Re: Bertisch et al.: Chronic hepatitis C virus infections in Switzerland in 2020: Lower than expected and suggesting achievement of WHO elimination targets. J Viral Hepat. 2023;00:1–18.

Detailed list of concerns

1. Calculations and estimates

1.1. General population

The prevalence calculation for the general population is not comprehensible: The calculation in this groups which should rather be called “low-risk population” is based on 10 studies (Table 2, page 9). For 9 studies, HCV RNA prevalence was only taken from study participants who were neither PWID nor persons from high prevalence country of origin. There were only 4 viraemic cases, but the denominator remains unclear, because only the total N of study participants is provided for each study. The tenth study with 60 viraemic persons among 392,861 draftees is unpublished data from the Swiss Army, in which some preselection e.g. towards active PWID is discussed. The average prevalence among the low-risk subpopulations of these 10 heterogeneous publications is established (possibly by adding the 10 bold numbers and dividing by 10) and applied to a population size of 6 million. No statistical analysis is performed despite the fact that the populations and time periods vary to a great extent from study to study.

A key paper which Bertisch et al. used to calculate the prevalence in the general population is Djebali-Trabelsi et al 2021. The authors of this study however discuss that the study is only relevant for patients who are undergoing outpatient treatment for minor surgical procedures. *“(…) at risk groups for HCV infection were not adequately represented. Indeed, a large majority of the people included in this study benefited from private insurance and , thus, were not fully representative of the general Swiss population.” (Djebali-Trabelsi et al. 2021, P. 1758)*. This limitation in terms of reliability and representativeness is not discussed by Bertisch et al.

1.2. People who inject drugs (PWIDs)

Underestimation of HCV RNA prevalence among PWID: Since 75% of MSM living with HIV participate in the Swiss HIV Cohort Study (SHCS), SHCS data are quite representative for this group. In contrast, the Swiss Association for the Medical Management in Substance Users (SAMMSU) cohort covers only about 7% of the approximately 20'000 opioid agonist therapy (OAT) patients in Switzerland (BAG), with an enrollment bias towards OAT patients in centralized settings (institutions), where HCV management has been shown to be better (Bregenzer et al., 2017; Schürch et al., 2020). Extrapolating data from the SAMMSU cohort ("best case scenario") to the whole OAT/PWID population, leads to a dramatic underestimation of the HCV RNA prevalence in this risk group. According to the National OAT registry, only 20% receive their OAT at an institution (centralized setting), while the huge majority is cared for in a decentralized setting (OAT provision by the treating physician (about 25%) or the pharmacy (about 50%)) (https://www.substitution.ch/de/jahrliche_statistik.html&year=2021&canton=ch). There is a publication bias towards successful HCV micro-elimination efforts ("low-hanging fruits") in centralized settings (https://smw.ch/index.php/smw/article/view/2868/4684), while data from decentralized settings is still scarce.

1.3. People born abroad

Calculations of HCV prevalence among Swiss residents born in Italy: Persons with a birth year after 1953 are excluded from the authors’ calculations. However, in the literature we can find 2 peaks in

the birth cohort distribution in Italy: before 1953 and between 1960 and 1980. (Andriulli, 2018; Nevola et al., 2022). Neither of these studies is referenced. Kondili et al. (2020) recommend a birth cohort screening for persons born in Italy between 1969 and 1987. This paper isn't mentioned either.

Calculations for other groups of persons born abroad "*few persons from high-prevalence countries such as Egypt and Pakistan migrated to Switzerland*" (p. 16): The authors miss to mention and discuss the numerous mid-range prevalence countries like Kosovo, Portugal, Ukraine, Serbia, Bosnia-Herzegovina which make up a substantial part of the Swiss HCV population with country of origin other than Switzerland. (Bihl et al., 2021)

1.4. Mortality estimates

According to Bertisch et al. estimations, mortality rates have fallen from 2.5 per 100,000 to "considerably below" 2.0 per 100,000, but no calculation is shown anywhere, it is solely based on assumptions.
Furthermore, in Table 3, discussing WHO elimination targets, the authors claim that most deaths among PWIDs were due to comorbidities (e.g. due to alcohol) and thus not due to the HCV infection. This contradicts another publication examining the attributable fraction of death, which showed that alcohol was not a major contributor to mortality (Rüeger et al. 2015). The author fail to discuss this paper.
Furthermore it is important to know that the mortality rate in the WHO elimination targets (i.e., the number to be reduced) does not correspond to the total number of liver-related deaths minus those due to comorbidities, but to all liver-related deaths. As a result, if a correction due to comorbidities is to be applied, this should be applied to both the estimates for 2015 and 2020, and the difference calculated after the correction to both estimates. Such calculations are not shown anywhere in the paper.

1.5. Nosocomial infections

It is unclear how Bertisch et al. come to the conclusion that nosocomial infections other than infections acquired by blood products for persons with haemophilia do not play a role for prevalence estimates (eg. at the dentist, endoscopies). The proportion of unknown transmission routes in the notification system of the Swiss Federal Office for Public Health FOPH has always been high (Richard et al, 2018).

1.6. Undiagnosed cases

The number of undiagnosed chronic hepatitis C cases in the different risk groups and the general population is of great significance for the prevalence estimations, because HCV treatment uptake is 0% in this group, which means that all of them are still viraemic. There are no robust prevalence studies for the general population in Switzerland, and in a risk-based screening setting, low-risk patients are less likely to be screened and treated. However, Bertisch et al. do not mention their assumptions regarding the proportion of undiagnosed cases.

1.7. Effects of measures

The authors do not distinguish between adopted measures and their effects in their prevalence estimates. Eg there is most probably an overestimation of the effect of point-of-care tests and guidelines: In Table 1 (page 4), Bertisch et al. talk about "*gradual introduction*" of capillary antibody (Ab) testing and point-of-care RNA determination. However, in contrast to HIV capillary Ab tests, HCV capillary Ab tests are currently not reimbursed by the health care insurance in Switzerland, and the capillary point-of-care HCV RNA quantification requires an expensive analyser on-site. Thus, these diagnostic tools are only used within specific projects and not yet in routine care, making their impact

rather small. Although "*yearly retesting is advocated in OST*" (Table 1, page 4) in the Federal Office of Public Health (FOPH) guideline (BAG, 2019) is rarely performed. Even in the SAMMSU cohort, OAT patients are screened on average only every two years (Bregenzer et al., 2021). Besides, the risk-based HCV screening is not fully implemented outside the cohort (Bregenzer et al., 2017; Schürch et al., 2020).

1.8. Overestimation of the spontaneous clearance rate

The spontaneous clearance rate is set rather high at 30% or 35%. According to Grebely et al., it is only 25% (Grebely et al., 2014). The PWID/OAT population is predominately male (80%) and HCV genotype 3 is more common. Both characteristics were associated with a lower spontaneous clearance rate in the study by Grebely et al. (Grebely et al., 2014). In the cited meta-analysis by Smith et al., the spontaneous clearance rate was also lower (24.4% for PWID and 15.4% for HIV-positive MSM) (Smith et al., 2016).

2. Missing relevant publications

As mentioned under 2.3. relevant publications to support prevalence estimations among people born in Italy are missing.

An important paper which discusses prevalence in the Swiss population and among Swiss residents born abroad was published in 2021 (Bihl et al., 2021). Since it was published after the end of the time period that Bertisch et al. were looking at, the authors cannot be expected to include it in their review. However, as it was published in November 2021, and Bertisch et al. submitted their paper in September 2022. The authors should have at least addressed this publication in their discussion.

3. Weakness in the methods: Systematic literature review and expert opinion

Bertisch et al. state to have undertaken a systematic literature review. However, the search strategy is not clearly stated, and important publications are missing (see 2.3. and 3.). How did the authors choose the additional journals beside the mentioned German speaking journals not listed in Pubmed? Why searching only one database (Pubmed)? Why only German-speaking journals, no French or Italian? How did they choose the conferences? No conference by the Swiss Society for Infectious Diseases SSI, on addiction medicine or of the American Association for the Study of the Liver AASLD is mentioned. A PRISMA flow diagram is missing. It is not clear, based on what inclusion and exclusion criteria the publications were retrieved. The retrieved publications were not systematically discussed in terms of their validity and reliability.

The HCV prevalence among former experimental drug users is estimated by expert opinion. The method, assessment of the expert opinion and how the experts have been chosen is not mentioned.

4. Limitations and failure of discussing representativeness of data

Bertisch et al. mention very few limitations and fail to discuss representativeness of data., see also Letter to the Editor and section on PWID above (1.2.)

5. References

References are not consistent which makes it very difficult to comprehend the authors' approach. There are three different referential systems in the document (main references, references in tables). The same publication appears with different numbers in various referential lists. Furthermore, important statements are referenced by secondary literature instead of primary literature (for more see details below).

Some examples for citing secondary literature instead of primary sources:

- Statement on antibody positivity among region of origin in Italy, page 3, 2.3.1. iv): Ref 4 and 5 do not contain any primary data on HCV prevalence in Italian regions. Ref 23 contains data from 1978. More recent studies on HCV epidemiology in Italy and its subregion are not cited or discussed (Andriulli et al., 2018; Kondili et al., 2019; Nevola et al., 2022).
- Statement on reported new transmissions among PWID in 2020, table 3, page 12: Ref 7 does not provide OAT specific data on new HCV transmissions.
- Statement on SVR 2001-2014 vs SVR under DAA, page 3, 2.2.2.: Ref 1 does not provide any primary data on that topic.
- Page 14, discussion, first paragraph: Ref 19 is a commentary without providing any primary data.
- Page 16, discussion "*and special efforts were undertaken to identify HCV-infected persons from this group in order to offer treatment*": Table 1 is mentioned as reference. Table 1 is five pages of text. In the whole table 1 there is one reference (Ref 48, cited separately in table 1: "*Piga doctoral thesis, University of Zurich, 2008*") on measures against HCV in southern Switzerland, which seems to be a dissertation (Is "Piga" the author?), but cannot be found in the dissertation database of the University of Zurich.
- Page 16 discussion, "…*people undergoing infertility testing or immunosuppressive therapy*": The cited Ref 4 is a paper on the epidemiology of HCV in Switzerland, based on the Swiss mandatory reporting system. There is no primary data on screening of people undergoing infertility testing or immunosuppressive therapy. The only sentence in Ref 4 about the topic is as follows and does not provide references for these subgroups either: "*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.*"