UNIVERSITÉ DE GENÈVE

Impact of Screening and Treatment for Hepatitis C Virus (HCV) Infection in Switzerland

A Comprehensive Mathematical Model of the Swiss HCV Epidemic

Final report

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Table of abbreviations

DAA	Direct acting antivirals
DC	Decompensated cirrhosis
EASL	European Association for the Study of Liver
FOPH	Federal Office of Public Health
FSO	Federal Statistical Office
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD-10	International Classification of Diseases, 10th revision
IDU	Injection drug user
LT	Liver transplantation
MSM	Men having sex with men
NSP	Needle and syringe program
OST	Opiate substitution therapy
PCR	Polymerase chain reaction
RR	Rate ratio
SCCS	Swiss Hepatitis C Cohort Study
SVR	Sustained virological response

Summary

Background and objective

An estimated 40,000 people were chronically infected with Hepatitis C virus (HCV) in Switzerland in 2016. HCV is one of the leading causes of liver disease, but a considerable proportion of the infected people may remain unaware of their infections until the onset of severe symptoms. A few years ago, the new effective therapy with direct acting antivirals (DAA) became available, and since October 2017, all HCV infected patients in Switzerland are eligible to be treated.

The aim of our project was to estimate the effect of various screening strategies on identifying the currently undiagnosed patients, and to project the number of annual new diagnoses, treated patients achieving sustained virological response (SVR), liver related deaths among HCV infected people, and the size of the HCV viremic population, between 2018 and 2029. We compared the following screening interventions with the current practice of screening (baseline scenario): intensified testing of current injection drug users (IDU); screening of former IDU; screening of people originating in high prevalence regions (South Europe, Asia, Africa); screening of people born 1951-1985; and universal screening of the entire population.

Methods

We developed a mathematical model of HCV disease progression that simulates individual patients from HCV infection until death. The progression of the disease is represented using health states that account for the current stage of liver disease (F0-F4, decompensated cirrhosis, hepatocellular carcinoma, transplanted liver) and stage of the infection and care (acute, chronic undiagnosed, diagnosed, on treatment, SVR/cured). Patients are assigned demographic and behavioral baseline characteristics. Transition times between health states are sampled from hazard functions, which were parameterized based on a comprehensive literature search and consulting experts. Because of uncertainty in input parameters, we conducted four alternative analyses, combining two assumptions about the rate of fibrosis progression (dynamic age- and stage-dependent vs. constant) and past diagnosis rate among IDU (low increasing vs. constant high).

The outputs of the model were converted into the assumed HCV infected population of Switzerland by giving each simulated patient a weight based on his/her baseline characteristics, corresponding to the representativeness of this simulated patient among the true infected population. We used the

notification database of the Federal Office of Public Health and the data collected by the Swiss Hepatitis C Cohort Study to estimate the distribution of the characteristics among the individuals diagnosed by 2016. We estimated the size of the undiagnosed population in 2016 by assuming a total infected population of 40,000 individuals. We assumed that the distribution of the characteristics was the same among the individuals infected in a particular year regardless of being diagnosed or not by 2016, and that the number of annual new cases of HCV would continue in the future on the same level as in the recent years. We also conducted sensitivity analyses where we either increased or decreased the total size of the infected population, or the proportion of individuals with high-risk behavior among the undiagnosed, or increased the liver related mortality rate.

Results

In this summary, we present the results comparing the future strategies from the main analysis assuming dynamic fibrosis progression and low diagnosis rate among IDU in the past (see Section 6 and Appendix E of the full report for the other analyses).

The expected number of new diagnoses in 2018 was about 700 in the baseline scenario, which represents a substantial drop from 2017 due to the decreasing number of undiagnosed patients in the easy-to-identify population groups (Figure i). Afterwards, the annual new diagnoses continued to slightly decrease. More intensive screening of current IDU did not considerably change the number of new diagnoses. With origin based screening, the new diagnoses were slightly above the baseline scenario, with similar pattern across the years. The number of diagnoses in 2018 was considerably higher with birth cohort screening (3,000) and universal screening (3,900). After the first years, the diagnoses decreased rapidly.

The model predicted in the baseline scenario that over 7,000 patients would achieve SVR in 2018. Afterwards, the number decreased fast, with only about 200 patients achieving SVR in 2029. The differences in annual number of SVR across the scenarios followed those of the new diagnoses. In particular universal and birth cohort screening scenarios will be able to cure over 1,000 patients more than the baseline scenario in the first years.

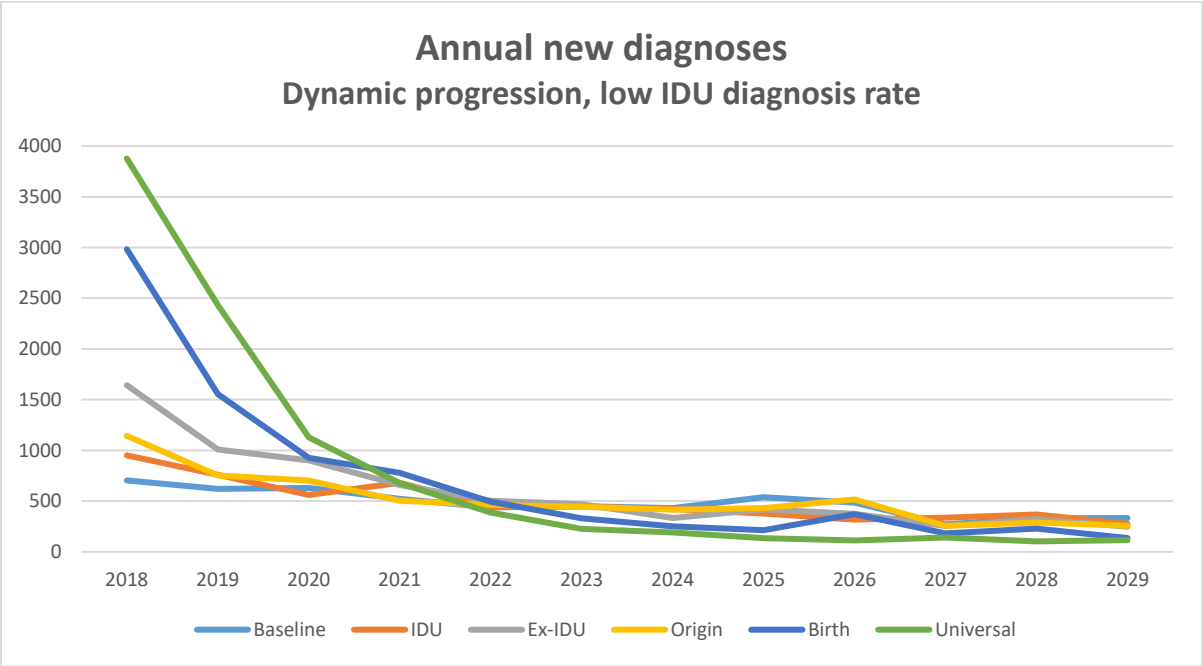

Figure i. Annual new diagnoses 2018-2029 according to the model. *Different curves present different screening scenarios.*

No differences between scenarios were seen in liver related mortality (Figure ii). About 100 to 250 HCV infected patients are expected to die of liver related cause during every year over the next decade, with a slowly decreasing trend.

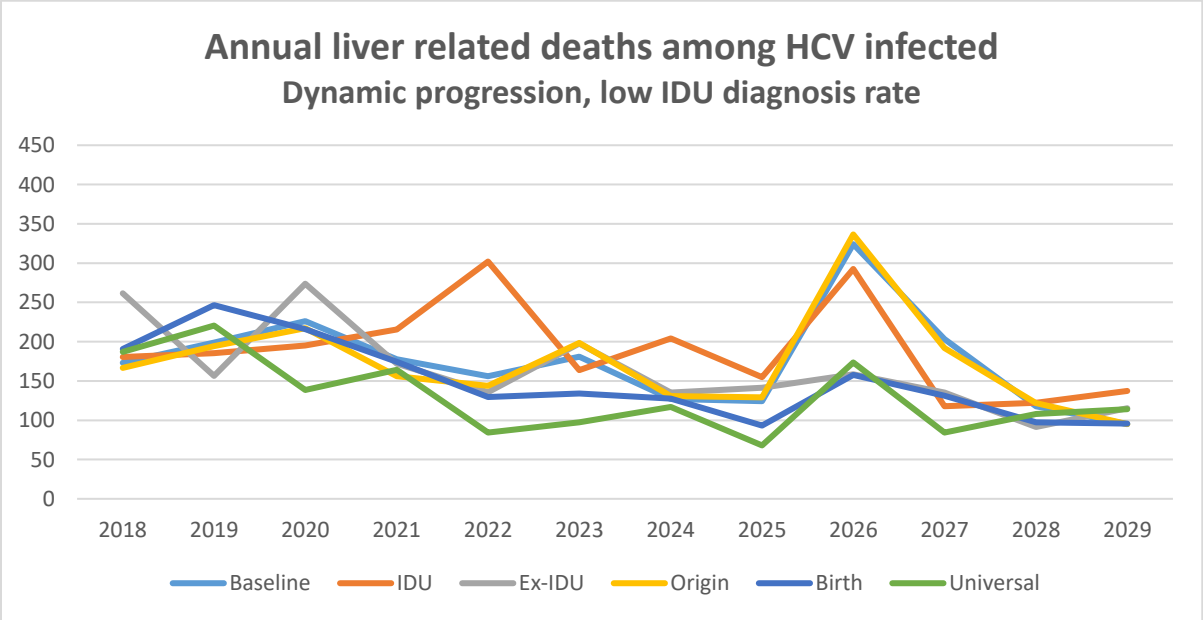

Figure ii. Annual liver related deaths among hepatitis C virus (HCV) infected patients 2018-2029 according to the model. *Different curves present different screening scenarios.*

The number of chronically infected viremic patients decreased continuously in all scenarios (Figure iii). In all scenarios except birth cohort and universal screening, about 5,000 viremic individuals were still living in Switzerland in 2029. With birth cohort screening, this number decreased to below 2,000, and with universal screening, below 1,000. Of the viremic patients, only about 150-350 belonged to the groups with high risk of onward transmission in all scenarios.

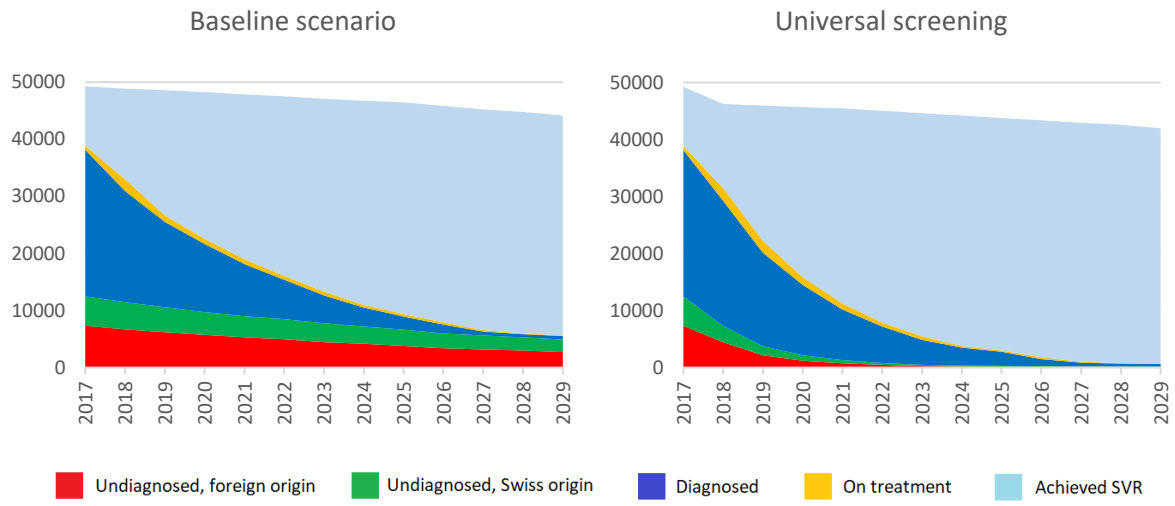

Figure iii. Distribution of undiagnosed, diagnosed, currently treated and cured among the infected population 2017-2029 according to the model (baseline and universal scenarios). *Spontaneously cleared patients are not shown.*

Conclusion

We compared six strategies of screening for hepatitis C virus between 2018 and 2029. We found that the size of the viremic population is likely to decrease in the future continuously, but with universal screening or screening of a broad birth cohort would yield the clearly lowest number of viremic patients by 2030.

The study had however several limitations. The results are consequences of the assumptions and input parameters, which in many cases were uncertain. The probably most important limitation concerned the assumptions about the currently unknown HCV infected population. The model we used is also not a transmission model, meaning that the future new infections were based on an assumption and not produced by the model.

Our study supports the continuation of testing population groups based on risk behavior, but at the same time shows that this alone will not be sufficient to reach all HCV infected individuals in the next

12 years. More information is needed about the characteristics of the currently undiagnosed population, in order to allow more detailed evaluations of the various screening strategies.

1 Introduction

1.1 Hepatitis C virus infection: Background

About 40,000 people were estimated to be chronically infected with the Hepatitis C virus (HCV) in Switzerland in 2016.[1] HCV poses a serious public health threat, and is one of the leading causes of liver disease. Of people living with HCV, a considerable proportion are expected to be unaware of their infection until the onset of severe symptoms.[2] Within 20-30 years of getting infected, about 7 to 30% of the patients will develop cirrhosis, and 1 to 5% progress further to hepatocellular carcinoma (HCC).[2–4] Thus, HCV infection may lead to elevated morbidity and mortality, the need of risky and expensive procedures such as liver transplantation, and other direct and indirect disease-related costs.

Until 2014, pegylated interferon alpha with ribavirin was the standard treatment against HCV. However, this therapy had several limitations. Permanent eradication occurred in about half of patients infected with genotype 1 (which is the most common genotype in Europe); the drug was administered by subcutaneous injection; and there were several side effects, part of which severe.[2] A few years ago, direct acting antivirals (DAA) for HCV became available, and are now the gold standard of HCV treatment. DAAs have substantially higher cure rates and can be administered orally without the addition of interferon alpha. The treatment is however expensive, and several countries have restricted the reimbursement to patients in an advanced stage of the disease. In Switzerland, DAA treatment was until recently reimbursed only for patients in fibrosis stage F2 or above, as well as certain population groups. In October 2017, these restrictions were lifted and all people living with hepatitis C virus can now receive treatment.

The current epidemic in Switzerland is mainly concentrated among injection drug users (IDU). Sexual transmission is possible but rare. However, increased HCV incidence has been reported among HIV positive men who have sex with men (MSM).[5] Elevated HCV prevalence may also be found among other population groups, such as migrants originating from countries with a high HCV prevalence, and patients who underwent invasive medical procedures before the introduction of disposable tools and safe sterilization of the equipment.

Currently, the Federal Office of Public Health (FOPH) maintains a database for all HCV cases notified in Switzerland. Blood donations are systematically screened for HCV, and HCV testing is recommended for persons who show clinical symptoms of hepatitis and/or have risk factors (medical, demographic, occupational, or other) associated with HCV. However, there is no national policy to screen wider population groups (based on e.g. a birth cohort).[2]

1.2 Current state of research

Several mathematical models have been published to estimate the progression, transmission and epidemiological and financial burden of HCV infection in Switzerland and other settings. Müllhaupt *et al.* have published a national-level model, showing that unless interventions are implemented, the number of patients in an advanced stage of the disease will continue to grow.[6] They estimated that the annual costs related to HCV (excluding antiviral treatment) will peak at about 97 million euros in 2030. This study applied a model developed by Razavi *et al.* that has been widely used for different countries.[7] However, this model also has limitations. As a compartmental model, the model did not take into account some major individual-level risk factors. The increasing liver-related mortality predicted by this model was not confirmed by a recent analysis.[1] The model was also not a transmission model: the assumptions about annual new infections were extrapolated from historical data, meaning that the model cannot take into account the impact of future interventions that target transmission.

Other mathematical models have been developed to study the course of the HCV infection and the epidemic in more detail. The models are however usually limited to a specific sub-population, or tailored to a particular research question. For example, our group has developed two models for HCV in Switzerland, one investigating the disease progression, and the other the transmission.[8,9] Both models were restricted to HIV-coinfected MSM, covering only a small part of the total HCV infected population. The questions relevant to this group are also not necessarily relevant for other risk groups, and the models cannot be directly generalized to the national level. To our knowledge, there is no comprehensive national-level model for any country that would take the transmission, detailed disease progression, and individual-level risk factors into account.

We have recently completed a situation analysis for the HCV epidemic in Switzerland.[1] According to this analysis, the reported HCV related mortality has remained stable during the past 20 years. Drug use was associated with over half of all reported HCV cases between the years 1988 and 2015,

further supporting the role of injection drug use as the main route of transmission. The large majority of new notifications happened among people originating from Switzerland or other European countries. Among Swiss-born people, the number of notifications has been decreasing since 2000. Among people born abroad, the number of notifications has remained stable during the past 20 years. Among people born in Switzerland and selected other countries, the majority of new notifications were associated with injection drug use. However, in people coming from countries outside of Europe, and in older persons originating from southern Europe, most people had no history of IDU. These infections are probably related to unsafe medical procedures in the past.

1.3 Objectives of the current project

The aim of this project is to investigate the future development of the Swiss HCV epidemic using a mathematical model of disease progression. Specifically, we will aim to study what the expected epidemiological outcomes under various screening scenarios are, and to assess the most effective policy for HCV screening in Switzerland.

The availability of effective and well-tolerated treatment with DAAs has raised the question if HCV infections should be actively screened among people without obvious liver-related symptoms, in order to cure the infection already before the liver disease advances and to interrupt ongoing transmission. Different countries apply different policies for screening. In the United States, universal HCV screening is recommended among people born between 1945 and 1965: the prevalence in this age group is about five times higher than in the population overall.[10] In Europe, the European Association for the Study of Liver (EASL) recommends to screen the most-at-risk populations, which should be determined according to country context.[11] For example, in France screening was until recently recommended for men aged between 18-60 years, as well as pregnant women. Meanwhile, this recommendation has been extended to screen all adults at least once in life.[12,13] In Switzerland, population groups with high HCV prevalence include IDU, HIV-positive MSM and people who have migrated from high-prevalence countries. Among persons not engaging in high-risk behavior, prevalence tends to be higher among older people, and in particular older migrants, who were exposed to transmission through e.g. unsafe procedures in healthcare.[14]

HCV testing among patients with high-risk behavior is already recommended and to some extent implemented. We will model two screening strategies focusing on IDU: one where testing is intensified among current IDU; and one where screening is applied to former drug users as well. In

Switzerland, studies show that the prevalence varies depending on the year of birth.[15] This suggests that birth cohort screening may be advantageous. We will therefore investigate a strategy where all people born between the years 1951 and 1985 will be intensively screened from 2018 onwards. Other plausible screening strategies would include those based on country of origin:[14] we will model one scenario where patients originating from countries with known elevated prevalence will be screened. Finally, we will model a universal scenario where the entire population will be actively screened.

The results of the intervention scenarios will be compared to a baseline scenario, where patients continue to be tested as before 2018, including testing of patients based mainly on risk behavior and symptoms. As Switzerland lifted the restrictions on DAA therapy from October 2017 and all HCV infected people are now eligible for therapy, we will not investigate different strategies of treatment. We will assume that in the future all patients diagnosed with chronic HCV infection will be eligible for treatment.

1.4 Methods

We implemented the model using the R package *gems* (GEneralized Multistate Simulation model).[16] In brief, this package simulates cohorts of patients from a multistate model that is determined with a set of states and transitions between them. The model represents the progression of HCV infected individuals from time of infection until death, across the different stages of liver disease, infection, and cascade of care.

We started the project with a review of the existing literature, which is presented in Section 2. In Section 2, we also present the key parameter values that were selected for the model, as well as an overview of the choice and distribution of baseline characteristics. We then developed the simulation and applied it to model the expected HCV infected population. The simulation model's internal structure is shown in Section 3, together with a formal description of the hazard functions and how the parameters selected in Section 2 are used in the model. The adaption of the model's raw output to the Swiss epidemic is shown in Section 4. Section 5 presents a comparison of the model's projections in the past using various parameterizations, and Section 6 presents the results comparing the outcomes under different screening strategies.

2 Literature review and parameterization

2.1 Liver disease progression in HCV infected individuals

In our model, liver disease is divided into seven stages: F0, F1, F2, F3, F4, decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). Progression can follow from each stage to the subsequent one only, with the exception of F4, from where it is also possible to proceed to HCC directly. In addition, we include liver transplantation (LT), to which the patients can progress from DC or HCC. We reviewed the available literature, including observational studies and parameterizations used for mathematical models, to identify the relevant cofactors and estimate the rates of disease progression. In this section, we summarize the approaches that different studies used to evaluate the rates of progression across the different stages of liver disease until cirrhosis (F4 and DC). Additional studies, as well as a summary of the findings, are shown in Appendix A.1. **Values that were chosen to be used in the model are highlighted in bold face at the end part of each sub-section.**

2.1.1 Progression from F0 to DC

One of the earliest studies we identified, by Poynard *et al.*, assessed the natural history of liver fibrosis progression due to hepatitis C, and the factors associated with the progression.[17] According to their study, old age at infection, excessive alcohol consumption and male sex were more strongly associated with faster fibrosis progression than virological factors of the HCV infection. The study found no association between fibrosis progression and HCV genotype. The rates were estimated by dividing the number of the current fibrosis stage by the expected duration since infection. This approach therefore has several limitations: for example, it implies that the rates for all steps for fibrosis progression are identical (i.e. given a set of factors, the average duration at each fibrosis stage is the same). Age was considered as age at infection, not the current age, meaning that for individuals infected at young age the progression rate will remain low throughout lifetime.

In contrast, Thein *et al.* considered stage-specific fibrosis progression rates.[18] They undertook a systematic review and meta-analysis of prognostic studies with which they computed the annual stage-specific transition probabilities using the Markov maximum likelihood estimation method. The duration of infection was found to be the most consistent factor significantly associated with progression of fibrosis. They assumed that alcohol consumption only affects fibrosis progression between F1 and F3, but not from F0 to F1 or F3 to F4. The meta-regression analysis by Thein *et al.*

was applied also by Ward *et al.* in a study assessing the clinical and economic burden of chronic hepatitis C in the UK.[19]

Razavi *et al.* studied the impact of treatment to reduce HCV incidence and mortality in different countries including Switzerland.[7] They modeled the hepatitis C disease progression and mortality. Fibrosis progression rates were back-calculated from data from the US (US Surveillance, Epidemiology and End Results; SEER). They used the results of Harris *et al.*, who used a similar back-calculation method for calculating the fibrosis progression rates for patients from the UK, as a guidance.[20] The following stages were considered: F0, F1, F2, F3, cirrhosis and HCC. The rates were defined for each 10-year age group and both genders separately. The age variable was defined as current age, i.e. each individual patient's progression rates are updated as the patient gets older.

Further studies identified in our review are listed in Appendix A.1.[21–44]

Based on the findings from the literature review, we decided to include two alternative parameterizations for our model regarding progression from F0 to F4: one based on **dynamic age- and stage-specific progression as suggested by Razavi *et al* including dependency on gender and alcohol consumption,**[7] and one based on **constant rates according to Poynard *et al* depending only on baseline age.**[17] Both approaches have their advantages. It has been shown that the progression of liver disease is likely to accelerate in older age, and the use of constant rates may thus underestimate the true potential of end-stage liver disease among patients infected while young, but meanwhile in older age. The estimates from Razavi *et al.* are also fairly well in line with the estimates from other studies, such as those of Thein *et al.*[18] In contrast, the approach using dynamic progression is subject to substantial uncertainty. Poynard's approach, although very basic, may correspond better to the present level of knowledge. In addition, the average progression rate using Poynard's parameterization was substantially lower, meaning that the use of these two alternative analyses serves also as a sensitivity analysis. For **progression from F4 to DC, we used the estimate of Hutchinson *et al.***[24]

2.1.2 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) represents a serious complication of HCV-related cirrhosis. The risk of HCC depends on a background of chronic liver disease, including chronic hepatitis C or hepatitis B infection (2-5%), genetic predisposition, older age and abuse of alcohol.[45,46]

Planas *et al.* conducted a study of 200 patients with HCV related cirrhosis, and found that 33% of the patients developed HCC.[47] Conti *et al.* evaluated the early occurrence and recurrence of HCC in cirrhotic patients treated with DAA.[48] They found that in patients with HCV-related cirrhosis, DAA-induced resolution of HCV infection does not seem to reduce occurrence of HCC, and patients previously treated for HCC have still a high risk of tumor recurrence, in the short term. Cabibbo *et al*. estimated the recurrence and survival probabilities of HCV-related early HCC following complete response after potentially curative treatment.[49] **We selected the results of Planas *et al* for the model.**[47]

2.1.3 Liver transplantation

We included also liver transplantation in our model. Liver transplantation is performed for patients who are at an end-stage liver disease,[50] and fulfill certain conditions of eligibility. **We chose a rate of 0.05 for progression from DC and HCC to transplanted liver.**

2.1.4 Fibrosis progression and regression after treatment

It can be expected that the progression of liver disease will either stop, slow down, or turn into regression as the patient achieves sustained virological response (SVR). Morgan *et al.* systematically reviewed observational studies in order to determine the association between response to HCV therapy and development of HCC among persons at any stage of fibrosis and those with advanced liver disease.[51] They found that achieving SVR is associated with a reduction in the relative risk for HCC for persons at all stages of liver disease (hazard ratio, 0.24 [95% CI, 0.18 to 0.31] for all patients, and 0.23 [95% CI, 0.16 to 0.35] for patients with advanced liver disease). People who responded to treatment were approximately six times less likely to develop HCC than the ones who did not respond. Viral eradication prevented 14 (12-15) cases of HCC per 1,000 person-years including people in all stages of fibrosis, or 23 (18-26) cases of HCC per 1,000 person-years including people in advanced fibrosis (F3-F4).

Zahnd *et al.* assumed that clearing HCV decreased the rate at which fibrosis progressed from F0 to F4 (rate ratio, RR = 0.1), from F4 to DC (RR = 0.1), and from F4 to HCC (RR = 0.38).[8] This study was however focusing on people co-infected with HIV which may affect the progression. Cordero-Ruiz *et al.* studied the impact of fibrosis on treatment response among people who were treated with α-interferon and ribavirin.[52] They found that among 66 individuals with SVR, the fibrosis progressed in

10, remained stable in 54, and regressed in 2 cases. The outcomes were significantly better than among the 59 non-responders (31 with fibrosis progression, 28 stable).

Other studies are described in Appendix A.2.[53–57] After reviewing the literature and consulting experts in the field, **we decided to follow the approach of Zahnd *et al*, using a residual progression with hazard ratio of 0.1.**[8] This means that liver disease continues to progress also after sustained virological response or spontaneous clearance, but with a 10 times slower rate.

2.2 Acute and chronic stages of HCV disease, spontaneous clearance

The focus of our model is in chronic HCV, but for generalizability we also include the entire course of the disease from infection, and thus also model acute HCV and spontaneous clearance explicitly.

In general, 50% to 85% of infected adult persons will develop chronic HCV infection.[58,59] According to Hoofnagle, 75% to 85% of individuals infected with HCV progress to chronic infection, persisting for at least 6 months after onset, with the rate varying by age, sex, race, and the status of the immune system.[60] Ayoub *et al.* estimated the duration of acute HCV stage in primary and secondary infections to be 16.5 weeks and 4.1 weeks, respectively.[61] Razavi *et al*. and Müllhaupt *et al*. have used a spontaneous clearance rate of 18% (15-45%) for Switzerland.[6,7] Other studies also reported spontaneous clearance rates ranging from 20% to 40%.[62–66]

In our model, we define acute infection as the **first 6 months since HCV infection**, regardless of whether the virus will be cleared or if chronic infection develops. Similarly, we determine chronic infection as HCV infection that has been present for at least 6 months.[67] This distinction is thus based only on a formal definition. **Spontaneous clearance in the model will be included analogically to Zahnd *et al.*[8]** The details of the function will be shown in Section 3.

2.3 Diagnosis and treatment

2.3.1 Diagnosis

Diagnosis of the HCV infection consists of finding the potentially infected people, performing the diagnostic test, receiving the test result and informing the tested person. In our model, we calculated the rate of diagnosis as a combination of two factors: the rate of testing, and the probability of completing the testing process including receiving a correct positive test result. Since one of the overall aims of the model is to compare future diagnosis strategies, the rate of diagnosis will depend

on the calendar year: until 2017, the diagnosis rate should correspond to the reality as close as possible, whereas from 2018 onwards, multiple strategies will be modelled and compared.

Switzerland lacks a national action plan for the prevention and control of viral hepatitis. In 2013, healthcare provider initiated HCV testing had been proposed.[2] We therefore considered the following routes of getting tested before 2018: **liver-related symptoms and clinical signs of advanced liver disease; testing based on drug use or other high-risk practices; testing as a part of regular HIV care.** We also included a **background testing of people without risk factors.** We excluded screening of patients who may have been infected due to blood transfusions or other nosocomial risk factors in Switzerland before the virus was identified: a number of factors such as their comorbidities make it likely that their number is rather low.[1,2] We **also did not consider any non-risk behavior related testing**, based on e.g. origin, birth cohort or history of drug use. Screening based on country of origin and/or birth cohort are recommended in many countries. For example, in the United States, it was shown that persons born between 1945 and 1965 comprised the clear majority of all people infected with HCV, and thus it has been recommended to screen this birth cohort regardless of symptoms or risk factors.[10] It has been also shown that in Switzerland, people born in certain countries in Southern Europe aged above 60 were clearly overrepresented among patients infected with HCV, as compared with the proportion of this group in the general population. A likely reason for this can be the unsafe medical and paramedical practices in some countries from 1950s to 1970s.[14] In addition, the prevalence of HCV varies greatly across countries, with a number of countries such as Egypt having a notably high prevalence. These findings show that screening of people based on their country of origin, regardless of other risk factors, could be a strategy to consider. At the moment, there is however no action plan for such screening in place in Switzerland.

It is not very likely that early stage of fibrosis (F1-F2) would cause symptoms that would make the patient suspect a liver-related condition. The further the disease progresses, the more likely it will become that the patient will seek care and be tested. We therefore **restricted the symptom-based testing to F3 and above.** It is unlikely that HCV in a cirrhotic patient would be missed, thus we **increased the rate substantially in F4.** Liver related values may be elevated in the earlier stage of fibrosis as well, but the observation of these would require a blood test taken for some other reason. This route of diagnosis is included in the background testing rate.

Current intravenous drug users and their physicians are likely aware of their high risk of acquiring infectious diseases, and are therefore tested regularly, especially when participating in substitution treatment. However we assume that, in Switzerland, during the former "peak times" of intravenous heroin consumption there were considerable numbers of persons with short-time or intermittent consumption, or even lengthy consumption but without social disintegration. These individuals may never have been tested for hepatitis C. Among them there may be persons who may not consider themselves at risk. In addition, intranasal consumption of drugs (mainly cocaine) can pose a transmission risk if the paraphernalia for nasal consumption are shared. Thus, the risk of HCV infection may also extend to completely different societal groups with intermittent cocaine consumption.

Although injecting drug users have now good access to support and healthcare including testing of blood borne infectious diseases, the situation in the 1980s and 1990s, at the peak of the drug consumption, was probably worse. Since this is a key assumption that determines the stage of patients at diagnosis but we did not have any data on this parameter, we decided to consider two alternatives: in the first analysis we used a **relatively high constant rate of testing among active IDU**, and in the second analysis we assumed a **lower rate which increased over time**.

In Switzerland, HCV tests are performed for patients who report anal sex and who report intravenous or nasal drug use with sharing of drug paraphernalia. Moreover, HIV infected patients who are aware of their status visit the clinic regularly. As a consequence, for HIV infected individuals the average time from HIV infection to HIV diagnosis can be considered as an estimate for the time that an HCV test is performed. According to a study conducted by van Sighem *et al.*, average time from HIV infection to diagnosis among MSM has decreased to 2.6 years for those infected in recent years.[68] The probability to detect HIV among infected MSM within the first year of HIV infection, possibly already during the primary infection, is even higher in Switzerland.[69] We therefore assumed in the model that the **HIV coinfected MSM with high-risk behavior would be tested annually, HIV uninfected high-risk MSM every second year, and other HIV coinfected individuals after about 5 years from HIV infection.**

Apart from the reasons mentioned above, there are also other reasons to get tested regardless of risk factors or baseline characteristics. For example, hepatitis C testing is standard for blood donors, and elevated liver values may indicate a need for test. Because of this, we included a **background**

testing rate that is applied to all individuals, regardless of baseline characteristics and liver disease stage.

The sensitivity of HCV testing depends on the type and protocol of tests used. We considered only the standard testing protocol, which consists of an antibody test followed by PCR. Antibody tests have a high sensitivity, except during the first three months since infection, and for immunosuppressed patients whose antibody formation may be delayed or missing.[70–72] Antibody testing will also detect patients who have cleared the infection. This does not influence the model's results as only chronically HCV infected people are included. It would however have economic consequences that will be relevant should cost-effectiveness be assessed at a later stage. The PCR test, which has both a high sensitivity and specificity, is performed thereafter to confirm the active infection. The sensitivity of the PCR test has been estimated between 91% and 100%, depending on the detection limit**.** According to Anderson *et al.*, 82% of patients who were tested anti-HCV positive took and completed a PCR test.[73] However, this study was done in an emergency setting in the United States, where the situation is likely to be considerably different from routine care in Switzerland. We therefore decided not to consider drop-out during the testing process in our model.

2.3.2 Treatment

Throughout this project, we refer by "treatment" only to the new therapies based on direct acting antivirals (DAAs), which became available in 2014.[74] Patients who were successfully cured with the pre-DAA therapy were excluded from the model. Since this type of treatment is no longer used, including pre-DAA therapy into the model would have increased its complexity substantially, without being able to help answering any of the questions of interest. Unsuccessful pre-DAA treatment was also not explicitly included: we assumed that treatment attempts without virological response would not influence the progression of liver disease.

Under optimal circumstances, DAA treatment should be initiated as soon as the infection is detected. However, due to financial constraints, restrictions for DAA treatment existed even in high-income settings. In Switzerland, DAA treatment was reimbursed only for patients in liver disease stage F2 or above, or to certain other specific population groups, until recently. In October 2017, these restrictions were lifted.

Patients who are already eligible during the time of diagnosis can be expected to start treatment about 6 months after diagnosis. For those diagnosed earlier, initiation of treatment will depend on

meeting the eligibility criteria (i.e. progression to a higher METAVIR stage) and the average interval of visits to a clinician. According to the sales data, about 7,900 patients were treated with DAAs during the years 2014-17. Based on the estimates of the total HCV infected population (n=36,000-43,000) and the cumulative number of notifications (>40,000), we can assume that a considerable part, or even the majority, of diagnosed patients eligible for treatment are still waiting. Thus, we **assumed an additional random delay between eligibility/treatment availability and initiation of treatment for all patients diagnosed before 2014**.

Several studies have investigated the optimal treatment duration for different HCV genotypes.[25,75–79] Treatment duration can vary based on HCV genotype and stage of liver disease (cirrhotic and non-cirrhotic). Most commonly, **a treatment course of 12 weeks** is recommended, and this was also assumed in our study.

The probability of virological response has been shown to depend on HCV genotype and may vary based on the liver disease stage (cirrhotic vs. non-cirrhotic).[2,7,20,25,75–77,80] In most cases, SVR probability was estimated above 90% or even close to 100%, and the differences between genotypes are also disappearing, although some lower rates were also found for particular treatment regimens. We decided to use a **98% probability of SVR regardless of genotype and other characteristics.**

2.4 Mortality

We divided mortality in the model according to cause. We included liver-related mortality, HIV-related mortality, mortality related to drug use, and other (background) mortality. Modelling the mortality due to extrahepatic manifestations associated with HCV infection was discussed but not considered due to the lack of reliable data. These causes of mortality can be interpreted as competing risks: the parameters that we would ultimately need are the risks of death due to a particular cause in the absence of other causes.

All-cause mortality rates for different age and gender groups can be found in the Federal Statistical Office (FSO) database.[81] **We decided to use these data directly for the background mortality in our model,** since the competing causes of liver disease, HIV and injection drug use can be expected to be negligible at the general population level.

The cause-specific transition rates from DC, HCC and transplanted liver to death have been noted in several studies.[6,19,21,25,82] **After a review of the literature (Appendix A.3)[69,83–89], we decided to adapt**

the values used by a previous model of Martin *et al*.[90] Since other studies proposed higher values, we considered these for a sensitivity analysis.

Razavi *et al*. used a standardized mortality ratio of 5.5 (ratio of mortality rates between active IDUs and the overall population) for active IDUs under the effective harm reduction systems in place for people who use drugs.[7] This ratio contains the effect of all reasons related to drug use, including HIV infection and liver related causes due to HCV which are included separately. We however took this estimate together with the FSO all-cause mortality rates[81] as a basis for the IDU related mortality, as the resulting cause-specific IDU mortality remained very low.

2.5 Baseline characteristics

2.5.1 Inclusion of baseline characteristics

Our model includes 10 different variables for baseline characteristics: age at infection, year of birth, gender, country or region of origin, HCV genotype, intravenous drug use (starting and stopping times), excessive alcohol use, time of HIV co-infection, and high-risk MSM behavior (Table 1). The different characteristics correlate substantially with each other, and therefore it would be inappropriate to sample the final distribution assuming independence between the variables. However, due to the large number of variables, many of which contain several possible values, the total number of possible combinations would be very high, making it practically impossible to estimate the full distribution. In Appendix B, we show a brief summary of the baseline characteristics of the Swiss Hepatitis C Cohort for reference. The characteristics of this cohort are however not generalizable for the entire infected population.

We therefore consider the following approach: The model will be run in two steps. First, a large number of patients will be simulated one by one, to create a cohort where all relevant combinations of characteristics are represented. In the second step, the characteristics are matched to the estimates about the true Swiss HCV infected population (see Section 4). In the first step, we will therefore not aim to estimate the full distribution of characteristics, but assure that all relevant combinations are included, and the most essential ones are represented with a high enough number of patients to reduce stochastic variability.

Since some baseline characteristics include continuous variables, there are in theory an infinite number of possible sets of characteristics. To make the number of combinations finite, we simplified

the situation by representing the year of birth and age at infection using discrete groups based on intervals, and times of HIV infection and drug use with dichotomous variables (yes or no). We also reduced the number of genotypes to 4, keeping only the most common ones. Without loss of generality, we can sample the exact values in most cases from uniform distributions.

Table 1 shows all the possible combinations for the patient's baseline characteristics. The total number of over 110,000 combinations was reduced slightly when impossible combinations (e.g. female MSM, combinations of early birth year and old age), and in addition some combinations that are in theory possible but deemed irrelevant, were excluded.

In the next sections we present some additional findings from our literature search.

Table 1. List of possible baseline characteristics in the model.

Characteristic	Number of values	Description
Alcohol consumption	3	Excessive, moderate, abstinent
Genotype	4	1,2,3,4
HIV	2*	No, yes
MSM	2	No, yes
Gender	2	Male, female
IDU	2*	No, yes
Origin	4	Switzerland/Liechtenstein, Western Europe/Americas/Oceania, Eastern Europe/Central Asia/Balkans, Southern Europe/Asia/Africa
Age at infection	8*	[< 21), [21 - 31), [31 - 41), [41 - 51), [51 - 61), [61 - 71), [71 - 81), [81 - ∞)
Year of birth	8*	[1937 - 1947], [1947 - 1957], [1957 - 1967], [1967 - 1977], [1977 - 1987], [1987 - 1997], [1997 - 2007], [2007-2016]
Total	14,152	

MSM, men having sex with men; IDU, injection drug user.*The actual variables in the model are defined continuously (in the case of IDU and HIV, referring to the time of drug consumption or HIV infection).

2.5.2 Country of origin

Bertisch *et al.* compared characteristics of anti-HCV-positive individuals in the Swiss Hepatitis C Cohort Study (SCCS) and of HCV cases reported to the Federal Office of Public Health (FOPH), with

those of the general population in Switzerland,[14] showing an overrepresentation of certain countries of origin among the people both in the SCCS database and the FOPH hepatitis C registry.

For simplicity, we divided the patients' countries of origin into four categories: Switzerland and Liechtenstein; Western Europe, Americas and Oceania; Eastern Europe, Central Asia and the Balkans; and Southern Europe, Asia and Africa (Appendix C). This division correlates roughly with the types of epidemic, although it is not exhaustive.

2.5.3 Injection drug use

Injection drug use is a major route of transmission, and several studies have studied hepatitis C among IDU. Injection drug use in our model is included as the time period of active drug use.

Martin *et al.* modeled treatment scale-up in the age of DAAs among people who inject drugs.[91] A dynamic HCV transmission model was parameterized to three settings with differing chronic HCV prevalence: UK, Australia, and Canada. They used 11 years as the average injecting duration until cessation point value in all the sites, but varied this injecting duration from 6 years up to 20 or 27 years in the uncertainty/sensitivity analyses based on seroprevalence survey data.

Turner *et al.* designed a meta-analysis and pooled analysis, with logistic regression allowing adjustment for gender, injecting duration, crack injecting and homelessness, to investigate whether opiate substitution therapy (OST) and needle and syringe programs (NSP) can reduce HCV transmission among IDUs.[92] The analysis covered five studies conducted in six sites in the UK. The mean age of the individuals ranged from 29.6 years to 34.9 years, and the mean injecting duration from 8.5 years to 12.0 years.

Fazito *et al.* reviewed literature in order to calculate regional estimates of the average duration of time individuals maintain a specific high risk behavior.[93] People who inject drugs and men who have sex with men were considered in this review.

We assumed that duration of intravenous drug use would range **up to a period of 20 years.**

2.5.4 HIV coinfection and high-risk sexual practices

Based on a systematic review and meta-analysis conducted by Urbanus *et al.* to synthesize the epidemiology, and the risk factors for hepatitis C virus (HCV) among HIV co-infected and HIV negative men who have sex with men (MSM), incident HCV predominantly affects HIV positive MSM.[94] Several

studies suggest that HCV seems to predominantly affect HIV-positive MSM, whereas HIV-negative MSM are significantly less affected.[45,46,94–97]

3 Mathematical model: structure and hazard functions

3.1 Overview of the model

In this section, we will present the mathematical formulation of all hazard functions included in the model, as well as describe how the parameters selected in Section 2 will be applied in the model.

The model is implemented using the R package *gems*. We will consider a total of 52 health states (Figure 1). Of these, 48 states combine the progression of the patient through the eight stages of liver disease (F0, F1, F2, F3, F4, DC, HCC and LT) and six stages of the infection and cascade of care (acute, chronic undiagnosed, diagnosed, treated, retreated, cured). The remaining four states represent death, divided according to the four included causes (liver disease, IDU, HIV coinfection, others).

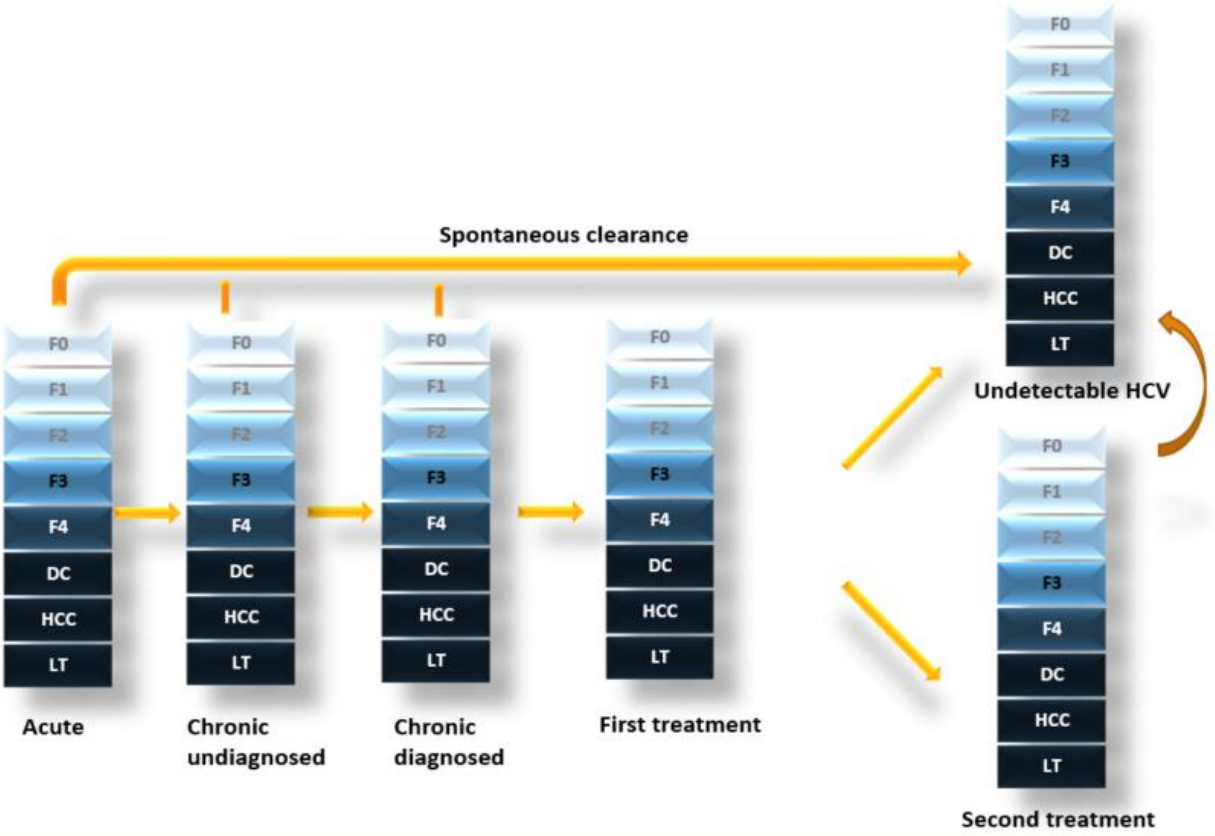

Figure 1. Schematic representation of the model. *The patients progress simultaneously through the stages of liver disease (vertically) and infection and cascade of care (horizontally). Death is possible from any stage but not shown here. F0-F4, fibrosis according to METAVIR scale; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; HCV, hepatitis C virus.*

3.2 Fibrosis progression

In our model, progression of fibrosis may depend on the individual patient's current age, gender, alcohol consumption, and viremia. The fibrosis hazard functions from stage F*x* to stage F*y*, where F*y* is either the immediate successor of F*x* (when F*x* = F0,…,F3), DC or HCC (when F*x* = F4), HCC or LT (when F*x* = DC), or LT (when F*x* = HCC), are of the following form:

$$h_{Fx,Fy}(t, bl, history) = r_{Fx,Fy,bl}\left(t + \sum history + bl(age)\right)\lambda_{SVR}(t)\, R_{Fx,Fy,bl},$$

where $r_{Fx,Fy,bl}(\tau)$ is the progression rate depending on gender and current age τ, and the hazard ratios $R_{Fx,Fy,bl}$ and $\lambda_{SVR}(t)$ modify the progression depending on the patient's alcohol consumption and virological response, respectively. Moderate alcohol consumption is considered as between 20 and 40 g of alcohol per day on average, and excessive consumption as more than 40 g/day on average, regardless of gender. We consider alcohol consumption as a fixed parameter, and thus a constant hazard ratio will be applied to each individual patient over the lifetime, even though in reality it is expected that the alcohol consumption may vary over age. The parameter $\lambda_{SVR}(t)$ is 1 for all patients before treatment and also the patients who failed treatment, and 0.10 for patients with either SVR or who spontaneously cleared the infection.

As mentioned in Section 2, we used two alternative approaches for the parameter $r_{gender}(\tau)$. The first alternative uses rates derived from estimates by Razavi *et al.* and Harris *et al.* (Table 2).[7,20] The main reason for choosing these rates was to catch the accelerating disease progression over age, which has been suggested by e.g. Poynard *et al.*[98] We acknowledge that these data have limitations: they are based on the incidence of liver cancer, from which it was back-calculated using assumptions on the attributability of liver cancer to HCV. In this approach, the basic rates $r_{Fx,Fy,bl}(\tau)$ are taken from Table 2, depending on the gender and current age τ. The rate was multiplied by a coefficient depending on the patient's alcohol consumption (Table 3). In the second alternative parameterization, we used the constant rates proposed by Poynard *et al.*(Table 4).[17] Age is taken into account only as "age at infection": this means that, for example, a patient who was infected at a young age will continue to progress slowly even as he gets older. This could potentially delay the progression to cirrhosis and/or HCC among these patients, leading to an underestimation of the effect of timely treatment. In this analysis, we did not distinguish the rates by gender or alcohol

consumption either. In practice, this means that $r_{Fx,Fy,bl}(\tau)$ does not depend on time τ, but instead only on the age at baseline.

Table 2. Disease progression rates between fibrosis stages F0 and F4 according to gender and current age: parameters for analysis with dynamic fibrosis progression.[7,24]

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

Table 3. Hazard ratio to modify the progression rate if the patient is a moderate, or excessive alcohol consumer.

Stage	$R_{bl(alcohol)}$	References
$F0 \longrightarrow F1$	$x \in \{0\ (non), 1\ (moderate), 2\ (excessive)\}$ $\begin{cases} 1, & for\ x = 0 \\ 1.16, & for\ x = 1 \\ 1.33, & for\ x = 2 \end{cases}$	17,99
$F1 \longrightarrow F2$	$\begin{cases} 1, & for\ x = 0 \\ 1.3, & for\ x = 1 \\ 2.22, & for\ x = 2 \end{cases}$	100
$F2 \longrightarrow F3$	$\begin{cases} 1\ , & for\ x = 0 \\ 1.3, & for\ x = 1 \\ 2.22, & for\ x = 2 \end{cases}$	17,18
$F3 \longrightarrow F4$	$\begin{cases} 1, & for\ x = 0 \\ 1.16, & for\ x = 1 \\ 4, & for\ x = 2 \end{cases}$	17,99

Table 4. Disease progression rates between fibrosis stages F0 and F4 according to age at infection: parameters for analysis with constant fibrosis progression.[17]

Age at infection	Value
≤20	0.091
21-30	0.105
31-40	0.138
41-50	0.200
≥51	0.333

These values are applied to all steps from F0 to F4.

The hazards of end-stage liver disease are shown in Table 5. This parameterization, based on the studies of Hutchinson *et al.* and Planas *et al.*, was used in both analyses.[24,47]

Table 5. Disease progression rates to end stages of liver disease according to current age.[24,46]

Age	0-29	30-39	40-49	50-59	60-69	70+
$F4 \longrightarrow DC$	0.0651 (0.0139, 0.2610)	0.0641 (0.0219, 0.1750)	0.0648 (0.0324, 0.1186)	0.0649 (0.0403, 0.0951)	0.0635 (0.0336, 0.1186)	0.0630 (0.0229, 0.1675)
$F4 \longrightarrow HCC$	0.0079 (0.0040, 0.0159)	0.0130 (0.0075, 0.0219)	0.0212 (0.0142, 0.0311)	0.0347 (0.0249, 0.0475)	0.0565 (0.0381, 0.0792)	0.0913 (0.0561, 0.1469)
$DC \longrightarrow HCC$	0.0155 (0.0074, 0.0328)	0.0252 (0.0137, 0.0440)	0.0410 (0.0248, 0.0644)	0.0665 (0.0416, 0.1026)	0.1091 (0.0646, 0.1751)	0.1762 (0.0945, 0.3251)

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma

Our model does not include the possibility of disease regression, i.e. once the patient's infection is cleared, he or she will either remain in the same fibrosis stage, or progress further (with a rate of 0.1 times the corresponding rate with no SVR). As mentioned in Section 2, it is likely that fibrosis may in reality regress after SVR, at least for some patients. Including this feature explicitly would however have added substantial complexity to the model. While interpreting the results, it should therefore be noted that the burden of liver disease may be overestimated among patients who have achieved SVR.

The rate of liver transplantation from DC and HCC was assumed to be 0.05 regardless of baseline characteristics.

3.3 Spontaneous clearance

The progression from acute to chronic infection will follow at exactly 6 months after infection. Spontaneous clearance may in theory happen at any time. We assumed that the probability of spontaneously clearing HCV, follows a logistic decrease, with a probability p of 32% at one year. The formula of the logistic function is

$$f(t) = \frac{1}{1 + \left(\frac{t}{a}\right)^b}$$

The parameters were taken from Zahnd *et al*[8], with a = 0.25 and b = 2.23. The probability of spontaneous clearance is highest at the beginning, after which the decrease in probability accelerates until the inflection point a, and decelerates thereafter, approaching zero in infinity.

3.4 Screening and diagnosis

The probability of diagnosis over time depends on three factors: the probability of initiating HCV testing, the probability of completing the testing, and receiving the correct test result. Assuming that less than 100% of people tested positive will complete the diagnosis process with the correct positive test result, some patients will be diagnosed as false negatives and thus should be able to get retested later. However, this would increase the complexity of the model, and because the probability of false negative tests is very low, bring only minimal benefit. Therefore, we ignore the possibility of multiple tests and use only the crude rates, i.e. the sum

$$c(bl,t) = c_{background} + c_{symptoms}\big(F(t)\big) + c_{HIV,MSM}(bl,t) + c_{IDU}(bl,t) + c_{origin}(bl) + c_{birth}(bl)$$

where $c_{background}$ is constant over time and independent of baseline characteristics; $c_{symptoms}$ depends on the fibrosis stage $F(t)$ at time t; $c_{HIV,MSM}$ depends on the baseline characteristics (MSM behavior, HIV coinfection and its timing) as well as time; c_{IDU} depends on the baseline characteristics (timing of active intravenous drug use) and time; and c_{origin} and c_{birth} on baseline characteristics only (origin and year of birth, respectively). The rate is applied until 2018. The parameterization has been explained in Section 2 and the parameters are shown in Table 6. By rates, we mean constant hazard functions, and the time to event is therefore exponentially distributed. For example, a rate of 0.5/person-year

means that at any point of time, the mean time for an undiagnosed person until diagnosis is equal to the inverse of the rate, i.e. 2 years. This is equivalent to a proportion of $1 - e^{-0.5} = 39\%$ of the remaining undiagnosed population being tested every year.

Original and birth cohort based diagnosis rates are set to zero. For IDU based screening, we used two alternatives, as described in Section 2. In the first alternative, IDU screening was assumed to be 0.5/person-year during the entire active injection drug use period. In the second alternative, it was assumed to be 0.05/person-year before 1990, 0.15/person-year between 1990 and 1995, and 0.25/person-year between 2018. In both analyses, this rate was set to zero outside the period of active injection drug use.

For the period from 2018 onwards, an alternative rate $c'(bl,t)$ is used. This will be determined according to the scenario. As described in the Introduction, we considered the following six scenarios about future testing and screening:

1) No additional screening
2) Intensified screening of active IDU
3) Screening of former IDU
4) Screening based on country of origin
5) Screening based on birth cohort
6) Universal screening

The basic diagnosis rate, using the same values as before 2018 (and a rate of 0.5/person-year for IDU for both analyses) was used as the basis of all scenarios. With intensified screening of active IDU, the rate of diagnosis among IDU was doubled to 1.0/person-year. With screening of former IDU, the screening rate for IDU was kept at 0.5/person-year after the end of active injection drug use. In country-based screening, a rate of 0.5/person-year was applied to people originating from high-risk countries, and in birth cohort screening, to people born between 1951 and 1985. Finally, with universal screening, the background testing rate was replaced with a rate of 0.5/person-year.

Table 6. Rate of diagnosis due to different routes until 2018.

Risk indicator	When applied	Value (rate/year)	Source or explanation
Symptoms and clinical signs of advanced liver disease	Fibrosis F3 or higher	1 in F3, 2 in F4, 5 in DC or HCC	Assumption: The probability of visiting a doctor increases with fibrosis stage, patients in DC or HCC will be identified immediately
Background testing (for the whole population)	Regardless of fibrosis stage or baseline characteristics	0.01	Assumption: There is a continuous probability of being tested due to e.g. elevated liver values or blood donation
Drug use	Active IDU	0.5 or 0.05-0.25*	Assumption: active IDU are tested regularly
HIV infection, high-risk MSM	High-risk MSM 1 year after HIV infection	1	High-risk MSM with diagnosed HIV infection are routinely tested for HCV
High-risk MSM (HIV negative)	High-risk MSM until 1 year after HIV infection	0.5	High-risk MSM are likely to come regularly for testing infectious diseases
HIV infection (not MSM)	Other HIV infected patients since time of infection	0.2	Assumption: a considerable proportion of HIV infected patients are still late presenters

The rates are based on assumptions and discussion with experts. DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDU, injection drug user; MSM, men having sex with men.
*We conducted two separate analyses: in one, this rate was 0.5/person-year throughout, and in the other 0.05 until 1990, 0.15 between 1990 and 1995, and 0.25 between 1995 and 2018.

3.5 Treatment with DAA

We assume that DAA treatment was available from 2014 to diagnosed patients in METAVIR stage F2 or higher, and from 2018 to all patients regardless of liver disease stage. This follows approximately the policy and availability in Switzerland, as shown in Section 2. Since there are no longer any restrictions on the eligibility to treatment, we did not study any more restrictive treatment scenarios.

Transition from diagnosis to treatment is based on a time-to-event function, where the basic assumption is that if the patient was eligible and treatment was available at the time of diagnosis, the time from diagnosis to treatment is sampled from a uniform distribution between 0 and 1 year, resulting in an average delay of 6 months. For people diagnosed between 2014 and 2018 but who were at disease stage F0 or F1, the same delay was applied from the beginning of year 2018. For people who were already diagnosed before 2014, we applied a considerably longer delay (starting from 2014 if already at F2 or above by then; or, if not, from either 2018 or the time of entering F2, whichever occurred first). After initial model runs, this delay was chosen to be sampled from a uniform distribution between 0 and 15 years.

We also do not account for the limitations of the early DAAs regarding genotypes. According to expert opinion, we consider 12 weeks for the treatment duration regardless of the HCV genotype and liver disease stage. We assume that the probability of SVR is 98% regardless of genotype. In the model, 98% of patients therefore moved 12 weeks after starting treatment to the cured stage, and the remaining 2% stayed in the treatment stage. As the model does not account for possible liver disease regression, going to the “cured” stage will not affect the stage of liver fibrosis.

In our model, we keep the patients who fail treatment in their respective “on treatment” (first or second) health states also after the end of the respective treatment, until either death, second treatment, or clearance.

In case of a treatment failure, the patient should continue with a second course of treatment, with a different regimen. We assume that there is a delay of at least another 12 weeks from ending first treatment to determination of the treatment response. After this, the second treatment will start immediately for half of the patients. For simplicity and due to the fact that second-line treatment is rare, we use the same parameters as for first-line treatment, despite there being differences in reality. After second-line treatment, no further options exist, and the patients will stay viremic for the rest of their lifetime. Due to the high cure rate, such cases are very unlikely.

3.6 Mortality

We define four different hazard functions for mortality in order to capture death due to liver disease, IDU, HIV, and other causes.

Liver related mortality is assumed to be zero in the early stages of fibrosis (F3 and below). The proposed values for rates from F4, DC, HCC and LT are given in Table 7.[90] These parameters are fixed rates that do not depend on age, gender or other baseline characteristics. We also conducted a sensitivity analysis using the upper limit of the range for liver related mortality.

Drug use related mortality, 0.0017 per person-year, was derived from the standardized mortality ratio of 5.5 and average all-cause mortality rate of 0.0001 to 0.001.[6,81] We chose a rate lower than most literature estimates. This may underestimate the drug related mortality in the past, but should be more appropriate for the future. Moreover, the parameterization of "drug use related mortality" based on the standardized mortality ratio contains also liver- and HIV-related mortality, whereas in the model these causes were included separately and "drug use related mortality" was intended to contain only deaths directly related to the use of drugs. The low drug use related mortality is therefore in line with this latter assumption. Also, in our model active drug users include persons on substitution therapy, which further explains the low drug related mortality rate among this population. HIV-related mortality was assumed to be 2/100,000 person-years in 2000 to 2007 and 1/100,000 person-years in 2007 to 2014.[83]

We approximated the background mortality with all-cause mortality as reported by the Federal Statistical Office (FSO) for Switzerland (Appendix D).[81] Although in reality this data includes also deaths due to the explicitly modelled causes (liver disease, drug use, HIV), these can be expected to contribute only minimally to the overall population level mortality in Switzerland, and it is plausible to use all-cause mortality as a proxy for background mortality.

Table 7. Rates of mortality from F4, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) and liver transplantation (LT).

Mortality Rate	Value: main analyses*	Value: sensitivity analysis*
$F4 \longrightarrow death$	0.010	0.034
$DC \longrightarrow death$	0.129	$\begin{cases} 0.550, & \text{for the first year} \\ 0.156, & \text{thereafter} \end{cases}$
$HCC \longrightarrow death$	0.430	$\begin{cases} 0.770, & \text{for the first year} \\ 0.480, & \text{thereafter} \end{cases}$
$LT \longrightarrow death$	$\begin{cases} 0.160, & \text{for the first year} \\ 0.057, & \text{thereafter} \end{cases}$	$\begin{cases} 0.331, & \text{for the first year} \\ 0.069, & \text{thereafter} \end{cases}$

*All values are per year.

4 Transforming the model's output into a realistic representation of the Swiss HCV infected population

4.1 Main analysis

In this section, we present how we transformed the output of the simulation into a realistic representation of the Swiss HCV infected population. First, we analyzed the notification data from the FOPH and the SCCS cohort data to determine the currently diagnosed HCV infected population which we denote from now on as *known population*. We then make assumptions about the currently undiagnosed infected population and future infections, based on the information on the known population and expected disease dynamics; this group will be denoted as the *unknown population*. We will give the simulated patients weights defining how many real patients each simulated patient represents.

From each simulated patient, we collect the indicators that can be matched to the observed data. These include the year of diagnosis, the fibrosis stage (or presence of DC or HCC) at the time of diagnosis, as well as the following baseline characteristics: year of birth, age at infection, sex, country of origin, intravenous drug use (ever), high-risk MSM behavior, HIV coinfection (at any time), and alcohol consumption. Table 8 and Table 9 show the output of the simulation and baseline characteristics for a randomly chosen patient. The patient was born in 1964 and infected at the age of 40.17 years, and she entered a diagnosed state (states 11-15, 33, 39, 45) at the time of 1.29 years since infection. Therefore, her year of diagnosis can be calculated by summing 1964+40.2+1.3, meaning she was diagnosed in 2005, and infected in 2004. From the baseline characteristics, we can also for example find out that the patient is female, HIV uninfected, born in Switzerland, and never used intravenous drugs. We also note that the transition from undiagnosed (states 1-10, 31-32, 37-38, 43-44) to diagnosed happened from state 7 to state 12, meaning that she was in fibrosis stage F1 (represented by states 2, 7, 12, 17, 22 and 27) at the time of diagnosis.

Calendar time T_i for each simulated patient *i* can be calculated as

$$T_i = t + bl_i(birthyear) + bl_i(age)$$

where t is the time variable in the raw output of the simulation, and bl_i the set of baseline characteristics for patient *i*.

Table 8. Raw output of the model for one simulated patient. Each state represents a combination of stages of liver disease, infection and cascade of care.

State 1	State 2	State 3	State 4	State 5	State 6	State 7	State 8	State 9	State 10	State 11	State 12	State 13	State 14
0	**0.29**	NA	NA	NA	NA	0.5	NA	NA	NA	NA	**1.29**	**4.61**	**8.81**
State 15	**State 16**	**State 17**	**State 18**	**State 19**	**State 20**	**State 21**	**State 22**	**State 23**	**State 24**	**State 25**	**State 26**	**State 27**	**State 28**
9.96	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
State 29	**State 30**	**State 31**	**State 32**	**State 33**	**State 34**	**State 35**	**State 36**	**State 37**	**State 38**	**State 39**	**State 40**	**State 41**	**State 42**
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**11.49**	NA	NA	NA
State 43	**State 44**	**State 45**	**State 46**	**State 47**	**State 48**	**State 49**	**State 50**	**State 51**	**State 52**				
NA	NA	**12.92**	NA	NA	NA	NA	NA	NA	**14.93**				

The states that the patient attended are shown in red. All times are in years. NA, not applicable (i.e. the patient was never in this state)

Table 9. Baseline characteristics of one simulated patient.

Variable	Value
Age at infection	40.17
Gender	0 [female]
Year of birth	1964
HIV infection time	999
MSM	0 [no]
IDU starting time	999
IDU stopping time	999
Country of origin	0 [Switzerland]
Alcohol use	0 [moderate or abstinent]
Genotype	1

The size and characteristics of the known population were determined from the notification data of the Federal Office of Public Health (FOPH) and the data of the Swiss Hepatitis C Cohort (SCCS). The FOPH notification data had a total of 49,943 records. Records indicating the death of the patient were excluded from our analyses. Records of patients who were noted to have been treated with pre-DAA treatment were weighted with 0.5 to take into account that about half of the treated patients would achieve SVR and thus should be excluded from the model, since the simulation did not include the pre-DAA treatment. We then collected for each patient the following characteristics:

year of notification; sex; year of birth; country of origin; types of exposure; presence of cirrhosis and/or HCC; acuteness of infection. Year of birth and country of origin were further combined into categories. Birth years were categorized as <1937, 1937-47, 1948-57, 1958-67, 1968-77, 1978-87, 1988-97, 1998-2007 and 2008-16. Countries of origin were grouped into four categories: Switzerland and Liechtenstein; Western Europe, Americas and Oceania; Eastern Central Europe, the Balkans and former Soviet republics; Southern Europe, Asia and Africa (Appendix C). Types of exposure were transformed into two variables: IDU (using the IDU exposure variable directly); and MSM (notifications indicating sexual exposure and homo/bisexual preferences). Only 58% of all records had all variables available. Due to the large number of missing data especially regarding routes of exposure, we corrected the distribution of the characteristics by imputing missing values. All notification records with a particular variable missing were distributed to different values of the missing variable in the same relation as the values were among those records with otherwise identical characteristics. This approach is in line with the "missing (not completely) at random" assumption: the probability to have a missing value does not depend on the missing variable itself, but it may depend on the other variables. The assumption may not be completely true: for example, people with previous drug use may be reluctant to report this. Since the missing values were most common among exposure routes, which also are important in the model for estimating the rate of diagnosis, the uncertainty may influence the characteristics of the population.

In the next step, we used the SCCS data to refine the distribution of fibrosis stage at diagnosis, and to include the distribution of alcohol consumption and HIV co-infection. The variable in our distribution representing the presence of cirrhosis or HCC was updated to include also information on the fibrosis stage. Each patient was also assigned an alcohol consumption pattern (abstinent or rare; moderate; excessive) and HIV status. All analyses were done in a similar way to filling the missing data: we calculated the distribution of the desired variable among those with otherwise matching characteristics. If there were no patients in the SCCS for some combination of baseline characteristics, we assumed an equal distribution across alcohol consumption categories, and that HIV coinfection coincided with MSM behavior. These approaches may not be completely realistic as there are also other groups who may be HIV-HCV coinfected (IDU, people originating in countries with high prevalence for both diseases). However, for the purposes of the model, this simplifying assumption is not expected to play a major role. The main effect of HIV coinfection in the model is to

allow a faster detection of HCV. If a large proportion of the low-risk population infected with HCV would be coinfected with HIV, it would increase the proportion of detection among these individuals.

Each simulated patient i was then given a weight w_i according to the formula

$$w_i = \frac{n_{real,i} N_{sim}}{n_{sim,i} N_{real}}$$

where $n_{real,i}$ and $n_{sim,i}$ correspond to the total number of patients with the same characteristics as patient i, in the simulation and the observations (FOPH data) respectively, and , N_{sim} and N_{real} the total number of simulated and observed (FOPH data) patients respectively.

To estimate the unknown population, we first calculated the distribution of years of infection from the simulated weighted data (i.e. the simulated cohort representing the currently diagnosed population, with weights determined as above). The potential unknown population was divided according to the country of origin (Switzerland versus others), and both groups were estimated separately. For the population of Swiss origin, we assumed that the number of annual new infections would follow approximately the distribution of infection years among the already diagnosed people, although the relative proportion of undiagnosed would be expected to increase over time. We also assumed that the new infections would peak in the early 1990s, during the time of the major changes in drug policy, and that the total viremic population in 2016 would be about 40,000. The number of new infections every year was chosen so that these conditions would be valid, assuming that the distribution of characteristics is the same as among the known population infected in that year. For the patients of foreign origin, we assumed that the number of new infections would decline over the years, to take into account the healthcare related epidemics. Since the model does not include the current place of residence, the simulated patients of foreign origin also include those that may still be abroad but will later migrate to Switzerland. Between years 2016 and 2029, we assumed that the number of new infections would remain constant on the level of 2015.

We assigned weights to simulated patients based on the assumptions above using the same method as for the currently diagnosed population.

4.2 Sensitivity analyses

In addition to the sensitivity analysis regarding liver-related mortality described in Section 3.6, we conducted four sensitivity analyses including the entire comparison of scenarios, by only changing

the weights determined using the approach shown in Section 4.1. In sensitivity analyses 1 and 2, we increased or decreased the total size of the undiagnosed population, respectively. In sensitivity analysis 1 we increased the number of newly infected individuals up to year 1990 who still remain undiagnosed approximately three-fold. In sensitivity analysis 2, this number was halved.

In sensitivity analyses 3 and 4, the size of the population was kept as in the main analysis, but the proportion of high- and low-risk individuals among the patients not diagnosed by 2016 was modified. For this purpose, we defined high-risk population as IDU and high-risk MSM, and low-risk population as the rest. In sensitivity analysis 3, we decreased the size of the undiagnosed low-risk population infected each year to a half of the original, and in turn increased the number of undiagnosed high-risk individuals infected in the same year to have the same total as in the main analysis. In sensitivity analysis 4, we did the opposite.

Sensitivity analyses 1 to 4 were all based on the assumptions with dynamic fibrosis progression (according to the parameters as by Razavi *et al*),[7] and a low but increasing diagnosis rate among IDU in the past. All six scenarios for future screening were included. The analysis described in Section 3.6, where higher mortality rates for liver related causes were applied, will be referred to as sensitivity analysis 5. In this case, we used the assumptions of dynamic fibrosis progression but high IDU diagnosis rate. For sensitivity analysis 5, we only modelled the baseline scenario.

5 Model projections in the past: comparison of analyses and data

5.1 Alternative analyses

In this section, we present the main results from the time period 1970-2015 from four alternative models (color of the curves refers to Figures 2, 3, 4, 5, 6, 7 and 8):

- Dynamic fibrosis progression, high diagnosis rate among IDU (black curves)
- Constant fibrosis progression, high diagnosis rate among IDU (red curves)
- Dynamic fibrosis progression, low diagnosis rate among IDU (blue curves)
- Constant fibrosis progression, low diagnosis rate among IDU (green curves)

Dynamic fibrosis progression refers to the parameterization according to Razavi *et al.*,[7] and constant fibrosis progression to the parameterization according to Poynard *et al.*[17] High diagnosis rate among IDU means a constant rate of 0.5/person-year in the past, low diagnosis rate increased over time until 0.25/person-year. The rationale and details of these alternatives are described in Section 2.

When available, the model projections are compared with original data (grey dashed curves).

5.2 New infections

According to the models with high IDU diagnosis rate, the annual number of new infections remained around 800 until the early 1980s, and increased thereafter, reaching a peak of 2000 annual infections in the mid-1990s (Figure 2). Since 1997, the annual infections have decreased, going below 400 by 2015. There were no differences between the models with dynamic and constant fibrosis progression rates.

If we assumed a lower diagnosis rate among IDU, the peak levelled out and appeared in general 5-10 years earlier, with over 1500 people infected annually between 1985 and 1995. Based on the knowledge that we have on the peak in intravenous drug use, this is likely to be more realistic. It should be noted that the model does not consider most patients who were infected and died undiagnosed. Because of this, the projected number of patients infected until 1971 was also considerably lower than thereafter: this does not mean that there would have been a true increase in 1972. Because of the mortality related to drug use, the curves for all analyses do not exclude the possibility that the actual peak may have been earlier. In 2015, the back-calculation predicted slightly over 200 new infections; based on this, we assumed that 200 new persons would be newly infected every year between 2016 and 2029.

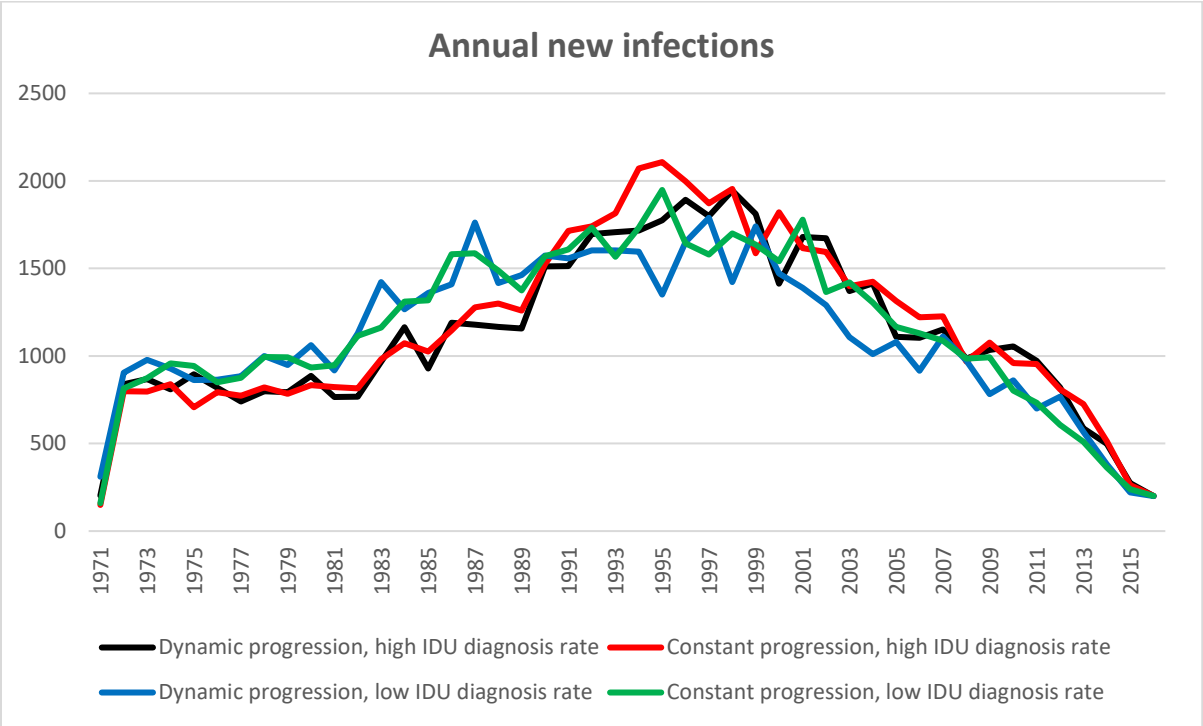

Figure 2. Annual new infections 1971-2016 according to the model. *The figure excludes patients who were expected to have died, or achieved SVR with pre-DAA treatment, before 2016. IDU, injection drug user.*

5.3 New diagnoses

The new diagnoses were directly matched to the notification data, and we therefore expect no differences between the analyses. The total number of diagnoses predicted by the model was below the notification data, which is explained by patients who by definition were not included in the model (such as those with documented death, or who were expected to have been successfully treated) (Figure 3).

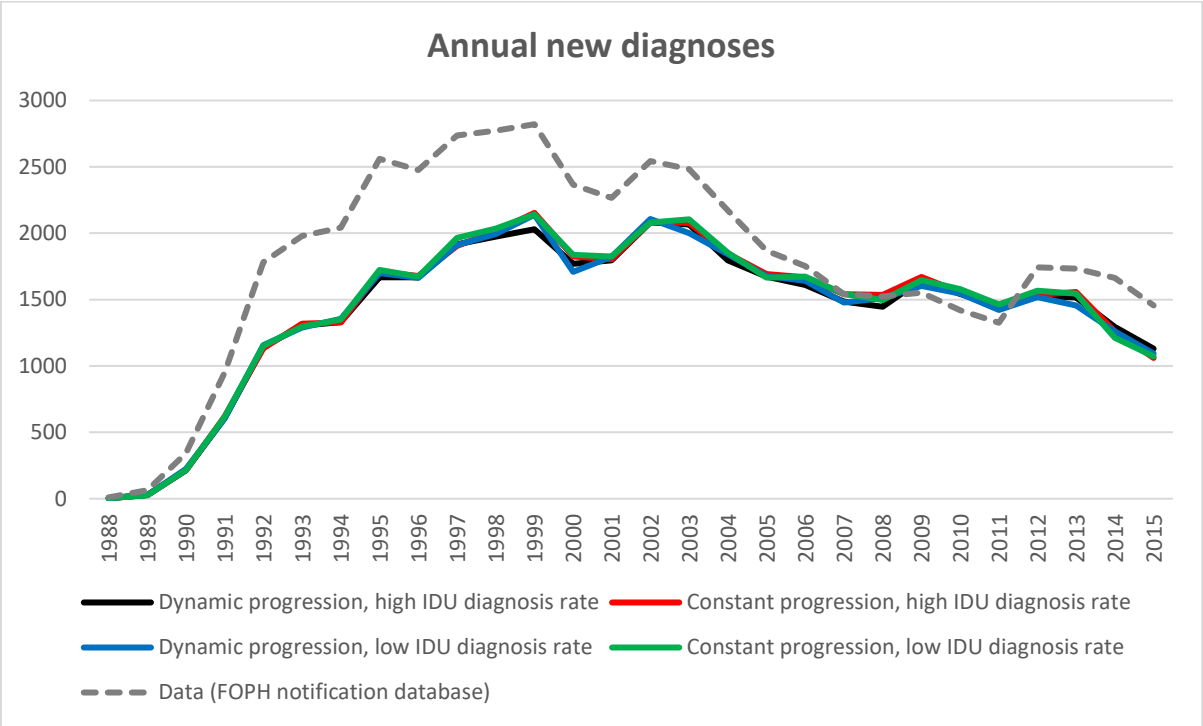

Figure 3. Annual new HCV diagnoses 1988-2015 according to the model and the Federal Office of Public Health (FOPH) notification data. *IDU, injection drug user.*

5.4 HCV related mortality

The increasing pattern in mortality was seen in all four analyses (Figure 4). Mortality in the analyses with constant fibrosis progression rates was about half of that in analyses with dynamic progression, reflecting that the disease progression was on average slower. There were no differences between the analyses with different IDU diagnosis rates.

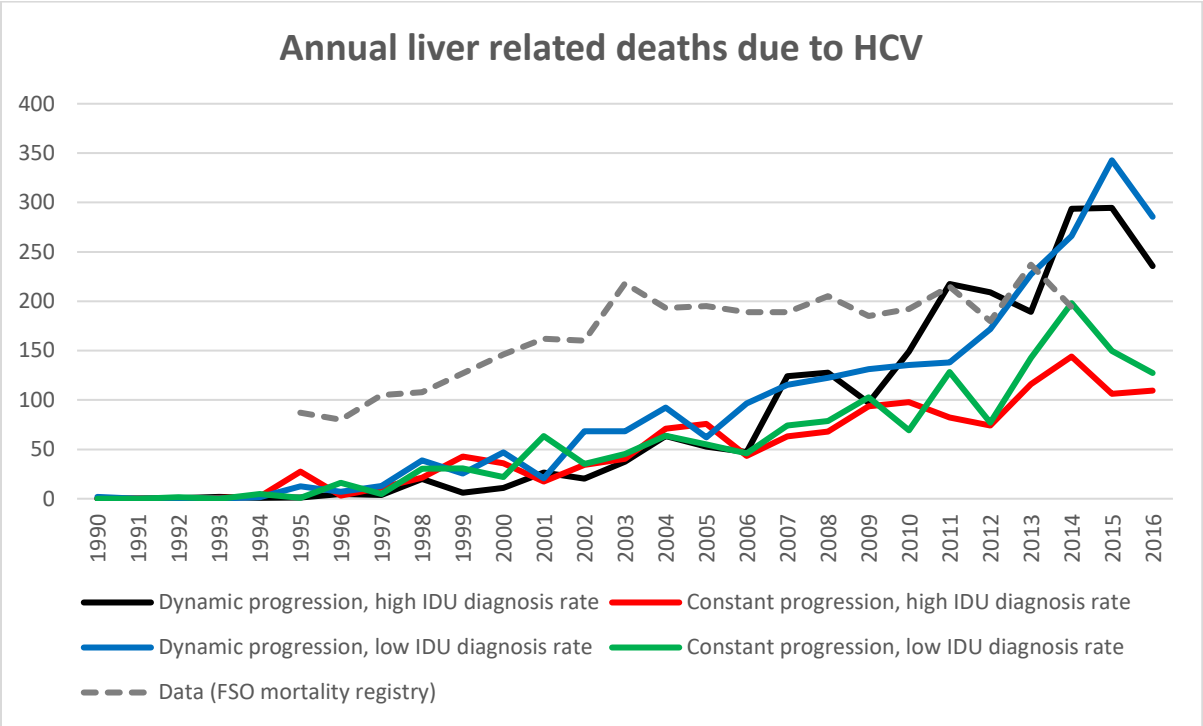

Figure 4. Annual liver related deaths due to hepatitis C virus (HCV) 1990-2016 according to the model and the Federal Statistical Office death registry data. *IDU, injection drug user.*

We compared the mortality predicted by the model to the HCV related mortality from the database of the Federal Statistical Office (FSO). In Figure 4, the dashed curve shows all deaths where hepatitis C (ICD-10 code 17.1 or 18.2) was mentioned as any factor: primary cause, or initial, consecutive, or concomitant condition. The deaths predicted by the models with dynamic fibrosis progression matched well with these data in the recent years (2012-13), with about 200 to 250 deaths every year, but substantially lower in the earlier years. The mortality in the analyses with constant fibrosis progression was lower than the data throughout, although it also became close to the observed data in 2014. Moreover, our model did not show any liver-related deaths prior to 1990. The model did by definition exclude patients who could have been expected to have died until now. For example, up to about one third of the cases notified in the 1990s were excluded from the model. Some of the registered deaths could be among these patients. This also explains why our model projects no deaths before 1990: patients infected in the early years were either excluded from the model since the aim was to model the currently alive and in particular undiagnosed population, or they already died of other causes before progressing into liver related death. It should be noted that the data are not directly comparable with the model's output. The model measures essentially liver related

mortality among all HCV infected people. The data contain only patients who were known to be HCV infected i.e. diagnosed, but may contain deaths not related to liver disease, such as deaths related to intravenous drug use or HIV coinfection. In Figure 5 we show mortality estimates from the FSO data using alternative definitions. If we only include deaths with ICD-10 code B18.2 (chronic hepatitis C) as any cause, the number of deaths was lower until 2002, but followed the original curve thereafter. This may be due to misclassification in the earlier years between acute and chronic infection, but also due to more patients dying of other causes during acute infection. If we included both codes for HCV, but in addition required a condition indicating either cirrhosis or hepatocellular carcinoma, the curve was flatter, being about half of the original level. Inclusion of only cases where hepatitis C was mentioned as a primary cause were substantially lower, staying at 10 to 20 cases every year throughout the time period. Moreover, it has been shown using probabilistic linkage that based on data from the SCCS, more than half of the cases that were determined to be associated with hepatitis C had HCV mentioned as a cause on the death certificate.[83]

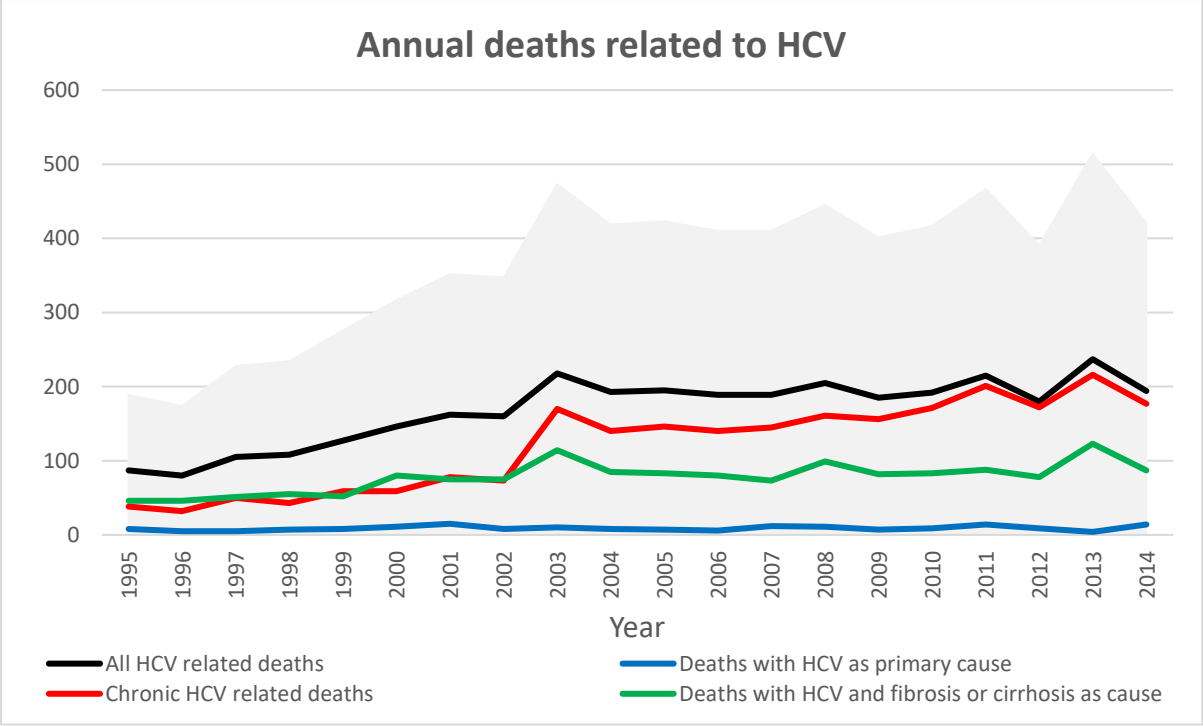

Figure 5. Comparison of annual number of hepatitis C virus (HCV) related deaths in Switzerland from the Federal Statistical Office death registry using different definitions. *The grey shaded area represents all HCV related deaths corrected by a correction factor derived from Keiser et al.*[83]

Based on this information, we can only conclude that the upper limit of HCV related mortality is around 2 times the highest curve (400-500 cases per year), but it is not possible to make further

reliable conclusions about the level or shape of the true mortality. In our model, HCV related mortality includes only deaths that are due to liver disease, which would advocate for the use of a definition which also requires the presence of a liver related disease. However, we are not aware how systematically the different causes have been recorded.

5.5 End-stage liver disease

The numbers of annual cases of DC and HCC projected by the model followed the same pattern as liver related deaths, increasing over time (Figure 6, Figure 7). In both analyses with dynamic fibrosis progression, on average about 150 cases of DC and 250 cases of HCC were expected annually during the last few years. In the analyses with constant fibrosis progression, the level was about half of this.

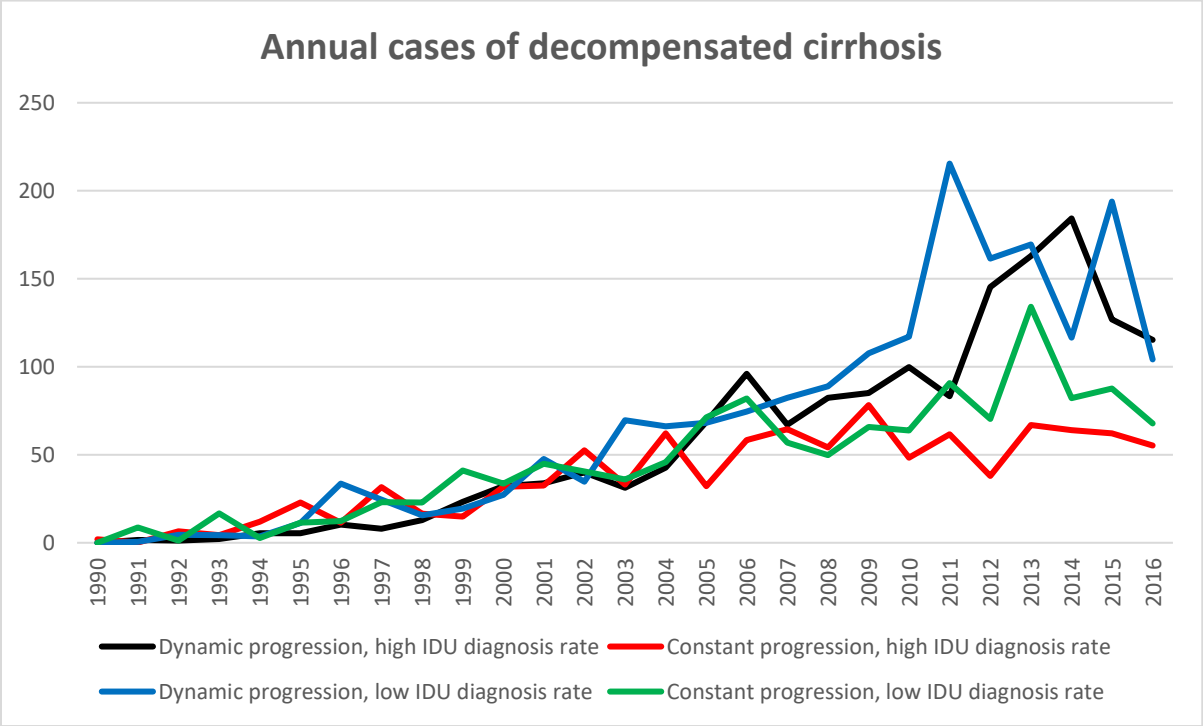

Figure 6. Annual cases of decompensated cirrhosis among HCV infected patients 1990-2016 according to the model. *IDU, injection drug user.*

A comparison of the model projections and data from the Swiss cancer registry shows that the model projections were lower than expected until about 2010, but in line thereafter, if we assumed dynamic fibrosis progression (Figure 7). The data were calculated from the total number of liver related cancers, assuming that 90% of all liver cancers were HCC, and 40% of HCC attributable to HCV.[101,102] Although this is in line with literature estimates, the data need to be interpreted with

caution. The difference in the early years may partly be due to the same reason as the difference in mortality, i.e. exclusion of patients known to have died according to the notification data.

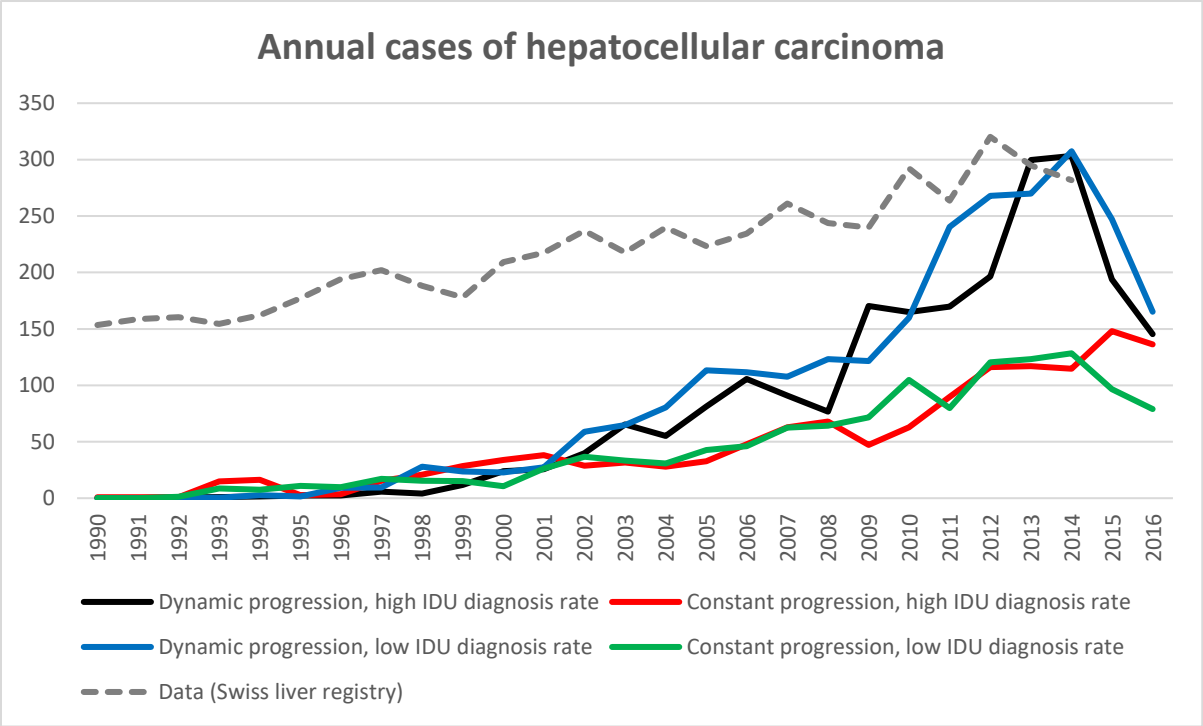

Figure 7. Annual new cases of hepatocellular carcinoma among HCV infected patients 1990-2016 according to the model and the Swiss cancer registry data. *The cancer registry data are available at http://www.nicer.org/en/statistics-atlas/cancer-incidence/, and were corrected using a constant coefficient representing the share of HCV related cancers.*

5.6 Treatment

We assumed that from 2014, patients in stage F2 or higher may be treated. The lower number of patients treated in the analysis with constant progression rates is again a consequence of the overall slower disease progression. Moreover, the analysis with lower diagnosis rates showed a larger number of patients treated than the analysis with higher past IDU diagnosis rates. This is probably due to the fact that patients are in a more advanced stage of the disease on average, therefore being eligible for treatment in 2014 already. The numbers in three out of four analyses are still higher than observed, the total numbers of patients being treated reached between 7,100 and 12,400, as compared with 7,900 in the sales data (Figure 8). In reality, some patients who according to the model were treated, may only receive treatment in 2018 or later.

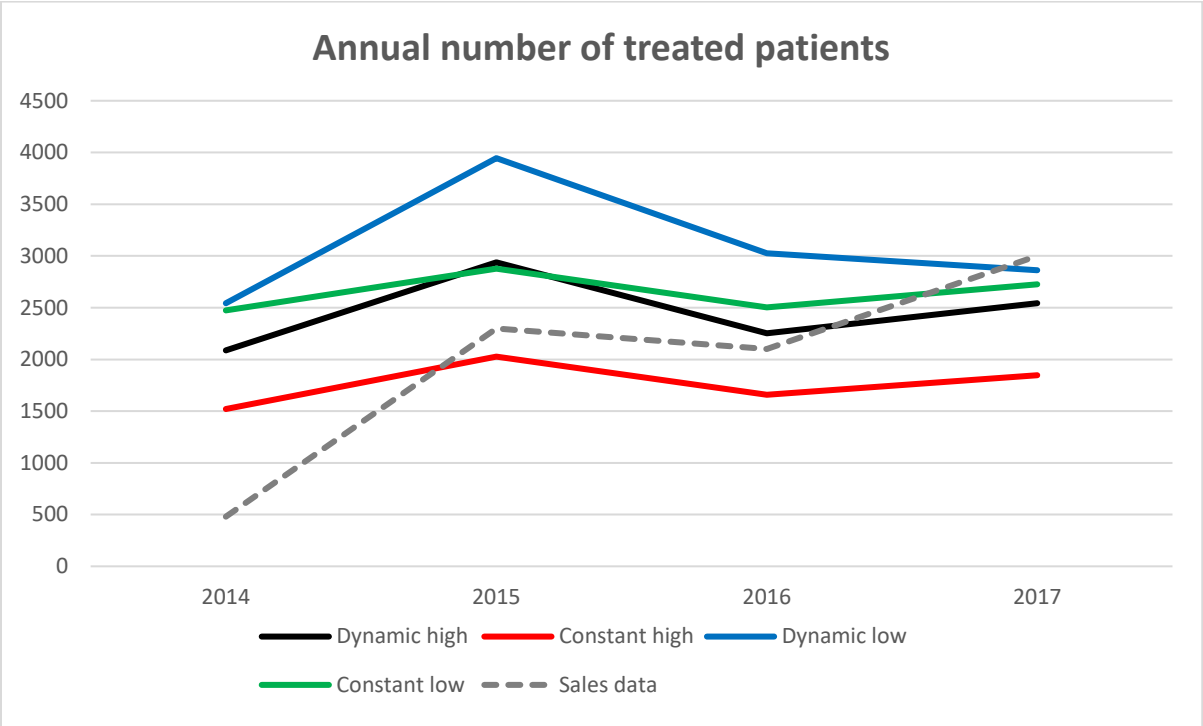

Figure 8. Annual number of treated patients 2014-2017 according to the model and sales data.

5.7 Characteristics of the viremic population

Since the current location (in Switzerland or abroad) is not modelled explicitly, the graph can only be seen as an approximation for the true HCV infected population of Switzerland (Figure 9): in particular, the "unknown foreign population" (red area) may be an overestimation. The total population size in all analyses in 2016 is slightly above 40,000, which is in line with the estimates of the sensitivity analysis (36,000-43,000).[1] According to the model, about one third of the infected population was undiagnosed in 2013 before DAA therapy became available. Since then, the proportion has decreased. In the analysis with constant progression rate, the proportion of patients in more advanced stage of liver disease was higher (Figure 10).

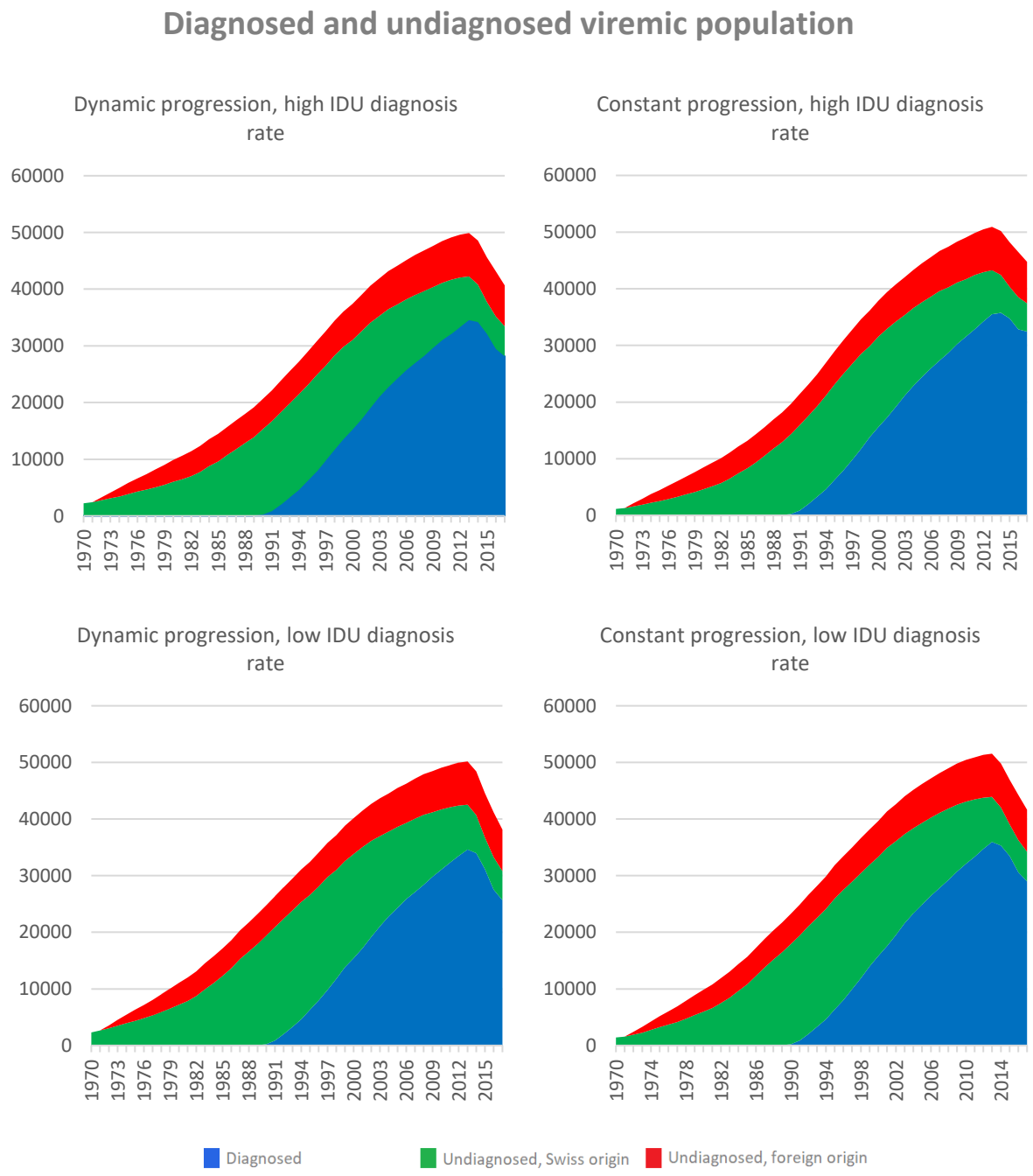

Figure 9. Diagnosed and undiagnosed viremic population in Switzerland 1970-2016. *IDU, injection drug user.*

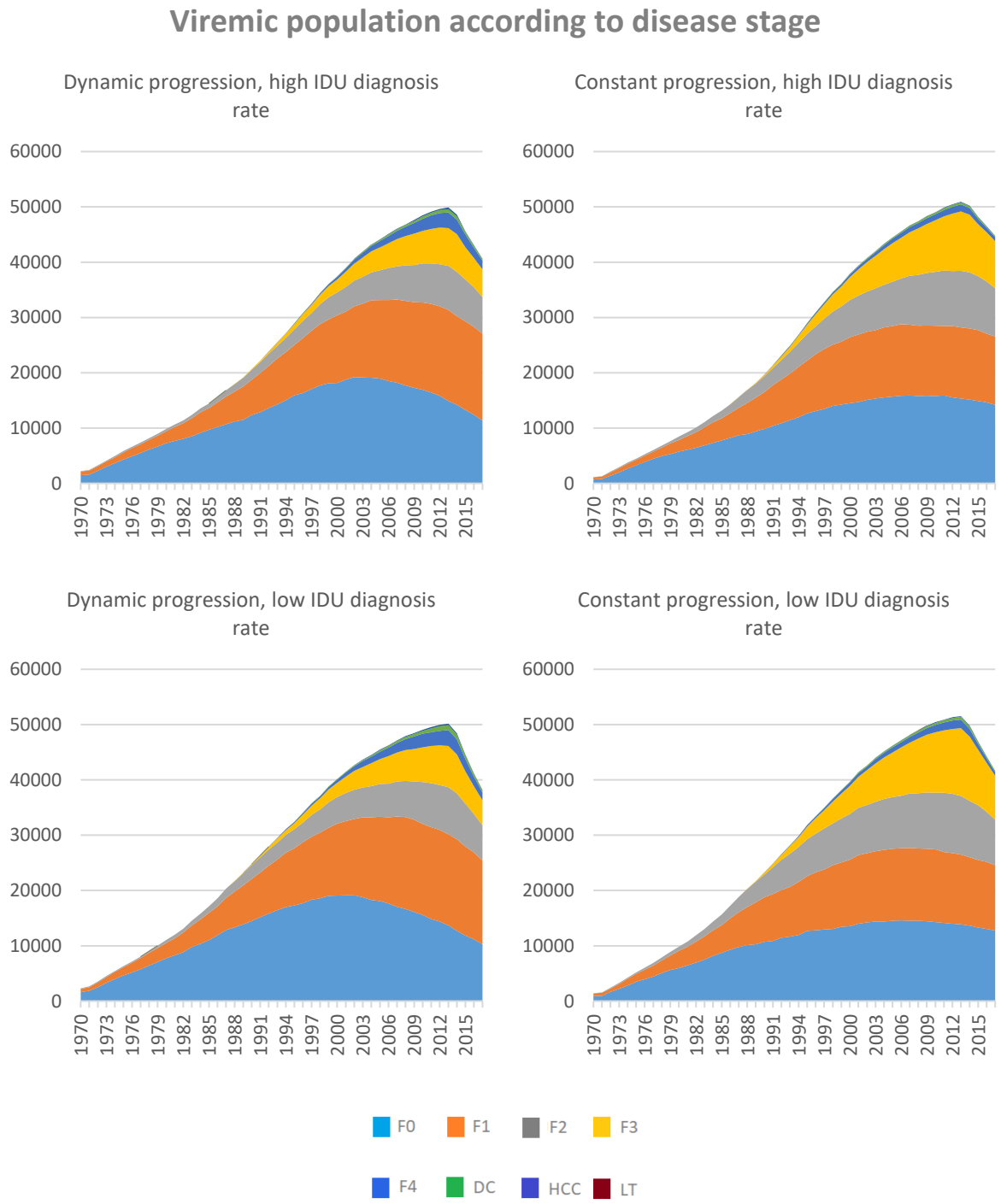

Figure 10. Viremic population according to stage of liver disease 1970-2016. *DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; IDU, injection drug user; LT, liver transplantation.*

5.8 Sensitivity analyses

The sensitivity analyses 1 to 4 did not differ in terms of the diagnosed population, and we thus did not expect any differences in the outcomes prior to 2018. These sensitivity analyses will be presented in detail in the next section.

In the sensitivity analysis 5, we used the higher limits for liver-related mortality (Table 7). Figure 11 shows a comparison of liver related mortality in the corresponding main analysis (with dynamic fibrosis progression and high IDU diagnosis rate). Despite the higher average mortality, the number of liver related deaths did not differ much from the main analysis.

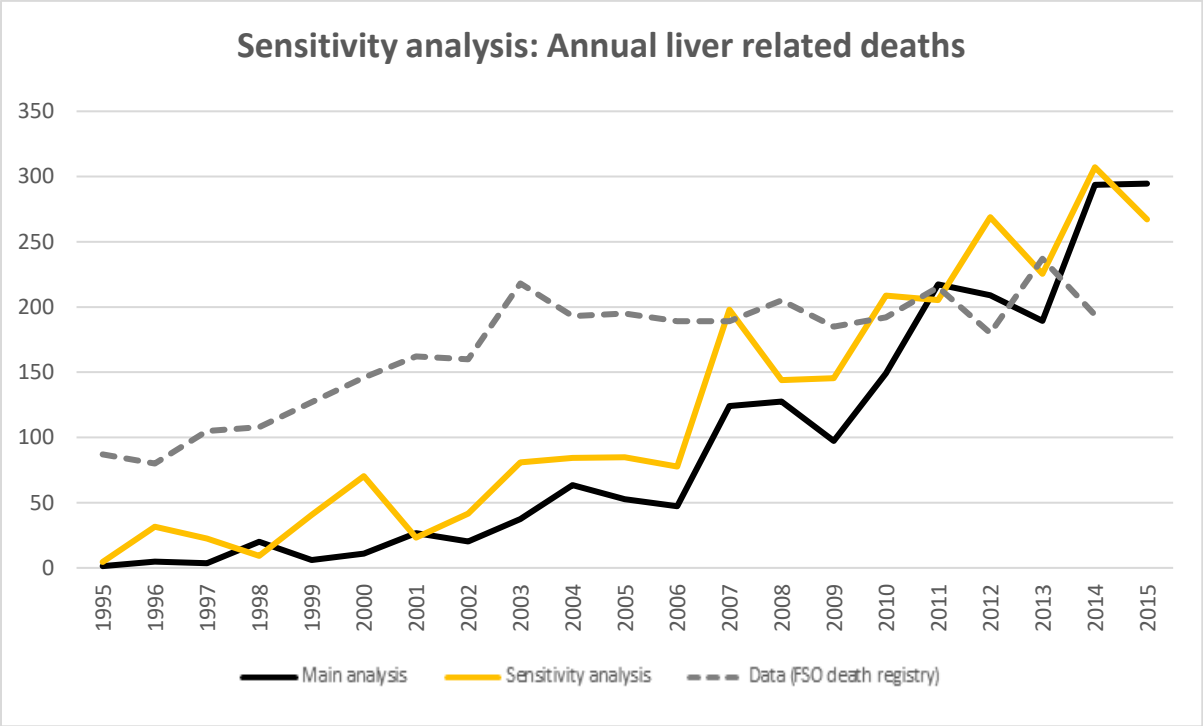

Figure 11. Liver related deaths: comparison between one of the main model analyses, sensitivity analysis with higher mortality rate, and the Federal Statistical Office (FSO) data.

6 Main results: Different screening scenarios for Switzerland

6.1 Introduction to results

We present the results of the model for six screening scenarios. In the *baseline* scenario, patients are screened as before 2018 (see Table 6). In the *intensified IDU screening,* the rate of screening active IDUs is increased to 1.0/person-year. In the *former IDU screening* scenario, patients with a history of IDU who have stopped using drugs are also screened with a rate of 0.5/person-year. In the *origin based scenario* patients who are originating in the fourth country group (South Europe, Asia and Africa) are screened with a rate of 0.5/person-year. In the *birth cohort screening* scenario, individuals born between 1951 and 1985 are screened with a rate of 0.5/person-year. Finally, we included a universal screening scenario where a screening at a rate of 0.5/person-year is applied to all population groups. All scenarios are built on the baseline scenario, meaning that testing according to the baseline scenario is always included separately, and e.g. in the universal screening scenario active IDU and HIV coinfected MSM are tested faster than patients outside specific risk groups.

We performed the analysis using the same four alternative parameterizations as in Section 5. **However, as the differences between the analyses were minimal, we only present the results of two of the four analyses for clarity: the analysis with dynamic fibrosis progression and low past IDU diagnosis rate; and the analysis with constant fibrosis progression and high past IDU diagnosis rate.** The two remaining combinations are shown in Appendix E.

6.2 New diagnoses

The number of new diagnoses was between 1,000 and 1,500 during the years preceding 2018 (see Section 5.3 for details). The decrease in the baseline strategy (600 to 700 diagnoses expected in 2018) is due to the decreasing number of undiagnosed patients in the population groups that are easy to identify as high-risk, such as active IDU and HIV coinfected MSM (Figure 12). Preliminary data on notifications for 2018 suggests that this may be an underestimation, meaning that the rate of diagnosis in some patient groups is higher than expected. This difference could also be partly explained by possible double-counting of cases after the partial anonymization in 2011: this could have led to an overestimation of the diagnoses in the recent years, thus reducing the size of the remaining undiagnosed population. In the analysis with constant disease progression and high past IDU diagnosis rate, there was a temporary increase in the new diagnoses in 2019, which most likely is due to random variability.

More intensive screening of current IDU does not considerably increase the number of diagnoses in the next few years since this group is already tested frequently. However, in this scenario the rate of diagnosis remained at about 500 cases per year also in the long term. Since this is a patient group with ongoing transmission, it will be efficient to detect those who become newly infected. The results of screening former IDUs were sensitive to the IDU diagnosis rate in the past. In the analyses where diagnosis rate among IDUs was already high in the past, this strategy increased the number of diagnoses slightly during the coming few years, and the number of diagnoses remained also in the future at about 500 per year. If it was assumed that the diagnosis rate was however lower in the past, screening former IDUs increased the number of diagnoses considerably in the next years, with over 1,600 patients detected in 2018 and about 1,000 each year in the following years. With origin based screening, the new diagnoses were slightly above the baseline scenario, with similar pattern across the years. Highest increase in the near future is expected in scenarios where large population groups are regularly screened. With universal screening, about 8,000 new patients would be expected to be diagnosed within the next four years, compared with about 3,000 in the baseline scenario. The initial peak in new diagnoses also resulted in a decreasing trend: from year 2022 onwards, birth cohort and universal screening had the lowest number of annual diagnoses. It is however questionable if and how the assumed rate of 0.5/person-year could be achieved. Universal or birth cohort screening would require testing a large population with low prevalence, indicating a high cost per detected patient.

The results are not expected to be sensitive to the internal parameters of the model, because disease progression does not essentially influence the probability of being tested in a screening strategy. Assumptions about the currently undiagnosed population are however essential.

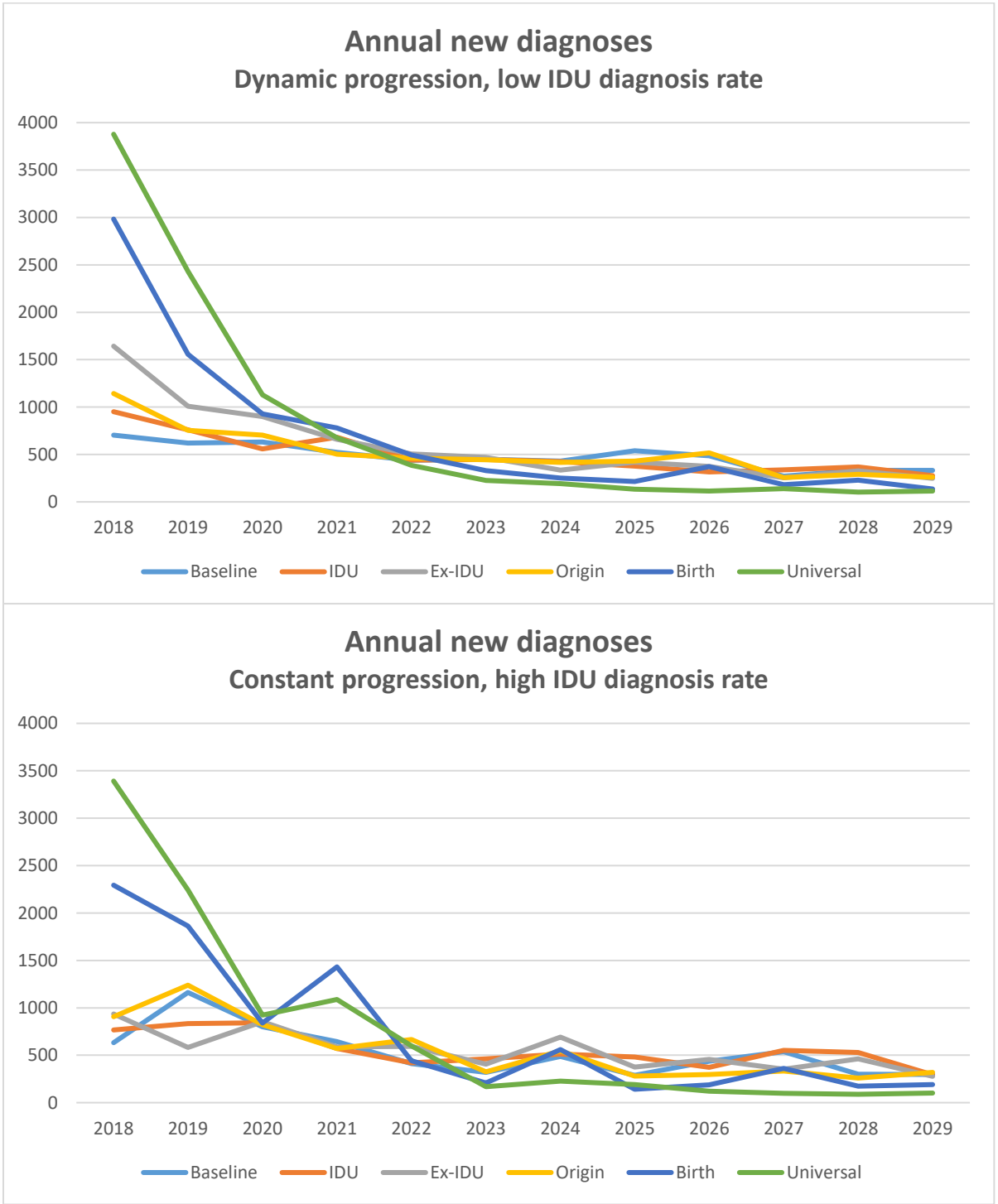

Figure 12. Annual new diagnoses 2018-2029 according to the model. *Analyses using dynamic fibrosis progression and low past injection drug user (IDU) diagnosis rate are shown in the upper panel, and constant fibrosis progression and high past IDU diagnosis rate in the lower panel. Different curves present different screening scenarios.*

6.3 Sustained virological response

The number of patients achieving SVR in 2018 was sensitive to the assumptions about fibrosis progression: with dynamic progression, over 7,000 patients were expected to be cured in 2018, compared with only about 4,500 with constant progression. In all analyses, the number of patients achieving SVR each year decreased over the next decade, but in the analyses assuming dynamic fibrosis progression, this decrease was faster, with a leftover of only about 200 additional patients achieving SVR in 2029. On the contrary, in the analyses with constant fibrosis progression, the decrease was smaller, and in 2029, still over 1,500 patients were successfully treated. The high number of new cured infections in 2018 is due to the changes in eligibility criteria: all patients in the model who were diagnosed before 2018 with HCV but were in stage F0 or F1, will be treated in 2018. This follows theoretically from the treatment initiation parameters, which do not account for factors such as the availability of treatment. In reality, it may be that the peak observed in 2018 will be distributed over a longer time period.

The differences in annual cured infections follow those in new diagnoses (Figure 13). In particular universal and birth cohort screening strategies will be able to cure over 1,000 patients more than the baseline scenario each year in the first years. Assuming constant disease progression the relative benefit is even larger. In the analyses with dynamic disease progression, there were no major differences between the scenarios after 2022 anymore. In the analyses with constant fibrosis progression, the differences were clearer: between 2024 and 2026, the scenarios screening current or former IDU, and from 2027, the baseline and origin based screening scenarios, had the highest number of patients achieving SVR. Universal and birth cohort screening strategies had clearly the least patients achieving SVR after 2026.

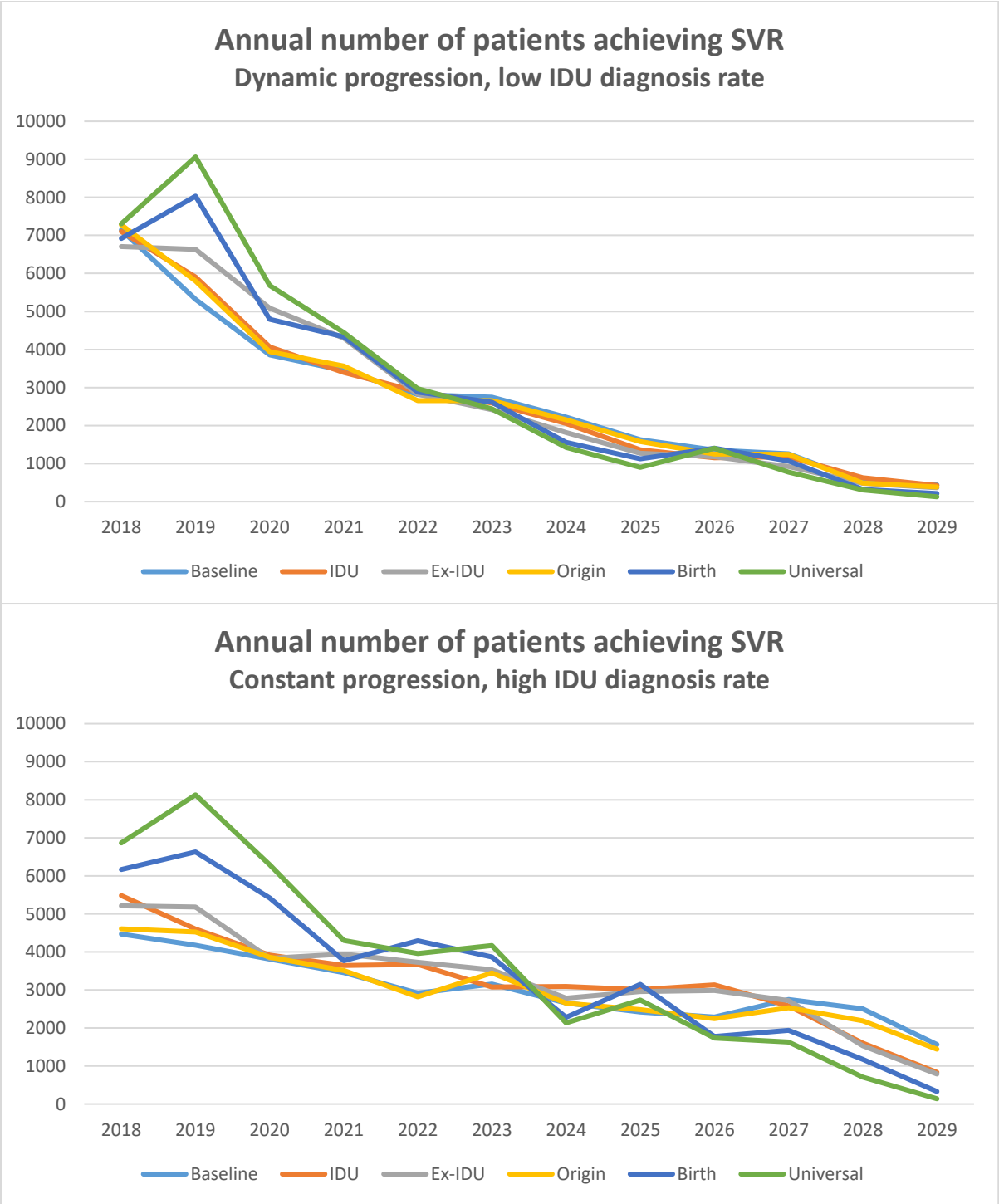

Figure 13. Annual number of patients achieving SVR 2018-2029 according to the model. *Analyses using dynamic fibrosis progression and low past IDU diagnosis rate are shown in the upper panel, and constant fibrosis progression and high past IDU diagnosis rate in the lower panel.*

6.4 Mortality

No considerable differences in liver related deaths between the strategies were seen (Figure 14): about 100 to 250 liver related deaths associated with HCV are expected in the future. There was a slight overall difference between the analyses: the trend in liver-related deaths was increasing in the analyses using constant fibrosis progression, but decreasing with dynamic fibrosis progression.

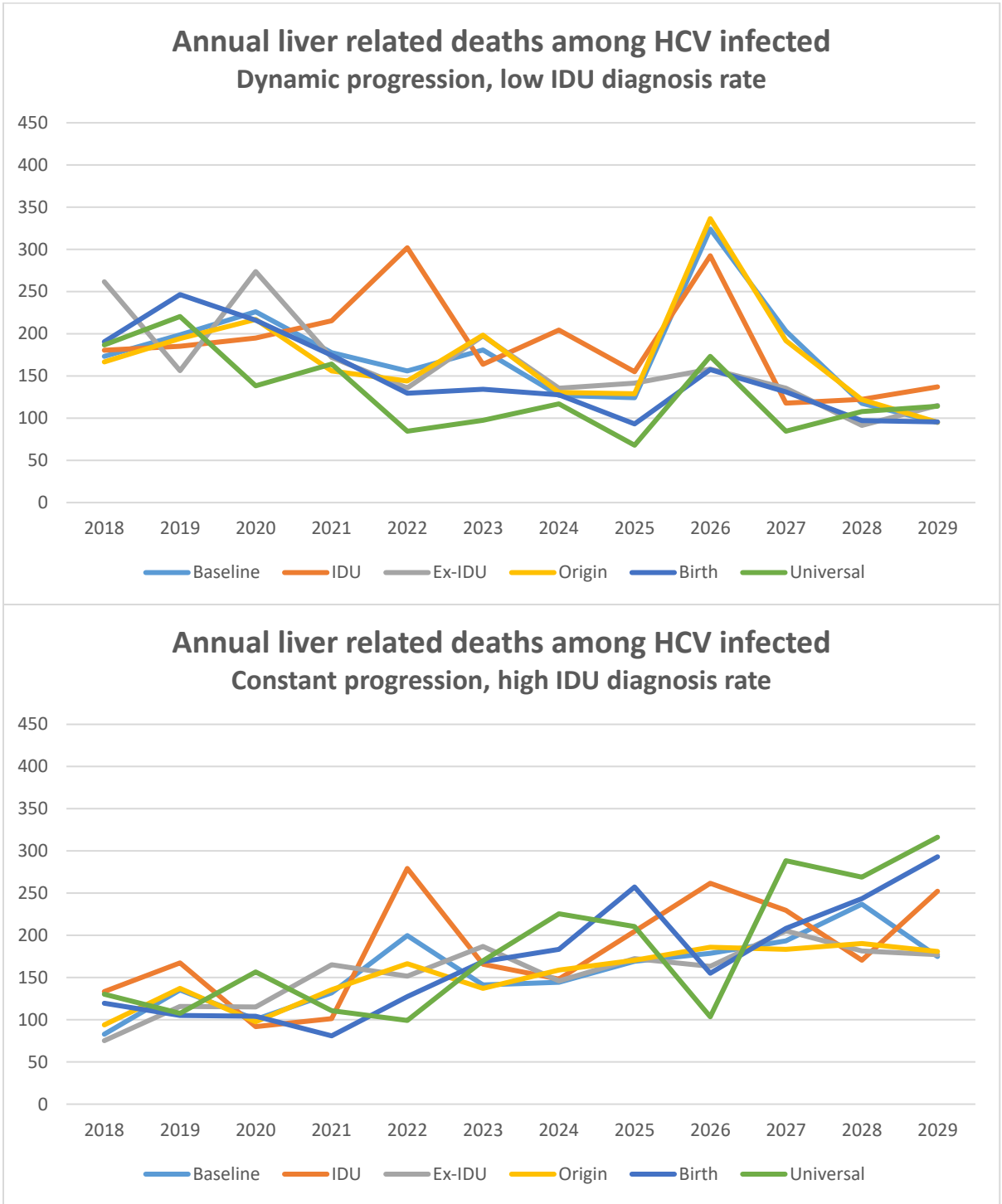

Figure 14. Annual liver related deaths among hepatitis C virus (HCV) infected patients 2018-2029 according to the model. *Analyses using dynamic fibrosis progression and low past injection drug user (IDU) diagnosis rate are shown in the upper panel, and constant fibrosis progression and high past IDU diagnosis rate in the lower panel.*

6.5 Characteristics of the infected population

The number of viremic patients decreased continuously in all scenarios (Figure 15, Figure 16). In 2017, the model predicted that depending on the assumptions, 11% to 22% of the people chronically infected with HCV had achieved SVR. This proportion grew rapidly in the next years: in 2023, the majority of people who were once chronically infected had been successfully treated. In the baseline scenario and the scenarios with intensified screening of current IDU and origin-based screening, there will be still around 5,000 viremic people by 2030 in Switzerland. In the analyses with constant disease progression, this number was even higher (6,000-8,000) in some scenarios. About half of the patients undiagnosed in 2029 were originating abroad. The origin-based screening did not change this result: a large part of the foreign-born patients do not come from the regions with very high HCV prevalence. With birth cohort screening, the viremic population decreased to about 2,000, and with universal screening, to below 1,000 patients, in 2029. The results of the screening of former IDU were sensitive to the assumption about past IDU diagnosis rate: In the analyses with low IDU diagnosis rate in the past, the size of the viremic population in 2029 was about 4,000 and thus lower than in the baseline scenario. In the analyses with high IDU diagnosis rate, the size of the viremic population was about 5,000.

The distribution of fibrosis stages among viremic patients did not differ considerably between scenarios either (Figure 17, Figure 18). However, there was a clear difference between the analyses with dynamic disease progression and constant disease progression. In the analyses with dynamic progression, about two thirds of the viremic population were in stages F0 or F1 during the first years. In the analyses with constant progression, the absolute number of patients in F0 and F1 was approximately the same as in the dynamic progression analyses, but there were more viremic patients in stages F2 and F3. The proportion of patients with cirrhosis or HCC was minimal, since the rate of diagnosis in these stages is already high regardless of scenario.

Depending on the scenario and analysis, about 150 to 350 HCV infected, viremic active IDUs are expected to be living in Switzerland in 2029 (Figure 19). The differences between screening strategies are small. Universal screening reduced the number of viremic active IDUs mainly in the analyses where the IDU diagnosis rate was low in the past, the difference not exceeding 200.

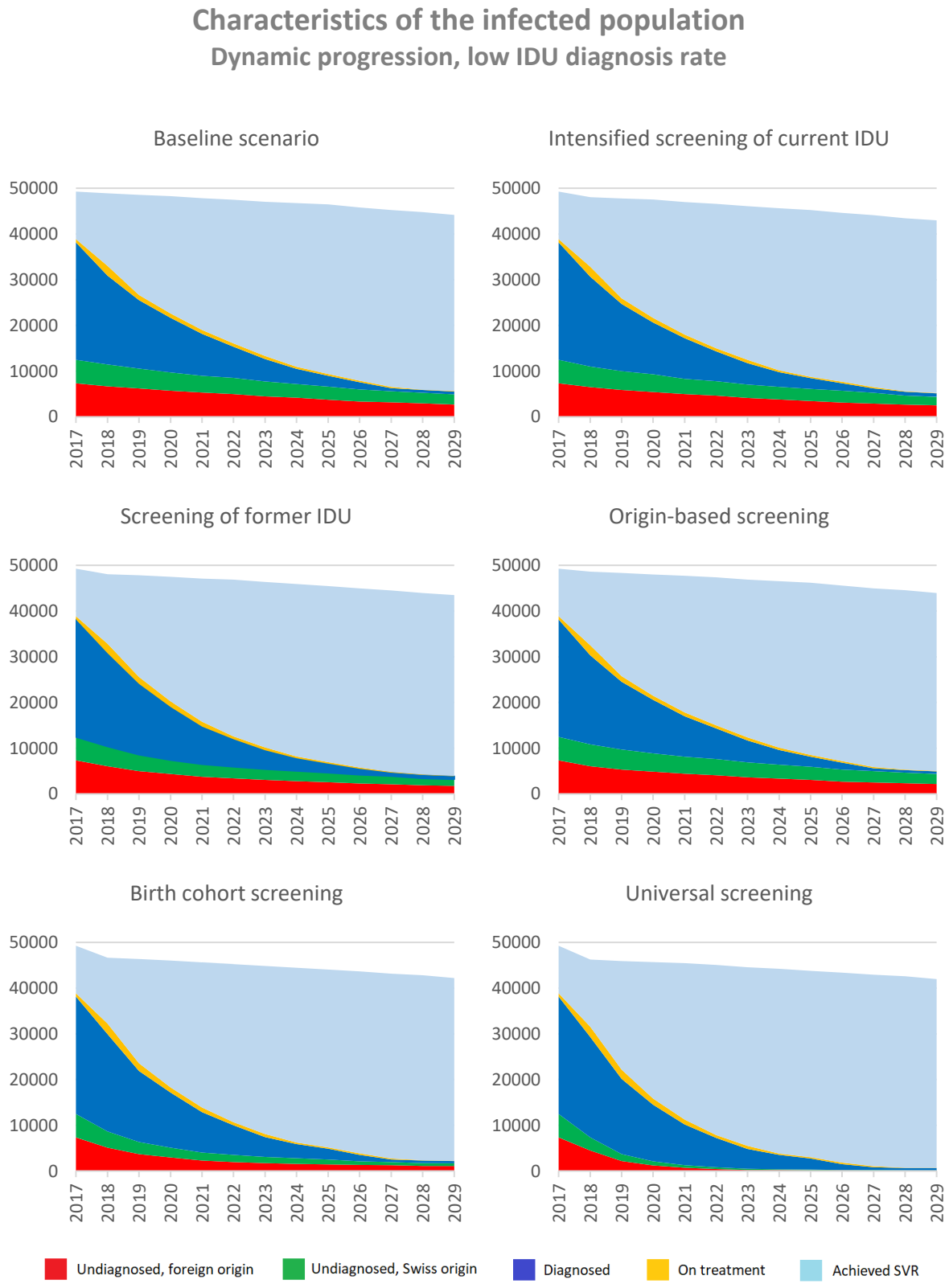

Figure 15. Distribution of undiagnosed, diagnosed, currently treated and cured among the infected population 2017-2029 according to the model using dynamic fibrosis progression and low diagnosis rate among injecting drug users (IDU) in the past in in the six modelled screening scenarios. *Spontaneously cleared patients are not shown.*

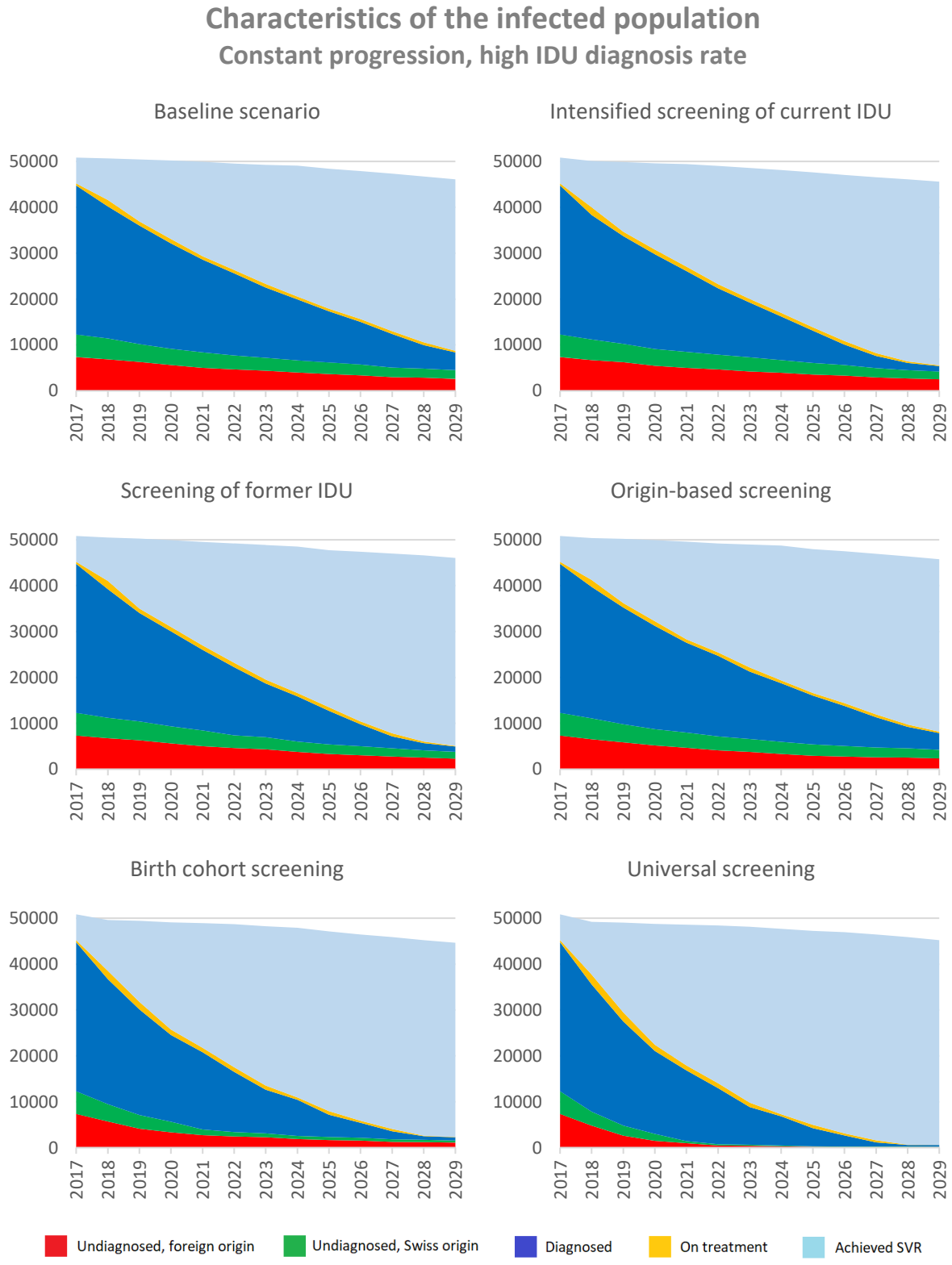

Figure 16. Distribution of undiagnosed, diagnosed, currently treated and cured among the infected population 2017-2029 according to the model using constant fibrosis progression and high diagnosis rate among injecting drug users (IDU) in the past in the six modelled screening scenarios. *Spontaneously cleared patients are not shown.*

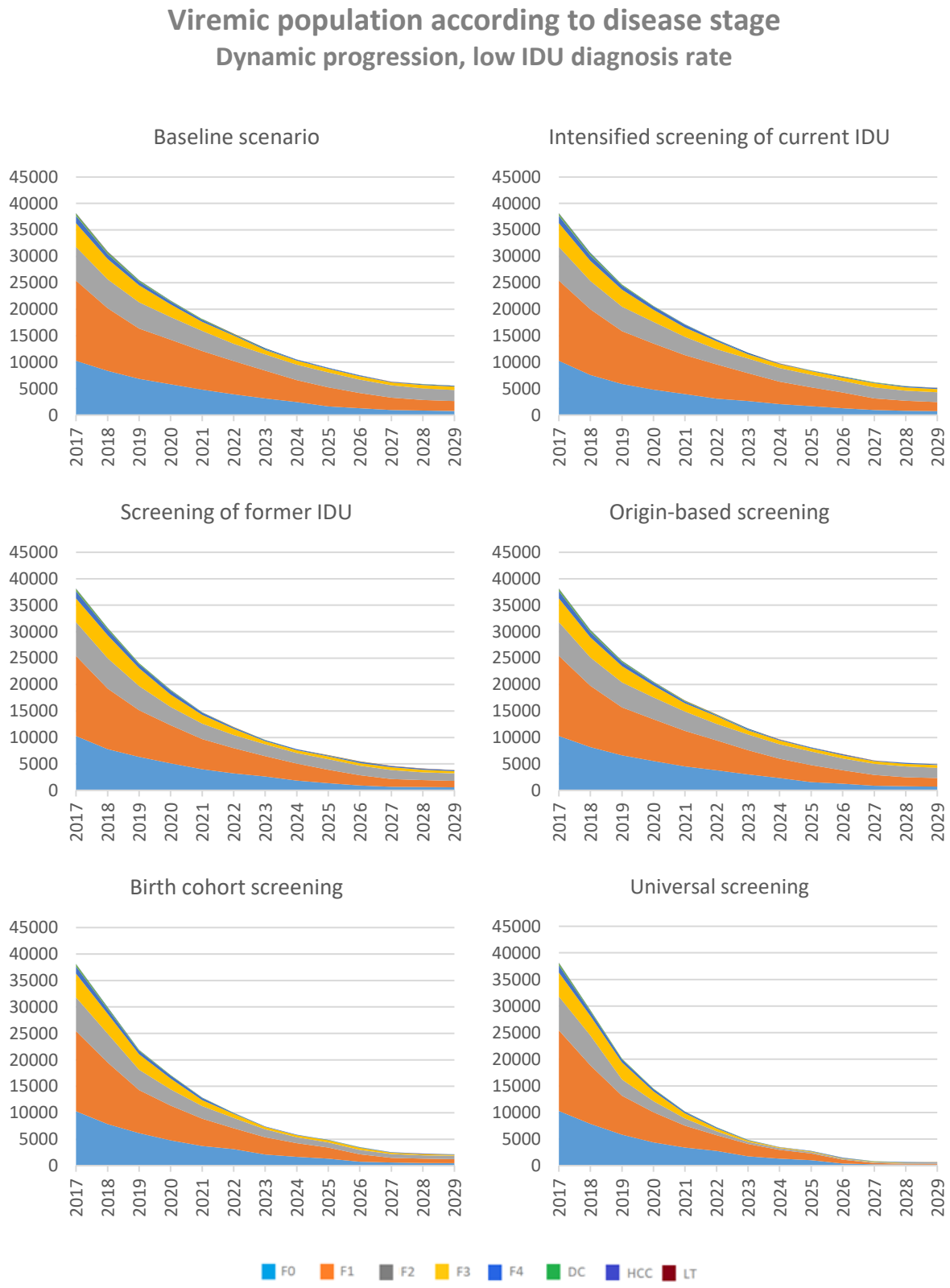

Figure 17. Viremic population by fibrosis stage 2017-2029 according to the model using dynamic progression and low past injection drug user (IDU) diagnosis rate in the six modelled screening scenarios. *DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation.*

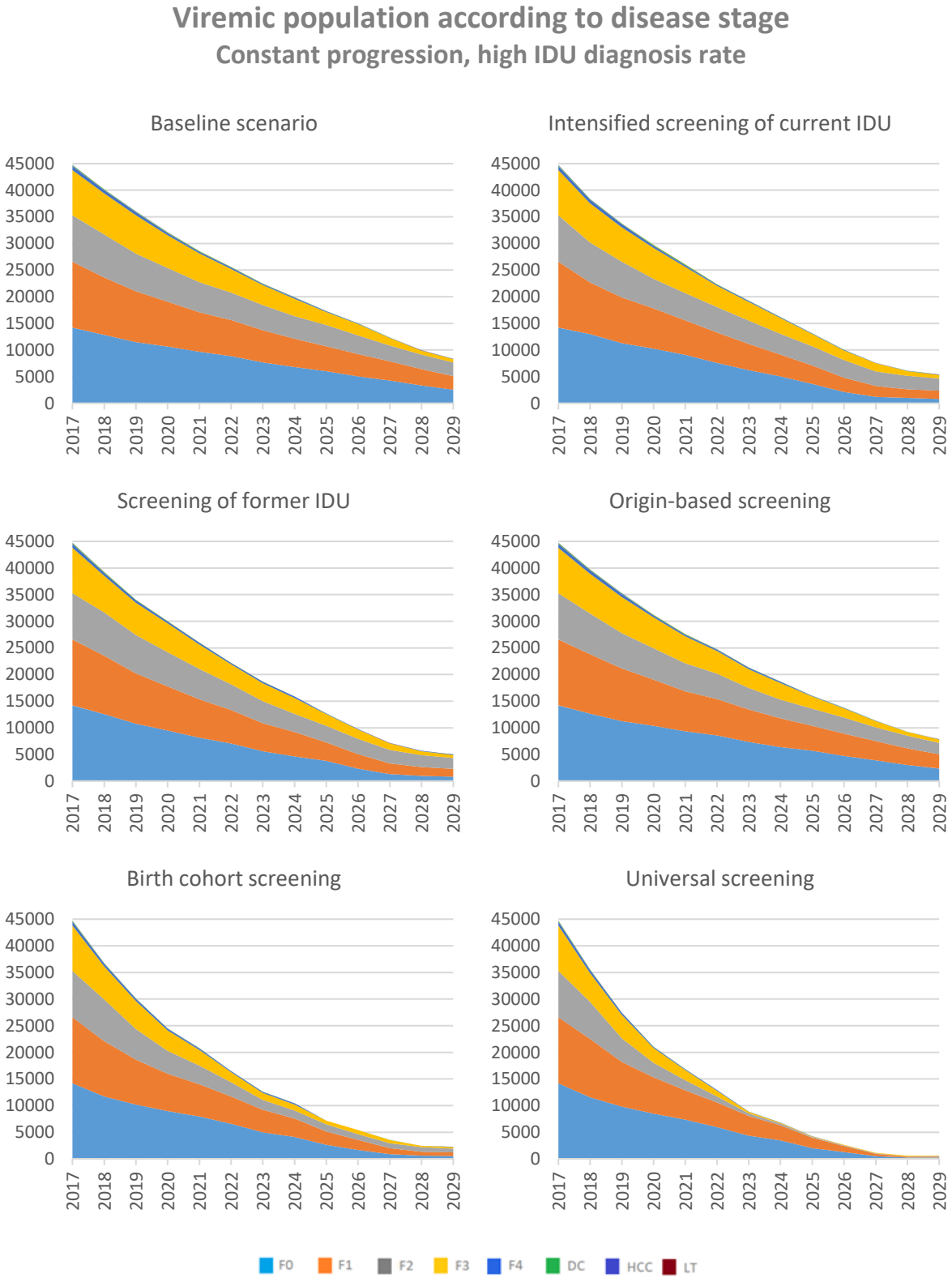

Figure 18. Viremic population by fibrosis stage 2017-2029 according to the model using constant progression and high past injection drug user (IDU) diagnosis rate in the six modelled screening scenarios. *DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation.*

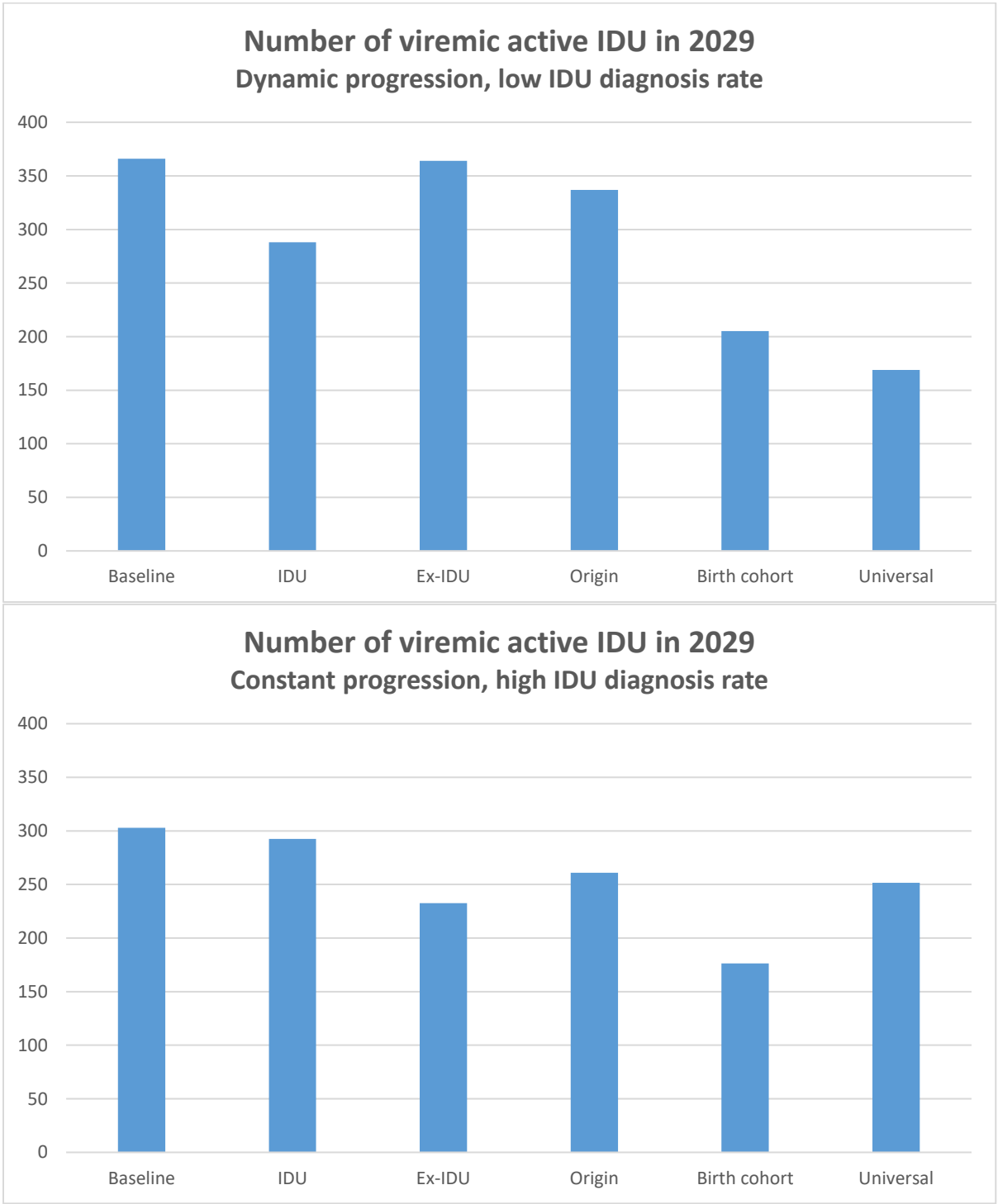

Figure 19. Number of viremic active injection drug users (IDU) in 2029 in different screening scenarios. *Results from the model with dynamic fibrosis progression and low past IDU diagnosis rate are shown in the upper panel, and constant fibrosis progression and high past IDU diagnosis rate in the lower panel.*

6.6 Sensitivity analyses

In sensitivity analysis 1, the current undiagnosed population was assumed to be substantially larger. In 2016, the size of the undiagnosed population was projected at 31,000, as opposed to 14,000 in the main analysis. This corresponds to a total population of about 60,000 HCV infected individuals in 2016, which is considerably more than estimated in the situational analysis, 36,000-43,000 (Figure 20)[1] However, the scenario is also equivalent with the situation where the total population was within this range, but the share of the diagnosed population lower. This could be a result of e.g. an underestimation of the mortality or number of patients who achieved SVR through pre-DAA treatment, or if the notification data contained some double-counting or false positive results.

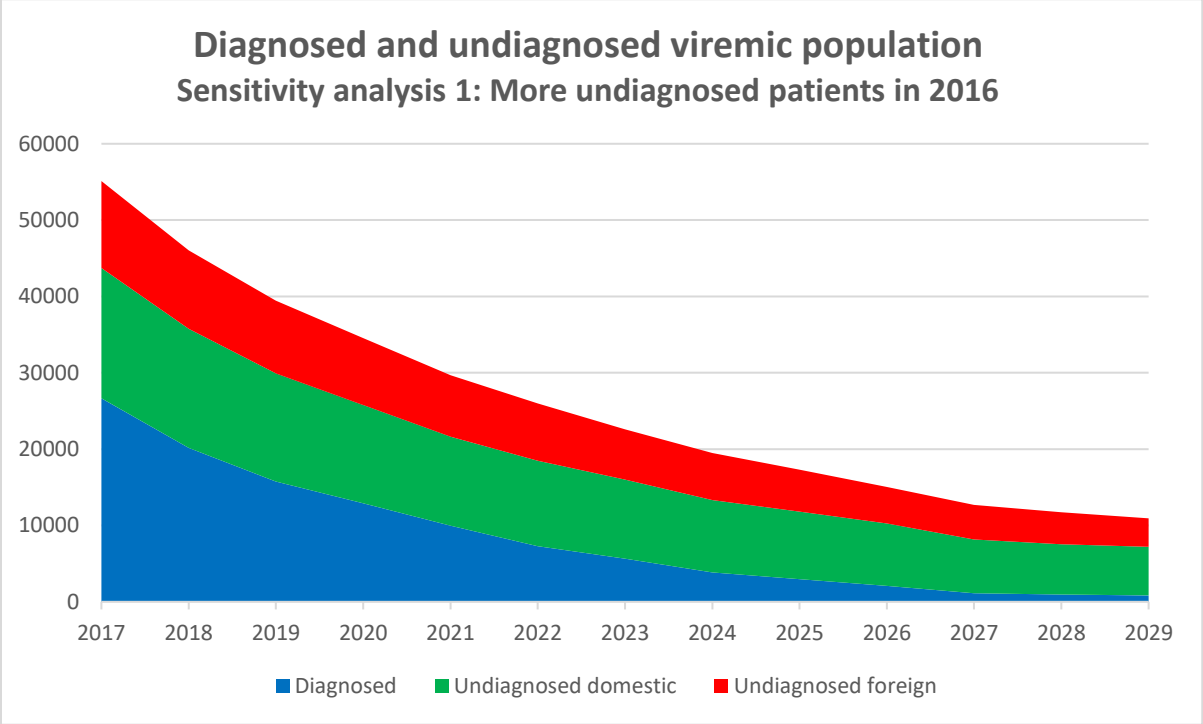

Figure 20. Diagnosed and undiagnosed viremic population 2017-2029 according to the model in the sensitivity analysis 1, baseline scenario.

The pattern in the number of new diagnoses and treated patients followed the main analysis, being only proportionally larger. In 2018, the model predicted 1,400 to 8,300 new diagnoses depending on the scenario, and this decreased gradually to 100-500 in 2029 (Figure 21). Universal screening was the most effective strategy, followed by birth cohort screening. Former IDU screening diagnosed 3,700 patients in 2018, being the third-most effective scenario; origin based screening and intensified

screening of active IDU also increased the number of diagnoses slightly compared with the baseline scenario.

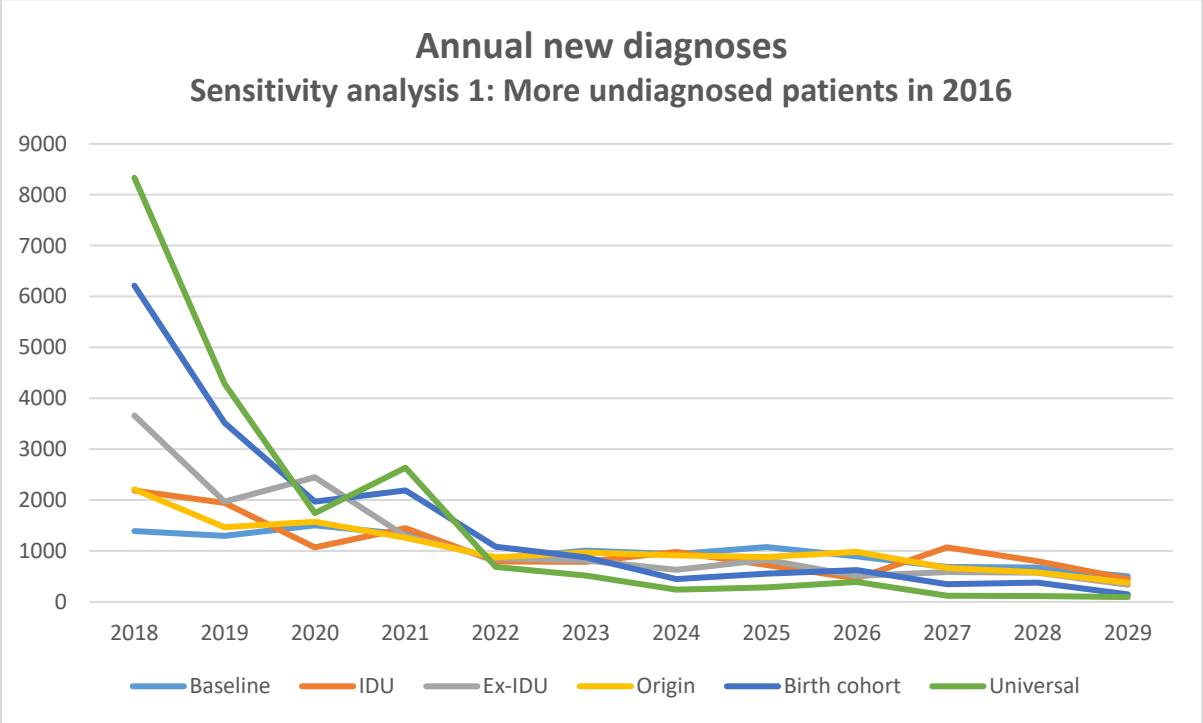

Figure 21. Annual new diagnoses 2018-2029 according to the model, Sensitivity analysis 1. *Different curves present different screening scenarios.*

Mortality followed the same pattern as in the corresponding main analysis, with a slightly decreasing trend (Figure 22). Because of the higher overall number of infected individuals, the number of liver related deaths was also higher, ranging 170-260 in 2018, and 110-260 in 2029, with some outliers across the years.

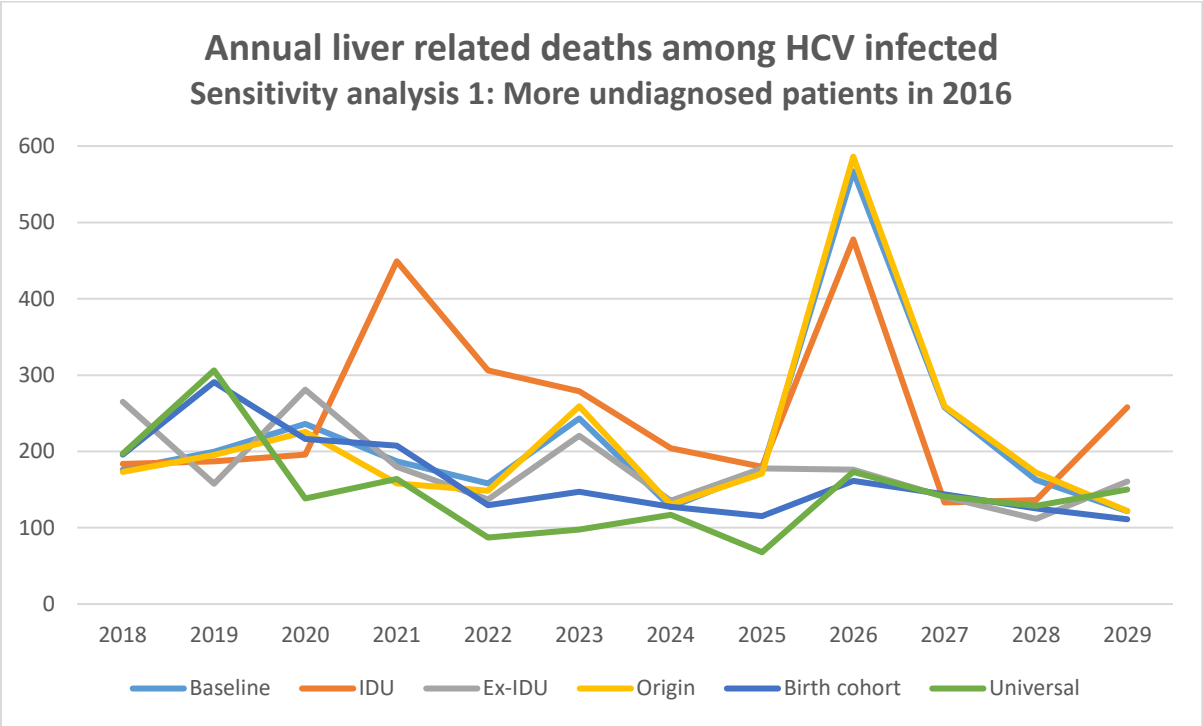

Figure 22. Annual liver related deaths among hepatitis C virus (HCV) infected patients 2018-2029 according to the model, Sensitivity analysis 1. *Different curves present different scenarios.*

In sensitivity analysis 2, we assumed the opposite, i.e. a considerably lower number of undiagnosed patients at present. The model projected about 9,000 undiagnosed patients in 2016, making the total infected population close to the lower limit estimated in the recent situation analysis, 36,000 (Figure 23)[1] Similarly to sensitivity analysis 1, the results were in line with the main analysis, except for the lower number of diagnoses and treatments. In 2018, depending on the scenario, 500 to 2,700 patients were diagnosed (Figure 24). The relative differences between the scenarios were smaller than in the main analysis, but universal, birth cohort and former IDU screening strategies were the most effective ones also in this analysis. In mortality, the pattern was the same (slight decrease) as in the corresponding main analysis and sensitivity analysis 1, but with slightly lower absolute numbers (Figure 25).

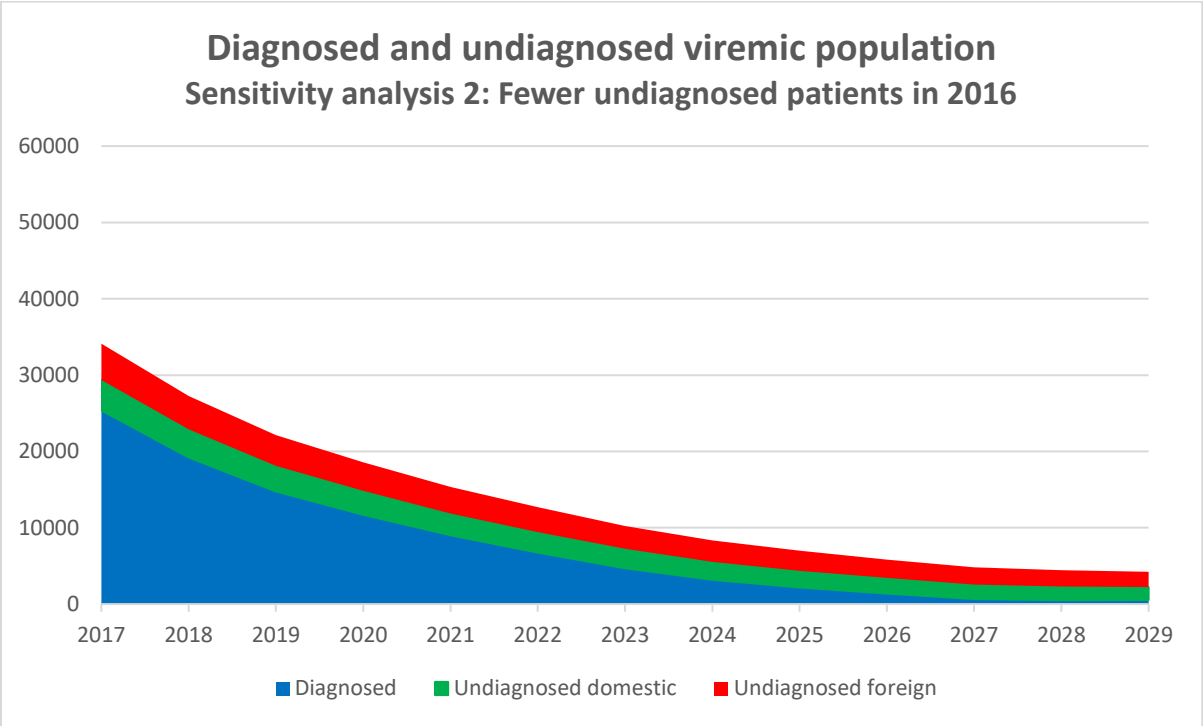

Figure 23. Diagnosed and undiagnosed viremic population 2018-2029 according to the model in the sensitivity analysis 2, baseline scenario.

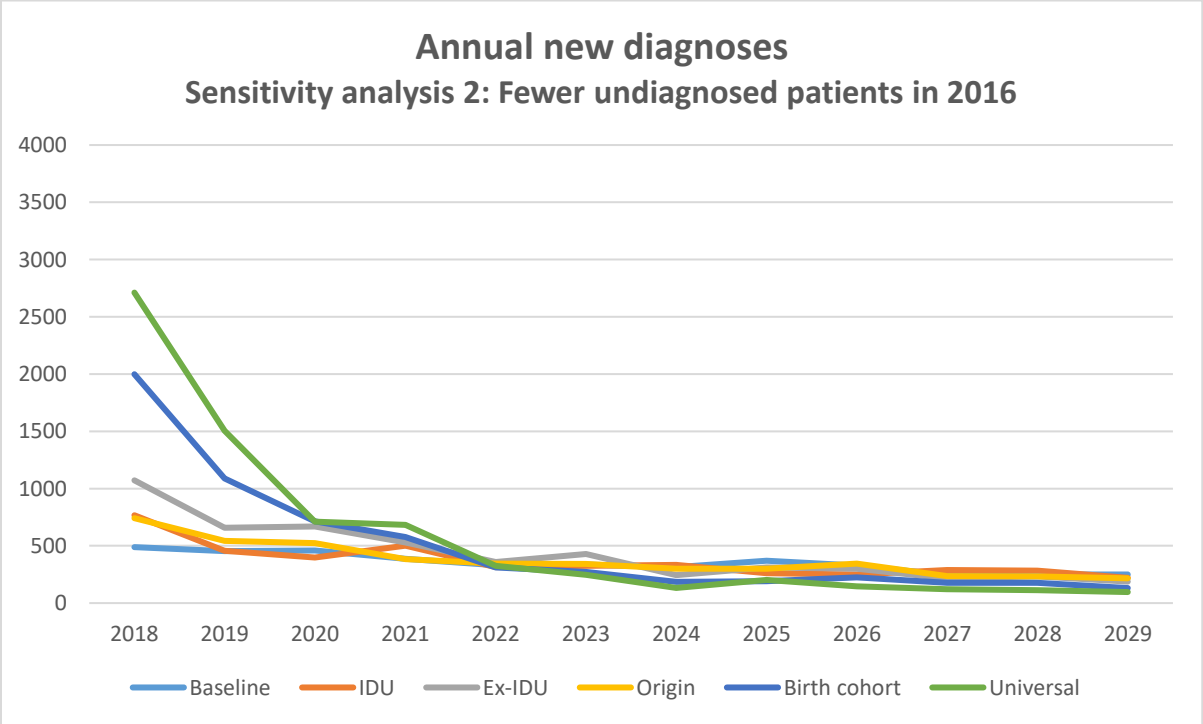

Figure 24. Annual new diagnoses 2018-2029 according to the model, Sensitivity analysis 2. *Different curves present different screening scenarios.*

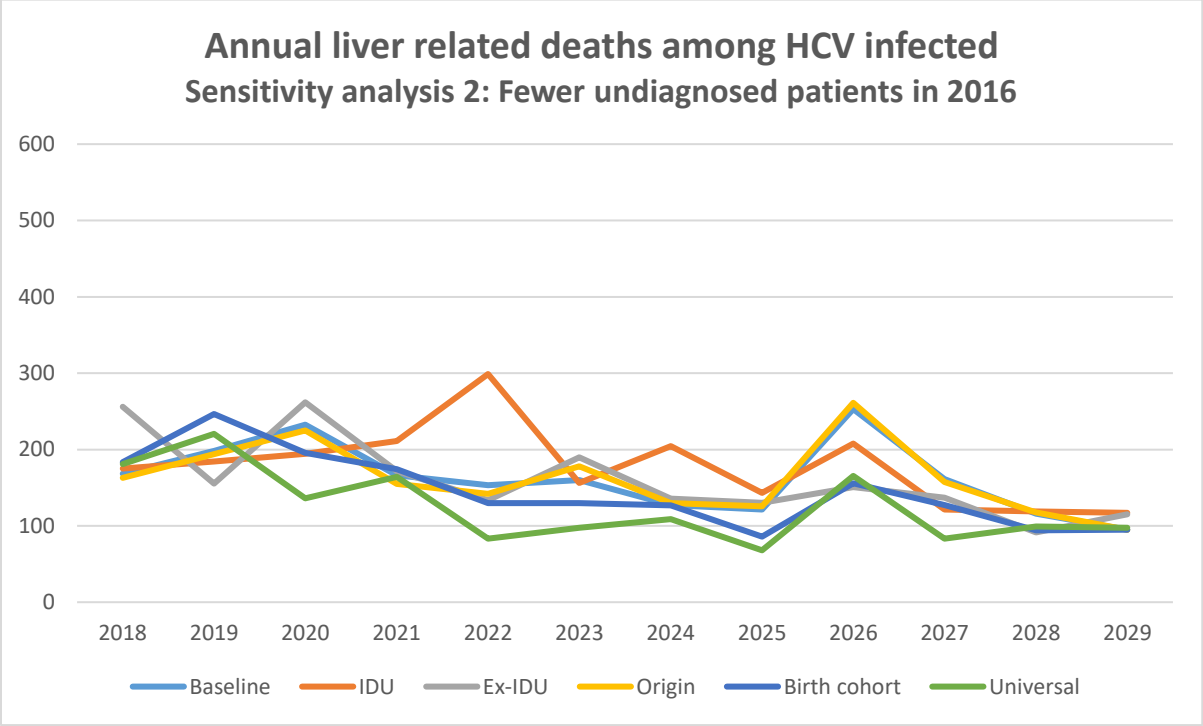

Figure 25. Annual liver related deaths among hepatitis C virus (HCV) infected patients 2018-2029 according to the model, Sensitivity analysis 2. *Different curves present different scenarios.*

Sensitivity analyses 3 and 4 addressed the assumptions regarding the characteristics of the population who were not diagnosed by 2016. In sensitivity analysis 3, where the proportion of patients belonging to high-risk groups was larger (Figure 26), there were corresponding differences in the efficacy of different screening scenarios. The outcomes with universal screening, birth cohort screening, origin based screening and baseline scenarios were as in the main analysis, with universal screening being the most effective (Figure 27). Screening former IDUs performed clearly better than in the main analysis, with outcomes similar to those of birth cohort screening. Intensified screening of active IDUs did not considerably increase the number of diagnoses or treated patients, despite the larger overall number of IDUs. Mortality did not differ from the corresponding main analysis, with the exception of some of the outlier values that were lower (Figure 28).

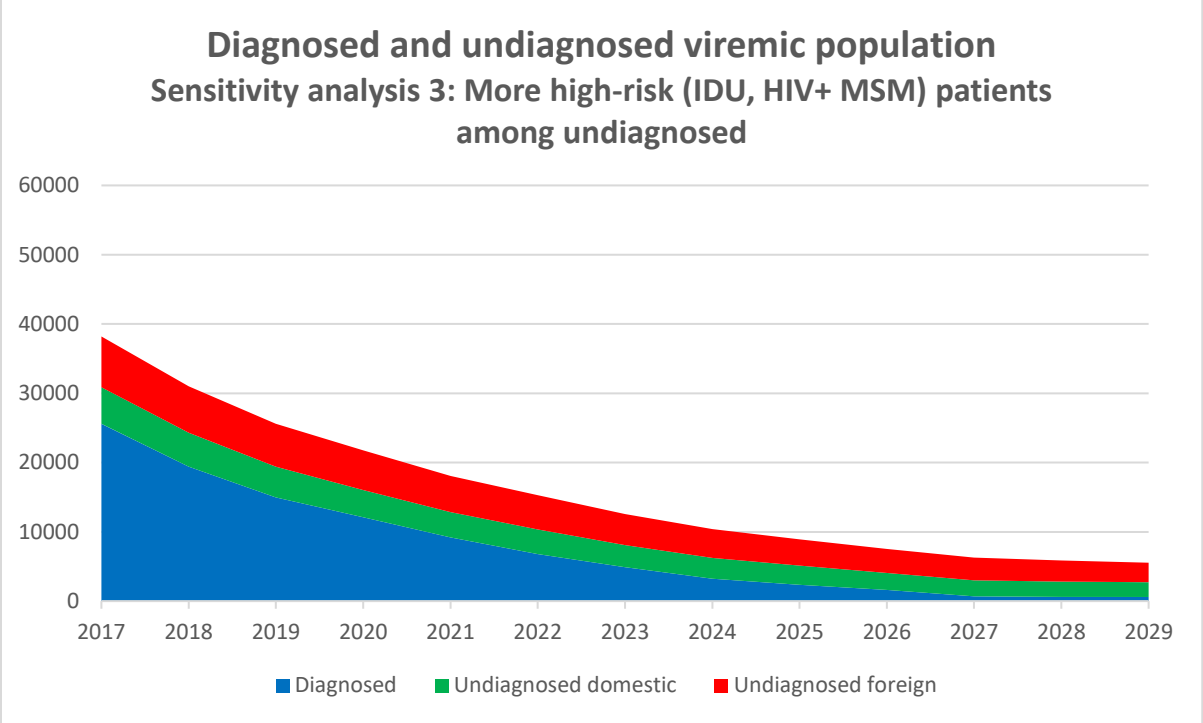

Figure 26. Diagnosed and undiagnosed viremic population 2018-2029 according to the model in the sensitivity analysis 3, baseline scenario. *HIV+ MSM, HIV infected men having sex with men; IDU, injection drug user.*

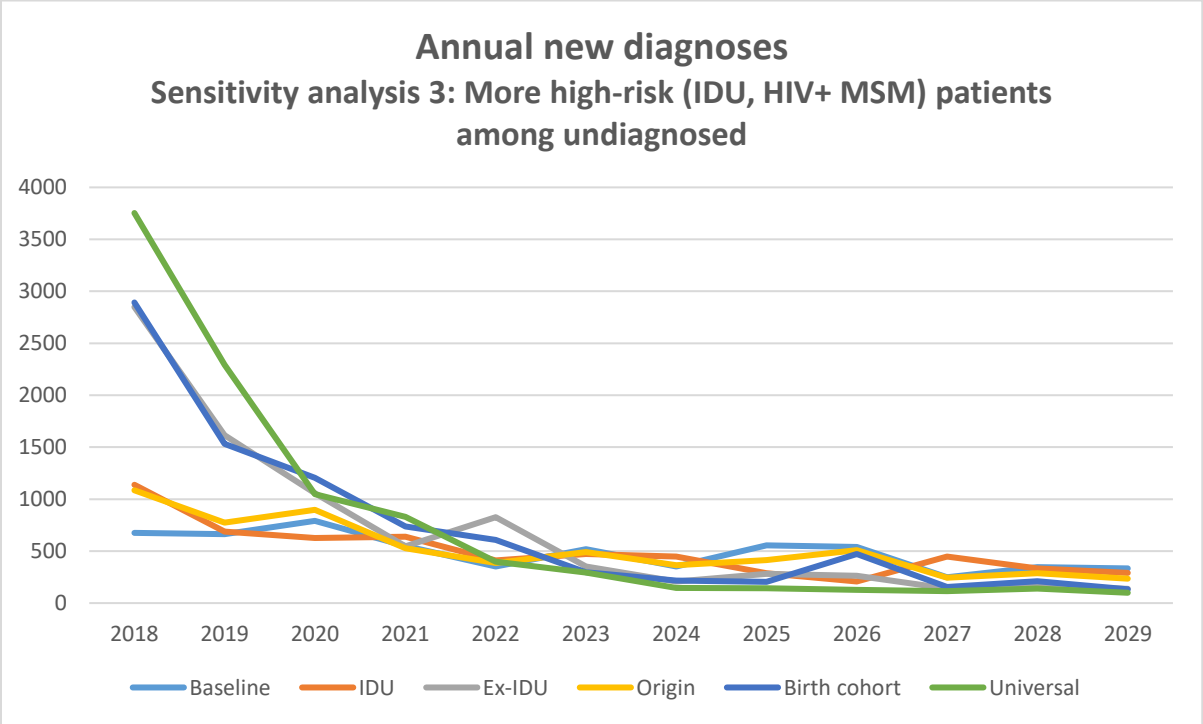

Figure 27. Annual new diagnoses 2018-2029 according to the model, Sensitivity analysis 3. *Different curves present different screening scenarios. HIV+ MSM, HIV infected men having sex with men; IDU, injection drug user.*

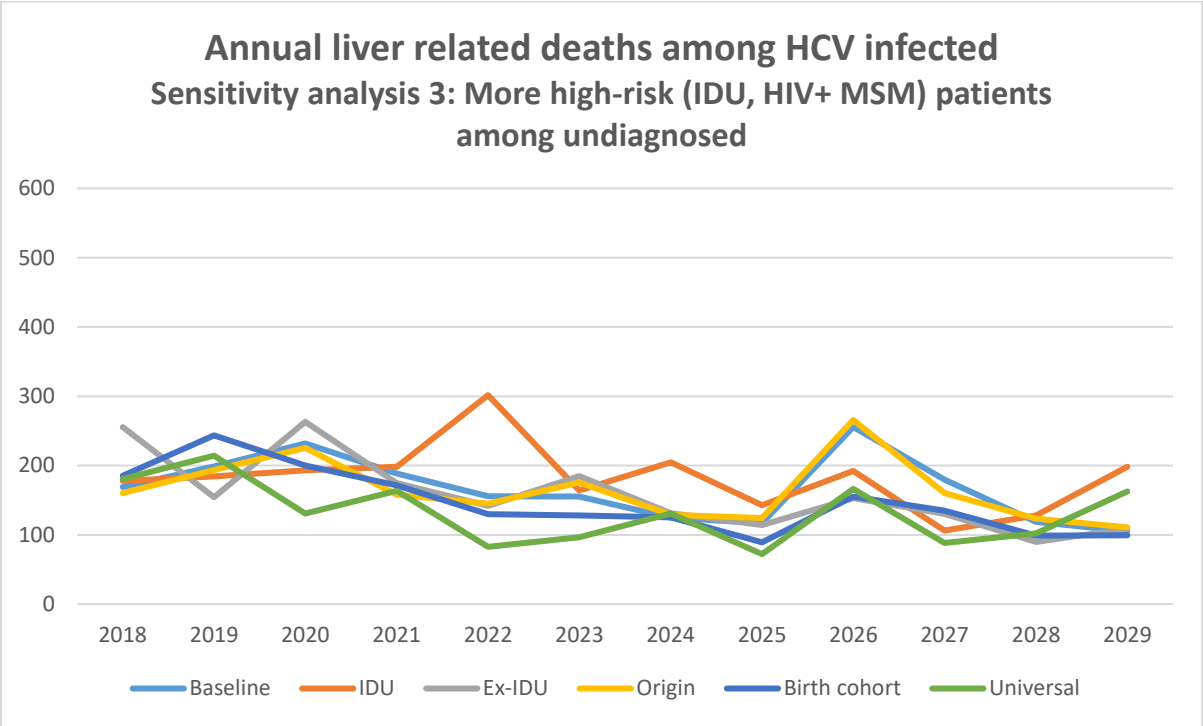

Figure 28. Annual liver related deaths among hepatitis C virus (HCV) infected patients 2018-2029 according to the model, Sensitivity analysis 3. *Different curves present different scenarios. HIV+ MSM, HIV infected men having sex with men; IDU, injection drug user.*

In sensitivity analysis 4, the situation was the opposite, with the proportion of high-risk individuals being considerably lower than in the main analysis (Figure 29). The only differences to the main analysis were in the scenarios with screening former or active IDUs (Figure 30). Former IDU screening had similar outcomes to the origin based screening scenario, diagnosing about 25% fewer patients in the next few years than in the main analysis. The benefit of intensified screening of active IDU was also smaller than in the main analysis. Mortality was similar to the corresponding main analysis (Figure 31).

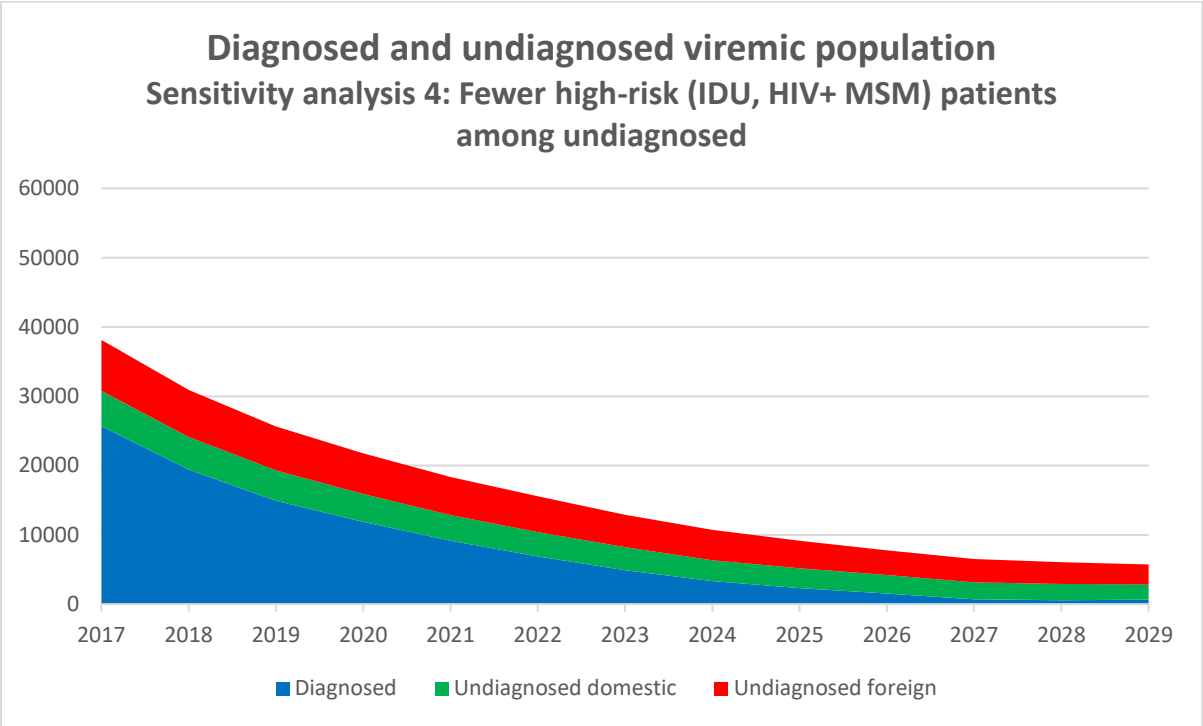

Figure 29. Diagnosed and undiagnosed viremic population 2018-2029 according to the model in the sensitivity analysis 4, baseline scenario. *HIV+ MSM, HIV infected men having sex with men; IDU, injection drug user.*

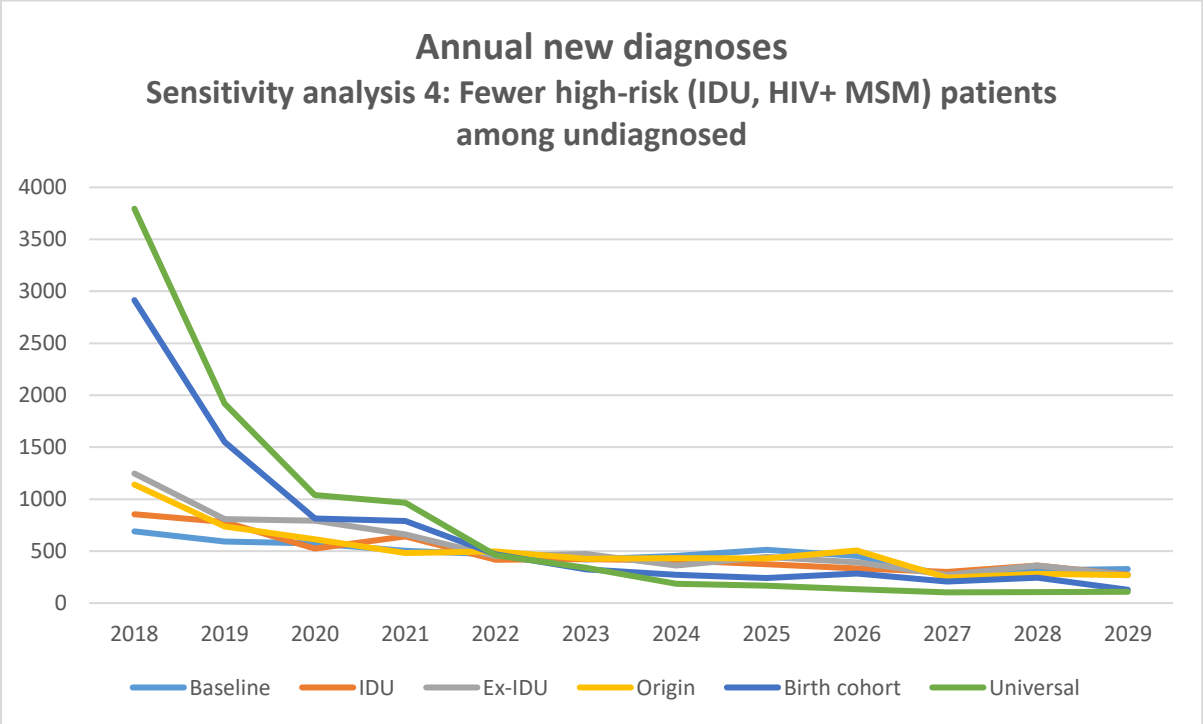

Figure 30. Annual new diagnoses 2018-2029 according to the model, Sensitivity analysis 4. *Different curves present different screening scenarios. HIV+ MSM, HIV infected men having sex with men; IDU, injection drug user.*

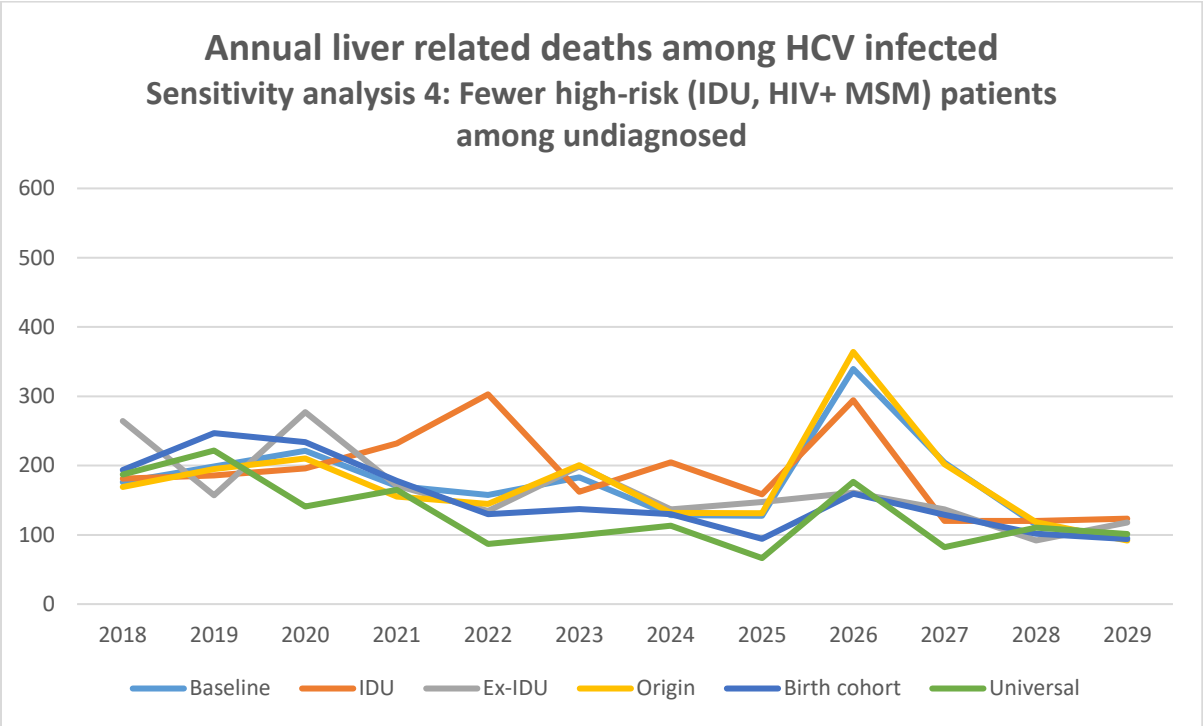

Figure 31. Annual liver related deaths among hepatitis C virus (HCV) infected patients 2018-2029 according to the model, Sensitivity analysis 4. *Different curves present different scenarios. HIV+ MSM, HIV infected men having sex with men; IDU, injection drug user.*

7 Conclusions

In this study, we built a mathematical model for disease progression among HCV infected individuals in Switzerland, and made comparisons between six different screening strategies for the period 2018-2029. The results show that the size of the viremic population is likely to continue to decrease, regardless of the screening strategy. We expect that by 2030, there will be 5,000 to 7,000 viremic individuals infected with HCV in Switzerland if all diagnosed patients are treated, but no additional screening strategies are applied. Only either universal screening, or a strategy that targets a large proportion of the population, such as the birth cohort screening, can substantially decrease the number of viremic individuals. Such intensive population-based strategies would also lead to a lower number of diagnoses in the long term, compared with the current situation of testing people mainly based on symptoms or risk behavior. Under some assumptions, a strategy targeting screening to patients with a history of IDU could also be efficient. However, we also expect that in the future, only a small proportion of the viremic individuals will belong to groups contributing to onward transmission. Among the key populations of transmission, testing is already performed on a regular basis.

This study has several limitations. As in any mathematical modelling study, the results are consequences of the assumptions and input parameters, which in many cases were uncertain. We conducted four separate analyses combining two different assumptions on fibrosis progression and two different assumptions about testing IDUs in the past. Although the pre-2018 results showed some differences between the analyses, the relative differences between the scenarios in the future were essentially the same in all analyses, with a few exceptions. In particular the benefit of screening former IDUs was sensitive to the assumptions we made about the testing rate among IDUs in the past. The lower the past rate, the more effective it will be to try to identify those who injected drugs in the past.

The probably most important limitation concerns the characteristics of the unknown population. Whereas the currently diagnosed population could be modeled relatively accurately by matching the simulated patients to the notification data, the undiagnosed population was based completely on assumptions. Moreover, as the main outcome of the model were the future diagnoses, the results were based only on this undiagnosed population. We conducted several sensitivity analyses where the key assumptions were changed. As expected, the absolute size of the unknown population did

not affect the relative benefit of the screening scenarios. If the true undiagnosed population is larger, intensive screening strategies will lead to even more diagnoses and treatments. On the other hand, it will also increase the efficacy especially for strategies that require the screening of large low-risk populations. If we assumed that the characteristics of patients infected each year are similar between patients diagnosed or not diagnosed by 2016, we found that screening former IDUs could double the number of detected cases in the next few years, while only large-scale birth cohort or universal screening could end the epidemic. Different assumptions about the proportion of patients infected through high-risk behavior among the currently undiagnosed population led to differing estimates in particular regarding the effectiveness of screening strategies focusing on IDUs. If we assumed that two thirds of all undiagnosed patients were infected by injecting drug use, screening among people with a history of drug use would have the same effect as screening the entire birth cohort born 1951-1985. Correspondingly, if the proportion of IDU among the undiagnosed was below 20%, former IDU screening would not be very efficient. Similar results could be expected for origin based screening: the higher the proportion of undiagnosed patients originating from high-prevalence countries, the more effective it will be to screen these populations.

Our model is not a transmission model either. The number of new infections was an input to the model, based on the available data on the diagnosed population and estimates of the true size of the epidemic. We also could not reproduce some of the observed outcomes in the past, such as the high mortality and HCC incidence in the earlier years of the epidemic. This is due to the approach we used, excluding patients who were diagnosed in the early years of the epidemic who are expected to either have died or been successfully treated. This approach limits the validation of the model, but it does not influence the future outcomes. Moreover, most indicators projected by the model were close to the observed data in the last few years, when the modeled population should be almost equivalent to the true HCV infected population of Switzerland. The data available were not directly comparable to the model's outputs. Even though included in the proposal, we did not include an economic evaluation, mainly due to time constraints. In particular, when considering to screen large population groups in situations with low prevalence, implementation of such a screening strategy needs to be carefully assessed (e.g. how many patients need to be tested, and what are the possible consequences of false positive results).

The representation of liver disease progression in our model may be an oversimplification of the reality. We used two different parameterizations for the fibrosis progression: one based on detailed

age- and stage-specific rates. This approach accounts for the accelerated disease progression in older age, but is subject to uncertainty. In the second approach, we used a simpler parameterization, where the duration of liver disease from F0 to F4 was divided into steps of equal length, the progression being based on baseline characteristics at the time of infection only. Both approaches yielded similar results: the main difference was rather due to the average progression being slower in the second approach, than the differences in the complexity of the parameterization. Furthermore, we did not take into account the possibility of regression of the fibrosis stage after successful treatment. This report does not show the burden of liver disease after SVR, nor did we include an economic evaluation; therefore this assumption does not affect the current results. If the results of the model were used for a more comprehensive evaluation of the disease and economic burden, it should be noted that the model would likely overestimate the stage of the liver disease among patients with SVR after treatment.

In conclusion, our study supports the continuation of testing population groups based on risk behavior, but at the same time shows that this alone will not be sufficient to reach all HCV infected individuals in the next 12 years. More information is needed about the characteristics of the currently undiagnosed population, in order to allow more detailed evaluations of the various screening strategies.

Acknowledgments

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References

1. Zahnd C, Brezzi M, Bertisch B, Giudici F, Keiser O. Analyse de Situation des Hépatites B et C en Suisse: Rapport Intégral [Internet]. Office fédéral de la santé publique (OFSP); 2017. Available from: https://www.bag.admin.ch/situationsanalyse-hepatitis
2. Fretz R, Negro F, Bruggmann P, Lavanchy D, De Gottardi A, Pache I, et al. Hepatitis B and C in Switzerland - healthcare provider initiated testing for chronic hepatitis B and C infection. Swiss Med Wkly. 2013;143:w13793.
3. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. Lancet. 2015;385(9973):1124–35.
4. Moradpour D, Müllhaupt B. [Hepatitis C: epidemiology natural course and diagnosis]. Rev Médicale Suisse. 2015;11(471):896–901.
5. Wandeler G, Gsponer T, Bregenzer A, Günthard HF, Clerc O, Calmy A, et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. Clin Infect Dis. 2012;55(10):1408–16.
6. Müllhaupt B, Bruggmann P, Bihl F, Blach S, Lavanchy D, Razavi H, et al. Modeling the Health and Economic Burden of Hepatitis C Virus in Switzerland. PloS One. 2015;10(6):e0125214.
7. Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat. 2014;21 Suppl 1:34–59.
8. Zahnd C, Salazar-Vizcaya L, Dufour J-F, Müllhaupt B, Wandeler G, Kouyos R, et al. Modelling the impact of deferring HCV treatment on liver-related complications in HIV coinfected men who have sex with men. J Hepatol. 2016;65(1):26–32.
9. Salazar-Vizcaya L, Kouyos RD, Zahnd C, Wandeler G, Battegay M, Darling KEA, et al. Hepatitis C virus transmission among HIV-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. Hepatol. 2016;
10. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo C-G, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep Cent Dis Control. 2012;61(RR-4):1–32.
11. European Liver Patients Association, European Association for the Study of the Liver. Recommendations for the promotion of case-finding for viral hepatitis B and C, including targeted screening measures for risk groups [Internet]. Available from: http://www.elpa-info.org/tl_files/elpa_downloads/recommendations-consolidated-version-final.pdf
12. Bottero J, Brouard C, Roudot-Thoraval F, Deuffic-Burban S, Hofliger P, Abergel A, et al. 2014 French guidelines for hepatitis B and C screening.A combined targeted and mass testing strategy of chronic viruses namely HBV, HCV and HIV. Liver Int. 2016;
13. Association française pour l'étude du foie (AFEF). Recommandations AFEF pour l'élimination de l'infection par le virus de l'hépatite C en France [internet]. Available from: http://www.afef.asso.fr/ckfinder/userfiles/files/recommandations-textes-officiels/recommandations/VF%20INTERACTIF-%20RECO-VHC%20AFEF%20v2103.pdf
14. Bertisch B, Giudici F, Negro F, Moradpour D, Müllhaupt B, Moriggia A, et al. Characteristics of Foreign-Born Persons in the Swiss Hepatitis C Cohort Study: Implications for Screening Recommendations. PloS One. 2016;11(5):e0155464.
15. Bruggmann P, Richard J-L, Swiss Hepatitis C Cohort Study Group. Birth year distribution in reported hepatitis C cases in Switzerland. Eur J Public Health. 2015;25(1):141–3.
16. Blaser N, Vizcaya LS, Estill J, Zahnd C, Kalesan B, Egger M, et al. gems: An R Package for Simulating from Disease Progression Models. J Stat Softw. 2015;64(10):1–22.
17. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349(9055):825–32.
18. Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatol. 2008;48(2):418–31.
19. Ward T, Gordon J, Bennett H, Webster S, Sugrue D, Jones B, et al. Tackling the burden of the hepatitis C virus in the UK: characterizing and assessing the clinical and economic consequences. Public Health. 2016;141:42–51.
20. Harris RJ, Thomas B, Griffiths J, Costella A, Chapman R, Ramsay M, et al. Increased uptake and new therapies are needed to avert rising hepatitis C-related end stage liver disease in England: modelling the predicted impact of treatment under different scenarios. J Hepatol. 2014;61(3):530–7.
21. Martin NK, Hickman M, Miners A, Hutchinson SJ, Taylor A, Vickerman P. Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons. BMJ Open. 2013;3(8).

22. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess Winch Engl. 2007;11(11):1–205, iii.
23. Townsend R, McEwan P, Kim R, Yuan Y. Structural frameworks and key model parameters in cost-effectiveness analyses for current and future treatments of chronic hepatitis C. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2011;14(8):1068–77.
24. Hutchinson SJ, Bird SM, Goldberg DJ. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. Hepatol. 2005;42(3):711–23.
25. Deuffic-Burban S, Boursier J, Leroy V, Yazdanpanah Y, Castera L, Mathurin P. Are targeted treatment recommendations in chronic hepatitis C tailored to diagnostic methods of fibrosis? J Hepatol. 2017;66(2):304–12.
26. Armstrong GL. Commentary: Modelling the epidemiology of hepatitis C and its complications. Int J Epidemiol. 2003;32(5):725–6.
27. McEwan P, Kim R, Yuan Y. Assessing the cost utility of response-guided therapy in patients with chronic hepatitis C genotype 1 in the UK using the MONARCH model. Appl Health Econ Health Policy. 2013;11(1):53–63.
28. McEwan P, Ward T, Chen C-J, Lee M-H, Yang H-I, Kim R, et al. Estimating the Incidence and Prevalence of Chronic Hepatitis C Infection in Taiwan Using Back Projection. Value Health Reg Issues. 2014;3:5–11.
29. McGarry LJ, Pawar VS, Panchmatia HR, Rubin JL, Davis GL, Younossi ZM, et al. Economic model of a birth cohort screening program for hepatitis C virus. Hepatol Baltim Md. 2012;55(5):1344–55.
30. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138(2):513–21, 521.e1-6.
31. Marcellin P, Asselah T, Boyer N. Fibrosis and disease progression in hepatitis C. Hepatol Baltim Md. 2002;36(5 Suppl 1):S47-56.
32. Cramp ME, Rosenberg WM, Ryder SD, Blach S, Parkes J. Modelling the impact of improving screening and treatment of chronic hepatitis C virus infection on future hepatocellular carcinoma rates and liver-related mortality. BMC Gastroenterol. 2014;14:137.
33. Smith DJ, Combellick J, Jordan AE, Hagan H. Hepatitis C virus (HCV) disease progression in people who inject drugs (PWID): A systematic review and meta-analysis. Int J Drug Policy. 2015;26(10):911–21.
34. Simon TG, King LY, Zheng H, Chung RT. Statin use is associated with a reduced risk of fibrosis progression in chronic hepatitis C. J Hepatol. 2015;62(1):18–23.
35. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatol. 2001;34(4 Pt 1):809–16.
36. Xu F, Moorman AC, Tong X, Gordon SC, Rupp LB, Lu M, et al. All-Cause Mortality and Progression Risks to Hepatic Decompensation and Hepatocellular Carcinoma in Patients Infected With Hepatitis C Virus. Clin Infect Dis O. 2016;62(3):289–97.
37. Tovo CV, Becker SC da C, Almeida PRL de, Galperim B, Chaves S. Progression of liver fibrosis in monoinfected patients by hepatitis C virus and coinfected by HCV and human immunodeficiency virus. Arq Gastroenterol. 2013;50(1):19–22.
38. Kielland KB, Delaveris GJM, Rogde S, Eide TJ, Amundsen EJ, Dalgard O. Liver fibrosis progression at autopsy in injecting drug users infected by hepatitis C: a longitudinal long-term cohort study. J Hepatol. 2014;60(2):260–6.
39. Li J-F, Liu S, Ren F, Liu M, Wu H-L, Chen Y, et al. Fibrosis progression in interferon treatment-naive Chinese plasma donors with chronic hepatitis C for 20 years: a cohort study. Int J Infect Dis. 2014;27:49–53.
40. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med. 1999;340(16):1228–33.
41. Wiese M, Fischer J, Löbermann M, Göbel U, Grüngreiff K, Güthoff W, et al. Evaluation of liver disease progression in the German hepatitis C virus (1b)-contaminated anti-D cohort at 35 years after infection. Hepatol. 2014;59(1):49–57.
42. Hissar SS, Kumar M, Tyagi P, Goyal A, Suneetha PV, Agarwal S, et al. Natural history of hepatic fibrosis progression in chronic hepatitis C virus infection in India. J Gastroenterol Hepatol. 2009;24(4):581–7.
43. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatol. 1999;30(4):1054–8.
44. Bräu N, Salvatore M, Ríos-Bedoya CF, Fernández-Carbia A, Paronetto F, Rodríguez-Orengo JF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol. 2006;44(1):47–55.
45. Triolo M, Della Corte C, Colombo M. Impact of HBV therapy on the incidence of hepatocellular carcinoma. Liver Int O. 2014;34 Suppl 1:139–45.
46. Sacco R, Mirabile A, Giacomelli L, Bresci G, Attardo S, Cabibbo G. Report from European Association for the Study of the Liver: HCC Summit, Geneva, Switzerland, 2-5 February 2017. Future Oncol. 2017;13(15):1297–300.

47. Planas R, Ballesté B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol. 2004;40(5):823–30.
48. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016;65(4):727–33.
49. Cabibbo G, Petta S, Barbàra M, Missale G, Virdone R, Caturelli E, et al. A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma. Liver Int. 2017;37(8):1157–66.
50. Ericzon BG, Wilczek HE, Larsson M, Stangou AJ, Wijayatunga P, Suhr O. To transplant or not to transplant-Lessons learned from 20 years global collaboration in liver transplantation for hereditary transthyretin amyloidosis. Hepatology. 2013;58(S1):1011A.
51. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158(5 Pt 1):329–37.
52. Cordero-Ruiz P, Carmona-Soria I, Rodríguez-Téllez M, Caunedo-Alvarez A, Quezada-Pacheco RH, Flores-Cucho A, et al. Long-term follow-up of patients with chronic hepatitis C treated with α-interferon and ribavirin antiviral therapy: clinical and fibrosis impact of treatment response. Eur J Gastroenterol Hepatol. 2017;29(7):792–9.
53. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology. 2002;122(5):1303–13.
54. van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. J Hepatol. 2016;65(1 Suppl):S95–108.
55. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. Hepatol. 2009;49(3):729–38.
56. Sáez-Royuela F, Badia E. Hepatitis C: Is regression of advanced fibrosis possible after treatment? EMJ. 1(3):126–32.
57. Serfaty L. Follow-up of patients with chronic hepatitis C and a sustained viral response. Liver Int. 2016;36 Suppl 1:67–71.
58. Innes HA, Hutchinson SJ, Allen S, Bhattacharyya D, Bramley P, Delahooke TES, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatol. 2011;54(5):1547–58.
59. El-Akel W, El-Sayed MH, El Kassas M, El-Serafy M, Khairy M, Elsaeed K, et al. National treatment programme of hepatitis C in Egypt: Hepatitis C virus model of care. J Viral Hepat. 2017;24(4):262–7.
60. Hoofnagle JH. Course and outcome of hepatitis C. Hepatol. 2002;36(5 Suppl 1):S21-29.
61. Ayoub HH, Abu-Raddad LJ. Impact of treatment on hepatitis C virus transmission and incidence in Egypt: A case for treatment as prevention. J Viral Hepat. 2017;24(6):486–95.
62. Schmidt AJ, Falcato L, Zahno B, Burri A, Regenass S, Müllhaupt B, et al. Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection? BMC Public Health. 2014;14:3.
63. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006;13(1):34–41.
64. Di Bisceglie AM. Natural history of hepatitis C: its impact on clinical management. Hepatol. 2000;31(4):1014–8.
65. Grebely J, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatol. 2014;59(1):109–20.
66. Sakem B, Madaliński K, Nydegger U, Stępień M, Godzik P, Kołakowska A, et al. Hepatitis C virus epidemiology and prevention in Polish and Swiss population - similar and contrasting experiences. Ann Agric Environ Med. 2016;23(3):425–31.
67. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 2013;10(9):553–62.
68. van Sighem A, Nakagawa F, De Angelis D, Quinten C, Bezemer D, de Coul EO, et al. Estimating HIV Incidence, Time to Diagnosis, and the Undiagnosed HIV Epidemic Using Routine Surveillance Data. Epidemiol Camb Mass. 2015;26(5):653–60.
69. HIV, Syphilis, Gonorrhoe und Chlamydiose in der Schweiz im Jahr 2015: eine epidemilologische Übersicht. BAG-Bull. 2016;46:12–36.
70. Spach DH. Screening and Diagnosis of Hepatitis C Infection Overview [Internet]. 2018. Available from: https://www.hepatitisc.uw.edu/go/screening-diagnosis
71. Kim S, Oh HB, Cha CH, Choi SE, An HY, Lee KJ. [Quality Evaluation of the Performance Study of Diagnostic Tests Using STARD Checklist and Meta-Analysis for the Pooled Sensitivity and Specificity of Third Generation Anti-HCV EIA Tests.]. Korean J Lab Med. 2006;26(4):307–15.
72. Filice G, Patruno S, Campisi D, Chiesa A, Orsolini P, Debiaggi M, et al. Specificity and sensitivity of 3rd generation EIA for detection of HCV antibodies among intravenous drug-users. New Microbiol. 1993;16(1):35–42.

73. Anderson ES, Galbraith JW, Deering LJ, Pfeil SK, Todorovic T, Rodgers JB, et al. Continuum of Care for Hepatitis C Virus Among Patients Diagnosed in the Emergency Department Setting. Clin Infect Dis. 2017 Jun;64(11):1540–6.
74. Swiss Hepatitis Strategy 2014-2030. Time to Act Now! Process Paper - A Living Document [Internet]. Swiss Hepatitis Strategy; 2016. Available from: http://www.hepatitis-schweiz.ch/files/Dokumente/PDF/2016_10-Process_paper.pdf
75. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370(21):1993–2001.
76. Kohli A, Kapoor R, Sims Z, Nelson A, Sidharthan S, Lam B, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis. 2015 Sep;15(9):1049–54.
77. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889–98.
78. Zeuzem S. Treatment Options in Hepatitis C. Dtsch Arzteblatt Int. 2017;114(1-02):11–21.
79. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370(16):1483–93.
80. Young J, Weis N, Hofer H, Irving W, Weiland O, Giostra E, et al. The effectiveness of daclatasvir based therapy in European patients with chronic hepatitis C and advanced liver disease. BMC Infect Dis. 2017;17(1):45.
81. STAT-TAB - interactive tables (FSO). Deaths by sex, nationality, marital status and age [Internet]. Swiss Federal Statistical Office; Available from: https://www.pxweb.bfs.admin.ch/pxweb/en/px-x-0102020206_103/-/px-x-0102020206_103.px
82. Stahmeyer JT, Rossol S, Liersch S, Guerra I, Krauth C. Cost-Effectiveness of Treating Hepatitis C with Sofosbuvir/Ledipasvir in Germany. PloS One. 2017;12(1):e0169401.
83. Keiser O, Giudici F, Müllhaupt B, Junker C, Dufour J-F, Moradpour D, et al. Trends in hepatitis C-related mortality in Switzerland. J Viral Hepat. 2018;25(2):152–60.
84. Calzadilla-Bertot L, Vilar-Gomez E, Torres-Gonzalez A, Socias-Lopez M, Diago M, Adams LA, et al. Impaired glucose metabolism increases risk of hepatic decompensation and death in patients with compensated hepatitis C virus-related cirrhosis. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2016;48(3):283–90.
85. Giudici F, Bertisch B, Negro F, Stirnimann G, Müllhaupt B, Moradpour D, et al. Access to therapy and therapy outcomes in the Swiss Hepatitis C Cohort Study: a person-centred approach. J Viral Hepat. 2016;23(9):697–707.
86. May MT, Justice AC, Birnie K, Ingle SM, Smit C, Smith C, et al. Injection Drug Use and Hepatitis C as Risk Factors for Mortality in HIV-Infected Individuals: The Antiretroviral Therapy Cohort Collaboration. J Acquir Immune Defic Syndr 1999. 2015;69(3):348–54.
87. Aghemo A, Colombo M. Hepatocellular carcinoma in chronic hepatitis C: from bench to bedside. Semin Immunopathol. 2013;35(1):111–20.
88. Kershenobich D, Razavi HA, Cooper CL, Alberti A, Dusheiko GM, Pol S, et al. Applying a system approach to forecast the total hepatitis C virus-infected population size: model validation using US data. Liver Int. 2011;31 Suppl 2:4–17.
89. United Nations Office on Drugs and Crime [Internet]. Available from: www.unodc.org
90. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations." Hepatology. 2012;55(1):49-57.
91. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatol. 2013;58(5):1598–609.
92. Turner KME, Hutchinson S, Vickerman P, Hope V, Craine N, Palmateer N, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. Addict. 2011;106(11):1978–88.
93. Fazito E, Cuchi P, Mahy M, Brown T. Analysis of duration of risk behaviour for key populations: a literature review. Sex Transm Infect. 2012;88 Suppl 2:i24-32.
94. Urbanus AT, van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS. 2009 Jul 31;23(12):F1-7.
95. Witt MD, Seaberg EC, Darilay A, Young S, Badri S, Rinaldo CR, et al. Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis, 1984-2011. Clin Infect Dis. 2013;57(1):77–84.
96. Jin F, Prestage GP, Matthews G, Zablotska I, Rawstorne P, Kippax SC, et al. Prevalence, incidence and risk factors for hepatitis C in homosexual men: data from two cohorts of HIV-negative and HIV-positive men in Sydney, Australia. Sex Transm Infect. 2010;86(1):25–8.
97. Alary M, Joly JR, Vincelette J, Lavoie R, Turmel B, Remis RS. Lack of evidence of sexual transmission of hepatitis C virus in a prospective cohort study of men who have sex with men. Am J Public Health. 2005;95(3):502–5.
98. Poynard T, Mathurin P, Lai C-L, Guyader D, Poupon R, Tainturier M-H, et al. A comparison of fibrosis progression in chronic liver diseases. J Hepatol. 2003;38(3):257–65.
99. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol. 2001;34(5):730–9.

100. Serfaty L, Poujol-Robert A, Carbonell N, Chazouillères O, Poupon RE, Poupon R. Effect of the interaction between steatosis and alcohol intake on liver fibrosis progression in chronic hepatitis C. Am J Gastroenterol. 2002;97(7):1807-12.
101. Vitali GC, Laurent A, Terraz S, Majno P, Buchs NC, Rubbia-Brandt L, et al. Minimally invasive surgery versus percutaneous radio frequency ablation for the treatment of single small (≤3 cm) hepatocellular carcinoma: a case–control study. Surg Endosc. 2016;30(6):2301-7.
102. de Martel C, Maucort-Boulch D, Plummer M, Franchesci S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. Hepatology. 2015;62(4):1190-1200.

Appendix A. Further details of the literature search

A.1 Fibrosis progression

This section presents some additional details and findings from the literature regarding the progression of fibrosis. The studies that were considered for the parameterization of the model are described in Section 2.1.

Martin *et al.* considered the liver disease stages as mild (F0-F1), moderate (F2-F3), cirrhotic (F4), DC and HCC.[21] They used a beta distribution, based on a systematic review by Shepherd *et al.*,[22] to estimate the transition rate for each of the five transitions excluding factors such as time at HCV infection. Townsend *et al.* reviewed the structural framework and key model parameters from economic evaluations for treatment for chronic hepatitis C published in 2000-2011.[23] They modeled the impact of variability across parameters on the results.

Hutchinson *et al*. developed a Markov model for estimating the disease burden of hepatitis C among drug users in Scotland.[24] They reviewed the available literature to estimate the annual transition probabilities from compensated cirrhosis to various end points. The pooled estimate for transition from compensated to decompensated cirrhosis was 6.5% in a year.

Deuffic-Burban *et al.* used a country-specific Markov model to predict clinical outcomes in patients with chronic HCV mono-infection over 5 years in Italy, France, and the UK.[25] They used country-specific rates for progression from F0 to F4, and universal (common for all countries) rates for progression from cirrhosis (i.e., F4) to end stage liver disease (DC, HCC and liver transplantation). Gender and age were included as factors. They divided DC further to three separate parts: first DC, stable DC and progressive DC. They assumed that the fibrosis progression rates were 3 to 4.5 times higher for patients with alcohol abuse (>50 g/day) than for patients without alcohol abuse.

Armstrong *et al*. conducted a critical overview of modelling approaches.[26] According to their study, data from natural history studies suggest that progression to cirrhosis is much slower in people infected as children or young adults, of whom fewer than 5% have progressed to cirrhosis in the first 20 years, than in people infected as older adults, of whom 10–20% have progressed to cirrhosis in the first 20 years. They suggest that beyond 20 years there are no data to suggest whether disease progression will accelerate or decelerate.

McEwan *et al*. describe an economic model designed to assess the costs and benefits of response guided therapy compared with standard duration of therapy in hepatitis C virus genotype 1 patients.[27] Their fibrosis progression rates were based on Thein *et al*.[18]

Moreover, McEwan *et al.* estimated the number of patients living with chronic HCV infection in Taiwan and quantified the expected numbers in each of the five Metavir fibrosis stages.[28]

McGarry *et al.* assessed the cost-effectiveness of screening 100% of U.S. residents born 1946-1970 over 5 years (birth-cohort screening), compared with current risk-based screening, by projecting costs and outcomes of screening over the remaining lifetime of this birth cohort.[29] A Markov model of the natural history of HCV was developed using data synthesized from surveillance data, published literature, expert opinion, and other secondary sources. The fibrosis progression rate was estimated directly from Davis *et al.*[30]

Marcellin *et al.* found that the major factors known to be associated with faster fibrosis progression are older age at infection, male gender, and excessive alcohol consumption.[31] According to their study, viral load and genotype did not seem to influence significantly the progression rate. Progression of fibrosis is more rapid in immunocompromised patients. They discussed the different rates of cirrhosis progression, with a critical appraisal of influencing factors.

The impact of increasing diagnosis and treatment of HCV as new therapies become available in England, was modelled by Cramp *et al*.[32] Fibrosis progression rates through the disease stages was based on the study conducted by Razavi *et al.*[7]

Long-term outcome data with serial biopsies can be found in the studies by Smith *et al.*[33;a], Simon *et al.*[34], Freeman *et al.*[35;b], Xu *et al.*[36;c], and Tovo *et al.*[37;d].

Long-term outcome data without biopsies can be found in studies by Kielland *et al.*[38;e], Li *et al.*[39;f], Kenny-Walsh *et al.*[40;g], Wiese *et al.*[41;h], and Hissar *et al.*[42;i]

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[a] Biopsy was the preferred criterion for measuring fibrosis/cirrhosis.
[b] A systematic review including 57 studies by Freeman et al.
[c] Biopsy at start, then clinical endpoints; US, mostly white males
[d] Brazilian study; serial biopsies over 5 years
[e] drug users, autopsy
[f] Chinese, untreated persons infected at plasma donation
[g] Irish, untreated women infected with Rhesus prophylaxis
[h] East German women infected with Rhesus prophylaxis; part treated
[i] Calculation of progression in Indian patients

Special aspects of HCV-HIV coinfection are discussed by Benhamou *et al.*[43;j] and Bräu *et al.*[44;k] There are more studies that investigate the liver disease advancement under co-infection; however we do not cite them here, as they either contain only one biopsy, or serial Fibroscan tests without biopsies.

A.2 Fibrosis progression after sustained virological response

A description of the studies that were used to parameterize the mathematical model is shown in Section 2.1.4.

Poynard *et al.* combined the results of four large prospective studies in which patients undertook their second liver biopsy 24 weeks after cessation of IFN.[53] According to their study, the patients who achieved SVR in stages F2, F3, or F4 had an average negative annual fibrosis progression rate of −0.591 (−0.627 to −0.550). For non-responders this value was 0 (−0.443 to 0). Moreover, patients with or without SVR in stages F0 and F1 had no fibrosis progression during and after treatment.

Van der Meer *et al.* reviewed the current data regarding the beneficial clinical outcomes with antiviral therapy as well as the remaining uncertainties in this field.[54] They found that fibrosis regression has been demonstrated in several studies among patients with sustained virological response (SVR). According to their study, as fibrosis takes a long time to develop, it seems natural to take also a long time to regress. However, even with a long follow-up, not all patients with the highest fibrosis score showed fibrosis regression.

George *et al.* determined the long-term clinical, virological, histologic, and biochemical outcomes of 150 patients with SVR after treatment of chronic HCV infection.[55] They found that the majority of patients had improving outcomes, and some patients had even normal or nearly normal liver tissue. Patients with pretreatment cirrhosis remained at risk for developing HCC.

In order to determine whether liver stiffness decreases after treatment in patients with HCV genotype 1, Sáez-Royuela *et al.* analyzed data from HCV patients with advanced fibrosis (F3 and F4).[56] They found that 57% of cirrhotic patients with SVR had cirrhosis regression. In their study, patients with decompensated cirrhosis were excluded. However, they believed that in HCV, it is still uncertain whether severe fibrosis could be reversed to some extent. Moreover, they believed that for reasons not known, advanced fibrosis and cirrhosis did neither regress nor progress in some patients, despite

[j] 122 HIV co-infected persons compared to 122 HCV mono-infected persons
[k] Focus on the influence of ART in HIV-HCV co-infected persons

the presence of SVR. Comorbidities such as alcohol consumption, diabetes and obesity probably play a major role in the progression of liver disease in SVR patients.[57]

A.3 Mortality

A description of the studies that were included in the parameterization of the model is shown in Section 2.4.

Keiser *et al.* analyzed time trends in HCV-specific mortality rates in the Swiss general population using the death registry of the Federal Statistical Office (FSO).[83] According to their study HCV-related mortality increased between 1995 and 2003, and remained constant afterward. Their study suggests that the overall mortality for patients with HCV remained almost constant at 2.5/100,000 person-year.

Calzadilla-Bertot *et al.* examined the influence of glucose abnormalities on overall mortality and liver-related complications in cirrhotic patients.[84] They showed that adjusted overall mortality was significantly higher in diabetic patients than in those without diabetes.

Adjusted median times to death for males with excessive alcohol consumption and IDU have been estimated by Giudici *et al*. using the SCCS data.[85] Liver-related mortality rate in HIV-HCV co-infected people is estimated by May *et al*.[86] Aghemo *et al.* estimated the liver-related mortality for HCV infected patients with or without SVR.[87]

Kershenobich *et al.* developed a model to estimate the mortality rate in different countries based on age, liver related deaths due to HCV infection and the proportions of the prevalent population infected by intravenous drug users (IDU) and transfusion.[88] The mortality rates were adjusted for being an active IDUs between ages 15 and 44, and transfusion. They used a dynamic system approach with inflows and outflows to build a simulation model to estimate the future size of the HCV-infected population regardless of the severity of the disease. The model did not take into account future events such as the introduction of new therapies or a significant increase in treatment rates. They assumed that HCV infected IDU had an excess mortality ratio of 22.0 between the ages 15 and 44.

A systematic review found a crude mortality rate of 2.3 per 100 person-years among IDUs in Western Europe.[69] The United Nations Office on Drugs and Crime reported mortality related to drug use as 24.2 per one million person-years for the total population aged between 15 and 64 in Switzerland.[89]

Appendix B. Baseline characteristics of the Swiss Hepatitis C Cohort Study (SCCS) in 2017

Table 10 (Appendix). Distribution of genotypes across regions of origin.

Region	Genotype 1	Genotype 2	Genotype 3	Genotype 4
Switzerland	48.24	7.58	27.00	9.62
Southern Europe	49.76	8.86	25.03	9.48
Western Europe	46.24	10.15	25.18	11.27
Eastern Europe	54.94	6.59	24.17	6.59
North Europe	54.16	4.16	25.00	8.33
Asia/Oceania	43.36	11.50	30.97	7.96
America	48.78	4.87	21.95	15.85

All values are in %.

Table 11 (Appendix). Distribution of birth years across regions of origin.

Year of Birth	Switzerland	Southern Europe	Western Europe	Eastern Europe	North Europe	Asia /Oceania	America	Africa
> 1987	0.30	0.10	0.37	0.00	4.10	0.00	1.21	0.79
1983-1987	1.05	0.00	0.75	1.098	0.00	2.65	3.66	2.38
1978-1982	3.65	3.11	4.13	10.98	0.00	10.62	3.66	1.58
1973-1977	7.54	7.93	3.08	20.87	8.30	11.50	4.88	8.73
1968-1972	16.22	9.02	11.65	10.98	12.50	21.33	14.63	15.07
1963-1967	12.04	11.19	13.90	6.59	12.50	8.84	2.44	14.28
1958-1962	19.59	15.55	19.92	5.49	16.66	12.38	20.73	19.84
1953-1957	12.71	10.73	17.29	19.78	8.33	9.73	21.95	19.04
1948-1952	4.17	3.88	3.75	1.10	12.50	6.19	6.10	8.73
1943-1947	4.28	8.55	3.00	8.79	16.66	7.96	7.31	3.17
1933-1943	5.65	20.52	8.64	10.98	0.00	4.42	2.43	7.14

All values are in %.

Appendix C. Categorization of countries of origin

Table 12 shows the categorization of countries located geographically in Europe. Countries located geographically in North, Central and South America, Caribbean and Oceania were categorized into group 2 (Western Europe, Americas, Oceania), and countries in Africa and Asia into group 4 (Southern Europe, Asia, Africa), with the exception of the Asian former members of the USSR which were categorized into group 3 (Eastern Europe, Central Asia, Balkans).

Table 12 (Appendix). Categorization of European countries.

Country	Category
Albania	3: Eastern Europe, Central Asia and the Balkans
Andorra	2: Western Europe, Americas and Oceania
Austria	2: Western Europe, Americas and Oceania
Belarus	3: Eastern Europe, Central Asia and the Balkans
Belgium	2: Western Europe, Americas and Oceania
Bosnia and Herzegovina	3: Eastern Europe, Central Asia and the Balkans
Bulgaria	3: Eastern Europe, Central Asia and the Balkans
Croatia	3: Eastern Europe, Central Asia and the Balkans
Cyprus	4: Southern Europe, Asia, Africa
Czech Republic	3: Eastern Europe, Central Asia and the Balkans
Denmark	2: Western Europe, Americas and Oceania
Estonia	3: Eastern Europe, Central Asia and the Balkans
Finland	2: Western Europe, Americas and Oceania
France	2: Western Europe, Americas and Oceania
Germany	2: Western Europe, Americas and Oceania
Greece	4: Southern Europe, Asia, Africa
Hungary	3: Eastern Europe, Central Asia and the Balkans
Iceland	2: Western Europe, Americas and Oceania
Ireland	2: Western Europe, Americas and Oceania
Italy	4: Southern Europe, Asia, Africa
Kosovo	3: Eastern Europe, Central Asia and the Balkans
Latvia	3: Eastern Europe, Central Asia and the Balkans
Liechtenstein	1: Switzerland and Liechtenstein
Lithuania	3: Eastern Europe, Central Asia and the Balkans
Luxembourg	2: Western Europe, Americas and Oceania

Country	Category
Macedonia	3: Eastern Europe, Central Asia and the Balkans
Malta	4: Southern Europe, Asia, Africa
Moldova	3: Eastern Europe, Central Asia and the Balkans
Monaco	2: Western Europe, Americas and Oceania
Montenegro	3: Eastern Europe, Central Asia and the Balkans
Netherlands	2: Western Europe, Americas and Oceania
Norway	2: Western Europe, Americas and Oceania
Poland	3: Eastern Europe, Central Asia and the Balkans
Portugal	4: Southern Europe, Asia, Africa
Romania	3: Eastern Europe, Central Asia and the Balkans
Russia	3: Eastern Europe, Central Asia and the Balkans
San Marino	4: Southern Europe, Asia, Africa
Serbia	3: Eastern Europe, Central Asia and the Balkans
Slovakia	3: Eastern Europe, Central Asia and the Balkans
Slovenia	3: Eastern Europe, Central Asia and the Balkans
Spain	4: Southern Europe, Asia, Africa
Sweden	2: Western Europe, Americas and Oceania
Switzerland	1: Switzerland and Liechtenstein
Turkey	4: Southern Europe, Asia, Africa
Ukraine	3: Eastern Europe, Central Asia and the Balkans
United Kingdom	2: Western Europe, Americas and Oceania
Vatican City	4: Southern Europe, Asia, Africa

Appendix D. Background mortality

Table 13 (Appendix). Background mortality rates for men and women according to age in 2014 and 2015 (based on FSO).[81]

	2014		2015	
Age	Male	Female	Male	Female
0 years	0.004089	0.003121	0.004003	0.003326
1 year	0.000466	0.000345	0.000614	0.000336
2 years	0.000231	0.000148	0.000323	0.000171
3 years	2.34E-05	0.000124	4.58E-05	7.33E-05
4 years	6.97E-05	9.71E-05	0.000139	4.93E-05
5 years	2.35E-05	9.97E-05	6.91E-05	4.81E-05
6 years	2.36E-05	0	0.000116	9.87E-05
7 years	2.42E-05	5.09E-05	0.000117	7.48E-05
8 years	7.31E-05	0.000103	4.79E-05	5.04E-05
9 years	9.77E-05	2.59E-05	2.42E-05	0.000102
10 years	0.000123	0	7.26E-05	2.56E-05
11 years	7.48E-05	0.000105	0	0.000102
12 years	9.8E-05	0.000104	9.89E-05	0.000104
13 years	7.3E-05	0.000155	0.000146	5.13E-05
14 years	6.88E-05	4.87E-05	0.000121	0.000179
15 years	0.000116	0.000171	9.09E-05	0.000145
16 years	0.000228	0.000144	0.000298	4.83E-05
17 years	0.000291	0.000118	0.000247	9.5E-05
18 years	0.000367	0.000136	0.000351	0.000162
19 years	0.000471	4.48E-05	0.000441	0.000222
20 years	0.000272	8.78E-05	0.000525	8.77E-05
21 years	0.000369	0.000128	0.000534	8.61E-05
22 years	0.000412	0.000242	0.000521	0.000125
23 years	0.000305	0.000216	0.000515	9.82E-05
24 years	0.000299	0.000154	0.00048	0.00021
25 years	0.000446	0.00019	0.000471	0.00013
26 years	0.000467	0.000202	0.000558	7.35E-05

	2014		2015	
Age	Male	Female	Male	Female
27 years	0.000525	0.000129	0.000453	0.000178
28 years	0.000531	0.00018	0.000526	0.000161
29 years	0.000333	0.000319	0.000431	0.000157
30 years	0.000549	0.000299	0.000428	0.000208
31 years	0.000395	0.00023	0.000335	0.000241
32 years	0.000472	0.00024	0.000607	0.000243
33 years	0.000524	0.000259	0.000564	0.000304
34 years	0.000637	0.000361	0.000517	0.000288
35 years	0.000606	0.000228	0.000446	0.000255
36 years	0.000507	0.000302	0.000615	0.000365
37 years	0.000507	0.000391	0.000587	0.000351
38 years	0.000849	0.000391	0.000725	0.000317
39 years	0.000868	0.000465	0.000752	0.000528
40 years	0.00093	0.000597	0.000719	0.000549
41 years	0.000876	0.0004	0.000786	0.000435
42 years	0.000862	0.000629	0.000989	0.000414
43 years	0.001358	0.000588	0.001003	0.000641
44 years	0.001288	0.000742	0.001412	0.000698
45 years	0.001197	0.00069	0.001185	0.001027
46 years	0.001365	0.00089	0.001438	0.00092
47 years	0.001394	0.000945	0.001797	0.000932
48 years	0.001812	0.001199	0.001703	0.0012
49 years	0.001828	0.001158	0.002071	0.001242
50 years	0.002392	0.001273	0.002508	0.001382
51 years	0.002872	0.001429	0.002391	0.001536
52 years	0.00294	0.001504	0.002668	0.001902
53 years	0.002871	0.001959	0.002619	0.001647
54 years	0.003248	0.002185	0.003228	0.002223
55 years	0.003394	0.002564	0.00395	0.002138
56 years	0.004308	0.002718	0.004281	0.002587
57 years	0.004981	0.002912	0.004171	0.002616

	2014		2015	
Age	Male	Female	Male	Female
58 years	0.00535	0.002773	0.004904	0.003055
59 years	0.005633	0.003468	0.005619	0.003252
60 years	0.006311	0.00296	0.00635	0.00369
61 years	0.006836	0.003677	0.006699	0.00384
62 years	0.007481	0.004355	0.008207	0.004426
63 years	0.008244	0.004682	0.008815	0.004324
64 years	0.009357	0.004873	0.009666	0.004798
65 years	0.010476	0.005241	0.010491	0.005712
66 years	0.011504	0.006441	0.010085	0.006859
67 years	0.013043	0.006892	0.012261	0.007184
68 years	0.013701	0.007779	0.014167	0.007176
69 years	0.014601	0.007609	0.015148	0.0083
70 years	0.01592	0.008784	0.015674	0.008848
71 years	0.018229	0.010211	0.018598	0.009921
72 years	0.017999	0.011739	0.019801	0.011236
73 years	0.021368	0.012269	0.022057	0.011182
74 years	0.02228	0.012551	0.024331	0.014513
75 years	0.025763	0.015071	0.026651	0.015111
76 years	0.029439	0.016336	0.028528	0.018423
77 years	0.031307	0.019085	0.034784	0.0209
78 years	0.035795	0.022592	0.037438	0.022147
79 years	0.038258	0.024912	0.043058	0.025207
80 years	0.048137	0.028492	0.046955	0.028308
81 years	0.055583	0.034111	0.055816	0.03561
82 years	0.061403	0.039902	0.066068	0.03739
83 years	0.070615	0.044507	0.069463	0.048144
84 years	0.081032	0.051116	0.083079	0.056441
85 years	0.090628	0.064589	0.093036	0.06082
86 years	0.109028	0.072927	0.105946	0.078281
87 years	0.128267	0.088903	0.123602	0.090188
88 years	0.142296	0.10103	0.149383	0.106278

	2014		2015	
Age	Male	Female	Male	Female
89 years	0.162824	0.12704	0.170915	0.122572
90 years	0.180525	0.133641	0.20857	0.142943
91 years	0.210397	0.160615	0.225931	0.173739
92 years	0.245631	0.188521	0.251538	0.196493
93 years	0.30122	0.209084	0.315588	0.239773
94 years	0.309412	0.244569	0.311947	0.265862
95 years	0.361933	0.280126	0.370759	0.319672
96 years	0.409231	0.310084	0.423347	0.364224
97 years	0.482916	0.388713	0.484018	0.406737
98 years	0.519856	0.402428	0.55477	0.453456
99 years	0.42268	0.447439	0.674699	0.515789
100 years or older	0.651724	0.606544	0.672414	0.562893

Appendix E. Results of the analyses assuming dynamic fibrosis progression and high IDU diagnosis rate in the past, and constant fibrosis progression and low IDU diagnosis rate in the past

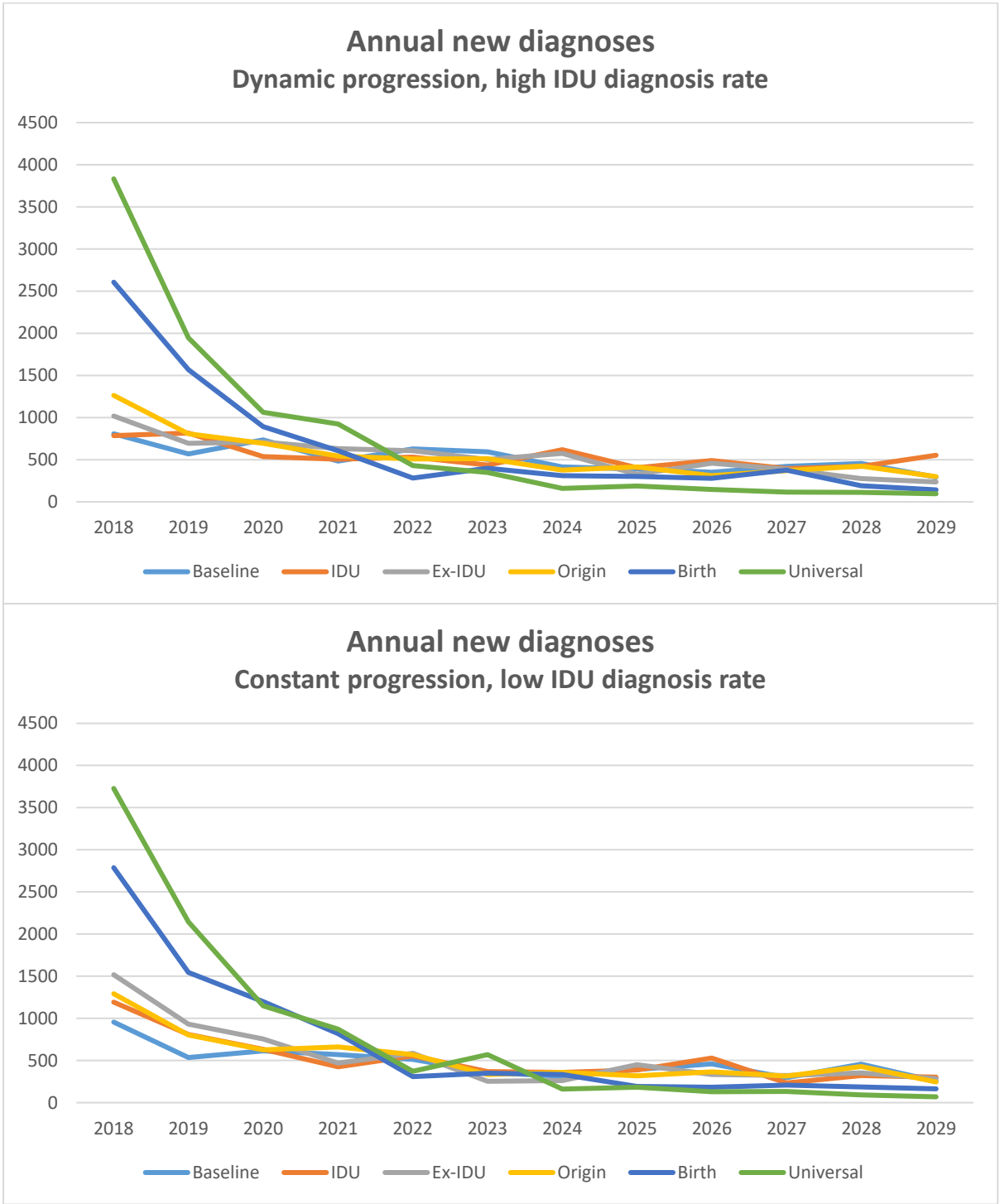

Figure 32 (Appendix). Annual new diagnoses 2017-2029 according to the model. *Analyses using dynamic fibrosis progression and high past injection drug user (IDU) diagnosis rate are shown in the upper panel, and constant fibrosis progression and low past IDU diagnosis rate in the lower panel. Different curves present different screening scenarios.*

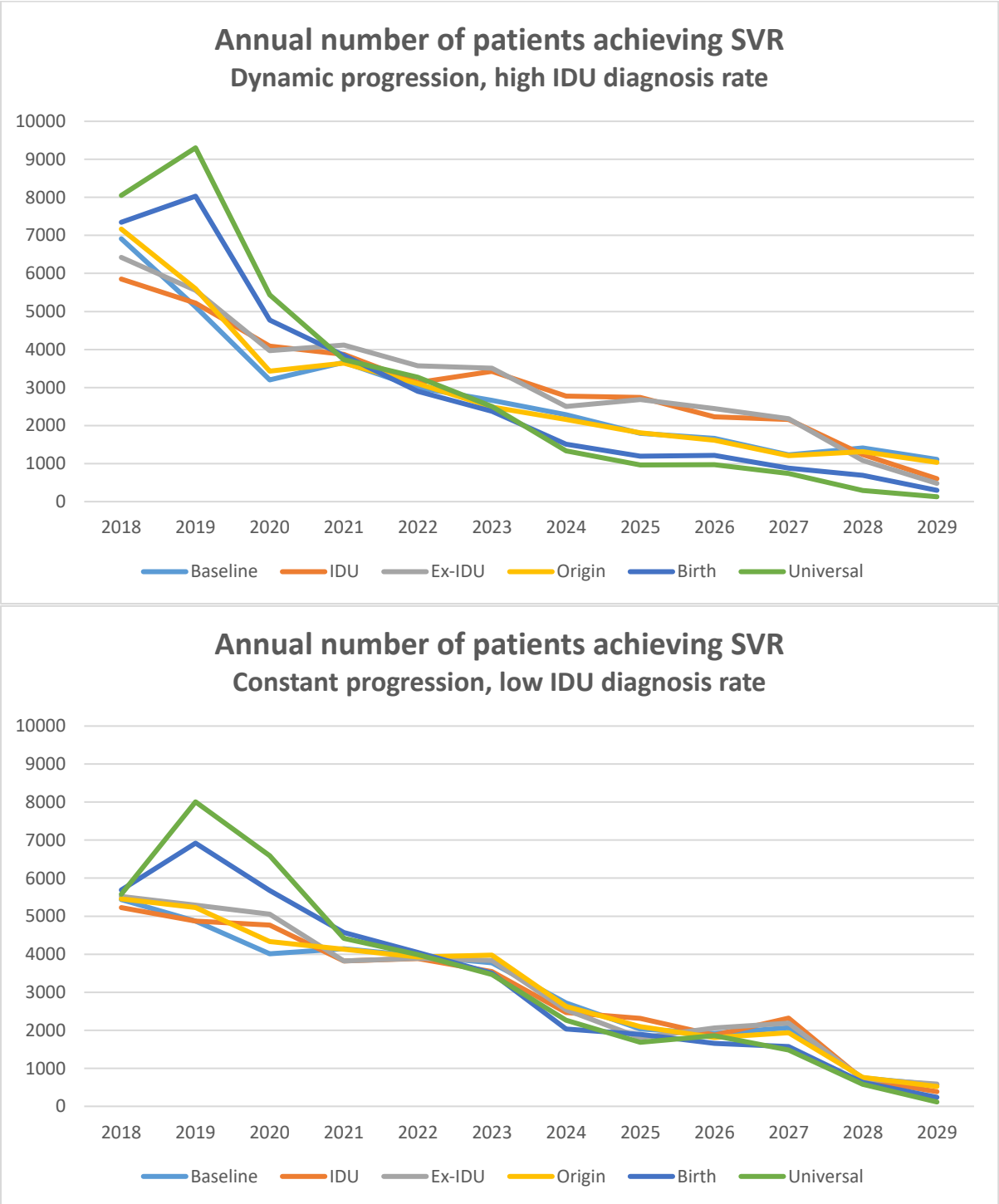

Figure 33 (Appendix). Annual number of cured patients 2018-2029 according to the model. *Analyses using dynamic fibrosis progression and high past IDU diagnosis rate are shown in the upper panel, and constant fibrosis progression and low past IDU diagnosis rate in the lower panel.*

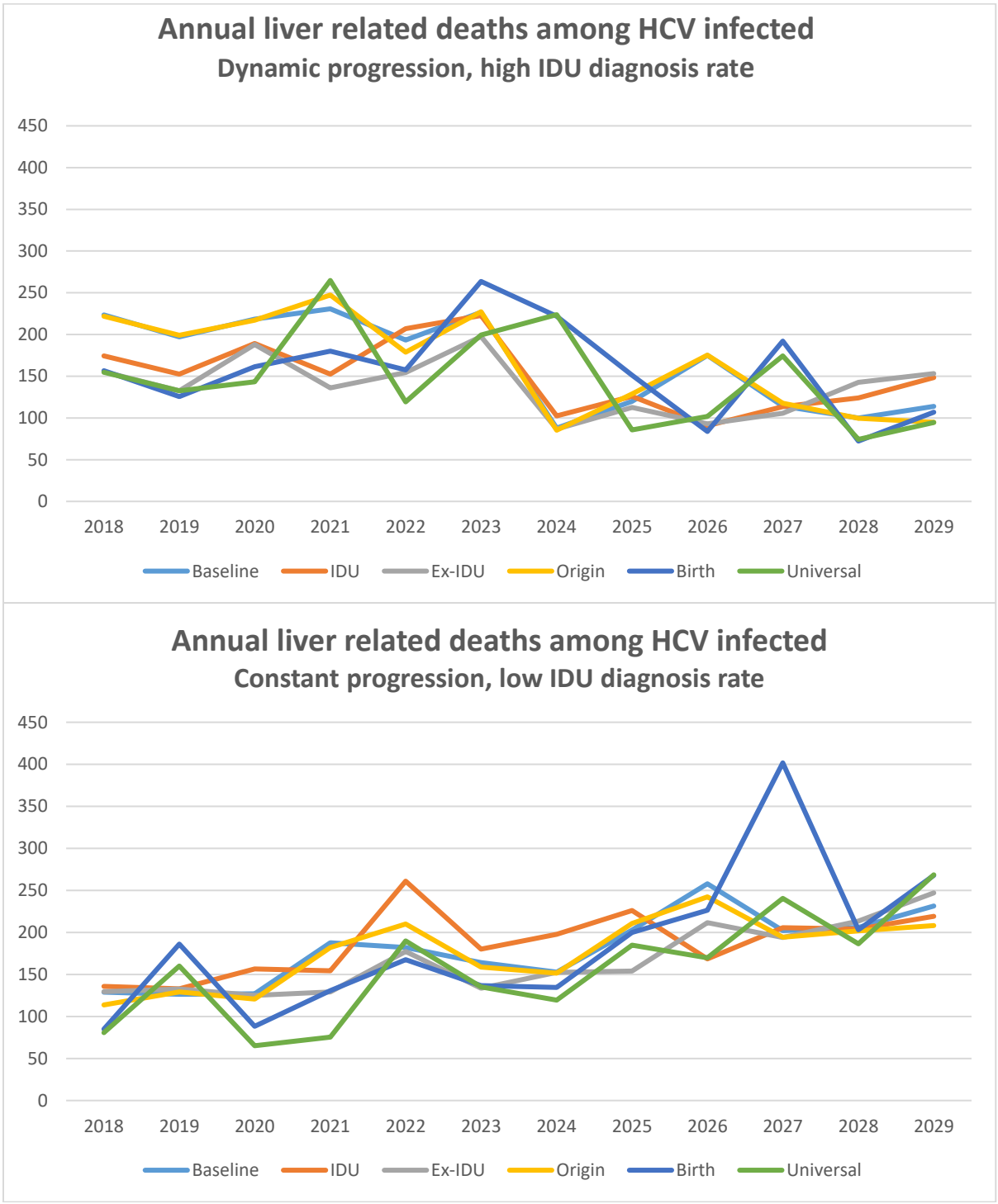

Figure 34 (Appendix). Annual liver related deaths among hepatitis C virus (HCV) infected patients 2018-2029 according to the model. *Analyses using dynamic fibrosis progression and high past injection drug user (IDU) diagnosis rate are shown in the upper panel, and constant fibrosis progression and low past IDU diagnosis rate in the lower panel.*

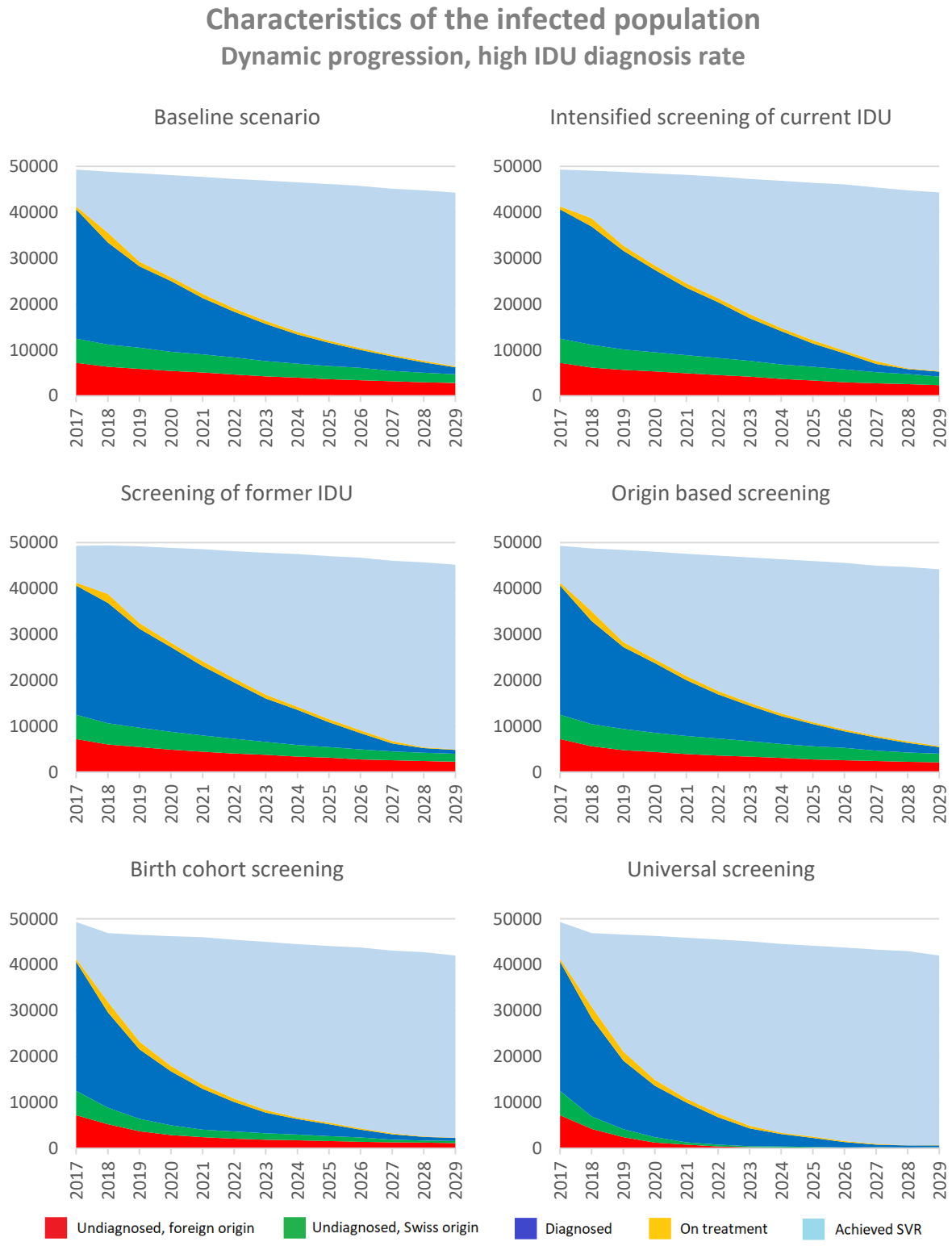

Figure 35 (Appendix). Distribution of undiagnosed, diagnosed, currently treated and cured among the infected population 2017-2029 according to the model using dynamic fibrosis progression and high diagnosis rate among injecting drug users (IDU) in the past in in the six modelled screening scenarios. *Spontaneously cleared patients are not shown.*

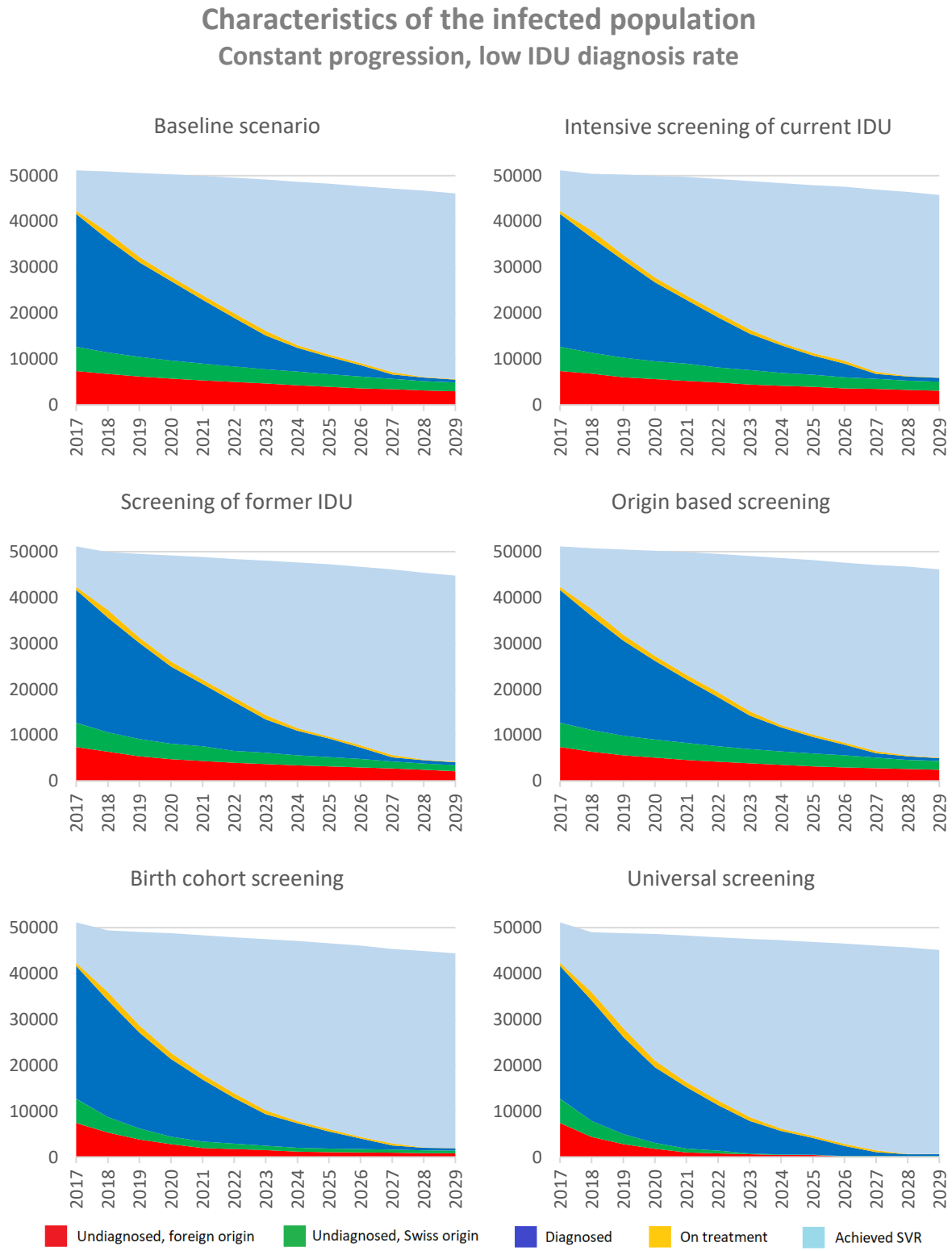

Figure 36 (Appendix). Distribution of undiagnosed, diagnosed, currently treated and cured among the infected population 2017-2029 according to the model using constant fibrosis progression and low diagnosis rate among injecting drug users (IDU) in the past in in the six modelled screening scenarios. *Spontaneously cleared patients are not shown.*

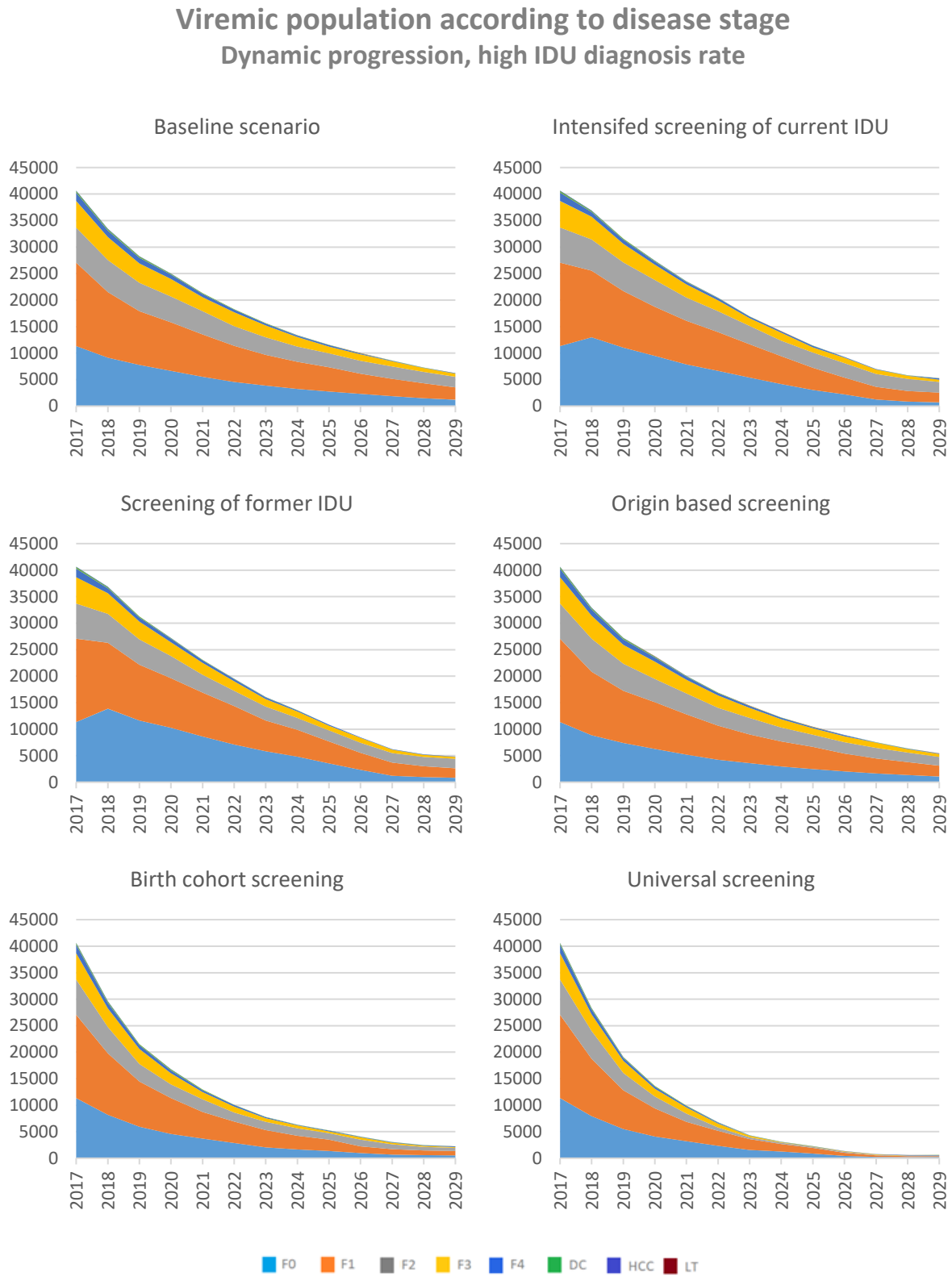

Figure 37 (Appendix). Viremic population by fibrosis stage 2018-2029 according to the model using dynamic progression and high past injection drug user (IDU) diagnosis rate in the six modelled screening scenarios. *DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation.*

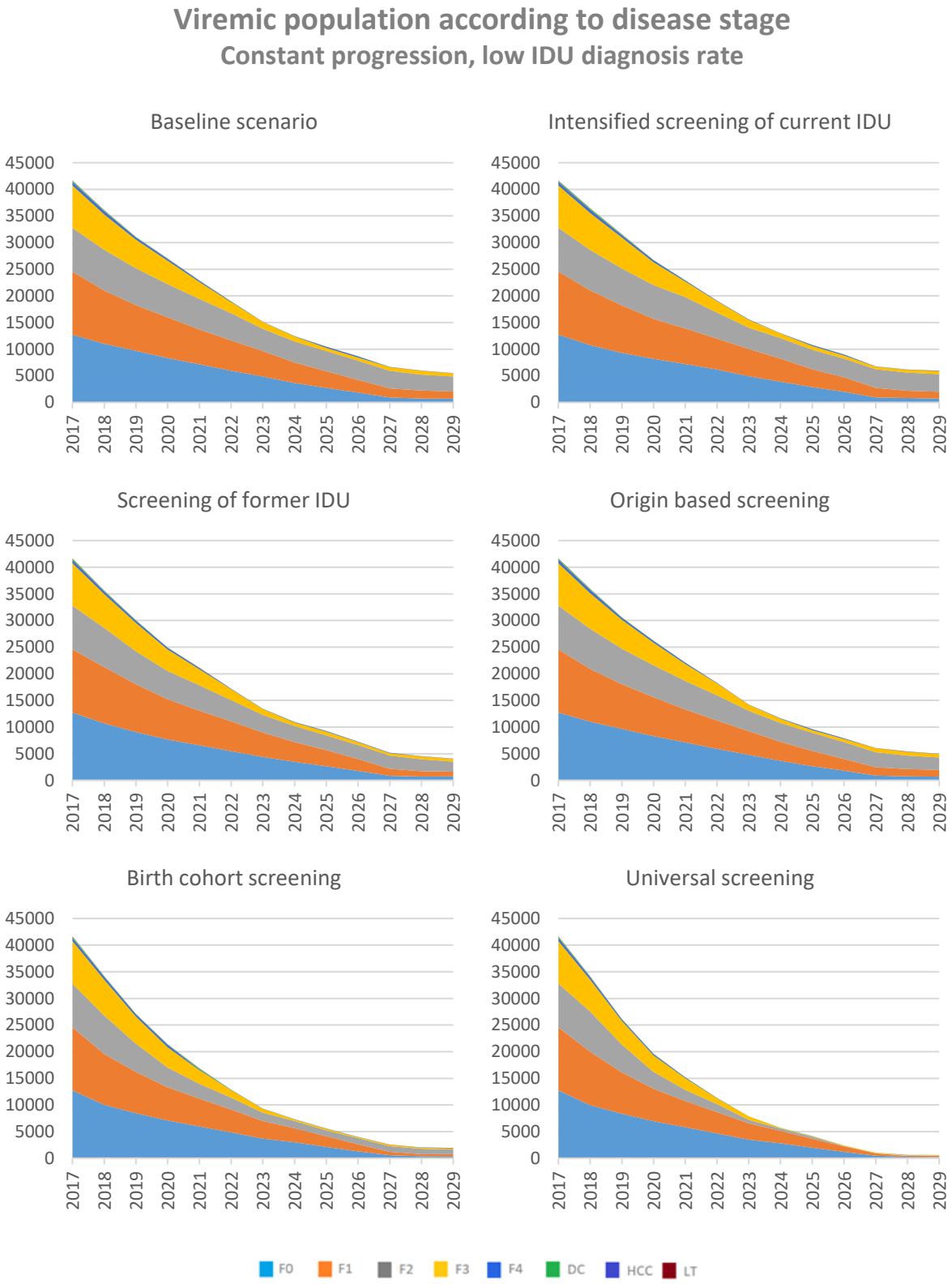

Figure 38 (Appendix). Viremic population by fibrosis stage 2018-2029 according to the model using constant progression and low past injection drug user (IDU) diagnosis rate in the six modelled screening scenarios. *DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation.*

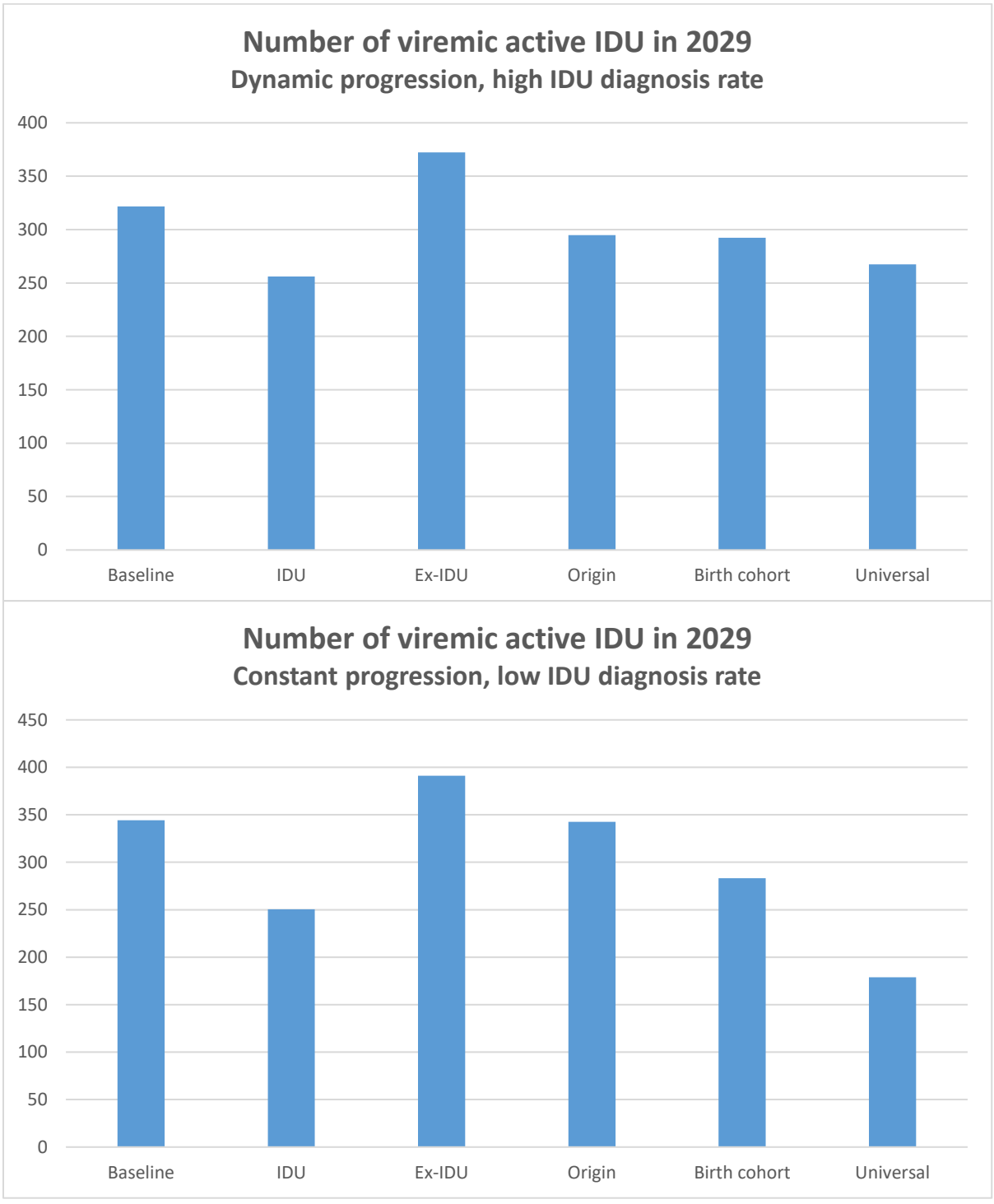

Figure 39 (Appendix). Number of viremic active injection drug users (IDU) in 2029 in different screening scenarios. *The results according to the model with dynamic fibrosis progression and high past IDU diagnosis rate are shown in the upper panel, and constant fibrosis progression and low past IDU diagnosis rate in the lower panel.*