

# Simulation of hepatitis C based on a mandatory reporting system

Markus Sagmeister<sup>a,b</sup>, Eberhard L. Renner<sup>a</sup>, Beat Mullhaupt<sup>a</sup>  
and John B. Wong<sup>b</sup>

**Objective** Hepatitis C is a major cause of liver disease in European countries. We aimed to assess the current and future disease burden of hepatitis C.

**Setting** A representative data set of hepatitis C was applied to a validated computer model.

**Methods** The mandatory reporting of positive hepatitis C virus (HCV) test results by all medical laboratories in Switzerland and the clinical data obtained by questionnaire for each positive test from the treating physicians created a unique, representative epidemiological database allowing the determination of the age distribution of acute (i.e. newly acquired) and chronic HCV infections. Based on these data and a simulation model of the natural history of hepatitis C, we estimated the prevalence of HCV infection, future morbidity/mortality from cirrhosis/hepatocellular carcinoma and costs.

**Results** Our analysis estimates a prevalence of anti-HCV in Switzerland of 1.25–1.75%, which is slightly higher than prior reports (0.5–1%) derived by extrapolation from selected populations. Although new HCV infections decreased after 1990, our analysis predicts that HCV-related morbidity and mortality will increase by 70–90%, reaching a maximum in 2015–2020, largely from

complications in cases already prevalent in 1998. The model predicts that the incidence of cirrhosis will begin to decrease after 2005–2010. Antiviral treatment reduces disease burden by approximately 5%. Undiscounted HCV-related annual direct costs will more than double and reach a maximum of almost US\$33 million in 2020.

**Conclusions** The incidence of HCV-related cirrhosis is predicted to decrease after 2005–2010, while disease burden and costs due to complications are estimated to continue to increase until 2015–2020. *Eur J Gastroenterol Hepatol* 14:25–34 © 2002 Lippincott Williams & Wilkins

*European Journal of Gastroenterology & Hepatology* 2002, 14:25–34

**Keywords:** cirrhosis, hepatitis C, hepatocellular carcinoma, prevalence, simulation

<sup>a</sup>Division of Gastroenterology and Hepatology, University Hospital, Zürich, Switzerland; and <sup>b</sup>Division of Clinical Decision Making, Informatics and Telemedicine, Department of Medicine, New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA

Correspondence to E. L. Renner, MD, Division of Gastroenterology and Hepatology, University Hospital, Rämistrasse 100, CH-8091 Zürich, Switzerland  
Tel: +41 1 255 25 53; fax: +41 1 255 45 98;  
e-mail: eberhard.renner@dim.usz.ch

Received 8 March 2001 Revised 4 May 2001  
Accepted 24 July 2001

## Introduction

Infection with the hepatitis C virus (HCV) becomes chronic in 80% of cases [1,2], with a 10–20% risk of developing cirrhosis over 20 years [2–5]. Once established, cirrhosis carries a 4% annual risk of decompensation [4] and a 1–5% annual risk of developing hepatocellular cancer (HCC) [6]. Thus, patients infected for 20–30 years have had the HCV infection for sufficient duration to now be at risk for complications from chronic liver disease including HCC.

Because HCV was not identified until 1988 [7], few studies have a sufficiently long follow-up to reliably assess the lifetime consequences of chronic HCV infection [2,8,9]. Nonetheless, in selected populations (limiting the generalizability of these studies), significant HCV-related mortality was observed [2,8]. Recently, when compared with an age-matched and sex-matched general population, the life expectancy of patients with

chronic hepatitis C has been shown to be decreased, with the cirrhotic stage accounting fully for the excess mortality [10].

In Switzerland, reporting of positive tests for hepatitis has been mandatory since 1988 [11]. Since the availability of tests for hepatitis C in late 1988, all registered medical laboratories have to report any positive anti-HCV serology or HCV-RNA polymerase chain reaction to the Swiss Federal Office of Public Health (BAG). To avoid duplicate reporting, each report is cross-checked with the existing database to determine whether the patient has been registered previously. For any newly reported HCV cases, the BAG requests further complementary clinical and epidemiological information from the patient's primary care physician. These data provide insight into changes in the epidemiology of the route of transmission and assist with differentiating acute from chronic hepatitis C. Collec-

tively, this dataset creates a unique opportunity to perform epidemiological studies of HCV in Switzerland.

To predict future epidemiological and clinical developments in the midst of uncertainty, modelling techniques have proven useful. Bennett *et al.* [12] published a Markov model to estimate the morbidity, mortality and costs associated with chronic HCV in the USA. Using a Markov model to back-calculate the hepatitis C epidemic in France, Deuffic *et al.* predicted a 33–100% increase in HCC mortality from HCV infection in the next 30 years [13]. Similarly, Wong *et al.* [14] predicted a twofold increase in mortality related to HCV infection in the USA over the next 10–20 years.

We sought to examine the hepatitis C epidemic in Switzerland by estimating the current prevalence and predicting future HCV-related morbidity, mortality and economic burden. In contrast to the aforementioned modelling studies, by applying the BAG's representative epidemiological database for hepatitis C in Switzerland, we could account not only for prevalence, but also for incidence, thus enabling the development of a comprehensive model.

## Methods

Using standard decision analysis software (Decision Maker, Version 7, Division of Clinical Decision Making, New England Medical Center, Boston, USA) [15], we applied a previously published and validated computer simulation model for the natural history of HCV [12,16]. The model is based on a Markov simulation, in which cohorts of patients move through predefined health states over time until all patients have entered the dead state. The health states include mild hepatitis, moderate hepatitis and cirrhosis as the three histopathological stages. The likelihood that patients may progress to more advanced disease states or death over time was specified by transition probabilities derived from the literature. Time is represented by annual cycles. The model considers morbidity and mortality from hepatitis C and mortality from other causes as occurring in the general Swiss population.

## Prevalence

As in other countries, the BAG used the anti-HCV prevalence in blood donors and pregnant women to estimate the prevalence of hepatitis C at 0.5–1% in the 1998 Swiss population, translating into 35 000–70 000 persons who were HCV infected in 1998 [17]. When applied in the United States, prevalence estimates based on a similar approach underestimated the prevalence actually observed when screening was applied to a representative sample of the US population [18,19]. In the absence of such a population-based seroprevalence study in Switzerland, we attempted to

compute the prevalence of HCV infection in Switzerland using simulation techniques.

From the BAG data, we assumed in a first scenario an anti-HCV prevalence of 0.75% (median BAG estimate) and assumed that the age distribution of all 'non-acute' hepatitis C cases (Table 1) applied to the entire HCV-infected Swiss population. As found in the NHANES III study [19], we assumed that 73.9% of those positive for HCV antibody had HCV RNA detectable in their blood so that 38 797 Swiss subjects have chronic HCV RNA positive infection. To estimate the age-specific prevalence of cirrhosis in this Swiss population, we used a previously published linear relationship between HCC-related cirrhosis and age ( $R^2 = 0.97$ ) in a data set of 2235 liver biopsies [14,20]. The age-specific prevalences of moderate and mild hepatitis were back-calculated from the age-specific prevalence of cirrhosis, assuming a 7.3% annual probability of developing cirrhosis from moderate hepatitis [12]. About 30–40% of all chronically infected patients have persistently normal liver transaminases for more than 12 months [21]. We assumed that these patients would not develop progressive liver disease. Many of these patients may still have histological hepatitis [21]. Thus, our results may underestimate future morbidity and mortality from hepatitis C.

## Incidence

Since 1993, about 60 cases of acute hepatitis C have been consistently documented annually [22]. Assuming that symptomatic acute hepatitis C occurs in only 10–20% of those infected, the BAG estimates an annual incidence of seven to 14 new HCV infections per

**Table 1** Age distribution of a cohort (base-case scenario) of anti-hepatitis C virus (HCV)-positive patients (reported as chronic infected) (prevalence)

Base scenario (prevalence: 52 500 anti-HCV-positive)			
Age group (years)	Swiss population	anti-HCV-positive (%)	Number of anti-HCV-positive
0–4	329 700	0.74	388
5–9	430 200	0.14	73
10–14	408 800	0.18	94
15–19	406 000	1.48	777
20–24	418 000	7.87	4130
25–29	514 400	15.87	8334
30–34	611 300	19.84	10 417
35–39	583 300	16.96	8906
40–44	525 200	11.28	5920
45–49	499 300	5.62	2949
50–54	484 300	3.48	1826
55–59	396 200	4.25	2230
60–64	343 000	3.62	1900
65–69	396 000	2.95	1548
70–74	267 600	2.74	1438
75–79	212 500	1.72	903
80+	280 800	1.27	666
Total	7 106 600	100.00	52 500

100 000 inhabitants or 497–995 new infections per year in Switzerland [22]. In the base case, we assumed that 746 newly infected patients would occur per year, i.e. the median of the BAG's estimated range. We assumed that the age distribution of future newly HCV-infected cases in Switzerland would be identical to the age distribution of all cases of acute hepatitis C reported to the BAG between 1992 and 1998 (Table 2). In these newly infected patients, 80% will develop chronic infection [21].

### Extension of the model

To represent treatment patterns within Switzerland, we modified the published hepatitis C model to include the possibility of partial hepatectomy or orthotopic liver transplantation (OLT) for surgically treatable small HCC. The likelihood of, risks of and survival after OLT and partial hepatectomy were based on literature (Medline search) and expert opinion, and are detailed in the Appendix and Figure. 1 and Table 3.

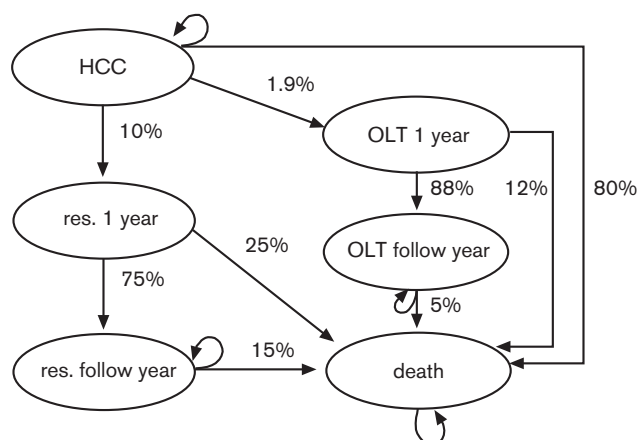
### OLT for HCV-associated end-stage liver disease

Because 27% of OLTs (all indications) at the University Hospital Zürich were for HCV-related end-stage liver disease (without HCC) in a consecutive series (E. L. Renner, unpublished data 1997), we assumed that 16 (range, 14–18) of the 60 OLTs being performed in Switzerland in 1994 for non-HCC-related causes were for HCV-related liver disease. In the USA, 730 OLTs were performed for HCV-related liver disease in 1994 [44], translating to a rate of 2.74 OLTs for HCV-related liver disease per million inhabitants (USA population in 1994, 266 600 000 [45]). This rate was 2.33 in 1994 for Switzerland (population in 1994, 7 062 400 [46]). Thus, the overall annual probability of OLT for HCV-related

**Table 2** Age distribution of a cohort (base-case scenario) of anti-hepatitis C virus (HCV)-positive patients (reported as acute infected) (incidence)

Base scenario (incidence, 746)		
Age group (years)	Number of anti-HCV positive	anti-HCV positive (%)
0–4	2	0.3
5–9	18	2.4
10–14	18	2.4
15–19	18	2.4
20–24	180	24.2
25–29	194	25.9
30–34	113	15.2
35–39	46	6.2
40–44	28	3.7
45–49	32	4.2
50–54	15	2.0
55–59	32	4.2
60–64	17	2.2
65–69	15	2.0
70–74	9	1.3
75–79	4	0.5
80+	6	0.8
Total	746	100.0

**Fig. 1**



Modification of a previously published Markov model to include states of health for hepatocellular carcinoma (HCC). res, Resection; follow, following; OLT, orthotopic liver transplantation.

liver disease seems similar (population based) in the USA and Switzerland, differing only by about 15% (not considering alternative assumptions regarding the prevalence of hepatitis C).

### Death from liver disease

In 1994, 644 subjects died from chronic liver disease in Switzerland [Swiss Federal Office of Statistics (BFS), unpublished data 1999]. The proportion of these deaths related to HCV infection, however, is unknown. Due to imprecise and incomplete coding by the reporting physicians, cases registered by the BFS (five deaths caused by chronic hepatitis C, 59 deaths caused by HBV-related or HCV-related cirrhosis; BFS, unpublished data 1999) are not only very likely to underestimate, but do even not allow one to reliably determine, the fraction of deaths attributable to HCV-related cirrhosis. In a seroprevalence study on 253 unselected patients with cirrhosis treated in a Swiss general hospital, 17% of cirrhotics (excluding HCC cases) were found to be positive for anti-HCV [35]. Reflecting referral patterns, alcoholic cirrhosis may be over-represented in this series, thus leading to underestimation of the fraction of HCV-related liver disease. Of all OLTs performed for end-stage chronic liver disease (excluding other indications such as HCC, metabolic disorders and fulminant liver failures) in a recent series of consecutive OLTs at the University Hospital Zürich, 44% were performed for HCV-related end-stage liver disease (E. L. Renner, unpublished data 2000). This latter figure, however, probably overestimates the true fraction of deaths attributable to HCV-related cirrhosis, since among OLT candidates alcoholic cirrhosis is likely to be under-represented. Based on the aforementioned, we therefore assume the pro-

**Table 3 Rates and probabilities of disease progression**

Transition probabilities		Baseline estimate (annual)	Range (sensitivity analysis)
From	To		
HCC	Resection first year	0.1	0.08–0.12
HCC	OLT first year	0.019	0.014–0.024
HCC	Death	0.8	0.7–0.9
Resection first year	Death	0.25	0.20–0.30
Resection following years	Death	0.15	0.13–0.17
OLT first year	Death	0.12	0.1–0.14
OLT following years	Death	0.05	0.04–0.06

HCC, hepatocellular cancer; OLT, orthotopic liver transplantation.

portion of deaths from chronic liver disease related to HCV to range between 17 and 44%, which extrapolates to 109–283 deaths in 1994. This compares with an estimate of 40% for the USA [47].

#### Effect of antiviral treatment

To approximate the effects of antiviral therapies (i.e. the interferon/ribavirin combination) on our results, we estimated a percentage of 14% with known hepatitis C (15 069 documented patients with anti-HCV positivity [17] out of an assumed 105 000 anti-HCV-positive patients). To consider the effect of these therapies, we assumed that all non-cirrhotic patients with known HCV infection would have been treated, except those with normal transaminases and those with HCC. We applied the age distribution of chronic infected HCV patients (Table 1) and calculated with a sustained response rate to antiviral treatment of 40% [48,49].

#### Costs

Costs were calculated using a societal perspective, and included direct and indirect costs. The present value of future costs applied a 3% annual discount rate [50].

#### Direct costs (Table 4)

*Outpatient care.* In the absence of national data, a panel of gastroenterologists and hepatologists estimated the annual frequency and type of medical care provided in outpatient settings for each health state. Costs were based on countrywide reimbursement tariffs [51].

*Inpatient care.* Similarly, the same panel estimated the annual frequency of hospitalizations. The average length of stay was based on the database of the Swiss Hospital Association (VESKA) [52] and on separate evaluations (E. L. Renner, unpublished data 1997). Information on individual cost elements was obtained from the VESKA and two large hospitals. We updated

**Table 4 Costs per year due to hepatitis C**

Disease state	Costs per year (US\$)		
	Outpatient care	Hospital care	Total
Chronic hepatitis (mild/moderate)	200		200
Compensated cirrhosis	295		295
Ascites, diuretic-sensitive	1470		1470
Ascites, refractory	3217	19 009	22 226
Variceal haemorrhage, 1 year	1715	17 066	18 781
Variceal haemorrhage, following years	1701	3168	4869
Encephalopathy, 1 year	3601	9505	13 106
Encephalopathy, following years	3606	9505	13 111
Hepatocellular carcinoma (no operation), 1 year	3603	9505	13 108
Hepatocellular carcinoma (no operation), following years	3125		3125
Hepatocellular carcinoma (PH), 1 year	3603	34 920	38 523
Hepatocellular carcinoma (PH), following years	3125		3125
Hepatocellular carcinoma (OLT), 1 year	13 351	130 254	143 605
Hepatocellular carcinoma (OLT), following years	11 385	1046	12 431
OLT, 1 year	13 351	120 747	134 098
OLT, following years	11 385	1046	12 431

PH, partial hepatectomy; OLT, orthotopic liver transplantation.

the 1998 Swiss Hospital Institute data for OLT [53] to reflect the current shortened length of stay [52] and the expanded costs for hospital care [46]. Cost data are similar to those in the United States [54] We assumed that asymptomatic patients with unknown disease would not incur additional health costs until the occurrence of decompensated cirrhosis or HCC.

#### Indirect costs

Indirect costs were evaluated using the human capital approach [55]. To provide a conservative estimate of indirect costs, we only assumed permanent disability for patients with decompensated cirrhosis or HCC.

## Results

### Prevalence of hepatitis C in Switzerland

To estimate the prevalence of HCV infection in Switzerland, we compared model predictions regarding the incidence of death from HCV-related HCC and chronic liver disease, and that of HCV-related OLT, with the same events presumably having occurred in 1998 (Table 5). Applying the median 0.75% BAG HCV prevalence estimate resulted in outcome predictions that fell below outcome assumptions for HCC and OLT, while the model prediction for deaths from HCV-related chronic liver disease (107 deaths) was at the lower limit of the assumed range (109–283 deaths). According to our model's estimates, 1.25–1.75% of anti-HCV prevalence provided the best fit to the assumed HCV complications.

### Disease burden by prevalence

In the absence of population-based seroprevalence data for Switzerland, we assumed an anti-HCV prevalence of 1.5% (see earlier) in our analyses to predict future HCV-related disease burden. Thus, we examined future complications for a cohort of 77 595 HCV-RNA-positive subjects exhibiting an age distribution identical to that of the chronically HCV-infected patients reported to the BAG (Table 6). Excluding new HCV infections (i.e. future incidence), the analysis suggests that annual HCC incidence and HCV-related mortality (i.e. death from decompensated cirrhosis and death

from liver disease) will increase by 70 and 90%, respectively, reaching their maxima in about 15–25 years from now. By excluding any future new HCV infections, the incidence of HCV-related cirrhosis would decline rapidly after 2005 (Fig. 2).

### Disease burden by prevalence and future incidence

Calculating with an annual 746 future new HCV infections according to BAG estimates, this analysis considers both, existing HCV infections (prevalence) and new infections (incidence), and permits a simulation of the entire HCV epidemic in Switzerland (Table 7). The simulation was limited up to 2015, since projecting future incidence rates more than 15 years into the future seems to carry a too high uncertainty. Projected HCV-related complications increased only slightly compared with the prior analysis, reflecting the slow progression rate of hepatitis C. The incidence of HCV-related cirrhosis (first complication of HCV infection) rose until 2005 but declined thereafter, even if the annual incidence of new HCV infections was increased by two-thirds to 1238 (Fig. 3). The decline occurs because of the decrease in new infections since 1990 (after mandatory screening of blood products) and the ageing and dying (due to all causes) of the cohort of currently infected patients. This result remained stable even with the variations to base-case estimates used in the simulation model (Table 3).

### Effect of antiviral treatment

Antiviral therapy would reduce annual HCV-related mortality by about 5%, measured as the annual reductions of death of HCV-related chronic liver disease or HCC in 15–25 years. This small reduction in annual mortality is mainly caused by the small fraction of HCV infected subjects diagnosed today (14%) and a response rate of 40%.

### Costs

#### Direct costs

Based on our simulation of the HCV epidemic (see earlier) and the annual cost per disease state (cf. Table 4), we estimate the total direct costs of HCV-related

Table 5 Complications of hepatitis C virus (HCV) as a function of anti-HCV prevalence

Events 1998	Assumed	Predicted regarding to anti-HCV prevalence					
		0.75%	1%	1.25%	1.50%	1.75%	2%
Death due to HCV-related hepatocellular carcinoma	98–132	55	73	92	110	128	147
Death due to HCV-related chronic liver disease	109–283	107	143	179	216	251	287
Liver transplantation for HCV-related end-stage liver disease	14–18	8	11	14	16	19	22

HCV, hepatitis C virus.

**Table 6 Future complications of hepatitis C based on prevalent cases in 1998**

	1998	2005	2010	2015	2020	2025	2030	2035
Incidence of HCV-related hepatocellular carcinoma	114	163	186	196	195	183	165	141
Orthotopic liver transplantation for HCV-related end-stage liver disease	16	22	28	33	35	35	33	29
Incidence of HCV-related liver cirrhosis	1046	1058	982	873	749	622	500	386
Incidence of decompensated HCV-related liver cirrhosis	256	379	443	471	472	448	406	348
Death due to HCV-related chronic liver disease	216	256	325	378	406	410	389	348

HCV, hepatitis C virus.

diseases in Switzerland to be US\$16.1 million (i.e. US\$2.3 million/million inhabitants) for 1998. To be conservative, we only estimated future costs for HCV-infected subjects prevalent in 1998. The yearly (undiscounted) costs will double until 2020, reaching a maximum of US\$32.9 million in 2020 (Table 8). The cumulated (discounted) costs of the entire cohort of HCV-infected subjects will sum up to US\$32.8 million by 2025.

**Indirect costs**

For the modelled cohort of 77 595 HCV-infected subjects prevalent in 1998 in Switzerland, our analysis estimates a loss of 479 500 years of future life due to complications of HCV infection. Restricting the analysis to those between 20 and 60 years of age (as years of productivity) results in a loss of 94 800 years. For 1998, our model estimates a loss of 699 years due to disability

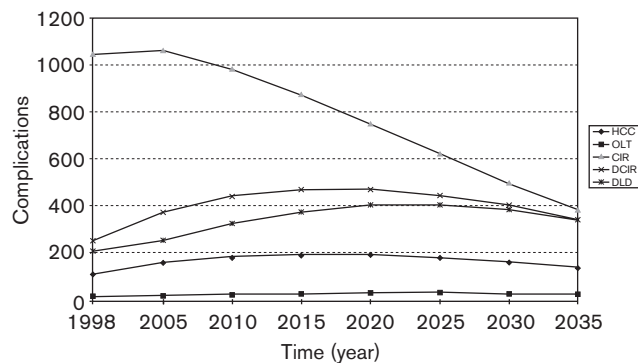
in individuals aged 20–60 years, with a loss of productivity of US\$25.9 million.

**Discussion**

The mandatory reporting of diagnostic tests positive for HCV markers to the BAG combined with detailed clinical information from primary care physicians creates a unique epidemiological data set on HCV infection in Switzerland. The data collected by the BAG allow the differentiation of acute from chronic infections and permit determination of the age distribution of infected subjects. This database, therefore, enabled a comprehensive computer simulation, going further than previous approaches [13,14]. The results of our modelling of the HCV epidemic in Switzerland can be summarized as follows.

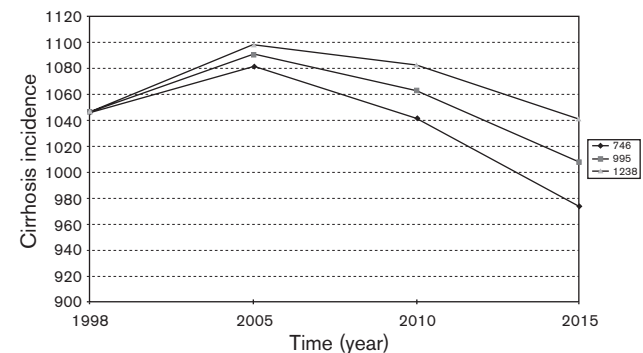
1. The anti-HCV prevalence in the Swiss population was estimated to be 1.25–1.75% using a validated model of the natural history of HCV infection and

**Fig. 2**



Future complications based on the hepatitis C virus (HCV) cohort prevalent in 1998. HCC, incidence of HCV-related hepatocellular carcinoma; OLT, orthotopic liver transplantation for HCV-related end-stage liver disease; CIR, incidence of HCV-related liver cirrhosis; DCIR, incidence of decompensated HCV-related liver cirrhosis; DLD, death of HCV-related chronic liver disease.

**Fig. 3**



Future incidence of hepatitis C virus (HCV)-related cirrhosis, based on the HCV cohort prevalent in 1998 and different incidence rates for new HCV infections (annual HCV infections, 746–1238).

**Table 7 Future complications of hepatitis C based on prevalent cases in 1998 and future incident cases**

	1998	2005	2010	2015
Incidence of HCV-related hepatocellular carcinoma	114	164	190	205
Orthotopic liver transplantation for HCV-related end-stage liver disease	16	22	28	34
Incidence of HCV-related liver cirrhosis	1046	1082	1042	974
Incidence of decompensated HCV-related liver cirrhosis	256	380	450	490
Death of HCV-related chronic liver disease	216	257	328	387

HCV, hepatitis C virus.

back-calculation of observed events (i.e. incidence of HCV-related HCC, death from HCV-related liver disease, OLT for HCV-related end-stage liver disease). This is slightly higher than BAG estimates (i.e. up to 1.0%) because of differences in methodology, i.e. modelling and back-calculation of observed events versus projection from prevalences in highly selected populations.

- The model predicts increasing HCV-related disease burden for the next 20 years, with HCV-related morbidity and mortality almost doubling by approximately 2020. These predictions are similar to those made by the US Centers for Disease Control and Prevention [47], and model calculations performed by Wong *et al.* [14] and Deuffic *et al.* [13] for the USA and France, respectively. Because of the decrease in new HCV infections since 1990 due to screening of blood donors, the annual incidence of HCV-related cirrhosis in Switzerland is predicted to rise up to 2005 and decline afterwards, indicating that the epidemic might decrease.
- The model also predicts that HCV-related morbidity and mortality will lead to rising societal costs over the next 20 years, reaching a maximum in 2020. Thus, annual (undiscounted) direct costs for treating complications of HCV-related liver disease may double by 2020, reaching almost US\$32.9 million per year. The estimated HCV-related direct costs in 1998 of US\$16.1 million are, however, relatively small compared with the US\$801 million direct costs attributable to coronary heart disease in Switzerland

[56] (inflated from 1993 to 1998 health care dollars [46]).

As with any modelling approach, our analysis required making assumptions in the absence of clinical and epidemiological data. Thus, our estimate of the prevalence of HCV infection in Switzerland depends on the likelihood of developing HCV complications (e.g. death from HCV-related HCC or liver disease) and the availability of OLT for HCV-related end-stage liver disease. Even with a lower assumed number of HCV-related complications in 1998, however, our analysis would suggest that the incidence of HCV-related complications would still increase during the next 20 years, albeit with a lower annual burden.

Our simulation may have underestimated the future disease burden for the following reasons: we assumed that HCV-infected patients exhibiting persistently normal transaminases do not develop progressive liver disease. While this assumption seems to hold true for the majority of this subgroup of patients [57], the potential of a minority eventually progressing to more advanced disease states is not entirely excluded. Because patients with persistently normal transaminases account for 30–40% of all chronically HCV-infected subjects [21], even a minority progressing to advanced disease states may significantly increase future HCV-related disease burden and costs.

**Table 8 Direct costs of hepatitis C**

	Direct costs (US\$ millions)					
	1998	2005	2010	2015	2020	2025
Costs undiscounted	16.1	26.1	29.7	32.1	32.9	32.3
Costs discounted (3%)	16.1	21.7	21.4	20.1	17.5	15.2
Costs undiscounted, cumulative	16.1	162.6	304.1	460.3	623.9	787.1
Costs discounted (3%), cumulative	16.1	146.3	254.1	357.3	451.3	532.8

Our simulation did not take age at infection, co-infection with HIV or HBV or concomitant alcohol consumption into account, although some data clearly indicate that rates of progression increase with each of the three [10,58–60]. Because the majority of the prevalent and newly incident cases fell into the 20- to 44-year-old group and because the progression rate increases for age groups at infection over and older than 45 years, age at infection may not substantially alter our results. A considerable fraction of the prevalent cases of HCV infection, however, may have co-infections with HBV or HIV or concomitant alcohol consumption. Presumably, this holds true for even a larger fraction of the newly incident cases because a major risk factor for acquiring HCV infection is injection drug use. In particular, alcohol has been demonstrated to have a significant impact for the progression of hepatitis C [59,60]. Wiley *et al.* have shown that alcohol intake of > 60 g/day in men and > 40 g/day in women may increase the risk of cirrhosis two- to threefold for patients with chronic hepatitis C [60]. Thus, considering these risk factors for disease progression (and today's highly effective anti-HIV therapies) would probably increase future HCV-related disease burden.

Finally, we considered the effect of antiviral therapies (i.e. standard interferon/ribavirin combination) on patients with known disease [48,49,61]. By obviating progression to advanced disease states in a proportion of patients, these therapies may reduce disease burden in the future. Nevertheless, only a small percentage (14%) of prevalent HCV-infected patients are diagnosed and a significant proportion of these were diagnosed with established cirrhosis only partly amenable to antiviral therapy. Therefore, even with the benefit of antiviral treatment, the future disease burden would only be decreased by 5% in the absence of systematic screening for HCV. New therapies such as pegylated interferon in combination with ribavirin that have overall sustained response rates up to 54% [62] will have the same limitations (small percentage of infected patients known, diagnosis with already established cirrhosis) as standard interferon/ribavirin, and therefore will only have a limited effect on the future disease burden.

Systematic screening for chronic hepatitis C has been evaluated neither clinically nor in relation to its cost-effectiveness and is not performed routinely in Switzerland. Nevertheless, screening for hepatitis C could be cost-effective and is recommended for certain risk groups (i.e. patients with transfusion of blood products before 1990, former injecting drug users, etc.) [47,63]. To answer the question on the benefit of a large-scale screening programme for hepatitis C, further research is needed.

### Acknowledgement

The authors would like to thank Dr Raoul Kammerlander, Federal Office of Public Health, Switzerland,

for generously providing insight into the BAG's epidemiological database. This work was supported by a research grant of the Department of Gastroenterology and Hepatology at the University Hospital Zürich and partly by unrestricted grants from Essex Chemie AG Lucerne, Switzerland, and Roche Pharma (Schweiz) AG, Reinach, Switzerland.

### References

- 1 Esteban JI, Lopez-Talavera JC, Genesca J, Madoz P, Viladomiu L, Muniz E, *et al.* High rate of infectivity and liver disease in blood donors with antibodies to hepatitis C virus. *Ann Intern Med* 1991; **115**:443–449.
- 2 Seeff LB, Buskell-Bales Z, Wright EC, Durako SJ, Alter HJ, Iber FL, *et al.* Long term mortality after transfusion-associated non-A, non-B hepatitis. *N Engl J Med* 1992; **327**:1906–1911.
- 3 Di Bisceglie AM, Goodman ZD, Ishak KG, Hoofnagle JH, Melpolder JJ, Alter HJ. Long term clinical and histopathological follow-up of chronic posttransfusion hepatitis. *Hepatology* 1991; **14**:669–674.
- 4 Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, *et al.* Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; **112**:463–472.
- 5 Tremolada F, Casarin C, Alberti A, Drago C, Tagger A, Ribero ML, *et al.* Long-term follow-up of non-A, non-B (type C) post transfusion hepatitis. *J Hepatol* 1992; **16**:273–281.
- 6 Di Bisceglie AM, Order SE, Klein JL, Waggoner JG, Sjogren MH, Kuo G, *et al.* The role of chronic viral hepatitis in hepatocellular carcinoma in the United States. *Am J Gastroenterol* 1991; **86**:335–338.
- 7 Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B hepatitis. *Science* 1989; **244**:362–364.
- 8 Darby SC, Ewart DW, Giangrande PL, Spooner RJ, Rizza CR, Dusheiko GM, *et al.* Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. *Lancet* 1997; **350**:1425–1431.
- 9 Kenny-Walsh E, Irish Hepatology Research Group. Clinical outcomes after hepatitis C infection from contaminated anti D immune globulin. *N Engl J Med* 1999; **340**:1228–1233.
- 10 Niederau C, Lange S, Heintges T, Erhardt A, Buschcamp M, Hurter D, *et al.* Prognosis of chronic hepatitis C: results of a large, prospective cohort study. *Hepatology* 1998; **28**:1687–1695.
- 11 Bundesamt für die Gesundheit. *Verordnung über die Meldung übertragbarer Krankheiten des Menschen (Meldeverordnung)*. Bern, 21 September 1987.
- 12 Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon- $\alpha$ 2b in patients with histology mild chronic hepatitis C. *Ann Intern Med* 1997; **127**:855–865.
- 13 Deuffic S, Buffat L, Poynard T, Valleron AJ. Modeling the hepatitis C virus epidemic in France. *Hepatology* 1999; **29**:1596–1601.
- 14 Wong JB, McQuillan GM, McHutchinson JG, Poynard T. Estimating future hepatitis C morbidity, mortality and costs in the United States. *Am J Public Health* 2000; **10**:1562–1569.
- 15 Sonnenberg FA, Pauker SG. *Decision Maker 7.0*. Boston, MA: New England Medical Center.
- 16 Wong JB, Bennett WG, Koff RS, Pauker SG. Pretreatment evaluation of chronic hepatitis C; risks, benefits, and costs. *JAMA* 1998; **280**:2088–2093.
- 17 Bundesamt für die Gesundheit. Schweizerische Expertengruppe für virale Hepatitis: Hepatitis C; Infektionen mit dem Hepatitis C Virus – Epidemiologie, Prävention und Behandlung. *Bulletin* 49. Bundesamt für die Gesundheit, Bern; 1998.
- 18 Alter MJ, Kruszon-Moran D, Neinan OV, McQuillan GM, Gao F, Linda A, *et al.* The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999; **341**:556–562.
- 19 National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. *Vital Health Stat* 1994; **1**:32.
- 20 Poynard T, Bedossa P, Opolon P, BSVIRC, METAVIR, and DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997; **349**:825–832.
- 21 Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, *et al.* The natural history of community-acquired hepatitis C in the United States. *N Engl J Med* 1992; **327**:1899–1905.

- 22 Bundesamt für die Gesundheit. Infektionskrankheiten in der Schweiz 1997: Akute Hepatitis C. *Arzt- und Labormeldungen: Fallzahlen nach hauptsächlichlichen Risikogruppen*. Bundesamt für die Gesundheit, Bern; 1998.
- 23 Schafer DF, Sorrell MF. Hepatocellular carcinoma. *Lancet* 1999; **353**:1253–1257.
- 24 Chalasani N, Said A, Ness R, Hoen H, Lumeng L. Screening for hepatocellular carcinoma in patients with cirrhosis in the United States: results of a national survey. *Am J Gastroenterol* 1999; **94**:2224–2229.
- 25 Zaman SN, Johnson PJ, Williams R. Silent cirrhosis in patients with hepatocellular carcinoma. Implications for screening in high-incidence and low-incidence areas. *Cancer* 1990; **65**:1607–1610.
- 26 The Liver Study Group of Japan. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. *Ann Surg* 1990; **211**:277–287.
- 27 Collier J, Shermann M. Screening for hepatocellular carcinoma. *Hepatology* 1998; **27**:273–278.
- 28 Calvet X, Bruix J, Bru C, Gines P, Vilana R, Sole M, *et al.* Natural history of hepatocellular carcinoma in Spain. Five years' experience in 249 cases. *J Hepatol* 1990; **10**:311–317.
- 29 Livraghi T, Bolondi L, Buscarini L, Cottone M, Mazziotti A, Morabito A, *et al.* No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis, Italian Cooperative HCC Study Group. *J Hepatol* 1995; **22**:522–526.
- 30 Stuart KE, Anand AJ, Lenkins RL. Hepatocellular carcinoma in the United States; prognostic features, treatment outcome, and survival. *Cancer* 1996; **77**:2217–2222.
- 31 Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a western center. *Ann Surg* 1999; **229**:790–800.
- 32 Franco D, Capussotti L, Smadja C, Bouzari H, Meakins J, Kemeny F, *et al.* Resection of hepatocellular carcinomas; results in 72 European patients with cirrhosis. *Gastroenterology* 1990; **98**:733–737.
- 33 Gozetti G, Mazziotti A, Grazi GL, Jovine E, Gallucci A, Morganti M, *et al.* Surgical experience with 168 primary liver cell carcinomas treated with hepatic resection. *J Surg Oncol* 1993; **3**:S59–S61.
- 34 Fuster J, Garcia-Valdecasas JC, Grande L, Tabet J, Bruix J, Anglada TA, *et al.* Hepatocellular carcinoma and cirrhosis. Results of surgical treatment in European series. *Ann Surg* 1996; **223**:297–302.
- 35 Zala G, Havelka J, Altdorfer J, Joller-Jemelka H, Risti B, Meier B, *et al.* Hepatitis-C-Virus und Hepatom. *Schweiz med Wschr* 1992; **122**:194–197.
- 36 Swisstransplant. *Liver transplantation*. Swisstransplant, Geneva; 1999.
- 37 Mazzafero V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**:693–699.
- 38 McPeake JR, O'Grady JG, Zaman S, Portmann B, Wight DG, Tan KC, *et al.* Liver transplantation for primary hepatocellular carcinoma: tumor size and number of lesions determine outcome. *J Hepatol* 1993; **18**:226–234.
- 39 Llovet JM, Bruix J, Fuster J, Castells A, Garcia-Valdecasas JC, Grande L, *et al.* Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. *Hepatology* 1998; **27**:1572–1577.
- 40 Bronowicki JP, Vetter D, Dumas F, Boudjema K, Bader R, Weiss AM, *et al.* Transcatheter oily chemoembolization for hepatocellular carcinoma. A 4-year study of 127 French patients. *Cancer* 1994; **74**:16–24.
- 41 Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the 'Deale'). I. Validation of the method. *Am J Med* 1982; **73**:883–888.
- 42 Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decision Making* 1993; **13**:322–338.
- 43 Bundesamt für Statistik. *Sterbetafel 1996/1997*. Bundesamt für Statistik, Neuchatel; 1999.
- 44 Health Resources and Services Administration. *1997 Annual Report of the US Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network – Transplant Data: 1988–1996*. Rockville, MD: UNOS, Richmond, VA, and the Division of Transplantation, Office of Special Programs, US Department of Health and Human Services; 1997.
- 45 US Department of Commerce. *Statistical Abstract of the United States 1998*. Department of Commerce, Washington; 1999.
- 46 Bundesamt für Statistik. *Statistisches Jahrbuch der Schweiz 1997*. NZZ Verlag, Zürich; 1998.
- 47 Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *Morbidity Mortal Wkly Rep* 1998; **47**:1–3.
- 48 Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, *et al.* Randomised trial of interferon  $\alpha$ 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon  $\alpha$ 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998; **352**:1426–1432.
- 49 McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, *et al.* Interferon Alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998; **339**:1485–1492.
- 50 Gold MR, Siegel JE, Russel LB, Weinstein MC. *Cost Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.
- 51 Verbindung der Schweizer Aerzte, Versicherer gemäss UVG, Militärversicherung, Invalidenversicherung. *Aerztetarif*. Verbindung der Schweizer Aerzte, Luzern; 1998.
- 52 VESKA. *VESKA Diagnosenstatistik 1996*. VESKA, Aarau; 1997.
- 53 Arbeitsgruppe Schweizerisches Institut für Gesundheits- und Krankenhauswesen (SKI). *Lebertransplantation in der Schweiz*. Schweizerisches Institut für Gesundheits- und Krankenhauswesen, Aarau; 1989.
- 54 Showstack J, Katz PP, Lake JR, Brown R, Dudley RA, Belle S, *et al.* Resource utilization in liver transplantation. Effect of patient characteristics and clinical practice. *JAMA* 1999; **281**:1381–1386.
- 55 Hodgson TA, Meiners MR. Cost-of-illness methodology: a guide to current practices and procedures. *Milbank Mem Fund Quart* 1982; **60**:429–462.
- 56 Sagmeister M, Gessner U, Oggier W, Horisberger B, Gutzwiller F. An economic analysis of ischaemic heart disease in Switzerland. *Eur Heart J* 1997; **18**:1102–1109.
- 57 Mathurin P, Moussalli J, Cadranet JF, Thibault V, Charlotte F, Dumouchel P, *et al.* Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. *Hepatology* 1998; **27**:868–872.
- 58 Soto O, Sanchez-Quijano A, Rodrigo L, Angel del Olmo J, Garcia-Bengoechea M, Hernandez-Quero J, *et al.* Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusual rapid progression of cirrhosis. *J Hepatol* 1997; **26**:1–5.
- 59 Corrao G, Arico S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *Hepatology* 1998; **27**:914–919.
- 60 Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998; **28**:805–809.
- 61 Reichard O, Norrkrans G, Fryden A, Braconier JH, Sonnerborg A, Weiland O. Randomised, double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C. The Swedish Study Group. *Lancet* 1998; **351**:83–87.
- 62 McHutchison J, Manns M, Harvey J, Albrecht JK. Adherence to therapy enhances sustained response in chronic hepatitis C patients receiving peg-interferon alfa-2b plus ribavirin [Abstract]. *J Hepatol* 2001; **34**:2A.
- 63 Swiss Experts on Viral Hepatitis (SEVHEP). *Hepatitis C; 50 Fragen und Antworten*. Zürich: University Hospital Zürich; 2000.

## Appendix

### Extension of the model

We modified the published hepatitis C model [12,16] to include the possibility of partial hepatectomy or OLT for small surgical curable HCC (Fig. 1).

### Assumptions

We assumed that asymptomatic HCC would only be detected in an early (surgically treatable) stage by screening measurements. We assumed that HCC resection or OLT would only be considered for small ( $\leq 5$  cm), unifocal tumours or for not more than three tumours  $\leq 3$  cm without evidence of vascular invasion, because most surgeons would not operate on multifocal tumours [23]. After partial hepatectomy or OLT for HCC, we did not consider re-operation, nor did we consider non-surgical treatments of HCC such as transcatheter chemoembolization or percutaneous ethanol injection, which are still under clinical evaluation.

### Partial hepatectomy and HCC

In a survey (response rate, 54%) of US members of the American Association for the Study of Liver Diseases (AASLD), 84% perform routine screening of cirrhotic

patients for HCC [24]. This survey probably overestimates screening practice because it only includes AASLD members. In Switzerland, routine screening of cirrhotic patients for HCC by sonography and alpha-fetoprotein is common, so we assumed that 50–70% (base-case, 60%) of patients with known HCV-associated cirrhosis are screened routinely. However, 30–56% (base-case, 40%) of patients with HCC have silent, unrecognized cirrhosis at the time of HCC diagnosis and will therefore not be recruited in a screening procedure [25,26]. In a screened cirrhotic population, about 80% (66–100%) of all HCC will present as a small, single lesion with a diameter  $\leq$  5 cm at diagnosis (50–75% as a tumour  $\leq$  3 cm) that is possibly amenable to resection [27]. Not all of these patients, however, undergo surgery because only 29–54% (base-case, 40%) are ultimately resected. The high portion of undiagnosed cirrhosis and the low resection rate may be the main limitations of successful screening programmes for HCC in cirrhotic patients. Because of these considerations, we assumed that about 10% of all HCC will be resected. This is consistent with prospective and retrospective (possibly biased to more intensive treating) studies showing a range of surgical treatment from 6% (partial hepatectomy) [28] to 11–20% (partial hepatectomy and OLT) [29,30].

One-year survival after partial hepatectomy for HCC ranges from 68 to 79%, and 5-year survival ranges from 37 to 38.6% [30–34]. The biggest series with 412 patients and partial hepatectomy was reported recently by Fong *et al.* [31], with a reported 1-year and 5-year survival for patients with cirrhosis of 77 and 37%, respectively (base-case: 1-year survival, 75%; 5-year survival, 38%).

#### OLT and HCC

In 1996, 327 patients died of HCC in Switzerland (BFS, unpublished data 1999). As reported in other countries, about 35% of all HCC (range, 98–132 HCC) are estimated to be related to HCV in Switzerland [35]. Based on an evaluation of 62 consecutive OLTs at the University Hospital Zürich (E. L. Renner, unpublished data 2000), two HCC were related to HCV (3.2%). Taking the same rate for all OLTs in Switzerland (67 OLTs in 1996) [36], we assumed 2.2 OLTs for HCV-associated HCC in 1996. Collectively, this led us to assume a probability of 1.9% for a HCV-related HCC to undergo OLT.

The literature shows considerable overall variability in the survival after OLT for HCC as post-operative tumour recurrence correlates with tumour size and with the number of lesions. In well-selected patients with small tumours  $\leq$  5 cm, the perioperative mortality and 5-year survival are 6 and 57–75%, respectively [37–39].

#### Advanced HCC

The 1-year survival of patients with advanced HCC (tumour exceeding 5 cm in diameter, more than three nodules, or invasion of blood vessels) is about 20% [28,29,40].

#### Transition probabilities from HCC

To adjust mortality rates ( $r$ ) to probabilities ( $P$ ), we applied the declining exponential approximation of life expectancy ('Deale') [41]. Thus, mortality rates ( $r$ ) were converted to annual transition probabilities ( $P$ ) using the expression  $P = e^{-r}$  [42], where  $t = 1$  year (Table 3). Age-specific mortality data (from all other causes) were obtained from official Swiss mortality tables [43].