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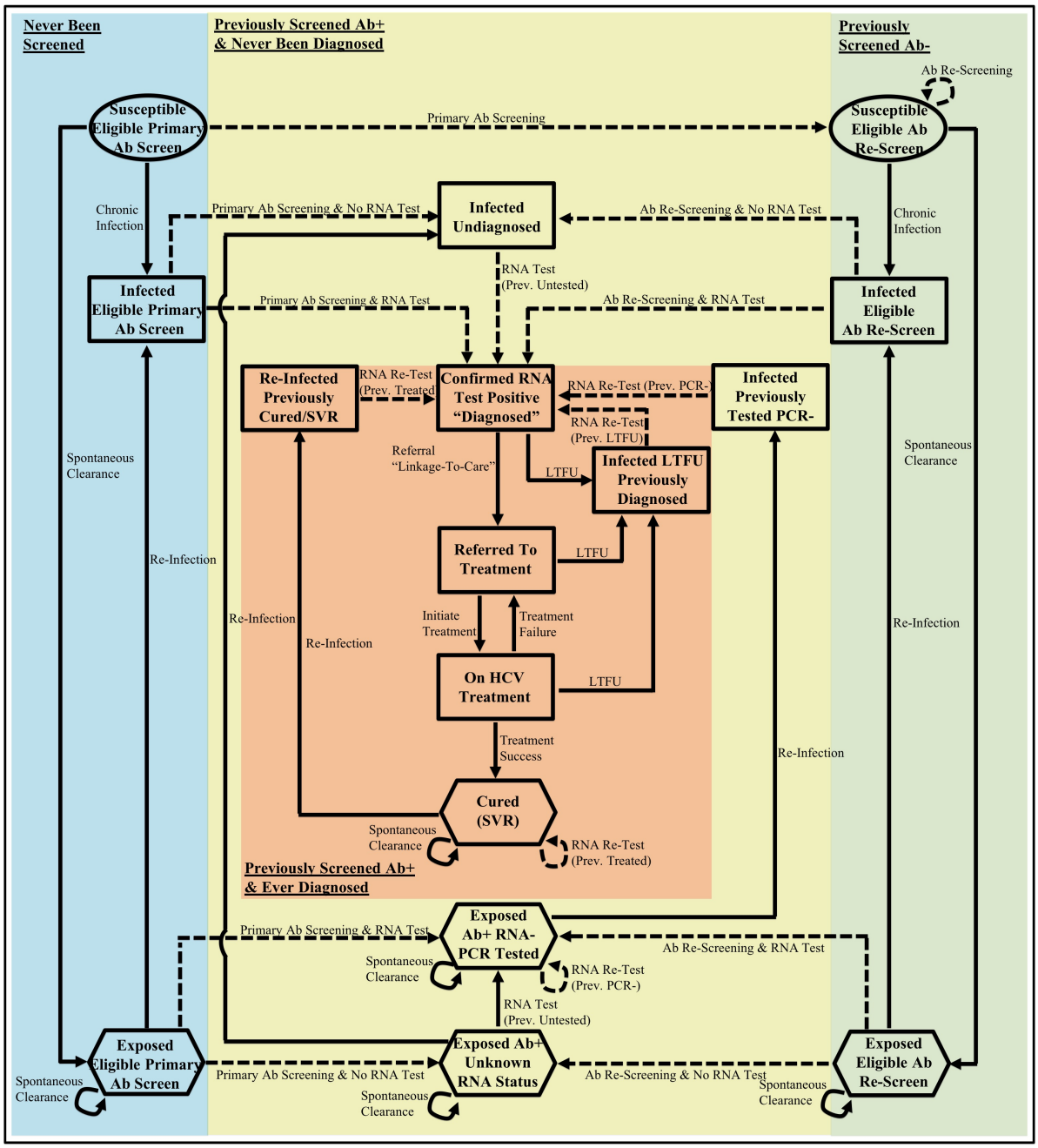
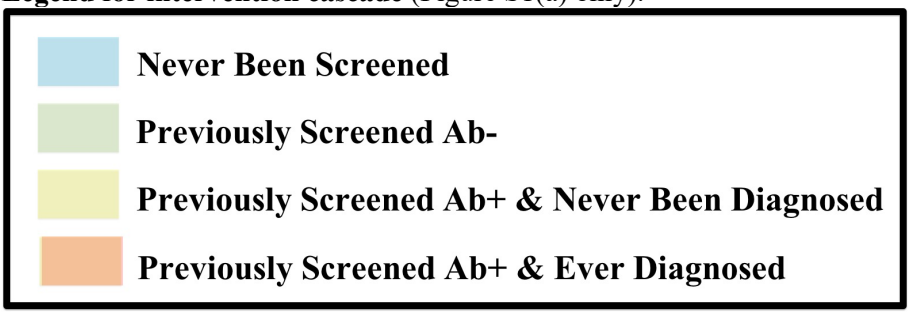
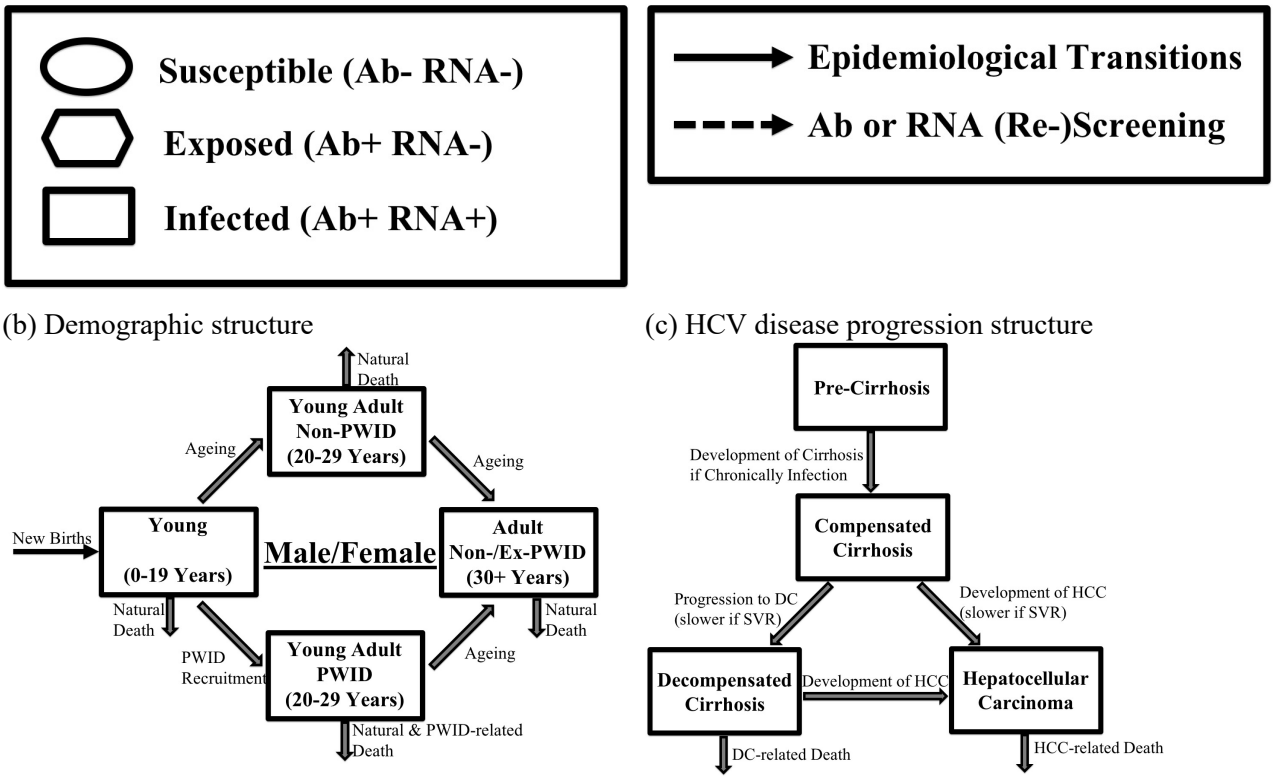
## Supplementary Methods




**Legend for intervention cascade** (Figure S1(a) only).






**Supplementary Figure S1.**
Schematics showing the structure of the full HCV screening model, namely, (a) the transmission dynamics integrated with the complete screening and treatment intervention cascade, (b) the demographic compartments with stratification by sex, age/behaviour, and population growth, and (c) the HCV disease progression stages. In (a), the colour shading represents grouped compartments according to Ab screening and HCV diagnosis status: Never been screened (blue shading), previously screened as Ab- (green shading), previously screened as Ab+ & never been diagnosed (yellow shading), and previously screened as Ab+ & ever diagnosed (orange shading). A simplified representation of the intervention cascade is shown in Figure 1 in the main text. HCV: hepatitis C virus; Ab: Antibody (indicating past exposure to HCV); RNA: ribonucleic acid (indicating active HCV infection); PCR: polymerase chain reaction, a method to diagnose and measure levels of HCV RNA; SVR: sustained virologic response (indicating effective cure from active HCV infection).

**General Description of Model Structure**
The model stratifies the population into three broad categories based on their prior Ab screening experience (Figure 1 and Supplementary Figure S1): Individuals who have never been Ab screened and are eligible for first-time Ab screening; individuals who have been previously screened Ab-negative (Ab-) and could be re-screened; and individuals who have previously been screened Ab-positive (Ab+), regardless of chronic infection or treatment status. To incorporate possible engagement with services, the last category is then stratified into those who have ever been diagnosed with active infection, and those who have never been diagnosed with active infection. Individuals with known Ab+ status who have never been diagnosed captures all persons who have never received treatment and are unaware of their present HCV RNA status, including those who were never tested for RNA and those whose last RNA test was negative. Meanwhile, individuals with known Ab+ status who have ever been diagnosed encompasses all persons who have been diagnosed with chronic HCV infection, including those referred to, undergoing, and completed treatment; those lost-to-follow-up; and any post-treatment re-infections (Figure 1, shaded region; or Supplementary Figure S1, orange-shaded region). The model also allows for the development of a positive antibody response following spontaneous resolution of an acute infection in a proportion of new infections.

**Model Structure and Model Equations**
Here we describe the full HCV screening model equations shown schematically in Supplementary Figure S1, which is equivalent to the simplified model schematic as illustrated in Figure 1 of the main text. Supplementary Figure S1 separates out the different strata of the model structure into components, representing separately the baseline HCV epidemic and screening cascade (Supplementary Figure S1a), the demographic and behavioural aspects of the model, namely stratification by sex, age, injecting drug use (Supplementary Figure S1b), and the progression stages of HCV-associated disease (Supplementary Figure S1c). The latter two components of the model, namely, the demographic/behavioural component and disease transmission and progression component, were the basis of our

previous model.[1] To obtain the current model, the previous model was adapted to incorporate a detailed cascade of care, including Ab and RNA screening and re-screening, linkage-to-care, treatment, and loss-to-follow-up.

The full model is a system of 512 non-linear ordinary differential equations. However, it is foundationally based on a Susceptible-Exposed-Infectious-Treatment (S-E-I-T) model structure comprised of four broad categories, corresponding to respective compartments of individuals who are Susceptible (have never been infected), Exposed (previously infected), Infectious (chronically infected), and undergoing Treatment (chronically infected but not infectious). These states are dependent on HCV antibody (Ab) status, namely, Ab-positive (Ab+) or Ab-negative (Ab-), and HCV RNA status, namely, RNA-positive (RNA+) or RNA-negative (RNA-). Denote the broad S-E-I-T categories by:

$S(t)$ = Susceptible, Actual HCV status Ab- & RNA-
$E(t)$ = Exposed, Actual HCV status Ab+ & RNA-
$I(t)$ = Chronically Infected and Infectious, Actual HCV status Ab+ & RNA+
$T(t)$ = Undergoing Treatment, Actual HCV status Ab+ & RNA+

Broadly speaking, Susceptible individuals who have never been infected do not display HCV Ab (i.e. both HCV Ab- and RNA-), whereas Exposed individuals who have been previously infected but are not actively infected display HCV Ab but not HCV RNA (i.e. HCV Ab+ and RNA-). Meanwhile, those who are Infectious or chronically infected display both HCV Ab and HCV RNA (i.e. HCV Ab+ and RNA+). However, it is not possible to for an individual to be Ab- but RNA+ (except in rare cases of acute HCV infection before the development of anti-HCV antibodies, which is outside the focus of this modelling). Each of these four broad S-E-I-T categories are further split into a total of 16 variables according to their screening and diagnosis status, as follows:

**Susceptible ($S_{ij}^{g}$), Actual HCV status Ab- & RNA-**

$Sp_{ij}^{g}(t)$ = Susceptible, Eligible for Primary Ab Screening
$Sr_{ij}^{g}(t)$ = Susceptible, Eligible for Ab Re-Screening

**Exposed ($E_{ij}^{g}$), Actual HCV status Ab+ & RNA-**

$Ep_{ij}^{g}(t)$ = Exposed, Eligible for Primary Ab Screening
$Er_{ij}^{g}(t)$ = Exposed, Eligible for Ab Re-Screening
$Eu_{ij}^{g}(t)$ = Exposed, Known Ab+, Never Tested for RNA
$Ek_{ij}^{g}(t)$ = Exposed, Known Ab+, Previously Tested RNA-
$Ec_{ij}^{g}(t)$ = Exposed, Cured (SVR)

**Infectious ($I_{ij}^{g}$), Actual HCV status Ab+ & RNA+**

$Ip_{ij}^{g}(t)$ = Infected, Eligible for Primary Ab Screening
$Ir_{ij}^{g}(t)$ = Infected, Eligible for Ab Re-Screening
$Iu_{ij}^{g}(t)$ = Infected, Known Ab+, Never Tested for RNA
$Id_{ij}^{g}(t)$ = Infected, Known Ab+, Diagnosed RNA+
$In_{ij}^{g}(t)$ = Infected, Known Ab+, Previously Tested RNA-
$Ic_{ij}^{g}(t)$ = Infected, Previously Cured (SVR), Unknown Current RNA Status
$Ik_{ij}^{g}(t)$ = Infected, Previously Diagnosed Ab+ & RNA+, but since then LTFU
$Rf_{ij}^{g}(t)$ = Infected, Referred to Treatment

**Treatment ($T_{ij}^{g}$), Actual HCV status Ab+ & RNA+**

$Tt_{ij}^{g}(t)$ = Treatment, Undergoing Treatment

For each of the variables, subscripts specify the more detailed demographic and disease progression structures, while the superscripts indicate the sex structure, extending from the baseline HCV epidemic model structure incorporating the screening cascade as defined in Supplementary Table S0.

The 16 variables can be re-arranged according to four screening and diagnosis criteria, namely: (i) Never been screened, (ii) Previously screened Ab-, (iii) Previously screened Ab+ and never been diagnosed, and (iv) Previously screened Ab+ and ever diagnosed, as described in more detail below.

(i) **Never been screened.** This can include individuals from Susceptible ($Sp$), Exposed ($Ep$), and Infected ($Ip$) categories, all of whom are unaware of their HCV Ab and RNA status.
(ii) **Previously screened Ab-negative (Ab-).** This encompasses all individuals whose primary Ab test was negative, but whose present Ab or RNA status is unknown. can also include individuals from Susceptible

($Sr$), Exposed ($Er$), and Infected ($Ir$) categories, with the latter two compartments possible if infection (and spontaneous viral clearance) occurs after primary Ab screening.

(iii) **Previously screened Ab-positive (Ab+) and never been diagnosed.** Here all individuals are aware of their Ab+ status. Two possible compartments each of Exposed and Infected can be distinguished: Persons who may have never been RNA-tested, whether Exposed ($Eu$) or Infected ($Iu$); or those whose last RNA test was negative, whether Exposed ($Ek$) or Infected at some point in time after having been RNA-tested negative ($In$).

(iv) **Previously screened Ab+ and ever diagnosed.** This encompasses all individuals who have ever been diagnosed, and includes those Exposed persons who have been cured ($Ec$) along with five compartments of Infected persons. These Infected compartments are those who are diagnosed with a confirmed RNA-positive test ($Id$), those lost-to-follow-up at any stage following diagnosis ($Ik$), those re-infected after being cured ($Ic$), those referred to treatment ($Rf$), and those undergoing treatment ($Tt$).

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 Supplementary Figure S1), specifically, (a) baseline HCV epidemic and screening structure, (b) demographic structure, (c) disease progression structure.

**Baseline HCV Epidemic Structure and Screening Cascade**

We first detail the transmission dynamics of HCV infection. Uninfected individuals, whether Susceptible or Exposed (previously infected), may become infected at a time-varying rate, $\lambda_i(t)$ for $i \in \{1, 2, 3, Y\}$ (i.e. the force of infection), which is dependent on age or behaviour. A proportion, $\delta$, of new infections spontaneously clear, returning such individuals to an Exposed state; meanwhile, the remainder of new infections that do not clear become Infectious or chronically infected. Re-infection can occur from Exposed to Infectious states.

Next, we describe the HCV screening and treatment cascade with reference to the four screening and diagnosis criteria:

(i) **Never been screened.** Individuals who have never been screened are eligible for primary, or first-time, Ab screening at a rate $\chi_1$. There are two possibilities. Those who are Susceptible ($Sp_{ij}^g$) will have a negative Ab test and move into a compartment of previously screened Ab-. Meanwhile, those who are Exposed ($Ep_{ij}^g$) or Infectious ($I_{ij}^g$) will have a positive Ab test, a proportion $\psi_1$ of which will subsequently undergo a HCV RNA test, with the remainder $(1 - \psi_1)$ being untested for RNA.

(ii) **Previously screened Ab-.** Previously screened Ab- persons are eligible for Ab re-screening at a rate $\chi_2$. Those who are Susceptible ($Sr_{ij}^g$) will be have a negative Ab test and return into the same compartment of previously screened Ab-. Infection (and spontaneous viral clearance) may occur among previously screened Ab- persons. Those who are Exposed ($Er_{ij}^g$) or Infectious ($Ir_{ij}^g$) will have a positive Ab test, a proportion $\psi_2$ of which will subsequently undergo a HCV RNA test, with the remainder $(1 - \psi_2)$ being untested for RNA.

(iii) **Previously screened Ab+ and never been diagnosed.** Among Exposed individuals, the proportions $\chi_1(1 - \psi_1)$ from primary Ab screening and $\chi_2(1 - \psi_2)$ from Ab re-screening without an RNA test will enter the $Eu_{ij}^g$ compartment, with the remaining proportions $\chi_1\psi_1$ from primary Ab screening and $\chi_2\psi_2$ from Ab re-screening with confirmed RNA- tests entering the $Ek_{ij}^g$ compartment. RNA testing of previously untested Exposed individuals may occur at a rate $\tilde{\chi}_1$, moving persons from the $Eu_{ij}^g$ compartment to the confirmed RNA- compartment $Ek_{ij}^g$. Similarly, among Infectious individuals, the proportions $\chi_1(1 - \psi_1)$ from primary Ab screening and $\chi_2(1 - \psi_2)$ from Ab re-screening without an RNA test will be infected but undiagnosed and enter the $Iu_{ij}^g$ compartment. Exposed individuals who are aware of their Ab+ status, but have not been RNA-tested, may become chronically infected, moving into the infected and undiagnosed compartment $Iu_{ij}^g$. Additionally, Exposed individuals who are aware of their Ab+ status and have been previously RNA-tested negative may also become chronically infected, moving into the infected and previously RNA- compartment, $In_{ij}^g$.

(iv) **Previously screened Ab+ and ever diagnosed.** Among Infectious individuals, the proportions $\chi_1\psi_1$ of primary Ab-screened and $\chi_2\psi_2$ of previously screened Ab-, along with RNA testing of previously untested individuals at a rate $\tilde{\chi}_1$, will obtain a confirmed RNA+ test, thus becoming diagnosed and entering the $Id_{ij}^g$ compartment. Following diagnosis, a proportion $\rho$ are referred to treatment and enter the $Rf_{ij}^g$ compartment, while the remaining proportion $(1 - \rho)$ are lost-to-follow-up (LTFU). Individuals who are referred to treatment initiate treatment and enter the $Tt_{ij}^g$ compartment at a rate $\tau_{ij}$ which may be dependent on age or behaviour (e.g. non-PWID versus PWID) and disease progression stage (e.g. pre-cirrhotic versus post-cirrhotic patients), with some being LTFU at a rate $\zeta_R$. Treatment duration $(1/\omega_j)$ depends on disease progression stage. A proportion $\alpha_i$ of those undergoing treatment are successfully cured and achieve SVR, entering the $Ec_{ij}^g$ compartment, while the remaining proportion $(1 - \alpha_i)$ who fail

treatment re-enter the treatment $Tt_{ij}^{g}$ compartment and are either re-treated or LTFU. Re-infection can occur after being cured. Individuals who were previously tested RNA- or previously cured can be re-tested for HCV RNA at respective rates $\tilde{\chi}_2$ and $\tilde{\chi}_3$, with those who have since become infected being diagnosed. Infectious individuals who were previously diagnosed, but lost-to-follow-up, are re-tested for HCV RNA and re-diagnosed at a rate $\tilde{\chi}_4$.

The equations for the baseline epidemic and HCV screening structure are categorised under the broad S-E-I-T headings as follows (refer to Supplementary Figure S1a). The full model is obtained by iteration of these 16 variables and corresponding equations to incorporate the aforementioned strata (detailed in the subsequent sections): demographic and behavioural characteristics, including sex ($g = g_1, g_2$), age structure and injecting drug use ($i = 1, 2, 3, Y$), and disease progression stages from no pathology to cirrhosis, decompensation, and HCC ($j = I, C, D, H$). Note that below, the explicit dependence on time ($t$) is dropped from the force of infection ($\lambda_i$, which is described in the subsection below) and variables to simplify notation.

**Susceptible ($S_{ij}^{g}$), Actual HCV status Ab- & RNA-**

$$\frac{dSp_{ij}^{g}}{dt} = -\lambda_i^g Sp_{ij}^{g} - \chi_1 Sp_{ij}^{g}$$
$$\frac{dSr_{ij}^{g}}{dt} = \chi_1 Sp_{ij}^{g} - \lambda_i^g Sr_{ij}^{g}$$

**Exposed ($E_{ij}^{g}$), Actual HCV status Ab+ & RNA-**

$$\frac{dEp_{ij}^{g}}{dt} = \delta\lambda_i^g Sp_{ij}^{g} - (1-\delta)\lambda_i^g Ep_{ij}^{g} - \chi_1 Ep_{ij}^{g}$$
$$\frac{dEr_{ij}^{g}}{dt} = \delta\lambda_i^g Sr_{ij}^{g} - (1-\delta)\lambda_i^g Er_{ij}^{g} - \chi_2 Er_{ij}^{g}$$
$$\frac{dEu_{ij}^{g}}{dt} = \chi_1(1-\psi_1)Ep_{ij}^{g} + \chi_2(1-\psi_2)Er_{ij}^{g} - \left[(1-\delta)\lambda_i^g + \tilde{\chi}_1\right]Eu_{ij}^{g}$$
$$\frac{dEk_{ij}^{g}}{dt} = \chi_1\psi_1 Ep_{ij}^{g} + \chi_2\psi_2 Er_{ij}^{g} + \tilde{\chi}_1 Eu_{ij}^{g} - (1-\delta)Ek_{ij}^{g}$$
$$\frac{dEc_{ij}^{g}}{dt} = \alpha_j\omega_j T_{ij}^{g} - (1-\delta)Ec_{ij}^{g}$$

**Infectious ($I_{ij}^{g}$), Actual HCV status Ab+ & RNA+**

$$\frac{dIp_{ij}^{g}}{dt} = (1-\delta)\lambda_i^g\left[Sp_{ij}^{g} + Ep_{ij}^{g}\right] - \chi_1 Ip_{ij}^{g}$$
$$\frac{dIr_{ij}^{g}}{dt} = (1-\delta)\lambda_i^g\left[Sr_{ij}^{g} + Er_{ij}^{g}\right] - \chi_2 Ir_{ij}^{g}$$
$$\frac{dIu_{ij}^{g}}{dt} = \chi_1(1-\psi_1)Ip_{ij}^{g} + \chi_2(1-\psi_2)Ir_{ij}^{g} + (1-\delta)\lambda_i^g Eu_{ij}^{g} - \tilde{\chi}_1 Iu_{ij}^{g}$$
$$\frac{dId_{ij}^{g}}{dt} = \chi_1\psi_1 Ip_{ij}^{g} + \chi_2\psi_2 Ir_{ij}^{g} + \tilde{\chi}_1 Iu_{ij}^{g} + \tilde{\chi}_2 In_{ij}^{g} + \tilde{\chi}_3 Ic_{ij}^{g} + \tilde{\chi}_4 Ik_{ij}^{g} - (\rho + \zeta_D)Id_{ij}^{g}$$
$$\frac{dIn_{ij}^{g}}{dt} = (1-\delta)\lambda_i^g Ek_{ij}^{g} - \tilde{\chi}_2 In_{ij}^{g}$$
$$\frac{dIc_{ij}^{g}}{dt} = (1-\delta)\lambda_i^g Ec_{ij}^{g} - \tilde{\chi}_3 Ic_{ij}^{g}$$
$$\frac{dIk_{ij}^{g}}{dt} = \zeta_d Id_{ij}^{g} + \zeta_R Rf_{ij}^{g} + \zeta_T T_{ij}^{g} - \tilde{\chi}_4 Ik_{ij}^{g}$$
$$\frac{dRf_{ij}^{g}}{dt} = \rho Id_{ij}^{g} + \left(1-\alpha_j\right)\omega_j Tt_{ij}^{g} - (\tau_{ij} + \zeta_R)Rf_{ij}^{g}$$

**Treatment ($T_{ij}^{g}$), Actual HCV status Ab+ & RNA+**

$$\frac{dTt_{ij}^{g}}{dt} = \tau_{ij} Rf_{ij}^{g} - (\omega_j + \zeta_T)Tt_{ij}^{g}$$

**Demographic Structure**

For each sex, 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. These broad age categories reflect the variation in HCV prevalence by age observed in the 2007-2008 national survey on viral hepatitis in Pakistan (i.e. HCV prevalence in Age 0-19: 1.5%, Age 20-29: 3.2%, and Age 30+: 6.9%). Although there is uncertainty surrounding the initiating age of injecting drug use (IDU) and the duration of IDU among PWID in Pakistan, according to the United Nations Office on Drugs and Crime report on Drug Use in Pakistan 2013[2], the mean initiation age of IDU in Pakistan was 26 years with the mean duration of IDU being 8-10 years. 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 of 20-29 years of age. Although this is a simplification of reality, we think that our model still captures the main characteristics of how injecting drug use contributes to overall levels of HCV transmission in Pakistan, with PWID making up a certain percentage of the population and having a high prevalence of HCV, both of which have been calibrated to context-specific data from Pakistan. The Young and Adult Non-/Ex-PWID categories then represent the remainder of the general population. Importantly, because PWID contribute a small proportion of HCV infections in Pakistan, this simplification should not affect our model projections.

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. 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 and non-HCV-related deaths and $\Lambda_2^g$ is the growth rate, given below.

$$\Lambda_1^g = \mu_1^g(\text{Young})_g + \mu_2^g(\text{Young Adult Non-PWID})_g + (\mu_2^g + \mu)(\text{Young Adult PWID})_g + \mu_3^g(\text{Adult})_g$$

$$\Lambda_2^g = b_g(\text{Total Population})_g,$$

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

If we sum together the population in each age/behaviour category by sex, then these categories satisfy the set of equations (refer to Supplementary Figure S1b):

$$\frac{d}{dt}(\text{Young})_g = \Lambda_g - (\eta_1 + \mu_i^g)(\text{Young})_g$$

$$\frac{d}{dt}(\text{Young Adult})_g = (1-\phi_g)\eta_1(\text{Young})_g - (\eta_2 + \mu_2^g)(\text{Young Adult})_g$$

$$\frac{d}{dt}(\text{Young Adult PWID})_g = \phi_g\eta_1(\text{Young})_g - (\eta_2 + \mu_2^g + \mu)(\text{Young Adult PWID})_g$$

$$\frac{d}{dt}(\text{Adult})_g = \eta_2[(\text{Young Adult})_g + (\text{Young Adult PWID})_g] - \mu_3^g(\text{Adult})_g$$

**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 Supplementary Figure S1c). Each of the health states is stratified using the same S-E-I-T structure as described in the baseline HCV 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 to re-infection by HCV, 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, $\xi_{CH}$. Resolution of HCV infection (i.e. SVR) at the cirrhotic stage is associated with slower progression either to decompensation or HCC, with a decreased relative risk of $\epsilon_{CD}$ for the former and $\epsilon_{DH}$ for the latter. Meanwhile, decompensation can also progress to HCC at a rate $\xi_{DH}$; 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.[3] 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, $\mu_5$. Note that our model simulates different causes of death, including natural death, drug-related death in PWID, and disease-related death for HCV-infected persons with advanced stages of liver disease (i.e. decompensated cirrhosis and HCC), which incorporates a measure of competing mortality risk.

Disease progression follows the set of equations below (refer to Supplementary Figure S1c):

$$\frac{d}{dt}(\text{Pre-Cirrhotic}) = -\sigma(\text{Pre-Cirrhotic Infected})$$

$$\frac{d}{dt}(\text{Cirrhotic}) = \sigma(\text{Pre-Cirrhotic Infected}) - (\hat{\epsilon}_{CD}\gamma + \hat{\epsilon}_{CD}\xi_{CH})(\text{Cirrhotic})$$

$$\frac{d}{dt}(\text{Decompensated}) = \hat{\epsilon}_{CD}\gamma(\text{Cirrhotic}) - (\hat{\epsilon}_{DH}\xi_{DH} + \mu_4)(\text{Decompensated})$$

$$\frac{d}{dt}(\text{HCC}) = \hat{\epsilon}_{CH}\xi_{CH}(\text{Cirrhotic}) + \hat{\epsilon}_{DH}\xi_{DH}(\text{Decompensated}) - \mu_5(\text{HCC}),$$

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

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

**Force of Infection**

For notational convenience, we can define the broad categories in the S-E-I-T structure by summing the corresponding compartments. For each $i \in \{1, 2, 3, Y\}$, $j \in \{I, C, D, H\}$, and $g \in \{g_1, g_2\}$, let

$$S_{ij}^g(t) = Sp_{ij}^g(t) + Sr_{ij}^g(t),$$

$$E_{ij}^g(t) = Ep_{ij}^g(t) + Er_{ij}^g(t) + Eu_{ij}^g(t) + Ek_{ij}^g(t) + Ec_{ij}^g(t),$$

$$I_{ij}^g(t) = Ip_{ij}^g(t) + Ir_{ij}^g(t) + Iu_{ij}^g(t) + Id_{ij}^g(t) + In_{ij}^g(t) + Ic_{ij}^g(t) + Ik_{ij}^g(t) + Rf_{ij}^g(t),$$

$$T_{ij}^g(t) = Tt_{ij}^g(t).$$

The force of infection (FOI), $\lambda_i(t)$, describes the time-varying rate of HCV transmission and incorporates factors that can influence this transmission rate, such as age or behaviour. The force of infection specifically associated with HCV transmission due to injecting drug use among PWID is denoted by $\pi_Y(t)$. 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, $\theta_Y$, associated with injecting drug use.

Define the various populations as follows:

$$\text{Total} = \sum_{\substack{i\in\{1,2,3,Y\} \\ j\in\{I,C,D,H\} \\ g\in\{g_1,g_2\}}} \left[S_{ij}^g + E_{ij}^g + I_{ij}^g + T_{ij}^g\right],$$

$$\text{Total Infectious} = \sum_{\substack{i\in\{1,2,3,Y\} \\ j\in\{I,C,D,H\} \\ g\in\{g_1,g_2\}}} I_{ij}^g,$$

$$\text{Total PWID} = \sum_{\substack{j\in\{I,C,D,H\} \\ g\in\{g_1,g_2\}}} \left[S_{Yj}^g + E_{Yj}^g + I_{Yj}^g + T_{Yj}^g\right],$$

$$\text{PWID Infectious} = \sum_{\substack{i\in\{1,2,3,Y\}\\ j\in\{I,C,D,H\}\\ g\in\{g_1,g_2\}}} I_{ij}^{g}.$$

For $i = 1, 2, 3$, define:

$$\bar{\lambda}_i = \beta_i \left(\frac{Total\ Infectious}{Total}\right),\ \pi_Y = \theta_Y \left(\frac{PWID\ Infectious}{Total\ PWID}\right).$$

The forces of infection, for each age/behaviour group $i = 1, 2, 3, Y$, at baseline are defined as:

$$\lambda_i = \begin{cases} \bar{\lambda}_i, & if\ i = 1, 2, 3, \\ \bar{\lambda}_2 + \pi_Y, & if\ i = Y. \end{cases}$$

Note that for the PWID subpopulation (denoted by index $i = Y$), the force of infection consists of two terms: an age-related contribution due to being a Young Adult, $\bar{\lambda}_2$, and an additional behaviour-related contribution due to injecting transmission risks, $\pi_Y$. Also, 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.

**Calculating HCV Infected Incidence**

The HCV infected incidence $Inc_G$ for a particular subgroup $G$ of all compartments can be calculated from the force of infection, $FOI_G$, using the general formula

$$Inc_G = \frac{\sum_{s\in G}(FOI_s \times Susceptible_s)}{\sum_{s\in G} Susceptible_s}.$$

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 $G_1$ for Non-PWID and $G_2$ for PWID, respectively. Then,

$$Inc_{(Non-PWID)} = \sum_{\substack{i\in\{1,2,3\}\\ j\in\{I,C,D,H\}\\ g\in\{g_1,g_2\}}} \lambda_i S_{ij}^{g} \Bigg/ \sum_{\substack{i\in\{1,2,3\}\\ j\in\{I,C,D,H\}\\ g\in\{g_1,g_2\}}} S_{ij}^{g},$$

and

$$Inc_{(PWID)} = \sum_{\substack{j\in\{I,C,D,H\}\\ g\in\{g_1,g_2\}}} \lambda_Y S_{Yj}^{g} \Bigg/ \sum_{\substack{j\in\{I,C,D,H\}\\ g\in\{g_1,g_2\}}} S_{Yj}^{g}.$$

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

$$Inc_{(Non-PWID)} = \sum_{\substack{i\in\{1,2,3,Y\}\\ j\in\{I,C,D,H\}\\ g\in\{g_1,g_2\}}} \lambda_i S_{ij}^{g} \Bigg/ \sum_{\substack{i\in\{1,2,3,Y\}\\ j\in\{I,C,D,H\}\\ g\in\{g_1,g_2\}}} S_{ij}^{g}.$$

HCV incidence is estimated at every timestep using the above formula, using parameter values presented in Supplementary Tables S1a-c and the unknown transmission coefficient parameter $\beta$. The value of $\beta$ is estimated through calibrating the modelled HCV prevalence to available HCV prevalence data from the 2007-2008 national survey on viral hepatitis in Pakistan and changes in HCV prevalence over time based on trends among blood donors. To capture these prevalence trends, the $\beta$ parameter is varied for each sampled model parameter set to minimise the difference between the modelled prevalence in 2007 and the national survey data by age profile, and in the modelled changed in prevalence by 2017 (one decade following the 2007-2008 national survey) and the projected data estimated increased in HCV prevalence by 2017. The calibrated model then automatically produces projections of what HCV incidence trends were needed over time to capture these HCV prevalence trends.

## Temporal Trends in HCV Seroprevalence in Non-PWID Risk Groups in Pakistan

**Background**
We have previously conducted a review of HCV seroprevalence trends among non-PWID populations in Pakistan, which quantified the changes in HCV seroprevalence among existing blood donor and antenatal data across five Pakistan cities from 1994 to 2014.[1] To summarise, first 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. Second, 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.

**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 computerised 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 computerised 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. In total, 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.

**Results and 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).

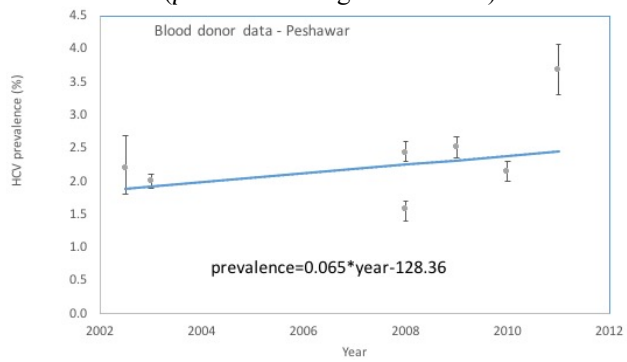
HCV prevalence data was collected on the following population groups: general population (n= 44), paediatric populations (n=9), recruitment for employment (n=23), pregnant women (n=21), blood donors (n=64), patients seeking hospital care (not related to HCV) (n=8), and students (n =1). Studies used a 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), particle 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.

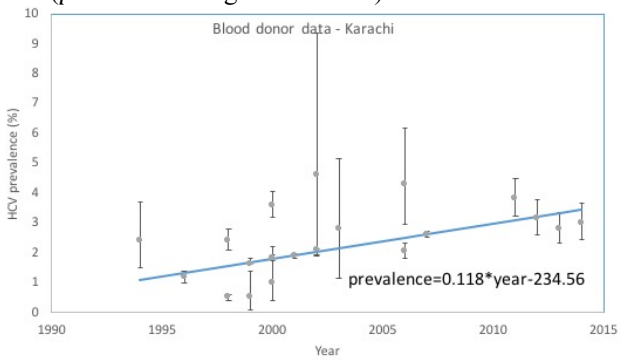
The HCV prevalence trends for blood donors in different cities, with associated 95% confidence intervals, are presented in Supplementary Figures S2(a)-(e). Although the trends in most cities suggest considerable variation, they consistently suggest a stable or slow upward trend over the last 10 to 20 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. 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 prevalence trends for antenatal women in Lahore are presented in Supplementary Figure S2(f). This data also suggests a fairly stable HCV prevalence 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 prevalence over the recent past.

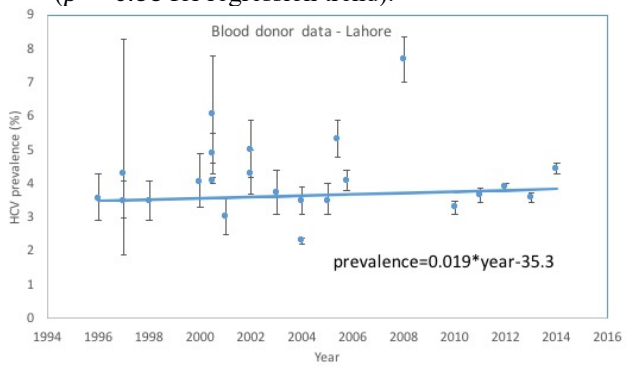
(a) HCV prevalence trends for blood donors in Peshawar ($p = 0.18$ for regression trend).



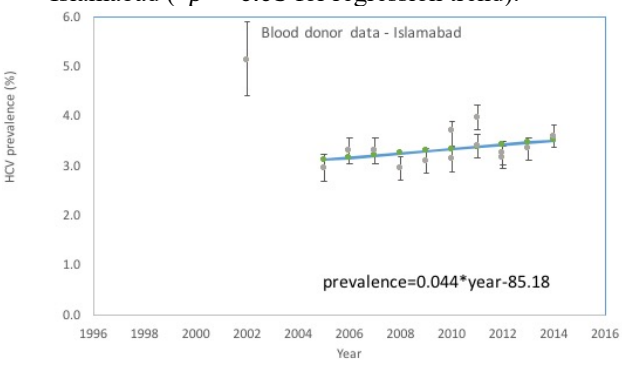

(b) HCV prevalence trends for blood donors in Karachi ($p < 0.01$ for regression trend).



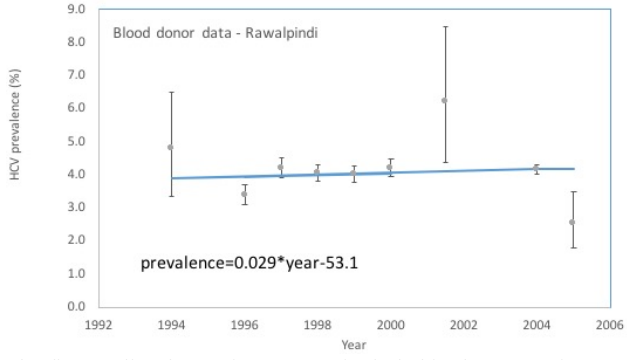

(c) HCV prevalence trends for blood donors in Lahore ($p = 0.66$ for regression trend).



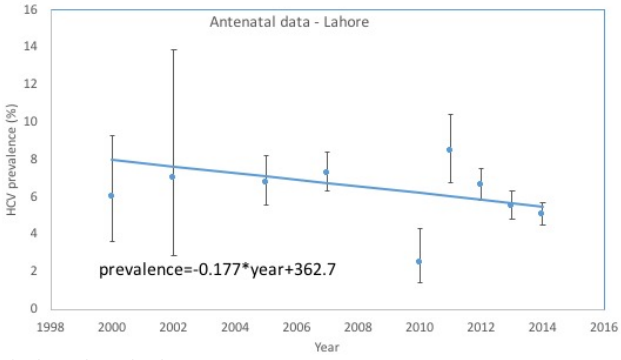

(d) HCV prevalence trends for blood donors in Islamabad (*$p = 0.03$ for regression trend).




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




(f) HCV prevalence 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.

**Supplementary Figure S2.**
HCV 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.

## Methods for Model Uncertainty Analysis: Model Parameterisation & 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 S1, whereas baseline values and uncertainty ranges for the demographic and epidemiological data used to calibrate the model is shown in Supplementary Table S2.

**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])[4-6], 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).[4] 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, $\mu_1^g$, $\mu_2^g$, and $\mu_3^g$ 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.[4,5]

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.[4-6] Current estimates from various sources also appear to indicate that the population growth rate is continuing to decrease.[4-8] 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.[4] Moreover, the US Census Bureau projects the average growth rate to fall to 1.33% by the year 2030.[7] To better represent this shift in the demographics of the population, for each sex, 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.

**Injecting Drug Use**

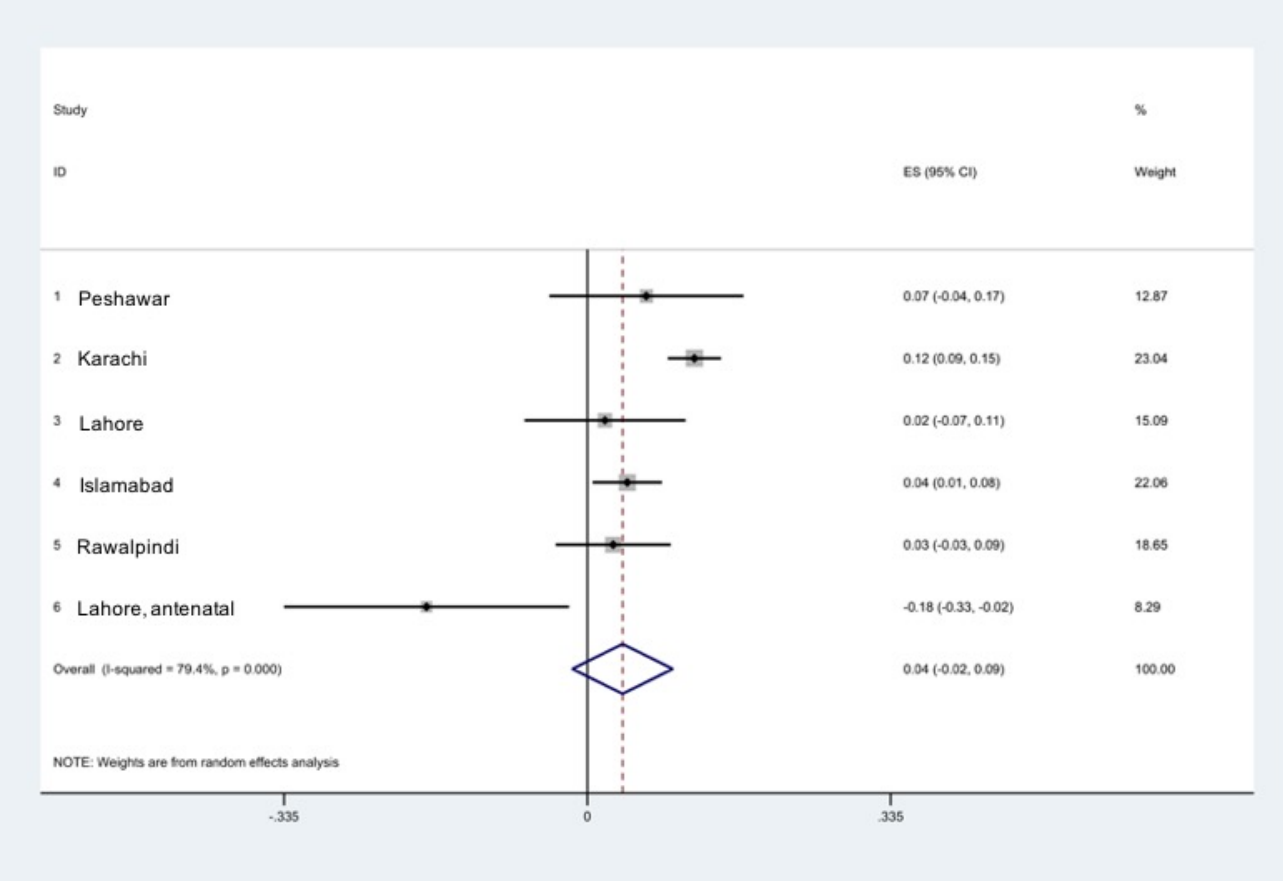
There is a great deal of uncertainty in the proportion of the general population that are PWID. Mathers et al. estimated the prevalence of PWID in 2006 to be 0.14% of persons 15-64 years of age, with low and high estimates of 0.13% and 0.16%.[9] This equates to 0.09% [0.08-0.1%] of the whole population. 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.[10] 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.[11] 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.[2] 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.[2] 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 sex, 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.[2,12] The UNODC 2013 report considered PWID prevalence by sex 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.[13]

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 42.2% +/- 13.1% (57.0 +/- 17.7% anti-HCV).[14] Aceijas and Rhodes reported a national chronic HCV infected prevalence estimate of 65.9% (89.0% anti-HCV), alongside a capital city estimate of 57.7-69.6% (78.0-94.0% anti-HCV), and an estimate for other sites of 55.5-68.9% (78.0-93.0% anti-HCV).[15] Other studies have reported chronic HCV infected prevalence to lie over a broad range from 5.9% to 67.3% (8.0-91.0% anti-HCV).[16] 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 62.2% (84.0% anti-HCV), with respective low and high estimates of 55.5% (75.0% anti-HCV) and 68.8% (92.9% anti-HCV).[17] 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.

**Meta-Analysis of HCV Seroprevalence Trends**

Our review of HCV among non-PWID risk groups in Pakistan yielded six temporal seroprevalence trend estimates as described in the previous section and in Lim et al.[1]. A random-effects meta-analysis was carried out on these trends to assess the expected change in HCV seroprevalence accounting for the effect sizes of each of the estimates. This yielded a pooled estimate of 0.39% (95%CI -0.17 to 0.94%) change in HCV seroprevalence per decade over 1994 to 2014 (Supplementary Figure S3).




**Supplementary Figure S3.**

Forest plot for random-effects meta-analysis on HCV seroprevalence trends among blood donor and antenatal data across five Pakistan cities from 1994 to 2014, suggesting an increase in anti-HCV prevalence of 0.39% (95%CI -0.17 to 0.94%) per decade.

**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 2007-2008 national survey on hepatitis B and C involving 47,043 individuals sampled from 7,000 households across Pakistan.[18] 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.[18] A systematic review from 2006 found that 26% [95%CI 22-29%] of acute infections are spontaneously cleared[19], 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 2007-2008 national survey results, we calculate the chronic HCV infected prevalence across both sexes 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, a meta-analyses of HCV seroprevalence trends over a 20-year period between 1994 and 2014 from blood donor and antenatal data across five major cities in Pakistan indicate a change of 0.39% [-0.17 to 0.94%] every 10 years (see previous section for details) – this range of temporal HCV prevalence trends is sampled uniformly. We calibrated the transmission parameters in the model and the approximations for the initial size of the HCV epidemic in Pakistan to capture the changes in chronic infected prevalence trend from 2007 to 2017.

**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.[20] 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.[3,21,22] Because data suggests 80% of HCV-infected individuals are genotype 3 in Pakistan[23-25], and studies suggest genotype 3 infections are associated with increased disease progression[26-29], 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.[27] The uncertainty distributions for the different transition and mortality probabilities were obtained from the literature (as indicated in Supplementary Table S1), which were sampled and then converted to instantaneous rates for parameterisation of the mathematical model.

**SVR and Disease Progression**

Chronic HCV infection leads to compensated cirrhosis if left untreated, and eventually to end-stage liver disease (ESLD), referring to decompensated cirrhosis and hepatocellular carcinoma (HCC).[30] It is assumed that achieving SVR halts disease progression in pre-cirrhotic patients, and reduces disease progression in post-cirrhotic patients. The latter is based on evidence that disease progression occurs at a reduced rate from compensated cirrhosis to decompensated cirrhosis or to HCC following SVR.[31] 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[32] and DAA treatment[33] 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.

**Existing and Future Treatment**

The public sector has been involved in procuring conventional treatments for HCV using interferon (IFN) or pegylated 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.[34] Data from the public sector on historical and existing treatment numbers are shown in Supplementary Table S3. 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.[34] 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 discernible change over time.[35-39] A report on health services utilisation using data from the World Health Survey of 2003 from a number of low- and lower-middle income countries suggest

that the share of inpatient visits at government facilities in Pakistan was approximately 40-45%. 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 150,000-160,000 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[24], 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.[40] 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%.[41-45] We sample the SVR for conventional treatments uniformly between the lower and upper bound estimates.

**HCV Treatment SVR Rates and DAAs in Pakistan**

Prior to 2016, conventional treatments were used in Pakistan, which had estimated SVR rates of 61% [50-73%]. Following the introduction of DAAs into the market in 2016, we assume that SVR rates improved to 90% [80-95%]. This is based on evidence that 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.[46-51] However, recent studies on DAA treatment efficacy, both outside and within Pakistan healthcare settings, 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.[52,53] The wide range of SVR for DAAs reflect the challenges in treating HCV genotype 3 in the Pakistan context, with reported SVR 12 rates of 84% in a Pakistan-specific treatment cohort.[54] Moreover, we assume the duration of DAA treatment to be 12 weeks for pre-cirrhotic patients and 24 weeks for post-cirrhotic patients, including those with compensated cirrhosis, decompensated cirrhosis, and HCC. Nevertheless, in our analyses, we consider treatment with the pangenotypic regimen of sofosbuvir and daclatasvir (SOF+DCV), which has shown high cure rates (88-98%) across genotypes, including genotype 3[51], and is being used as the standard of care at the province level in Pakistan.[34]

**Model Calibration**

To incorporate uncertainty, the parameters and calibration data were sampled 4,000 times from their respective uncertainty distributions as in Supplementary Tables S1 and S2. 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'). Chronic HCV prevalence in 2007 was fit by age and behaviour (i.e. PWID) categories. The parameter sets were then validated by comparing the output of the model for each simulation with the overall chronic HCV prevalence from the 2007-2008 national survey data[18], and the changing HCV prevalence trends from blood donor data as described above. A total of 2,849 model simulations failed to fit within the 95% CI of the HCV prevalence data overall and were excluded. The remaining (n = 1,151) model fits were used for subsequent analyses. The model was solved numerically using an explicit fourth order Runge-Kutta method in Matlab.[55,56] All model simulations were performed using Matlab Version R2018b, and the random-effects meta-analyses on HCV seroprevalence trends was conducted in Stata Version 14. Our model calibration and projections were robust to sampling 500, 1000, 2000, and 4000 initial parameters sets and yielded consistent results.

**Collection of Cost Data from the MSF HCV Programme in Machar Colony, Karachi, Pakistan**

Screening and treatment costs were collected and analysed by using a retrospective, cohort-based micro-costing approach from the provider's perspective[57] for an ongoing HCV treatment programme in Karachi, Pakistan, which was established by MSF in 2015.[58] These consist of two main types of costs: direct costs and indirect costs. Direct costs include any costs that can be directly linked to treatment of a patient, such as diagnostics tests, DAA drug costs, staff time, and other materials. Meanwhile, indirect costs include expenses that are incurred which cannot necessarily be broken down into individual unit costs for a patient, but are required for the activity to be conducted, such as estates, overheads, electricity, etc. Taking both of these into consideration, the total unit costs for diagnosis and treatment, by pre-cirrhotic or post-cirrhotic stages, which are used in the modelling projections are shown in Supplementary Table S4.

Supplementary Table S5 includes details of the costing assumptions made and how costs were derived for HCV screening and treatment. These costs have primarily been calculated from our ingredients-based costing analysis[57] of the local MSF HCV intervention in Karachi[58], however, several changes were made to more realistically represent a potential national scale-up. Specifically, the Ab test kits in the MSF HCV treatment protocol were Oraquick (test kit cost of USD $13.74), but we have assumed use of SD Bioline (test kit cost of USD $2.15 from our costing analysis of

the MSF HCV intervention in Machar Colony, Karachi, Pakistan), which is the WHO pre-qualified HCV rapid diagnostic test[59] and is widely available in Pakistan. In the baseline cost analysis, we have not explicitly included costs of referral; however, the intervention on which our cost estimates are based included activities such as extensive individual counselling at each step of the treatment pathway to ensure high referral from diagnosis to treatment assessment. We therefore assume that costs for improving referral up to 80% are implicitly included in our cost estimates. Additional costs to further increase referral to 90% are explored in the sensitivity analyses and is shown to have minimal impact on the overall costs.

**Intervention Scenarios for the HCV Screening and Treatment Cascade**

The calibrated model was used to evaluate various screening and treatment intervention scenarios from 2018, with corresponding model parameters detailed in Supplementary Table S1. In all scenarios, we assume that individuals with a positive HCV Ab test are tested for HCV RNA, i.e. $\psi_1, \psi_2 = 1$.

*Intervention Scenarios*

We used the model to investigate the following scenarios from 2018 onwards (see Supplementary Figure S4 for a visualisation of the intervention scenarios).

- **Scenario S0:** No further treatment from 2018 onwards.
- **Scenario SQ:** Assuming screening and referral rates to maintain levels of treatment (`Status Quo'), which is ~150,000-160,000 treatments per year. In this scenario, referral rates were sampled uniformly between 35% and 70% per year across model runs, and then overall screening rates were fitted (2.6-5.9% of the population per year) to yield an average treatment rate of approximately 150,000-160,000 annually over 2018 to 2030.
- **Scenario S1:** One-time random screening of 90% of the 2018 Pakistan population by the end of 2030, equating to 6.2% [6.1-6.3%] screened annually, with 80% of diagnosed individuals referred to care.
- **Scenario S2:** One-time screening (as Scenario S1) but targeted first to individuals over 30 years of age and PWID, who have higher HCV prevalence. In particular, this means that those aged over 30 and PWID are selected for screening first, and then others are screened thereafter to make up the annual screening quota.
- **Scenario S3:** Prioritised one-time screening (as Scenario S2), but with periodic RNA re-screening of cured individuals and those previously screened RNA-, and Ab re-screening of individuals previously screened Ab-. Re-screening starts from 2020 and occurs every 10-years for non-PWID and annually for PWID.
- **Scenario S4:** Prioritised one-time screening as in Scenario S3, but with an increased referral rate (90% instead of 80%), double the primary Ab screening rate (12.4% per year instead of 6.2%), increased re-screening every 5-years for non-PWID (from every 10-years), and re-engaging LTFU non-PWID every 5-years and PWID every year (not included previously).

*Referral Rates*

The referral rate represents the rate at which individuals who are diagnosed with chronic HCV infection initiate treatment, with the remaining individuals lost to follow up (LTFU). In the Status Quo Scenario SQ, the current levels of screening and referral that result in 150,000-160,000 average annual treatments over 2018 to 2030 is unknown. For each model fit, we sampled the referral rate between 35% and 70%, and then fitted the corresponding overall screening rate (2.6-5.9% of the population per year) to obtain the status quo treatment rate. A 35% referral rate was selected as the lower bound based on data from an intervention in Karachi[57], which corresponded to an overall screening rate of approximately 6.2% [6.1-6.3%] per year as in Scenario S1. The 70% referral rate was selected as the upper bound based on evidence of higher rates of referral achieved in a testing and treatment programme in Lahore, Pakistan[60] In Scenarios S1 to S4, we consider referral rates of 80-90%, which are based on recommendations of the WHO Global Health Sector Strategy for the elimination of viral hepatitis[61], with similar referral rates to these having recently been achieved in Egypt (https://www.who.int/hepatitis/news-events/egypt-hepatitis-c-testing/).

*Loss to Follow-Up (LTFU)*

For simplicity, the model focusses primarily on one aspect of LTFU in our analysis, namely, LTFU between diagnosis and referral to treatment. However, the end effect of other forms of LTFU will be equivalent in reducing the overall proportion of individuals that complete treatment and are cured. This is especially true for LTFU following diagnosis and during referral, with this effectively reducing the proportion of diagnosed individuals that start treatment, and so can easily be seen as one LTFU occurring between diagnosis and treatment initiation. Also, testing and treatment studies in Pakistan evaluated by our team have generally found very low LTFU rates after starting treatment (8%) and high cure rates (SVR = 94-97%) among all those that completed treatment (and attended their SVR12 visit). Because it is likely that this latter aspect of LTFU plays a less substantial role than the potential LTFU that can occur between diagnosis and treatment initiation, we assume that little LTFU occurs after starting treatment and is accounted for in our intention to treat SVR rates.

*Impact on HCV Incidence and HCV-Related Mortality*

For each scenario, impact was measured in terms of reductions in HCV incidence and mortality by 2030 compared with 2015 levels. Estimation of other measures of impact such as the number of new infections averted or the number of

HCV-related deaths averted between 2018 and 2030 for each intervention scenario were compared to Scenario S0 (the counterfactual scenario of no further treatment from 2018 onwards).

*Metrics for the Cascade of Care*

We calculated the total number of persons falling into the following categories for each year, as well as the cumulative sum across 2018-2030: (i) screened, (ii) diagnosed (both Ab+ and RNA+), (iii) referred to treatment, (iv) initiated treatment, and (v) cured (i.e. achieved SVR). The cascade of care (Figure 3 of the main text) for each scenario was constructed by evaluating the proportions that were diagnosed, referred to treatment, initiated treatment, and achieved SVR, as compared with the chronic HCV burden in 2018, which was set at 100%. The full burden of infections over 2018-2030 was defined as the number of chronic HCV infections in 2018 plus all new chronic infections that would have occurred from 2018-2030.

(a) Visualisation of the counterfactual scenario S0, Status Quo SQ, and Intervention Scenarios S1-S3.

| **Baseline** | | **Intervention Scenario** | | | |
|---|---|---|---|---|---|
| **S0** | **SQ** | **S1** | **S2** | **S3** | |
| | | | | | **No Intervention** From 2018 Onward |
| | | | | | '**Status Quo**' (~150,000-160,000 Treatments Per Year) |
| | | | | | **One-Time 90% Screen**^ By 2030 with **80% Referred** |
| | | | | | + **Target** Ab Screening Age 30+ & PWID |
| | | | | | + **Re-Screen SVR & Ab-/RNA-** Every 10 Years From 2020† |

(b) Visualisation of additional Intervention Scenario S4 in relation to incremental improvements to Scenario S3.

| **Additional Incremental Intervention Scenario** | | | | | |
|---|---|---|---|---|---|
| **S3** | **---** | **---** | **---** | **S4** | |
| | | | | | **One-time 90% Ab Screen** with **80% Referral**<br>+ **Target** Screening Age 30+ & PWID<br>+ **Re-Screen** SVR, RNA-, and Ab- every 10 years† |
| | | | | | + **Increase Referral to 90%** |
| | | | | | + **Double One-time Screening**^ so that >90% of population screened once by 2025 |
| | | | | | + **Re-Screen Every 5 Years†** |
| | | | | | + **Re-Engage LTFU Every 5 Years†** |

^A 6.2% [6.1-6.3%] annual primary Ab screening rate will screen approximately 180 million by 2030. Doubling this rate to 12.4% [12.1-12.6%] primary Ab screened per year will screen over 180 million by 2024.
†Re-screening refers to repeat Ab-screening of individuals previously screened Ab- as well as RNA-screening of individuals who have previously been tested Ab+, but may not be aware of their present HCV RNA status, including those who have never been RNA-tested, or were previously tested RNA-, lost-to-follow-up (LTFU), or previously cured. Frequency of re-screening is varied as indicated, except for PWID, who are re-screened every year from 2020.

**Supplementary Figure S4.**
Graphical representation of Intervention Scenarios S0, SQ, and S1-S4 explored in our analyses.

## Supplementary Model Projections and Results

**Screening and Re-screening for HCV Ab and RNA**

The number of persons screened is estimated by including all individuals who receive at least one of Ab and/or RNA test(s) (Supplementary Table S6). Those who are Ab- would undergo a single test for HCV Ab, while those who are known Ab+ would undergo a single test for HCV RNA. Meanwhile, those who receive a positive Ab test result and subsequently undergo a confirmatory RNA test would require two tests for the same individual.

**Annual Primary Screening Rate**

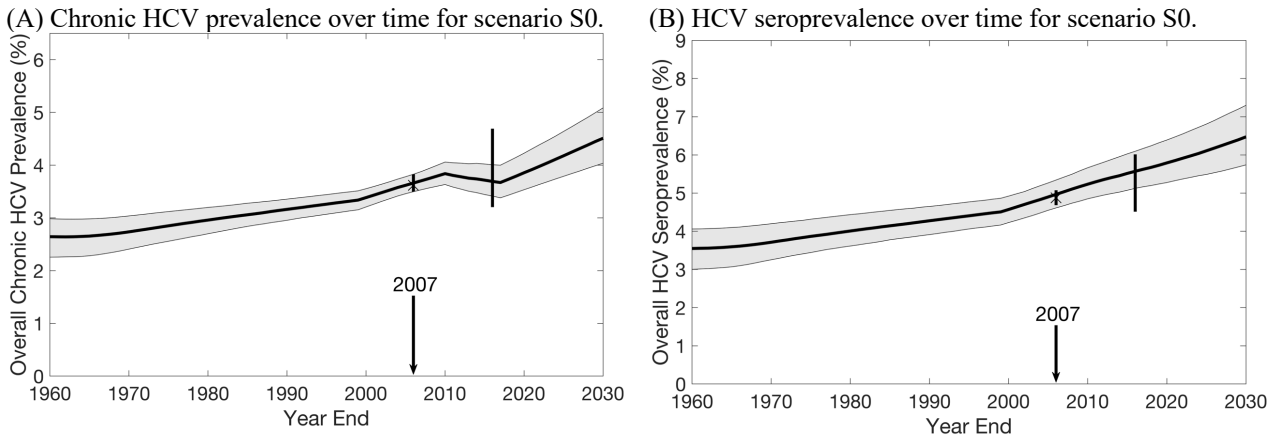
An annual primary Ab screening rate of 6.2% [95% uncertainty interval of modelled runs, 6.1-6.3%], a total of 179 [174-183] million people will have been screened by 2030, which is 90% of the population in 2018. Considering the rapid population growth in Pakistan, this would only cover 72.4% [69.5-75.2%] of the projected total population size by the end of 2030. Doubling the rate of primary Ab screening to 12.4% [12.1-12.6%] per year will instead result in 278 [265-291] million people, or 112.4% [111.4-113.6%] of the projected 2030 population, screened by 2030, which is equivalent to 139.7% [135.5-144.6%] of the total population in 2018. Note that a doubled primary Ab screening rate would screen >90% of the 2018 population by 2025.

**Re-Screening is Necessary to Reduce Incidence Long-Term**

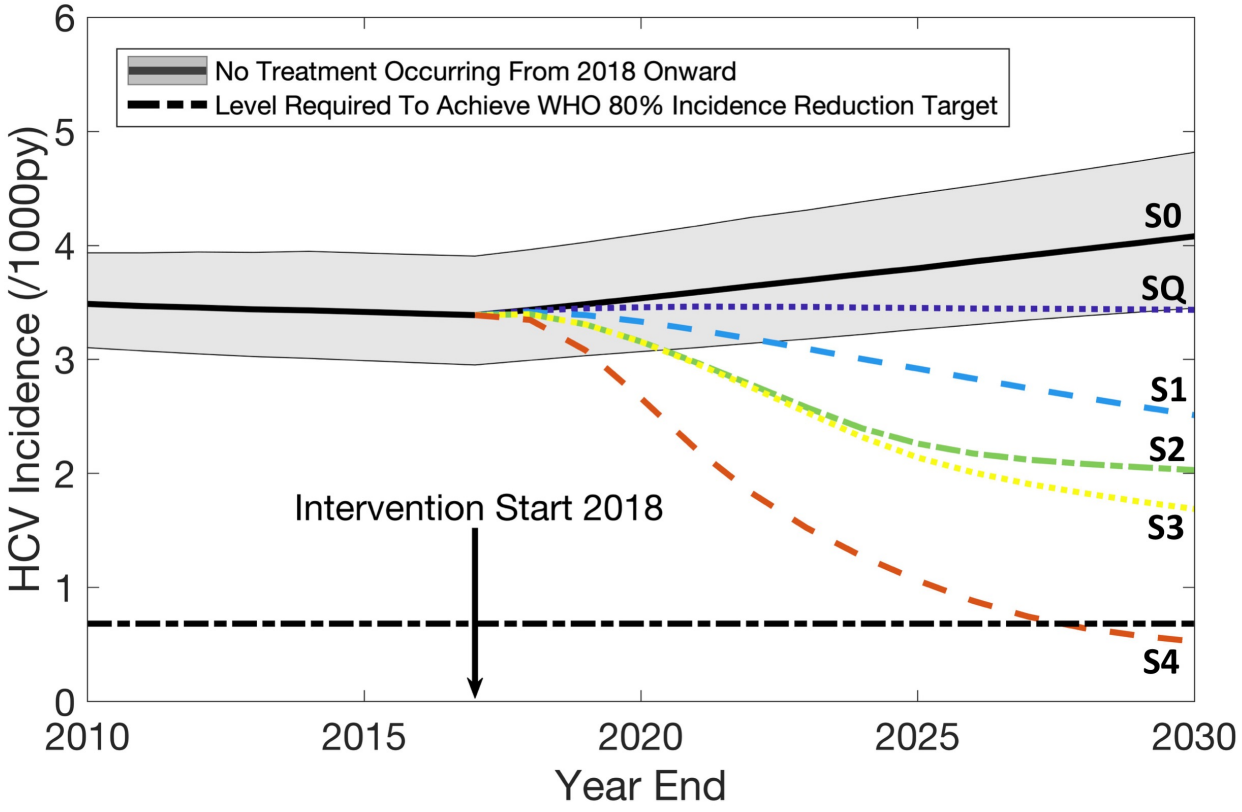
Although screening the whole population as rapidly as possible leads to the greatest impact in terms of reduction in incidence (e.g. one-time screen everyone in the first year, and subsequently one-time screen only new-borns), this differed minimally from spreading out one-time screening evenly over the period from the start of the intervention to the end of 2030. In this scenario, even perfect referral rates of 100%/year and one-time screening everyone in the first year would reduce incidence by at most 69% [63-74%] and mortality by at most 60% [50-65%] by 2030. The reason for this is because re-screening is necessary to identify new infections that occur following first-time or primary Ab screening in the case of previously screened Ab- individuals, or RNA re-screening for cured individuals and those previously screened RNA-.

**Reaching WHO HCV Targets for Reducing Mortality**

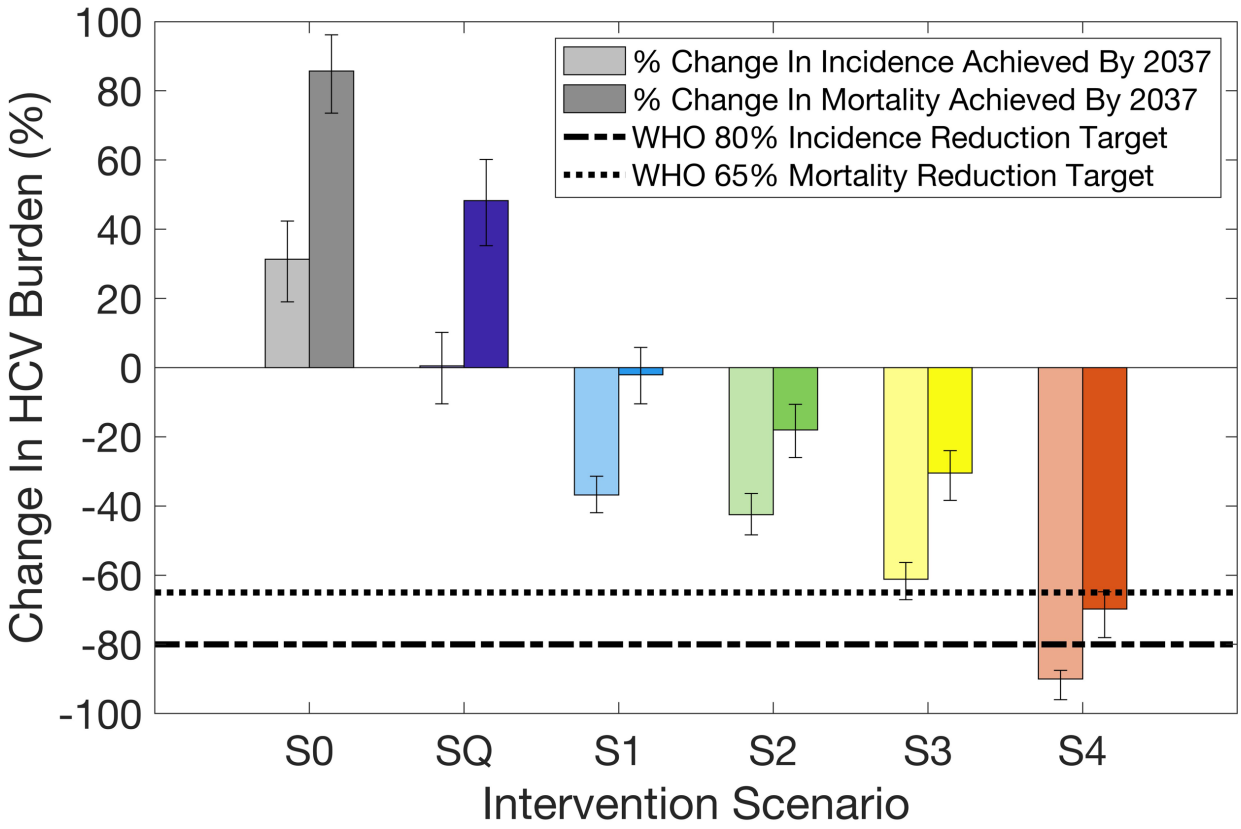
In the counterfactual Scenario S0 and the Status Quo Scenario SQ, HCV-related mortality was projected to increase by 49% and 32%, respectively, compared to 2015. Even with a further doubling of the treatment numbers, as in the one-time screening Scenario S1, HCV-related mortality was still projected to increase by 7% over the same period, although it is a decrease by 2030 compared to both the counterfactual Scenario S0 and the Status Quo Scenario SQ. This highlights the challenges in reducing HCV-related mortality by 2030 in a setting that has an increasing epidemic. A comprehensive screening and treatment intervention, as in Scenario S4, achieves over an 80% reduction in HCV incidence by 2030 compared to 2015, but only reaches the target of reducing HCV-related mortality by 65% by 2035 (Supplementary Table S6, see also Supplementary Figure S7 for the changes in HCV incidence and HCV-related mortality under each interventions scenario by the end of 2037, i.e. 20 years after the start of intervention in 2018). Further intervention scale-up is needed to achieve the 65% mortality reduction target by 2030.




**Supplementary Figure S5.**
Model projections from 1960 to 2030 for (A) overall chronic HCV prevalence and (B) HCV seroprevalence (i.e. HCV Ab prevalence) over time for the baseline scenario S0 of no treatment from 2018 onwards. The model was calibrated to chronic HCV prevalence in 2007 from the 2007-2008 National Survey for each age group[18] and from surveys amongst PWID[17], as well as to the changing HCV prevalence trends a decade later in 2017 according to a meta-analysis on blood donor data from 1994-2014. Our model projections estimate an increase in HCV Ab prevalence of 0.61% [95% of model runs: 0.40 to 0.87%] over the 10-year period between 2007 and 2017. This is consistent with our random-effects meta-analysis on HCV seroprevalence trends among blood donors and antenatal data over 1994-2014, which suggested an increase in anti-HCV prevalence of 0.39% (95%CI -0.17 to 0.94%) per decade (Supplementary Materials, Section 3; see also Supplementary Figure S3).The kink in model projections for chronic HCV prevalence (Figure S5A) is due to the scale-up in treatment from 2010, which is then stopped in 2018 for scenario S0. This is not shown in the figure of HCV seroprevalence (Figure S5B) because treatment does not affect antibody prevalence as directly. The timeseries line represents the median of 1,151 final model runs, with the shaded area showing the 95% uncertainty intervals of runs.



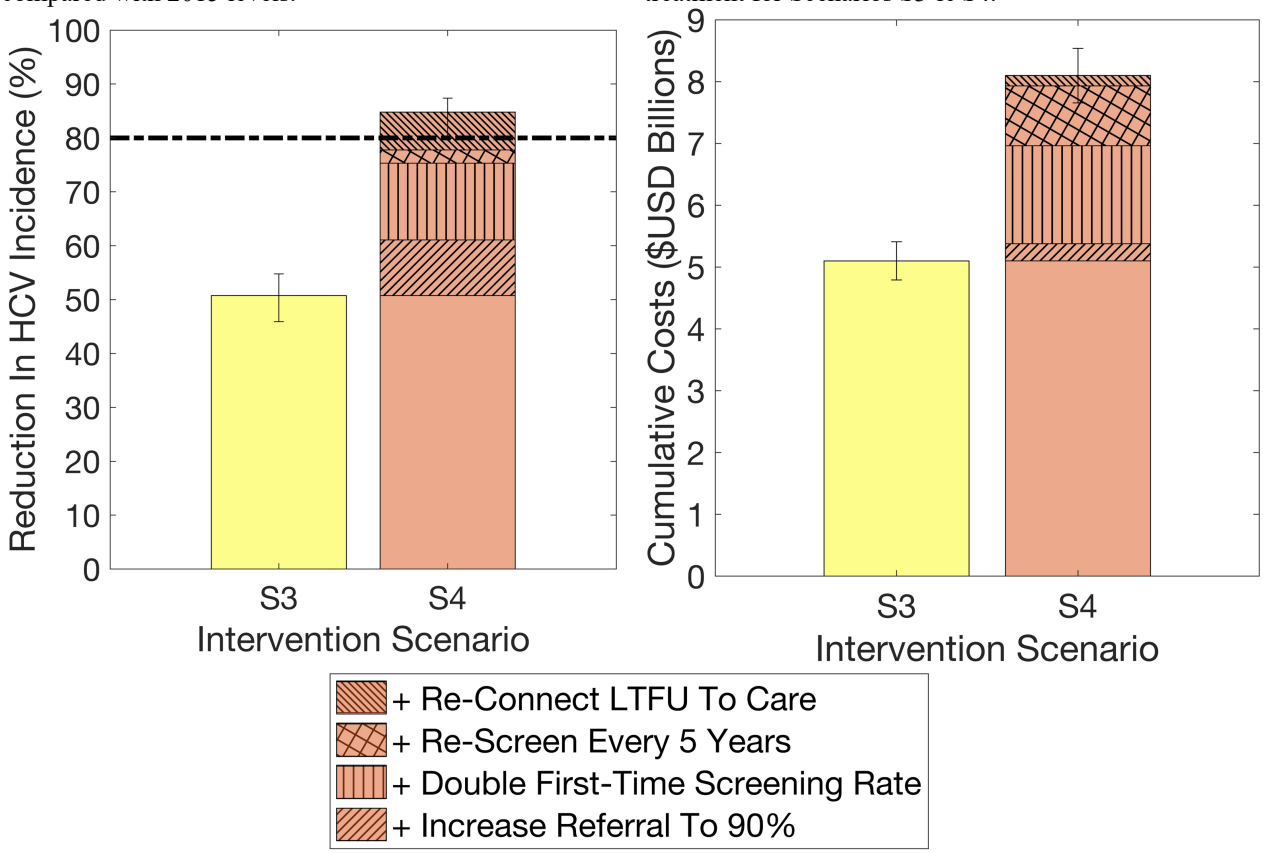

**Supplementary Figure S6.**
Model projections showing the changes in HCV incidence until 2030 for the modelled intervention scenarios. At the start of 2018, HCV incidence was projected to be 3.4 [3.0-3.9] per 1000 person-years, with an estimated 660,000 [580,000-750,000] new HCV infections in 2018. The lines for each scenario indicate the medians of 1,151 final model runs. The shaded area shows the 95% uncertainty intervals for the counterfactual baseline Scenario S0.




**Supplementary Figure S7.**
Reductions in incidence and mortality achieved for Scenarios S0, SQ, and S1-S4 by the end of the year 2037 (i.e. 20 years after the start of intervention). Although the most aggressive scenario S4 allows the 80% incidence reduction target to be reached by 2030 (Figure 2 in main text), achieving the 65% reduction in mortality requires further scale-up and would take longer to realise. In our main analyses, we have shown that a 65% reduction in HCV-related mortality can be achieved by 2035 (Supplementary Table S6). Intervention scenarios are as follows. **Scenario S0:** No screening or treatment from 2018 onwards. **Scenario SQ:** Maintaining status quo treatment of 150,000-160,000 annual treatments. **Scenario S1:** One-time screening 90% of the general population by 2030. **Scenario S2:** One-time screening as in Scenario S1, with prioritisation for PWID and adults (30+ years). **Scenario S3:** One-time prioritised screening as in Scenario S2, along with re-screening cured and previously Ab-negative individuals from 2020 (every ten years for non-PWID and annually for PWID). **Scenario S4:** Scenario S3 with incremental improvements as described in the main text. The height of each bar represents the median of 1,151 final model runs, with whiskers indicating 95% uncertainty intervals of runs.

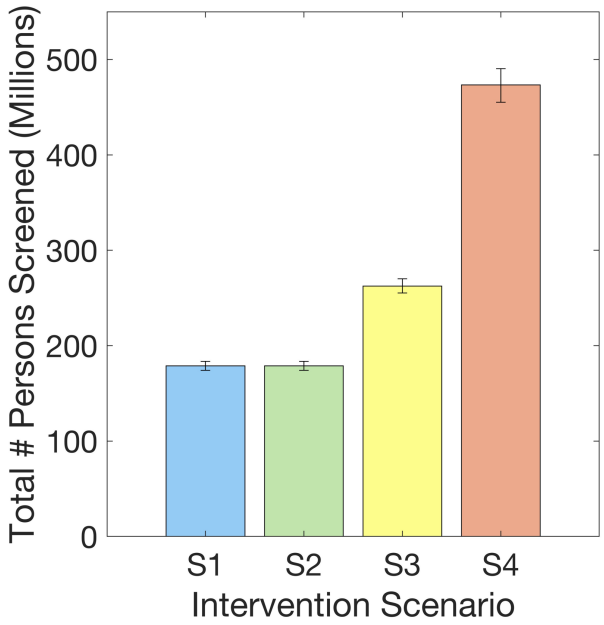
(A) Relative reduction in incidence achieved by 2030 compared with 2015 levels.

(B) Cumulative costs of further scale-up in screening and treatment for Scenarios S3 & S4.

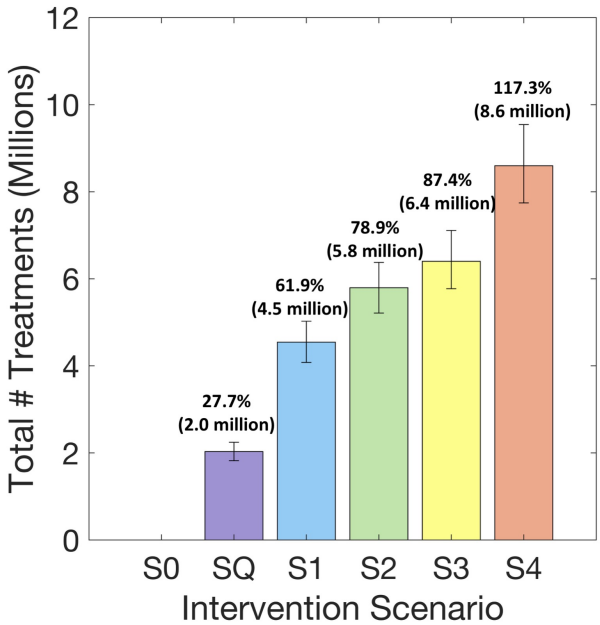



**Supplementary Figure S8.**
Relative reduction in (A) incidence and (B) total screening and treatment costs (2018-2030) resulting from further improvements in screening interventions (Scenario S4) compared with Scenario S3. Intervention scenarios are as follows. **Scenario S3:** One-time prioritised screening of 90% of the general population by 2030, along with re-screening cured and previously Ab-negative/RNA-negative individuals from 2020 (every ten years for non-PWID and annually for PWID). **Scenario S4:** Scenario S3 with incremental improvements as described in the figure legend. The height of each bar represents the median of 1,151 final model runs, with whiskers indicating 95% uncertainty intervals of runs.

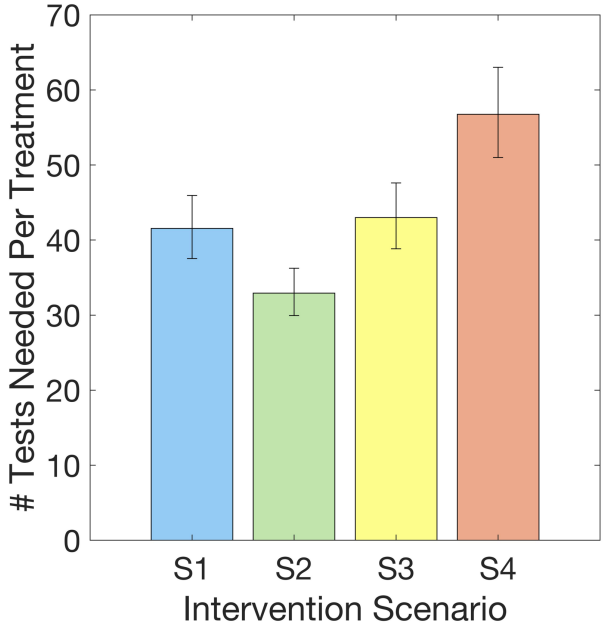
(A) Total number of people screened over 2018 to 2030



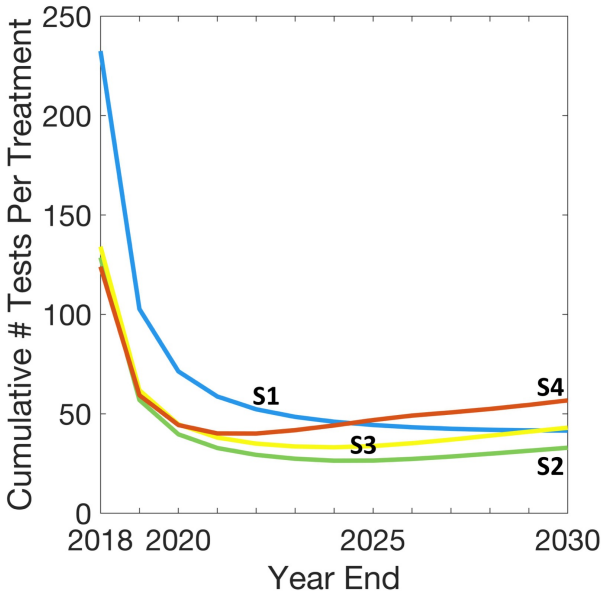

(B) Treatment uptake over 2018 to 2030

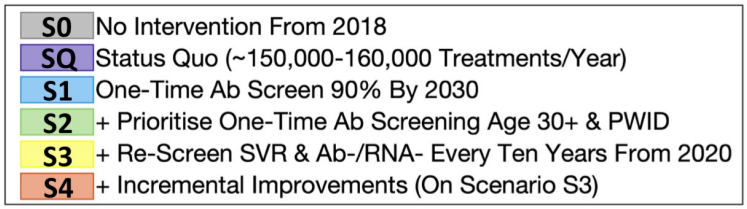



(C) Average number of screening diagnostics tests needed per treatment over 2018 to 2030



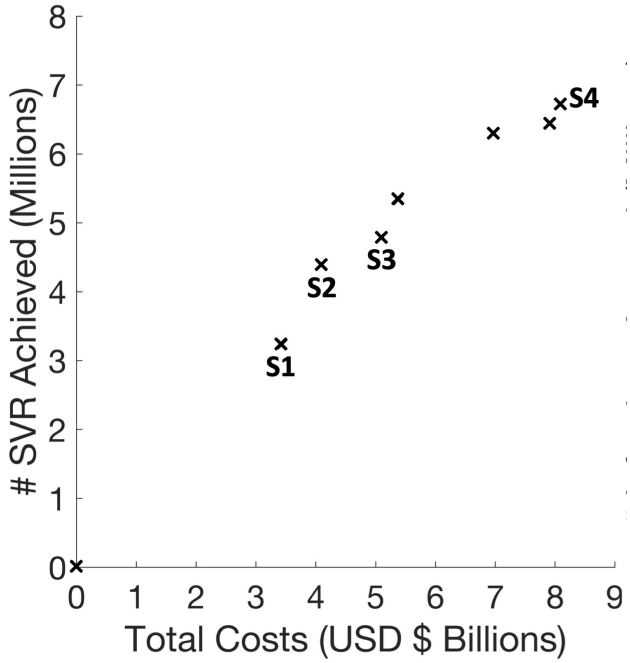

(D) Cumulative number of screening diagnostics tests needed per treatment each year from 2018 to 2030.



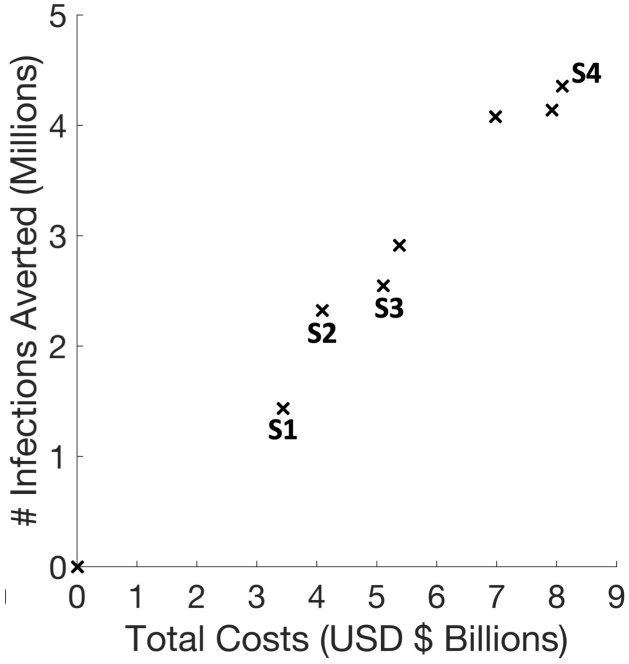




**Supplementary Figure S9.**
Screening and treatment measures for Scenarios S1-S4. (A) Total number of persons screened; (B) Total number of treatments initiated; (C) Average number of screening diagnostics tests (both Ab and RNA) needed to initiate one treatment over 2018 to 2030; and (D) Cumulative number of screening diagnostics tests needed to initiate one treatment by the end of each year from 2018 to 2030. The large values in the first few years from the intervention start in 2018 reflects that there is a delay between when patients are screened and when they are initiated on treatment. The figure indicates that as intervention is scaled up and chronic HCV prevalence declines, there are diminishing yields on the number of tests needed to initiate one treatment. The height of each bar (A-C) or timeseries curve (D) represent the median of 1,151 final model runs, with whiskers indicating 95% uncertainty intervals of runs.

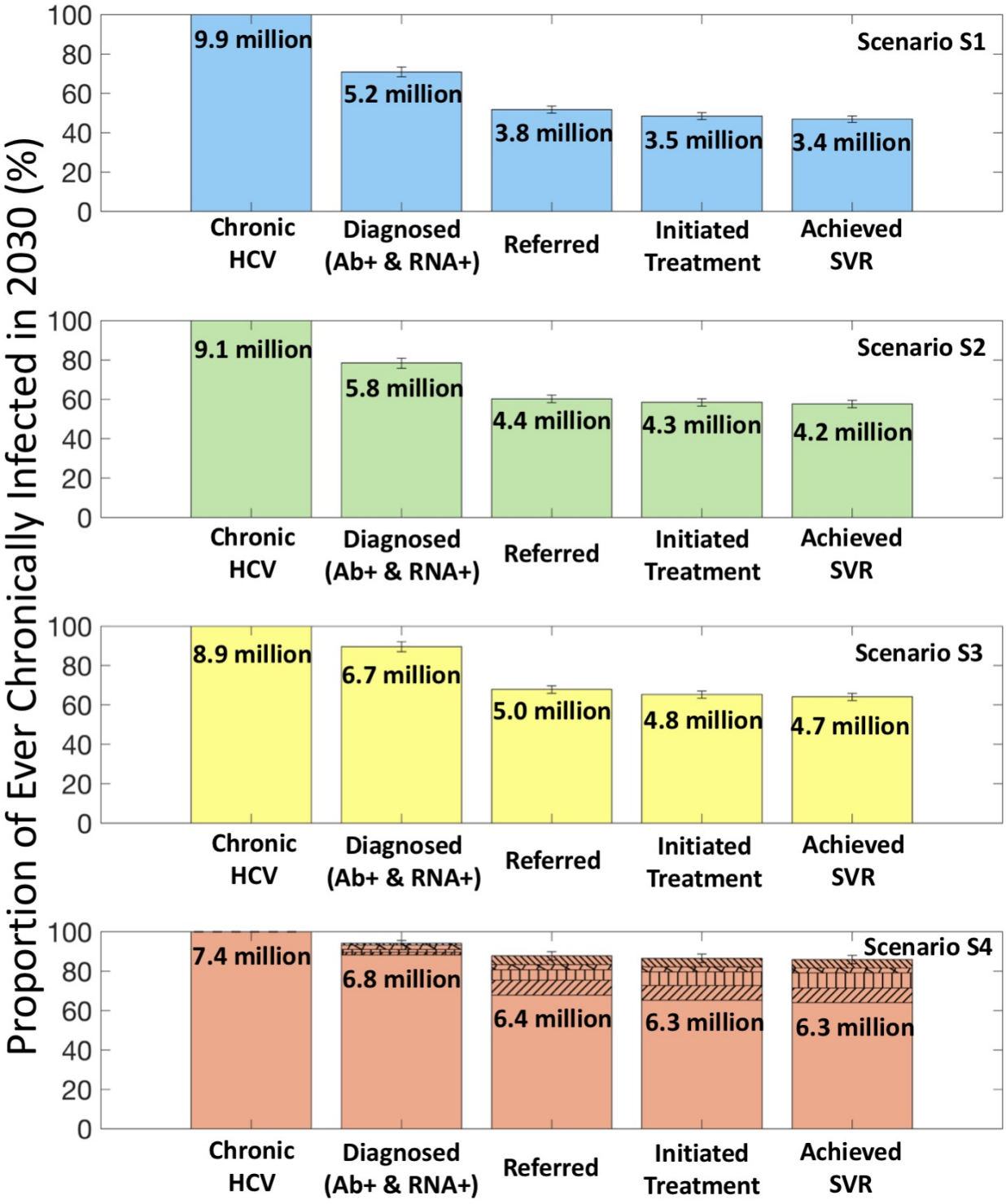
(A) Number of cures achieved versus total costs over 2018-2030



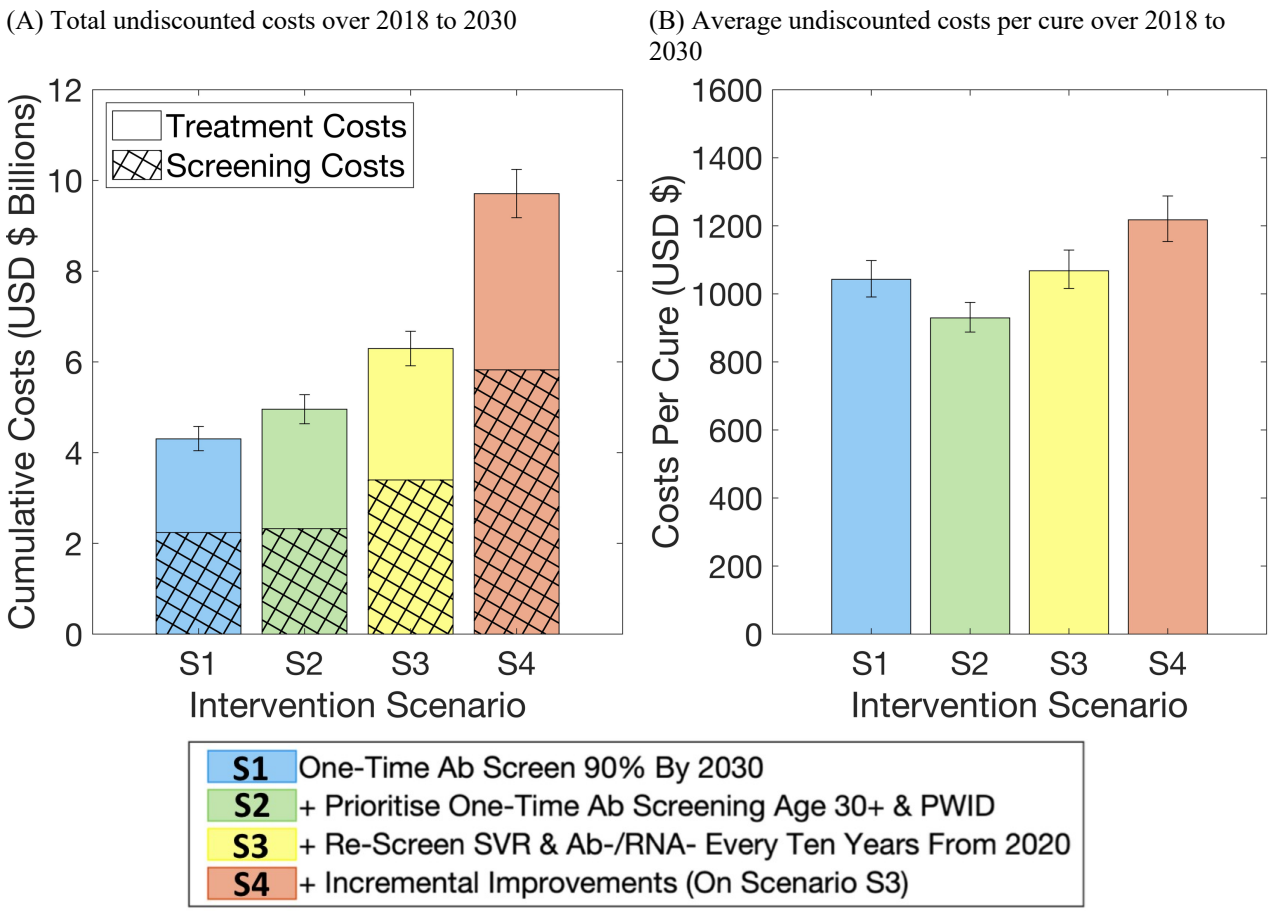

(B) Number of new infections averted versus total costs over 2018-2030



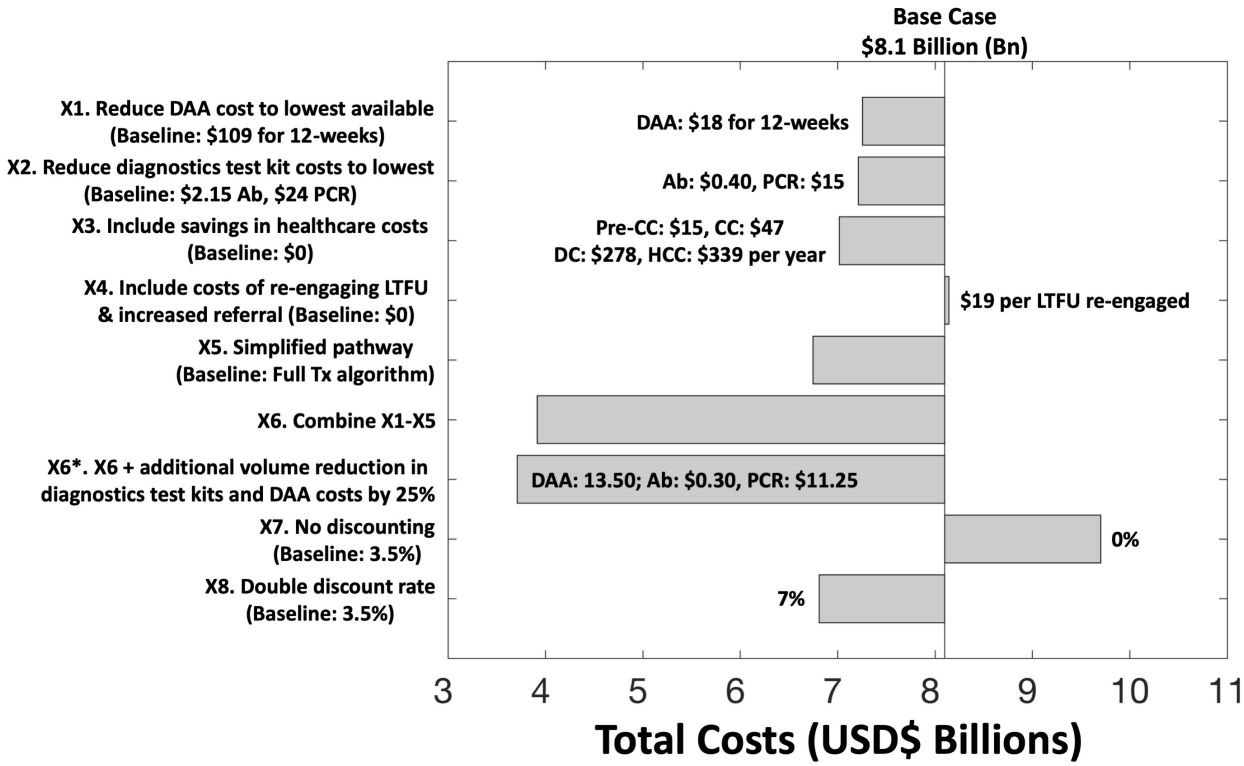

**Supplementary Figure S10.**
Scatter plots of (A) number of cures achieved, or (B) number of new infections averted, compared to total estimated screening and treatment costs over 2018-2030 for each of the intervention scenarios. The plotted values show the median of 1,151 final model runs. Costs and outcomes are discounted at a standard rate of 3.5% per year.




**Supplementary Figure S11.**
Cascade of care for Scenarios S1-S4 showing a snapshot of the infected population at the end of 2030. Each column shows a proportion relative to all persons in the model at that timepoint who have ever been infected. The number corresponding to 100% of chronically infected persons in 2030 will be different for each of the scenarios because the prevention benefits achieved by 2030 in each scenario will vary. Comparing with the model schematic in Figure 1 or Supplementary Figure S1, for example, a snapshot of the diagnosed proportion would include all persons who are presently in the "Confirmed RNA Test Positive Diagnosed", "Infected LTFU Previously Diagnosed", "Referred to Treatment", "On HCV Treatment", and "Cured (SVR)" compartments because all of these individuals would have had to be diagnosed to be in any one of those states. Note that "Re-infected Previously Cured/SVR" persons are not considered to have been diagnosed because they have since acquired infection. The height of each bar represents the median of 1,151 final model runs, with whiskers indicating 95% uncertainty intervals of runs.




**Supplementary Figure S12.**
Estimated total screening and treatment costs and cost per cure for each screening intervention scenario over 2018-2030 without discounting. The height of each bar represents the median of 1,151 final model runs, with whiskers indicating 95% uncertainty intervals of runs.




**Supplementary Figure S13.**
Univariate sensitivity analysis on total costs for Scenario S4 showing all sensitivity analyses scenarios as described in Supplementary Table S4b. DAA: direct-acting antiviral; Ab: antibody; PCR: polymerase chain reaction; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LTFU: lost-to-follow-up; Tx: treatment. The length of each bar represents the median of 1,151 final model runs.

## Supplementary Tables

**Supplementary Table S0.**
Definition of indices that characterise the full set of model equations.

| Indexed Structure | Index | Index Values | Meaning |
|---|---|---|---|
| Sex | $g$ | $g_1, g_2$ | Male ($g = g_1$)<br>Female ($g = g_2$) |
| Age/Behaviour | $i$ | $1, 2, 3, Y$ | Young ($i = 1$)<br>Young Adult Non-PWID ($i = 2$)<br>Young Adult PWID ($i = Y$)<br>Adult Ex-/Non-PWID ($i = 3$) |
| Disease Progression | $j$ | $I, C, D, H$ | Chronic Pre-Cirrhosis ($j = I$)<br>Cirrhosis ($j = C$)<br>Decompensation ($j = D$)<br>Hepatocellular Carcinoma ($j = H$) |

**Supplementary Table S1a.**
Baseline model parameters with associated uncertainty ranges. Rates are per year.

| Parameter | Symbol | Baseline value or fitted range when stated [Uncertainty Distribution/Range] | Source |
|---|---|---|---|
| **Demographic Parameters** | | | |
| Average population growth rate per annum Δ | $b_g$ | Pre-2000: Fitted 2.76% [2.53 %-2.99%]<br>Interim 2000-2015: Fitted 1.92% [1.54-2.31%]<br>Post-2015: [Uniform 1.35-2.08%] | 4-6 |
| 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: 0.032 [0.026-0.039],<br>Female: 0.009 [0.0004-0.017] | Calibrated to fit PWID proportions as given in Supplementary Table S2[2] |
| Average mortality rate for each age group | $\mu_{1,g}$<br>$\mu_{2,g}$<br>$\mu_{3,g}$ | 1/56<br>1/41 Fitted: 0.024<br>Fitted values: Male: 0.023 [0.020-0.026]<br>Female: 0.020 [0.017-0.024] | Based on a life expectancy at birth estimate of 66 years in 2015[4], but also adjusted in model calibration |
| Additional drug-related mortality rate | $\mu$ | 0.028 [Lognormal 0.017-0.039] | Based on estimates of drug-related mortality across Asia[13] |
| **Epidemic/Transmission Parameters** | | | |
| HCV transmission rate per susceptible in each age group (fitted values) | $\beta_1$<br>$\beta_2$<br>$\beta_3$ | $\beta_1$ = 0.059 [0.052-0.066]<br>$\beta_2$ = 0.053 [0.023-0.085]<br>$\beta_3$ = 0.12 [0.10-0.14] | Fit to chronic prevalence in each age category in 2007[18] as given in Supplementary Table S2 |
| Additional HCV transmission rate for injecting drug use | $\theta$ | Fit to data on HCV prevalence amongst PWID<br>Fitted values: 0.61 [0.51-0.74] | Fit to chronic prevalence in PWID[17,19] in 2012: 62.2% [55.5-68.8%] |
| Proportion of infections that spontaneously clear | $\delta$ | 0.26 [Uniform 0.22-0.29] | [19] |
| **Disease Progression Parameters** | | | |
| Relative risk of progression from cirrhosis to decompensated if SVR | $\epsilon_{CD}$ | 0.07 [Lognormal 95% CI 0.03, 0.20] | 62 |
| Relative risk of progression from cirrhosis to HCC if SVR | $\epsilon_{CH}$ | 0.23 [Lognormal 95% CI 0.16, 0.35] | 31,62 |
| 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† | | 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 | 27 |
| Transition probability (TP) of chronic HCV to cirrhosis†‡ | $\sigma$ | 0.027 [Normal – mean = 0.027, std = 0.0008] | 20 |

| | | | |
|---|---|---|---|
| TP of compensated cirrhosis to decompensation†‡ | $\gamma$ | 0.039 [Beta– $\alpha = 14.6, \beta = 360.2$] | [3,21,22] |
| TP of cirrhosis or decompensation to HCC†‡ | $\xi$ | 0.014 [Beta– $\alpha = 1.9, \beta = 136.1$] | [3,21,22] |
| TP of additional mortality due to decompensation‡ | $\mu_4$ | 0.13 [Beta– $\alpha = 147.0, \beta = 984.0$] | [3,21,22] |
| TP of death due to HCC‡ | $\mu_5$ | 0.43 [Beta– $\alpha = 117.1, \beta = 155.2$] | [3,21,22] |

Δ Baseline values for $b$ for the pre-2000 and interim 2000-2015 growth rates are taken from the UN Department of Economic and Social Affairs, Population Division[4]; 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[7]
† 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.[27]
‡ Transition probabilities have been converted to instantaneous rates for use in the model.

**Supplementary Table S1b.**
Screening and treatment model parameters with associated uncertainty ranges. Rates are per year. See Table 2 in the main text or Supplementary Table S1c for specific values used in each of the scenarios.

| Parameter | Symbol | Baseline value or fitted range when stated [Uncertainty Distribution/Range] | Source |
|---|---|---|---|
| **Screening Parameters** | | | |
| Primary Ab screening rate annually | $\chi_1$ | Baseline: 0<br>Status Quo: 2.6-5.9%<br>Scenarios S1-S4: 6.2-12.4%<br>Range: 0-1 | Varied in scenarios |
| Ab re-screening rate annually | $\chi_2$ | | Varied in scenarios |
| Proportion of primary Ab-screened persons tested for HCV RNA | $\psi_1$ | Set to 1<br>Range: 0-1 | It is assumed that everyone who is tested Ab-positive, either from primary Ab screening or Ab re-screening, are subsequently tested for HCV RNA, i.e. there is no LTFU at this stage |
| Proportion of Ab re-screened persons tested for HCV RNA | $\psi_2$ | Set to 1<br>Range: 0-1 | |
| RNA screening of previously untested annually | $\tilde{\chi}_1$ | Initially set to 0 | Varied in scenarios |
| RNA re-screening of previously tested RNA-negative annually | $\tilde{\chi}_2$ | Initially set to 0 | |
| RNA re-screening of previously cured annually | $\tilde{\chi}_3$ | Initially set to 0 | |
| RNA re-screening of previously LTFU annually | $\tilde{\chi}_4$ | Initially set to 0 | |
| **Referral Parameters** | | | |
| Referral rate to treatment | $\rho$ | Range: 0-100%<br>Status Quo: 35-70%<br>Scenarios S1-S4: 80-90% | Varied in scenarios |
| **Treatment Parameters** | | | |
| Treatment rate per capita | $\tau_{ij}$ | Calibrated to historical treatment rate at baseline. From 2018, the value is set to 1.6094 so that approx. 80% of referred individuals will initiate treatment within the next year | Note: A rate $r$ corresponds to a proportion $p = (1 - e^{-rt})$ transitioning by time $t$ |
| Average duration on treatment | $1/\omega_j$ | 24-weeks for conventional treatment with IFN and RBV, which was the standard for treatment of HCV genotype 3 in Pakistan before 2016. Shortened to 12 weeks for pre-cirrhotic patients when DAA treatments were introduced from 2016 onwards; patients with cirrhosis or ESLD commence HCV treatment for 24 weeks | [51,63] |
| Proportion of individuals achieving SVR with IFN and RBV treatment | $\alpha_j$ | 0.66 [Uniform 0.50-0.81] | [41,43,45] |
| Proportion of individuals achieving SVR with new DAA treatments | $\alpha_j$ | 0.9 [Uniform 0.80-0.95] | [51,53,63] |

| | | | |
|---|---|---|---|
| **Lost to Follow Up (LTFU) Parameters** | | | |
| LTFU following diagnosis | $\zeta_D$ | Set to $(1-\rho)$ | It is assumed that those who have been diagnosed and are not referred to treatment are LTFU |
| LTFU during referral | $\zeta_R$ | Initially set to 0 | |
| LTFU during treatment | $\zeta_T$ | Initially set to 0 | |

**Supplementary Table S1c.**
Specific model parameters for each screening and treatment intervention scenario for 2018 onwards, including the parameters selected for the incremental improvements to Scenario S3 that define Scenario S4.

| | **Ab screening & re-screening** | | | **RNA re-screening of known Ab+ status** | | | | **Referral** |
|---|---|---|---|---|---|---|---|---|
| **Intervention scenario** | **Primary Ab screening rate‡** | **Re-screening rate of SVR and previously screened uninfected‡** | | **Previously treated** | | **Rate previously diagnosed LTFU linked back to care** | | **% diagnosed HCV infections linked to treatment** |
| | **All** | **Gen.[c]** | **PWID** | **Gen.** | **PWID** | **Gen.** | **PWID** | **All** |
| **Scenario S0.** No further treatment from 2018 | -- | -- | -- | -- | -- | -- | -- | -- |
| **Scenario SQ.** ~150,000-160,000 treatments/year | 2.6-5.9% | -- | -- | -- | -- | -- | -- | 35-70% |
| **Scenario S1.** One-time 90% screen by 2030 with 80% referred[a] | 6.2% [6.1-6.3%] | -- | -- | -- | -- | -- | -- | 80% |
| **Scenario S2.** S1+ Target primary Ab screening Age 30+ & PWID | 6.2% [6.1-6.3%] | -- | -- | -- | -- | -- | -- | 80% |
| **Scenario S3.** S2+ Re-screen SVR & Ab/RNA- from 2020 | 6.2% [6.1-6.3%] | 10% | 100% | 10% | 100% | -- | -- | 80% |
| **Scenario S4** | | | | | | | | |
| S3+ Increase referral to 90% | 6.2% [6.1-6.3%] | 10% | 100% | 10% | 100% | -- | -- | 90% |
| + Double primary Ab screening rate[b] | 12.4% [12.1-12.6%] | 10% | 100% | 10% | 100% | -- | -- | 90% |
| + Re-screen every 5 years | 12.4% [12.1-12.6%] | 20% | 100% | 20% | 100% | -- | -- | 90% |
| + Re-engage RNA+ LTFU | 12.4% [12.1-12.6%] | 20% | 100% | 20% | 100% | 20% | 100% | 90% |

[a]A 6.2% [6.1-6.3%] annual primary screening rate is equivalent to first-time Ab screening 180 [175-185] million individuals, or 90% of the 2018 population, by 2030.
[b]A 12.4% [12.1-12.6%] annual primary screening rate is equivalent to first-time Ab screen 280 [265-290] million individuals, or 140% of the 2018 population, by 2030.
[c]Gen: General population rate for non-PWID groups.
*Incremental improvements to Scenario S3.
‡We assume that all persons tested Ab-positive, either from primary Ab screening ($\psi_1$) or Ab re-screening ($\psi_2$), are subsequently tested for HCV RNA, i.e. there is no loss-to-follow-up at this stage

**Supplementary Table S2.**
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] | [4-6] |
| | 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] | [4-6] |
| | 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] | [4-6] |
| | 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% | [4] |
| | 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[2] |
| | Male | 0.42% [Uniform 0.36-0.54%] | |
| | Female | 0.006% [Uniform 0.0006-0.24%] | |
| HCV chronic prevalence in 2007 (estimated as 74% of antibody prevalence) | Overall | 3.62% [3.45-3.79%] | [18], 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 PWID | | 62.16% [55.50-68.75%] | [17] |
| Projected change in HCV seroprevalence over 10 years | | 0.39% [-0.17 to 0.94%] | Meta-analysis on blood donor data trends in Pakistan from 1994 to 2014 |
| Projected change in chronic HCV prevalence over 10 years | | [Uniform -0.13 to 0.73%] | Assume full range of viraemic rate from spontaneous clearance[19] |

**Supplementary Table S3.**
Pre-Intervention Treatment

| Year | Punjab | Sindh | KPK | Baluchistan | Total Treatments 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[a] | 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 |
| 2016[b] | - | - | - | - | - | 152,710[b] |
| 2017[b] | - | - | - | - | - | 152,710[b] |
| **Total** | | | | | | **1,036,828** |

ND: No data available
*To estimate the total number of historical HCV treatments each year across both public and private sectors, a split of Public 40%, Private 60% was assumed. DAAs became available from 2016 onwards.
[a]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.
[b]Data was not available for the pre-intervention years 2016 and 2017, so it was assumed that the total number of treatments nationally remained the same as in 2015.

**Supplementary Table S4a.**
Screening and treatment costs used in the modelling projections. All costs are in 2018 US Dollars (USD$).

| | Values or Range | | Source/Comments |
|---|---|---|---|
| | **Baseline** | **Complete Simplified Pathway∆** | |
| **Screening/Diagnostics Costs*** | | | |
| Ab Test (each) | | | MSF-SINA 'Longitudinal Cohort to Evaluate Hepatitis C Treatment Effectiveness in Karachi, Pakistan', based at Machar Colony MSF clinic in Karachi, Pakistan[54,58] |
| Ab-negative | $10.13 | $8.38 | |
| Ab-positive | $16.67 | $14.92 | |
| PCR Test (each) | | | MSF-SINA Costing analysis[57] |
| PCR-negative | $34.01 | $24.21 | |
| PCR-positive | $40.77 | $30.97 | |
| **Treatment Costs** | | | |
| Drug regimen costs | | | |
| SOF (12-week supply) | $45 | $18.00 (SOF+DCV) | Global Hepatitis Report 2017[64], Pakistan Health Research Council[65] |
| DCV (12-week supply) | $63.84 | | MSF-SINA |
| Visit costs | | | Costing analysis[57] |
| Pre-cirrhosis | $143.85 | $74.30 | Simplified treatment pathway based on [60] |
| Post-cirrhosis | $203.37 | $129.35 | |
| Laboratory costs | | | |
| Pre-cirrhosis | $150.55 | $31.83 | |
| Post-cirrhosis | $165.08 | $38.88 | |
| Total Treatment* (Full-course) | | | Costing analysis[57], including monitoring/consultation costs |
| Pre-cirrhosis | $403.24 | $124.13 | 12-weeks |
| Post-cirrhosis | $586.13 | $204.23 | 24-weeks |
| **Total Costs of Diagnosis & Treatment** | | | |
| Pre-cirrhosis | $460.68 | $170.02 | Positive Ab and PCR test, plus 12-weeks of DAA treatment |
| Post-cirrhosis | $643.57 | $250.12 | Positive Ab and PCR test, plus 24-weeks of DAA treatment |

*Total screening/diagnostics costs include staff time and overheads, as well as the costs of diagnostics test kits. Total treatment costs include monitoring costs (specifically, visit and laboratory costs), as well as the costs of DAA therapy (12 weeks for pre-cirrhotic patients and 24 weeks for post-cirrhotic patients). See Supplementary Table S5 for details on how costs were derived.
∆The complete simplified treatment pathway refers to sensitivity analysis scenario X6 (i.e. the combination of sensitivity analysis scenarios X1-X5), which considers the costs of a simplified treatment algorithm that is being implemented by the Hepatitis Prevention and Treatment Programme[60] at the Pakistan Kidney and Liver Institute (PKLI) in Lahore, Pakistan, combined with using the cheapest available diagnostics test costs and DAA costs, including potential healthcare savings (see Supplementary Table S4b for details).

**Supplementary Table S4b.**
Ranges used for the univariate costing sensitivity analyses with respect to the total costs of Scenario S4.

| Sensitivity Analyses | Description of changes to Scenario S4 |
|---|---|
| **X1.** Reduce DAA cost to lowest known | Reduce cost of drug regimen for combined 12-week supply of generic SOF+DCV to USD$18 instead of USD$109 based on lowest known price available in Pakistan.[65] This changes total treatment costs to USD$312.40 and USD$404.45 for pre-cirrhotic and post-cirrhotic patients, respectively. |
| **X2.** Reduce diagnostics test costs lowest known | Reduce cost of diagnostics tests kits to lowest known price available in Pakistan, namely, to USD$0.40 (from USD$2.15) for HCV rapid antibody test and USD$15 (from USD$24.09) for RNA test.[65] This changes the diagnostics costs for Ab testing to USD$8.38 and USD$14.92, respectively, for Ab-negative and Ab-positive patients, and for RNA testing to USD$24.92 and USD$31.68, respectively, for PCR-negative and PCR-positive patients. |
| **X3.** Include savings in healthcare costs | Include healthcare costs of managing HCV-related disease based on data from a HCV patient survey that we collected and analysed from Cambodia[66] and adjusted to the Pakistan context[57] by applying WHO-CHOICE Health service delivery costs for Pakistan.[67] For pre-cirrhosis, we considered the average over the mean health state medical costs for all pre-cirrhotic stages (METAVIR score F0-F3) for an estimated cost of USD$14.80. We also assumed the mean health state medical costs for compensated cirrhosis (METAVIR score F4) (USD$46.70), decompensated cirrhosis (USD$277.60), and hepatocellular carcinoma (USD$339.20). |
| **X4.** Include costs of re-engaging LTFU and improving referral incrementally from 80% to 90% | Assume that a nurse in Pakistan is utilised to re-engage patients lost-to-follow-up (LTFU) and makes an average salary of USD$600 per month, and that there are 22 working days in one month, and travel costs of USD$10 per day. This works out to approximately USD$37.27 (USD$600/22 + USD$10) per day. Assuming that one nurse can re-engage 2 LTFU patients per day (one in the morning and one in the afternoon), this equates to USD$18.64 per LTFU who is re-engaged. Similarly, we assume that the same cost of USD$18.64 per patient is needed to improve referral from 80% to 90%, i.e. this is a 12.5% increase in referral from 80% to 90%, so 12.5% of newly referred patients each year would have incurred this cost. This cost was varied by half to double to account for uncertainty, and values for each valid model run were sampled uniformly from the range [USD$9.32-37.27] per LTFU re-engaged or new patient referred. |
| **X5.** Implement a complete simplified treatment pathway | Assume a simplified treatment algorithm as implemented by the Hepatitis Prevention and Treatment Programme at the Pakistan Kidney and Liver Institute (PKLI) in Lahore, Punjab, Pakistan[60], which is based on the WHO treatment guidelines.[51] The simplified treatment pathway involves fewer laboratory investigations, fewer follow-up visits, and task shifting. Details can be found in Supplementary Table S5. |
| **X6.** Combine **X1**-**X5** | Reduce DAA (X1) and diagnostics test costs (X2) to lowest known, include savings in healthcare costs (X3), include costs of re-engaging LTFU and improving referral incrementally (X4), and implement a simplified treatment algorithm (X5). |
| **X6*.** Scenario **X6** plus additional 25% volume reduction in diagnostics test kits and DAA costs | Sensitivity analysis scenario X6 combined with assuming a further volume reduction in diagnostics test kits (both Ab and RNA) and DAA costs by 25% on the lowest available price in Pakistan (X1 & X2). Specifically, HCV Ab test kits are reduced from USD$0.40 to USD$0.30 and HCV RNA test kits are reduced from USD$15 to USD$11.25. Meanwhile, DAA drug costs are reduced from USD$18 to USD$13.50 for 12-weeks of treatment. |
| **X7.** No discounting | Assume a 0% discount rate (from 3.5% at baseline). |
| **X8.** Double discount rate | Assume a 7% discount rate (from 3.5% at baseline). |

**Supplementary Table S5a.**
Activities, resources, and estimated unit costs at baseline and for a complete simplified HCV model of care. These have been derived from our costing analysis[57] of the MSF HCV intervention in Pakistan[54,58] and adjusted to reflect local staff costs. The complete simplified pathway is based on a simplified treatment algorithm implemented by the Hepatitis Prevention and Treatment Programme at the Pakistan Kidney and Liver Institute (PKLI) in Lahore, Punjab, Pakistan[60] and the WHO treatment guidelines[51], combined with using the cheapest diagnostics test and DAA drug costs, and including healthcare savings that arise from the management of HCV-associated disease (see sensitivity analysis scenario X6 in Supplementary Table S4b for details).

| **Activity** | **Ingredients** | **Resource Type** | **Economic Unit Cost (US$)** | |
|---|---|---|---|---|
| | | | **Baseline** | **Simplified** |
| Out-patients department (OPD) consultation | OPD receptionist | Staff time | 0.16 | 0.16 |
| | OPD nursing | Staff time | 1.05 | 1.05 |
| | OPD medical Doctor | Staff time | 3.60 | 3.60 |
| | OPD clinic visit | Space/Materials | 1.54 | 1.54 |
| RDT negative result counselling session | Patient support nurse | Staff time | 0.85 | 0.85 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |
| RDT positive result counselling session | Patient support nurse | Staff time | 1.32 | 1.32 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |
| | Laboratory technician | Staff time | 0.68 | 0.68 |
| | Laboratory visit | Space/Materials | 5.39 | 5.39 |
| PCR negative result counselling session | HCV clinic receptionist | Staff time | 0.25 | 0.25 |
| | HCV nurse | Staff time | 3.10 | 3.10 |
| | HCV medical doctor | Staff time | 0.71 | - |
| | HCV clinic visit | Space/Materials | 4.23 | 4.23 |
| | Patient support nurse | Staff time | 0.85 | 0.85 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |
| PCR positive result counselling session | HCV clinic receptionist | Staff time | 0.25 | 0.25 |
| | HCV nurse | Staff time | 3.10 | 3.10 |
| | HCV medical doctor | Staff time | 0.71 | - |
| | HCV clinic visit | Space/Materials | 4.23 | 4.23 |
| | Patient support nurse | Staff time | 1.32 | 1.32 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |
| | Laboratory technician | Staff time | 0.90 | 0.90 |
| | Laboratory visit | Space/Materials | 5.39 | 5.39 |
| Baseline initial assessment | HCV clinic receptionist | Staff time | 0.25 | 0.25 |
| | HCV nurse | Staff time | 3.10 | 3.10 |
| | HCV medical doctor | Staff time | 1.51 | 1.51 |
| | HCV clinic visit | Space/Materials | 4.23 | 4.23 |
| | Patient support nurse | Staff time | 0.79 | 0.79 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |
| | Laboratory technician | Staff time | 0.68 | 0.68 |
| | Laboratory visit | Space/Materials | 5.39 | 5.39 |
| Family planning (maternal and child health clinic-MCH) referral | MCH receptionist | Staff time | 0.58 | 0.58 |
| | MCH nurse | Staff time | 2.62 | 2.62 |
| | MCH visit | Space/Materials | 0.16 | 0.16 |
| Baseline subsequent assessment | HCV clinic receptionist | Staff time | 0.25 | 0.25 |
| | HCV nurse | Staff time | 3.10 | 3.10 |
| | HCV medical doctor | Staff time | 0.56 | - |
| | HCV clinic visit | Space/Materials | 4.23 | 4.23 |

| | | | | |
|---|---|---|---|---|
| Treatment initiation | HCV clinic receptionist | Staff time | 0.25 | 0.25 |
| | HCV nurse | Staff time | 3.10 | 3.10 |
| | HCV medical doctor | Staff time | 0.87 | - |
| | HCV clinic visit | Space/Materials | 4.23 | 4.23 |
| | Patient support nurse | Staff time | 0.94 | 0.94 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |
| | Pharmacist | Staff time | 1.85 | 1.85 |
| | Pharmacy visit | Space/Materials | 2.29 | 2.29 |
| Treatment follow up (Pre-cirrhosis) | HCV clinic receptionist | Staff time | 0.25 | - |
| | HCV nurse | Staff time | 3.10 | - |
| | HCV medical doctor | Staff time | 0.56 | - |
| | HCV clinic visit | Space/Materials | 4.23 | - |
| | Laboratory technician | Staff time | 0.68 | - |
| | Laboratory visit | Space/Materials | 5.39 | - |
| | Pharmacist | Staff time | 1.85 | 1.85 |
| | Pharmacy visit | Space/Materials | 2.29 | 2.29 |
| Treatment follow up (Post-cirrhosis) | HCV clinic receptionist | Staff time | 0.25 | 0.25 |
| | HCV nurse | Staff time | 1.12 | 1.12 |
| | HCV medical doctor | Staff time | 1.20 | 1.20 |
| | HCV clinic visit | Space/Materials | 4.61 | 4.61 |
| | Laboratory technician | Staff time | 0.68 | 0.68 |
| | Laboratory visit | Space/Materials | 5.43 | 5.43 |
| | Pharmacist | Staff time | 1.85 | 1.85 |
| | Pharmacy visit | Space/Materials | 2.44 | 2.44 |
| On treatment counselling | Patient support nurse | Staff time | 0.71 | 0.71 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |
| End of treatment | HCV clinic receptionist | Staff time | 0.25 | 0.25 |
| | HCV nurse | Staff time | 3.10 | 3.10 |
| | HCV medical doctor | Staff time | 0.60 | 0.60 |
| | HCV clinic visit | Space/Materials | 4.23 | 4.23 |
| | Laboratory technician | Staff time | 0.68 | 0.68 |
| | Laboratory visit | Space/Materials | 5.39 | 5.39 |
| | Patient support nurse | Staff time | 0.71 | 0.71 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |
| SVR12 | HCV clinic receptionist | Staff time | 0.25 | 0.25 |
| | HCV nurse | Staff time | 3.10 | 3.10 |
| | HCV medical doctor | Staff time | 0.80 | 0.80 |
| | HCV clinic visit | Space/Materials | 4.23 | 4.23 |
| | Laboratory technician | Staff time | 0.68 | 0.68 |
| | Laboratory visit | Space/Materials | 5.39 | 5.39 |
| | Patient support nurse | Staff time | 0.74 | 0.74 |
| | Patient support visit | Space/Materials | 0.78 | 0.78 |

**Supplementary Table S5b.**
Unit costs for visits, laboratory tests, test kits, and medicines used to estimate the costs of HCV screening and treatment.

| Item | Resource Type | Economic Unit Cost (US$) | |
|---|---|---|---|
| | | Baseline | Simplified |
| **Consultations/ visits** | | | |
| Outpatient department consultation | Visit | 6.35 | 6.35 |
| RDT negative result | Visit | 1.63 | 1.63 |
| RDT positive result | Visit | 8.17 | 8.17 |
| PCR negative result | Visit | 9.92 | 9.21 |
| PCR positive result | Visit | 16.68 | 15.97 |
| Baseline initial assessment | Visit | 16.73 | 16.73 |
| Family planning referral | Visit | 3.36 | 3.36 |
| Baseline subsequent assessment | Visit | 8.14 | 7.58 |
| Treatment initiation | Visit | 14.31 | 13.44 |
| Treatment follow up (Pre-cirrhosis) | Visit | 18.35 | 4.14 |
| Treatment follow up (Post-cirrhosis) | Visit | 18.35 | 18.35 |
| On treatment counselling | Visit | 1.49 | 1.49 |
| End of treatment | Visit | 15.74 | 15.74 |
| SVR12 | Visit | 15.97 | 15.97 |
| **Laboratory tests, test kits and medicines** | | | |
| Albumin | Laboratory test | 0.12 | 0.12 |
| Alkaline phosphatase | Laboratory test | 1.20 | 1.20 |
| ALT (also called SGPT) | Laboratory test | 1.29 | 1.29 |
| Anti HEV | Laboratory test | 6.88 | 6.88 |
| AST (also called SGOT) | Laboratory test | 1.29 | 1.29 |
| Bilirubin - Total & Direct | Laboratory test | 1.12 | 1.12 |
| Complete blood count | Laboratory test | 2.15 | 2.15 |
| Creatinine | Laboratory test | 1.20 | 1.20 |
| Glucose | Laboratory test | 1.03 | 1.03 |
| Hepatitis surface antigen test (HBsAg) | Laboratory test | 3.87 | 3.87 |
| HCV RDT | Laboratory test | 2.15 | 0.40 |
| HCV RNA (VL) | Laboratory test | 47.31 | 15.00 |
| HCV RNA (Qualitative) | Laboratory test | 24.09 | 15.00 |
| Haemoglobin | Laboratory test | 1.29 | 1.29 |
| HIV RDT | Laboratory test | 3.01 | 3.01 |
| Pregnancy test | Laboratory test | 1.72 | 1.72 |
| Prothrombin /International Normalized Ratio (PT/INR) | Laboratory test | 1.89 | 1.89 |
| Daclatasavir 60mg (per tablet) | DAA medicines | 0.76 | 0.21 |
| Sofosbuvir 400mg (per tablet) | DAA medicines | 0.54 | |
| Ultrasound | Laboratory test | 5.16 | 5.16 |

**Supplementary Table S5c.**
Number of units of consultations/visits and resource usage for each patient type. B – Baseline; S – Simplified.

| Item | Resource Type | Number of Units | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Never Infected | | Exposed | | Infected Pre-Cirrhosis | | Infected Post-Cirrhosis | |
| | | B | S | B | S | B | S | B | S |
| **Consultations/ visits** | | | | | | | | | |
| Outpatient department consultation | Visit | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| RDT negative result | Visit | 1 | 1 | - | - | - | - | - | - |
| RDT positive result | Visit | - | - | 1 | 1 | 1 | 1 | 1 | 1 |
| PCR negative result | Visit | - | - | 1 | 1 | - | - | - | - |
| PCR positive result | Visit | - | - | - | - | 1 | 1 | 1 | 1 |
| Baseline initial assessment | Visit | - | - | - | - | 1 | 1 | 1 | 1 |
| Family planning referral[a] | Visit | - | - | - | - | 4 | - | 4 | - |
| Baseline subsequent assessment[b] | Visit | - | - | - | - | 1 | - | 1 | - |
| Treatment initiation | Visit | - | - | - | - | 1 | 1 | 1 | 1 |
| Treatment follow up (Pre-cirrhosis) | Visit | - | - | - | - | 3 | 3 | 0 | 3 |
| Treatment follow up (Post-cirrhosis) | Visit | - | - | - | - | 0 | 0 | 6 | 3 |
| On treatment counselling[c] | Visit | - | - | - | - | 3 | - | 6 | - |
| End of treatment | Visit | - | - | - | - | 1 | 1 | 1 | 1 |
| SVR12 | Visit | - | - | - | - | 1 | 1 | 1 | 1 |
| **Laboratory tests, test kits and medicines** | | | | | | | | | |
| Albumin | Laboratory test | - | - | - | 1 | 1 | 2 | 1 | 2 |
| Alkaline phosphatase | Laboratory test | - | - | - | 1 | - | 2 | - | 2 |
| ALT (also called SGPT) | Laboratory test | | | 0 | 0 | 3 | 1 | 3 | 1 |
| Anti HEV[d] | Laboratory test | - | - | - | - | 0 | - | 1 | - |
| AST (also called SGOT) | Laboratory test | | | 0 | 0 | 1 | 1 | 1 | 1 |
| Bilirubin - Total & Direct | Laboratory test | - | - | - | 1 | 1 | 2 | 1 | 2 |
| Complete blood count | Laboratory test | - | - | 1 | 1 | 3 | 2 | 3 | 2 |
| Creatinine | Laboratory test | - | - | 1 | 1 | 3 | 1 | 4 | 1 |
| Glucose | Laboratory test | - | - | - | - | 1 | - | 1 | - |
| Hepatitis surface antigen test (HBsAg) | Laboratory test | - | - | 1 | 1 | 1 | 1 | 1 | 1 |
| HCV Genotype[e] | Laboratory test | - | - | - | - | 1 | - | 1 | - |
| HCV RDT | Laboratory test | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| HCV RNA (VL) | Laboratory test | - | - | - | 1 | 1 | 2 | 1 | 2 |
| HCV RNA (Qualitative) | Laboratory test | - | - | 1 | - | 1 | - | 1 | - |
| Haemoglobin | Laboratory test | - | - | - | - | 3 | - | 6 | - |
| HIV RDT | Laboratory test | - | - | 1 | - | 1 | - | 1 | - |
| Pregnancy test[f] | Laboratory test | - | - | - | - | 2 | - | 3.5 | - |
| Prothrombin /International Normalized Ratio (PT/INR) | Laboratory test | - | - | - | - | 1 | - | 1 | 1 |
| Daclatasavir 60mg (per tablet) | DAA medicines | - | - | - | - | 84 | 84 | 168 | 168 |
| Sofosbuvir 400mg (per tablet) | DAA medicines | - | - | - | - | 84 | 84 | 168 | 168 |
| Ultrasound | Laboratory test | - | - | - | - | 1 | - | 1 | 1 |

[a]At baseline, there are 4x family planning referral appointments which occur at initial assessment, during treatment, at end of treatment, and SVR12.
[b]Also referred to as the pre-treatment assessment.
[c]Assume that on treatment counselling occurs at every visit, so this means 3x for pre-cirrhosis and 6x for post-cirrhosis at baseline.
[d]Anti-HEV testing is only done for "selected patients with persistent evidence of liver damage", so assume this is conducted for post-cirrhotic patients only at baseline. In the simplified route, assume anti-HEV testing is not done.
[e]The MSF protocol did genotyping at baseline assessment, but we have removed this for the simplified pathway since SOF/DCV is considered to be a pangenotypic regimen.[51]
[f]Assume roughly half of population are women and they receive a pregnancy test only if confirmed HCV RNA+ in the baseline case.

**Supplementary Table S6.**

Screening, diagnoses, and treatment uptake for intervention scenarios from 2018 to 2030 inclusive, compared with a baseline scenario of no treatment from 2018. The values represent the median of 1,151 final model runs, with ranges indicating 95% uncertainty intervals of runs.

| Comparator scenario | Total population of Pakistan at start of 2018 (millions) | Total population of Pakistan by end of 2030 (millions) | Chronic HCV prevalence at start of 2018 | Number of prevalent chronic HCV infections at start of 2018 (millions) | HCV incidence at start of 2018 (per 1000 person-years) | Expected chronic HCV prevalence by end of 2030 | Expected number of prevalent chronic HCV infections by end of 2030 (millions) | Expected HCV incidence by end of 2030 (per 1000 person-years) | % change in incidence by 2030§ | % change in HCV-related mortality by 2030§ | % change in chronic HCV prevalence by 2030§ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Counterfactual**. No intervention from 2018 | 199 [194-204] | 247 [234-261] | 3.7% [3.4-4.0%] | 7.3 [6.7-8.0] | 3.4 [3.0-3.9] | 4.5% [4.0-5.1%] | 11.2 [10.1-12.4] | 4.1 [3.5-4.8] | +19.5 [+12.5 to +27.1] | +48.9 [+42.7 to +56.1] | +21.5 [+14.3 to +29.1] |

| Intervention scenario | Average annual number of Ab and RNA tests needed between 2018-2030 (millions) | Average annual number of persons screened (either Ab or RNA) between 2018-2030 (millions) | Average Annual Number of treatments initiated between 2018-2030 (1000s) | % of chronic infections diagnosed by end of 2030‡ | % of chronic infections referred by end of 2030‡ | % of chronic infections treated by end of 2030‡ | % of chronic infections cured by end of 2030‡ | % change in incidence by 2030§ | % change in HCV-related mortality by 2030§ | Year that 65% reduction in HCV-related mortality target is reached |
|---|---|---|---|---|---|---|---|---|---|---|
| **Status Quo.** (~150,000-160,000 treatments/year) | N/A | N/A | 155 [150-160] | N/A | N/A | 27.5% [25.1-30.3%] | 25.0% [22.5-28.0%] | 0.7 [-6.3 to +8.3] | +32.3 [+25.0 to +40.0] | Never |
| **Scenario S1.** One-time 90% screen by 2030 with 80% referred[a] | 14.5 [14.1-14.8] | 13.8 [13.4-14.1] | 350 [315-385] | 88.0% [85.7-90.3%] | 66.4% [63.1-69.9%] | 61.9% [58.9-65.2%] | 56.4% [54.8-58.0%] | -26.5 [-30.7 to -22.5] | +7.0 [+1.1 to +13.5] | Reaches a peak of 3.2% reduction in 2040 |
| **Scenario S2.** S1+ Target primary Ab screening Age 30+ & PWID | 14.6 [14.3-15.0] | 13.8 [13.4-14.1] | 445 [400-490] | 104.3% [102.7-105.9%] | 82.2% [78.5-86.2%] | 78.9% [75.4-83.0%] | 72.9% [71.4-74.3%] | -40.8 [-45.4 to -36.4] | -14.8 [-21.1 to -7.8] | Reaches a peak of 18.4% reduction in 2035 |
| **Scenario S3.** S2+ Re-screen SVR & Ab/RNA- every ten years from 2020† | 21.1 [20.6-21.7] | 20.2 [19.7-20.7] | 490 [445-545] | 117.8% [114.5-121.6%] | 91.6% [87.0-96.8%] | 87.4% [82.9-92.3%] | 80.5% [78.2-82.8%] | -50.8 [-55.0 to -46.1] | -17.9 [-24.3 to -10.8] | Reaches a peak of 37.3% reduction in 2047 |
| **Scenario S4*.** | | | | | | | | | | |
| S3+ Increase referral to 90% | 21.2 [20.6-21.7] | 20.3 [19.7-20.8] | 545 [495-605] | 115.8% [112.6-119.5%] | 101.6% [96.4-107.4%] | 97.1% [92.1-102.5%] | 89.5% [87.0-92.1%] | -61.1 [-64.8 to -56.5] | -26.1 [-32.9 to -18.5] | Reaches 57.7% reduction by 2050 |
| + Double primary Ab screening rate | 30.1 [28.9-31.3] | 29.1 [27.9-30.2] | 615 [555-680] | 124.3% [121.7-128.0%] | 112.0% [106.3-118.1%] | 109.1% [103.7-114.9%] | 101.4% [99.6-103.6%] | -75.3 [-78.8 to -69.9] | -46.4 [-53.0 to -37.8] | Reaches 61.8% reduction by 2050 |
| + Re-screen every 5 years | 37.3 [36.0-38.7] | 36.3 [35.0-37.7] | 630 [570-700] | 128.0% [125.1-132.0%] | 115.2% [109.2-121.4%] | 112.1% [106.5-118.0] | 104.2% [102.3-106.5%] | -77.7 [-81.1 to -72.3] | -47.8 [-54.8 to -39.1] | Reaches 65.0% reduction by 2042 |
| + Re-connect RNA+ LTFU to care & re-screen previously RNA- every 5 years† | 37.4 [36.1-38.8] | 36.4 [35.1-37.8] | 660 [595-735] | 134.6% [131.7-138.7%] | 120.6% [114.5-127.1%] | 117.3% [111.5-123.6%] | 109.0% [107.0-111.4%] | -84.8 [-87.4 to -79.7] | -52.1 [-59.3 to -43.0] | Reaches 65.0% reduction by 2035 |

[a]A 6.2% [6.1-6.3%] annual primary screening rate will screen approximately 180 [175-185] million individuals, or 90% of the 2018 population, by 2030. Doubling this to a 12.4% [12.1-12.6%] annual primary screening rate is equivalent to first-time Ab screen 280 [265-290] million individuals, or 140% of the 2018 population, by 2030.

§Compared with end of 2015 levels.

*Incremental improvements to Scenario S3. The values for Scenario S4 are in the final row of the table.

†Except for PWID, who are re-screened every year from 2020.

‡Compared to the number of chronic infections at the start of intervention in 2018.

**Supplementary Table S7.**
Costs and efficiency of screening and treatment intervention scenarios from 2018 to 2030 inclusive. Costs and outcomes are discounted at a standard rate of 3.5% per year. The values represent the median of 1,151 final model runs, with ranges indicating 95% uncertainty intervals of runs.

| Intervention scenario | Total screening and treatment costs over 2018-2030 ($ billions)‡ | Proportion of total costs due to screening over 2018-2030 (%) | Average number of tests§ needed to initiate one treatment over 2018-2030 | Total number of persons achieving SVR over 2018-2030 (millions) | Total number of new infections averted over 2018-2030 (millions) | Total number of HCV-related deaths averted over 2018-2030 (100,000s) | Costs per cure over 2018-2030‡ ($) | Costs per new infection averted over 2018-2030 ($) | Costs per HCV-related death averted over 2018-2030 ($) |
|---|---|---|---|---|---|---|---|---|---|
| **Scenario S1.** One-time 90% screen by 2030 with 80% referred[a] | 3.4 [3.2-3.7] | 52.7 [50.5-55.1] | 41.6 [37.6-45.9] | 3.2 [2.9-3.6] | 1.4 [1.2-1.7] | 1.0 [0.6-1.5] | 1,060 [1,010-1,120] | 2,400 [2,110-2,780] | 36,400 [22,700-57,200] |
| **Scenario S2.** + Target primary Ab screening Age 30+ & PWID | 4.1 [3.8-4.4] | 46.7 [44.5-49.0] | 32.9 [29.9-36.2] | 4.4 [4.0-4.8] | 2.3 [1.9-2.7] | 1.7 [1.1-2.5] | 930 [890-980] | 1,750 [1,540-2,040] | 24,800 [15,700-38,600] |
| **Scenario S3.** + Re-screen SVR & Ab/RNA- every ten years from 2020† | 5.1 [4.8-5.4] | 53.5 [51.2-55.8] | 43.0 [38.8-47.6] | 4.8 [4.3-5.3] | 2.5 [2.1-3.0] | 1.7 [1.1-2.6] | 1,060 [1,010-1,130] | 2,000 [1,750-2,320] | 30,200 [19,100-47,100] |
| **Scenario S4*.** | | | | | | | | | |
| + Increase referral to 90% | 5.4 [5.0-5.7] | 50.9 [48.6-53.2] | 38.8 [35.0-42.9] | 5.3 [4.8-5.8] | 2.9 [2.5-3.4] | 1.9 [1.2-2.9] | 1,010 [960-1,060] | 1,840 [1,620-2,130] | 28,300 [17,900-44,200] |
| + Double primary Ab screening rate | 7.0 [6.6-7.4] | 55.6 [53.4-58.0] | 49.0 [44.3-54.4] | 6.3 [5.7-6.9] | 4.1 [3.5-4.7] | 2.7 [1.8-4.2] | 1,110 [1,050-1,170] | 1,710 [1,500-1,970] | 25,500 [16,200-39,500] |
| + Re-screen every 5 years | 7.9 [7.5-8.4] | 60.2 [57.9-62.4] | 59.3 [53.3-65.8] | 6.4 [5.9-7.1] | 4.1 [3.5-4.8] | 2.7 [1.8-4.2] | 1,230 [1,170-1,300] | 1,910 [1,680-2,220] | 28,800 [18,400-44,600] |
| + Re-engage RNA+ LTFU† | 8.1 [7.7-8.5] | 59.2 [57.0-61.5] | 56.7 [51.0-63.0] | 6.7 [6.1-7.4] | 4.4 [3.7-5.1] | 2.8 [1.9-4.4] | 1,200 [1,140-1,270] | 1,860 [1,640-2,140] | 28,600 [18,200-44,300] |

[a]A 6.2% [6.1-6.3%] annual primary screening rate will screen approximately 180 million by 2030, or 90% of the 2018 population, by 2030. Doubling this to a 12.4% [12.1-12.6%] annual primary screening rate is equivalent to first-time Ab screen 280 [265-290] million individuals, or 140% of the 2018 population, by 2030.
*Incremental improvements to Scenario S3. The values for Scenario S4 are in the final row of the table.
†Except for PWID, who are re-screened every year from 2020.
‡All costs in $USD.
§Both Ab & RNA tests

**Supplementary Table S8.**
Undiscounted costs and efficiency of screening and treatment intervention scenarios from 2018 to 2030 inclusive. The values represent the median of 1,151 final model runs, with ranges indicating 95% uncertainty intervals of runs.

| Intervention scenario | Total screening and treatment costs over 2018-2030 ($ billions)‡ | Total number of persons achieving SVR over 2018-2030 (millions) | Total number of new infections averted over 2018-2030 (millions) | Total number of HCV-related deaths averted over 2018-2030 (100,000s) | Costs per cure over 2018-2030‡ ($) | Costs per new infection averted over 2018-2030 ($) | Costs per HCV-related death averted over 2018-2030 ($) |
|---|---|---|---|---|---|---|---|
| **Scenario S1.** One-time 90% screen by 2030 with 80% referred[a] | 4.3 [4.0-4.6] | 4.1 [3.7-4.6] | 1.9 [1.6-2.2] | 1.3 [0.9-2.0] | 1,040 [990-1,100] | 2,210 [1,940-2,550] | 32,600 [20,400-51,200] |
| **Scenario S2.** + Target primary Ab screening Age 30+ & PWID | 5.0 [4.6-5.3] | 5.3 [4.9-5.8] | 3.1 [2.6-3.7] | 2.3 [1.5-3.5] | 930 [890-980] | 1,580 [1,390-1,840] | 21,700 [13,700-33,700] |
| **Scenario S3.** + Re-screen SVR & Ab/RNA- every ten years from 2020† | 6.3 [5.9-6.7] | 5.9 [5.3-6.5] | 3.4 [2.9-4.0] | 2.3 [1.5-3.6] | 1,070 [1,020-1,130] | 1,830 [1,600-2,120] | 26,800 [17,000-41,800] |
| **Scenario S4*.** | | | | | | | |
| + Increase referral to 90% | 6.6 [6.2-7.0] | 6.5 [5.9-7.2] | 3.9 [3.3-4.6] | 2.6 [1.7-4.1] | 1,010 [960-1,070] | 1,680 [1,470-1,940] | 25,100 [15,900-39,100] |
| + Double primary Ab screening rate | 8.2 [7.8-8.7] | 7.4 [6.8-8.1] | 5.4 [4.6-6.3] | 3.8 [2.5-5.7] | 1,110 [1,060-1,170] | 1,520 [1,340-1,760] | 22,000 [14,000-33,900] |
| + Re-screen every 5 years | 9.5 [9.0-10.0] | 7.6 [6.9-8.3] | 5.5 [4.7-6.4] | 3.8 [2.5-5.8] | 1,250 [1,180-1,320] | 1,720 [1,510-1,990] | 25,000 [16,000-38,700] |
| + Re-engage RNA+ LTFU† | 9.7 [9.2-10.2] | 8.0 [7.3-8.7] | 5.8 [4.9-6.7] | 3.9 [2.6-5.9] | 1,220 [1,150-1,290] | 1,670 [1,470-1,920] | 24,800 [15,900-38,400] |

[a]A 6.2% [6.1-6.3%] annual primary screening rate will screen approximately 180 million by 2030, or 90% of the 2018 population, by 2030. Doubling this to a 12.4% [12.1-12.6%] annual primary screening rate is equivalent to first-time Ab screen 280 [265-290] million individuals, or 140% of the 2018 population, by 2030.
*Incremental improvements to Scenario S3. The values for Scenario S4 are in the final row of the table.
†Except for PWID, who are re-screened every year from 2020.
‡All costs in $USD.

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