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ORIGINAL ARTICLE

Chronic hepatitis C virus infections in Switzerland in 2020: Lower than expected and suggesting achievement of WHO elimination targets

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Abstract

In this multi-method study, we investigated the prevalence of chronic infections with the hepatitis C virus (HCV) in Switzerland in 2020, and assessed Switzerland's progress in eliminating HCV as a public health problem by 2030 with regard to the World Health Organization (WHO) criteria targeting infections acquired during the preceding year ('new transmissions') and HCV-associated mortality. Based on a systematic literature review, the reappraisal of a 2015 prevalence analysis assuming 0.5% prevalence among the Swiss population and data from many additional sources, we estimated the prevalence among subpopulations at increased risk and the general population. For new transmissions, we evaluated mandatory HCV notification data and estimated unreported new transmissions based on subpopulation characteristics. For the mortality estimate, we re-evaluated a previous mortality estimate 1995–2014 based on new data on comorbidities and age. We found a prevalence of ≤0.1% among the Swiss population. Discrepancies to the 2015 estimate were explained by previous (i) underestimation of sustained virologic response numbers, (ii) overestimation of HCV prevalence among PWID following bias towards subgroups at highest risk, (iii) overestimation of HCV prevalence among the general population from inclusion of high-risk persons and (iv) underestimation of spontaneous clearance and mortality. Our results suggest that the WHO elimination targets have been met 10 years earlier than previously foreseen. These advancements were made possible by Switzerland's outstanding role in harm-reduction programmes, the longstanding micro-elimination efforts concerning HIV-infected MSM and nosocomial transmissions, little immigration from high-prevalence countries except Italian-born persons born before 1953, and wealth of data and funding.

Abbreviation: COO, country of origin; DAA, direct-acting antiviral; FOPH, Federal Office of Public Health; FSO, Federal Statistical Office; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MSM, men having sex with men; OST, opioid substitution therapy; PCR, polymerase chain reaction; PWID, people who inject drugs; SAMMSU, Swiss Association for the Medical Management in Substance Users; SCCS, Swiss Hepatitis C Cohort Study; SHCS, Swiss HIV Cohort Study; SVR, sustained virologic response (following HCV treatment); WHO, World Health Organization

KEYWORDS
elimination, hepatitis C, prevalence, Switzerland, WHO

1 | INTRODUCTION

In 2015, 36,000–43,000 persons (0.5% of the population) were living with chronic hepatitis C virus (HCV) infection in Switzerland, according to a prevalence estimate commissioned by the Swiss Federal Office of Public Health (FOPH).[1] However, the authors faced many data gaps—most available data concerned people who inject drugs (PWID).[1] But even those estimates from 2010 and 2012[2] were outdated, with PWID being among the first to receive direct-acting antivirals (DAA) in Switzerland starting in March 2014.[3] Very little information was available on HCV infections among vulnerable subpopulations other than PWID (non-PWID) and the general population.[1] The majority of HCV infections had been diagnosed and reported to the FOPH in the 1990s,[4] and numbers declined after 1999.[4,5] However, little was known about the number of people who had cleared their HCV infection naturally, had been cured by treatment or had died.[1] The 2015 HCV prevalence estimate used the few data available at the time to make assumptions about the general population and non-PWID subpopulations, added data for PWID, and considered treatment and mortality data as best as possible.[1]

After 2015, more data became progressively available after intensive test-and-treat activities among PWID, allowing new estimates of chronic HCV infection[5,6] for this largest subgroup.[1,4,5,7] New data also emerged on non-PWID subpopulations. A nationwide HCV micro-elimination program was performed among HIV-infected men having sex with men (MSM).[8,9] Special efforts were undertaken to find persons born in Italy before 1953 who acquired HCV before migrating to Switzerland, constituting the largest group of foreign-born HCV patients.[10,11] General population studies, including one investigating large-scale screening in a sample from the general population, found a much lower prevalence than assumed in the 2015 prevalence estimate.[12] Mortality data suggested that more HCV-infected persons had already died than previously assumed.[13] Currently, the findings of the 2015 prevalence estimate, corrected for persons who have since achieved sustained virologic response (SVR), are used as guidance for test-and-treat strategies in Switzerland. The new data, however, suggest a much lower prevalence. A lower HCV prevalence will have an impact on new HCV transmissions and HCV-related mortality that are used by the World Health Organization (WHO) as criteria for elimination of HCV as a public health problem by 2030.[14,15]

This paper aims to update the current (i.e. by 2020) number of people living with chronic HCV infection in Switzerland and improve the reliability of this prevalence estimate. It will also assess Switzerland's progress in HCV elimination regarding the WHO criteria.

2 | METHODS

2.1 | Subpopulations, general population

We investigated the HCV prevalence in Switzerland across seven subpopulations at increased infection risk and in the remaining general population. The seven subpopulations are as follows:

(i) PWID, defined as active or former injecting drug users ever in needle/syringe exchange programs, opioid substitution therapy (OST), or as inpatients,
(ii) Former experimental drug users. Persons with short-period drug use not enrolled in PWID services have been described in the 1980–90s,[16,17]
(iii) MSM living with HIV,
(iv) Persons born in Italy before 1953,
(v) Other foreign-born persons (i.e. except subpopulation (iv)),
(vi) Persons with nosocomial infections acquired in Switzerland,
(vii) Prison inmates.

We defined the general population as persons not belonging to the above subpopulations; they had been infected by 'other risks' such as sexual contacts among people who are not MSM living with HIV,[5,12,18] non-sterile tattooing, piercings, manicure, pedicure or mother-to-child transmissions.

2.2 | Data sources

2.2.1 | Systematic review of HCV data published 2016–20

We searched for published information providing estimates of HCV prevalence, SVR, re-infection or HCV-associated mortality in Switzerland, including all published information on HCV cases mandatorily reported to the FOPH. The previous literature review was limited to publications until 30 April 2016.[1] The current study adds data published between 1 January 2016 and 31 December 2020. We searched Pubmed but also the non-English Swiss weekly journals 'Swiss Medical Forum', 'Schweizerische Ärztezeitung/Bulletin des médecins suisses', the FOPH bulletin ('BAG-Bulletin/Bulletin OFSP') and the bimonthly journal 'Suchtmedizin' (addiction medicine) with the predefined search terms 'hepatitis C' OR HCV AND (switzerland OR swiss OR schweiz). We added data from abstracts/posters of the following conferences: *International Liver Congress* 2016–2020, annual meetings of the *Swiss Society of Gastroenterology* 2016–19, *European AIDS Clinical Society* conferences 2017 and 2019,

European Society of Clinical Microbiology and Infectious Diseases conferences 2016–19, and *International Network on Hepatitis C in Substance Users* conferences 2016–19, using the predefined search terms 'Switzerland' and 'hepatitis C'.

2.2.2 | Additional information from various sources

We followed the activities of 'Hepatitis Switzerland', a network developing strategies for viral hepatitis elimination.[19] The Swiss Army provided unpublished data on HCV prevalence among draftees 2004–2020; positive antibody results were verified by immunoblot and followed by viraemia testing.

(i) We evaluated a PWID prevalence estimate commissioned by the FOPH (2015 PWID analysis)[2] and the national guidelines on HCV among PWID.[20]
(ii) For former experimental drug users, two of the authors (BB and LP) evaluated publications from Pubmed and PWID-focused research institutes, documents of the Zürich City-, Swiss Social- and Swiss Federal Archives, and contacted health professionals, academic experts and civil society representatives involved in the 1980–90s.
(iii) For persons born in Italy before 1953, we evaluated Italian publications concerning HCV epidemiology[21,22] and migration patterns.[5,23]
(iv) For nosocomial transmissions in Switzerland, we included an expert assessment on HCV among haemophilic persons.

Concerning HCV treatment data for 2001–2016[1] and 2017–2020, we used sales data made available via the FOPH. For DAAs obtained abroad, we searched for information on buyers' clubs. SVR was achieved by 64% following treatment in 2001–2014,[1] and by ≥95% following treatment with DAAs.[1,24–26] We used Pubmed publications for frequency and predisposing factors of spontaneous HCV clearance. We used general population demographics for Swiss residents (age, gender, country of origin, canton of residence) and for prison inmates provided by the Swiss Federal Statistical Office (FSO). Additional sources of information are listed in Supplemental Information Table S1.

2.3 | Analyses

2.3.1 | Prevalence estimates

Subpopulations

(i) PWID: We assessed the 2015 PWID analysis for HCV prevalence among PWID subgroups, converted their antibody-based data into viraemia considering likely spontaneous clearance and subtracted PWID numbers who likely achieved SVR, or died in 2015–2020.
(ii) Former experimental drug users: We evaluated their number, mortality, and the likelihood of past intravenous drug use and HCV treatment.
(iii) MSM living with HIV: About 75% of them participate in the Swiss HIV Cohort Study (SHCS),[8,9,27] where a nationwide trial with biannual HCV screening and immediate treatment was performed in 2015–2017, preventing further transmission as a welcome side effect[8,9]; and where new occurrence of viraemic HCV infection is detected at least yearly[8,9] and subsequently treated. To the remaining viraemic persons, we added estimates for SHCS participants outside the HCV screening study and outside the SHCS.
(iv) Persons born in Italy before 1953: We estimated antibody positivity based on their probable region of origin in Italy,[4,23] Italian regional age-adjusted antibody positivity,[22] potential HCV-associated health problems reducing migration likelihoods[21,22] and multiplied it with this group's number of persons residing in Switzerland (FSO). To estimate viraemia, we subtracted those who fulfilled the following criteria: (likely) spontaneous clearance (Table 1); SVR following general[1,28] and regional ([4,5,11] Table 1) test-and-treat efforts; and liver-associated mortality.[10,11]
(v) Other foreign-born persons (i.e. except subpopulation (iv)): To the general population prevalence, we added this group's increased proportion in the *Swiss Hepatitis C Cohort Study* (SCCS),[10] compared with their proportion among the general population (FSO).
(vi) Persons with nosocomial infections acquired in Switzerland: We evaluated notification data[4,5,7] and publications concerning HCV transmissions through blood transfusions, dialysis, sharps exposures of healthcare workers and other healthcare exposures; we considered preventive strategies,[29] age- and comorbidity-associated mortality, and HCV treatment.
(vii) Prison inmates: We searched for imprisoned persons with Swiss residency not belonging to any of the other subpopulations.

General population

Studies were divided into two groups: prevalence of viraemic HCV infections based directly on PCR versus prevalence of viraemic infections based on HCV seroconversion. We added information on transmission routes, if available, highlighting PWID and persons from high-prevalence countries of origin (COO). Across these studies, the average prevalence of laboratory-based viraemia among persons who are not PWID/do not come from high-prevalence COO was calculated and multiplied by the number of Swiss-born persons (Table 2).

2.3.2 | Elimination estimates

The WHO recently defined the targets for elimination of HCV as a public health problem by 2030. As targets for validation of HCV transmission, countries are to document ≤5 new transmissions

TABLE 1 Estimated number of persons with chronic HCV infection residing in Switzerland in 2020.

Subpopulations	Subpopulations *N* with HCV viremia, method	Method, supporting data, uncertainties	Total population *N* with HCV viremia, method, supporting data
PWID = active or former injecting drug users ever in needle/syringe exchange programs, OST or as inpatients	2750–4750 based on 6600–11,300 HCV Ab-positive PWID in 2015 and, consecutively: minus 30% spontaneous clearance; minus 35% SVR; minus 8% mortality	*Subpopulation details, with explanation of the number*: The assumption of 6600–11,300 *HCV Ab-positive PWID in 2015* had been based on 1650 PWID in heroin-based treatment in 2015 [1] and 17,350 PWID receiving other OST in 2015 [2] among 23,100 PWID in total (estimate based on data from [2,3]); with 60% HCV Ab prevalence among those in heroin-based treatment, and 26% to 48% among the 21,450 PWID outside heroin-based treatment [3]. *Spontaneous clearance* was assumed for 30% of all HCV Ab-positive PWID in Switzerland; based on 24% spontaneous clearance among PWID in data mostly from the 1990s and 2010s [4], doubling of spontaneous clearance in the US 1998–2017 [5], and a high prevalence of positive predictive factors for spontaneous clearance among PWID in Switzerland: genotype 3 [6] (in 32–40% [7,8]); white race [5,9]; and young age at infection [4–6,10] (47.3% of acute HCV cases among PWID in Switzerland were diagnosed in persons aged <30 years [11]). *SVR following HCV treatment* was assumed for 35% of those who had not cleared HCV spontaneously. Based on SAMMSU cohort data (9% treatment/y among PWID in 5/2015–5/2017 [12]) and considering smaller, less specialized centres [7,12], 6% treatment/y was assumed for 2015–2020. These data were supported by the Swiss test-and-treat focus on PWID [11,13–15], publications confirming early and continuous DAA treatment in OST [16–19], awareness campaigns [20] and the gradual introduction of test-and-treat support in Switzerland (capillary Ab testing, point-of-care RNA determination, pangenotypic DAA treatment and on-site treatment [12]). After DAA treatment in OST, 97% acquired SVR [12]. Increasing numbers of PWID with SVR are also described in the SCCS [8,21,22]. The *mortality* of 8% was calculated based on FSO death registry and SCCS data 2000–2014 (10% mortality, 20% LTFU) [23] and SCCS data 2008–16 (10% mortality, 5% LTFU) [24], considering the increased mortality among PWID [24]. The major death cause in the SCCS was liver-related [24]; PWID also died from non-liver cancers, cardiovascular diseases, overdoses and poisonings [24]. PWID in Switzerland are an ageing population: in 2020, average age 55 years [8,11,13] *Supporting data*: (a) The estimate is *in line with data reported to the FOPH* that showed a sharp decrease of PWID since 2000 [11,13,14]. (b) The upper estimate of 15,400 persons in the 2015 PWID prevalence estimate commissioned by the FOPH was likely too high, because based on persons in heroin-based treatment, with the highest HCV prevalence of all PWID [3]. (c) The number of PWID ever screened for HCV is high: in 2014, it was likely 80% [3]; since then, it likely increased, following the many test-and-treat activities [7,12,16–19,21,25]. (d) Reinfections among PWID are rare [7,11–13,25], aided by a 'treatment as prevention' benefit [12]. (e) Switzerland has elaborate prevention and harm reduction strategies [7,11,13–15,25–28]. (f) Yearly retesting is advocated in OST [12,15]. (f) The mortality calculation is in accordance with reductions in OST numbers 2015–2020 [1,2] *Uncertainties*: Considerable measurement uncertainty derives from the variable estimates (26%–48%) of HCV Ab positivity outside heroin-based treatment [3]	5900–9200 persons with chronic HCV infection Calculated as sum of all subpopulations. Supported: by declining overall rates of viraemic infections and increasing age among persons reported to the FOPH [11,13,14] by increasing evidence that the previous gaps in test-and-treat services were addressed (e.g. among PWID [7,61]) by a very similar total population number in a modelling study, except that those prevalence numbers were predicted for 2025 instead of 2020 [63] by decreasing HCV-associated liver transplantations [13]
Former experimental drug users	50–150 based on a few thousand persons in this group, with around 2.7% Ab positivity; minus 50% SVR	*Subpopulation details, with explanation of the number*: Based on evaluations of literature [26,28–31], archived data and expert interviews [32], the number of former drug users with self-limited and rather 'experimental' drug use without contact to drug treatment services was low (a few thousands [32]); these persons usually had non-injecting drug use [29,31,32] for which HCV Ab positivity of 2.7% has been described [3]. Including a few persons with injecting drug use, they may have been 100–300 HCV Ab-positive persons. ≥50% of them may have undergone HCV testing/treatment following 'Hepatitis Switzerland' campaigns [33] or, with HCV acquired ≥30 years ago, following HCV-associated signs or symptoms [34]. A part of them likely died, with their advanced age and with potential comorbidity [32] *Supporting data*: Similar patient groups were described abroad [e.g. 35] *Uncertainties*: The variation of the estimate expresses uncertainties concerning their number, SVR and mortality	

TABLE 1 (Continued)

Subpopulations	Subpopulations *N* with HCV viremia, method	Method, supporting data, uncertainties	Total population *N* with HCV viremia, method, supporting data
MSM living with HIV	50–150 based on the results of a HCV micro-elimination program among this group in Switzerland, and estimates for persons of this group outside that program	*Subpopulation details*: The HCV epidemic among MSM is concentrated among HIV-infected MSM [36–42], with increasing incidence during the early DAA years [39,40]. Sharing of injections equipment ('Chemsex', intracavernosal injections), sexual practices leading to rectal bleeding, sharing of anal douching devices, and snorting drugs in settings of increased HCV prevalence are risk factors for sexual hepatitis C transmission [36–38,41] *Explanation of the numbers*: A nationwide, systematic, population-based *HCV micro-elimination program* 2015–2017 with (re)screening among 80% of the 4640 HIV-infected MSM in the SHCS (Swiss *HCVree Trial*) found 190 viraemic persons, with 176 achieving SVR [42]. For the 20% of HIV-infected MSM in the SHCS, but outside the trial, and ≤25% outside the SHCS [40,41], we assumed 5.1% prevalence of viraemic HCV as at start of the Swiss *HCVree Trial* [42], and 50% SVR, resulting in around 50 persons with viraemic infection *Supporting data*: New- or reinfections are decreasing, likely aided by information campaigns, e-health-assisted behavioural counselling interventions [41] and testing efforts [36–38,40–42] (in the SHCS, viraemic infection is excluded ≥yearly [40,42]). In 2020, 9 infections were notified among MSM [14], conform to SHCS data [14] *Uncertainties*: We added an upper estimate of 150 persons to show measurement uncertainty from undiagnosed infections despite the very advanced Swiss HIV diagnosis and treatment cascade [43], and high HIV and HCV testing activity among MSM in Switzerland [42,43]	
Persons born in Italy before 1953	650–900 based on 2600–3450 Ab-positives among the 86,600 Swiss residents born in Italy before 1953; and, consecutively: minus 35% spontan. clearance; minus 50% SVR; minus 50% SVR in a subgroup of 25%; minus 10% mortality	*Subpopulation details, with explanation of the number*: Estimate calculated with 3%–4% Ab prevalence, based on: (a) Ab data in Italy by age group and geographic area (≥4.6% South, 1.3% North [44–46]), (b) origin of these persons within Italy (≥50% South [11,47,48]), and (c) reduced migration likelihood with hospitalisations, frequent transfusions or dialysis, all at HCV risk [44,46]. A total of 86,600 persons born in Italy before 1953 resided in Switzerland in 2020[a] (FSO), resulting in 2600–3450 Ab-positive persons. 35% may have spontaneously cleared their HCV (high prevalence of predictive factors: young age at infection [4–6,10] among many Italian-born migrants born before 1953 [44–47]; white race [5,9]; female gender [4,5,9,10] with more females than males infected in Italy in the 1950–1970s [43,45] and high female immigration [44,46–48]). Among the remaining 1700–2250 viraemic persons, 50% were likely tested and treated, following recommendations [34] or symptoms [34]. Of the remaining 850–1126 persons, 25% reside in Southern Switzerland (FSO), among whom 50% likely achieved SVR after special test-and-treat efforts [11,13,14,28,34] including awareness campaigns focused on the population and on general practitioners [48]. Among the remaining 739–985 viraemic persons, 10% mortality is assumed [8,21] Supporting data: *NNSID observations after 2015* showed many notifications of 'old and very old' chronic infections, especially in the Italian-speaking part of Switzerland [13,14] and in *SCCS data* where persons born in Italy before 1953 emerged as the biggest foreign-born group, with a high percentage of advanced liver disease and mortality [8,21]. Awareness of HCV is likely high among this group, supported by media coverage, campaigns, and considerable awareness also in Italy *Uncertainties*: Some level of measurement uncertainty was expressed in the Ab prevalence estimate ('3%–4%')	

(Continues)

TABLE 1 (Continued)

Subpopulations	Subpopulations *N* with HCV viremia, method	Method, supporting data, uncertainties	Total population *N* with HCV viremia, method, supporting data
Other foreign-born persons	1000–1300 based on 1119 persons with HCV viraemia, from a viraemia calculation factor of 0.044% among foreign-born persons except persons born in Italy before 1953 (2,543,400[a]); minus 10–30% SVR; plus 300 persons to mirror uncertainty	*Subpopulation details*: In Switzerland, there is a *low prevalence of persons from HCV high-prevalence countries/regions* (except Italian-borns): FOPH data showed a small peak for Georgian-born [8,28], partly also Russian-born persons [8,28], but these usually had a limited stay (e.g. as asylum seekers; coming for treatment purposes) and do not reside in Switzerland [8]. Few persons from other high-prevalence countries including Egypt, Mongolia and Pakistan reside in Switzerland [8,11,28]. In the FOPH and the SCCS, few HCV-infected persons were registered originating from Africa, Asia and the Americas [8,11,13,14,28] *Explanation of the number*: The 1119 persons with HCV viraemia are the result of a viraemia calculation factor of 0.044%, multiplied with the number of persons in this group residing in Switzerland (FSO); the factor is based on data in the *SCCS and FOPH until 2014* [8] with a viraemia of 0.032% for the Swiss-born general population, augmented by 39% representing the increase in the SCCS of the proportion of persons in this group (41%), compared to their proportion (29.6%) in the Swiss general population ([8], FSO), with similar data reported to the FOPH [11]. After 2014, SCCS data showed similar SVR between Swiss-born and foreign-born persons [21]; as those data may have been biased towards persons born in Italy before 1953 [21], we calculated the SVR as 10%–30% to express variance *Supporting data*: Supported by other publications from Switzerland on HCV among foreign-born persons, with the only viraemic infection among 586 FSW (98% of foreign origin) likely acquired in the country of origin [49,50], and no infections among 107 Eritrean refugees [51]; and by publications from other European countries, highlighting the prevalence variations by countries of origin of major migrant groups [8]. In 2018, the FOPH reported 'hardly any increase of chronic HCV infections by persons infected before their immigration' [13] *Uncertainties*: (a) In addition to the variable number of SVR, we added 300 persons to compensate for insufficiently represented or undiagnosed foreign-born persons. (b) True numbers were likely lower: the proportion of foreign-born persons among persons with HCV detected in 2020 [14] was considerably higher than their proportion of 30% in the general population (FSO), with 45% among the 61% of new infections with a known COO, and likely higher among those with unknown COO. In analogy to previous findings [8], some of these may have no Swiss residency, or may no longer be present in Switzerland	

TABLE 1 (Continued)

Subpopulations	Subpopulations *N* with HCV viremia, method	Method, supporting data, uncertainties	Total population *N* with HCV viremia, method, supporting data
Persons with nosocomial infections acquired in Switzerland	250–500 based on 300 infections from transfusions, dialysis and sharps injuries; plus 0–200 infections from other healthcare exposures	*Subpopulation estimate by types of exposure, details*: *≤150 transfusion-associated infections*; based on ≤3300 cases of transfusion-associated HCV ever reported to the FOPH [11,13,14,52], continuously declining since 1992–1995 [11,13]. These persons were infected ≥30 years ago, often in connection with grave diseases, accidents or giving birth [28]; their mortality is likely high, from those pre-existing diseases or accidents [28], their advanced age [28], and HCV-associated complications [24]. Among persons with haemophilia in Switzerland, <150 remained untreated in 2016; almost all have since achieved SVR [53]. *≤50 dialysis-associated infections*; based on ≤200 cases of dialysis-associated HCV ever notified to the FOPH [11,13] and high HCV awareness among this group. *≤50 infections from sharps exposures*; based on 600 cases of Ab positivity ever notified in association with sharps exposures in healthcare [11], with likely only slightly higher total numbers [54,55]; most of those exposures happened long in the past [11]; there is high awareness [14,34,56], and likely high SVR [e.g. 55]. *Between 0 and 200 cases infected by other exposures in healthcare*, such as a break in safety precautions that happened a few years ago [57]; but such events are likely very rare, following the broad implementation of prevention strategies [11,13,28,34,57]; once suspected, testing and treatment is high [57] *Supporting data*: Also in the 2015 prevalence estimate commissioned by the FOPH, viraemic persons with HCV acquired from blood products (≤1986) or transfusions (≤1992) had been estimated 'to be few'; however, no number was provided [28] *Uncertainties*: True numbers are likely lower; reasons: infections usually acquired decades ago; testing and treatment following symptoms; high awareness	
Prison inmates	Contained among PWID/ acquired abroad	*Subpopulation details*: In the largest Swiss prison, 91% of those positive for HCV Ab were born outside Western Europe [58], and the majority of foreign nationals in prison had no Swiss residency [58, FSO]. HCV-infected Swiss inmates were mostly PWID [58,59] and included in the above data on PWID *Supporting data*: The 2015 PWID prevalence estimate commissioned by the FOPH also included this group among PWID or infections acquired abroad [3]. In 2007, a low number (0.8%) of HCV infections had been found among prisoners in Switzerland outside injecting drug use [60] *Uncertainties*: HCV infections among non-PWID Swiss residents acquired through non-sterile tattoos while in prison are listed among the General Population	

(Continues)

TABLE 1 (Continued)

Subpopulations	Subpopulations *N* with HCV viremia, method	Method, supporting data, uncertainties	Total population *N* with HCV viremia, method, supporting data
General population = persons not in other subpopul.; infected by sexual contacts except as HIV-infected MSM, tattooing, piercings, manicure, pedicure, MTCT	1150–1550 calculated as HCV viraemia of 0.019–0.026% (based on average of general pop. studies = 0.032 (Table 2) from data 8–16 y before, reduced by 20–40% for mortality and SVR), among 6,040,000[a] Swiss-born persons	*Subpopulation estimate by types of exposure, details*: *Sexual transmission of HCV except among HIV-infected MSM* is very rare [11,36–38,41]; supported by FOPH observations with heterosexual transmissions little reported after 2000–2003 [14] and likely overestimated, as often associated with other types of exposure [14]; by very low prevalence among female sex workers [49,50]; and by a prevalence similar to the general population among HIV-uninfected MSM in Switzerland [14,36–38]. Transmissions from *non-sterile tattoos, piercings, manicure and pedicure* are marginal [11,13,14] and expected to further decrease, with prevention strategies implemented since decades [14,56]. *Mother-to-child transmissions* are rare [11,13,14,34]. Among persons from the general population presenting for blood donations 1996–2003, continuously decreasing HCV incidence was observed [52] *Supporting data*: The 2015 prevalence estimate commissioned by the FOPH [28] overestimated HCV among this group, because the viraemia was calculated with Ab data and a viraemic rate set too high, and because four of the eight contributing studies had no information on HCV transmission pathways, with bias towards inclusion of high-risk persons (Table 2) *Uncertainties*: The general population estimate may still be too high, because based on higher-than-average numbers of persons with sexualized drug use and exposure to sharps injuries (Table 2); in fact, the only study designed to represent the general population showed no viraemic infection outside PWID among 2732 participants (Table 2 and [61]). We expressed some measurement uncertainty with the 20–40% estimate for mortality and SVR, with mortality based on FSO death registry and SCCS data 2000–2014 (10% mortality, 20% LTFU) [23] and SCCS data 2008–16 (10% mortality, 5% LTFU) [24]; and SVR based on DAA sales- and treatment data [21,22,28,62]	

Note: References (references not listed in the main document are provided with journal/conference information): [1] HeGeBe Jahresberichte; Sucht Schweiz, [2] National substitution statistics, available at: www.substitution.ch, [3] Cominetti 2015, [4] Smith BMC Infect Dis 2016, [5] Seo 2020, [6] Lehmann J Med Virol 2004, [7] Bregenzer 2017, [8] Bertisch 2016, [9] Kimble BMC Infect Dis 2019, [10] Bulteel J Hepatol 2016, [11] Richard 2018, [12] Bregenzer 2021, [13] FOPH 2019, [14] FOPH 2021, [15] FOPH guidelines for persons with intravenous drug use 2013, [16] Brunner poster INHSU 2017, [17] Larribau poster INHSU 2016, [18] Moriggia poster INHSU 2016, [19] Weber 2018, [20] Bruggmann SÄZ 2016, [21] Brezzi 2019, [22] Bachofner 2018, [23] Keiser J Viral Hepat. 2018, [24] Roelens 2020, [25] Bruggmann Swiss Med Wkly 2017, [26] Csete 2012, [27] Frey Situationsanalyse der heroingestützten Behandlung. Zürich: KEK – CDC 2021; [28] Zahnd 2017; [29] Röhrig 1990, [30] Kuebler Addiction 1997, [31] Kuebler 2000, [32] Archive findings dated 1989–1994 and interviews with 16 experts in 2017 and 2019: available from the corresponding author, [33] Activities of "Hepatitis Switzerland", available at: https://en.hepatitis-schweiz.ch, [34] Fretz 2013, [35] Harris J Viral Hepat 2016, [36] Schmidt 2020, [37] Apers JAIDS 2015, [38] Schmidt & Bremer AIDS 2016, [39] Wandeler Open Forum Infect Dis 2015, [40] Braun Clin Inf Dis 2019, [41] Künzler-Heule BMC Infect Dis 2019, [42] Braun 2020, [43] FOPH Bulletin 45/2022, [44] Chiaramonte 1991, [45] Ansaldi J Med Virol 2005, [46] Di Stefano J Med Virol 2002, [47] Rosoli Centro Studi Emigrazione, Roma 1978, [48] Piga doctoral thesis, University of Zürich 2008, [49] Vernazza 2020, [50] Vu Swiss Med Wkly 2020, [51] Chernet Int J Public Health 2018, [52] Niederhauser 2005, [53] Expert interview 2018; details available from the corresponding author, [54] Weber J Hepatol 2001, [55] Bertisch poster ECCMID 2013, [56] Swiss National Accident Insurance Fund 2009, [57] Balmelli J Hosp Infect 2020, [58] Chacowry Pala 2018, [59] Baggio J Infect Public Health 2020, [60] Wolff BMC Public Health 2011, [61] Djebali-Trabelsi 2021, [62] Brunner poster INHSU 2016, [63] Estill Comprehensive mathematical model of the Swiss HCV epidemic; on behalf of the FOPH 2018.

Abbreviations: Ab, antibody; Chemsex, sexualized use of stimulant drugs (via injection or snorting); DAA, direct-acting antiviral; FOPH, Federal Office of Public Health; FSO, Federal Statistical Office; FSW, female sex workers; HBV, hepatitis B virus; HCV, hepatitis C virus; LTFU, lost to follow-up; MSM, men having sex with men; MTCT, mother-to-child transmission; OST, opioid substitution therapy; PWID, people who inject drugs; SAMMSU, Swiss Association for the Medical Management in Substance Users; SCCS, Swiss Hepatitis C Cohort Study; SHCS, Swiss HIV Cohort Study; SVR, sustained virologic response (following HCV treatment).

[a]Swiss population in 2020 = 8,670,000, with Swiss-born persons = 6,040,000 and foreign-born persons = 2,630,000 (FSO 2020), including persons born in Italy before 1953 = 86,600.

TABLE 2 HCV antibody and viraemia in studies representing the general population in Switzerland, by transmission routes.

First author, year, journal	Data collect.	Study aim, method, population	Total, *N*	HCV-antibody[a] positive *N* (%)	Viraemia based on HCV-PCR		
					PWID and persons from high-prevalence COO, *N* (%)	Others, *N* (%)	
Studies with viraemic infections based directly on HCV-PCR, with information on HCV transmission routes							
Study designed to represent the general population							
Trabelsi 2019, EASL, poster	2014–18	To investigate whether large-scale screening identifies HCV infection in a general population sample. Prospective observation, patients aged 18–80 y of a general surgical outpatient clinic before minor surgery	2732	12 (0.44)	2 (0.07); both PWID, HCV already known	**0 (0.00)**	Average prevalence of 0.032%
Studies among general population segments							
Weber 2001, J Hepatol	1999	Evaluation of HCV prevalence among dentists (79%, equivalent to 23% of all Swiss dentists) and dental assistants. Study situation (during congress) may contain bias	1056	1 (0.09)	0 (0.00)	**0 (0.00)**	
Bertisch 2013, ECCMID, poster	2005–07	Cross-sectional investigation of the HCV prevalence among hospital staff (healthcare, administration, housekeeping; 80% with patient contact)[b] of a tertiary care hospital	5766	7 (0.12)	2[b] (0.03); one PWID, one high-prev. COO	**1 (0.02)** likely inf. by sharps injury (nurse)	
Schleiffenbaum 2006, SMW	2004	68% of draftees (>95% males, median age 19.3y ± 1y) of six army recruitment centres (voluntary testing, offering the choice of three different laboratory test blocks)	7364	5 (0.07)[c]	0 (0.00)	**1 (0.01)** little inform.; heterosexual male	
Clerc 2016, Sex Transm Dis	2011–12	Non-HIV-diagnosed MSM at a gay health centre and meeting areas, French-speaking Switzerland; 11% had sexually transmitted infection in the previous year	633	1 (0.16)	0 (0.00)	**1 (0.16)**[b] MSM	
Schmidt 2014, BMC Public Health	2009–10	Non-HIV-diagnosed MSM at a gay health centre in Zurich; 3% reporting current injection drug use, 13% non-injection drug use of cocaine or amphetamines	821	3 (0.37)	0 (0.00)	**1 (0.12)** MSM	
Schmidt 2020, SMW	2016–17	HIV-negative multi-partner men, mostly from gay health centres; 44% of MSM and 17% of other multi-partner men reported history of sexually transmitted infection	693	2 (0.29)	0 (0.00)	**0 (0.00)**	
Vernazza 2020, SMW	2016–17	FSW, German-speaking Switzerland	488	2 (0.41)	1 (0.20) high-prev. COO	**0 (0.00)**	
Vu 2020, SMW	2015–16	FSW, French-speaking Switzerland	96	0 (0.00)	0 (0.00)	**0 (0.00)**	
Study with viraemic infections based directly on HCV-PCR, with partial information on HCV transmission routes							
Swiss Army 2021, unpublished[d]	2004–20	Draftees (>95% males, aged 18–25 y); some preselection possible (e.g. active PWID); may contain persons from high-prevalence COO, some PWID and MSM engaging in Chemsex	392,861	87 (0.02)	**≤60 (≤0.015)**		

97% non-Swiss nationality, 92% no Swiss residency[e]

(Continues)

TABLE 2 (Continued)

First author, year, journal	Data collect.	Study aim, method, population	Total, *N*	HCV-antibody[a] positive *N* (%)	Viraemia based on HCV-PCR: PWID and persons from high-prevalence COO, *N* (%)	Viraemia based on HCV-PCR: Others, *N* (%)
Study with viraemic infections based directly on HCV-PCR, without information on HCV transmission routes						
Candinas 1994, J Med Microbiol	1986–92	To determine, among dead persons whose organs were transplanted at Zürich university hospital, the frequency of positive HCV results with different antibody tests and RNA. The organ donors were considered 'more likely to belong to socioeconomic risk groups for HCV'	207	4 (1.93)	≤3 (≤1.45) (likely to contain PWID)	ND
Studies with viraemic infections based on HCV seroconversion, without information on HCV transmission routes						
Prasad 2007, SMW	1990–91	Material originally used for a toxoplasma and hepatitis B study among women giving birth at the largest hospital per canton. No information except nationality. 'Likely bias towards PWID' (anti-HBc positivity in 39% of HCV antibody positive women as observed in PWID; choice of hospital)	9057	64 (0.71)	ND (no viraemia based on HCV-PCR; no information on PWID; only partial information on COO)	
Nicolosi Guidicelli 2012, Hematol Oncol	2001–02	Participants serving as matched controls in a study on the relationship of HCV and B-cell lymphoma. They were hospitalized in the same hospital as the lymphoma patients, in the Italian-speaking part of Switzerland. No patient information except 'no PWID'	81	2 (2.47)	ND (no viraemia based on HCV-PCR; no information on COO)	
Russmann 2007, BMC Gastroenterol	2003–04	Study to screen hepatitis B, HCV antibody, haemochromatosis among patients of all ages admitted to the emergency room of a university hospital. Bias: proximity to drug scene; 'disproportionally high numbers of foreign-born persons'. Positive antibody test not confirmed by a confirmatory assay	5036	135 (2.68)[f]	ND (no viraemia based on HCV-PCR; 41% were PWID; only partial information on COO)	

Note: Name of first author and year in italics: The 2015 prevalence estimate (Zahnd, 2017) had calculated the HCV prevalence among the non-PWID population based on the antibody results of these studies, including a preliminary version of the *Trabelsi* study ($N = 1345$). Bold numbers: These numbers were used to calculate the average prevalence among the general population estimates that used viraemia based on HCV-PCR.

Abbreviations: Chemsex, sexualized use of stimulant drugs (via injection or snorting); COO, country of origin; FSW, female sex workers; HCV, hepatitis C virus; MSM, men having sex with men; Others, people who are neither PWID, nor originating from high HCV prevalence countries; with possible infection routes such as tattoos, piercings, manicure, pedicure, mother-to-child transmissions, sexual contacts (except as HIV-infected MSM); PWID, people who inject drugs; SMW, Swiss Medical Weekly.

[a]With confirmation of the antibody positivity by a confirmatory assay, except *Russmann*.

[b]Personal information by study author.

[c]In four of the five persons: confirmatory assay with indeterminate result.

[d]Conscription is compulsory in Switzerland; recruitment examinations reach >95% of a year's Swiss male population (Schleiffenbaum 2006).

[e]FSW are recorded in this category based on interlinkage with the general population; among them, only Swiss residents add to the prevalence estimate in Table 1.

[f]Unconfirmed antibody tests.

per year per 100,000 adults representative of the general population at the country level and ≤2 new transmissions per year per 100 PWID.[14,15] As targets for validation of mortality reduction, the WHO requests a HCV-related mortality rate of ≤2 per year per 100,000 adults.[14,15] For new transmissions among adults residing in Switzerland, we evaluated the number and subpopulation representation of all HCV cases reported as 'acute cases' to the FOPH in 2020[7] (see definition of 'acute cases' in Table 3). We estimated additional new transmissions that may have been missed from lack of reporting (as new transmissions) or lack of testing, and complemented the estimate with trends over the last 20 years among new HCV diagnoses reported to the FOPH[4,5,7] and with subpopulation analyses of the likelihood that new HCV transmissions might have happened in 2020. To estimate new transmissions among PWID in 2020, we used the reported new transmissions among HCV-tested PWID in OST[7] and added estimates of the unreported fraction for new transmissions among non-screened PWID in OST, and for (un) tested PWID outside OST (Table 3).

For the HCV-related mortality rate in 2020, we re-evaluated the mortality rate estimate based on FSO death registry data 1995–2014[30] in light of new data on comorbidities and subpopulation characteristics of HCV-infected persons, including their alcohol consumption,[11,31] and considered the updated HCV prevalence for 2020 (Table 3).

3 | RESULTS

All types and sources of data used for the study are listed in Table S1. The systematic review yielded 484 journal articles and 21 congress abstracts. A total of 382 journal articles were excluded based on title or abstract, and 48 based on the full text. The resulting 54 journal articles and 21 congress abstracts are listed in Table S2. After the 2015 HCV prevalence estimate and the 2015 PWID analysis, no data had provided an estimate of HCV prevalence in Switzerland or in a subpopulation. But they provided data or background information that helped to create the prevalence and elimination estimates.

3.1 | Prevalence estimates

A total of 13,100 persons likely achieved SVR until 2016.[1] A total of 8600 SVR may be added for 2017–20, based on 8668 DAA treatments sold in Switzerland, likely 200 obtained from abroad (Table 1), and 97% treatment success.[24–26] Mortality: 10% of the 4700 SCCS participants died between 2008–16, and more may have died among the 5.2% who were lost to follow-up[13] (Table 1). Mortality was particularly high among PWID[11,13] (Table 1) and among persons from Italy born before 1953[10,11] (Table 1). SVR and mortality were specifically identified among PWID and the general population; among other subgroups, they were already included in the prevalence estimates.

Subpopulations

We arrived at the following estimates of viraemic persons by subpopulations, with details, explanations, supporting data and additional references listed in Table 1:

(i) PWID: Among the 23,100 Swiss PWID in 2015, 26–48% HCV antibody positivity was assumed for those 17,350 receiving OST and those outside OST; and 60% for those 1650 receiving heroin-based treatment.[2,32] Of the resulting 6600–11,300 antibody positives, likely 30% cleared HCV spontaneously, based on international observations[33,34] and favourable factors[35] among Swiss PWID.[2,6,10] Starting in 2014, several campaigns and projects helped to intensify test-and-treat activities among PWID[6,26,31,37] (Table 1). In the Swiss Association for the Medical Management in Substance Users (SAMMSU)-cohort, treatment rates of 9% per year have been documented from May 2017 to May 2019[26]; for less specialized centres,[6,26] we assumed yearly treatment rates of 6% during 2015–2020, with 97% SVR.[7] 8% of PWID likely died in 2015–2020.[13] In line with declining HCV notifications among PWID 1995–2020,[4,5] we found 2750–4750 viraemic PWID.

(ii) Former 'experimental' drug users: Based on our evaluations[4,16,17,36] (Table 1), persons in this group were few (some thousands), usually with non-injection drug use[16,36] carrying little HCV risk.[2] Including test-and-treat efforts following HCV-associated complications[27] or awareness-raising campaigns,[37] our estimate resulted in 50–150 viraemic persons.

(iii) MSM living with HIV: A total of 190 HCV-viraemic persons emerged when screening 80% of the 4640 HIV-infected MSM in the SHCS, with 176 achieving SVR.[9] For the 20% SHCS participants outside that trial and the ≤25% HIV-infected MSM outside the SHCS,[8,27] we assumed 5.1% viraemic infections[9] and 50% treatment-associated SVR (details: Table 1). With a safety margin for new and re-infections despite preventive measures[8,9,27] and undiagnosed infections, we arrived at 50–150 viraemic persons.

(iv) Persons born in Italy before 1953: We estimated 3–4% antibody prevalence among the 86,600 persons born in Italy before 1953 residing in Switzerland in 2020 (FSO)[4,21,22]; 35% of those likely spontaneously cleared HCV[34] (details and additional references in Table 1). Several test-and-treat activities focused on these persons, including a special campaign in a part of Switzerland where many of them reside.[37] Following HCV treatment[1,4,7,10,11] and age- and liver-associated mortality,[9,10] 650–900 viraemic persons likely remain.

(v) Other foreign-born persons (except subpopulation (iv)): Among notified cases[4,5,7] and in the SCCS,[10,11] HCV cases among this group were slightly higher than among the Swiss-born general population; among groups of foreign-born persons, hardly any cases of HCV were found.[38–40] Based on data in the SCCS,[10] we calculated the HCV prevalence among this group as increased by 39% in comparison with the prevalence among the general Swiss population (FSO). Added to the viraemia percentage of the Swiss-born general population, multiplied by 2,536,000 persons of this group residing in Switzerland (FSO), with calculation of 10%–30% SVR, and

TABLE 3 WHO targets for elimination of HCV as a public health problem per 2030: estimates for Switzerland per 2020.

		WHO target, per 2030 [1]	Switzerland, per 2020	
			Target estimate	Method, supporting data, uncertainties
New HCV transmissions	Adult population	≤5 new HCV transmissions per 100,000 adults[a], corresponding to ≤336 new HCV transmissions based on 7,114,731 adults in Switzerland in 2020[b]	≤2.5 new HCV transmissions per 100,000 adults[b], i.e. ≤179 new HCV transmissions among the 7,114,731 adults in Switzerland[b]	*Groups at increased risk of new HCV transmission, 2020*: New HCV transmissions in 2020 occurred predominantly among PWID and HIV-infected MSM [2]: of the 17 persons with new transmissions reported to the FOPH (= 2% of the 903 reported cases [2]), 4 were reported as PWID and 6 as (likely HIV-infected[c]) MSM [2]. For all PWID in Switzerland, we assumed a maximum of 160 new transmissions (see below). For (HIV-infected) MSM, we assumed all new transmissions to be included in the cases reported to the FOPH, because ≥75% of HIV-infected MSM in Switzerland participate in the SHCS [3–5] where yearly HCV screening is mandatory [3,4], and those outside the SHCS are also regularly screened [3,5, Table 1]. Thus, ≤13 new transmissions likely occurred among MSM (= the 6 reported cases, and likely ≤7 cases with unknown transmission route [2]). *Supporting data*: (a) The same predominance of PWID and (HIV-infected) MSM among new transmissions emerged in reports to the FOPH since the early 2000s [6,7]. (b) Among all other subpopulations, very few new transmissions were to be expected: HCV had been acquired decades ago among former experimental drug users, persons born in Italy before 1953 and persons with nosocomial infections acquired in Switzerland; it was acquired before coming to Switzerland among foreign-born persons not born in Italy before 1953 [8–10, Table 1]; strategies to avoid infections by tattooing, piercings, manicure and pedicure [Table 1] had been implemented decades ago; no new transmissions had occurred among MTCT [2] and were very unlikely among non-MSM sexual contacts [2]. To account for uncertainties, we assumed ≤20 new transmissions outside PWID and (HIV-infected) MSM, part of which may be among the 7 new transmissions with unknown route [2]. Total: ≤2,5 new HCV transmissions per 100,000 adults = ≤179 new transmissions among 7,114,731 adults
	PWID	≤2 new HCV transmissions per 100 PWID, corresponding to 436 new HCV transmissions based on 21,814 PWID in Switzerland in 2020	0.35–0.73 new HCV transmissions per 100 PWID, i.e. 77–160 new HCV transmissions among 21,814 PWID in Switzerland	*New transmissions among PWID with positive HCV antibody status reported in 2020*: Among the 903 persons with positive HCV antibody status mandatorily reported to the FOPH in 2020[d] [2], information on transmission routes was available for 35%. Among those, 77% (179 persons) were PWID, among whom 2,2% (4 persons) were detected as new transmissions [2]. Applying the same results to the 65% persons with missing information would have resulted in 695 PWID with 11–12 new transmissions; but we suspected reporting bias towards PWID and new transmissions[#]. Instead, in accordance with their prevalence in the FOPH and SCCS [2,6,7,11], we assumed PWID to be 68% (614 persons) of all persons with positive HCV antibody status reported in 2020, and assumed 1% new transmissions among them (6 persons). *New HCV transmissions among all PWID in Switzerland in 2020, including uncertainties*: We assumed 25–75% of PWID in OST and heroin-based treatment as tested for HCV in 2020, based on yearly testing recommended in OST in Switzerland [13,14] and testing triggered by risk behaviour [14,15]. Among untested PWID in OST, we assumed new transmissions in 0.25%. Thus, among 16,144 PWID in OST in 2020 [16] and 1634 persons in heroin-based treatment [17], there were likely 77–144 new transmissions in 2022. Among the 4036 persons not in OST (calculation: Table 1), we expected very few (0–5) new transmissions: in Switzerland, a reduction of injecting opioid use has long been observed [2,6,7,15] and, as world leader in harm reduction [6,14,18,19], OST is very accessible [6,14,15]. To express the uncertainty that, with COVID-19-associated restrictions, some at-risk persons may not have been tested for HCV, we re-analysed untested PWID in OST and heroin-based treatment assuming new transmissions in 0.5%, which added 11 new transmissions (= total 77–160 new transmissions). The 2020 data likely showed effects of intensified campaigns during previous years, with support of OST centres and general practitioners to test-and-treat their OST patients [20,21]. *Supporting data*: Even with the added uncertainties, the reported numbers were in accordance with the declining trend since 1999–2002 [2,6,7]. Total: 0.35–0.73 new transmissions per 100 PWID = 77–160 new transmissions among 21,814 PWID

TABLE 3 (Continued)

	WHO target, per 2030 [1]	Switzerland, per 2020	
		Target estimate	Method, supporting data, uncertainties
HCV-related mortality rate	≤2 HCV-related mortality rate per 100,000 adults[a], corresponding to a mortality of ≤142 persons based on the adult population in Switzerland in 2020[b]	HCV-related mortality rate considerably below 2 per 100,000 adults[b]	The HCV-related mortality rate in Switzerland had previously been assumed as ≈2,5 per 100,000 Swiss residents based on the FSO death registry 1995–2014, with probabilistic linkage to deaths in the SCCS 2000–2014 [22]. With limited data, death from chronic liver disease was assumed as HCV-related although other types of chronic liver disease could have been the real cause [22], and death from sepsis was generally assumed as caused by infected ascites in HCV-related cirrhosis [22]. True numbers were likely lower: (a) A substantial part of the chronic liver disease attributed to HCV in the FSO death registry analysis was likely caused or aggravated by alcohol: long-term daily intake of >40 grams of alcohol was documented among 25–30% of SCCS participants and of PWID in a cantonal survey [12,23]. (b) Death from sepsis was likely frequently caused by bacteriaemia associated with injection drug use [24], in contrast to the assumptions in the FSO death registry analysis [22]. (c) The majority of HCV-infected Swiss persons belong to subpopulations with a high mortality from non-HCV causes: many PWID died from non-liver cancers and cardiovascular diseases (partly associated with their high smoking rate [25]), opioid overdoses and poisonings [25]; many persons born in Italy before 1953 and persons with nosocomial infections acquired in Switzerland died from old age or complications of pre-existing diseases or accidents [10–12]. (d) DAA treatments starting in 2014 are likely associated with mortality reductions [25]; less liver transplantations were already observed in 2015–18 [7]. (e) The FSO death registry analysis was based on the HCV prevalence in 1995–2014 [22] that was considerably higher than the 2020 estimate. We thus assume the HCV-related mortality rate in 2020 as considerably below 2 per 100,000 adults.

Note: New HCV transmission = cases with confirmed HCV antibody with increased transaminases and/or icterus without indications of a chronic infection; including cases with documented seroconversion in the preceding 2 years [1,2,6,7]. References (references not listed in the main document are provided with journal/conference information): [1] WHO 2021, [2] FOPH 2021, [3] Braun Clin Inf Dis 2019, [4] Braun 2020, [5] Künzler-Heule BMC Infect Dis 2019, [6] Richard 2018, [7] FOPH 2019, [8] Röhrig 1990, [9] Chiaramonte 1991, [10] Zahnd 2017, [11] Bertisch 2016, [12] Brezzi 2019, [13] Bregenzer 2021, [14] FOPH guidelines for persons with intravenous drug use 2013, [15] Cominetti 2015, [16] National substitution statistics, available at: www.substitution.ch, [17] HeGeBe Jahresberichte; Sucht Schweiz, [18] Csete 2012, [19] Bruggmann 2016, [20] Bruggmann SÄZ 2016, [21] Activities of "Hepatitis Switzerland", available at: https://en.hepatitis-schweiz.ch, [22] Keiser J Viral Hepat. 2018, [23] Schürch 2020, [24] Martinez SMW 2020; [25] Roelens 2020.

Abbreviations: COO, country of origin; DAA, direct-acting antiviral; FOPH, Federal Office of Public Health; FSO, Federal Statistical Office; HCV, hepatitis C virus; MSM, men having sex with men; MTCT, mother-to-child transmission; OST, opioid substitution therapy; PWID, people who inject drugs; SCCS, Swiss Hepatitis C Cohort Study; SHCS, Swiss HIV Cohort Study; WHO, World Health Organization.

[a]Representative of the general population at country level [1].

[b]Residing in Switzerland.

[c]No information on HIV status [2,7], but in accordance with HCV cases in the SHCS [2,7].

[d]Reports from physician and laboratory, due within 1 week; with information on potential seroconversion, testing reasons, exposure, clinical manifestations, disease course, nationality, country of origin; # PWID likely overrepresented among persons with reported (newly transmitted) HCV infection, following high awareness, frequent testing in OST [14,15], more straightforward identification of their transmission route compared to other HCV subpopulations.

increased by 300 potentially insufficiently represented foreign-born persons, this amounted to 1000–1300 viraemic persons.

(vi) Nosocomial infections acquired in Switzerland: Reported to the FOPH were ≤3300 transfusion-,[4,5,7,41] ≤200 dialysis-associated infections[4,5] and ≤600 infections associated with sharps injuries among healthcare workers.[4,5] Notifications continuously declined after a peak in the 1990s[4,5], associated with broadly implemented preventive strategies[1,5,7,29] and few new infections.[4,5,7] With considerable SVR[1] and mortality from advanced age[4] and serious concomitant diseases[1] (Table 1), 250–500 viraemic persons are assumed.

(vii) Prison inmates: In Swiss prisons, HCV-infected persons are usually foreign-born, often without Swiss residency; or PWID[42] (Table 1).

We found little overlap between the subpopulations, except for prison inmates who were near-completely merged into PWID or foreign-born subpopulations. Where an overlap occurred, we assigned those persons to the transmission route assumed as the most likely, in descending order: PWID, former experimental use of opioids, HIV-infected MSM, persons with nosocomial infections acquired in Switzerland, both groups of foreign-born persons.

General population

We found ten studies from (segments of) the general population with viraemia based on HCV-PCR and information on HCV transmission routes (Table 2). Among nine studies (19,705 participants), transmission route information was complete; five of them (including one study designed to represent the general population (2732 participants)) contained no viraemic infection from 'other risks', while four contained one such infection each, with transmission routes shown in Table 2. The tenth study, with 60 viraemic persons among 392,861 draftees, contained partial information on transmission routes (Table 2). From the average viraemia of 0.032% among the 10 studies, 20%–40% were subtracted to account for SVR and mortality following the advanced age (8–16 years) of the studies' data (Table 1, Table 2). Multiplication by 6,040,000 Swiss-born persons resulted in 1150–1550 viraemic persons, supported by few transmissions from 'other risks' in the notification-,[4,5,7] blood bank-[41] and other data.[18,38,36,43]

An overview of the findings and their comparison with the methods, subpopulations and results of the 2015 prevalence estimate is provided in Table 4.

In total, we arrived at an estimated 5900–9200 viraemic persons (≤0.1% of the population) in Switzerland by 2020, in line with declining overall rates of HCV infections with evidence of viral replication,[44] the increasing age of HCV-infected persons reported to the FOPH[4,5,7] and decreasing HCV-associated liver transplantations.[5]

3.2 | Elimination estimates

Among all 903 persons with HCV infection reported to the FOPH in 2020, 17 persons (2%) were reported with new transmissions.[7] Among these, 6 persons were MSM (likely HIV-infected) and 4 were PWID[7] (Table 3). Based on data and evaluations presented in Table 3, we concluded that the rather few new transmissions were mostly experienced by individuals belonging to the two subpopulations MSM (likely HIV-infected) and PWID, and very unlikely to be experienced by other individuals. Conclusions were similar for new transmissions among reported infections without information on new transmissions, and untested persons with HCV infection (Table 3). Including some uncertainties, we arrived at an estimate of ≤2.7 new HCV transmissions per 100,000 adults residing in Switzerland in 2020 (Table 3).

For new transmissions among PWID, our analysis was based on the following data (Table 3): HCV tests mandatorily reported to the FOPH (in 2020)[7]; as a trend[4,5,7]; numbers of PWID in OST including heroin-based treatment; HCV testing frequency in OST; and estimates for PWID outside OST (Table 3). We arrived at an estimate of 0.35–0.73 new HCV transmissions per 100 PWID (Table 3).

For the HCV-related mortality rate in Switzerland in 2020, we found new data that would lower the mortality rate of ≈2,5 per 100,000 Swiss residents that had been estimated with data 1995–2014[30] (Table 3), likely resulting in a mortality rate considerably below 2 per 100,000 adults.

Thus, all three estimates resulted lower than the targets that the WHO had set for 2030[14,15] (Table 3).

4 | DISCUSSION

This study concludes that in 2020, around 5900–9200 persons in Switzerland lived with chronic HCV infection, corresponding to ≤0.1% of the population. This estimate is surprisingly low compared with the 36,000–43,000 persons assumed in the 2015 prevalence estimate,[1] even when subtracting the 8600 persons with SVR (Table 4). The discrepancy is even more pronounced compared with previous estimates of 80,000 persons,[19] corresponding to 1% of the population.

We found the following principal explanations for this large discrepancy: First, previous prevalence estimates used estimates from persons in heroin-based treatment as the highest estimate for all PWID[1,2]; but only 6.6% PWID were in heroin-based treatment,[32] with the highest prevalence of all PWID subgroups.[2] Second, for the prevalence among non-PWID, the 2015 prevalence estimate relied on studies from (segments of) the general population, but half of those studies likely contained PWID or persons from high-prevalence COO (Table 2).[1] Third, previous estimates assumed a spontaneous clearance rate[1] that was too low, as detailed in Table 1 and supported by FOPH observations.[4,5,7] Fourth, previous mortality estimates had not considered the high daily alcohol intake of many HCV-infected persons[11,31] (Table 3), and that mortality was also elevated from non-liver cancers, cardiovascular diseases and overdoses among PWID[13]; from pre-existing diseases that required transfusions and dialysis among persons infected in Swiss healthcare[1] (Table 1); and from advancing age, particularly among persons

TABLE 4 HCV prevalence estimates 2015 and 2020: comparison of subpopulations and results, outline of the method of the prevalence estimate 2015.

	HCV prevalence estimate 2015 [1]				HCV prevalence estimate 2020			
Subpopulations	**Subpopulations *N*, based on antibody positivity**	**Subpopulations *N*, converted to viraemia by a viraemic rate of 79.7%[a]**	**Corrections for mortality, SVR**	**Total population *N***	**Subpopulations**		**Subpopulations *N*, with viraemia based on HCV-PCR; corrections for mortality and SVR included[b]**	**Total population *N***
PWID	7700–15,400 PWID, based on data from [2]	6000–13,000 PWID	4000 persons assumed to have died from HCV ≤2015 13,000 persons with SVR following HCV treatment ≤2016	36,000–43,000	Opioid-using population	PWID	2750–4750	5900–9200
						Former experimental drug users	50–150	
All others	58,000 persons, based on an HCV antibody prevalence of 0.7% in studies assumed to represent the general population[a], calculated for a population of 8,327,126[c]; may have included non-PWID persons at increased risk	47,000 persons			MSM living with HIV		50–150	
					Foreign-born population	Persons born in Italy before 1953	650–900	
						Other foreign-born persons	1000–1300	
					Persons with nosocomial infections acquired in Switzerland		250–500	
					Prison inmates		Contained among PWID/ foreign-born population	
					General population = persons not in other subpopulations; infected by non-sterile tattooing, piercings, manicure, pedicure, MTCT, sexual contacts among people who are not MSM living with HIV		1150–1550	

Note: References: [1] Zahnd 2017, [2] Cominetti 2015 (full references see main document).

Abbreviations: FOPH, Federal Office of Public Health; MSM, men having sex with men; MTCT, mother-to-child transmission; PWID, people who inject drugs; SVR, sustained virologic response.

[a]Details: see Table 1.

[b]Method used for the 2020 prevalence estimate: see main document and Table 1.

[c]Swiss population in 2015 (Federal Statistical Office).

born in Italy before 1953,[10,11] among persons with nosocomial infections acquired in Switzerland (Table 1),[1,5] and among PWID with their average age of 55 years in 2020.[4,5,10]

Our estimate of the reduction of HCV incidence and prevalence in Switzerland appears higher than estimates from other European countries. However, the difference might just reflect a limited availability of HCV incidence and prevalence data in Europe.[7] Nevertheless, some epidemiological features are unique for Switzerland: with strong commitment to HCV prevention, counselling, testing and treatment among PWID,[3–5,7,17,20,26] Switzerland is a world leader in harm reduction.[4,17,19,20] Centres providing OST are highly diversified, from general practitioners to heroin substitution centres.[6,17,20] Many of them started HCV test-and-treat services very early.[3,4,6] During the last years, the gaps in HCV test-and-treat services[1,6] were addressed.[7,20,26] The Swiss healthcare system early recognized and addressed the HCV risk among MSM living with HIV[8,18,43] (Table 1). Specific treatment programs were initiated early (the Swiss *HCVfree Trial*).[9] HCV screening is performed at least annually among all HIV-positive MSM in the SHCS,[8,9,27] considered as a key group among this HCV subpopulation.[9] The only major group of HCV-infected foreign-born persons residing in Switzerland are persons born in Italy before 1953,[1,5,10,11] and special efforts were undertaken to identify HCV-infected persons from this group in order to offer treatment (Table 1). In contrast to some other European countries such as the Netherlands and the UK, few persons from high-prevalence countries such as Egypt and Pakistan migrated to Switzerland.[10]

Few countries may dispose of such a wealth of data,[17] including three nationwide cohort studies (SCCS, SHCS, SAMMSU-cohort) that provided essential HCV data.[9–11,13,26,30] Also, growing numbers of persons not belonging to the above risk groups have been screened for HCV, reducing the pool of undiagnosed infections: blood donors,[4] army recruits 2004–2020, people undergoing infertility testing or immunosuppressive therapy[4]; often also patients with signs/symptoms compatible with HCV infection,[1,28] MSM, people before surgery, pregnant women and healthcare personnel.[4] This is reflected by the high proportion of FOPH notifications without evidence of viral replication.[44] Finally, our prevalence results are supported by a modelling study in Switzerland, except that the predicted prevalence numbers apply for 2020 instead of 2025 as in the model output.[45]

The risk of newly acquired HCV infections is low in Switzerland. Few are expected among PWID,[9] benefitting from yearly screening recommended in OST,[20,26] early treatment approaches[26] and dropping re-infection rates.[4–6,26] Among MSM, particularly those with HIV, HCV infections are limited to a small subgroup with sexual practices involving blood contact and/or injecting stimulant or erectile enhancement drugs[18,27,43] and may further decline following prevention efforts.[9,27,46] New HCV infections acquired in healthcare and through tattooing, piercings, manicure and pedicure are very rare,[4,5,7] with the broad implementation of preventive measures established for decades.[29] Some nosocomial infections may have been imported from abroad. They are rare and contained in the above data.

Starting in February 2022, a large number of refugees from Ukraine moved to Switzerland. Ukraine has a considerably higher HCV prevalence than other European countries.[46] Refugees, persons involved in their care and all physicians in Switzerland received information concerning the continuation of HCV treatment started before arrival in Switzerland, and the provision of testing and treatment.[46]

With an increasing HCV prevalence gap between Switzerland and many other countries, similar information with focus on persons newly arriving in Switzerland is likely to increase in the future.[47]

Our findings support the continuation of the risk-based HCV testing strategy that Switzerland has been applying up to now.[4,5,7,28] As shown above, new transmissions are rather rare, and the true HCV-related mortality is so low in Switzerland that the country is very likely to have already met the WHO targets for HCV elimination in 2030.[14,15] Additional requests of the WHO[14] have equally been met: Switzerland has a high level of safety for blood transfusions[41] and other interventions targeting nosocomial transmissions,[4,5,7,29] and a high implementation level regarding harm reduction in people who inject drugs.[17] The experiences made in Switzerland demonstrate the effectiveness of an elimination strategy based on: (i) efforts in reducing nosocomial HCV transmissions,[4,5,7] (ii) pioneering harm reduction,[17] (iii) followed by a micro-elimination program among HIV/HCV-co-infected MSM,[9] and (iv) investing in HCV-prevention programmes and in information on HCV among persons at risk[37] (Table 1). Switzerland is one of few countries worldwide to have surpassed the 2030 UNAIDS HIV elimination targets in 2020.[44,48] With some subgroup overlap, and much overlap of transmission interventions, there was likely mutual benefit for the elimination of both HIV and HCV.

Strengths and limitations: The study focuses on Switzerland, but some of its epidemiologic considerations may apply in countries with similar epidemics. PWID data are mostly from Zürich, where the biggest open drug scene was located in the 1980–90s.[16,17] The impact of the COVID-19 pandemic on the number of new HCV infections reported in 2020 is likely to be small; the numbers in 2020 all follow a long-term declining trend.[5,7]

5 | CONCLUSIONS

Following investigations that improved the reliability of the prevalence estimate, this paper documents a reduction of the HCV prevalence to ≤0.1% in the Swiss population. This result was likely achieved already in 2020, indicating the successful achievement of the 2030 WHO elimination targets for HCV by then.

AUTHOR CONTRIBUTIONS

Barbara Bertisch and Axel Jeremias Schmidt contributed to the study design, analysis of the data and writing of the article. Barbara Bertisch, Christian Schaetti, Patrick Schmid, Pietro Vernazza and Axel Jeremias Schmidt contributed to the interpretation of the data. Barbara Bertisch, Christian Schaetti, Laura Peter, Patrick Schmid,

Marc Isler and Robert Oppliger contributed to the collection of the data. All authors contributed to the editing of the manuscript and read and approved the final version of the article.

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Barbara Bertisch, Christian Schaetti, Patrick Schmid, Laura Peter, Pietro Vernazza, Marc Isler, Robert Oppliger and Axel Jeremias Schmidt: no conflict.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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