The epidemiology of hepatitis C in Switzerland: trends in notifications, 1988–2015

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Summary

With an estimated antibody prevalence of 0.7% in the low-risk population, hepatitis C virus (HCV) endemicity in Switzerland is low. We reviewed data from mandatory hepatitis C surveillance for 1988–2015 in order to describe the evolution of acute HCV infections and newly reported non-acute cases, and their epidemiological features. Crude and stratified annual incidence and notification rates and rate ratios were calculated using Poisson regression. Acute HCV incidence peaked in 2002 at 1.8 cases per 100,000 population, then declined sharply, levelling at around 0.7/100,000 from 2006. Notification rates for non-acute HCV cases peaked in 1999 (38.6/100,000), decreasing to 16.8/100,000 in 2015. Men constituted 65.5% of acute cases and 60.4% of non-acute cases. During the periods 1992–1995 and 2012–2015, the median age of acute cases increased from 28 to 37 and of non-acute cases from 32 to 48 years. The exposure leading to most acute (90.4%) and non-acute (71.9%) cases was presumably in Switzerland. Despite a sharp decrease since 2000, injecting drugs was the main reported exposure for both acute (63.8%) and non-acute (66.6%) cases, with a known exposure, followed by sexual contact with an infected person (18.9% and 10.3% respectively). Among all acute cases, the number of men who have sex with men increased sharply after the mid-2000s, totalling 41 during 2012–2015 (25.7%). Although the HCV epidemic peaked in 2000 – probably as a result of measures to control iatrogenic and percutaneous transmission – Switzerland must maintain prevention and surveillance.

Key words: hepatitis C, epidemiology, surveillance, incidence, injection drug users, men who have sex with men

Introduction

An estimated 1.75 million new hepatitis C virus (HCV) infections occurred worldwide in 2015, with the highest incidence in the World Health Organization's (WHO) European Region and the Eastern Mediterranean Region (both about 62 cases per 100,000 population) [1]. About 55–85% of the usually asymptomatic acute HCV infections become chronic, with a 15–30% risk of developing cirrhosis within 20 years [2]. Worldwide, 71 million people (1% of the global population) are chronically infected with HCV, with 14 million (1.5% of the population) living in the European region [1]. Each year, approximately 399,000 people, 86,000 in the European region, die of complications from a chronic HCV infection (cirrhosis and hepatocellular carcinoma) [1, 3].

With an estimated anti-HCV prevalence of 0.7% among the general population without risk groups and 45.8% among high-risk populations, the latter mostly injection drug users [4], Switzerland is among the regions with low prevalence (<1.5%), along with others in western and central Europe [5]. In contrast, Central Africa and Central Asia have high prevalence rates (>3.5%), and eastern Europe and most other parts of Africa and Asia have moderate prevalence rates. It is estimated that 36,000–43,000 chronically infected individuals live in Switzerland [4].

No vaccine exists. Consequently, primary prevention requires the avoidance of contact with contaminated blood, particularly in health services, in drug use involving injection drugs, and in sexual (rectal) bleeding in human immunodeficiency virus (HIV)-positive men who have sex with men (MSM). In Switzerland, it has been recommended since 1993 that physicians suggest HCV antibody testing to individuals with certain risk factors [6]. To date, routine screening has been limited to blood donations (detected with first generation tests since 1990, and with polymerase chain-reaction tests [PCR] after 1999) [6], injection drug users in substitution programmes [7] and people included in the HIV / acquired immunodeficiency syndrome (AIDS) study cohort [8]. Individuals belonging to other risk groups, such as health personnel, prison inmates [9], other injection drug users or MSM may also be screened, depending on the screening practice of their general practitioner, their employer or their prison, as well as populations that are not considered at-risk, such as pregnant women [10], people undergoing infertility testing and people before surgery or immunosuppressive therapy.

Currently, in Switzerland the development of a national strategy for the screening and care of infected people is under intense debate. Some suggest introducing or systematising the screening of at-risk groups [11–15], others propose the systematic screening of the most affected birth cohorts [16, 17], as recommended in, for example, the United States [18]. Since October 2017, health insurance covers the cost of direct-acting antivirals for all HCV-infected people.

Since the recent advent of potent and safe direct-acting antivirals, it has been possible to cure more than 90% of patients treated, thereby reducing transmission and the risk of complications and death. This paved the way for the WHO strategy, adopted in 2016, to eliminate hepatitis as a public health threat by 2030 [19]. The WHO also proposed an action plan for the European region, with ambitious targets to be achieved by 2020 for the detection, treatment and cure of chronically infected individuals, aiming at a 30% reduction in the number of new chronic HCV infections and a 10% reduction in the number of deaths [20]. As a consequence, detailed epidemiological data indicating trends in the HCV-infected population, including transmission risk factors, are necessary in order to implement or enhance measures for prevention, screening and treatment.

Because of immigration, countries with a low prevalence in the general population may have foreign populations or populations of foreign origin with HCV prevalence rates that are similar to those of their countries of origin. Switzerland has had a large number of immigrants since the 1950s, initially mainly from southern Europe and later of increasingly diverse origins. In 2015, 163,000 foreign people moved to Switzerland, representing a net migration of 76,000 individuals [21]. At 2.05 million people out of 8.33 million, foreigners accounted for 24.6% of the total population, 12.4% of them coming from Asia, Africa and eastern Europe.

The aim of this article is to describe epidemiological trends in HCV cases reported in Switzerland between 1988 and 2015 in terms of age, gender, nationality, Swiss linguistic region, and assumed places and sources of exposure at the time of the first notification. The results of this first comprehensive analysis of nationwide mandatory hepatitis C surveillance since its inception will contribute to an optimisation of ongoing and future control measures.

Materials and methods

Surveillance of HCV infection through mandatory notification

In Switzerland, laboratories and physicians have been obliged to notify the Federal Office of Public Health (FOPH) of individual cases of hepatitis since 1988. A few dozen cases of non-A non-B hepatitis were notified between 1988 and 1990. They were retrospectively reclassified as HCV cases. Laboratories are first required to report all positive results (anti-HCV antibody response confirmed by another test – usually an immunoblot test, HCV core antigen detection or HCV RNA detection). Afterwards, the treating physician completes a detailed notification form including clinical manifestations, and assumed places and sources of exposure. The FOPH classifies the cases in a centralised database. Children under 1 year of age with antibodies only and patients living abroad are excluded. All reports are registered with a person's full name. However, for legal and data protection reasons, cases of hepatitis C (and B) for which the FOPH had not received a new report in the previous 10 years were anonymised at the start of 2012. It was therefore no longer possible to assign some of the repeated reports to previously notified cases. No informed consent is required, since the notification of hepatitis C cases is mandatory under Swiss federal law.

Case definition

The case definition of an acute or recently acquired HCV infection – hereafter referred to as acute cases – is met if at least one of the following three criteria is fulfilled: (1) presence of at least one of the three laboratory markers mentioned above, with jaundice of recent onset *and* absence of indications suggesting a chronic infection (case known for over a year, onset of symptoms more than 1 year ago, cases considered chronic by the physician, presence of ascites, cirrhosis or hepatocellular carcinoma; (2) detection of HCV core antigen or RNA in a child under the age of 1 year; and (3) documentation of recent HCV seroconversion (presence of a negative anti-HCV test in the 24 months before the diagnosis of a HCV infection).

All other laboratory-confirmed cases of HCV infection are considered to be non-acute, including cases for which only laboratory notifications are available. This category also includes anti-HCV positive cases that were cured spontaneously or with treatment.

Statistical analysis

We conducted separate analyses of the acute and non-acute HCV cases notified through the Swiss mandatory notification system between 1988 and 2015. Analyses comprised the proportion of cases by year of first notification and 4-year notification period, gender, age, nationality, linguistic region, assumed place and source of exposure, and the presence of cirrhosis or hepatocellular carcinoma at the time of the physician's first notification. The crude incidence rate (IR) and the incidence rate ratio (IRR) by year were also calculated by means of Poisson regression for the acute cases, using Stata version 14.0. The same was performed for reported non-acute cases by using the notification rate (NR) and the notification rate ratio (NRR). Specific rates and ratios were also calculated for data stratified by gender, age group, linguistic region and nationality, as well as odd ratios (ORs) for exposure by gender, age and nationality. Multiple exposures for the same case have been weighted by the total number of exposures for this case. Thus, each case has only one exposure in total; this enabled calculation of the IR and NR stratified by exposure in relation to the general population. For cases notified by only laboratories, we hypothesised that the exposure structure observed for cases notified by physicians is similar, and applied it accordingly. All analyses related to trends were restricted to the period of 1992–2015, because the number of cases was limited, but increased rapidly during the first years after HCV surveillance implementation. An IRR or NRR >1 was considered a significant increase, an IRR or NRR <1 a significant rate decrease if $p < 0.05$ (z test). Differences between proportions were considered significant if $p < 0.05$ (chi-square test for differences between proportions and nonparametric test for trends across ordered groups to assess changes in proportion over time). The annual Swiss population statistics by gender, age and nationality that were used as denominators were provided by the Federal Statistical Office.

Results

Notification of HCV cases

Between January 1988 and December 2015, 49,908 HCV cases among people living in Switzerland were notified.

From 1988 to 1992, laboratory diagnostics, screening and surveillance of HCV were gradually implemented, which resulted in a strong initial increase in the number of notifications (fig. 1). Notification by physicians was absent for 6716 cases (13.5%) reported by a laboratory. Of the total of cases, 1585 were classified as acute (3.2%) and 48,923 as non-acute (96.8%). The annual numbers of acute (range for 1992–2015: 43–130) and non-acute HCV cases (range: 1260–2750), as well as annual IRs or NRs for acute, non-acute and total HCV, are shown in figure 1.

Acute HCV cases

Since the full implementation of HCV surveillance in 1992, the IR of acute cases has basically shown a long plateau levelling out at around 0.7–0.8 cases per 100,000 population, interrupted by a peak between 1999 and 2005, with a maximum of 1.8/100,000 in 2002 (fig. 1 and fig. 2). Overall, the IR decreased slightly between 1992 and 2015 (IRR 0.99, p <0.001).

The gender and age at the time of first notification were reported for 99.9% of acute HCV cases, 65.5% of whom were males (annual range 53.2–79.2%; table 1). The overall IR of acute cases between 1988 and 2015 was thus significantly higher for males (1.0/100,000) than for females (0.5/100,000; IRR 0.51, p <0.001). The IRs for males and females have changed largely in parallel over the past 28 years (fig. 2).

Figure 1: Notified acute and non-acute hepatitis C virus cases with incidence and notification rates, Switzerland, 1988-2015.
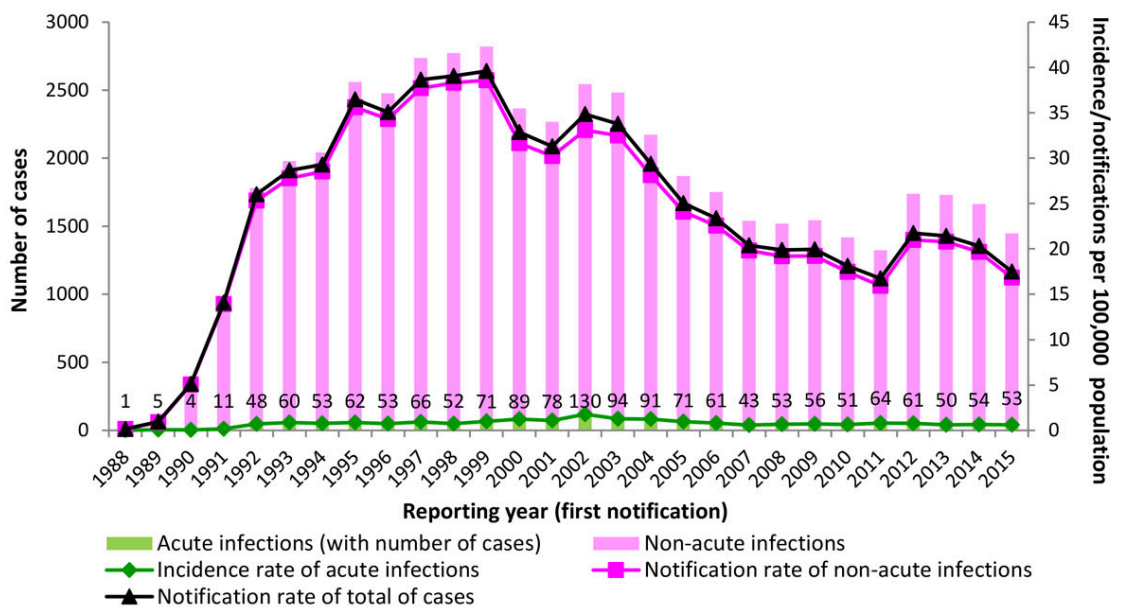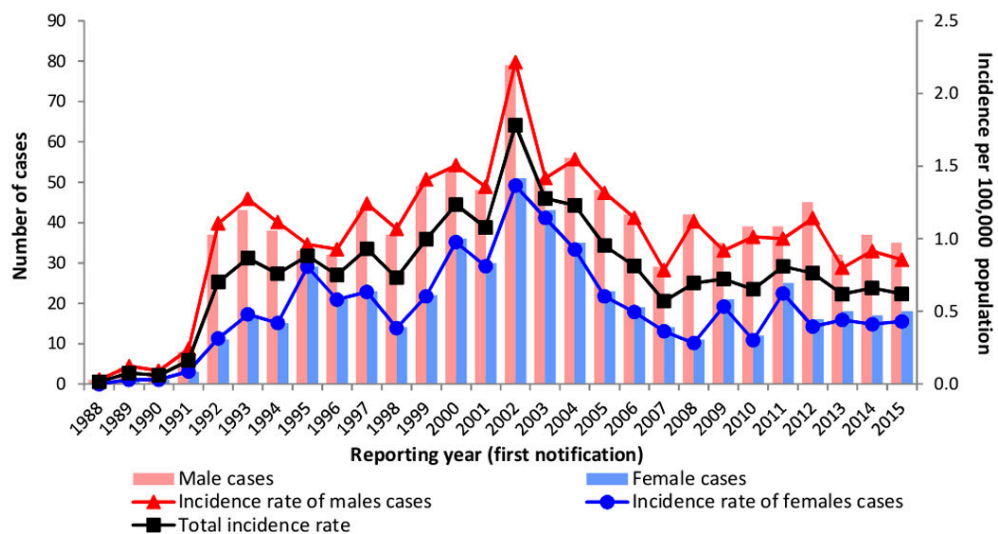

Figure 2: Notified acute hepatitis C virus cases with incidence rates by gender, Switzerland, 1988-2015.

The highest proportion of cases and IR between 1988 and 2015 were found in the group aged 25–29 years (21.5%, 2.4/100,000; table 1). The IR was particularly low among children under 15 years. Eleven acute cases (0.7%) were reported for infants, suggesting vertical transmission, the most recent being in 2012. Throughout the study period, the IR was generally highest in the age group 20–29 years, with a trend towards increasing age with time (fig. 3). The

Table 1: Comparison of characteristic features of notified acute and non-acute HCV cases, Switzerland, 1988–2015.

Category	Acute cases			Non-acute cases			p-value[*]
	n	%	IR[†]	n	%	NR[‡]	
Notification period							
1988–1991	21	1.3	0.08	1345	2.8	5.05	<0.001
1992–1995	223	14.1	0.80	8141	16.8	29.35	
1996–1999	242	15.3	0.85	10564	21.9	37.24	
2000–2003	391	24.7	1.34	9267	19.2	31.87	
2004–2007	266	16.8	0.89	7065	14.6	23.64	
2008–2011	224	14.1	0.72	5580	11.5	17.95	
2012–2015	218	13.7	0.67	6361	13.2	19.56	
Total	1585	100.0	0.77	48323	100.0	23.54	
Gender							
Males	1038	65.5	1.03	29090	60.4	28.92	<0.001
Females	546	34.5	0.52	19063	39.6	18.21	
Total	1584	100.0		48153	100.0		
Age (years)							
0–4	14	0.9	0.13	187	0.4	1.69	<0.001
5–9	0	0.0	0.00	54	0.1	0.48	
10–14	2	0.1	0.02	79	0.2	0.69	
15–19	97	6.1	0.81	816	1.7	6.78	
20–24	296	18.7	2.27	3663	7.6	28.09	
25–29	340	21.5	2.35	6182	12.8	42.65	
30–34	269	17.0	1.72	7389	15.3	47.34	
35–39	170	10.7	1.07	7052	14.6	44.19	
40–49	207	13.1	0.66	10182	21.1	32.58	
50–59	113	7.1	0.43	6033	12.5	23.18	
60–69	48	3.0	0.24	3422	7.1	16.98	
70–79	18	1.1	0.13	2325	4.8	16.39	
80–89	10	0.6	0.13	759	1.6	10.24	
≥90	0	0.0	0.00	60	0.1	4.57	
Total	1584	100.0		48203	100.0		
Nationality							
Swiss	1106	77.0	0.67	25846	72.4	15.76	<0.001
Foreign	330	23.0	0.80	9876	27.6	23.94	
Total	1436	100.0		35722	35722		
Region							
German-speaking Switzerland	1004	63.4	0.69	30610	63.5	21.02	<0.001
French-speaking Switzerland	500	31.5	0.98	13304	27.6	26.14	
Italian-speaking Switzerland	81	5.1	0.92	4300	8.9	49.03	
Total	1585	100.0		48214	100.0		
Assumed place of exposure (since 1999)							
Switzerland	792	67.7	0.61	7032	22.7	5.42	<0.001
Abroad	84	7.2	0.06	2747	8.9	2.12	
Unknown and missing	294	25.1	0.23	21244	68.4	16.38	
Total	1170	100.0		21244	100.0		
Assumed exposure[§]							
Injection drug use	854	53.9	0.42	18668	38.6	9.09	<0.001
Sexual contact with an infected person	253	16.0	0.12	2880	6.0	1.40	
Other contact (family, etc.)	67	4.2	0.03	1411	2.9	0.69	
Dialysis	44	2.8	0.02	130	0.3	0.06	
Blood transfusion	24	1.5	0.01	3090	6.4	1.51	
Accident among health care workers	25	1.6	0.01	573	1.2	0.28	
Other[¶]	71	4.5	0.03	1266	2.6	0.62	
Unknown and missing	247	15.6	0.12	20305	42.0	9.89	
Total	1584	100.0	0.77	48323	100.0	23.54	

* For differences between proportions. † Incidence rate per 100,000 population. ‡ Notification rate per 100,000 population. § Several-exposure proportions weighted by the number of exposures for each case. For cases only notified by laboratories (i.e. without mention of exposure), the exposure structure observed for cases with a physician's notification was applied. Incidence and notification rates were calculated by using the general population as the denominator, not the (unknown) specific at-risk population for each category. ¶ Especially exposure by medical injections, surgery, dental care, tattooing or perinatal transmission.

median age remained stable at 28 years until 2000–2003 (with interquartile range (IQR) 23–34), and increased afterwards, reaching 37 years in 2012–2015 (IQR 29–47). Overall, during the period 1992–2015, the IR decreased significantly each year by 6% in the age group 15–19 years (IRR 0.94, p <0.001), by 5% in the age group 20–24 (IRR 0.95, p <0.001) and by 2% among those aged 25–29 (IRR 0.98, p <0.05). By contrast, it increased by 3% in the age group 35–39 years (IRR 1.03, p <0.05) and 4% in the group aged 40–49 years (IRR 1.04, p <0.001).

The mean annual IR of acute cases for the whole period 1988–2015 was significantly higher in the French-speaking and Italian-speaking parts of Switzerland than in the German-speaking part, at 0.98 and 0.92 compared with 0.69 cases per 100,000 population, respectively (IRR 1.42, p <0.001 and IRR 1.34, p = 0.01, respectively). This difference arises from the incidence peak in the early 2000s, which was much less marked in the German-speaking part of Switzerland than in the two other regions. The range of IRs by canton over 28 years was very wide, with a minimum of 0.2 in the cantons of Obwalden and Schwyz and a maximum of 1.1 in the cantons of Vaud and Schaffhausen, and 1.5 in Geneva.

Nationality was reported for 90.6% of all acute HCV cases. Of these, 23.0% were foreigners: 76.0% of them from Europe, mainly from Italy, former Yugoslavia, and Portugal; 12.5% from Asia; 8.4% from Africa; 2.8% from America; and 0.3% from Oceania. Overall, the IR for people of foreign nationality was slightly higher than for Swiss nationals, including those naturalised (IRR 1.19, p = 0.006). However, the IR became identical for both groups in 2012–2015.

The place of exposure was reported for 74.9% of the acute cases notified between 1999 and 2015, and 90.4% of them had been exposed in Switzerland (table 1), which was the case less frequently for foreigners (74.5%) than for Swiss (94.8%, p <0.001). This proportion remained stable over time. A presumable exposure was reported for 84.4% of cases during 1988–2015. Cases were mainly exposed through the use of injection drugs (63.8% of cases with a known and weighted exposure), followed by sexual contact with an infected person (18.9%). Other sources of exposure, such as accidents among health care workers, blood transfusion, dialysis, medical injections, surgery, dental care, tattooing or perinatal transmission were reported less frequently (table 1). Injection drug use was less likely to be reported as the source of exposure for foreigners than for Swiss (OR 0.72, p = 0.006), whereas dialysis was more likely to be reported (OR 4.74, p <0.001). Of the 351 cases with at least a presumed sexual exposure to an infected person, 213 (60.7%) were male. Of these, 47.9% were presumably infected during heterosexual intercourse (but exposure through injection drug use was also reported for 63/102 or 61.8% of them), and 42.2% during homosexual intercourse (only 5/90 or 5.6% of them also reported such another exposure); 9.9% had an unknown sexual preference. Whereas the number of females and males presumably infected at least through exposure during heterosexual intercourse fell sharply after the 2000–2003 period, the total number of acute HCV cases among MSM rapidly increased to 41 during 2012–2015. This represented 89.1% of cases in males with sexual exposure, or 75.9% of all cases with sexual exposure, or 25.7% of all cases with a known exposure.

Figure 4 shows that injection drug use was the primary exposure source reported throughout the study period, with a maximum of 247 cases in 2000–2003. Sexual contact with an infected person was always the second most common form of exposure, with the number of cases remaining relatively constant since the early 2000s. Recently (2012–2015), injection drug users represented no more than 33.9% of the acute cases, compared with 23.9% for cases due to sexual contact. Exposures other than these were very rare, especially infection by transfusion and accident among healthcare workers, whereas unknown or missing sources of exposure were particularly numerous (30.3%).

Figure 3: Incidence rates of acute hepatitis C virus cases by age and notification period, Switzerland, 1992-2015.
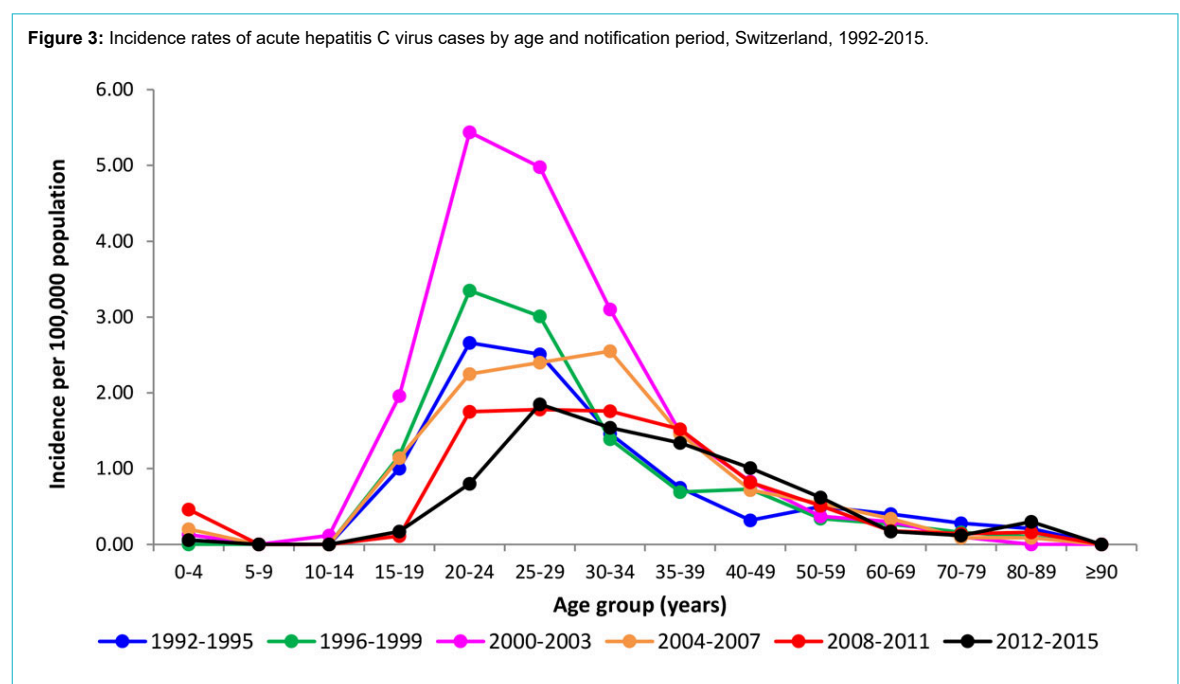
Exposure varied widely with age at the time of the first notification: 70.4% of cases of acute HCV in the age group 20–34 years had presumably been exposed as injection drug users, compared with 60.2% in the age group 0–19 years and only 26.1% in of those aged 35 years and over. Among the latter, the proportions of exposure through sexual contact with an infected person (22.4%), dialysis or transfusion (10.5%), as well as unknown exposure or missing sources (27.2%), were particularly high. The number of acute cases in those aged 20–34 years presumably infected through sexual contact decreased from the mid-2000s, the number of those aged 35 years and over increased steadily to 41 (of which 83.0% were MSM) in 2012–2015 (compared with 10 in the age group 20–34 years). In contrast, exposure was largely similar for both genders. However, exposure as a healthcare worker (OR 0.24, p <0.001) and non-sexual contacts, usually within the family, (OR 0.42, p <0.001) was less frequent in males than in females.

The epidemiological features of the acute cases notified during the last 4-year period (2012–2015) enabled us to define the typical profile of people who become infected nowadays. They are Swiss (75.6%) men (68.4%), aged 25–49 years (72.0%), and assumed to be infected in Switzerland (89.8% of cases with a known place of exposure), either by injection drug use (48.7% of cases with a known exposure) or by sexual contact with an infected person (34.2%), particularly as MSM (25.7%).

Non-acute HCV cases
The NR of non-acute HCV cases increased from 25.3 cases per 100,000 population in 1992 to a peak of 38.6/100,000 in 1999 (IRR 1.06, p <0.001) before decreasing to 16.8/100,000 in 2015 (IRR 0.95, p <0.001; fig. 1).

As with acute HCV cases, the majority of non-acute cases notified between 1988 and 2015 were males (60.4%, annual range 57.4–66.5%; table 1 and fig. 5), with a significantly higher mean annual NR (30.0/100,000 compared with 18.7/100,000; NRR 0.63, p <0.001). Throughout the period under surveillance, the NR has evolved in parallel for both genders.

The age at the time of the first notification was reported for 99.8% of non-acute HCV cases, of whom 2.4% were aged under 20, 50.3% between 20 and 39, 33.6% between 40 and 59 and 13.6% were 60 years or older (table 1 and fig. 5). The NR was highest in the age group 30–34 years (47.3/100,000). During 1992–2015, the NR decreased each year, almost always significantly, by 2–7% in all age groups under 40, and also significantly by 1–3% for people aged 60–79. In contrast, the NR increased significantly at a yearly rate of 2% in the 50–59 and 80–89 age groups. The highest NR by age group halved between 1992–1995 and 2012–2015, and shifted from 25–34 years to 40–59 years. The NR by gender was higher for males in the age group 20–59 years and similar for other ages (fig. 5).

Because the birth year of non-acute cases has increased only slightly throughout the 28 years under surveillance, with a median of 1961 (IQR 1951–1967) in 1992–1995 and of 1965 (IQR 1957–1974) in 2012–2015, most cases belonged to a limited number of birth cohorts (fig. 6). Indeed, 60.5% of notified non-acute HCV cases involved patients born in only 20 birth cohorts, i.e., between 1955 and 1974, and 73.9% patients were born during three decades (1950–1979). If the analysis is restricted to the recently reported non-acute cases (2012–2015), these proportions hardly decrease, at 56.1% and 71.4% respectively. For the period as a whole, these proportions were higher for males than for females, at 64.6 and 54.4%, respectively, for 20 birth cohorts, and 78.5 and 66.9%, respectively for 30 cohorts. For both genders, a maximum of patients were born in 1964 (median 1963). There were more females (55.3%) than males among patients born up to 1945. The opposite was observed among patients born after 1945 (63.5% of males, p <0.0001). As a consequence of these concentrated birth years, the median age at the time of first notification increased continuously between 1992–1995 (32 years, IQR 27–43) and 2012–2015 (48 years, IQR 39–56). The majority of non-acute cases born before 1950 resulted from ia-

Figure 4: Numbers of acute hepatitis C virus cases by exposure and notification period, Switzerland, 1992-2015. Other exposures cover especially exposure by medical injections, surgery, dental care, tattooing or perinatal transmission.
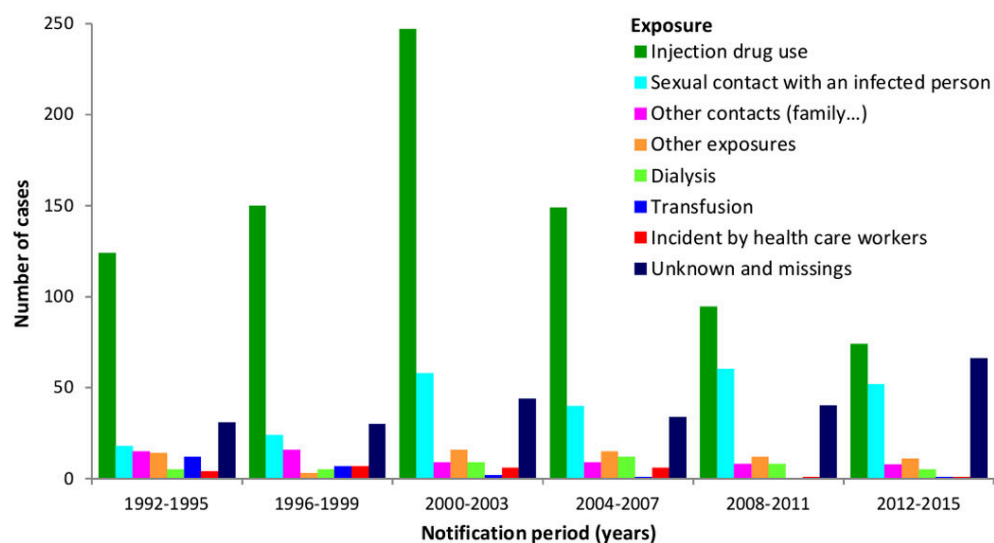
trogenic contamination: transfusion (56.4% of cases with a reported exposure), dialysis (1.8%), accident among health care workers (5.3%), and other exposures, which mainly include contamination through medical injections, surgery and dental care (13.8%); exposure through the use of injection drugs was rare (7.3%). On the contrary, injection drug use was by far the main source of exposure for cases born between 1950 and 1979, as well as those born in 1980 or after, at 74.4 and 67.6%, of cases with a reported exposure, respectively.

As for acute HCV cases, the mean annual NR of non-acute cases was higher in the French-speaking part of Switzerland (26.1/100,000; NRR 1.24, p <0.001) and above all in the Italian-speaking part (49.0/100,000; NRR 2.33, p <0.001; table 1) compared with the German-speaking region (21.0/100,000). The evolution of the NR in the three

language regions was largely parallel throughout the study period. The differences between cantonal NR were large (range 8.9–49.0/100,000), with a maximum in the Ticino canton (the Italian-speaking canton) and then in urban cantons (Basel, Geneva, Vaud and Zurich), and a minimum in sparsely populated rural cantons.

Among the 73.9% of non-acute HCV cases with a known nationality, 27.6% were foreigners, most of whom (72.6%) had European nationality, followed by citizens from Asia and Oceania (13.8%), Africa (9.6%) and America (4.0%). By nationality, the most numerous foreign nationals came from Italy (29.3% of 9573 cases with a known foreign nationality), followed by Portugal (9.0%), Georgia (6.1%), Spain (5.9%), former Yugoslavia (5.8%), Russia (4.3%), Germany (4.1%) and France (3.7%). For the period as a whole, the NR for foreigners was higher than for Swiss

Figure 5: Numbers and notification rates of non-acute hepatitis C virus cases by gender and age group at time of the first notification.
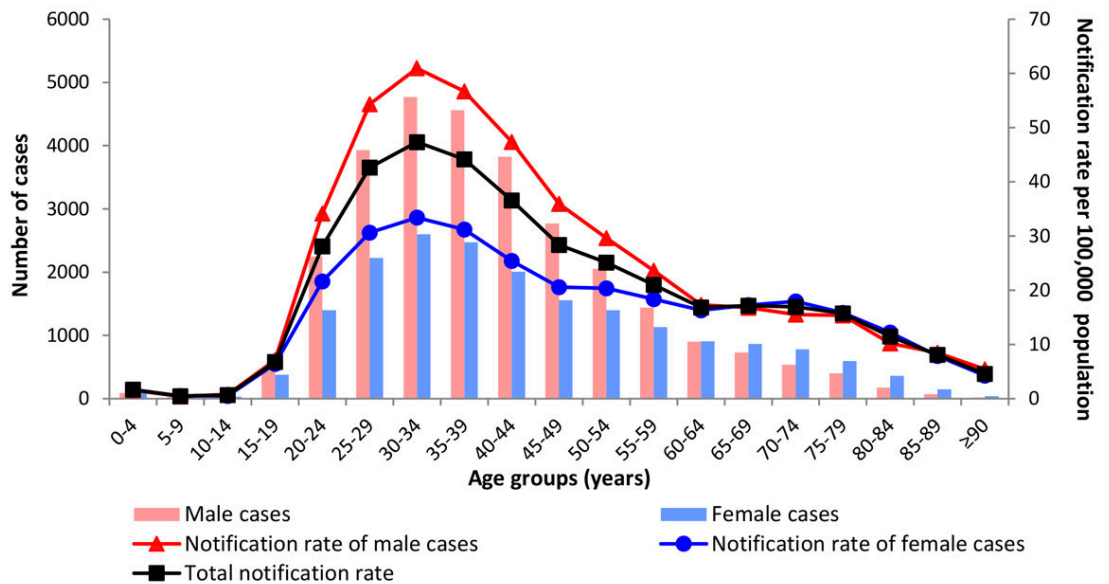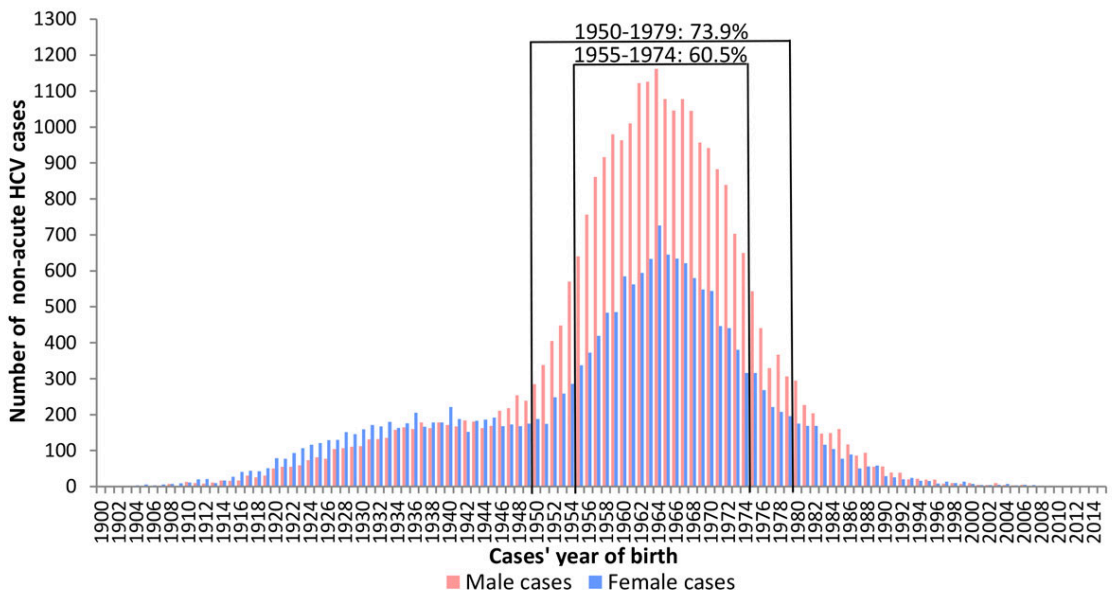

Figure 6: Number of reported non-acute hepatitis C virus cases by gender and birth cohort, and percentage of total cases for 20 or 30.

nationals (NRR 1.52, p <0.001). Unlike acute HCV cases, this difference persisted in 2012–2015 for non-acute cases (NRR 1.35, p <0.001). The NR peak was reached earlier for Swiss citizens (26.9 cases per 100,000 inhabitants in 1999) than for foreigners (37.2/100,000 in 2003). The proportion of foreigners among non-acute HCV cases increased continuously from 1992–1995 (20.7%) to 2008–2011 (39.5%), before declining to 32.8% in 2012–2015 (p <0.001). Among foreigners, the proportion of Europeans decreased from 85.4% in 1992–1995 to 66.5% in 2004–2007 (p <0.001) and then remained stable, mainly replaced by Asian nationals (4.4% in 1992–1995 compared with 19.1% in 2012–2015; p <0.001), predominantly from Georgia, Mongolia and Pakistan.

The presumed place of exposure was reported for only 31.6% of non-acute HCV cases notified between 1999 and 2015 (table 1). Among them, 28.1% had been exposed abroad, which was more often the case for foreigners (63.9%) than for Swiss citizens (9.8%, p <0.001). Moreover, the proportion of foreigners infected abroad increased from 54.0 to 72.2% (p <0.001) between 2000–2003 and 2012–2015.

The presumed exposure was also known far less often for non-acute HCV cases (42.0% unknown or missing) than for acute cases (table 1). Most non-acute cases were infected through the use of injection drugs (66.6% of cases with a known and weighted exposure), more rarely by blood transfusion (11.0%) or sexual contact with an infected person (10.3%). Injection drug users were less frequent among foreigners than Swiss (OR 0.59, p <0.001). In contrast, dialysis (OR 2.97, p <0.001) and other sources (mainly iatrogenic) (OR 2.43, p <0.001) were more frequent sources of exposure among foreigners than Swiss. Unlike the acute cases, the absolute number of non-acute cases in MSM tended to decrease slightly over time, so that since the late 2000s a similar number of acute and non-acute cases were notified yearly among MSM, i.e., a mere dozen. Compared with younger cases, those born before 1950 were more often infected by blood transfusion (OR 23.17, p <0.001), dialysis (OR 5.90, p <0.001), or other exposures such as medical or dental care (OR 4.48, p <0.001), and as a healthcare worker (OR 3.29, p <0.001), but less often by injected drugs (OR 0.02, p <0.001) and or sexual contact (OR 0.74, p <0.001). Exposure also partly differed by gender for non-acute cases: males were less frequently infected than females as healthcare workers (OR 0.29, p <0.001), by transfusion (OR 0.50, p <0.001) and by an unknown exposure (OR 0.76, p <0.001). The opposite was observed for injection drug users (OR 2.00, p <0.001).

Discussion

This article describes how the epidemiology of acute and non-acute HCV infections has developed in Switzerland since mandatory notification was introduced in 1988. The peak of notifications occurred at the turn of the year 2000 for both acute and non-acute cases, with 1.8 and 38.6 cases per 100,000 population, respectively. However, whereas the number of reports of non-acute cases continued to decline, the IR of acute cases stabilised over the last decade, at around 0.7 cases per 100,000. The majority of non-acute and, even more, acute cases were young adults, mainly males. Acute cases were younger than non-acute cases,

more often infected in Switzerland and through sexual contact or dialysis, but less frequently by blood transfusion, if we assume that the numerous cases with missing data had the same sources of exposure as cases with a documented source of exposure. The analysis of exposure, birth year and gender of acute cases enabled us to distinguish roughly three phases in the HCV epidemic in Switzerland: (1) an early phase mainly associated with iatrogenic transmission among individuals born before 1950, particularly affecting females for the elderly among them; (2) an intermediate phase (from the 1980s to the end of the 2000s) with a maximum incidence, strongly linked to injection drug use and affecting mostly males, and (3) a recent phase since the end of the 2000s, with the emergence of sexual transmission in MSM and moderate continuation of transmission in injection drug users.

In recent years, the NR of all HCV cases in Switzerland has been more than double the average in the European Union [22], where the NR varied considerably from one country to another and rather reflected the differences between surveillance systems, and screening and diagnostic practices, than real rates of incidence and prevalence. The NR was highest in countries with extensive screening programmes targeting at-risk groups for hepatitis, such us the United Kingdom, which in 2013 had the same NR as Switzerland (20.5/100,000) with a prevalence about two times lower. In the absence of repeated surveys among representative populations, the continuing decrease in NR observed in Switzerland since the turn of the last century suggests a decline in HCV prevalence. Except for France, which has very active programmes to manage HCV infection, a decreasing trend in prevalence was not observed in Europe [23, 24]. In contrast, the HCV prevalence is still rising in some countries with a dramatic increase in injection drug users, such as Russia, Poland and Czech Republic [23].

As has generally been observed in western and northern Europe, in Switzerland HCV infections were consistently more common in males than in females [22]. Injection drug use, by far the largest source of exposure to HCV, is indeed much more common among males in Switzerland [25]. Other exposures such as blood transfusion and accidents among healthcare workers were more frequent among females, but remained rare overall.

The age of cases at notification increased from 1988 to 2015, particularly for non-acute cases (median age 32 and 48, respectively, vs 28 and 37, respectively, for acute cases), but the birth cohorts involved remained largely focused on 1964, regardless of the 4-year notification period analysed (data not shown). This means (1) that acute cases nowadays become infected later in life than in the past, probably owing to the steeply decreasing number of cases among injection drug users, who – as in Germany [26] – were younger than cases infected through other sources of exposure, and (2) that recently reported non-acute cases were mostly old infections with increasingly late diagnosis within the context of a declining epidemic.

The frequency of reporting was higher in the two Latin regions than in German-speaking Switzerland, both for acute and non-acute cases. Italian-speaking Switzerland was characterised by a particularly high NR for non-acute cases. If we do not discount a more intensive screening practice in this region, this difference could also result

from the numerous Italian migrants living there (59,500 out of 352,000 inhabitants in 2015), as the prevalence of HCV is particularly high in southern Italy, which is the origin of the majority of Italian immigrants [27, 28]. Moreover, the proportions of non-acute HCV cases among Italians and of Italians in the population of this region were identical. This might suggest that a disproportionate share of cases have not yet been diagnosed in this subpopulation. More generally, it is likely that the proportion of diagnosed cases in people originating from areas of high endemicity, usually due to iatrogenic exposure, is lower than in other risk groups, who benefit from longer and more sustained screening. For example, injection drug users participating in a substitution programme or included in the Swiss HIV cohort are systematically tested for HCV at entry, and regularly retested if negative. It is estimated that over 80% of injection drug users have been tested for HCV at least once in their lifetime [29]. Despite this probable underdiagnosis, our data showed that foreigners were globally at higher risk of being infected with HCV than were Swiss citizens. This was particularly true for non-acute cases and among certain nationalities such as Italians, Spaniards, Georgians and Russians [13]. It should be noted that most acute cases, including foreigners, were presumably exposed in Switzerland, whereas the majority of foreigners with non-acute infection were exposed abroad, with an upward trend. Thus, the immigration of people with non-acute infections plays an increasing role in the maintenance and future burden of hepatitis C in Switzerland.

In Switzerland, as elsewhere in Europe, injection drug use was the main source of exposure for acute and especially non-acute cases [22]. Moreover, the use of non-injected drugs involves an additional risk of infection [30, 31]. The hepatitis C epidemic in Switzerland and its progressive resolution resulted largely from the sharp increase in the number of injection drug users during the 1980s and 1990s, and the subsequent implementation of harm reduction measures for HIV and hepatitis B and C among injection drug users [32, 33]. Access to these measures is high and the coverage is good in Switzerland, with programmes for the delivery of clean injection equipment in most major cities and free access to this equipment in pharmacies [29]. Consequently, the sharing of syringes is currently low (5%), but that of the equipment used to prepare the injection is higher, although decreasing. These measures led to a sharp drop in new infections through injection drug use since the mid-2000s. However, since the end of the 2000s, the number of notified non-acute cases among injection drug users has remained stable, at around 500 per year.

The decline in the total number of acute HCV cases was slowed by the emergence in Switzerland [8, 34], as in other western countries [35, 36], of a new at-risk population in the mid-2000s, with broad evidence of the sexual transmission of HCV: HIV-infected MSM [37–39]. The epidemic in this group occurred within a large international transmission network and coincided chronologically with the introduction of highly active anti-retroviral therapy and a subsequent increase in risky behaviour [40]. Moreover, the use of recreational non-injected drugs during sexual intercourse, which may increase the risk of transmission, is frequent [41–45]. Only HIV-positive MSM are generally considered at risk for HCV infection [39, 42, 46, 47], although some studies have also shown an increased risk in HIV-negative MSM [45, 48, 49]. A recent study showed that in Switzerland, the prevalence of HCV among non-HIV-positive MSM was similar to that of the general population, which does not justify the screening of this population [12].

There is increasing evidence that HCV is very rarely transmitted through sexual contact between HCV-serodiscordant heterosexual couples, especially among HIV-negative individuals [50–53]. Nevertheless, a sexual exposure was reported in Switzerland for 18.9% of acute cases and 11.6% of non-acute cases, with an assumed exposure among heterosexuals or individuals with an unspecified sexual preference. At 15.9 and 8.2% respectively, these proportions were similar and also surprisingly high in the European Union [54]. In our data, the actual proportion of infections attributable to sexual exposure is most likely overestimated among non-MSMs, as this exposure is often associated with other sources of exposure that are more likely to be the real source of infection, particularly injection drug use (in 60.2% of acute and 54.3% of non-acute cases) and to a lesser extent non-sexual contact such as a network injection drug users. Our weighting of multiple exposures has only partially corrected the excess of infections attributed to sexual exposure. As shown by an Italian study, HCV infections among spouses more probably result from them sharing risk factors for HCV infection than from sexual transmission [55].

Despite the decline in the number of acute notified cases, the risk of HCV transmission persists in Switzerland, owing to the remaining pool of chronically infected people. Additional efforts need to be made to prevent new cases among injection drug users and HIV-positive MSM. However, for Switzerland and other countries that have largely controlled the epidemic of acute HCV infection, the main challenge is to minimise the current and future burden of disease. Thus, secondary prevention in the form of testing initiated by healthcare providers (detection in risk groups, evaluation and eventual treatment of chronic infections with the new direct-acting antivirals leading to high cure rates) should continue [14].

The strengths of this analysis lie in the long-term surveillance of HCV infections covering the whole Swiss population, in the distinction made between acute and non-acute infections, and in the mandatory notification of all positive laboratory results, which increases the sensitivity of surveillance. Physicians completed a detailed form for a large proportion (86.5%) of cases notified by the laboratories.

This report has several limitations. HCV surveillance failed to capture most of the acute cases because newly acquired HCV infections are mainly asymptomatic. However, since the proportion of symptomatic cases among new infections is constant, the trends described here are likely to be reliable. Many non-acute cases have also not (yet) been notified because a large proportion of chronically infected cases remains asymptomatic at least for decades, which leads to late diagnosis. On the other hand, in order to allow comparability over the long term, non-acute cases include, without distinction, cases with unknown viraemic status, viraemic cases and cleared infections with HCV antibodies, which overestimates the number of cases with active infection. The diagnostic bias can be considered constant throughout the study period. Contrariwise, the inclusion of cleared infections may have decreased over time

with the increasing use of PCR in place of an antibody immunoblot test to confirm the serology. Thus, the downward trend observed for non-acute cases may have partly resulted from an increasing exclusion of spontaneously recovered or cured cases. However, PCR is not systematically used and the joint use of the two confirmatory tests remains common. Anonymisation carried out in 2012 led to the duplication of non-acute cases. This is the main reason for the increase in the number of non-acute HCV cases observed since 2012. A similar increase was recorded for hepatitis B after the same anonymisation process [56].

Conclusion

The surveillance over 28 years of hepatitis C in Switzerland indicates that the peak of the epidemic of acute and non-acute cases lies in the past. Since 1999, the NR of non-acute HCV infections has decreased almost continually, whereas the decline in IR of acute cases started 3 years later. This overall reduction was the result of the gradual introduction of measures aimed at preventing percutaneous transmission, mainly among injection drug users and focused on reducing the risk of HIV infection. The prevention of iatrogenic cases had started long before, through the use of disposable syringes and needles in medical settings. The IR has, however, stabilised at around 0.7 cases per 100,000 inhabitants over the last decade. This is probably partly a result of the emergence of sexual transmission among HIV-infected MSM engaging in at-risk behaviour involving blood. Although the peak of the HCV epidemic was passed at the turn of the century – probably because of measures aimed at controlling iatrogenic and percutaneous transmission – Switzerland needs to maintain its prevention and surveillance activities. With the availability of highly efficacious pangenotypic direct-acting antivirals, achieving the WHO objectives of eliminating HCV as a public health threat is potentially at hand, including in Switzerland [57].

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