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Appendices

Microelimination of chronic hepatitis C in Switzerland: modelling the Swiss Hepatitis Strategy goals in eastern, western and northern regions

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Appendix 1: Delphi process

		Activities
Phase 1 – Data Gathering	1a	**Identify country experts who are willing to collaborate** • Experts were identified through HCV-related scientific contributions, or through referrals and recommendations from leading researchers. Panels consisted of hepatologists, gastroenterologists, virologists, infectious disease specialists, epidemiologists, health economists, health scientists, and Ministry of Health representatives.
	1b	**Literature Search** • Review the internal database for previously identified sources • Review online sources (MOH, WHO, etc.) to capture non-indexed sources • Run a literature search from 2013 forward to identify recent publications • Summarize input data available through the literature • Gather empirical data for new HCC cases, liver transplants (LT), percent of HCC and LT due to HCV, annual newly diagnosed, annual treated, percent of infection due to transfusion, and percent of infections that are among active PWID • Build draft model based on published data or extrapolate inputs from countries with data when data are missing (as a placeholder) • Schedule meeting with experts
Phase 2 – Country Meetings and Modeling	2a	**Expert Meeting 1 (2-3 hours)** • Provide a background on the project, model, and methodology • Review data identified in Phase 1b and highlight gaps in data • Request data in local non-indexed journals, unpublished data, and any other available data (e.g., hospital-level data) that can be used to fill the gaps • Gain agreement on countries that can be used for extrapolation when no local data are available
	2b	**Follow-up with Experts Post Meeting 1** • Send minutes of the meeting and list of remaining action items to experts • Follow up with experts to collect missing data and get copies of publications in the local journals, unpublished data, relevant Ph.D. theses, government reports, and raw hospital or registry-level data • Analyze raw data and send to experts for approval
	2c	**Disease Burden Modeling** • Populate disease burden model with inputs and calibrate model to empirical data • Develop 2-3 scenarios to prepare for meeting 2, including a WHO target scenario (elimination by 2030) • Schedule second meeting • Develop a slide deck summarizing all inputs and associated data sources • Perform a final check of the model and slide deck and approve internally
	2d	**Expert Meeting 2 (2-3 hours)** • Review all inputs as well as data provided by experts since meeting 1 and results of analyses of any raw data provided • Gain agreement on all inputs to be used in the model • Update the model using any updated inputs • Run scenarios requested by experts (e.g., slow increase in the number of treated patients, disease control, WHO target) and review results and insights • Agree on final strategies that would be considered as part of a national strategy
Phase 3 – Follow-up Analyses	3a	**Follow-up Analyses** • Update model as necessary and send results to experts • Provide support to address follow-up questions • Lock down inputs and outputs as approved • Run additional scenarios to support the development of a national strategy (e.g., economic impact, birth cohort screening, and sources of transmission) • Report results to Polaris Observatory • Update analysis as new information becomes available (e.g., new national studies, updated treatment data)

Appendix 2: Forecasting viraemic HCV prevalence

Indicator – This analysis focused on estimating the viremic HCV infections, which reflects 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 end of the year 2015 viremic prevalence.

Time period – Available hospital and regional based data were used in this analysis. In St. Gallen, a retrospective analysis of electronic medical records between January 1st 2004 and December 31st 2016 of all patients with a positive anti-HCV screening test were considered. In Geneva and Zurich, reported liver cancer data between 1990-2013 and 1988-2014, respectively, were used.

Geographical scope – St. Gallen, containing the cantons of Appenzell Innerrhoden (AI), Appenzell Ausserrhoden (AR) and St. Gallen (SG) and the cantons of Geneva and Zurich were considered. Expert approval meetings were held with all cantons and three cantonal-specific disease burden models were built.

Modeling HCV Prevalence

The analysis started with a review of available hospital and regional data and was supplemented with Delphi method interviews with country experts to ensure that all relevant data (including unpublished data) are taken into consideration (see Section 1). A Markov model was used to forecast HCV prevalence over time. The prevalence of HCV is not constant over time. When incidence is higher than mortality and cured, 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 the HCV prevalence at the end of 2015 for each canton. The details of the model have been published previously.[1,2]

- **Required inputs –** The following inputs were required to build and calibrate each cantonal model.

Model input	Definition	Source
Canton population by 5-year age cohort	The number of people in the country, reported annually from 1950 to 2050 (by gender and 5-year age cohort)	[3]
Mortality rate by 5-year age cohort	The percent of deaths among the total population, reported annually from 1950 to 2050 (by gender and 5-year age cohort)	[4]
Anti-HCV + prevalence rate	Percent of total population who are anti-HCV(+)	[5], hospital specific data provided by experts
Viremic rate	Percent of anti-HCV(+) individuals who are HCV-RNA(+)	[6]
Age and gender distribution	Anti-HCV prevalence rate by age (5-year cohorts) and gender	[7]
Genotype distribution	Proportion of HCV-RNA(+) population categorized by HCV genotype (out of 100%)	[8], hospital-specific data provided by experts
Annually treated	Number of HCV infected individuals who have received treatment in a given year	[9], hospital-specific data provided by experts

Model input	Definition	Source
Total diagnosed	Viremic HCV cases diagnosed and alive in a given year	[7]
Newly diagnosed	Annual number of newly diagnosed HCV cases	[7]
Liver transplants	Annual number of liver transplants due to HCV	Hospital specific data provided by experts
HCC	Annual number of HCC incidence due to HCV	Hospital specific data provided by experts

Prevalence by age – Switzerland notification data were used to develop estimate prevalence by age. In this method, the annual number of newly diagnosed cases in Switzerland was collected and adjusted for mortality and cured. The birth year was used to calculate the age and consolidate data from multiple years into the last year of available data. It was assumed that screening was conducted randomly, and the number of diagnosed cases by each age cohort 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 prevalence by age and general populations by age equal to the estimated total 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. The above methodology was used to estimate the prevalence by age in all cantons, where diagnosed data by age were available through the Federal Office of Public.[7]

Treated patients – The number of individuals treated annually for HCV in St. Gallen was estimated through the previously described retrospective analysis. The annual number of treated patients in Geneva and Zurich was estimated through audit drug sales data, accounting for population of the cantons.

The annual number of units of Pegylated-Interferon (Peg-IFN), ribavirin (RBV), or direct acting anti-virals (DAAs) sold, as reported by IMS Health, was converted to treated patients using the average number of units per patient. The number of treated patients was calculated using the genotype distribution of the infected population (assumed the genotype distribution of the treated population was the same as the overall population), duration of treatment for each genotype, the number of Peg-IFN, RBV, or DAA units per week, and the percent of patients who completed their treatment (80% in most countries unless stated otherwise). The annual number of units was also adjusted to account for uses in HCV and any under-reporting using inputs from the expert panel.

Cured patients – In the absence of better information, it was assumed the genotype distribution of the treated population was the same as the total infected population (they have the same probability of being diagnosed and treated). The sustained viral response (SVR) rates by genotype were used to estimate the number of patients cured per year. Canton interviews were used to determine the real world SVR for the different treatment regimens – interferon based therapy in combination with ribavirin (RBV) (dual therapy), with RBV and a protease inhibitor (PI) (triple therapy), RBV with direct acting antivirals (DAAs), and DAAs. Experts took into consideration the percentage of the population who were treatment experienced and treatment naïve on each treatment option and disease stages of the patients being treated (e.g., F1, F2, F3, and F4). The average SVR by genotype by country has been reported previously.[2,10,11]

Liver transplants – The annual number of liver transplants was gathered from the cantonal hospitals and adjusted for the percentage attributed to HCV. For examples of such an adjustment factor, see references listed here. [12-17]

Diagnosed patients – Notification data from 1988-2015 from the Swiss Federal Office of Public Health was utilized.[7] Diagnosed cases were calculated by summing data from all years after taking into consideration the mortality among the diagnosed cases. It was assumed that the viremic rate among the diagnosed population was the same as the total infected population.

All-cause mortality – The all-cause mortality rates by age and gender were gathered from the United Nations mortality database. [4] The rates were adjusted for incremental increase in mortality due to injection drug use and transfusion. A standard mortality ratio (SMR) of 10 (9·5-29·9) was used for the portion of the HCV infected population who were people who inject drugs (PWID) between ages 15-44.[18-23] An SMR of 2·1 (1·3-17·6) was applied to all ages for the portion of the population infected due to transfusion.[24] The number of active PWID and HCV prevalence among PWID was gathered through published studies [25-28] and divided by the total HCV infected population to estimate percent of all HCV infections that is among active PWID.

Markov model – The Markov model described here is an open sourced model. Modelers and epidemiologists in France, Greece, Australia, Egypt, Spain, and Portugal have independently reviewed the model and provided feedback for modifications and updates. In addition, country experts in 59 countries continue to provide requests for updates to the model to enhance its functionality and algorithms. Since its inception in 2012 [29], the model has undergone over 80 revisions and updates.

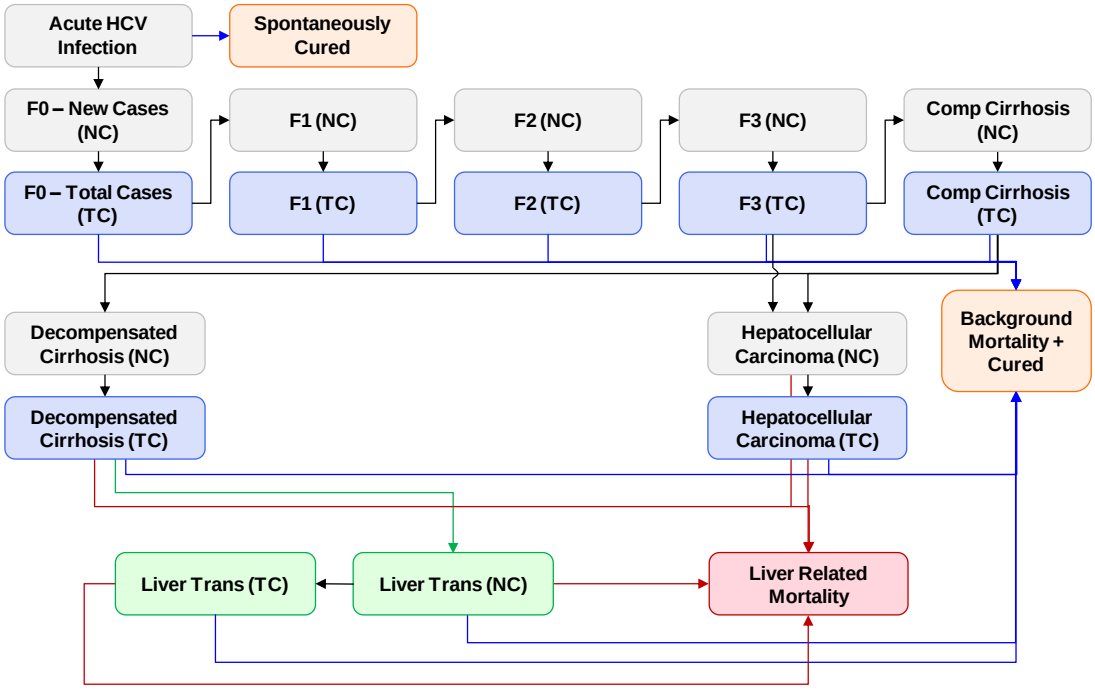
The Markov (disease progression) model was constructed in Microsoft Excel® 2007 (Microsoft Corp., Redmond, WA) to quantify the size of the HCV infected population, by the liver disease stages, from 1950-2050. The size and impact of the HCV infected population prior to 1950 was considered negligible for 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 modeled using the flow shown in the figure below and calculations shown in Equation 1.

The model started with the annual number of acute infections that progressed to chronic HCV (viremic) 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 specified, the scope of the model was limited to viremic, HCV ribonucleic acid (RNA) positive cases. Non-viremic cases (those exposed to the virus but spontaneously cleared the virus or were treated and cured) were not considered.

The number of new cases at each stage of disease (incidence) was calculated annually by multiplying the annual progression rates times the prevalent population (by age and gender) in the previous stage. Thus, the annual number of new F2 cases was calculated by multiplying the prevalent population in F1 (by age and gender) times the F1 to F2 progression rate (Equation 1).

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

The flow of the HCV disease progression model



F = Fibrosis; NC = New Cases (grey); TC = Total Cases (blue); Trans = Transplants (green); orange represents end of infection due to cure or background mortality; red represents end of infection due to liver related mortality.

Equation 1. Annual prevalence (total cases) calculations by stage, year, and age

$$\text{Total Cases}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} = \text{Total Cases}_{\text{Stage}_x\ \text{Year}_{y-1}\ \text{Age Cohort}_{z-1}} + \text{New Cases}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} - \text{Cured}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} - \text{Background Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} - \text{Progressed}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} - \text{Liver Related Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z}$$

where:

$$\text{New Cases}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} = \left(\text{Total Cases}_{\text{Stage}_{x-1}\ \text{Year}_{y-1}\ \text{Age Cohort}_{z-1}}\right)\left(\text{Progression Rate}_{\text{Stage}_{x-1}\rightarrow\text{Stage}_x\ \text{Age Cohort}_{z-1}}\right)$$

$$\text{Cured}_{\text{Stage}_x\text{Year}_y\text{Age Cohort}_z} = \left(\text{Total Cases}_{\text{Stage}_x\text{Year}_{y-1}\text{Age Cohort}_{z-1}}\right)\left(\text{Age Eligibility Flag}_{\text{Year}_{y-1}\text{Age Cohort}_{z-1}}\right)\left(\frac{\text{Cured}_{\text{Stage}_x\text{Year}_y}}{\text{Total Age Eligible Cases}_{\text{Stage}_x\text{Year}_{y-1}}}\right)$$

where:

$$\text{Cured}_{\text{Stage}_x\ \text{Year}_y} = \sum_{w=1}^{6}\left(\text{Total Treated}_{\text{Genotype}_w\ \text{Stage}_x\ \text{Year}_y}\right)\left(\text{SVR}_{\text{Genotype}_w\ \text{Year}_y}\right)$$

$$\text{Background Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} = \left(\text{Total Cases}_{\text{Stage}_x\ \text{Year}_{y-1}\ \text{Age Cohort}_{z-1}} - \text{Cured}_{\text{Stage}_x\text{Year}_y\text{Age}_z}\right)\left(\text{Adjusted Background Mortality Rate}_{\text{Year}_{y-1}\text{Age Cohort}_{z-1}}\right)$$

$$\text{Progressed}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} = \left(\text{Total Cases}_{\text{Stage}_x\ \text{Year}_{y-1}\ \text{Age Cohort}_{z-1}} - \text{Cured}_{\text{Stage}_x\text{Year}_y\text{Age Cohort}_z} - \text{Background Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z}\right)\left(\text{Progression Rate}_{\text{Stage}_x \rightarrow \text{Stage}_{x+1}\ \text{Age Cohort}_{z-1}}\right)$$

$$\text{Liver Related Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} = \left(\text{Total Cases}_{\text{Stage}_x\ \text{Year}_{y-1}\ \text{Age Cohort}_{z-1}} - \text{Cured}_{\text{Stage}_x\text{Year}_y\text{Age Cohort}_z} - \text{Background Mortality}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z} - \text{Progressed}_{\text{Stage}_x\ \text{Year}_y\ \text{Age Cohort}_z}\right)\left(\text{Liver Related Mortality Rate}_{\text{Year}_{y-1}\text{Age Cohort}_{z-1}}\right)$$

Progression rates – The progression rates by age, gender, and fibrosis score were back calculated. Data from the UK were used for the percentage increase in progression rate by age and gender.[30] 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 for F0, F1, F2, F3, and F4.[31] Finally, the modified progression rates were adjusted to fit historical HCC incidence by age and gender in the US [32] after adjusting for the portion of all HCC cases attributed to HCV.[33]

The progression rates to end stage liver disease and liver related deaths were based on previously published rates. Insufficient data were available to develop predictable rates by age and gender. Thus, the same rate was applied for all ages and genders.[30,34,35] The table below lists all progression rates along with the uncertainty intervals.

HCV disease progression rates

Back-Calculated Progression Rates – Males

Age Cohorts	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 Decomp	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%
Decomp 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 (Yr 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 Progression Rates – Females

Age Cohorts	**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 Decomp	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%
Decomp 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 (Yr 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%

*Low and High progression rates form the estimate range used in calculating uncertainty intervals of the outputs; F = Fibrosis; C = Compensated; Decomp = Decompensated; HCC = Hepatocellular Carcinoma; Yr = Year; Sub = Subsequent

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

Historical Incidence

Back calculation of incidence – A back calculation methodology was used to estimate incidence by year. The prevalence of HCV in 1950 (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. 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 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 beginning around the 1960s or 1970s (relative to 1950), and then decrease in the 1980s or 1990s as knowledge of blood safety spread following the HIV epidemic and as HCV screening tests became more prevalent in blood banks and transfusion centers. Incidence data on acute infections were also used to inform the incidence trends in the model.

The model was used to solve for the constant times the annual relative incidence that resulted in the known prevalence after adjusting for mortality and those cured. 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*

$$\text{Total HCV Infections}_{\text{Year}_y} = \sum_{t=1950}^{y} \left(\text{New Infections}_t - \text{Spontaneously Cured}_t - \text{Mortality}_t - \text{Cured}_t\right)$$

The annual incidence cases were distributed by age and gender, and the modeled 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 asking the cantonal experts if they expect 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 to achieve the desired growth rate. It was assumed the number of new infections per year would stay constant in the future in the absence of better information.

Validation of the model – The model was validated by comparing its output against empirical data. Switzerland has extensive data on their HCV cohort, including HCC cases, which was used to compare against modelled outcomes.

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