Supplementary Material

Planning the Hepatitis C virus elimination in Cyprus. A modeling study

Ilias Gountas[1], Ioanna Yiasemi[2], Evi Kyprianou[2], Christos Mina[2], Chrysanthos Georgiou[3], Petros Katsioloudes[4], Andri Kouroufexi[5], Anna Demetriou[6], Elena Xenofontos[7], Georgios Nikolopoulos[1]

Ilias Gountas, Georgios Nikolopoulos, Medical School, University of Cyprus, Nicosia, Cyprus

Ioanna Yiasemi, Evi Kyprianou, Christos Mina, Cyprus Monitoring Centre, Cyprus National Addictions Authority, Nicosia, Cyprus

Chrysanthos Georgiou, Nicosia General Hospital

Petros Katsioloudes, Evangelistria Medical Centre

Andri Kouroufexi, Pharmaceutical Services, Ministry of Health

Anna Demetriou, Health Monitoring Unit, Ministry of Health

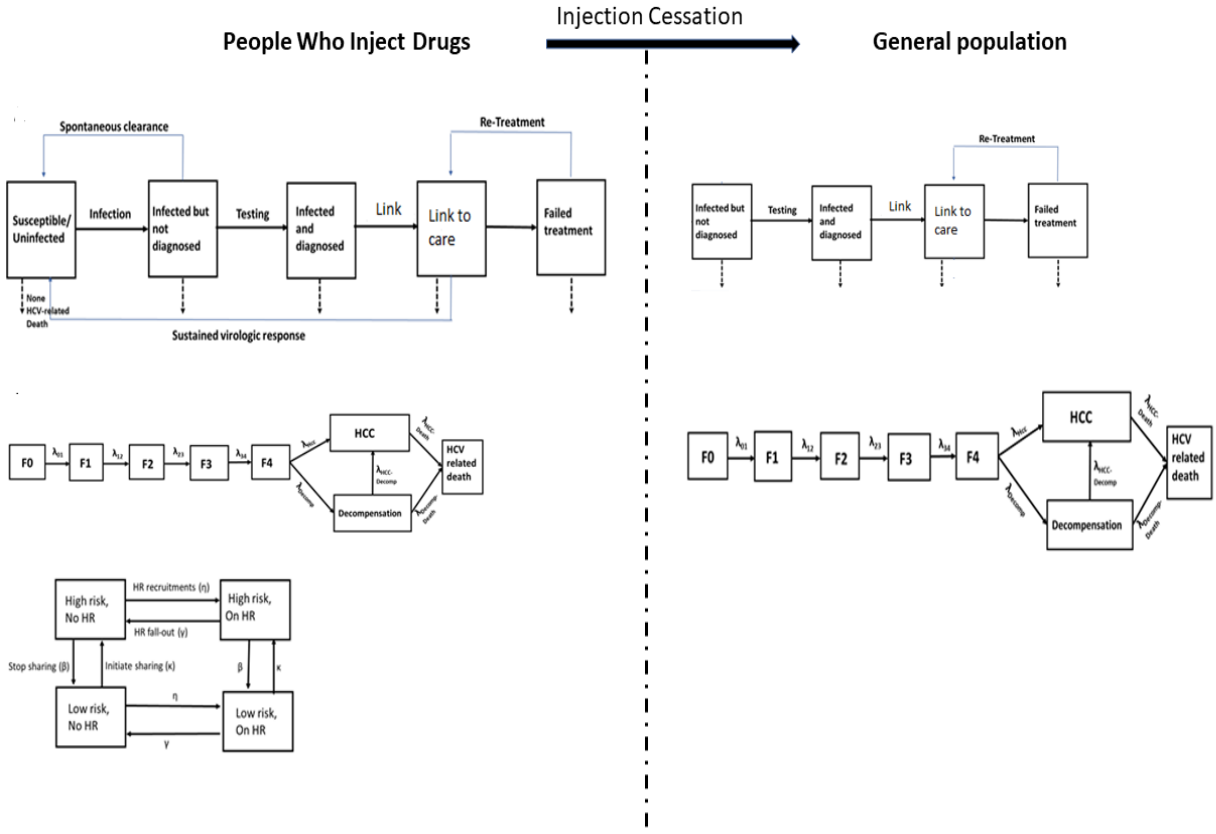
Elena Xenofontos, Department of Internal Medicine, Limassol General Hospital, Limassol, Cyprus

Content

Schematic outline of the mathematical model for Hepatitis C transmission 3
Probability of Infection 4
Model's type 5
Characteristics of the examined population 6
Evaluated scenarios 7
Annual diagnoses by each evaluated scenario 8
Scenario A 8
Scenario B 9
Scenario C 10
Scenario D 11
Scenario E 12
Treatment allocation during the first years of DAAs 13
Annual Treatment distribution by risk group under the elimination scenario 14
Cumulative incidence 15
Sensitivity Analysis 16
Sensitivity Analysis Table 16
Tornado diagram for the whole population 17
Tornado diagram for the PWID population 18
References 19

Schematic outline of the mathematical model for Hepatitis C transmission

Supplementary Figure 1 Schematic outline of the mathematical model for HCV disease transmission and treatment states, behavioral states, harm reduction states, and natural history states. (The infection rate per year depends on the prevalence of people who inject drugs and on whether they participate in a harm reduction programs).



Probability of Infection

The probability of infection for an uninfected sharer PWID from *m* unsafe injections is a non-linear function of the probability of transmission of HCV from one contaminated syringe, the number of unsafe injections (*m*), and the prevalence of HCV-infected syringes. It is derived as follows:

$$\text{Probability}_{\text{Infection from } m \text{ Unsafe Injections}} = 1 - \text{Probability}_{\text{Not Getting Infected from } m \text{ Unsafe Injections}} \quad (1)$$

$$\text{Probability}_{\text{Not Getting Infected from } m \text{ Unsafe Injections}} = \left(1 - \text{Probability}_{\text{Infection from One Unsafe Injection}}\right)^{m} \quad (2)$$

$$\text{Probability}_{\text{Infection from One Unsafe Injection}} = \text{Probability}_{\text{Transmission from One Contaminated Syringe}} \times \text{Prevalence}_{\text{Infected Syringes}} \quad (3)$$

Combining (1), (2), and (3):

$$\text{Probability}_{\text{Infection from } m \text{ Unsafe Injections}} = 1 - \left(1 - \text{Probability}_{\text{Transmission from One Contaminated Syringe}} \times \text{Prevalence}_{\text{Infected Syringes}}\right)^{m} \quad (4)$$

Furthermore, assuming that the rates of lending out and borrowing syringes among PWID are equal,

$$\text{Prevalence}_{\text{Infected Syringes}} = \frac{\sum_i \text{Unsafe Injections}_i \times \text{Fraction of PWID}_i \times \text{Prevalence of HCV Among Sharers}_i}{\sum_i \text{Unsafe Injections}_i \times \text{Fraction of PWID}_i}, \quad (5)$$

where *i* ranges over general population, OST only, NSP only, and OST and NSP and fraction of PWID represents the proportion of PWID in group *i*.

Specifically, for uninfected sharer PWID in group *i* (where *i* is general population, OST only, NSP only, or both OST and NSP), the probability of infection λ_i is:

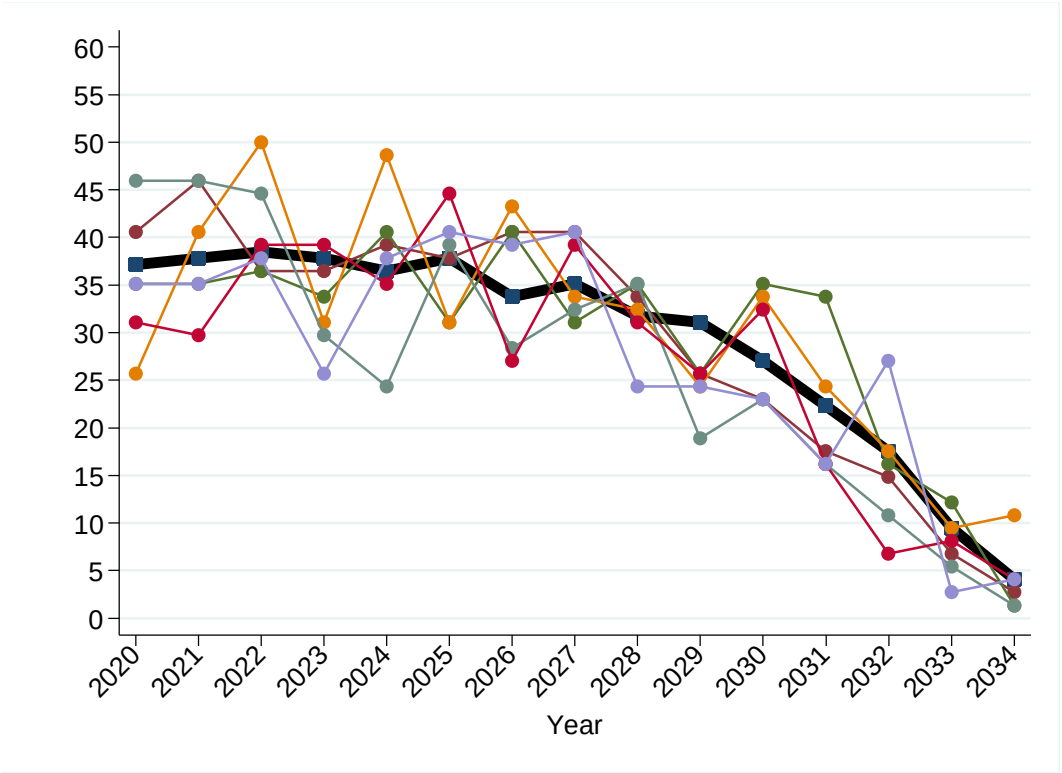
$$\lambda_i = 1 - \left(1 - \text{Probability}_{\text{Transmission from One Contaminated Syringe}} \times \text{Prevalence}_{\text{Infected Syringes}}\right)^{m_i} \quad (6)$$

For PWID in a harm reduction program, the number of unsafe injections per person per year was calculated by multiplying the number of unsafe injections per person per year in general population by a factor of *X*, *Y*, or *Z* (*X*, *Y*, and *Z* <1), respectively, thereby reducing the probability of infection.

Model's type

In our analysis, a discrete-time, stochastic, individual-based model (IBM) was used. IBM simulates the patients' trajectories at an individual level. It is important that those models possess some inherent randomness due to their methodology. The way that the model examines if a pseudo-individual would change state (e.g., from susceptible to infected) is through the draw of random numbers. More specifically, the model estimates the probability of moving from one stage to the next (e.g., from susceptible to infected). Then for each pseudo-individual, a random number from a Uniform (0,1) distribution is drawn. If the resulted random number (e.g., 0.3) is smaller than the estimated probability of changing stage (e.g. 0.4), then this pseudo-individual changes stage and vice versa. For example, regarding the transmission from susceptible to infected, if the risk of infection is 20 percent, then all the individuals with drawn random numbers lying in the range of (0-0.2) are assumed to become infected. As the outcome of each run depends on chance, every simulation leads to slightly different results (Figure S1). Uncertainty comes from a single set of parameters but across multiple simulations with randomness included. For that, results over all simulations are pooled and the median along a range is normally presented (stochastic variability). In those models, in order for the results to be reliable, several runs should be conducted since if the number of runs is limited, extreme results from simulations would affect significantly the pooled estimates. For more details regarding the IBM models one could look at (Vynnycky Emilia 2010).

Supplementary Figure 2 Model predictions for HCV incident cases under scenario E for the first 6 simulations (different colors) of the model. The solid black line shows the median estimation.



Characteristics of the examined population

According to the Pharmaceutical Services of the Ministry of Heath of Cyprus, the distribution of the fibrosis stage of the patients waiting for treatment is shown to the below table.

Supplementary Table 1 Fibrosis distribution of the patients waiting for treatment in the Republic of Cyprus

Fibrosis stage	**Percentages**
F0-F1	63.2%
F2	21.0%
F3	5.3%
F4	10.5%

The mean age of the population is 41.6 years old

Evaluated scenarios

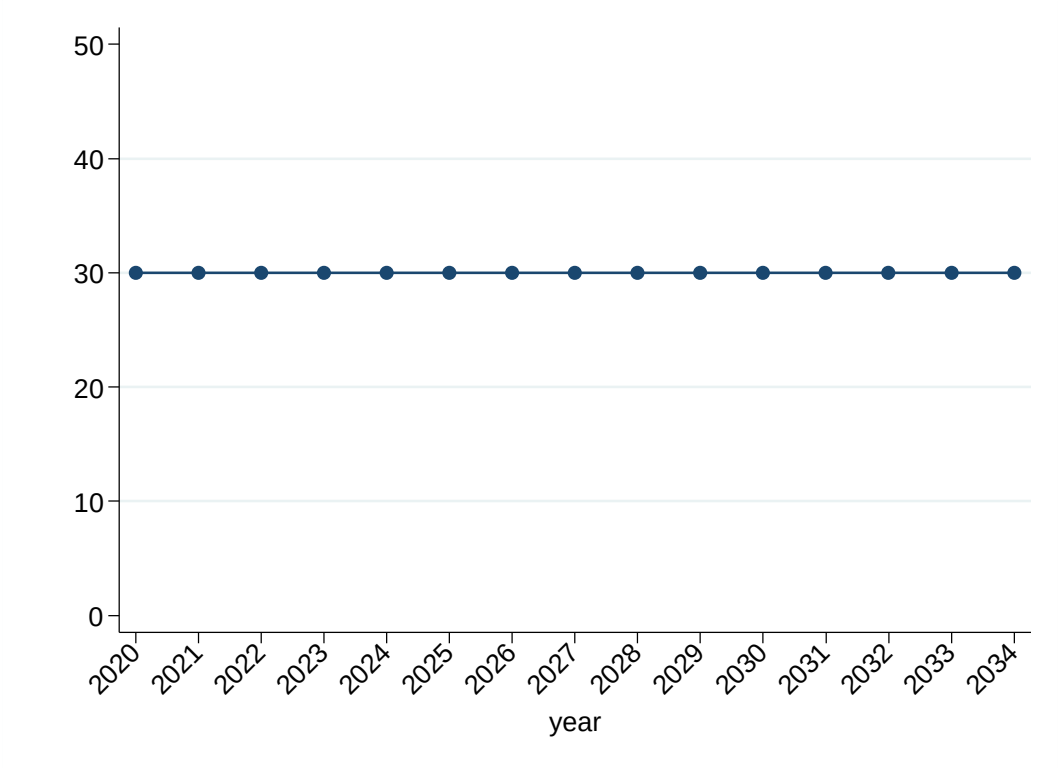
Table 2 Evaluated scenarios for projections of the future burden of hepatitis C infection in the Republic of Cyprus

	General population		PWID population		
	Increase treatment coverage	Increase diagnoses	Increase harm reduction coverage	Increase treatment coverage	Increase diagnoses
Scenario A	No	No	No	No	No
Scenario B	Yes	No	No	No	No
Scenario C	Yes	Yes	No	No	No
Scenario D	Yes	Yes	Yes	No	No
Scenario E	Yes	Yes	Yes	Yes	Yes

Annual diagnoses by each evaluated scenario

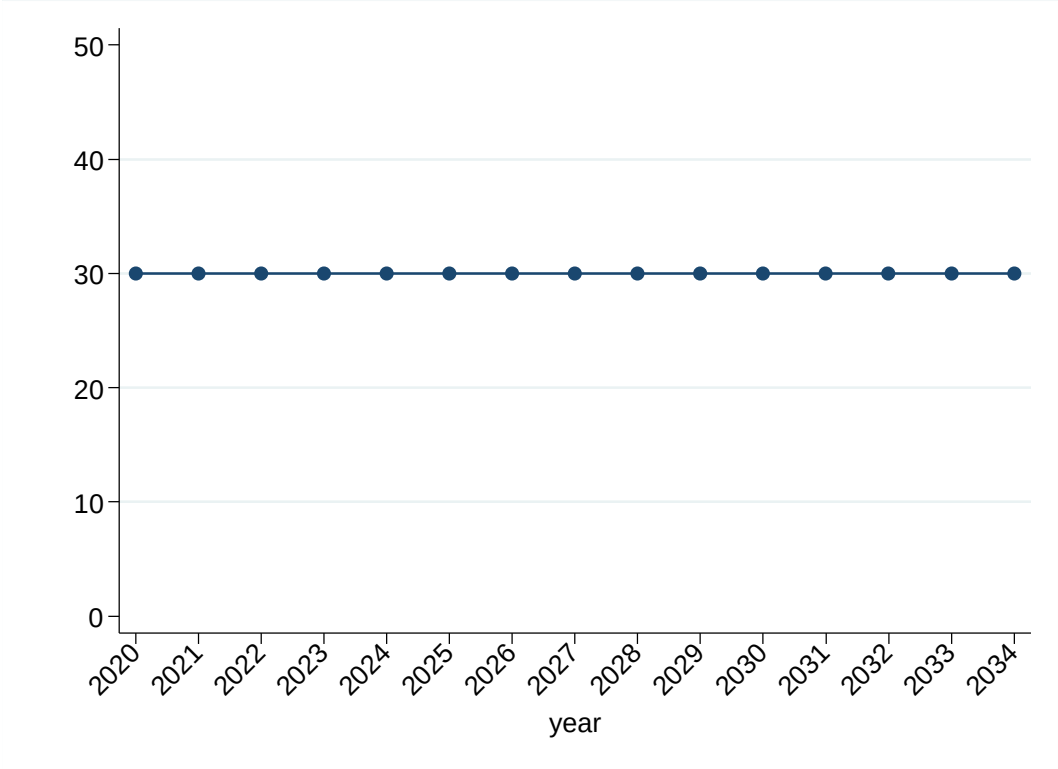
Scenario A

Supplementary Figure 3 Model predictions concerning the annual diagnoses under scenario A.



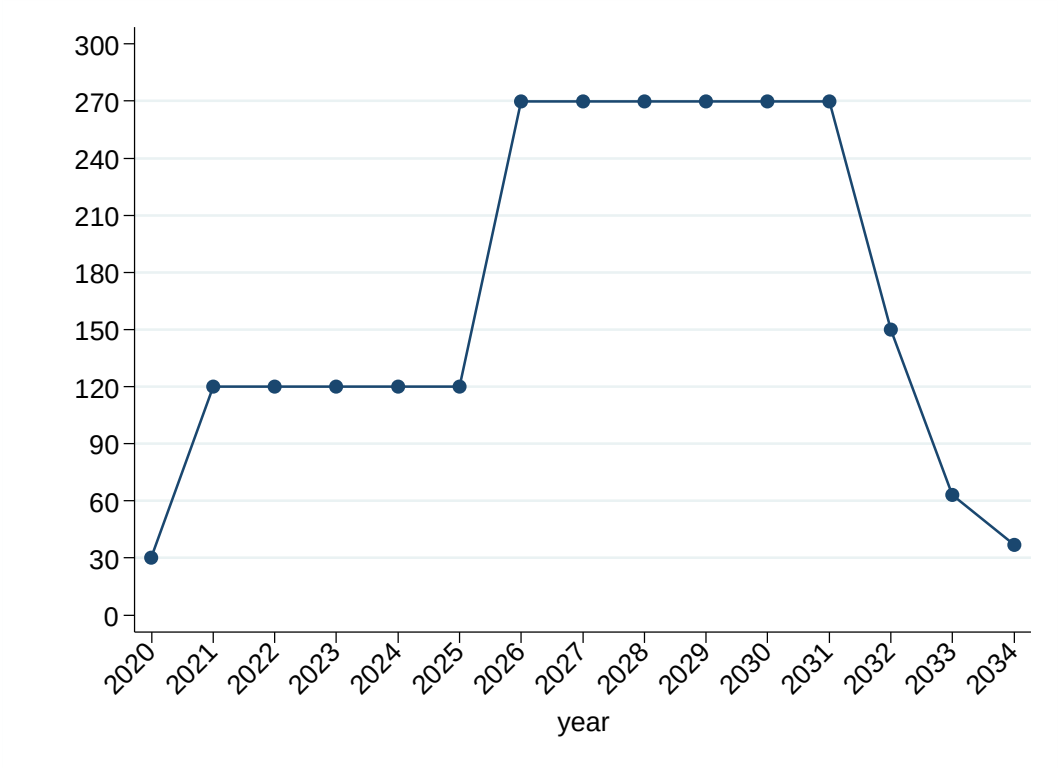
Scenario B

Supplementary Figure 4: Model predictions concerning the annual diagnoses under scenario B.



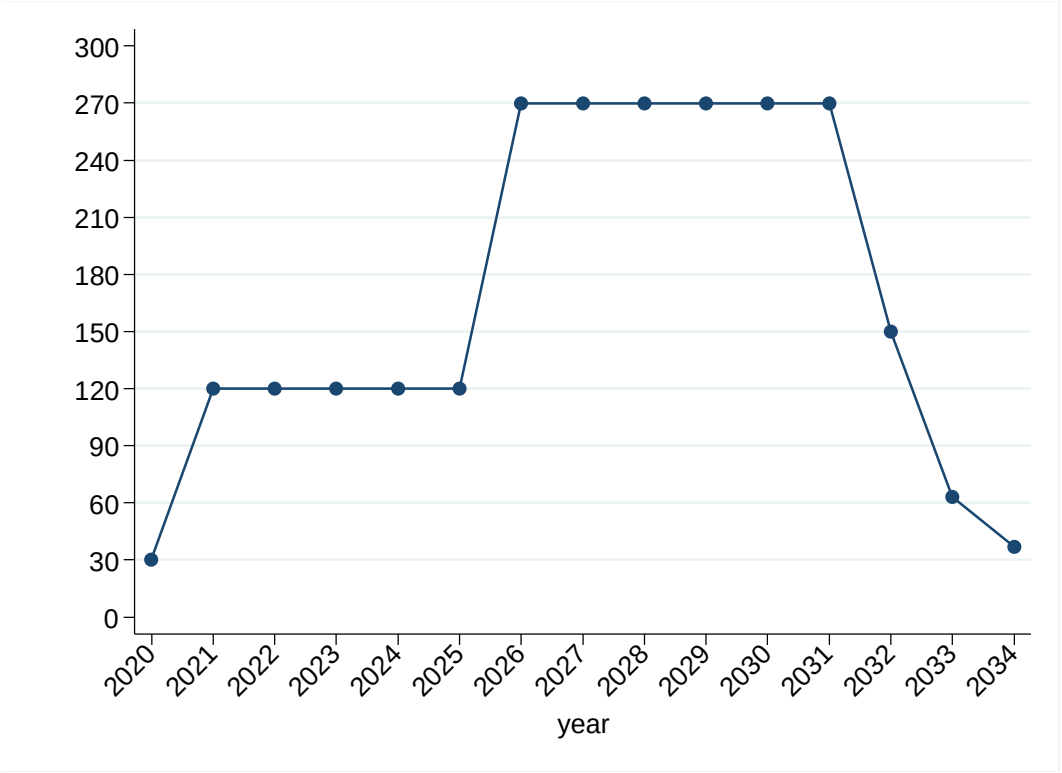
Scenario C

Supplementary Figure 5 Model predictions concerning the annual diagnoses under scenario C.



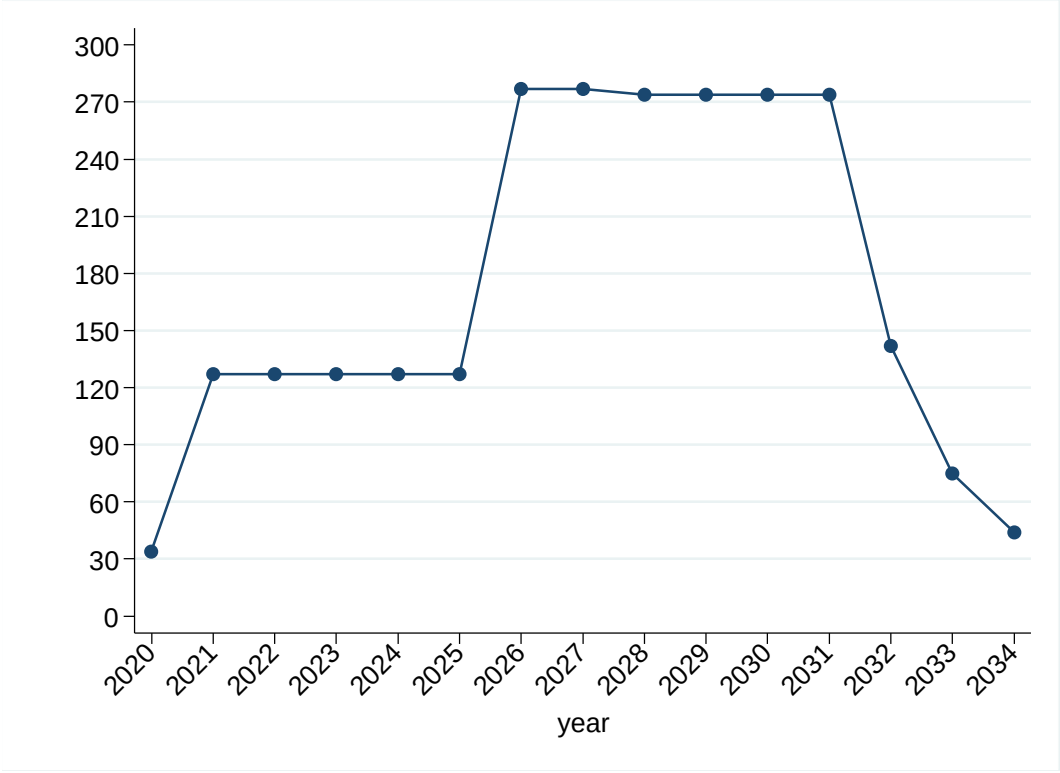
Scenario D

Supplementary Figure 6 Model predictions concerning the annual diagnoses under scenario D.



Scenario E

Supplementary Figure 7 Model predictions concerning the annual diagnoses under scenario E.



Supplementary Figure 8 Model predictions concerning the annual diagnoses under scenario E for PWID.

By increasing harm reduction coverage, there is no need to implement significant screening program in PWID. Most PWID would be diagnosed through the expansion of the HR coverage.

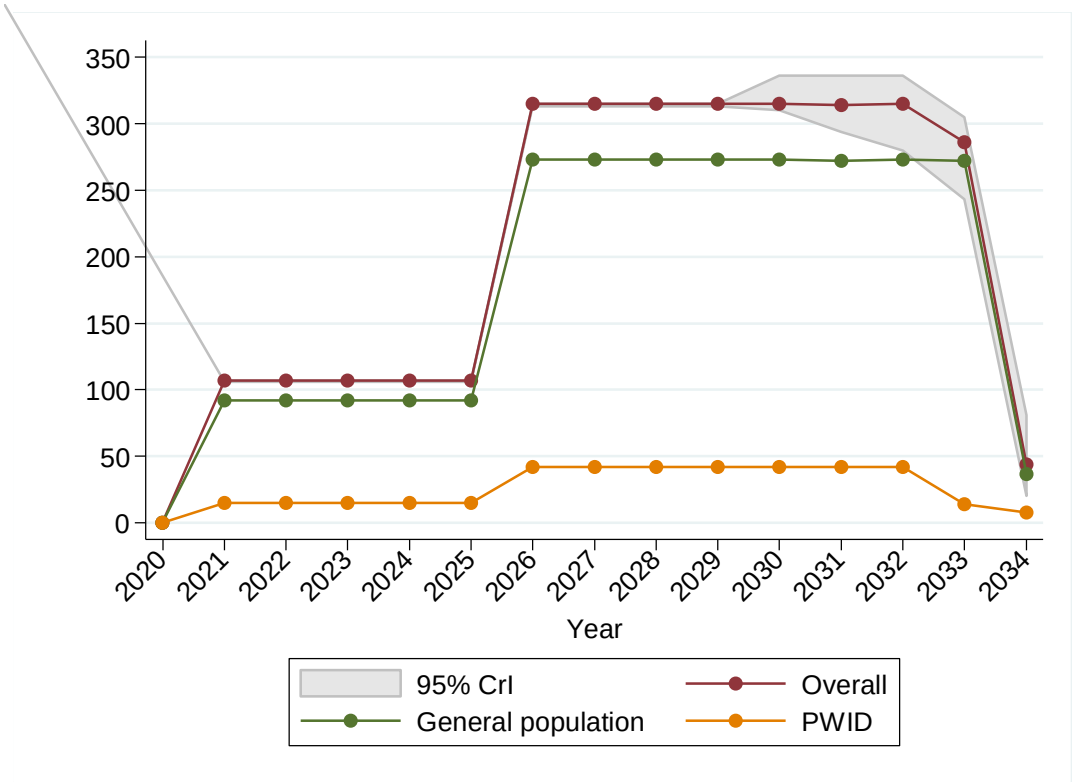
Treatment allocation during the first years of DAAs

It is expected that during the first years of the introduction of DAAs, patients from the general population with advanced disease (≥F3) or PWID who participate in HR would have a higher probability of initiating DAA therapy compared to those with mild disease or PWID who do not participate in HR, respectively. We took the above into account by modeling the proportion of annual treatments delivered among patients with advanced and mild disease to be 80% and 20%, respectively. Similarly, we hypothesized that the proportion of annual treatments delivered among PWID in HR and PWID not in a HR to be 66.6% and 33.3%, respectively. It is notable that if the number of available treatments exceeded the number of

diagnosed patients with advanced disease or PWID on HR program, then they would be allocated to patients with mild disease or in PWID not on HR program, respectively. The impact of this assumption was evaluated in the sensitivity analysis.

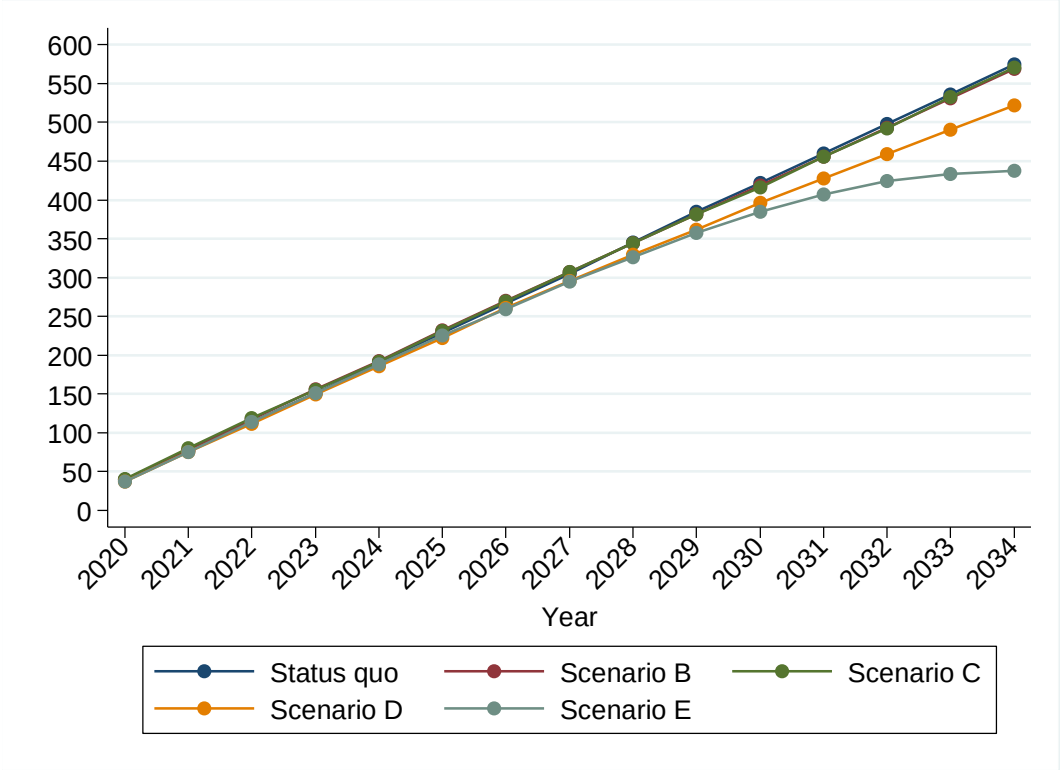
Annual Treatment distribution by risk group under the elimination scenario

Supplementary Figure 8 Distribution of treatment by risk group under elimination scenario.



Cumulative incidence

Supplementary Figure 8 Cumulative incident cases.



Sensitivity Analysis

Sensitivity Analysis Table

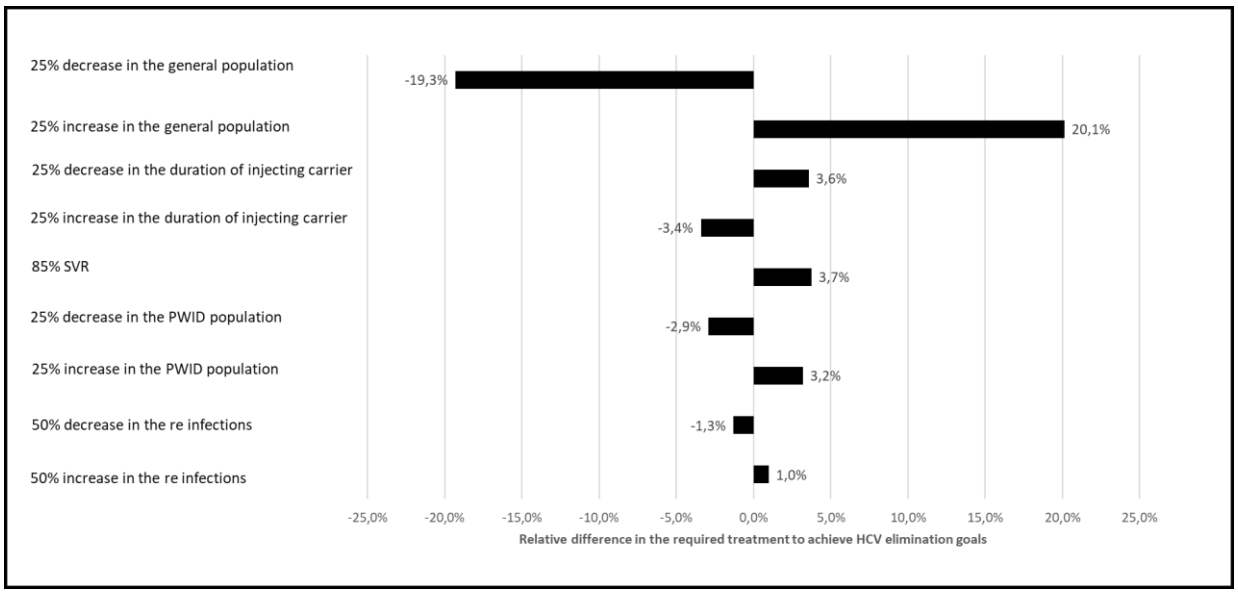
To examine the impact of different model assumptions on cumulative infections, we undertook a series of univariate sensitivity analyses, displayed in Table S3.

Supplementary Table 3 Sensitivity analysis table

Parameters	Value used in the primary analysis	Values examined in the sensitivity analysis
General population size	2600	1950 or 3250
PWID size	700	525 or 875
DAAs SVR	95%	85%
Duration of injecting carrier among PWID	13.5 yrs.	10 or 15 yrs.
Changes in risk behavior after successful treatment	No change	50% lower or higher probability of re-infection

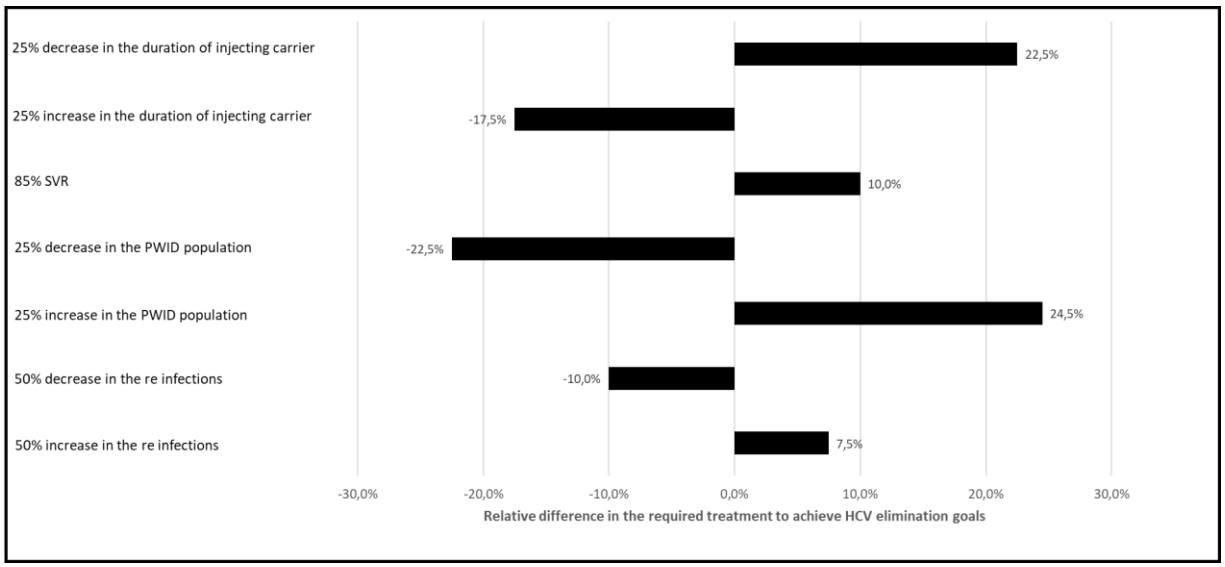
Tornado diagram for the whole population

Supplementary Figure 9 Results of one-way sensitivity analysis showing the relative difference in needed treatment to achieve HCV elimination goals for varying parameters of the model compared to the base parameter values in Table 1. A value of zero describes no change from estimated needed treatments compared to the base scenario. A positive or a negative value means that the required treatments are higher or lower to the estimated under the base scenario.



Tornado diagram for the PWID population

Supplementary Figure 10 Results of one-way sensitivity analysis showing the relative difference in needed treatment to achieve HCV elimination goals for varying parameters of the model compared to the base parameter values in Table 1. A value of zero describes no change from estimated needed treatments compared to the base scenario. A positive or a negative value means that the required treatments are higher or lower to the estimated under the base scenario.



References

Vynnycky Emilia 2010: AN INTRODUCTION TO INFECTIOUS DISEASE MODELLING