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# Appendix

## Cost-effectiveness analysis of strategies to manage the disease burden of hepatitis C virus in Switzerland

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### Section 1. HCV disease burden model, forecasting viremic prevalence

**Indicator —** This analysis focused on estimating viremic HCV infections, which are indicated by the presence of HCV RNA. The analysis used anti-HCV prevalence, serological evidence of past or present infection and the viremic rate in a Markov model to estimate the end-of-year viremic prevalence in 2015.

**Time period —** Available published and unpublished studies conducted before January 1, 2018 were considered for model input values. Model outcomes concerning disease burden (including viremic prevalence, incidence and prevalence of HCC, decompensated cirrhosis and mortality) were forecasted through to 2030, in line with the Global Health Sector Strategy Targets. Costs and health effects associated with these outcomes were assessed through to 2031 to ensure full realization of the scenario costs.

**Geographical scope —** The analysis focused on the HCV-infected population residing in Switzerland at a national level.

### Modelling HCV prevalence

The analysis started with a review of published studies and was supplemented with Delphi method interviews with national experts to ensure that all relevant data (including unpublished data) were taken into consideration. A Markov model was used to forecast HCV prevalence over time. The prevalence of HCV is not constant over time. When incident cases are higher than deaths and cures, the total number of infections will increase over time. The total number of infections will decrease over time when the opposite is true. The model was used to forecast HCV prevalence at the end of 2015. The details of the model have been published previously (1, 2).

**Required inputs —** The following inputs were required to build and calibrate the Swiss model.

| Model input | Definition | Source |
|---|---|---|
| **Country population by 5-year age group** | Number of people in the country, reported annually from 1950 to 2050 (by sex and 5-year age group) | (3) |
| **Mortality rate by 5-year age group** | Share of deaths among the total population, reported annually from 1950 to 2050 (by sex and 5-year age group) | (4) |
| **Anti-HCV prevalence** | Share of total population who are anti-HCV(+) | (5) |
| **Viremic rate** | Percentage of anti-HCV(+) individuals who are HCV RNA(+) | (6) |
| **Age and sex distribution** | HCV prevalence by sex and 5-year age group | Calculated using diagnosis data from the Swiss FOPH, adjusted to the size of the prevalent population (7, 8) (5) |
| **Genotype distribution** | Proportion of HCV RNA(+) population categorized by HCV genotype (out of 100%) | (9) |
| **Annually treated** | Number of HCV-infected individuals who have received treatment in a given year | IMS Health (8)<br>Expert Input (Prof. Franco Negro) |
| **Total diagnosed** | Viremic HCV cases diagnosed and alive in a given year | Calculated using data from (7, 8) |
| **Newly diagnosed** | Annual number of newly diagnosed HCV cases | (7, 8) |
| **Liver transplants** | Annual number of liver transplantations due to HCV | Swiss Transplant; Personal communication |
| **HCC** | Annual incident cases of HCC due to HCV | NICER; Geneva Tumour Registry; (10) |

**Prevalence by age —** Switzerland's notification data were used to estimate HCV prevalence by age. In this method, the annual number of newly diagnosed cases in Switzerland was collected and adjusted for mortality and cures. The birth year was used to calculate age and to consolidate data from multiple years into the last year with available data. It was assumed that screening was conducted randomly. The number of diagnosed cases in each age group was divided by the country's population in that age group (in the last year of data). A weighting factor was applied to get the sum-product of the rough prevalences by age and the general populations by age equal to the estimated total number of infections in the country. This weighting factor times the rough prevalence was used as an estimate of the true prevalence by age. The output was approved by the expert panel. Diagnosed data by age were available through the Federal Office of Public Health (11).

**Treated patients —** IMS data showed an estimated 2,300 (2,000–2,500) patients treated in Switzerland in 2015, approximately 1,280 of whom were ≥F3 and the remainder of whom were F2 (8). In 2016, the number of treated patients dropped to 2,100 ≥F2 (Table 1). In October 2017, treatment restrictions were lifted, making patients of all fibrosis stages eligible for treatment. In 2017, 3,000 patients were treated (IMS Health data), an increase of 43% compared to 2016, as previously warehoused F0 and F1 patients began to seek treatment.

**Cured patients —** In the absence of better information, it was assumed that the genotype distribution of the treated population was the same as that of the total infected population (they have the same probability of being diagnosed and treated). The sustained virological response (SVR) rates by genotype were used to estimate the number of patients cured per year. Interviews with national experts were used to determine the real-world SVR rates for the different treatment regimens: interferon-based therapy in combination with ribavirin (RBV) (dual therapy), with RBV and a protease inhibitor (PI) (triple therapy), and RBV with direct-acting antivirals (DAAs). Experts took into consideration the percentages of the population that were treatment-experienced and treatment-naïve for each treatment option and the disease stage of the patients being treated (e.g., F1, F2, F3 and F4). The average SVR rate by genotype and by country has been reported previously (2, 12, 13). The SVR rates in countries without expert interviews were extrapolated from countries with interviews.

**Liver transplantations —** The annual number of liver transplantations was obtained from Swiss Transplant and adjusted for the percentage attributed to HCV infection based on expert consensus. For examples of such an adjustment factor, see the references listed here (14-19).

**Diagnosed patients —** Notification data from 1988–2015 from the Swiss Federal Office of Public Health was utilized (11). The number of diagnosed cases was calculated by summing data from all years after taking into consideration the mortality among diagnosed cases. It was assumed that the viremic rate among the diagnosed population was the same as in the total infected population.

**All-cause mortality —** The all-cause mortality rates by age and sex were taken from the United Nations World Population Prospects (4). The rates were adjusted for an incremental increase in mortality due to injection drug use (IDU) and a history of blood transfusion in the HCV-infected population. A standardized mortality ratio (SMR) of 10 (9.5–29.9) was used for the portion of the HCV-infected population that were active PWID aged 15–44 (20-25). An SMR of 2.1 (1.3–17.6) was applied to all ages for the portion of the population infected due to transfusion (26). The number of active PWID and the HCV prevalence among PWID were taken from published studies (27-30) and divided by the total HCV-infected population to estimate the percentage of all HCV infections that were among active PWID.

**Markov model —** The Markov model described here is an open-source model that is provided to academic and government researchers upon request. Modellers and epidemiologists in France, Greece, Australia, Egypt, Spain and Portugal have independently reviewed the model and provided feedback for modifications and updates. In addition, experts in 59 countries continue to provide requests for updates to the model to enhance its functionality and algorithms. Since its inception in 2012 (31), the model has undergone over 80 revisions and updates.

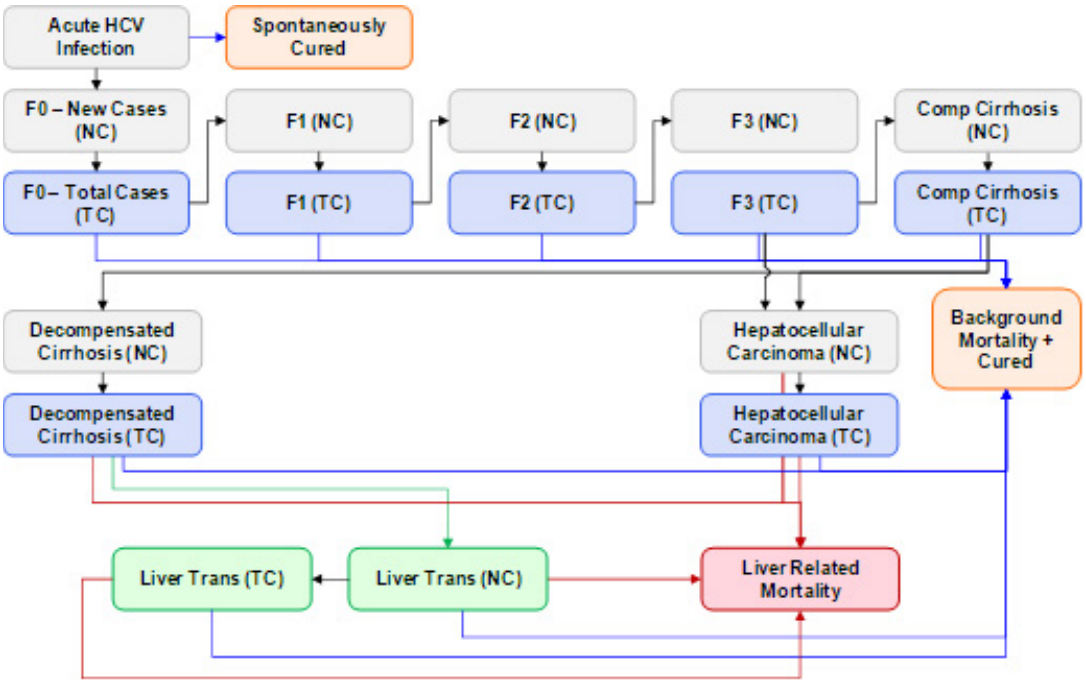
The Markov (disease progression) model was constructed in Microsoft Excel® (Microsoft Corp., Redmond, WA) to quantify the annual size of the HCV-infected population by stage of liver disease over 1950–2050. The size and impact of the HCV-infected population prior to 1950 was considered negligible for the purposes of this analysis. Microsoft Excel was selected as a platform due to its transparency, availability and minimal need for operator training. The disease progression was modelled using the flow shown in the figure below and the calculations shown in Equation 1.

The model started with the annual number of acute infections that progressed to chronic (viremic) HCV infection after accounting for spontaneous clearance of the virus. The methodology to calculate incidence is described below. The progression of these new cases was followed, along with all chronic infections from prior years. Unless otherwise specified, the scope of the model was limited to viremic, HCV ribonucleic acid (RNA)-positive cases. Non-viremic cases (those who were exposed to the virus but either spontaneously cleared it or were treated and cured) were not considered.

The number of new (incident) cases at each stage of disease was calculated annually by multiplying the annual progression rate by the prevalent population (by age and sex) in the previous stage, less cures and deaths. Thus, the annual number of new F2 cases was calculated by multiplying the prevalent population in F1 (by age and sex) less cures and deaths in the prevalent population in F1 by the F1–F2 progression rate.

The prevalent population at each stage of disease was tracked by one-year age group and was aged (progressed to the next age group) annually. The progression rates were back-calculated using five-year age groups (as described below). In this model, the progression rate was assumed to be constant over the five-year age group. Thus, for ages 5–9, the F1–F2 progression rate was assumed to be constant.

**The flow of the HCV disease progression model**



**Equation 1. Prevalent cases in stage of liver disease $x$, at time $t$, of sex $s$, and age $a$**

$$\text{Prevalent cases}_{x,t,s,a} = \text{Prevalent cases}_{x,t-1,s,a-1,} \times \left(1 - d_{t-1,s,a-1}\right) \times \left(1 - l_{x,t-1,s,a-1}\right) \times \left(1 - p_{x \to y_1,s,a-1}\right) \times \left(1 - p_{x \to y_2,s,a-1}\right) \times \cdots \times \left(1 - p_{x \to y_n,s,a-1}\right) \times \left(1 - c_{x,t-1}\right) \times \left(1 - s_{x,t-1}\right) + \text{New cases}_{x,t,s,a}$$

where:

$\boldsymbol{d_{t,s,a}}$ is the annual background mortality rate at time $t$, for sex $s$, at age $a$

$\boldsymbol{l_{x,t,s,a}}$ is the annual liver-related mortality rate for stage $x$, at time $t$, for sex $s$, at age $a$

$\boldsymbol{p_{x \to y_1,s,a}}$, $\boldsymbol{p_{x \to y_2,s,a}}$, …, $\boldsymbol{p_{x \to y_n,s,a}}$ are the annual progression rates from stage $x$ to $y_1$, stage $x$ to $y_2$, …, stage $x$ to $y_n$, respectively, for sex $s$, at age $a$

$\boldsymbol{c_{x,t}}$ is the annual cure rate for stage $x$, at time $t$, defined as

$$c_{x,t} = \frac{\text{Total annual treatments}_{x,t} \times \text{SVR rate}_t}{\text{Total treatment-eligible cases}_{x,t-1}}$$

$\boldsymbol{s_{x,t}}$ is the annual liver transplantation rate for stage $x$, at time $t$, defined as

$$s_{x,t} = \frac{\text{Total liver transplantations}_{x,t}}{\text{Total liver transplant-eligible cases}_{x,t-1}}$$

**New cases$_{x,t,s,a}$** is the number of cases incident or progressing to stage $x$, at time $t$, for sex $s$, at age $a$.

**Progression rates —** The progression rates by age, sex and fibrosis score were back-calculated. Data from the UK were used for the percentage increase in progression rate by age and sex (32). However, this study only reported progression from chronic HCV to moderate chronic HCV and from moderate chronic HCV to cirrhosis. These reported rates were modified using a meta-analysis of published work to calculate progression rates for F0, F1, F2, F3 and F4 (33). Finally, the modified progression rates were adjusted to fit historical HCC incidence by age and sex in the U.S. (34) having adjusted for the portion of all HCC cases attributed to HCV infection (35).
The progression rates to end-stage liver disease and liver-related death were based on previously published rates. Insufficient data were available to develop predictable rates by age and sex. Thus, the same rate was applied for all ages and both sexes (36-38). The table below lists all progression rates along with the uncertainty intervals.

## HCV disease progression rates

**Back-calculated annual progression rates — Males**

| Age group | 0–4 | 5–9 | 10–14 | 15–19 | 20–24 | 25–29 | 30–34 | 35–39 | 40–44 | 45–49 | 50–54 | 55–59 | 60–64 | 65–69 | 70–74 | 75–79 | 80–84 | 85+ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **F0 to F1** | 5.3% | 5.3% | 5.3% | 5.3% | 5.3% | 5.3% | 5.3% | 5.3% | 13.9% | 13.9% | 17.1% | 17.1% | 19.4% | 19.4% | 21.8% | 21.8% | 21.8% | 21.8% |
| **Low** | 3.1% | 3.1% | 3.1% | 3.1% | 3.1% | 3.1% | 3.1% | 3.1% | 8.2% | 8.2% | 10.1% | 10.1% | 11.4% | 11.4% | 12.8% | 12.8% | 12.8% | 12.8% |
| **High** | 8.1% | 8.1% | 8.1% | 8.1% | 8.1% | 8.1% | 8.1% | 8,1% | 21.3% | 21.3% | 26.2% | 26.2% | 29.7% | 29.7% | 33.4% | 33.4% | 33.4% | 33.4% |
| **F1 to F2** | 3.4% | 3.4% | 3.4% | 3.4% | 3.4% | 3.4% | 3.4% | 3.4% | 9.1% | 9.1% | 11.2% | 11.2% | 12.7% | 12.7% | 14.3% | 14.3% | 14.3% | 14.3% |
| **Low** | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 5.3% | 5.3% | 6.6% | 6.6% | 7.5% | 7.5% | 8.4% | 8.4% | 8.4% | 8.4% |
| **High** | 5.3% | 5.3% | 5.3% | 5.3% | 5.3% | 5.3% | 5.3% | 5.3% | 13.9% | 13.9% | 17.1% | 17.1% | 19.4% | 19.4% | 21.8% | 21.8% | 21.8% | 21.8% |
| **F2 to F3** | 5.4% | 5.4% | 5.4% | 5.4% | 5.4% | 5.4% | 5.4% | 5.4% | 14.3% | 14.3% | 17.5% | 17.5% | 19.9% | 19.9% | 22.4% | 22.4% | 22.4% | 22.4% |
| **Low** | 3.2% | 3.2% | 3.2% | 3.2% | 3.2% | 3.2% | 3.2% | 3.2% | 8.4% | 8.4% | 10.3% | 10.3% | 11.7% | 11.7% | 13.2% | 13.2% | 13.2% | 13.2% |
| **High** | 8.3% | 8.3% | 8.3% | 8.3% | 8.3% | 8.3% | 8.3% | 8.3% | 21.8% | 21.8% | 26.9% | 26.9% | 30.5% | 30.5% | 34.3% | 34.3% | 34.3% | 34.3% |
| **F3 to C Cirrhosis** | 5.7% | 5.7% | 5.7% | 5.7% | 5.7% | 5.7% | 5.7% | 5.7% | 9.3% | 9.3% | 9.3% | 9.3% | 10.4% | 10.4% | 20.0% | 20.0% | 20.0% | 20.0% |
| **Low** | 3.3% | 3.3% | 3.3% | 3.3% | 3.3% | 3.3% | 3.3% | 3.3% | 5.3% | 5.3% | 5.3% | 5.3% | 6.0% | 6.0% | 11.4% | 11.4% | 11.4% | 11.4% |
| **High** | 10.8% | 10.8% | 10.8% | 10.8% | 10.8% | 10.8% | 10.8% | 10.8% | 17.7% | 17.7% | 17.7% | 17.7% | 19.8% | 19.8% | 38.1% | 38.1% | 38.1% | 38.1% |
| **F3 to HCC** | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% |
| **Low** | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% |
| **High** | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% |
| **C Cirrhosis to DCC** | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% |
| **Low** | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% |
| **High** | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% |

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| **C Cirrhosis to HCC** | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% |
| **Low** | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% |
| **High** | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% |
| **DCC to Death** | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% |
| **Low** | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% |
| **High** | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% |
| **HCC to Death (Year 1)** | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% |
| **Low** | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% |
| **High** | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% |
| **HCC to Death (Sub Yrs)** | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% |
| **Low** | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% |
| **High** | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% |

**Back-calculated annual progression rates — Females**

| **Age group** | **0–4** | **5–9** | **10–14** | **15–19** | **20–24** | **25–29** | **30–34** | **35–39** | **40–44** | **45–49** | **50–54** | **55–59** | **60–64** | **65–69** | **70–74** | **75–79** | **80–84** | **85+** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **F0 to F1** | 4.4% | 4.4% | 4.4% | 4.4% | 4.4% | 4.4% | 4.4% | 4.4% | 11.6% | 11.6% | 14.3% | 14.3% | 16.2% | 16.2% | 18.2% | 18.2% | 18.2% | 18.2% |
| **Low** | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 6.8% | 6.8% | 8.4% | 8.4% | 9.5% | 9.5% | 10.7% | 10.7% | 10.7% | 10.7% |
| **High** | 6.7% | 6.7% | 6.7% | 6.7% | 6.7% | 6.7% | 6.7% | 6.7% | 17.7% | 17.7% | 21.8% | 21.8% | 24.8% | 24.8% | 27.8% | 27.8% | 27.8% | 27.8% |
| **F1 to F2** | 2.9% | 2.9% | 2.9% | 2.9% | 2.9% | 2.9% | 2.9% | 2.9% | 7.6% | 7.6% | 9.3% | 9.3% | 10.6% | 10.6% | 11.9% | 11.9% | 11.9% | 11.9% |
| **Low** | 1.7% | 1.7% | 1.7% | 1.7% | 1.7% | 1.7% | 1.7% | 1.7% | 4.5% | 4.5% | 5.5% | 5.5% | 6.2% | 6.2% | 7.0% | 7.0% | 7.0% | 7.0% |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **High** | 4.4% | 4.4% | 4.4% | 4.4% | 4.4% | 4.4% | 4.4% | 4.4% | 11.6% | 11.6% | 14.3% | 14.3% | 16.2% | 16.2% | 18.2% | 18.2% | 18.2% | 18.2% |
| **F2 to F3** | 4.5% | 4.5% | 4.5% | 4.5% | 4.5% | 4.5% | 4.5% | 4.5% | 11.9% | 11.9% | 14.6% | 14.6% | 16.6% | 16.6% | 18.6% | 18.6% | 18.6% | 18.6% |
| **Low** | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 2.6% | 7.0% | 7.0% | 8.6% | 8.6% | 9.8% | 9.8% | 11.0% | 11.0% | 11.0% | 11.0% |
| **High** | 6.9% | 6.9% | 6.9% | 6.9% | 6.9% | 6.9% | 6.9% | 6.9% | 18.2% | 18.2% | 22.4% | 22.4% | 25.4% | 25.4% | 28.6% | 28.6% | 28.6% | 28.6% |
| **F3 to C Cirrhosis** | 4.7% | 4.7% | 4.7% | 4.7% | 4.7% | 4.7% | 4.7% | 4.7% | 7.7% | 7.7% | 7.7% | 7.7% | 8.7% | 8.7% | 16.7% | 16.7% | 16.7% | 16.7% |
| **Low** | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 4.4% | 4.4% | 4.4% | 4.4% | 5.0% | 5.0% | 9.5% | 9.5% | 9.5% | 9.5% |
| **High** | 9.0% | 9.0% | 9.0% | 9.0% | 9.0% | 9.0% | 9.0% | 9.0% | 14.7% | 14.7% | 14.7% | 14.7% | 16.5% | 16.5% | 31.8% | 31.8% | 31.8% | 31.8% |
| **F3 to HCC** | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% |
| **Low** | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% | 0.2% |
| **High** | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% |
| **C Cirrhosis to DCC** | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% | 3.0% |
| **Low** | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% | 2.1% |
| **High** | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% | 4.1% |
| **C Cirrhosis to HCC** | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% | 3.6% |
| **Low** | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% | 2.7% |
| **High** | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% | 4.8% |
| **DCC to Death** | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% | 20.0% |
| **Low** | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% | 16.0% |
| **High** | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% | 24.0% |
| **HCC to Death (Year 1)** | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% | 70.7% |
| **Low** | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% | 43.0% |
| **High** | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% | 77.0% |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HCC to Death (Sub Yrs)** | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% | 16.2% |
| **Low** | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% | 11.0% |
| **High** | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% | 23.0% |

C Cirrhosis, compensated cirrhosis; HCC, hepatocellular carcinoma; DCC, decompensated cirrhosis; Sub Yrs, subsequent years

**Incidence —** The following methodologies were used to estimate incidence in each country.

*Historical Incidence*

*Countries with two prevalence studies* — When two prevalence studies with age and sex distribution were available, they were used to calculate the average number of incident cases between the two time points. Countries that have reported HCV prevalence at two points in time include the United States, France and Egypt. The prevalence by age in the older studies was fed into a model that aged the population while taking into consideration background deaths, liver-related deaths and the number of individuals treated and cured. The average annual incidence was calculated from the difference in prevalence between the older study (after the above adjustments) and the new study.

*Back-calculation of incidence* — When reliable prevalence estimates were available at only one point in time, a back-calculation methodology was used to estimate the incidence by year. In this case, the prevalence of HCV in 1950 (among those who are still alive at the time of known prevalence) was assumed to be zero, and the same methodology as above was used to estimate the average annual number of new infections per year between 1950 and the year of known prevalence. In countries with a long life expectancy and known sources of infection prior to 1950 (e.g., Japan), adjustments were made to the prevalent population in 1950 to account for cases that are still alive today. The analysis was refined by developing a relative incidence curve with the 1950 relative incidence set to 1. The relative incidence was mapped based on the known risk factors and the start of blood screening in the country. In approved models, these relative incidence curves were discussed at length with the expert panel in order to best estimate the historical "shape" of the epidemic relative to 1950. For example, in many counties the incidence of HCV was estimated to increase (relative to 1950) beginning around the 1960s or 1970s, and then decrease in the 1990s as HCV screening tests became more prevalent in blood banks and transfusion centres. Incidence data on acute infections were also used to inform the incidence trends in the model.

The model was used to find a value for the annual relative incidence that resulted in the known prevalence after adjusting for mortality and cures. In this *calibration* step, the number of new infections shown in Equation 2 was calculated to fit the known prevalence in a given year *y*.

**Equation 2. Total HCV infections in year *y***

$$\text{Total HCV infections}_{\text{Year}_y} = \sum_{t=1950}^{y} \left(\text{New infections}_t - \text{Spontaneous clearances}_t - \text{Deaths}_t - \text{Cures}_t\right)$$

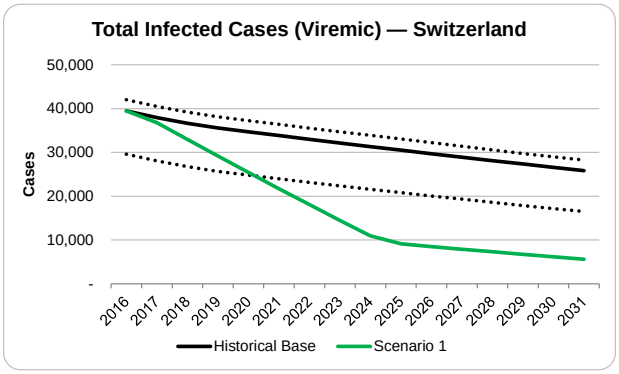
The annual incident cases were distributed by age and gender, and the modelled distribution was compared to the reported distribution. An iterative process of modifying the relative incidence curve and allocation by age was used to match the two curves and estimate the annual number of new infections by year.

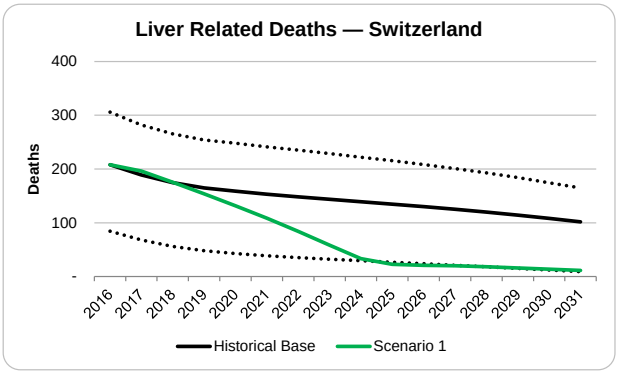
*Current & Future Incidence*

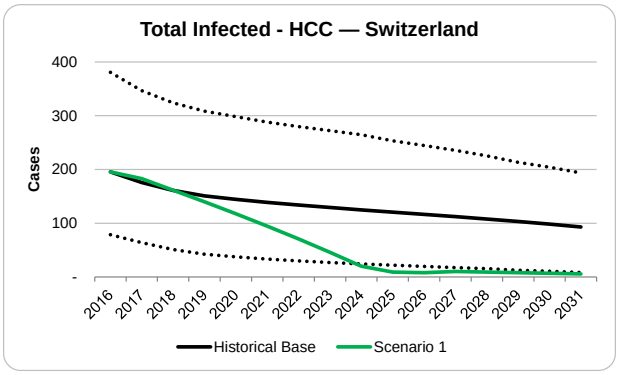
The current incidence (after the known prevalence) was calculated by using the last year's incidence and/or asking the experts from each country if they expected the future prevalence to decline, stay the same or increase. The rate of growth or decline was also collected. This was then used in the model to calculate the minimum annual incidence per year needed to achieve the desired growth rate. In the absence of better information, it was assumed that the number of new infections per year would stay constant in the future.

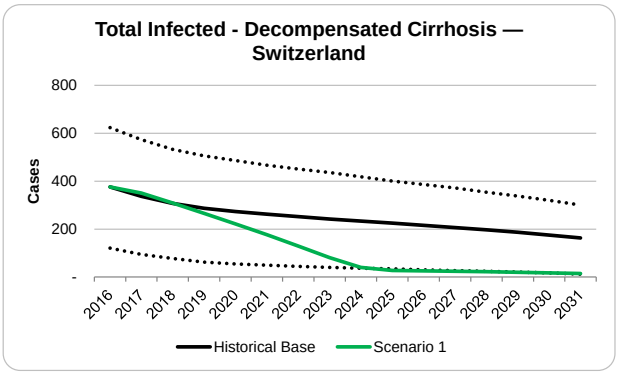
**Validation of the model —** The modelled outputs for 1990–2013 were validated against empirical data. Incident liver cancer data were obtained from the National Institute for Cancer Epidemiology and Registration and adjusted for hepatocellular carcinoma (HCC) based on histology data from the Geneva Tumour Registry. Histological data were available for 52% of tumours, of which approximately 91% were HCC. In the absence of better information, we assumed that the remaining 48% of tumours had a similar histological profile and included a range to capture the significant associated uncertainty: 91% (0–100%) HCC. The percentage of HCC attributable to HCV infection was estimated to be 44.5% (range 43.3–53.3%) (10).

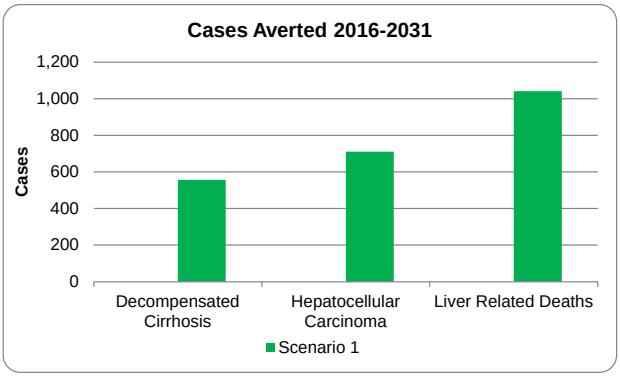
**Section 2 Disease burden model outcomes for total viremic infections, hepatocellular carcinoma, decompensated cirrhosis and liver-related deaths, by scenario, 2016–2031.**



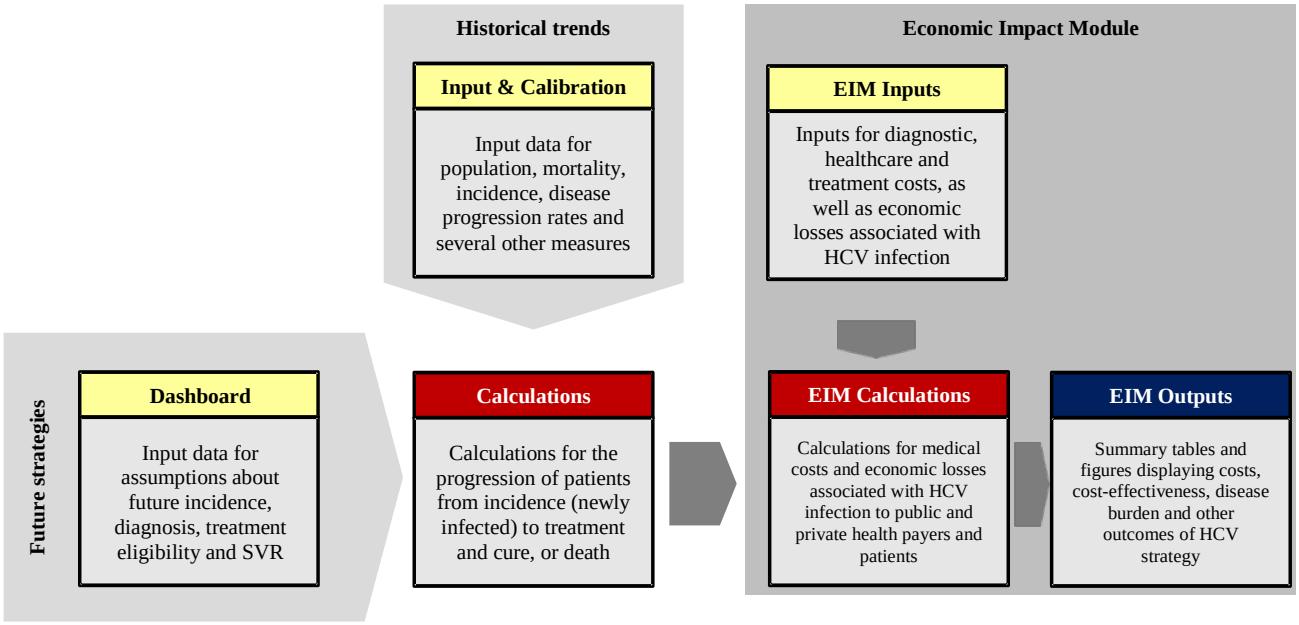



## Section 3 HCV economic impact model schematic and key calculations




Equation 1. Number of screenings needed to find one undiagnosed HCV-infected case in year $\boldsymbol{t}$

$$\text{Number of screenings needed to find one new case}_t = \frac{1}{\text{Prevalence of undiagnosed viremic HCV-infected cases}_t}$$

Equation 2. Total number of screens for HCV in year $\boldsymbol{t}$

$$\text{Total number of screens for HCV}_t = \text{Number of screenings needed to find one new case}_t \times \text{Newly diagnosed}_t$$

Equation 3. Incremental cost-effectiveness ratio (ICER) of a scenario

$$\text{ICER}_{\text{scenario}} = \frac{\sum_{t=2016}^{2031} \text{Medical costs of scenario}_t - \sum_{t=2016}^{2031} \text{Medical costs of base case}_t}{\sum_{t=2016}^{2031} \text{QALYs gained in scenario}_t - \sum_{t=2016}^{2031} \text{QALYs gained in base case}_t}$$

Equation 4. Cost savings of a scenario

$$\text{Cost savings}_{\text{scenario}} = \left( \sum_{t=2016}^{2031} \text{Medical costs of base case}_t - \sum_{t=2016}^{2031} \text{Medical costs of scenario } x_t \right)$$

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