

## Supplementary Material

# Treatment as prevention for hepatitis C virus in Pakistan: Mathematical modeling projections

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### S1 Text - Mathematical model

We developed a model based on adaptation of the deterministic compartmental mathematical models published in References (1, 2). The model was expressed in terms of a system of coupled nonlinear differential equations that stratify the population into compartments according to age group, HCV status and stage of infection, and level of risk of exposure:

Population aged 0-4 years old:

$$\begin{aligned} \frac{dS_1(1,i)}{dt} &= \varphi N(i) - (\eta(i) + \mu(1) + \delta(1) + \lambda_{S_1(1,i)}) S_1(1,i) + \left( \sum_{i'=1}^5 \eta(i') S_1(1,i') \right) \left( \frac{S_1(1,i)}{\sum_{i''=1}^5 S_1(1,i'')} \right) \\ \frac{dI_{Ac_1}(1,i)}{dt} &= \lambda_{S_1(1,i)} S_1(1,i) - (\eta(i) + \mu(1) + \delta(1) + \sigma_1) I_{Ac_1}(1,i) + \left( \sum_{i'=1}^5 \eta(i') I_{Ac_1}(1,i') \right) \left( \frac{I_{Ac_1}(1,i)}{\sum_{i''=1}^5 I_{Ac_1}(1,i'')} \right) \\ \frac{dS_2(1,i)}{dt} &= \varepsilon \beta I_{Ch}(1,i) + f \sigma_1 I_{Ac_1}(1,i) + g \sigma_2 I_{Ac_2}(1,i) - (\eta(i) + \mu(1) + \delta(1) + \lambda_{S_2(1,i)}) S_2(1,i) + \left( \sum_{i'=1}^5 \eta(i') S_2(1,i') \right) \left( \frac{S_2(1,i)}{\sum_{i''=1}^5 S_2(1,i'')} \right) \\ \frac{dI_{Ac_2}(1,i)}{dt} &= \lambda_{S_2(1,i)} S_2(1,i) - (\eta(i) + \mu(1) + \delta(1) + \sigma_2) I_{Ac_2}(1,i) + \left( \sum_{i'=1}^5 \eta(i') I_{Ac_2}(1,i') \right) \left( \frac{I_{Ac_2}(1,i)}{\sum_{i''=1}^5 I_{Ac_2}(1,i'')} \right) \\ \frac{dI_{Ch}(1,i)}{dt} &= (1-f) \sigma_1 I_{Ac_1}(1,i) + (1-g) \sigma_2 I_{Ac_2}(1,i) - (\eta(i) + \delta(1) + \mu(1)) I_{Ch}(1,i) + \left( \sum_{i'=1}^5 \eta(i') I_{Ch}(1,i') \right) \left( \frac{I_{Ch}(1,i)}{\sum_{i''=1}^5 I_{Ch}(1,i'')} \right) - \varepsilon \beta I_{Ch}(1,i) \end{aligned}$$

Population aged  $\geq 5$  years old:

$$\begin{aligned} \frac{dS_1(a,i)}{dt} &= \mu(a-1) S_1(a-1,i) - (\eta(i) + \mu(a) + \delta(a) + \lambda_{S_1(a,i)}) S_1(a,i) + \left( \sum_{i'=1}^5 \eta(i') S_1(a,i') \right) \left( \frac{S_1(a,i)}{\sum_{i''=1}^5 S_1(a,i'')} \right) \\ \frac{dI_{Ac_1}(a,i)}{dt} &= \mu(a-1) I_{Ac_1}(a,i) + \lambda_{S_1(a,i)} S_1(a,i) - (\eta(i) + \mu(a) + \delta(a) + \sigma_1) I_{Ac_1}(a,i) + \left( \sum_{i'=1}^5 \eta(i') I_{Ac_1}(a,i') \right) \left( \frac{I_{Ac_1}(a,i)}{\sum_{i''=1}^5 I_{Ac_1}(a,i'')} \right) \end{aligned}$$

$$\frac{dS_2(a,i)}{dt} = \varepsilon\beta I_{Ch}(a,i) + \mu(a-1)S_2(a-1,i) + f\sigma_1 I_{Ac_1}(a,i) + g\sigma_2 I_{Ac_2}(a,i) - (\eta(i) + \mu(a) + \delta(a) + \lambda_{S_2(a,i)})S_2(a,i) + \left( \sum_{i'=1}^5 \eta(i')S_2(a,i') \right) \left( \frac{S_2(a,i)}{\sum_{i''=1}^5 S_2(a,i'')} \right)$$

$$\frac{dI_{Ac_2}(a,i)}{dt} = \mu(a-1)I_{Ac_2}(a-1,i) + \lambda_{S_2(a,i)}S_2(a,i) - (\eta(i) + \mu(a) + \delta(a) + \sigma_2)I_{Ac_2}(a,i) + \left( \sum_{i'=1}^5 \eta(i')I_{Ac_2}(a,i') \right) \left( \frac{I_{Ac_2}(a,i)}{\sum_{i''=1}^5 I_{Ac_2}(a,i'')} \right)$$

$$\frac{dI_{Ch}(a,i)}{dt} = \mu(a-1)I_{Ch}(a-1,i) + (1-f)\sigma_1 I_{Ac_1}(a,i) + (1-g)\sigma_2 I_{Ac_2}(a,i) - (\eta(i) + \delta(a) + \mu(a))I_{Ch}(a,i) + \left( \sum_{i'=1}^5 \eta(i')I_{Ch}(a,i') \right) \left( \frac{I_{Ch}(a,i)}{\sum_{i''=1}^5 I_{Ch}(a,i'')} \right) - \varepsilon\beta I_{Ch}(a,i)$$

The population was stratified into five risk groups, defined with index  $i$  ( $i = 1, 2, \dots, 5$ )

representing the low to higher risk groups. This stratification by risk allows the model to accommodate for the heterogeneity in the level of risk of exposure in the population.

The population was also stratified into seven age groups, defined with the index  $a$  ( $a = 1, 2, \dots, 7$ )

. The first and second age groups represent the age bands 0-4 years old and 5-19 years old, respectively. Each group of the third, fourth, fifth, and sixth age groups represents a ten-year age band (20-29, 30-39, 40-49, and 50-59 years old). The last age group represents the age band >60 years old.

Definitions of all symbols in the equations can be found in Table S1.

**Table S1.** Definitions of symbols in the mathematical model equations.

Symbol	Definition
$S_1(a,i)$	HCV susceptible population
$S_2(a,i)$	Population of those who were previously exposed to HCV infection, but cleared their infection and are now susceptible to reinfection with HCV
$I_{Ac_2}(a,i)$	Population of individuals in secondary acute infection (following reinfection with HCV)
$I_{Ch}(a,i)$	Population of individuals in chronic HCV infection
$\varphi$	Population growth rate

$\delta$	Natural death rate
$N(i)$	Total population size in each risk group
$\sigma_1$	Rate of progression from primary acute HCV infection stage to chronic stage
$\sigma_2$	Rate of progression from secondary acute HCV infection stage to chronic stage
$f$	Fraction of individuals who clear their primary acute HCV infection spontaneously (first infection)
$g$	Fraction of individuals who clear their secondary acute HCV infection spontaneously (reinfection)
$\mu(a)$	Transition rate from one age group to the next age group
$1/\eta(i)$	Duration that an individual spends in a specific $i$ risk group
$\lambda_{S_k(a,i)}$	HCV force of infection experienced by each $S_k(a,i)$ susceptible population
$\beta$	Treatment rate starting from 2018
$\varepsilon$	Treatment success rate

The proportion of the population initially in each risk group  $i$  was determined using a gamma distribution (1-7). The population growth rate ( $\varphi$ ) and the natural mortality rate ( $\delta$ ) were described by the following functions, as they provided a robust fit of population growth and age structure in Pakistan (8, 9):

$$\varphi(t) = a_0 e^{-\left(\frac{t-t_0}{b_0}\right)^2}$$

and

$$\delta(t, a) = \frac{a_1 e^{-\left(\frac{t-t_1}{b_1}\right)^2}}{\left[1 + e^{-b_2(a-a_2)}\right]}$$

Here  $a_0$ ,  $a_1$ ,  $a_2$ ,  $t_0$ ,  $t_1$ ,  $b_0$ ,  $b_1$ , and  $b_2$  are fitting parameters.

The HCV force of infection (hazard rate of infection;  $\lambda_{S_k(a,i)}$ ) experienced by each  $S_k(a,i)$  susceptible population is expressed by

$$\lambda_{S_k(a,i)} = \rho_{S_k(a,i)} \sum_{a''=1}^7 \sum_{i''=1}^5 \sum_{\alpha=Ac_1,Ac_2,Ch} P_{I_\alpha(a'',i'') \rightarrow S_k(a,i)} \mathcal{G}_{i,i''} \mathcal{H}_{a,a''} \frac{\rho_{I_\alpha(a'',i'')} I_\alpha(a'',i'')}{\left( \sum_{k=1}^2 \rho_{S_k(a'',i'')} S_k(a'',i'') + \sum_{\alpha'=Ac_1,Ac_2,Ch} \rho_{I_{\alpha'}(a'',i'')} I_{\alpha'}(a'',i'') \right)}$$

Here,  $\rho_{X^{z(i)}}$  is the effective rate of contacts (parenteral exposures conducive to HCV

transmission) per year for each population variable  $X(a,i)$ . The parameter  $P_{I_\alpha(a,i) \rightarrow S_k(a,i)}$  defines

HCV transmission probability per contact between a member of the susceptible population

$S_k(a,i)$  and a member of the HCV infected population  $I_\alpha(a,i)$ . The mixing between the

different risk groups (and age groups) is dictated by the mixing matrices  $\mathcal{G}_{i,j}$  (and  $\mathcal{H}_{a,a''}$ ).

Mixing matrices: The matrices  $\mathcal{G}_{i,j}$  (and  $\mathcal{H}_{a,a''}$ ) provide the probability that an individual in the  $i$

(or  $a$ ) group will mix with an individual in the  $j$  (or  $a''$ ) group. The mixing matrices are given

by

$$\mathcal{G}_{i,j} = e_{Risk} \delta_{i,j} + (1 - e_{Risk}) \frac{\sum_{a=1}^7 \left( \sum_{k=1}^2 \rho_{S_k(a,j)} S_k(a,j) + \sum_{\alpha'=Ac_1,Ac_2,Ch} \rho_{I_{\alpha'}(a,j)} I_{\alpha'}(a,j) \right)}{\sum_{j'=1}^5 \sum_{a=1}^7 \left( \sum_{k=1}^2 \rho_{S_k(a,j')} S_k(a,j') + \sum_{\alpha'=Ac_1,Ac_2,Ch} \rho_{I_{\alpha'}(a,j')} I_{\alpha'}(a,j') \right)}$$

$$\mathcal{H}_{a,a''} = e_{Age} \delta_{a,a''} + (1 - e_{Age}) \frac{\sum_{j=1}^5 \left( \sum_{k=1}^2 \rho_{S_k(a'',j)} S_k(a'',j) + \sum_{\alpha'=Ac_1,Ac_2,Ch} \rho_{I_{\alpha'}(a'',j)} I_{\alpha'}(a'',j) \right)}{\sum_{a'=1}^7 \sum_{j=1}^5 \left( \sum_{k=1}^2 \rho_{S_k(a',j)} S_k(a',j) + \sum_{\alpha'=Ac_1,Ac_2,Ch} \rho_{I_{\alpha'}(a',j)} I_{\alpha'}(a',j) \right)}$$

Here,  $\delta_{i,j}$  (and  $\delta_{a,a''}$ ) are the identity matrices.  $e_{Risk}$  and  $e_{Age} \in [0,1]$  measure the degree of

assortativeness in the mixing. At the extreme  $e_{Risk} = e_{Age} = 0$ , the mixing is fully proportional

while at the other extreme  $e_{Risk} = e_{Age} = 1$ , the mixing is fully assortative, that is individuals mix

only with members in their own risk group.

Contact rate: The  $\rho_{X(a,i)}$  parameter describes the baseline rate of contacts (parenteral exposures) per year for each population variable. It is expressed by a power law function:

$$\rho_{X(a,i)} = F(a) \times C \times i^\theta$$

Here  $F(a)$  is the age-dependent factor of exposure to HCV among a specific age group  $a$ ,  $C$  is a constant determined by the average risk of exposure, and  $\theta$  is the exponent parameter that determines the growth in risk of exposure with risk group number  $i$ .

To account for temporal variation in HCV prevalence, we incorporated temporal changes in risk of exposure. We parameterized the temporal variation (time dependence of  $\rho_{X(a,i)}$ ) through a Gaussian function which provides the best fit for HCV prevalence data. This function is mathematically designed to describe and characterize the transitions (increase and decrease in the risk of exposure) in terms of their scale or strength, smoothness or abruptness, thickness (duration), and the turning point. Using the Gaussian parameterization,  $\rho_{X(a,i)}(t)$  is given by:

$$\rho_{X(a,i)}(t) = \rho_{X(a,i)} \times \left( 1 + Z \exp \left( \frac{-(t - \xi_{Turning})^2}{\xi_{Duration}^2} \right) \right)$$

Here,  $\rho_{X(a,i)}$  is the asymptotic value of  $\rho_{X(a,i)}(t)$  that describes the level of risk of exposure well before and well after the transition.  $\xi_{Duration}$  describes the transition duration parameter.  $\xi_{Turning}$  is the turning point year at which the effective rate of contacts per year crosses half the way towards its asymptotic value of  $\rho_{X(a,i)}$ . The level of risk of exposure changes during the transition from  $\rho_{X(a,i)}$  to a peak of  $\rho_{X(a,i)} \times (1 + Z)$ , and then declines eventually to  $\rho_{X(a,i)}$ .

## S2 Text - Parameter values

The parameters of the model were based on current empirical data on HCV epidemiology and natural history, and are listed in Table S2 along with their references. The demographic parameters  $a_0$ ,  $a_1$ ,  $a_2$ ,  $t_0$ ,  $t_1$ ,  $b_0$ ,  $b_1$ , and  $b_2$  were determined by fitting the population growth and age structure in Pakistan (8, 9). The age group mixing ( $e_{Age}$ ), the age-dependent factor of exposure to HCV ( $F(a)$ ), the exponent parameter ( $\theta$ ), the constant ( $C$ ) in the power law function, and the constants ( $Z$ ,  $\xi_{Turning}$ , and  $\xi_{Duration}$ ) in the Gaussian function were fitting parameters. They were determined by fitting simultaneously the overall and age-specific HCV antibody positive prevalence data in Pakistan (2, 10, 11). Furthermore, the treatment rate ( $\beta$ ) was assumed to be time-dependent, and was determined by fitting the model to the desired treatment program scale-up and sustainability.

**Table S2.** Model assumptions in terms of parameter values.

Parameter	Symbol	Value	Justification	Sources
Transmission probability per contact in chronic infection stage	$P_{I_{Ch}(a^*,i^*) \rightarrow S_k(a,i)}$	0.048	Combination of empirical data and quantitative estimates	(12-17)
Transmission probability per contact in primary acute infection	$P_{I_{Aq1}(a^*,i^*) \rightarrow S_k(a,i)}$	0.1296	Based on the relative level of viral load with respect to chronic infection stage	(14)
Transmission probability per contact in secondary acute infection	$P_{I_{Ac2}(a^*,i^*) \rightarrow S_k(a,i)}$	0.0648	Reduction of 50% in viral load during secondary acute infection with respect to initial primary acute infection	(18)
Duration of primary acute HCV infection stage	$1/\sigma_1$	16.5 weeks	Direct measurement from a prospective cohort study	(19)

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Duration of secondary acute HCV infection stage	$1/\sigma_2$	4.125 weeks	Direct measurement from prospective cohort studies	(18, 20)
Fraction of individuals who clear their primary acute HCV infection spontaneously (first infection)	$f$	25%	Direct measurement from a prospective cohort study	(19)
Fraction of individuals who clear their secondary acute HCV infection spontaneously (reinfection)	$g$	83%	Direct measurement from a prospective cohort study	(18)
Duration that an individual spends in a specific $i$ risk group	$\eta(i)$	12 - 40 years	A hierarchy of durations based on risk groups starting with an injecting career of 12 years among people who inject drugs (highest risk group) up to a low risk duration of 40 years (lowest risk group)	(1, 2, 21) and representative values
Degree of risk assortativeness	$e_{Risk}$	0.3	Informed by infectious disease modeling works	(1, 2, 16) and representative value
Relative risk of exposure by risk group	$\rho_{X(a,i)} / \rho_{X(a,1)}$		Quantitative estimates based on the plausible level of risk of exposure to HCV infection	Based on a power-law function motivated by analyses of the architecture of complex weighted networks (22, 23), and by an analysis of the average separation between individuals in a network or a sub-network (24)
First risk group (lowest risk group)		1.0 (reference group)		
Second risk group		5.6		
Third risk group		15.6		
Fourth risk group		32.0		
Fifth risk group (highest risk group including populations such as		56.0		

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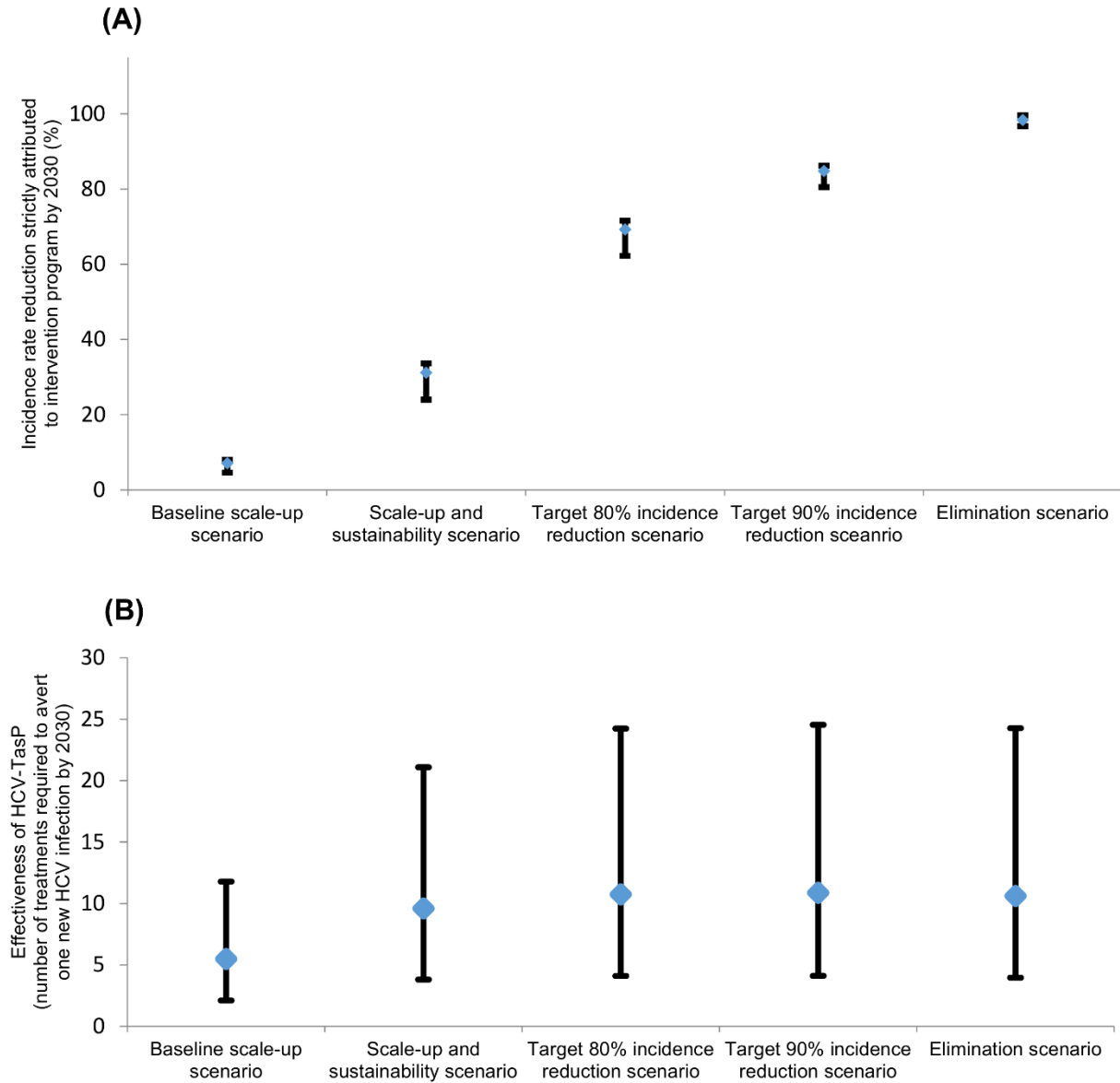
people who inject  
drugs)

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**Table S3.** Epidemiologic, programming, and health economic measures used to assess the impact of Pakistan’s treatment program, following our approach for Egypt (1).

<b>Measure</b>	<b>Definition</b>
<b>HCV chronic infection prevalence</b>	Proportion of a given population that are HCV antibody positive and ribonucleic acid (RNA) positive, that is, proportion of the population that are chronically infected with HCV.
<b>HCV incidence (also referred to as number of new HCV infections per year)</b>	Number of new HCV infections in a given population over a duration of a year.
<b>HCV incidence rate</b>	Number of new HCV infections per person-time of the at risk population, that is, HCV incidence divided by the population size of the at risk susceptible population.
<b>Incidence reduction</b>	Relative difference between incidence at a given time and incidence in 2010. This measure was used to define targets such as the 90% incidence reduction by 2030. The year 2010 was chosen as a reference year (25, 26), for comparisons over complete two decades (2010, 2020, and 2030), and for consistency with the approach for Egypt (1).
<b>Incidence rate reduction</b>	Relative difference between incidence rate at a given time in presence of intervention, and that in the no-intervention counter-factual scenario. This measure was used to disentangle incidence rate reduction attributed strictly to the program from that due to “natural” epidemic course.
<b>Annual reduction in incidence rate</b>	Relative difference between incidence rate at a given time with that exactly one year earlier. Of notice that this measure reflects reductions due to both intervention impact and natural epidemic course.
<b>Number of averted infections</b>	Difference between incidence after program implementation, and that in the no-intervention counter-factual scenario. An annual discount rate of 3% was applied on future savings (that is infections averted).
<b>Effectiveness of HCV treatment as prevention (also referred to as number of treatments required to avert one new infection)</b>	Cumulative number of treatments divided by number of averted infections over a chosen time horizon.
<b>Cost-effectiveness of HCV treatment as prevention (also referred to as cost to avert one infection)</b>	Cost of program divided by number of averted infections over a chosen time horizon. HCV treatment cost per person was assumed at \$100, mainly covering the direct cost of the generic DAAs. An annual discount rate of 3% was applied on future expenditures.
<b>Program treatment coverage</b>	Number of living treated persons at a given time divided by number of living chronically-infected persons at that time.

**Fig. S1. Uncertainty analyses.** A) Mean and 95% uncertainty interval (UI) of the estimated incidence rate reduction in the total population of Pakistan strictly attributed to the treatment intervention program by 2030. B) Mean and 95% UI for the effectiveness of HCV treatment as prevention (HCV-TasP) by 2030, defined as number of treatments required to avert one new HCV infection.



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