Modelling the impact of different testing strategies for HCV infection in Switzerland

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Abstract

Objective: Hepatitis C virus (HCV) infection is a major cause of liver disease. Since symptoms of chronic liver disease usually appear only late in the course of the disease, infected individuals may remain undiagnosed until advanced disease has developed. We aimed to investigate which screening strategies would be most effective to detect individuals unaware of their infection.

Methods: We developed a mathematical model for HCV disease progression and compared the current practice of HCV testing in Switzerland with the following screening strategies: intensive screening of active injection drug users (IDU), screening of former IDU, screening of individuals originating from countries with high HCV prevalence, screening of individuals born 1951–1985 (birth-cohort) and universal screening. All screening interventions were considered in addition to a baseline scenario that reflected the current practice of HCV testing.

Results: Within the first 4 years (2018–2021), every year, on average 650 cases were diagnosed in the baseline scenario, 660 with intensified IDU screening, 760 with former IDU screening, 830 with origin-based screening, 1420 with birth-cohort screening and 1940 with universal screening. No difference in liver-related mortality and incidence of end-stage liver disease between the screening scenarios was observed.

Conclusion: Our results suggest that only large-scale screening of the general population could substantially accelerate the rate of HCV diagnosis and treatment in Switzerland and other countries with similar epidemics. However, this implies screening of a large population with low prevalence, and may trigger considerable numbers of false-positive and borderline test results.

Keywords: hepatitis C infection, mathematical model, screening

Introduction

Hepatitis C virus (HCV) infection is a major cause of liver disease and liver-related mortality [1–3]. HCV prevalence of up to 15% has been reported in some countries; it may also be up to 1% in several high-income countries [1,4]. About 40,000 people (0.5% of the general population) were estimated to be chronically infected with HCV in Switzerland in 2016 [5].

As in many high-income countries, the majority of reported cases in Switzerland is concentrated among injection drug users (IDU) [5–8]. After 2000, the number of new infections among IDU has decreased following the intensified implementation of harm-reduction measures [5,7]. Sexual transmission of HCV is possible but rare in the general population [9,10]. However, increased HCV incidence has been reported among HIV-positive men who have sex with men (MSM) [5,11]. Most health care-associated HCV transmissions occurred before blood products were systematically screened for HCV and before adequate methods were introduced to prevent transmission by invasive medical procedures [5,12]. Increased HCV prevalence is also found in other groups such as migrants originating from high-prevalence countries [5,12,13]. In 2014, direct-acting antivirals (DAA) with a cure rate of >90% became available and are now the gold standard of HCV treatment [12,14]. Since October 2017, DAA treatment has been reimbursed for all HCV-infected patients in Switzerland, regardless of liver disease stage [6,15].

Infected persons may be unaware of their infection for decades [16]: liver-related complications develop slowly and may not appear for at least 10 years after infection [16,17]. Consequently, case detection based on symptoms and self-reported risk factors may be insufficient. Some countries have implemented policies of wider screening: for example, in France it is now recommended that every adult is tested at least once during their lifetime [18]. In Switzerland, like in many other countries, blood, organ and cell donations are systematically screened for HCV, and HCV testing is recommended for persons with clinical symptoms of hepatitis or medical, demographic, occupational or other risk factors associated with HCV [12]. However, there is no national policy or action plan to screen wider population groups [6,12]. Broader screening may accelerate the identification of HCV-infected individuals and, together with DAA treatment, reduce the long-term burden of the disease. We therefore developed a mathematical model to explore the impact of different screening strategies on HCV diagnosis and the number of cases of decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) and liver-related deaths in Switzerland.

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Methods

Model structure

We developed a mathematical model using the R package gems [19] to quantify HCV disease progression. In gems, disease progression is represented by a directed acyclic graph of health states. In each state, transition times to all possible destination states are sampled. The minimum of these times determines when and to which state the patient will move. The process is repeated until the patient reaches a terminal state. We adapted the model structure of Zahnd *et al*. [20] and simulated cohorts of patients from the time of infection until death. The patients progress along two dimensions, representing the progression of liver disease and the course of HCV infection including the cascade of care (Figure 1). The stage of liver disease is defined according to the METAVIR scoring system (F0–F4) followed by DC, HCC and liver transplantation (LT). The progression of HCV infection and care is divided into acute infection, chronic undiagnosed infection, chronic diagnosed infection, first treatment, second treatment and undetectable HCV. Death was represented using four separate states depending on the cause: liver-related, HIV-related, IDU-related and other causes. The patients who spontaneously clear HCV or achieve sustained virological response (SVR) after treatment move to the states with undetectable HCV viral load. We assumed that spontaneous clearance or achievement of SVR decreased the fibrosis progression rates by 90% [20]. Fibrosis regression after SVR was not considered in the model. For simplicity, we did not include a separate state for failing treatment. We only considered treatment with DAA and excluded patients treated successfully with pre-DAA treatment [21–24]. We assumed that patients could be treated with DAA in stage F2 or above between 2014 and 2017, and regardless of fibrosis stage from 2018 onwards [6]. Patients who were diagnosed before 2014 started treatment after a random delay between 0 and 15 years after becoming eligible for treatment. Patients diagnosed from 2014 onwards were treated on average 6 months after meeting the eligibility criteria [25]. Probability of achieving SVR was 98% regardless of genotype or other characteristics [14]. At the beginning of the simulation, patients were assigned the following characteristics: birth year, age at infection, sex, region of origin, HIV co-infection and its duration, alcohol consumption, high-risk sexual MSM behaviour, and the duration of injecting drug use (Supplementary Tables 1–2).

Data sources

We obtained the distribution of baseline characteristics among the currently diagnosed patients from the Swiss Federal Office of Public Health (FOPH) notification database (Supplementary Figure 1). This database contains all notified cases of HCV in Switzerland since 1988. We used the data on age, sex, region of geographic origin and the expected route of transmission at the year of notification. We assumed that half of the patients in the database who were treated in the pre-DAA era achieved SVR and were thus excluded from our analyses [21,23]. The FOPH database does not include information on alcohol consumption or HIV co-infection. These characteristics were estimated from the Swiss Hepatitis C Cohort Study (SCCS) [26] by matching the patients in the FOPH database with the patients in the SCCS based on the year of infection and common baseline characteristics. When there were no patients in the SCCS for a particular combination of infection year and baseline characteristics, we assumed that the proportions of individuals with severe, moderate and abstinent alcohol consumption were equal and that individuals with high-risk MSM behaviour were HIV co-infected.

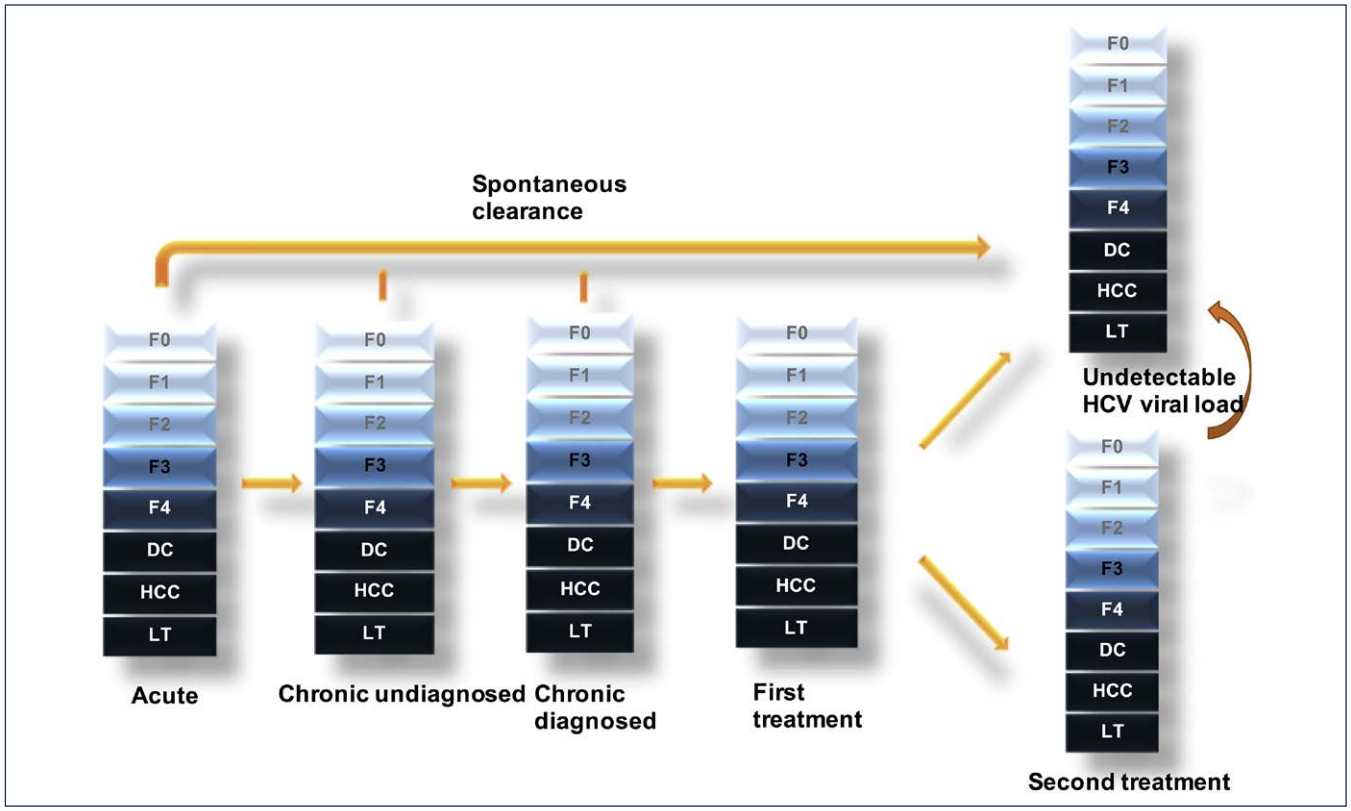

Figure 1. Structure of the simulation model. Individuals can progress vertically based on liver disease and horizontally through the hepatitis C virus (HCV) infection and cascade of care. First and second treatments contain the treatment episode itself and, in case of treatment failure, the time after ending therapy. Death can occur at any state (not shown in the graph for simplicity). F0–F4: stages of fibrosis according to the METAVIR scoring system; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplantation

Years of starting and ending active drug use, containing also substitution therapy, were assigned to all simulated IDU. Similarly, we assigned each HIV co-infected patient a year of HIV infection.

We reviewed the literature to parameterise the model. We chose parameter values that would best represent the situation in Switzerland, consulting experts if necessary. We parameterised fibrosis progression from F0 to F4 assuming stage- and age-dependent rates as proposed by Razavi *et al.* [27]. and Harris *et al.* [28]. (Supplementary Tables 3–5). Parameters for liver-related mortality and the cascade of HCV infection and care can be found in Supplementary Tables 6–7.

Fitting the model to the data of the local HCV registry

We first simulated generic cohorts of patients for all combinations of baseline characteristics. Then, we assigned each simulated patient a weight corresponding to the representativeness in the true HCV-infected population in Switzerland. The weights were based on the analyses of the FOPH and SCCS databases for the population diagnosed by 2015, and on our assumptions concerning the population that had not yet been diagnosed. We first determined the weights for the simulated individuals corresponding to the diagnosed patients in the FOPH data and used the model to back-calculate the year of infection in this population (Supplementary Figures 2–3). We assumed that the number of annual new infections among individuals of Swiss origin would follow approximately the distribution of infection years among people already diagnosed, with the probability of being diagnosed by year 2015 slightly decreasing over time. We then modified the number of new infections each year to account for the expected peak in new infections around the early 1990s, during the time of the major changes in drug policy [7,29,30]. For the patients of foreign origin, we assumed a decline in new infections over the years, influenced by differences in migration patterns and the HCV prevalence in the respective countries of origin [5,6,13]. The size of the viremic population living in Switzerland was assumed to be approximately 40,000 in 2016 [5].

We applied the distribution of baseline characteristics of the diagnosed patients infected in a particular year to the undiagnosed individuals infected in the same year. We assumed the number of annual new infections in the future would remain at the level of 2015 (Supplementary Table 8).

Screening strategies

We modelled a baseline scenario and five screening interventions from the year 2018 onwards. All five interventions were built on top of the baseline scenario. In the baseline scenario, HCV testing continued in the future as in 2017 (Table 1). With a scenario of intensified IDU screening, the rate of testing active IDU was increased from 0.5 to 1.0 per person-year. In the origin-based scenario, people from southern Europe, Africa and Asia were tested with a rate of 0.5 per person-year. In the birth-cohort screening scenario, the rate 0.5 per person-year was applied to individuals born between 1951 and 1985 [31], and with universal screening, to all individuals. In all scenarios, the patients had an HCV antibody test, followed by a confirmatory nucleic acid test in case of a positive antibody test result.

Sensitivity analyses

We conducted six sensitivity analyses (S1–S6) to address the uncertainty around parameters and assumptions (Supplementary Table 9). First, we conducted a sensitivity analysis around the size of the viremic population in 2016, assuming it was either 40% higher (sensitivity analysis S1) or 10% lower (S2) than in the main analysis. Second, we assumed that the proportion of individuals with high-risk behaviour was either higher (S3) or lower (S4) among the undiagnosed than the diagnosed population infected in the same year. Third, we reduced the rate of HCV diagnoses among IDU before 2018 (S5). Finally, we investigated the effect of fibrosis progression rates by using an alternative parameterisation of the liver disease progression (S6), assuming a constant rate of fibrosis progression across all stages [2].

Table 1. Rate of HCV testing based on different risk factors without screening interventions. The rates are based on assumptions and discussion with experts

Risk indicator	When applied	Value (rate per person-year)
Symptoms	Fibrosis F3 or higher	F3: 1 F4: 2 DC or HCC: 5
Background testing[a]	Regardless of fibrosis stage	0.01
Drug use	Active IDU	0.5
HIV infection, high-risk MSM	High-risk MSM 1year after HIV infection	1
High-risk MSM (HIV negative)	High-risk MSM until 1 year after HIV infection	0.5
HIV infection (not MSM)	Other HIV infected patients since the time of infection	0.2

DC: decompensated cirrhosis; F3, F4: fibrosis stage according to METAVIR score; HCC: hepatocellular carcinoma; IDU: injection drug user; MSM: men having sex with men.
[a] Background testing includes tests that are not triggered by any risk factor or symptom, such as suspicion based on high liver values observed in routine blood test, or HCV tests among blood donors.

Results

Screening scenarios

In the baseline scenario, on average 650 HCV-infected individuals were diagnosed annually during the first 4 years (2018–2021), and this number decreased to about 300 individuals by 2030 (Figure 2). Intensified screening among active IDU (660 diagnoses annually during years 2018–2021, 1% increase from baseline) and screening former IDU (760 diagnoses annually during years 2018–2021, 17% increase) led to similar results. Screening based on geographic origin slightly increased the number of diagnoses during the first 4 years, with 830 (28% increase from baseline) annual diagnoses. In the following years, the number remained stable in all of these four scenarios, at about 500 per year. With birth-cohort and universal screening, the number of new diagnoses was substantially higher in the year 2018 than in the other scenarios. Birth-cohort and universal screening strategies could identify on average 1420 (118% increase from baseline) and 1940 (198% increase from baseline) patients per year in 2018–2021, respectively. From 2022, the number started to decrease, reaching 140 (birth-cohort) and 100 (universal) diagnoses in 2029.

On average, 4720 patients can be expected to achieve SVR annually within the years 2018–2021 in the baseline scenario. The corresponding numbers (with increase compared with baseline) were 4760 (1%) for the intensified screening of active IDU, 5020 (6%) for the screening of former IDU, 4960 (5%) for the origin-based screening, 6000 (27%) for birth-cohort screening and 6600 (40%) for universal screening. From 2022 onwards the average number of patients achieving SVR ranged from 1200 to 2400 per year across the strategies.

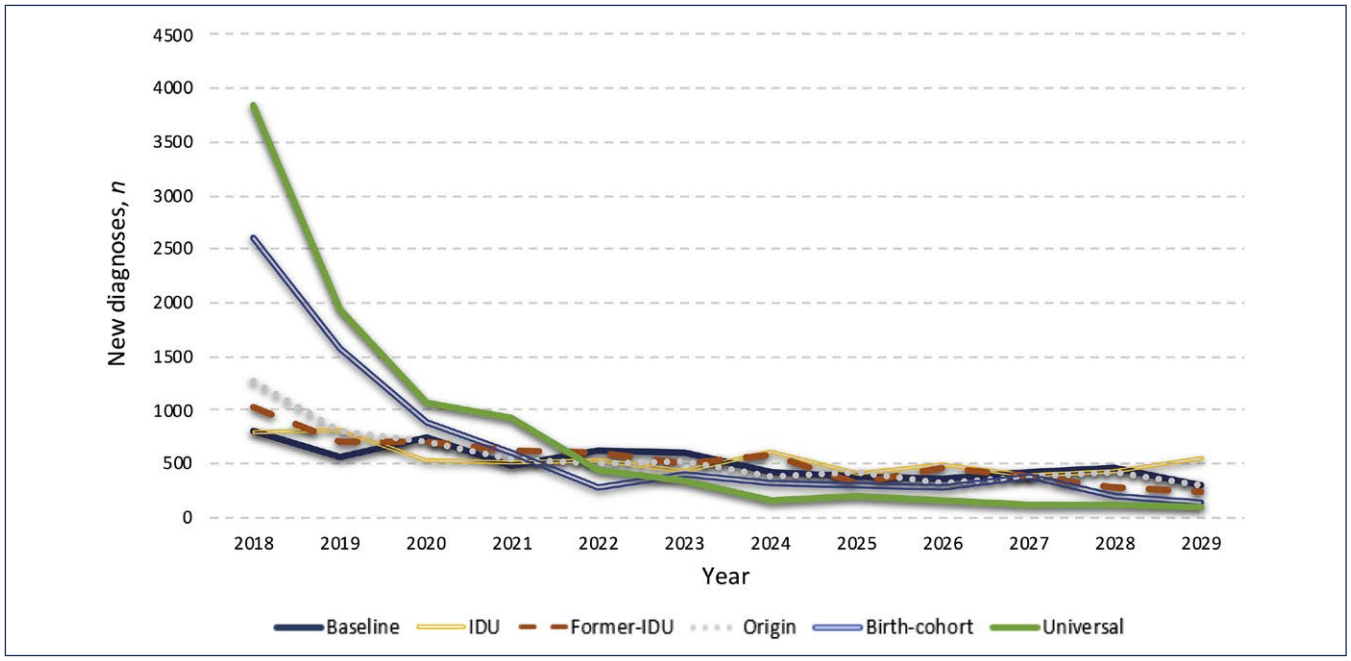

Figure 2. Number of annual new hepatitis C virus (HCV) diagnoses in Switzerland: a comparison between different screening scenarios (2018–2029). IDU: injecting drug user

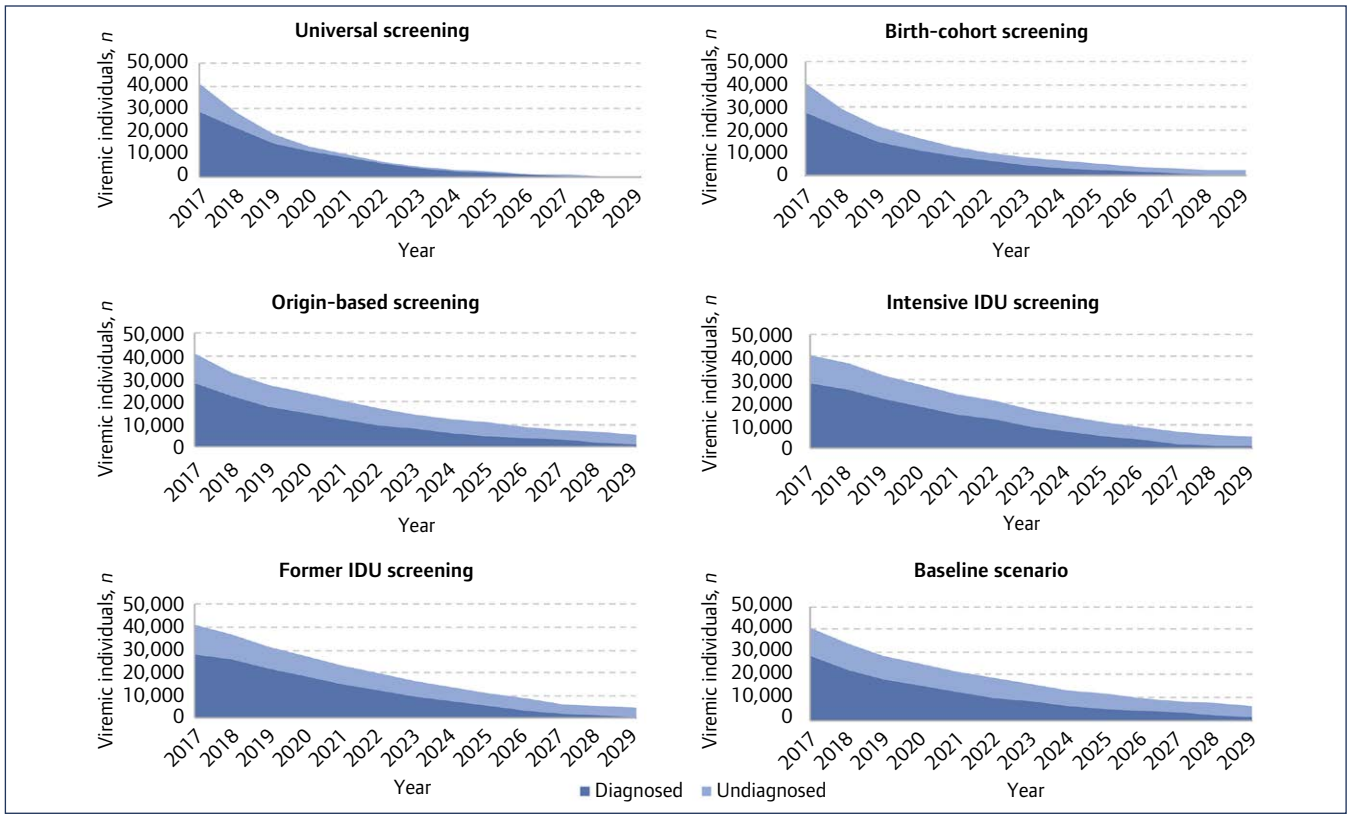

Figure 3. Number of viremic individuals, diagnosed and undiagnosed: a comparison between different screening scenarios (2018-2029). IDU: injecting drug user

The size of the viremic population is expected to remain above 5800 over the next decade in the baseline scenario and with intensified screening of current IDU, despite the initial decrease (Figure 3). Screening based on origin or screening former IDU decreased the size of the viremic population slightly, compared with the baseline scenario, leading to about 5000 (14% decrease from baseline) and 4000 (31% decrease from baseline) viremic individuals in 2029, respectively. Birth-cohort and universal screening led to a considerable decrease in the number of viremic individuals, with about 1900 (67% decrease from baseline; birth-cohort screening) and 600 (90% decrease from baseline; universal screening) viremic people living in Switzerland in 2029.

The model showed no major differences in liver-related morbidity and mortality between the scenarios during the years 2018–2029 (Supplementary Table 10). The total number of cases of DC, HCC and liver-related deaths within the period 2018–2029 ranged from 960 to 1430, 200 to 350 and 1700 to 2000, respectively, across the screening strategies (Figure 4). The differences among the strategies are likely due to stochastic variability.

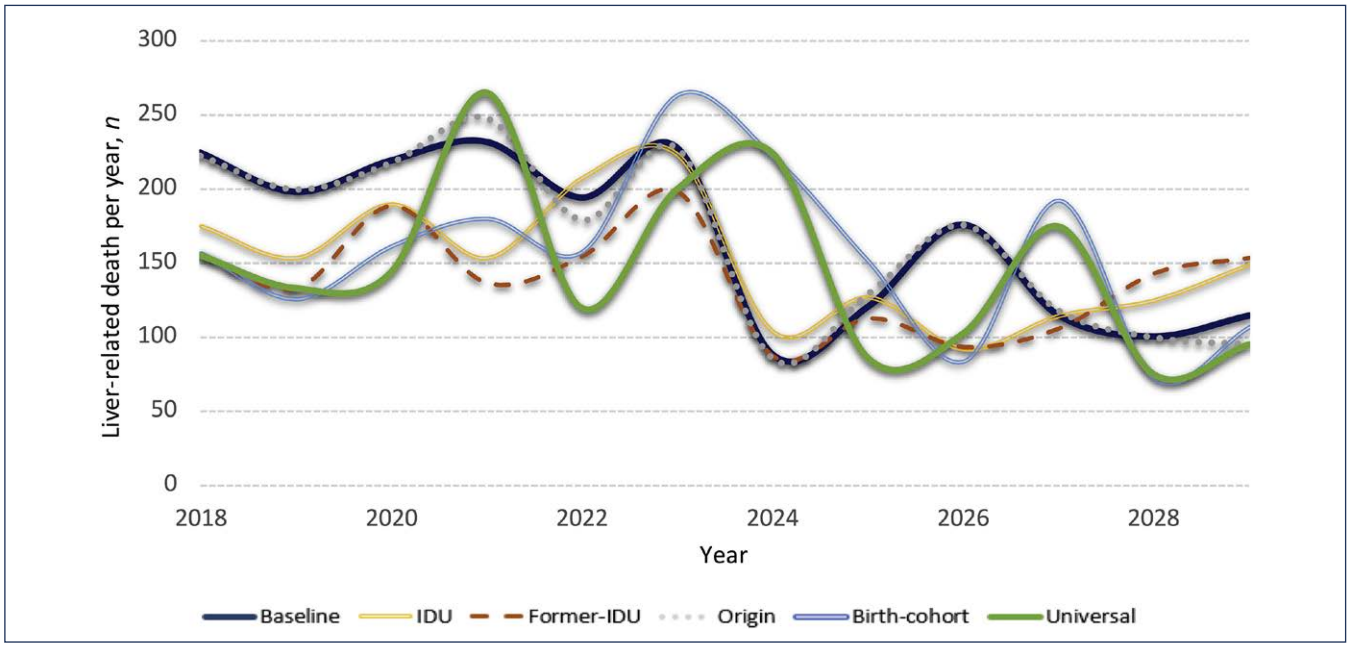

Figure 4. Number of liver-related deaths among hepatitis C virus (HCV)-infected individuals in Switzerland: a comparison between different screening strategies (2018-2029)

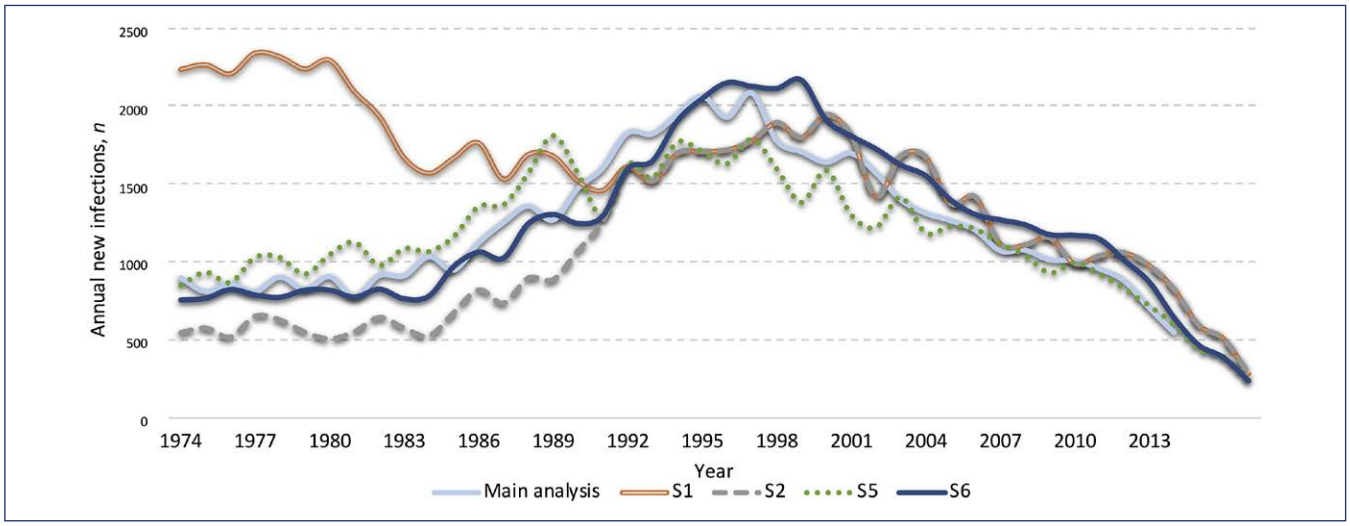

Figure 5. Number of new hepatitis C virus (HCV) infections per year in Switzerland in the past: a comparison of the main analysis and the sensitivity analyses. IDU, injecting drug user; S1: more undiagnosed people in 2016, S2: less undiagnosed people in 2016, S5: low IDU diagnosis rate; S6: constant progression rate

Sensitivity analyses

The annual number of new infections stayed around 1000 until the early 1980s in the main analysis, and started to increase thereafter, peaking at 1900 during the years 1995–1999 and followed by a decrease (Figure 5). A major difference was seen in the sensitivity analysis S1 with a larger viremic population: between 1971 and 1990, the number of new infections was twice as high as in the main analysis. There were no major differences between the main analysis and the analyses S2 and S5 in terms of newly infected individuals. However, for the analysis in which the diagnosis rate among IDU was lower (S5), the peak of new infections occurred 5–10 years earlier. The numbers of new infections in the analyses S3 and S4 were, by definition, the same as in the main analysis. In the analysis with constant fibrosis progression (S6) (Supplementary Table 11), the number of liver-related deaths and cases of DC and HCC were about half of those in the main analysis (Supplementary Table 10).

Regarding future projections, universal and birth-cohort screening yielded the same results in the main and sensitivity analyses (Supplementary Figure 4). The only major difference was in the analysis with more high-risk individuals (S3), where the effect of screening former IDU in 2018 was similar to birth-cohort screening.

Discussion

Principal findings

We forecasted the impact of several HCV testing strategies on the number of new HCV diagnoses, the size of the viremic population and the magnitude of liver-related complications and deaths in Switzerland between 2018 and 2029 using a disease progression model. Birth-cohort and universal screening seemed to be the most effective strategies for identifying the undiagnosed HCV-infected individuals within the next 4 years and for reducing the size of the viremic population. However, we could not show a clear difference in liver complications or mortality between the screening strategies, most probably due to stochastic variability in the model.

Implementing broad strategies such as birth-cohort or universal screening requires testing a large low-prevalence population, indicating a high cost per diagnosis. The feasibility of such screening strategies should be studied from the acceptability and cost-effectiveness perspective. Universal screening of 8 million residents over the next 12 years to identify about 10,000 infections would add a considerable burden to Switzerland's healthcare budget. The indirect costs related to false-positive and borderline test results should also be added [32–35]. Therefore, although universal screening could reduce the HCV viremic population by 2030, implementing such strategy would be challenging. Screening only the 3.6 million individuals born between 1951 and 1985 could halve the number of people tested [36]. Studies from the US have suggested that one-time birth-cohort screening could be cost-effective [37–40]. However, the eldest individuals, who have the highest rate of disease progression and may otherwise be more difficult to detect on time, would not benefit from birth-cohort screening [2,13].

Screening former IDU may also help to detect a substantial number of cases. However, the effectiveness of this strategy depends on the assumptions of the model. If we assumed that IDU were frequently tested in the past, screening former IDU provided almost no benefit. In contrast, assuming a considerably lower testing rate for active IDU in the past, screening of former IDU was almost as effective as birth-cohort screening, mainly because former IDU remained untested in the years of active drug use. Identifying former IDU can, however, be challenging. Despite the pragmatic, harm reduction oriented drug policy of Switzerland, persons who only occasionally injected drugs in the past will unlikely identify themselves as having been at risk for HCV infection [41]. Intensifying the screening of current IDU was, as expected, not very effective: we assumed a relatively high testing rate among IDU in our baseline scenario [5–7,12], although shortcomings of testing in this population are observed [7,42,43].

Liver-related mortality and the incidence of liver complications did not essentially differ between the scenarios. The observed differences were not systematic and thus mainly due to random variability. Furthermore, we only modelled the next 12 years. Therefore, we cannot exclude the possibility that screening would reduce mortality in the longer term. Background mortality also is a competing risk factor: patients who most benefit from additional screening tend to be older, and mortality is increased in persons with IDU [44].

Our results show that the number of viremic individuals will likely decrease over time in all screening strategies: in 2030, we expect to have no more than 5000 viremic individuals in Switzerland, with large-scale screening strategies even considerably less. This represents a multiple-fold decrease from the current level. Viremic individuals may transmit the virus onwards: however, the risk of transmission also depends on the risk behaviour. The analysed screening strategies target mainly populations outside the groups with most ongoing transmission such as active IDU and HIV-infected MSM. It is therefore unlikely that screening would substantially affect the transmission dynamics. Nevertheless, the impact of screening on the number of new infections needs verification with a transmission model before conclusions can be made.

Strengths and limitations

Our study is among the first to compare the effect of different HCV testing strategies on the epidemiological determinants of HCV infection in a nationwide setting. As in many other high-income countries, the epidemic in Switzerland is concentrated among injecting drug users and HIV-infected MSM, but other population groups may have also been exposed through, for example, unsafe medical procedures or one-time use of intravenous drugs. The results should be therefore applicable in a wide range of settings. Several mathematical models have estimated the progression, transmission and epidemiological and financial burden of HCV infection [45–48]. These models were usually limited to a specific subpopulation or tailored to a particular research question, or they did not take into account the individual-level risk factors. Our study benefited also from a systematic collection of HCV notification data since 1988.

Our study has several limitations. First, transmission is not included in our model. The absolute numbers should be interpreted with caution, as these are sensitive to several external factors, such as ongoing transmission and migration. Moreover, the number of new infections is a fixed input and the model thus does not take into account the impact of future interventions that target transmission. Second, to avoid complexity, we did not take into account the false-negative test results and retesting [49]. False-negative antibody tests can occur in very early infection and in immunosuppressed patients. However, as the majority of the HCV-infected population is not immunosuppressed [26], false-negative antibody tests are likely rare and should not essentially impact the results. Third, there are some limitations and uncertainty around the model parameters, including fibrosis progression rates and the assumptions regarding the currently undiagnosed population. The true HCV prevalence and the baseline characteristics of the undiagnosed individuals are difficult to estimate and cannot be determined without the collection of new primary data. Fourth, we did not model treatment with interferon and ribavirin, and the data for DAA treatment are limited to the period from 2014 when DAA became widely available. As the aim of the study was to compare screening strategies for identifying the undiagnosed infected individuals, the restriction to DAA treatment should not essentially influence the results. Exclusion of the pre-DAA therapy, however, complicates the validation of the model against past observations. Finally, the number of reported HCV-infected patients may be subject to various types of bias, such as possible inaccurate estimates of the number of HCV-infected persons who have emigrated or died.

Conclusion

Among the testing scenarios that we studied, only large-scale screening strategies could accelerate HCV detection. Screening people with a history of injecting drug use could also be effective, but the benefit of this strategy depends largely on assumptions of the characteristics of the undiagnosed population that cannot currently be verified. We could not show an essential difference in mortality and the incidence of DC or HCC across the screening scenarios. Our results underline the need to explore the feasibility of different HCV testing strategies in low-prevalence settings, and to evaluate the potential financial burden of implementing a large-scale screening strategy.

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Conflicts of interest

The views expressed in this publication are those of the authors and do not necessarily represent the view of the Federal Office of Public Health. OK and BB received an unrestricted grant from Gilead which is unrelated to the present project. GW received a research grant from Gilead Sciences, unrelated to this work. All other authors declare that they have no conflicts of interest.

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Modeling the impact of different screening strategies for HCV infection in Switzerland: supplementary documents

Supplementary Table 1. Baseline characteristics included in the model

Baseline characteristics	Value	Source of distribution
Alcohol consumption	Severe (on average >40 g/day), moderate (on average 20–40 g per day), abstinent	SCCS data
Sex	Male, Female	FOPH data
HIV	No, Yes	SCCS data
High-risk sexual MSM behaviour	No, Yes	FOPH data
IDU	No, Yes	FOPH data
Geographic origin	Switzerland, Western Europe, Eastern Europe, Others	FOPH data
Age (years)	<21, 21–31, 32–41, 42–51, 52–61, 62–71, 72–81, >81	FOPH data
Year of birth	1937–1947, 1948–1957, 1958–1967, 1968–1977, 1978–1987, 1988–1997, 1998–2006, 2007–2016	FOPH data

FOPH: Federal Office of Public Health; IDU: injecting drug user; MSM: men who have sex with men; SCCS: Swiss Hepatitis C Cohort Study.

Supplementary Table 2. Distribution of fibrosis stages at the beginning of the simulation [1]

METAVIR stage at HCV infection	Probability (%)
F0	85.90
F1	15.09
F2	1.84
F3	0.24
F4	1.50

Supplementary Table 3. Disease progression rates between METAVIR stages F0 and F4 according to sex and current age [2,3][a]

Age (years)	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80+
Fibrosis progression rate per 100 person-years: Male								
F0 → F1	4.5	3.7	2.7	9.9	12.1	13.8	15.5	12.7
F1 → F2	3.3	2.7	1.9	7.2	8.8	10.0	11.2	13.0
F2 → F3	4.7	3.8	2.8	10.2	12.4	14.1	15.9	13.0
F3 → F4	0.6	1.8	4.0	6.3	3.4	7.0	13.6	13.6
Fibrosis progression rate per 100 person-years: Female								
F0 → F1	3.8	3.1	2.2	8.2	10.2	11.5	12.9	10.6
F1 → F2	2.8	2.2	1.6	6.0	7.4	8.3	9.4	7.7
F2 → F3	3.9	3.1	2.3	8.5	10.4	11.8	13.2	10.9
F3 → F4	0.4	1.5	3.3	5.3	2.8	5.9	11.3	11.3

[a]We used the fibrosis progression rates between METAVIR stages F0 and F4 from a study conducted by Razavi *et al.* [3] where fibrosis progression rates were back-calculated from data from the US (US Surveillance, Epidemiology and End Results). They used the results of Harris *et al.* [2], who used a similar back-calculation method for calculating the fibrosis progression rates for patients from the UK, as a guidance.

Supplementary Table 4. Model parameters for liver disease progression from METAVIR stage F4 onwards (rate per 100 person-years)

Liver disease progression/age (years)	0-29	30-39	40-49	50-59	60-69	70+	References
F4 → DC	6.51	6.41	6.48	6.49	6.35	6.30	[2,4]
F4 → HCC	0.79	1.30	2.12	3.47	5.65	9.13	[2,4]
DC → HCC	1.55	2.52	4.10	6.65	10.91	17.62	[5]
DC → LT	3.1	3.1	3.1	3.1	3.1	3.1	[6]
HCC → LT	1.7	1.7	1.7	1.7	1.7	1.7	[7]

DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplantation.

Supplementary Table 5. Hazard ratio to modify the rate of liver disease progression for moderate or excessive alcohol consumption. The rates shown in Supplementary Table 4 are multiplied by these hazard ratios, depending on the patient's level of alcohol consumption

METAVIR stage/alcohol consumption	Abstinent	Moderate	Severe	References
F0 → F1	1	1.16	1.33	[8,9]
F1 → F2	1	1.3	2.22	[10]
F2 → F3	1	1.3	2.22	[8,11]
F3 → F4	1	1.16	4	[8,9]

Supplementary Table 6. Liver-related mortality rates per 100 person-years from F4, DC, HCC and LT

Event (state of liver disease → Death)	Value	References
F4 → Death	0.010	[7]
DC → Death	0.129	[6,7,12,13]
HCC → Death	0.430	[6,7,12,13]
LT → Death (first year)	0.160	[6,7,12,13]
LT → Death (second year)	0.057	[6,7,12]

Background mortality rates were taken from the Federal Office of Statistics database.
F4: cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplantation.

Supplementary Table 7. Model parameters for the cascade of HCV infection and care

Event	Origin state → Destination state	Description and parameter's value	Reference
Chronic	Acute → Chronic undiagnosed	Duration of acute infection is 6 months for all patients	[14]
Diagnosed	Undiagnosed → Diagnosed	Main text – Table 1	Assumption
Spontaneous clearance	Acute, Undiagnosed, Diagnosed → Cleared	We assumed that the probability of spontaneously clearing HCV follows a logistic decrease, with an overall probability of 32%	[1]
First treatment	Diagnosed → First treatment	Time from diagnosis to treatment by 2014 was sampled from a uniform distribution between 0 and 15 years Time from diagnosis to treatment after 2014 was sampled from a uniform distribution between 0 and 1 year	Assumption
Second treatment	First treatment → Second treatment	Time from diagnosis to treatment by 2014 was sampled from a uniform distribution between 0 and 15 years Time from the first treatment to the second treatment after 2014 was sampled from a uniform distribution between 0 and 1 year	Assumption
Duration	—	12 weeks regardless of the HCV genotype and liver disease stage	Assumption
Cure with DAA	Treatment → Cleared	98% regardless of genotype	[15,16]

Supplementary Table 8. Expected number of new hepatitis C infections 1970–2029, Switzerland

Year		**1971**	**1972**	**1973**	**1974**	**1975**	**1976**	**1977**	**1978**	**1979**	**1980**	**1981**	**1982**
Number of new infections		222	810	851	894	807	854	807	900	821	904	773	912
Year	**1983**	**1984**	**1985**	**1986**	**1987**	**1988**	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**
Number of new infections	908	1033	946	1120	1252	1357	1267	1471	1602	1826	1822	1944	2062
Year	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
Number of new infections	1927	2084	1777	1705	1639	1695	1570	1397	1311	1263	1202	1070	1073
Year	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019–2029**		
Number of new infections	1012	1004	953	876	704	543	221	200	200	200	200		

Supplementary Table 9. Description of the sensitivity analyses. High-risk population: IDUs and high-risk sexual MSM behaviour (and low-risk population is the remaining)

Sensitivity analysis	**Description (Assumption)**
S1	The size of viremic population in 2016 was assumed to be 40% higher than the main analysis.
S2	The size of viremic population in 2016 was assumed to be 10% lower than the main analysis.
S3	The size of the viremic population in 2016 was as in the main analysis, but the number of low-risk individuals among the undiagnosed individuals was decreased by 50%, and the number of high-risk individuals increased accordingly.
S4	The size of the undiagnosed low-risk population infected each year was increased to twice as the original, and the number of undiagnosed high-risk individuals infected in the same year was decreased to have the same total number of individuals as in the main analysis (the high-risk population is defined as S3).
S5	In S5, it is assumed that low diagnosis rate increased over time with the rate of 0.05/person-year until 1990, 0.1/person-year in 1990–1995, 0.15/person-year in 1996–2000,0.25/person-year in 2001–2018 and 0.5/person-year from 2018 onwards.
S6	A constant rate of fibrosis progression according to age at infection was applied across all stages (Supplementary Table 11).

IDU: injecting drug user; MSM: men who have sex with men.

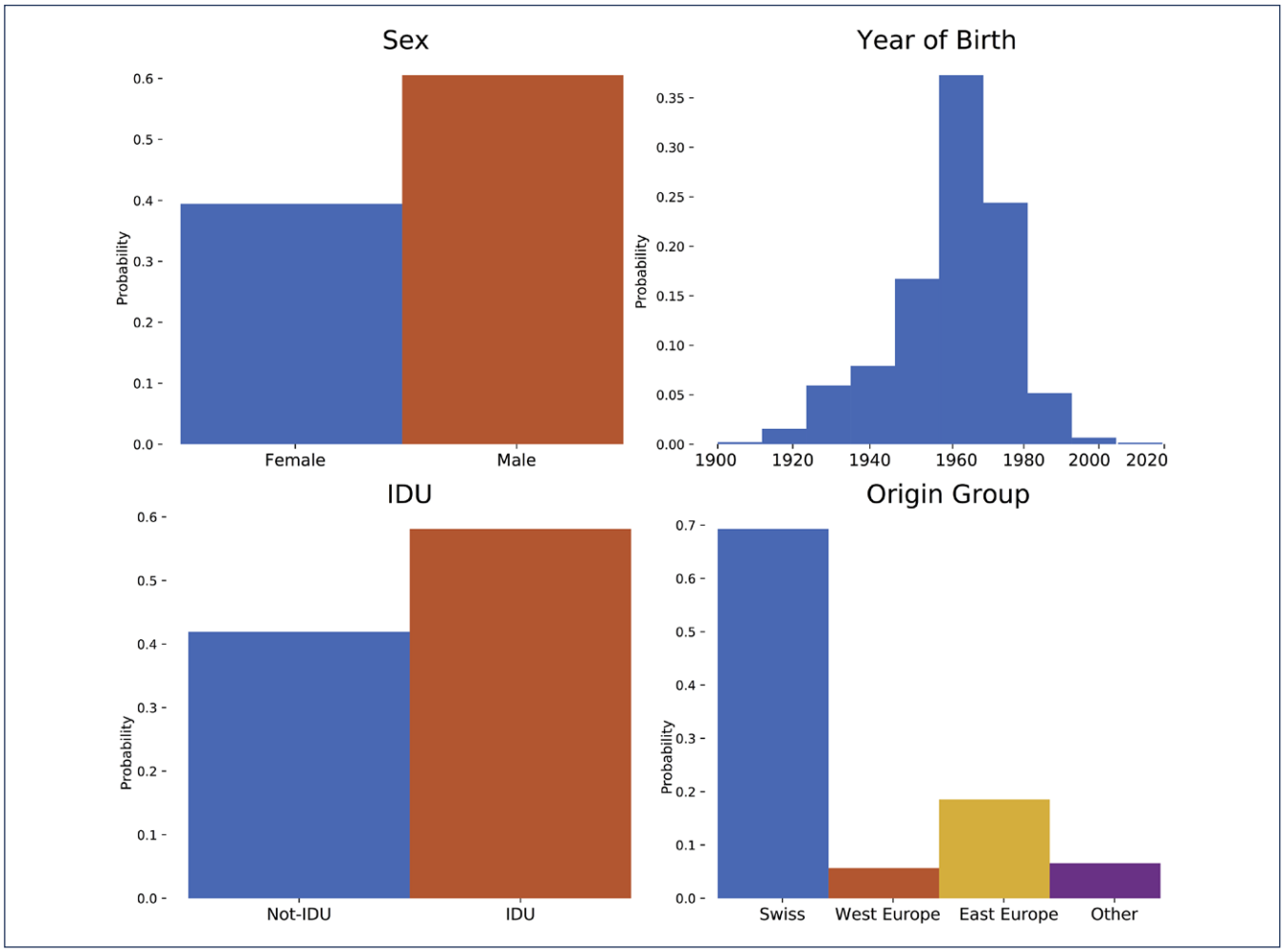
Supplementary Table 10. Number of liver complications in 2017–2018 for different screening strategies

Event-Year	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**
Baseline												
DC	264	231	163	124	80	73	54	46	30	25	20	25
HCC	71	39	63	20	26	13	14	5	16	10	2	3
Death	223	197	218	231	193	227	88	120	175	114	100	114
IDUs												
DC	234	164	134	104	58	50	33	28	7	16	17	19
HCC	69	18	29	20	22	9	6	5	16	10	26	2
Death	174	153	189	153	207	223	102	126	91	113	124	148
Former IDUs												
DC	228	158	134	103	58	49	33	36	8	17	15	15
HCC	68	16	29	19	20	8	5	5	14	10	21	2
Death	155	132	188	136	154	197	87	112	93	106	143	153
Geographic origin												
DC	236	188	178	117	66	44	32	18	12	21	19	22
HCC	80	23	52	6	10	5	6	4	2	0	1	5
Death	222	199	217	247	179	227	85	129	175	118	99	95
Birth-cohort												
DC	265	248	161	123	75	68	51	42	28	24	19	25
HCC	71	38	66	18	28	12	12	4	14	9	3	4
Death	157	126	161	180	158	264	222	151	84	192	72	107
Universal												
DC	236	142	116	79	38	11	8	7	6	6	6	10
HCC	40	28	12	1	41	0	8	2	0	0	2	6
Death	155	133	143	265	119	199	224	86	102	174	74	94

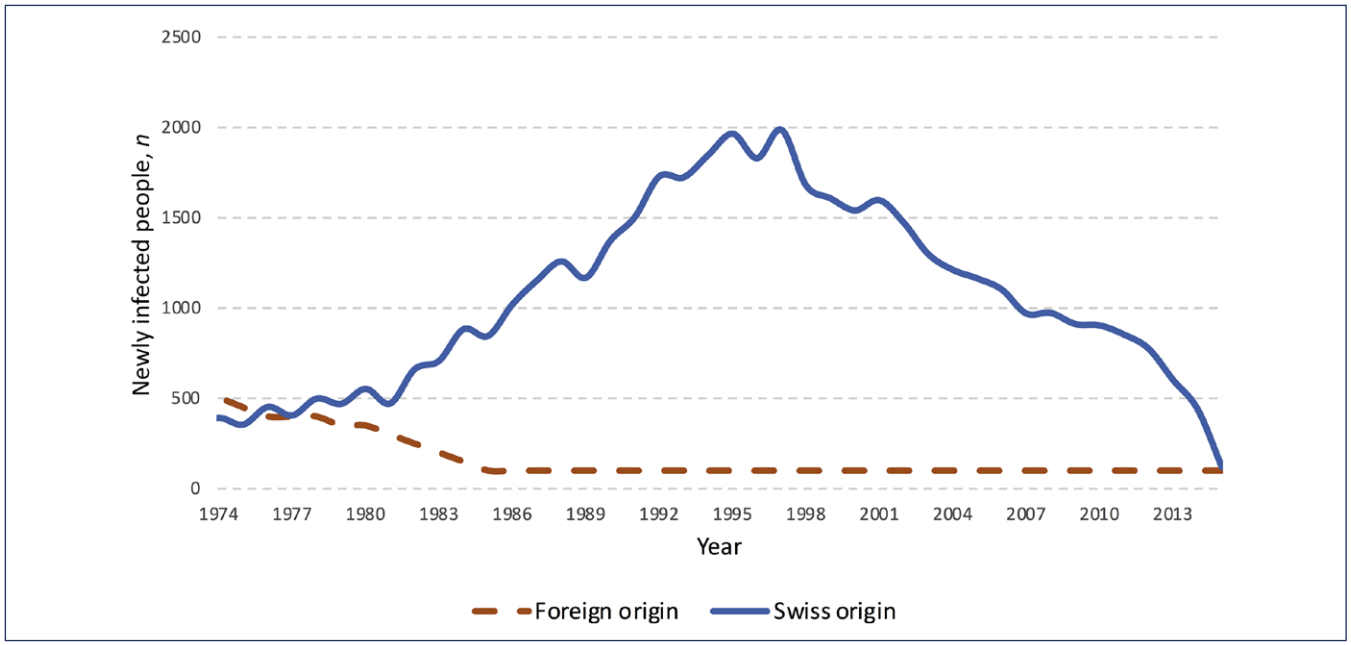
DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; Death: liver-related death; IDU: injecting drug user.

Supplementary Table 11. Disease progression rates between fibrosis stages F0 and F4 according to age at infection: parameters for analysis with constant fibrosis progression (sensitivity analysis S6) [8]

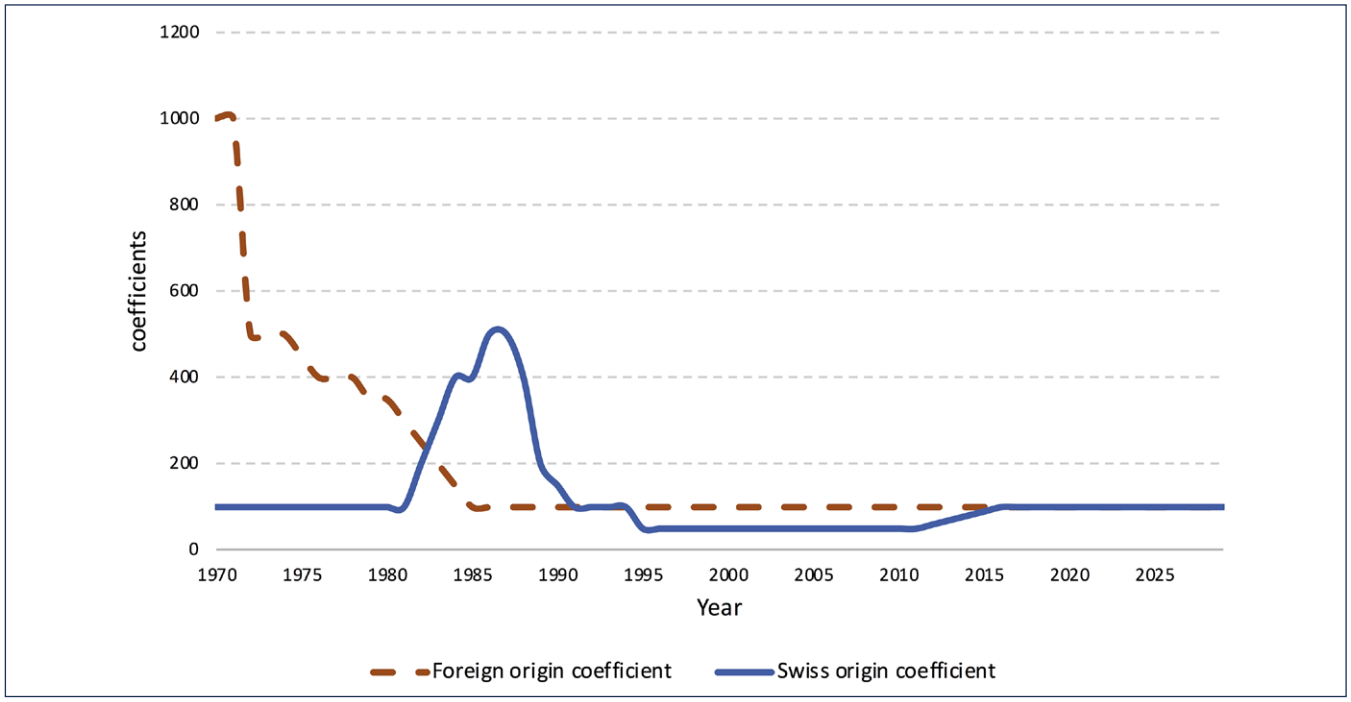
Age at infection(years)	Value	Description
<20	0.091	
21–30	0.105	These values are applied to all steps from F0 to F4.
31–40	0.138	
41–50	0.200	
>51	0.333	



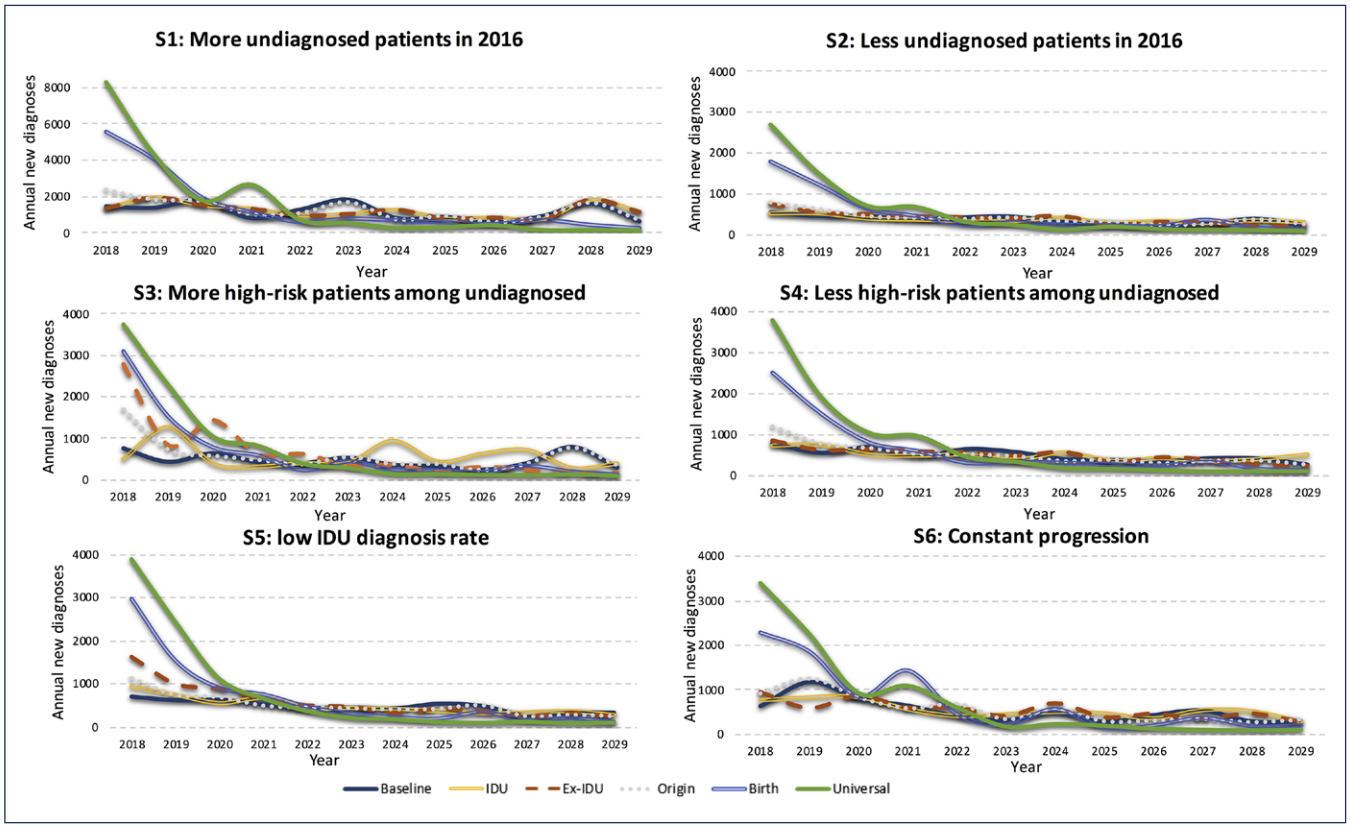
Supplementary Figure 1. Distribution of sex, year of birth, exposure through injection drug use and geographic origin in the Federal Office of Public Health database (from 1988 to 2015, and excluding the patients who had missing information on the presented characteristics). IDU: Injecting drug user; MSM: men who have sex with men



Supplementary Figure 2. Number of new infections per year in the past: comparison between persons of Swiss and foreign origin



Supplementary Figure 3. Coefficients for new infection in the Swiss origin and foreign origin populations. Each simulated patient is assigned a weight showing how often a similar patient appeared in the real data. As the real data do not include the undetected HCV-infected population, we defined an amplifying coefficient for Swiss origin and foreign origin population per year. This can give us a rough assumption about the true HCV incidence. The coefficients are chosen to emphasise the HCV incidence mainly among the persons of foreign origin in the early 1970s, and among the persons of Swiss origin in the late 1980s and early 1990s during the drug policy changes in Switzerland



Supplementary Figure 4. Sensitivity analysis around the size of viremic population (S1 and S2), proportion of the high-risk population (S3 and S4), past rate of diagnosis among IDU (S5), and fibrosis progression rate (S6). IDU: injecting drug user.

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