Received: 16 August 2023 | Revised: 14 September 2023 | Accepted: 23 September 2023

DOI: 10.1111/jvh.13892

JOURNAL OF VIRAL HEPATITIS JVH WILEY

LETTER TO THE EDITOR

Reply to 'Assessing the hepatitis C epidemiology in Switzerland: It's not that trivial'

Dear Editor,

We thank Sarah Blach et al.[1] for bringing attention to our update paper on the prevalence of HCV infections in Switzerland.[2]

Blach et al. aim to challenge our estimate of 5900–9200 persons living in Switzerland with chronic hepatitis C in 2020 (0.1% viraemic prevalence). Their main argument against our new estimates is the unfounded allegation that we did not handle the large number of publications we reviewed for this update according to scientific standards (implying that this slipped the reviewers and editors as well). We will counter their criticism point by point in the following. However, we would also like to mention that, in contrast, we have received positive feedback from other scientists in the field. The Principal Expert on Hepatitis of the European Centre for Disease Prevention and Control (ECDC), Dr Erika Duffell, wrote to us, '*The finding of a much lower HCV estimate compared to previous estimates has been a finding that has been noted elsewhere but few have undertaken such an elegant discussion around the factors accounting for these differences*.'

Blach et al. base their main argument on the results of their own modelling study (Bihl et al. 2022).[3] This model assumed a high HCV viraemic rate of 79.7% and resulted in an estimate of 32,100 viraemic individuals in Switzerland for 2019. However, the 79.7% assumption was based on data from the United States from 1999 through 2002.[3,4] They did so because of the unfounded claim that in Swiss notification data, *'the underlying HCV antibody or HCV RNA positive rates are not known'*.[5] However, this is incorrect. The Swiss notification system and hence the governmental epidemiology reports by the Federal Office of Public Health (FOPH) do distinguish between cases with evidence for viral replication versus cases based on confirmed antibody positivity only (suggesting that either there was no laboratory follow-up, for example, because the person with positive antibodies has left the country, or because the subsequent tests for HCV RNA and/or antigen were negative). FOPH's epidemiology report showed that in Switzerland in the years 2018/2019, for example, only in about half of reported cases (53%) there was evidence for viraemic HCV infection.[6] Hence it is surprising that Bihl et al.,[3] when updating their Markov model, did not adapt their assumption regarding the viraemic rate.

Furthermore, in their modelling study, they mention that *'people with a migration background account for the majority of HCV infections remaining in the country'*. However, most people in Switzerland with a migration background come from low HCV prevalence countries (such as Germany), and it is unclear to what extent people from high HCV prevalence countries remain in the country, particularly asylum seekers[7] and undocumented immigrants.[8]

We would like to underline the fact that despite documented massive increases in testing for HCV,[5] all of the following have been declining for many years: HCV positivity rates,[5] overall HCV notifications,[6] HCV notifications with evidence for replicating virus,[6] chronic hepatitis C with documented liver damage,[6] chronic HCV infections reported as asymptomatic[6] and acute hepatitis C.[6] Therefore, we stand by our conclusion that Switzerland has reached the WHO elimination targets, and prevalence estimates should be revised.

Regarding the publication by Djebali-Trabelsi et al.,[9] also published in this journal, there is indeed a declared participation bias concerning small differences in age and gender, but with respect to the prevalence of HCV in the general population, this hardly affects generalisability. More importantly, even if people with known HCV infections had been more likely to decline participation, this would not have affected the general population stratum as it excludes at-risk populations such as people who inject drugs (PWID). It is highly unlikely that a participation bias was associated with *unknown/undiagnosed* HCV infection. The main findings of that thorough study are that *'the lower prevalence of HCV infection (…) is likely related to the fact that several at-risk groups for HCV infection were not adequately represented'*, and that *'large-scale screening for hepatitis viruses does not seem to be effective in circumstances in which such testing is easy to do because, in these circumstances, several at-risk groups are often underrepresented'*. The claim of Blach et al. that we did not discuss the limitation in the publication of Djebali-Trabelsi et al.[9] is thus irrelevant: as shown by the study authors themselves, it limited the representation of at-risk groups, but not the study´s use for a general population estimate.[9]

Blach et al. also claim that retrieved publications *'were not systematically discussed in terms of their validity and reliability'*. This is not

[Correction added on 21 October 2023 after first online publication: Title and references have been revised in this version.]

correct either, since, for example, for the general population estimate, we provided a detailed discussion on which studies to include or reject, for questions of validity and reliability (main text, table 2).

They further criticise that we calculated the average prevalence for the general population from 10 publications and applied it to the Swiss general population. This is surprising, since the authors used exactly this methodology in their own prevalence estimate.[3] In addition, they have used data from the 2015 HCV prevalence estimate, building on fewer publications than in our update, with half of those clearly biased towards the inclusion of at-risk populations.[3,8,10] They obviously missed the point that we had validated our findings in comparison to the only Swiss study designed to represent the general population,[9] to the 2015 HCV prevalence estimate,[8] to national hepatitis C notification trends, and to other recent findings (tables 1 + 3). Further on that point: why should the denominators in our publication be *'mostly unclear'*? All denominators are listed (for the general population: table 2; for subpopulations: tables 1 + 3), and the source studies are carefully described concerning study aim, method and population.

Contrary to Blach et al.'s assertion, all our calculations can be traced (main text, detailed calculations tables 1–3). All references are supplied ('reference' section, references tables 1–3, additional reference information in S1 and S2) and are publicly accessible. The only exceptions (table 1) are the interview transcripts for the subpopulation of former experimental drug users and for persons with haemophilia, a subgroup of people with nosocomial infections, and documents retrieved from the physical archives we had searched for information on former experimental drug users.

The criticism of *'repeated references to secondary literature sources concerning mortality, spontaneous clearance and tested and treated'* is also unfounded. Regarding mortality, we referred to three publications that are based on primary source data from the *Swiss Hepatitis C Cohort Study*,[11–13] two of them also from the national death registry.[11,12] Regarding spontaneous clearance, we used primary source data and a systematic review from populations and HCV management settings that are comparable to the characteristics of the Swiss HCV subpopulations that we had stratified for. Regarding the percentage of tested and treated individuals, we used primary source data for all subpopulations and for the general population, except for the very small group of former experimental drug users, for which we used estimates from experts, see above.

Blach et al. claim that we performed no stratifications, *'even when populations and time periods vary to a great extent'*. This claim is again unfounded since stratification of populations is exactly what we did in great detail. As an example, the subpopulation of HIV-diagnosed men having sex with men (MSM) was dissected into those outside and inside the *Swiss HIV Cohort Study*, with the latter further subdivided by participation in the microelimination study ('*HCVree*'[14]); prevalence estimates were provided accordingly. Stratification concerning time periods was applied as shown in table 1; for subpopulations and the general population where (part of) the data were from before 2020, we calculated the 2020 prevalence based on data on mortality, sustained virologic response and up to date incidence data. In contrast to the 2015 HCV prevalence estimate,[8] we had a higher number of recent data at disposal due to increasing numbers of HCV publications, including FOPH annual epidemiological reports.

Blach et al also suggest that we did not support our claim that most deaths among PWID are due to comorbidities and not HCV-related sequelae. However, this information has been provided throughout our paper (see e.g. table 1). They also claim that this contradicts other publications—but the publication they cite discusses the influence of comorbidities on the progression of hepatitis C, not mortality, thus missing our point. There is ample evidence in the literature on the high mortality among PWID from drug overdoses, suicides and trauma,[15,16] infectious endocarditis,[17] cerebrovascular injury,[15] HIV-associated problems [16,17] and alcohol-associated liver disease.[16]

Blach et al. are incorrect when arguing that individuals born in Italy since 1953 were excluded from our analysis. Persons born in Italy before 1953 had been listed as a separate group because of their special characteristics, as shown in two publications with data from the *Swiss Hepatitis C Cohort Study* and the national notification system for infectious diseases.[7,13] As explained in section 3.1 of our study, persons with a subpopulation overlap were assigned to the most likely transmission route, for example, PWID born in Italy were assigned to the PWID group.

Blach et al. further argue that we failed to mention that, by extrapolation of the *SAMMSU* (i.e. Swiss Association for the Medical Management in Substance Users) *cohort* data as best practice HCV care,[18] viraemia among PWID could have been underestimated. However, we corrected for exactly that factor, as shown in table 1.

Finally, we would like to propose an explanation why Blach et al. cannot share our conclusion 'that Switzerland has reached the WHO elimination targets'. The first author and a co-author of this Letter to the Editor are the HCV group leader and the managing director of the Center for Disease Analysis Foundation (CDA) based in the United States.[19] CDA specialises in the *'study of complex diseases in order to provide countries with the data to create and implement successful elimination strategies'*[19] and provides HCV analyses for over 100 countries worldwide. 'Swiss Hepatitis', where most of the co-authors are members of, is a specialist network and lobby organisation developing strategies for viral hepatitis elimination.[20] Since 2014, 'Swiss Hepatitis' has requested the support of CDA for eight journal-published modelling studies on HCV in Switzerland, all but one financed by the pharmaceutical industry. Thus, Switzerland has been very present among the 104 HCV-focused CDA journal publications since 2014.[19] CDA bases their estimates on a self-developed Markov model, which they populate with country data.[3,10,19] CDA has an interest to use generalised parameters, for reasons of comparability and ease of application. Often, such data comes from the United States or from international collaborations.

But Switzerland differs greatly from many other countries inasmuch as it (i) is a pioneer in harm reduction,[21] (ii) pioneered the microelimination of HCV among HIV-diagnosed MSM,[14] (iii) is home to only one major group of HCV-infected foreign-born persons,[7] (iv) has a wealth of HCV data including three nationwide cohort studies with essential HCV data[7,11–14,18] and (v) is one of two countries

worldwide to have exceeded UNAIDS 2030 targets for HIV elimination in 2020,[22] with overlapping challenges of HCV and HIV.[23] For HCV data not related to characteristics inherent to the virus and subject to changes in population or disease management differences, this generalisation puts Switzerland at a disadvantage. In 2014, CDA and 'Swiss Hepatitis' published a modelled analysis of the HCV-associated health burden[24] that projected a steep increase in mortality. Two mortality studies (2017 and 2020) that had both used Swiss primary data sources did not show that increase.[11,12] For their estimate of 32,100 viraemic individuals in Switzerland for 2019,[3] CDA and 'Swiss Hepatitis' used their Markov model with generalised parameters, populated mostly with data from the 2015 HCV prevalence estimate,[8] which our study has shown to be outdated. CDA's country ranking is based on the same approach and has Switzerland listed among 21 countries *'working towards the WHO elimination targets by 2030–2050'*, behind 11 countries *'on track…by 2030'*.[25]

CONFLICT OF INTEREST STATEMENT

The authors have no potential conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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