged 15 to 64, with low and high estimates of 0.3% and 0.5%, respectively.[51] As the demographic data indicate that roughly 60% of the population are aged 15 to 64, we can calculate the estimated PWID prevalence in the total population to be 0.24% [0.18–0.30%]. However, in the data there is a disproportionate distribution of PWID by gender, namely, the vast majority of PWID participating in surveys are male. Whether or not this is due to low injecting drug use amongst females or a lack of representation in surveys by female PWID is unclear, however, it is likely that female PWID prevalence is underestimated due to low reporting arising from greater stigma associated with drug use as compared with men.[50,51] The UNODC 2013 report considered PWID prevalence by gender of people aged 15 to 64 to be 0.7% [0.6–0.9%] in males and 0.01% [0.001–0.4%] in females which, when adjusted to the total population, worked out to be roughly 0.42% [0.36–0.54%] of the total male population and 0.006% [0.0006–0.24%] of the total female population in 2012. We used these most recent estimates for the PWID prevalence and sampled from their respective uncertainty ranges assuming a uniform distribution.

Furthermore, injecting drug use is associated with heightened mortality due to drug-related poisonings; however, no studies to date have explored this issue for Pakistan. We estimate the parameter representing the additional drug-related mortality rate, $\mu$, to be 0.0281 per year for the Asian subcontinent based on a systematic review and meta-analysis from 2013, which calculated the crude mortality rates for PWID by region.[26]

Despite making up only a minority of the total population, the subpopulation of young adult PWID exhibits an exceptionally high chronic HCV infected prevalence. For instance, Waheed et al. performed a systematic review and observed an overall chronic HCV infected prevalence in PWID of 42.18% +/- 13.10% (57 +/- 17.7% anti-HCV).[54] Aceijas and Rhodes reported a national chronic HCV infected prevalence estimate of 65.86% (89.0% anti-HCV), alongside a capital city estimate of 57.72–69.56% (78.0–94.0% anti-HCV), and an estimate for other sites

of 55.50–68.82% (78.0–93.0% anti-HCV).[2] Other studies have reported chronic HCV infected prevalence to lie over a broad range from 5.92% to 67.34% (8.0–91.0% anti-HCV).[1] For the uncertainty analysis, we used the national estimate for chronic HCV prevalence amongst PWID in Pakistan obtained from a systematic review by Nelson et al., which reported HCV infected prevalence in 2003-2004 as 62.16% (84.0% anti-HCV), with respective low and high estimates of 55.5% (75.0% anti-HCV) and 68.8% (92.9% anti-HCV).[31] To represent the uncertainty in these estimates, we sampled from these ranges assuming a uniform distribution. This then yielded a range of fitted values for the force of infection (i.e. HCV transmission rate) in the subpopulation of young adult PWID.

### 3.3 Chronic HCV Prevalence in the General Population

We calibrate the model to available data on the HCV epidemic in the general Pakistan population. Estimates for HCV seroprevalence are taken from the 2007 national survey on hepatitis B and C involving 47,043 individuals sampled from 7,000 households across Pakistan.[38] The survey classified subjects in five-year age groups and reported HCV seroprevalence in each of these groups, along with an overall HCV sero-prevalence estimate of 4.8% in the general population.[38] A systematic review from 2006 found that 26% [95%CI 22–29%] of acute infections are spontaneously cleared[28], thus it is assumed that 74% [95%CI 71–78%] of anti-HCV positive individuals have chronic HCV infection (also called viraemic HCV infection), which equates to an overall mean chronic HCV infected prevalence of 3.62% in 2007. From the national survey results, we calculate the chronic HCV infected prevalence across both genders for each of the age categories as defined in the mathematical model and calculate their respective uncertainty ranges as follows: 1.50% [1.34–1.67%] for the 0-19 age category; 3.20% [2.84–3.59%] for the 20-29 age category; and 6.89% [6.50–7.30%] for the 30+ age category. We sample the uncertainty ranges for the chronic HCV infected prevalence within each age category assuming a normal distribution with mean and standard deviation derived from the binomial trials undertaken to estimate the prevalence for the national survey. This allows us to fit a range of values for the force of infection (i.e. HCV transmission rate) in each of the age categories. Moreover, trends in current data on the HCV epidemic indicate an increase in chronic HCV infected prevalence in the uncertainty range of [0.15–0.89%] every 10 years (i.e. corresponding to an increase in HCV sero-prevalence between 0.2% and 1.2% per decade), as estimated from data on the trends in HCV sero-prevalence amongst blood donors in 5 Pakistan cities observed over a 20-year period from 1994 to 2014 (see Section 2 for details). We calibrated the transmission parameters in the model and the approximations for the initial size of the HCV epidemic in Pakistan to capture this increasing chronic infected prevalence trend from 2007 to 2017.

### 3.4 HCV-Associated Disease Progression Including Increased Disease Progression Rates for HCV Genotype 3

Baseline HCV disease progression transition rates were obtained from a meta-analysis and systematic review of fibrosis progression, which estimated annual transition probabilities from F0 to F4 (with respect to the METAVIR scoring system) based on a random effects model.[45] From these stage-specific transition probabilities, we calculated the overall rate from chronic infection

without disease to cirrhosis, along with the corresponding uncertainty distributions. Meanwhile, mortality rates were estimated from the results of a UK-based clinical cohort study that estimated transition probabilities pertaining to mortality due to advanced stage liver disease, where the cohort consisted of around 60% men with 50% HCV genotype 1 infection and most of the remainder being genotypes 2 or 3.[17,43,56] Because data suggests 80% of HCV-infected individuals are genotype 3 in Pakistan[5,16,27], and studies suggest genotype 3 infections are associated with increased disease progression[19,21,33,37], these transition rates were adjusted for the higher proportion of genotype 3 in Pakistan. Specifically, HCV genotype 3 is associated with an increased relative risk of 1.30 [1.22–1.39] for disease progression to compensated or decompensated cirrhosis, and a relative risk of 1.80 [1.60–2.03] for the development of HCC, based on a large study cohort in the U.S.[21]. The uncertainty distributions for the different transition and mortality probabilities were obtained from the literature (as indicated in Supplementary Table S2), which were sampled and then converted to instantaneous rates for parameterisation of the mathematical model.

### 3.5 SVR and Disease Progression

There is evidence that achieving SVR is associated with reduced disease progression from compensated cirrhosis to decompensated cirrhosis or to HCC.[29,53] However, few studies have looked at the effect of SVR on progression from decompensated cirrhosis to HCC. Two studies evaluating the clinical outcomes of IFN-based HCV treatment[18] and DAA treatment[15] did not find an association between development of HCC and SVR status. Due to a lack of evidence, we assume that there is no benefit of SVR with respect to HCC progression for patients with decompensation.

### 3.6 Medical and Community Risk

In addition to age-stratified data on the HCV epidemic, the 2007 national survey collected detailed information on gender-stratified factors related to medical and community behaviours. We have performed a multivariate statistical analysis on the 2007 national survey data and identified group medical and community factors that were associated with HCV seroprevalence.[46] From the statistical analysis, high medical risk factors included: having greater than five therapeutic injections in the last year, history of blood transfusions, surgery, or haemodialysis. Meanwhile, high community risk factors included: barbering (males only), ear/nose piercings (females), tattoo/acupuncture, and sharing smoking equipment. The results from our statistical analysis show an accumulation of both medical risk and community risk with age amongst males and females, and also suggest that medical risks are shared between genders, whereas community risks are predominantly gender-specific, and we fit our model accordingly to take into account these features.

The model was calibrated to the chronic HCV prevalence within each grouped risk category by gender to estimate the gender-specific relative risk for HCV transmission for each risk category, and to the proportion of individuals within each risk category to estimate age and gender-specific one-way recruitment rates. Specifically, the proportions of individuals within each of

the following risk stages, namely, low medical risk & low community risk, low medical risk & high community risk, high medical risk & low community risk, and high medical & high community risk, according to age and gender, are as follows (refer to Supplementary Table S3). For males, (0-19 age category): 75.1% [74.3–75.9%], 5.1 [4.7–5.6%], 17.1% [16.4–17.8%], 2.7% [2.4–3.0%]; (20-29 age category): 39.7% [38.2–41.1%], 29.8% [28.5–31.2%], 15.0% [13.9–16.1%], 15.5% [14.5–16.6%]; (30+ age category): 33.3% [32.3–34.3%], 29.1% [28.1–30.1%], 16.9% [16.1–17.8%], 20.7% [19.8–21.6%]. For females, (0-19 age category): 37.2% [36.3–38.1%], 42.2% [41.3–43.2%], 5.7% [5.3–6.1%], 14.9% [14.2–15.6%]; (20-29 age category): 16.3% [15.2–17.4%], 49.6% [48.1–51.1%], 4.6% [4.0–5.3%], 29.5% [28.2–30.9%]; (30+ age category): 12.1% [11.4–12.9%], 45.1% [44.0–46.3%], 4.9% [4.4–5.4%], 37.9% [36.8–39.0%]. The uncertainty ranges for the medical and community risk groups are very small due to the large sample size, so we assume that there is no uncertainty present in the above proportions. We fit the recruitment rates for high medical risk and high community risk independently for each gender and age category to these proportions.

Next, we calculate from the national survey data the mean and binomial confidence intervals for infected prevalence by gender in each of the respective risk stages as before (i.e. low medical risk & low community risk, low medical risk & high community risk, high medical risk & low community risk, and high medical & high community risk), which yields the following: For males, 2.35% [2.10–2.62%], 6.21% [5.51–6.97%], 2.91% [2.42–3.48%], and 7.39% [6.44–8.45%]; for females, 1.81% [1.48–2.20%], 3.46% [3.11–3.83%], 2.81% [1.94–3.92%], and 5.68% [5.10–6.32%]. Fitting the corresponding model parameters to the risk-stratified HCV infected prevalence data allows us to determine the independent relative risks of acquiring chronic HCV infection associated with high medical and community factors by gender.

### 3.7 Existing and Future Treatment

The public sector has been involved in procuring conventional treatments for HCV using interferon (IFN) or peglyated interferon (Peg-IFN) and ribavirin (RBV) through National and Provincial Hepatitis Control Programmes from 2005 to 2015. Before 2005, we assume no HCV treatment occurred, but then assume a scale up of HCV treatment from 2005 to 2015 with about 23,000 total treatments being undertaken during the six-year period from 2005 to the end of 2010 and about 55,000 annual treatments thereafter.[36] Data from the public sector on historical and existing treatment numbers are shown in Supplementary Table S4. There is no data on the number of treatments provided by the private sector; however, it is estimated that the provision of HCV treatment from the public sector and private sector is split 40%/60%, based on discussions with the Provincial Hepatitis Control Programs.[36] This split represents a conservative estimate of the total number of historical HCV treatments that were provided nationally between 2005-2015, by considering healthcare system profile and usage data which suggest that, for 1994-2014, one-fifth to one-third of healthcare provision was from the public sector, with no discernable change over time.[32,34,35,41] Thus, we multiply the data for public sector treatment numbers 2.5-fold, yielding the total number of treatments procured between 2005 and 2015 when scaled up across both public and private sectors to be 731,408, with roughly 57,500 total treatments given from 2005 to 2010 and 115,000 up to 150,000 annual treatments thereafter. The HCV treatment rate was calibrated to give these annual historical treatment

numbers, with the treatments being assumed to be distributed proportionally to all chronically infected individuals with and without compensated cirrhosis.

Because the dominant HCV genotype in Pakistan is genotype 3, occurring in 80% of HCV infections, we calibrated the model to treatment efficacy for IFN + RBV therapy in such patients. A meta-analysis in 2008 across all relevant studies, not necessarily Pakistan-focussed, reported SVR rates of 68% across HCV genotype 3 patients.[4] The average duration of treatment using these conventional regimens was 24 weeks. Specific to the Pakistani perspective, a review of conventional HCV treatment collated data from numerous in-country studies and found that the reported SVR rates ranged between 50% and 81%.[3,22,39,40,47] We sample the SVR for conventional treatments uniformly between the lower and upper bound estimates.

From 2016 onwards, the treatment recruitment rate in the model is varied to investigate the range of intervention scenarios under consideration and compared with a treatment rate set to zero for a baseline comparison. Treatment with new direct acting antivirals (DAAs) are well-tolerated with a shorter average treatment duration of 12 weeks, and have demonstrated high efficacy in clearing HCV infection, with 90% or over of chronically infected individuals likely to achieve SVR following treatment.[14,20,23,24,55] However, recent studies on DAA treatment efficacy suggest that HCV genotype 3 is difficult to treat using DAAs, with lower SVR rates from about 80% and above for treatment combinations including sofosbuvir (SOF), RBV, and Peg-IFN.[57] Until late 2017, the only approved DAA in Pakistan was SOF, and so our analyses reflect the challenges associated with treating HCV genotype 3 infections using SOF in the Pakistan context, with reported SVR 12 rates of 84% in a Pakistan-specific treatment cohort.[7]

To reflect the uncertainty in the SVR rate for DAA therapy, we sample the model parameter $\alpha$ uniformly between 80% and 95%. We assume that treatment, when specified in the intervention scenarios, is applied to chronically infected individuals with no cirrhosis as well as to cirrhotic individuals, but is not extended to those who have advanced-stage disease, namely, decompensation and HCC.

### 3.8 Model Calibration

To incorporate uncertainty, the parameters and calibration data were sampled 1,000 times from their respective uncertainty distributions as in Supplementary Tables S2 and S3. For each set of sampled parameters and data, unknown model parameters were varied to fit the model to the calibration data using a non-linear least squares algorithm ('LSQNONLIN'). The parameter sets were then validated by comparing the output of the model for each simulation with the 2007 national survey data,[38] and the increasing HCV prevalence trends from blood donor data (refer to Section 2). A total of 672 model simulations failed to fit within the 95% CI of the HCV prevalence data overall and when stratified by medical and community risk factors and were excluded. The remaining ($n = 328$) model fits were used for subsequent analyses. The model was solved numerically using an explicit fourth order Runge-Kutta method in Matlab.[9,42] All model simulations were performed using Matlab Version R2016b, and the linear regression analysis of covariance (ANCOVA) was conducted in Stata Version 14.

Table S2: Model parameters with associated uncertainty ranges. Rates are per year.

| Parameter | Symbol | Baseline Value or Fitted Range [Uncertainty Distribution/Range] | Source |
|---|---|---|---|
| **Demographic Parameters** | | | |
| Average population growth rate per annum$\Delta$ | $b_g$ | Pre-2000: Fitted 2.81% [2.46–3.05%]<br>Interim 2000-2015: Fitted 2.08% [1.43–2.43%]<br>Post-2015: [Uniform 1.33–2.11%] | 8,13,49 |
| Rate of ageing from Young to Young Adult | $\eta_1$ | 1/20 | Based on average duration of 20 years in 0-19 age group |
| Rate of ageing from Young Adult to Adult | $\eta_2$ | 1/10 | Based on average duration of 10 years in 20-29 age group |
| Proportion of Young Adults who initiate injecting drug use | $\phi_g$ | Fitted values: Male: 0.028 [0.023–0.033]<br>Female: 0.008 [0.0004–0.015] | Calibrated to fit PWID proportions as given in Supplementary Table S3, [51] |
| Average mortality rate for each age group | $\mu_{1,g}$<br>$\mu_{2,g}$<br>$\mu_{3,g}$ | 1/56<br>1/41<br>Fitted values: Male: 0.025 [0.021–0.028]<br>Female: 0.022 [0.018–0.025] | Based on a life expectancy at birth estimate of 66 years in 2015 [49], but also adjusted in model calibration |
| Additional drug-related mortality rate | $\mu$ | 0.028 | Based on estimates of drug-related mortality across Asia [26] |
| **Epidemic and Treatment Parameters** | | | |
| HCV transmission rate per susceptible in each age group | $\beta_1$<br>$\beta_2$<br>$\beta_3$ | Fitted values: $\beta_1 = 0.044$ [0.036–0.051]<br>$\beta_2 = 0.058$ [0.034–0.089]<br>$\beta_3 = 0.099$ [0.078–0.12] | Fit to chronic prevalence in each age category in 2007 [38] as given in Supplementary Table S3 |
| Additional HCV transmission rate for injecting drug use | $\theta$ | Fitted values: 0.48 [0.38–0.57] | Fit to data on chronic HCV prevalence in PWID in 2012 [31]: 62.2% [55.5–68.8%] [28] |
| Proportion of infections that spontaneously clear | $\delta$ | 0.26 [Uniform 0.22–0.29] | 28 |
| Treatment rate per capita | $\tau_j$ | Set to 0 at baseline, calibrated to data at status quo, and varied to consider different treatment interventions | |
| Average duration on treatment | $1/\omega_j$ | 24-weeks, which is the standard for treatment of HCV genotype 3 in Pakistan with IFN and RBV. Shortened to 12 weeks when move to DAA treatments | 11 |
| Proportion of individuals achieving SVR with treatment with IFN and RBV | $\alpha_j$ | 0.66 [Uniform 0.50–0.81] | 3,40,47 |
| Proportion of individuals achieving SVR with treatment with new DAAs | $\alpha_j$ | 0.9 [Uniform 0.80–0.95] | 11,55 |
| **Progression Parameters** | | | |
| Relative risk of progression from cirrhosis to decompensated if SVR | $\epsilon_{CD}$ | 0.07 [Lognormal 95% CI 0.03, 0.20] | 53 |
| Relative risk of progression from cirrhosis to HCC if SVR | $\epsilon_{CH}$ | 0.23 [Lognormal 95% CI 0.16, 0.35] | 29,53 |
| Relative risk of progression from decompensation to HCC if SVR | $\epsilon_{DH}$ | 1.0 | Assume same progression for both SVR and non-SVR |
| Relative risks of disease progression if infected by HCV genotype 3$\nabla$ | — | 1.30 [Uniform 1.22–1.39] for chronic to cirrhosis, and cirrhosis to decompensation<br>1.80 [Uniform 1.60–2.03] for cirrhosis/decompensation to HCC | 21 |
| Transition probability (TP) of chronic HCV to cirrhosis$\nabla \bowtie$ | $\sigma$ | 0.027 [Normal, mean = 0.027, std = 0.0008] | 45 |
| TP of compensated cirrhosis to decompensation$\nabla \bowtie$ | $\gamma$ | 0.039 [Beta: $\alpha = 14.6, \beta = 360.2$] | 17,43,56 |
| TP of cirrhosis or decompensation to HCC$\nabla \bowtie$ | $\xi$ | 0.014 [Beta: $\alpha = 1.9, \beta = 136.1$] | 17,43,56 |
| TP of additional mortality due to decompensation$\bowtie$ | $\mu_4$ | 0.13 [Beta: $\alpha = 147.0, \beta = 984.0$] | 17,43,56 |
| TP of death due to HCC$\bowtie$ | $\mu_5$ | 0.43 [Beta: $\alpha = 117.1, \beta = 155.2$] | 17,43,56 |
| **Medical/Community Risk Parameters** | | | |
| Recruitment rate from low to high medical risk, by age and gender | $\nu_{i,g}$ | Fitted values: Male: 0.022 [0.021–0.023], 0.021 [0.018–0.024], 0.007 [0.006–0.009]<br>Female: 0.022 [0.021–0.023], 0.031[0.028–0.035], 0.009 [0.008–0.011] | Fit to data in each age and risk category by gender [38] as given in Supplementary Table S3 |
| Recruitment rate from low to high community risk, by age and gender | $\kappa_{i,g}$ | Fitted values: Male: 0.007 [0.007–0.008], 0.10 [0.096–0.11], 0.006 [0.004–0.007]<br>Female: 0.12 [0.11–0.13], 0.15 [0.14–0.17], 0.016 [0.011–0.023] | Fit to data in each age and risk category by gender [38] as given in Supplementary Table S3 |
| Relative risk of acquiring HCV if: | | | |
| High medical risk compared to low medical risk | $\psi_g$ | Fitted values: Male: 1.00[1.00–1.02], Female: 1.11 [1.00–1.75] | Fit to data on HCV prevalence in each risk category as given in Supplementary Table S3 |
| High community risk compared to low community risk | $\chi_g$ | Fitted values: Male:,1.50 [1.13–1.89], Female: 1.32 [1.09–1.73] | |
| Combined high medical and community risk compared to low risk | $\rho_g$ | Male: 1.45[1.11–1.89], Female: 1.54 [1.27–1.93] | |

$\Delta$Baseline values for $b_g$ for the pre-2000 and interim 2000-2015 growth rates are taken from the UN Department of Economic and Social Affairs, Population Division [49]; meanwhile, the projected post-2015 growth rate at baseline is obtained by averaging the point projections for the present year 2015 to the year 2030 from the International Data Base, US Census Bureau. [52]

$\nabla$The transition probabilities listed here are calibrated to reflect the higher proportion of HCV genotype 3 in Pakistan, which is associated with an increased transition probability of disease progression. [21]

$\bowtie$Transition probabilities are converted to instantaneous rates when parameterising the model.

Table S3: Demographic and epidemiological data used to calibrate and fit the mathematical model.

| Demographic and Epidemiological Data | | Baseline Value [Uncertainty Distribution/Range] | Source |
|---|---|---|---|
| Total population in 1960 | Total | [Uniform 44,912,000–51,719,000] | [8,13,49] |
| | Male | [Uniform 24,058,000–27,704,304] | |
| | Female | [Uniform 20,854,000–24,014,696] | |
| Total population in 2000 | Total | [Uniform 138,250,000–152,429,036] | [8,13,49] |
| | Male | [Uniform 71,330,000–78,324,451] | |
| | Female | [Uniform 66,921,000–74,104,585] | |
| Total population in 2015 | Total | [Uniform 188,925,000–199,085,847] | [8,13,49] |
| | Male | [Uniform 97,052,000–102,231,058] | |
| | Female | [Uniform 91,873,000–96,854,789] | |
| Proportion in each age group¶ | Young (0–19 years old) | 43.7% | [49] |
| | Young Adult (20–29 years old) | 19.3% | |
| | Adult (30+ years old) | 37.0% | |
| PWID size estimate | Whole population | 0.24% [Uniform 0.18–0.30%] | UNODC 2013 [51] |
| | Male | 0.42% [Uniform 0.36–0.54%] | |
| | Female | 0.006% [Uniform 0.0006–0.24%] | |
| Proportion of population in each age group by medical and community risk in 2007 from national survey | Male | | [38], Estimated 95% binomial CI |
| | 0–19: | | |
| | Low MR, Low CR | 75.1% [74.3–75.9%] | |
| | Low MR, High CR | 5.1% [4.7–5.6%] | |
| | High MR, Low CR | 17.1% [16.4–17.8%] | |
| | High MR, High CR | 2.7% [2.4–3.0%] | |
| | 20–29: | | |
| | Low MR, Low CR | 39.7% [38.2–41.1%] | |
| | Low MR, High CR | 29.8% [28.5–31.2%] | |
| | High MR, Low CR | 15.0% [13.9–16.1%] | |
| | High MR, High CR | 15.5% [14.5–16.6%] | |
| | 30+: | | |
| | Low MR, Low CR | 33.3% [32.3–34.3%] | |
| | Low MR, High CR | 29.1% [28.1–30.1%] | |
| | High MR, Low CR | 16.9% [16.1–17.8%] | |
| | High MR, High CR | 20.7% [19.8–21.6%] | |
| | Female | | |
| | 0–19: | | |
| | Low MR, Low CR | 37.2% [36.3–38.1%] | |
| | Low MR, High CR | 42.2% [41.3–43.2%] | |
| | High MR, Low CR | 5.7% [5.3–6.1%] | |
| | High MR, High CR | 14.9% [14.2–15.6%] | |
| | 20–29: | | |
| | Low MR, Low CR | 16.3% [15.2–17.4%] | |
| | Low MR, High CR | 49.6% [48.1–51.1%] | |
| | High MR, Low CR | 4.6% [4.0–5.3%] | |
| | High MR, High CR | 29.5% [28.2–30.9%] | |
| | 30+: | | |
| | Low MR, Low CR | 12.1% [11.4–12.9%] | |
| | Low MR, High CR | 45.1% [44.0–46.3%] | |
| | High MR, Low CR | 4.9% [4.4–5.4%] | |
| | High MR, High CR | 37.9% [36.8–39.0%] | |
| HCV Chronic Infected Prevalence in 2007 (estimated from antibody prevalence) | Overall | 3.62% [3.45–3.79%] | [38], Estimated 95% binomial CI |
| | Young (0–19 years old) | 1.50% [1.34–1.67%] | |
| | Young Adult (20–29 years old) | 3.20% [2.84–3.59%] | |
| | Adult (30+ years old) | 6.89% [6.50–7.30%] | |
| HCV chronic prevalence in 2007 by medical and community risk | Male | | [38] |
| | Overall | 3.65% [3.42–3.90%] | |
| | Low MR, Low CR | 2.35% [2.10–2.62%] | |
| | Low MR, High CR | 6.21% [5.51–6.97%] | |
| | High MR, Low CR | 2.91% [2.42–3.48%] | |
| | High MR, High CR | 7.39% [6.44–8.45%] | |
| | Female | | |
| | Overall | 3.57% [3.34–3.83%] | [38] |
| | Low MR, Low CR | 1.81% [1.48–2.20%] | |
| | Low MR, High CR | 3.46% [3.11–3.83%] | |
| | High MR, Low CR | 2.81% [1.94–3.92%] | |
| | High MR, High CR | 5.68% [5.10–6.32%] | |
| HCV Chronic Infected Prevalence in PWID | Overall | 62.16% [55.50–68.75%] | [31] |
| Projected increase in chronic HCV infected prevalence over 10 years | Overall | [0.15–0.89%] | Blood donor data in Pakistan |

¶We assume that the population proportions within each age group remains constant over the time period of interest. This assumption has arisen from observation of demographic data for Pakistan [48] which suggests that the age distributions for the age groups under consideration here has not fluctuated significantly between 1960 and 2015.

Table S4: Number of HCV Patients Treated by the National (2005–2010) and Provincial (2010–2015) Hepatitis Control Programmes.[36]

| **Year** | **Punjab** | **Sindh** | **KPK** | **Baluchistan** | **Total Treatment Public Sector** | **Total Treatments Across All Sectors*** |
|---|---|---|---|---|---|---|
| 2005–2010 | ND | ND | ND | ND | 23,000 | 57,500 |
| 2011 | ND | 25,394 | 8,928 | 866 | 55,188** | 137,970 |
| 2012 | 20,000 | 21,824 | 9,223 | 712 | 51,759 | 129,398 |
| 2013 | 20,000 | 28,221 | 6,212 | 731 | 55,164 | 137,910 |
| 2014 | 20,000 | 22,431 | 3,117 | 820 | 46,368 | 115,920 |
| 2015 | 34,500 | 21,847 | 3,837 | 900 | 61,084 | 152,710 |
| **Total** | 94,500 | 119,717 | 31,317 | 4,029 | 292,563 | 731,408 |

ND: No data available

*To estimate the total number of historical HCV treatments each year across both the public and private sectors, a split of Public 40%, Private 60% was assumed.

**There was no data available for Punjab province in 2011, so it was assumed that 20,000 HCV patients were treated in 2011 under the Provincial Hepatitis Program, which is consistent with the data from the subsequent years 2012 to 2014.

# 4 Supplementary Model Projections and Results

Table S5: (A) Uncertainty forecasts for the current and future demographic and epidemic projections from the model at baseline at the end of 2015 and after 15 years in 2030. (B) Total number and population attributable fraction (PAF) of new infections due to key risk factors/behaviours from 2016–2030 inclusive.

## Part A.

| Model Projections× | | Year End 2015 (Baseline) | Year End 2030 |
|---|---|---|---|
| Demographic projections | Total population (1000s) | 192,891 [188,467–197,160] | 248,079 [235,615–262,506] |
| | Male | 98,969 [96,449–101,744] | 126,745 [118,597–136,400] |
| | Female | 93,883 [91,136–96,431] | 120,877 [112,081–129,986] |
| | PWID prevalence (of total population) | 0.3% [0.2–0.4%] | 0.3% [0.2–0.4%] |
| | PWID population (1000s) | 564 [397–708] | 704 [490–881] |
| | Male | 439 [354–519] | 547 [432–675] |
| | Female | 124 [8–222] | 153 [10–274] |
| Epidemic projections | Infected prevalence in general population | 3.9% [3.7–4.1%] | 5.1% [4.6–5.5%] |
| | Infected prevalence in PWID# | 61.3% [55.0–67.1%] | 63.7% [57.6–69.6%] |
| | Total HCV incidence (per 1000 pyrs) | 3.7 [3.3–4.2] | 4.8 [4.1–5.5] |
| | Subgroup HCV incidence | | |
| | Non-PWID | 3.3 [2.9–3.7] | 4.4 [3.7–5.0] |
| | PWID | 366.9 [277.8–490.5] | 384.9 [294.4–510.8] |
| | Low MR, Low CR | 2.8 [2.4–3.2] | 3.5 [3.0–4.1] |
| | Low MR, HighCR | 4.3 [3.7–5.0] | 5.5 [4.6–6.7] |
| | High MR, Low CR | 3.3 [2.8–3.7] | 4.2 [3.5–4.8] |
| | High MR, High CR | 5.0 [4.1–5.9] | 6.5 [5.2–7.8] |
| Breakdown of infected population$^{\Omega}$ | Chronic, no disease | 75.6% [71.4–79.8%] | 75.5% [71.2–79.7%] |
| | Disease progression | 24.4% [20.2–28.6%] | 24.6% [20.3–28.8%]] |
| | Cirrhosis | 19.5% [14.8–24.5%] | 19.7% [14.9–24.6%] |
| | Decompensation | 4.2% [2.4–6.2%] | 4.1% [2.3–6.0%] |
| | HCC | 0.6% [0.1–1.7%] | 0.6% [0.1–1.7%] |
| Projected number of infected individuals by disease progression stage (1000s) | Total chronic infections | 7,542 [7,168–7,944] | 12,608 [11,781–13,581] |
| | Chronic, no disease | 5,692 [5,248–6,108] | 9,517 [8,651–10,351] |
| | Disease progression | 1,842 [1,493–2,150] | 3,100 [2,491–3,615] |
| | Cirrhosis | 1,466 [1,104–1,825] | 2,481 [1,871–3,104] |
| | Decompensation | 313 [171–463] | 517 [280–760] |
| | HCC | 47 [7–130] | 79 [12–212] |
| Exposure to high medical and community risk by gender | Male | | |
| | Low MR, Low CR | 53.3% [52.7–53.9%] | 51.9% [50.1–53.8%] |
| | Low MR, High CR | 17.9% [17.5–18.3%] | 18.2% [17.4–19.0%] |
| | High MR, Low CR | 16.8% [16.3–17.1%] | 16.9% [16.3–17.5%] |
| | High MR, High CR | 12.0% [11.6–12.4%] | 13.0% [12.1–13.8%] |
| | High CR, Any MR | 30.0% [29.3–30.5%] | 31.2% [29.7–32.6%] |
| | High MR, Any CR | 28.8% [28.2–29.4%] | 29.9% [28.6–31.0%] |
| | Female | | |
| | Low MR, Low CR | 24.2% [23.7–24.8%] | 23.3% [21.2–25.4%] |
| | Low MR, High CR | 44.4% [43.7–45.0%] | 43.9% [42.8–44.9%] |
| | High MR, Low CR | 4.3% [4.1–4.5%] | 4.2% [ 4.0–4.4%] |
| | High MR, High CR | 27.1% [26.6–27.9%] | 28.6% [27.3–30.1%] |
| | High CR, Any MR | 71.5% [70.8–72.1%] | 72.6% [70.3–74.7%] |
| | High MR, Any CR | 31.4% [30.8–32.2%] | 32.8% [31.5–34.3%] |
| Chronic infected prevalence by gender and medical/community risk | Male | | |
| | Overall | 4.0% [3.7–4.2%] | 5.1% [4.5–5.6%] |
| | Low MR, Low CR | 2.2% [2.0–2.4%] | 2.8% [2.4–3.1%] |
| | Low MR, High CR | 6.6% [5.9–7.4%] | 8.3% [7.2–9.4%] |
| | High MR, Low CR | 3.8% [3.4–4.1%] | 4.9% [4.2–5.3%] |
| | High MR, High CR | 7.8% [6.9–9.0%] | 9.7% [8.3–11.4%] |
| | High CR, Any MR | 7.1% [6.4–7.8%] | 8.9% [7.9–10.1%] |
| | High MR, Any CR | 5.5% [5.0–6.1%] | 7.0% [6.2–7.9%] |
| | Female | | |
| | Overall | 3.9% [3.5–4.2%] | 5.2% [4.5–5.8%] |
| | Low MR, Low CR | 1.3% [1.1–1.4%] | 1.63% [1.3–1.9%] |
| | Low MR, High CR | 3.9% [3.4–4.3%] | 5.08% [4.4–5.8%] |
| | High MR, Low CR | 3.2% [2.7–3.9%] | 4.20% [3.5–5.1%] |
| | High MR, High CR | 6.3% [5.7–7.0%] | 8.25% [7.2–9.4%] |

Continued on next page ⟶

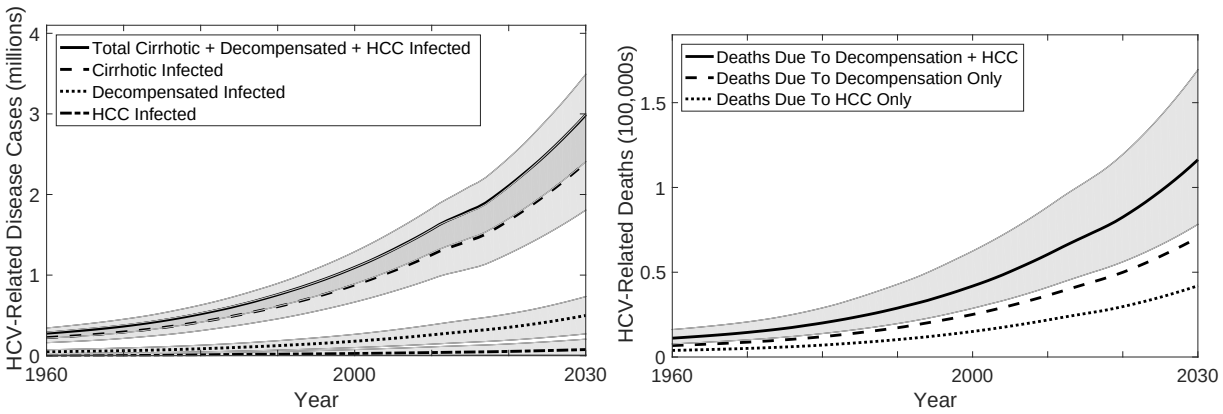
**Table S5 – Continued from previous page.**

| Model Projections[×] | | Year End 2015 (Baseline) | Year End 2030 |
|---|---|---|---|
| | High CR, Any MR | 4.8% [4.3–5.2%] | 6.3% [5.6–7.1%] |
| | High MR, Any CR | 5.9% [5.3–6.5%] | 7.8% [6.8–8.7%] |
| Estimated relative risk of HCV due to PWID, high medical, and high community risk factors | PWID risk | | |
| | Amongst PWID | 142.7 [107.0–191.1] | 114.3 [86.0–151.8] |
| | Overall | 8.9 [5.9–15.7] | — |
| | Community risk | | |
| | Male | 1.5 [1.1–1.9] | — |
| | Female | 1.3 [1.1–1.7] | — |
| | Medical risk | | |
| | Male | 1.0 [1.0–1.0] | — |
| | Female | 1.1 [1.0–1.8] | — |
| | Combined m/c risk | | |
| | Male | 1.5 [1.1–1.9] | — |
| | Female | 1.5 [1.3–1.9] | — |

## Part B.

| Model Projections for the Contribution of Key Risk Factors/Behaviours on the HCV Epidemic in Pakistan From 2016-2030[×] | Total Number of New Infections Attributable to Key Risk Factors From 2016–2030 (1000s) | Population Attributable Fraction of New Infections From 2016–2030 |
|---|---|---|
| PWID Risk Only | 1,861 [1,321–2,442] | 13.9% [9.8–18.2%] |
| High MR Only | 1,001 [294–2,393] | 7.5% [2.2–17.3%] |
| High CR Only | 3,777 [2,276–5,763] | 28.3% [17.8–40.9%] |
| Combined High MR & CR | 4,144 [2,495–6,559] | 30.8% [19.5–46.5%] |
| Combined PWID & High MR & CR | 5,674 [3,998–7,938] | 42.4% [30.0–58.0%] |

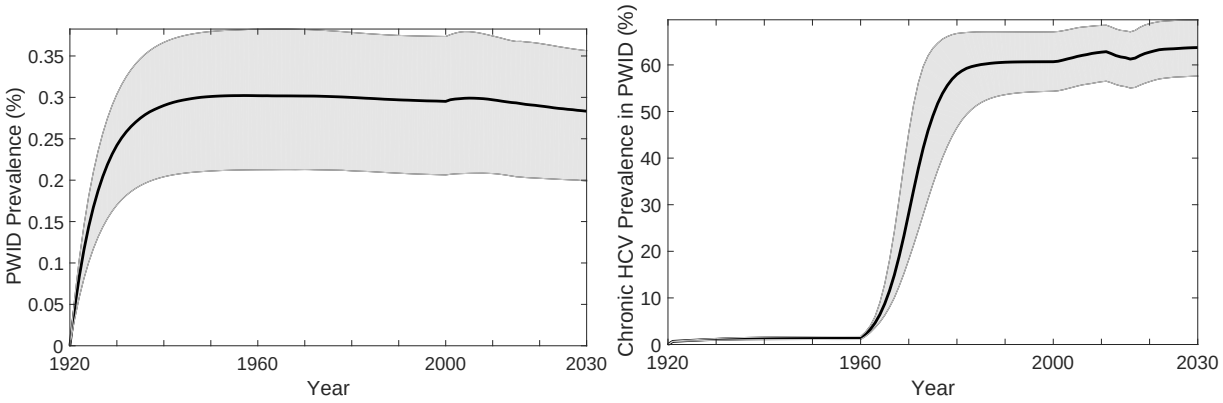
[×]Values in the table show the median of 328 model runs along with the 95% inter-percentile range for all runs.
[#]As a proportion of the PWID population.
[Ω]As a proportion of the total infected population.




(a) Number of prevalent HCV-associated disease cases.

(b) Prevalent cases of HCV-related mortality.

Figure S3: Model projections for (a) the number of chronically infected individuals who are living with HCV-associated disease, namely, cirrhosis, decompensation, and HCC; and (b) the mortality rate due to End Stage Liver Disease (ESLD), i.e. decompensation and HCC, in Pakistan from 1960 to 2030.




(a) PWID prevalence in the whole population.

(b) Chronic HCV prevalence in PWID.

Figure S4: Model projections for (a) the prevalence of PWID in the whole population, and (b) chronic HCV prevalence amongst PWID from 1920 to 2030. (a) Overall PWID prevalence is predicted to remain stable from around 1960 onwards at a prevalence of 0.3% [95%CrI 0.2–0.4%] of the total population in 2015 and 2030. (b) Chronic HCV prevalence in PWID is also projected to stabilise soon after the early 2000s, reaching 63.7% [95%CrI 57.6–69.6%] in 2030. The relative risk of HCV transmission due to PWID is estimated to be 8.9 [95%CrI 5.9–15.7] in the overall population. Amongst PWID, the relative transmission risk is substantially higher, at 142.7 [95%CrI 107.0–191.1] in 2015, but is expected to decrease over time to 114.3 [95%CrI 86.0–151.8] by 2030. This is likely due to accumulation of medical/community risks contributing a larger proportion of new infections as time goes on. Note: Although the model allows individuals to enter the PWID compartment from 1920 onwards, it only assumes that injecting drug use and associated HCV transmission starts in the early 1960s.

Table S6: Uncertainty forecasts for the potential impact of various illustrative intervention scenarios compared to the baseline scenario of no intervention from 2016.

| Intervention Scenario Projections[×] | | Initial Number of Treatments Needed Per Year From 2016–2030 | Total Number of New Infections Averted From 2016–2030 (1000s) | Proportion of Infections Averted From 2016–2030 | Total Number (%) of HCV Related Deaths Averted From 2016–2030 (1000s) | Reduction in Total Infected Prevalence by 2030‡ (%) | Reduction in Incidence Achieved by 2030‡ (%) | Reduction in Mortality Achieved by 2030‡ (%) |
|---|---|---|---|---|---|---|---|---|
| Reduction in HCV transmission risk | Reduce PWID, medical, community risk by 50% | N/A | 2,926 [1,737–4,432] | 21.5% [13.7–32.3%] | 34 (2.4%) [15–74] | -11.4% [-20.6–1.8%] | 5.0% [-9.7–21.8%] | -53.4% [-59.2–47.4%] |
| | Reduce all risk by 30% | N/A | 5,102 [4,483–5,785] | 38.1% [36.9–39.2%] | 62 (4.4%) [32–123] | 3.0% [-2.1–8.0%] | 29.4% [25.1–33.4%] | -45.1% [-50.7–37.4%] |
| | Reduce all risk by 50% | N/A | 7,970 [7,022–9,007] | 59.5% [58.2–60.7%] | 101 (7.1%) [52–198] | 21.69% [17.1–26.0%] | 58.1% [54.8–61.1%] | -33.8% [-41.0–23.8%] |
| Continuing current levels of treatment without scale-up (fixed treatment) | With conventional treatments | 150,000 per year | 910 [735–1,134] | 6.8% [5.6–8.3%] | 65 (4.6%) [40–108] | -13.3% [-20.7–5.7%] | -13.9% [-21.1–6.4%] | -47.6% [-54.6–41.3%] |
| | With new DAAs | 150,000 per year | 1,272 [1,107–1,476] | 9.6% [8.3–10.9%] | 96 (6.9%) [61–156] | -5.5% [-12.8–1.4%] | -7.4% [-14.6–0.3%] | -40.8% [-47.3–34.8%] |
| Continuing current rate or scaling up of treatment of all infections with new DAAs (proportional treatment) | Treat 2.0% per year (∼status quo treatment rate from the year 2016) | 151,000 [143,000–159,000] per year | 1,389 [1,177–1,616] | 10.4% [9.3–11.7%] | 101 (7.2%) [63–163] | -2.3% [-8.4–3.7%] | -4.3% [-11.0–2.1%] | -38.6% [-44.3–33.5%] |
| | Treat 5.0% per year | 372,000 [354,000–392,000] per year | 3,127 [2,653–3,618] | 23.4% [21.0–26.1%] | 229 (16.3%) [141–363] | 28.7% [23.1–34.7%] | 23.8% [17.3–30.0%] | -8.8% [-15.3–2.8%] |
| Combined approach (treatment & reducing transmission risk) | Reduce all risk by 50% & treat 5.0% per year | 366,000 [348,000–386,000] per year | 9,267 [8,197–10,393] | 69.1% [67.3–70.7%] | 304 (21.4%) [178–502] | 58.8% [55.0–62.4%] | 76.5% [73.1–79.1%] | 10.4% [2.8–20.4%] |

[×]Values in the table show the median of 328 model runs along with the 95% inter-percentile range for all runs.
‡As compared to 2015 levels.

### 4.1 ANCOVA Analysis

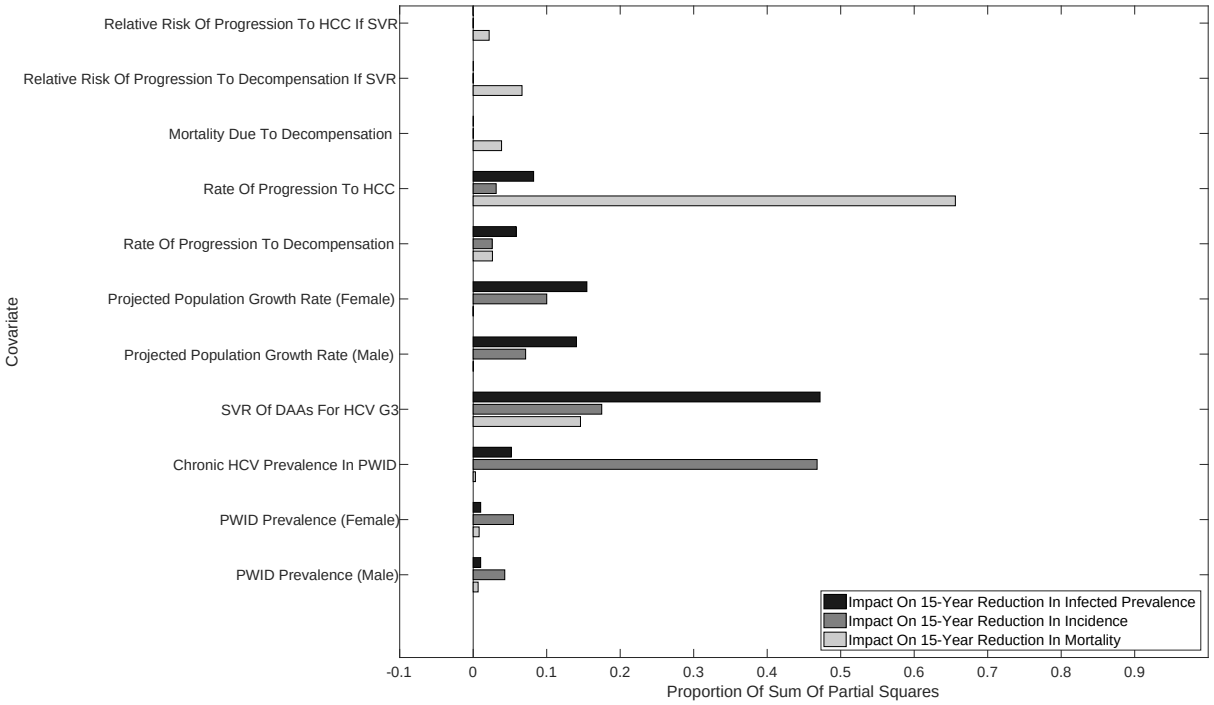



Figure S5: Outcome of uncertainty analysis using a linear regression of covariance (ANCOVA) to determine the variability in the 15-year impact on chronic infected prevalence, incidence, and mortality due to the parameter and calibration data for an intervention scenario with a 50% reduction in transmission risk across all groups, and a 5% treatment rate per year. The proportional contribution of each parameter on the model outcome's sum-of-squares was calculated to estimate their importance to the overall uncertainty.[6] Only those parameters and data quantities that contributed greater than 1% of the overall variability in at least one of the three metrics considered are shown.

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