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Trends in hepatitis C-related mortality in Switzerland

Short title: Trends in hepatitis C related mortality

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Abstract

Background & Aims: To accurately assess the burden of hepatitis C (HCV) and develop effective interventions, we must understand the magnitude and trends mortality related to the disease. In the United States, HCV-related mortality is continuously increasing. We have no comparable data for Switzerland and other European countries, though a modelling study predicted a similar increase.

Methods: We analysed time trends (1.1.1995-31.12.2014) in HCV-specific mortality rates in the Swiss general population using the death registry of the Swiss Federal Statistical Office (SFSO). We compared HCV-related mortality to HIV- and hepatitis B (HBV)-related mortality. To determine potential under-reporting in HCV-related mortality, we probabilistically linked the SFSO data to persons who died in the Swiss Hepatitis C Cohort (SCCS).

Results: SFSO data showed that HCV-related mortality more than doubled between 1995 and 2003, but has since stabilized at $\sim 2.5/100,000$ person-years. Since 2000, HCV-related mortality has been higher than HIV-related mortality and was about five-fold higher in 2014. HBV-related mortality remained low at $\sim 0.5/100,000$ person-years. Of 4,556 persons in the SCCS, 421 have died and 86.2% could be linked to the death registry. According to the SCCS, 133 deaths were HCV-related. HCV was not mentioned on the SFSO death certificate of 45% of these ($n=60/133$).

Conclusions: In conclusion, HCV-related mortality remained constant, possibly because quality of care was high, or because of under-reporting, or because mortality has not yet increased. However, HCV-related mortality is now much higher than HIV- and HBV-related mortality, and underreporting was common.

Keywords: cohort; hepatitis B; hepatitis C; HIV; mortality

Introduction

Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) (1, 2). New and more effective therapies for HCV may have changed the all-cause and cause-specific mortality. Instead of dying of HCV, persons who have cleared HCV may be more likely to die from other conditions like malignancies (other than HCC), cardiovascular disease, accidents, illicit drug overdose, suicide and other infections (2). Because chronic hepatitis C progresses slowly, these trends may emerge slowly, and some have predicted that liver-related complications and deaths will continue to increase for at least another decade (3, 4). For example, the Global Burden of Disease Study found that the absolute number of deaths attributable to hepatitis C increased from 303,000 in 1990 to 704,000 in 2013 (5).

To determine the burden of hepatitis C and develop effective interventions, we must quantify mortality, compare it to other diseases, and identify people at high risk of dying. Studies from the US found that HCV-related mortality is often underreported and mortality was particularly high in certain age groups. For example, in 1,600 persons of the Chronic Hepatitis Cohort Study who died from hepatitis C, HCV was listed on only 19% of their national death certificates (6). Most HCV-related deaths were recorded in persons born between 1945 and 1965. Another US study showed that, since 2007, HCV-related deaths have been more frequent than human immunodeficiency virus (HIV)-related deaths (7), but we have no comparable data for Switzerland or other countries.

The magnitude and trends in mortality in Switzerland are likely to differ from the US since the timing of HCV infection and the composition of the population are substantially different. We aimed to examine HCV-related mortality in Switzerland by first analyzing time trends in HCV-specific mortality using the official cause of death registry of the Swiss Federal Statistical Office

(SFSO). We then compared mortality in the SFSO death registry to the HCV-specific mortality in the Swiss Hepatitis C Cohort Study (SCCS) to determine potential underreporting in the SFSO.

Material and Methods

Trends in cause-specific mortality rates in the SFSO death registry

The SFSO has monitored the number and causes of death in Switzerland since 1876. Data were compiled until December 31, 2014. The SFSO uses the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (8) to code causes of death, based on initial, consecutive and concomitant diseases listed on the SFSO death certificate. We used data from the SFSO death registry to calculate trends in mortality caused by HCV (ICD-10 codes B17.1 or B18.2), hepatitis B virus (HBV) (B16.0, B17.0, B18.0, B18.1), and HIV (B20-B24) from 1995 to 2014. We classified causes either as primary cause of death, or mentioned anywhere on the SFSO death certificate.

We also recorded whether other causes potentially related to hepatitis C were mentioned on the SFSO death certificates (whether or not hepatitis C was mentioned). We grouped these potential causes into two sets of ICD-10 codes. The first set contains the causes of death that could be related to HCV, even though other types of chronic liver disease could have been the real cause of death: B94.2 (sequelae of viral hepatitis); C22.0 and C22.8 (hepatocellular carcinoma); D37.6 (neoplasm of uncertain behavior: liver, gallbladder and bile ducts); G93.4 (unspecified encephalopathy); I85.0 (esophageal varices with bleeding); K72.9 (unspecified hepatic failure); and K74.6 (other and unspecified cirrhosis of liver). The first set is a subset of the second set, which also includes deaths caused from sepsis. We assumed sepsis may have been caused by infected ascites associated with HCV-related cirrhosis: A40.3 (sepsis due to *Streptococcus pneumoniae*); A41.0 (sepsis due to *Staphylococcus aureus*); A41.1 and A41.2 (sepsis due to other specified or unspecified *Staphylococcus spp.*); A41.5 (sepsis due to other

Gram-negative organisms); and, A41.9 (unspecified sepsis). Two hepatologists (FN and BM) defined these sets by consensus.

We calculated time trends (with 95% confidence intervals) in crude and age-standardized mortality rates. Age-standardized rates were calculated by direct standardization. We used the official SFSO permanent resident population data as the annual denominator. We calculated the mid-year population for each year by averaging the end of year population in one year with the end of year population of the previous year. We grouped age into 5-year categories (0-4, 5-9, ..., 85+). For direct standardization, we used as reference the mid-2014 estimated permanent resident population.

The Swiss Hepatitis C Cohort Study

To analyze potential underreporting of HCV-related mortality in the SFSO registry, we compared the causes of death the SFSO reported with the causes of death the SCCS reported. The SCCS is a prospective observational cohort study that continuously enrolls HCV-infected persons (aged 18 years or older) who attend out-patient clinics at eight clinical centers (9). Enrollment began on September 18, 2000. Data are collected annually by standardized questionnaires and include demographic, psychosocial, clinical, laboratory, and treatment information. Persons who missed scheduled visits were actively traced with phone calls and letters. Causes of death were coded with ICD-10 codes by the treating physician and classified as related or unrelated to HCV. Non-HCV-related causes of death were categorized into suicide, overdose of narcotics, accident, other (for which an ICD-10 code had to be provided) and unknown. The study was approved by all local ethics committees, and all persons provided written informed consent.

Inclusion criteria and definitions

All persons enrolled into the SCCS were eligible for our analysis. Loss to follow-up (LTFU) was defined as “not seen for at least two years after the last visit to the clinic (excluding persons who have died)”. Only persons who were registered more than two years before the database closed could be considered LTFU (on December 31, 2014).

Linkage with the SFSO registry

To compare the causes of death reported by the SCCS with those of the official mortality registry of the SFSO, we used data from the Swiss National Cohort SNC (10, 11). In short, the SNC is a cohort of all Swiss residents which linked records from the 1990 and 2000 censuses to the deaths from the SFSO mortality registry. Deceased persons of the SCCS were anonymously linked with the mortality data of the SNC, using probabilistic record linkage (12). We used date of birth, date of death, gender, and nationality (Swiss vs. non-Swiss) to link records and allowed for typos in the linkage variables. We also used spatial information to improve the linkage, assigning the SCCS clinics and place of residence at time of death to one of the seven nomenclature of territorial units for statistics areas of Switzerland (13). We included deaths that occurred between September 18 2000 (start of the SCCS) and the end of 2014. We used G-Link software, developed by Statistics Canada (14), for linkage. We identified possible matches based on probability weights, and set the threshold so that only highly probable links were accepted. We compared characteristics between persons successfully linked and persons with failed linkage.

We determined how many deceased persons in the SCCS (related or unrelated to HCV, or cause of death unknown) had hepatitis C listed on their SFSO death certificate. We used the same definitions of (possibly) hepatitis-C related mortality: 1) HCV (B17.1 or B18.2) as primary

cause; 2) HCV anywhere on the SFSO death certificate; 3) first set of additional causes anywhere on the SFSO death certificate; and, 4) second set of additional causes anywhere on the SFSO death certificate.

All analyses were done with Stata version 14 (StataCorp, College Station, TX).

Results

SFSO mortality rates

Figure 1 shows the crude mortality rates for hepatitis C, HIV and hepatitis B, based on mention of corresponding ICD-10 codes anywhere on the SFSO death certificate. HCV-related mortality increased from 1.2/100,000 person-years in 1995 to 3.0/100,000 in 2003. After 2003, the rate remained more or less constant. HIV-related mortality declined rapidly, from 9.1/100,000 in 1995 to 2.5/100,000 in 1998. After 1998, HIV-related mortality continued to decrease but at a slower pace, reaching 0.6/100,000 in 2014. After 2000, HIV-related mortality was lower than HCV-related mortality. HBV-related mortality was below 1.0/100,000 most of the time, except for a small peak of 1.2/100,000 in 2005. When we included deaths that were possibly HCV-related (the extended set 1), death rate increased up to 18-20/100,000, with a slight drop-off between 2002 and 2004; it increased again thereafter (Figure 2). Additional inclusion of the extended set 2, minimally increased the reported death rate (data not shown). The death rate of HCC remained more or less constant, at 5/100,000 person-years (Figure 2). Age standardized rates were very similar to crude rates (data not shown).

Characteristics of persons in the SCCS

Of 4,556 SCCS participants, 443 (9.7%) died between September 18, 2000 and December 31, 2014; for 421/443 (95.0%) the date of death was known (Figure 3). The overall death rate was 16.3/1000 person-years of follow-up (95% CI 14.8-17.9). The median duration of follow-up was 5.8 years (interquartile range [IQR], 1.6-9.9). Table 1 shows the characteristics of all the persons in the SCCS and of deceased persons who could or could not be linked to the SFSO registry. At enrollment, persons in the SCCS were mostly male (63%), Swiss nationals (73%),

and had a median age of 44 years (IQR, 37-52 years). Slightly over half were former (11%) or current (44%) injecting drug users, a third reported previous or ongoing heavy alcohol consumption (> 40 g/day) and 15% had liver cirrhosis. A total of 941 (20.6%) persons were lost to follow-up before the database closed at the end of 2014. Deceased persons who could and those who could not be linked to the SFSO registry had similar characteristics.

Linkage SCCS – mortality registry

Of the 421 persons with a known date of death in the SCCS, 363 (86.2%) could be linked to one of the 995,393 records of the mortality registry with high linkage probability. Among the linked persons, reported date of death was identical in the SCCS and the mortality registry for 298 (82.1%), but was different for 65 (17.9%): 31 (10.7%) dates of death differed by ± 2 days, 5 (1.7%) had a different month and 3 (1.0%) differed by ± 1 year.

The SCCS physicians classified the 363 linked deaths as follows: 133 (36.6%) as HCV-related; 8 (2.2%) as suicide; 12 (3.3%) as overdose of narcotics; and, 5 (1.4%) as accidents. There were 105 (28.9%) deaths for reasons unrelated to HCV, and for 100 (27.6%) persons, cause of death was unknown.

Comparison between causes of death reported by the SCCS with the causes reported by the SFSO mortality registry

In the mortality registry, hepatitis C was mentioned as cause of death for a minority of persons (either as primary cause or anywhere on the SFSO death certificate), showing substantial underreporting ([Table 2](#)). Of the 363 SCCS deaths that could be linked, only for 13 (3.6%) the SFSO registry mentioned hepatitis C as primary cause of death, while for 138 (38.0%), hepatitis C was mentioned anywhere ([Table 2](#)). Considering additional causes of death, increased the percentage of deaths potentially associated with HCV to 59.5% (n=216), if we included the first set of causes of death, and to 62.3% (n=226) if we included the second set.

Similarly, when we considered only the 133 persons in the SCCS whose death was deemed HCV-related, the SFSO registry reported that 5 (3.8%) died primarily from HCV. Overall, for 73 deaths (54.9%) that the SCCS recorded as HCV-related, HCV also appeared on the SFSO death certificate. Therefore 45.1% (100% minus 54.9%) of HCV-related deaths were missed. When

we included the first and second sets of additional causes of death that could be attributed to HCV, the percentage of concordance between SCCS and SFSO increased to 90.2% for the first set and 91.7% for the second set.

When the SCCS coded deaths as unrelated to HCV ($n=130$), HCV was considered to be the primary cause of death in 3 (2.3%) SFSO death records, and was mentioned anywhere on the SFSO death certificate in 35 (26.9%) cases. When we included the first and the second sets of causes potentially attributable to HCV mentioned anywhere on the SFSO death certificate, this proportion increased to 41.5% for the first set and 46.1% for the second set.

Finally, among the 100 persons whose cause of death was unknown in the SCCS, the SFSO certificate reported that 5 (5%) died of HCV as primary cause, and HCV was reported anywhere for 30 (30%). These numbers increased to 42 (42.0%) after considering the first set of causes of death potentially related to HCV (mentioned anywhere on the death certificate) and 44 (44.0%) for the second set.

Discussion

Since 2000, HCV-related mortality in Switzerland has been higher than HIV- and HBV-related mortality. The national SFSO death registry showed that HCV-related mortality more than doubled between 1995 and 2003, but has since stabilized. In the same time-period, HIV-related mortality decreased substantially, and matched HBV-related mortality in 2005. In 2014, HCV-related mortality in Switzerland was about five-fold higher than HIV- and HBV-related mortalities. Underreporting of HCV-related mortality in the SFSO death registry was substantial. In almost half of the cases (45%) no HCV-related diagnosis was reported or coded.

The overall pattern of mortality for HCV, HBV and HIV was similar in the US and Switzerland, but there were some important differences. In 1999, HIV-related mortality was much lower in Switzerland than in the US (7) (about 2.5/100,000 vs. 6.0/100,000) but both subsequently declined at a similar pace. The introduction of effective combination therapy caused the initial steep decline in HIV-related mortality in Switzerland; thereafter, the decline was gentler, but continuous, probably because antiretroviral drugs continued to become more effective and were better tolerated (15, 16). The steep decline of HIV-related mortality in Switzerland may also explain why HCV-related mortality rose higher than HIV-related mortality sooner in Switzerland (2000) than in the US (2007). Although effective combination therapies against HIV became available at the same time in the US and in Switzerland, mortality among persons with HIV was higher in two US cohorts (17) than in European cohorts.

HBV-related mortality rates were low in both countries. In Switzerland there was no clear trend over time, and in the US there was a slightly decreasing trend. Our finding that HBV-related mortality was lower than HCV-related mortality in Switzerland is in line with findings

that the prevalence of HBV is lower than for HCV (18), that persons with HBV are mostly (60-70%) inactive carriers whose disease does not evolve over time, and that effective nucleoside and nucleotide analogues against HBV existed since about 2000 (19).

In contrast to the US (7) and to projections from a Swiss modelling study (3), we found no increase in documented HCV-related mortality in recent years in Switzerland. The modeling study by Müllhaupt *et al* projected that, based on the different time distribution when people were infected, HCV-related mortality in Switzerland would increase from about 120 cases in 1995 to 400 cases in 2014, and to 650 cases in 2030 (3). Both in Switzerland and in the US, most HCV notifications are related to intravenous drug use (IDU), and cases clustered in certain age groups (20, 21). In the US, 75% of all persons with HCV were born between 1945 and 1965 (21). In Switzerland 61% of all cases were born between 1955 and 1974 (20). We are not sure why we did not see an increase in HCV-related mortality in Switzerland in the past years. Perhaps the quality of care has improved over time, the simulation model was not accurate, or mortality was under-reported. Or, the increase may simply be delayed. If we assume that the time from HCV infection to cirrhosis takes about 30 years (22), and that the IDU epidemic in Switzerland peaked in 1990 (23), then we should expect HCV-related mortality to rise steeply around 2020. Müllhaupt *et al* may also have over-estimated HCV-related mortality because their model assumed an HCV prevalence of 1.6% (based on a modelling study from 1998 (24)), which may have been too high. Although no large-scale HCV prevalence surveys exist for Switzerland, a recent systematic review within a situation analysis showed that prevalence is probably lower (about 0.5%) (25). The initial increase of HCV-related mortality in Switzerland in 1995-2003 may have been caused by increase in awareness of HCV. We do not know what proportion of deaths possibly linked to HCV (including the extended sets 1 or 2) was really due to HCV. For example, HCC accounts for more than 20% of all causes

of death in extended set 1, but systematic reviews demonstrated that the relative importance of HCV in the etiology of HCC varies between settings and over time. Globally about 25-30% of HCC cases are attributable to HCV (26, 27). Raza *et al* showed that, in most European countries, the proportion of HCV-related HCCs was higher (mean anti-HCV positivity 34.3%) than the proportion of HBV-related HCCs (mean HBsAg positivity 23.1%), but they did not include any Swiss study. Two small studies from Switzerland showed that a similar proportion of HCC cases is probably HCV-related (28, 29). For the other deaths (sets 1 and 2) possibly related to HCV, it is also difficult to determine the proportion caused by HCV.

Our study was strengthened by the two complementary data sources we used to analyze HCV-related mortality in Switzerland. SFSO data are nationwide and include all deaths in Switzerland. The SCCS dataset allowed us to compare and validate causes of death. The SCCS covers most of Switzerland and includes probably >10% of the estimated 36,000-43,000 HCV-infected persons (25). The characteristics of the persons in the SCCS are similar to those reported by the national surveillance data of the Federal Office of Public Health (9, 30), so our findings can be generalized to other HCV-infected persons in Switzerland. However, the SCCS also has limitations. It includes a disproportionate high number of persons from large university hospitals at an advanced stage of the disease (9). Cause of death was unknown for 27.5% of all deceased persons in the SCCS who could be linked. These observations limit our comparison of causes of death between the two data sources. Moreover, linkage might also introduce some bias. Few variables could be used for linkage, but the high discriminatory power of two linkage variables (date of birth and date of death) allowed us to link most persons with a high probability. Some persons listed as deceased in the SCCS could not be linked to the SFSO registry. The reasons for this mismatch are unclear; it is possible that the linkage threshold was too strict (we favored this conservative choice to prevent false positive

linkages). It is likely that some persons who were lost to follow-up from the SCCS have died. In both the SCCS and the SFSO, deaths were often coded by different people, and coding practices may have changed over time, and between countries. However, all of the people who coded causes of death were experienced clinicians and/or specially trained. The main focus of our analysis was on liver-related mortality, but HCV also causes non-liver related mortality (2). Finally, we could not verify whether HIV and HBV-related mortality was under-reported in the SFSO registry, and to what extent underreporting occurred in the US. Although we could not exactly determine the magnitude of HCV-related mortality in Switzerland, we found that HCV-related mortality was lower in Switzerland than in the US, and that there was no increasing trend in recent years. Underreporting of HCV-related mortality was substantial, and in recent years, HCV-related mortality was about 5 times higher than HIV and HBV-related mortality. To prevent the development of long-term sequelae and mortality we must identify and treat HCV-infected people in time. The increasing availability and use of very effective new HCV therapies, should compel us to continuously monitor HCV-related mortality and causes of death over time.

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Author Contributions

Designed the study: OK with substantial contribution from FN, FG, AS, JE, BB, MB. Analyzed the data: AS, FG. Wrote the first draft of the paper: OK. Revised the paper: FN, FG, BM, CJ, JFD,

DM, PB, DS, BT, MB, BB, JE. Contributed data: FN, BM, CJ, JFD, DM, PB, DS, BT. Approved the final version of the manuscript: all.

Abbreviations:

HBV Hepatitis B; HCC hepatocellular carcinoma; HCV Hepatitis C; HIV Human Immunodeficiency Virus; SCCS Swiss Hepatitis C Cohort Study; SFSO Swiss Federal Statistical Office

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Table 1: Characteristics of persons at enrolment into the Swiss Hepatitis C Cohort Study**(SCCS)**

Variable	All persons in SCCS on December 31 st 2014 N = 4,556	Persons who died and could be linked to SFSO N = 363	Persons who died and could not be linked to SFSO N = 58	P-value linked vs non-linked
Age (median, IQR)	44 (37-52)	49 (41.5-58)	47.5 (39-57)	0.585
Gender				0.714
<i>Male</i>	2,861 (62.8)	265 (73.0)	41 (70.7)	
<i>Female</i>	1,695 (37.2)	98 (27.0)	17 (29.3)	
Nationality				0.203
<i>Swiss</i>	3,337 (73.2)	284 (78.2)	41 (70.7)	
<i>Non-Swiss</i>	1,214 (26.7)	79 (21.8)	17 (29.3)	
<i>Unknown</i>	5 (0.1)			
Genotype				0.421
1	2,183 (47.9)	176 (48.5)	32 (55.2)	
2	359 (7.9)	26 (7.2)	5 (8.6)	
3	1,195 (26.2)	99 (27.3)	10 (17.2)	
4	426 (9.3)	35 (9.6)	6 (10.4)	
<i>Other/unknown</i>	393 (8.7)	27 (7.4)	5 (8.6)	
Drug use				0.949
<i>Current</i>	2,024 (44.4)	165 (45.5)	27 (46.6)	
<i>Former</i>	512 (11.2)	26 (7.2)	4 (6.9)	
<i>Never</i>	1,982 (43.5)	170 (46.8)	25 (43.1)	
<i>Unknown</i>	38 (0.9)	2 (0.5)	2 (3.4)	
Alcohol consumption				0.941
<i>Current heavy drinker*</i>	386 (8.5)	52 (14.3)	8 (13.8)	
<i>Former heavy drinker*</i>	968 (21.2)	116 (32.0)	16 (27.6)	
<i>Curr/form moderate drinker</i>	734 (16.1)	49 (13.5)	7 (12.1)	
<i>No</i>	2,433 (53.4)	146 (40.2)	25 (43.1)	
<i>Unknown</i>	35 (0.8)	0	2 (3.4)	
Cirrhosis at enrolment				0.490
<i>Yes</i>	700 (15.4)	167 (46.0)	23 (39.7)	
<i>No</i>	3,828 (84.0)	196 (54.0)	33 (56.9)	
<i>Unknown</i>	28 (0.6)	0	2 (3.4)	
HIV				0.685
<i>Yes</i>	309 (6.8)	56 (15.4)	7 (12.0)	
<i>No</i>	3,296 (72.3)	247 (68.1)	40 (69.0)	
<i>Unknown</i>	951 (20.9)	60 (16.5)	11 (19.0)	
HBV chronic				1.000
<i>Yes</i>	93 (2.1)	11 (3.0)	1 (1.7)	
<i>No</i>	3,650 (80.1)	307 (84.6)	52 (89.7)	
<i>Unknown</i>	813 (17.8)	45 (12.4)	5 (8.6)	
Treated				0.892
<i>Yes</i>	2,654 (58.2)	185 (51.0)	29 (50.0)	
<i>No/unknown</i>	1,902 (41.8)	178 (49.0)	29 (50.0)	

* Heavy drinker was defined as >40g of alcohol per day; moderate drinker was defined as 20-40g/day.

P-values come from median tests for the continuous variable (age) and chi-squared or Fisher's exact test for categorical variables.

Table 2. HCV-related and unrelated deaths: comparison of causes of death between the Swiss Hepatitis C Cohort (SCCS) and the Swiss Federal Statistical Office (SFSO) using the successfully linked deceased persons

SFSO	Total SCCS linked deaths N = 363	SCCS deaths related to HCV N = 133	SCCS deaths unrelated to HCV N = 130	SCCS deaths unknown cause N = 100
HCV reported as primary cause of death in SFSO registry	13 (3.6%)	5 (3.8%)	3 (2.3%)	5 (5.0%)
HCV reported as any cause of death in SFSO registry	138 (38.0%)	73 (54.9%)	35 (26.9%)	30 (30.0%)
HCV (B17.1, B18.2, first set ¹) reported as any cause of death in SFSO registry	216 (59.5%)	120 (90.2%)	54 (41.5%)	42 (42.0%)
HCV (B17.1, B18.2, first set ¹ , second set ²) reported as any cause of death in SFSO registry	226 (62.3%)	122 (91.7%)	60 (46.1%)	44 (44.0%)

¹**First set:** B94.2 (sequelae of viral hepatitis), C22.0 and C22.8 (liver cell carcinoma), D37.6 (neoplasm of uncertain behavior: liver, gallbladder and bile ducts), G93.4 (unspecified encephalopathy), I85.0 (esophageal varices with bleeding), K72.9 (unspecified hepatic failure), K74.6 (other and unspecified cirrhosis of liver).

²**Second set:** A40.3 (sepsis due to *Streptococcus pneumoniae*), A41.0 (sepsis due to *Staphylococcus aureus*), A41.1 and A41.2 (sepsis due to other specified or unspecified *Staphylococcus*), A41.5 (sepsis due to other Gram-negative organisms), A41.9 (unspecified sepsis).

Figure 1: Crude mortality rates (with 95% confidence intervals) in the Swiss Federal Statistical Office (SFSO) of hepatitis C-related (HCV) mortality (B17.1, B18.2), Hepatitis B-related (HBV) mortality (ICD-10: B16.0, B17.0, B18.0, B18.1), and HIV-related mortality (B20-B24). Causes of death mentioned anywhere on the SFSO death certificate are shown.

Figure 2: Crude mortality rates (with 95% confidence intervals) in the Swiss Federal Statistical Office (SFSO) using hepatocellular carcinoma (HCC) (ICD-10 C22.0, C22.8) and the extended set 1 (C22.0, C22.8, B94.2, D37.6, G93.4, I85.0, K72.9, K74.6) as possibly HCV-related mortality. Causes of death mentioned anywhere on the SFSO death certificate are shown.

Figure 3: Flow chart.

SCCS: Swiss Hepatitis C Cohort Study; SFSO: Swiss Federal Statistical Office





