Author's response to reviews

Title: HCV-Related Burden of Disease in Europe: A Systematic Assessment of Incidence, Prevalence, Morbidity, and Mortality

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Author's response to reviews: see over
Dear Editors,

On behalf of all authors, I would like to thank you for keeping our manuscript under consideration after the split decision by the reviewers.

We are pleased to resubmit a revised version of the manuscript accounting for the concerns raised by the reviewers. A point-to-point reply to all each of the three reviewers is provided on the following pages.

We hope our revisions and answers are satisfying and suited to dissolve remaining concerns about the relevance of our manuscript.

If the reviewers feel that further changes should be made, we would be happy to address these issues.
Sincerely,

Uwe Siebert

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Point-to-Point Response to the Reviewers' Comments

Reviewer #1 (Mary E Ramsay):

General comments

The authors have aimed to review information on the incidence, prevalence and burden of hepatitis C in 22 European countries. The objective is important and admirable, given the difficulty of studying hepatitis C and the inconsistent methods of surveillance in use. The subject of the paper is of interest to the readership of BMC Public Health. The methods the authors have used are appropriate and include formal literature review and obtaining “grey” literature from national and international agencies. The article is very well written and clear.

The main weakness of this paper is the quality of the information available. The authors have acknowledged the limitations of the data and have chosen therefore to use the most consistent and comparable data sources available (such as data submitted to WHO). Because of this some of the more valid data sources are rejected and most of the extrapolations and conclusions are based upon these globally available data sources. This naturally weakens the conclusions and interpretation of the information.

The authors discuss the weaknesses of the data but do choose to make general conclusions (such as geographical trends, overall burden etc). I suspect that some of these conclusions cannot be justified given the weakness of the data sources and I wonder if they would be better acknowledging these weaknesses and refusing to comment (other than in terms of what it says about the data) on the potential differences between countries. It would be helpful to make more comments on how surveillance and data sources could be improved.

Response:

Thank you very much for acknowledging the importance of our objective and your thorough and critical review. Your general comment is in line with our own concern regarding the weakness of available burden of disease data and the risk of over-interpretation. In the revised version, we tried to be even more conservative in our interpretations than in the previous version of our manuscript, since some of our interpretations might still have been unjustified given the weakness of the data. In this version of the manuscript we completely avoided to interpret results for individual
countries, as those in deed might mostly reflect variations in data quality or be biased by our use of regional HCV-attributable fractions. Furthermore we deleted all references to individual countries in the result section, which originally were only meant to describe the data but carry the risk to be over-interpreted by the reader. In addition, we extended the discussion in order to explain why, despite the limited inter-country comparability, we presented country-specific burden of disease estimates in our tables (for more see our response to your third minor essential comment below). In response to your suggestion to comment more on possible data improvements, we more clearly addressed the role of intravenous drug users and their importance in incidence and prevalence estimations. Additional references were added as well. (for details see our response to your first minor essential comment below). In addition we followed you suggestion and the revised conclusion sections now puts a stronger emphasis on the fact that data on the burden of disease of hepatitis C in Europe are scarce, outdated or inconclusive. In the conclusion, we mention that, by revealing the paucity of available information, our study indicates that hepatitis C is still a neglected disease.

There are three areas where I think that minor essential revisions are required:

1. The first is the nature of the population affected. There is only one reference to injecting drug use in the paper and I think the fact that most recent infections in the region are likely to be in injectors deserves more acknowledgement and discussion – this has implications for the validity of incidence and prevalence estimates as they are largely a marginalised group. I wonder if some of the lessons learnt from the HIV epidemic in Eastern Europe – about second-generation surveillance for example – could be discussed with respect to HCV.

Response:

In response to that comment we added a passage and three more references to the background section, which address the role of intravenous drug users and the changing epidemiology of HCV infections. In addition, we addressed second-generation surveillance as a possible approach to better understand and prevent the spread of the HCV epidemic in the discussion. A reference describing the principles of second-generation screening was inserted as well. As a means to increase surveillance sensitivity, our previous manuscript already mentioned targeted screening programmes. Results from our PanEuropean Hepatitis C Project on screening, will be published separately. A statement that incidence and prevalence are underestimated
due to underassessment of intravenous drug users from our point of view would be speculation. As a known high risk group, IDUs are more frequently tested and targeted by screening programmes than the general population, which should be reflected in incidence figures. Some prevalence estimates, especially those available from national sources, are already corrected for under-representation of IDUs. This specific issue is also addressed in the first paragraph of the prevalence section in the discussion, which now has been rephrased in order to improve comprehensibility. A clarifying addition was also made to the last sentence of fourth paragraph of the prevalence section in the discussion. Our personal opinion is that the role of IDUs in deed might currently be underestimated in some Eastern countries like Romania and Poland, however, data are lacking to support our suspicion.

2. The second area that deserves more attention is the incidence data. Despite the statement that this data is acute hepatitis C I suspect in many cases, and know in some, that these diagnoses are not acute infections. I am not sure if the HFA database is clear but recent WHO joint reporting forms do specify acute and chronic infection separately, and when I looked today the on-line Euro database does not have hepatitis C incidence displayed. This may not have been the case in the past and may have mislead the authors of this manuscript. I understand that many countries feel obliged to report something even if they are not able to work out whether cases are acute or chronic. In addition, doctors often report chronic cases to schemes where acute infections are requested and national surveillance leads feel unable to contradict an incorrect report. This has been a long-standing issue for other forms of hepatitis and other authors have misinterpreted hepatitis B data from northern European countries in the past (eg. Zuckerman J, van Hattum J, Cafferkey M, et al. Should hepatitis B vaccination be introduced into childhood immunisation programmes in northern Europe? Lancet Infect Dis 2007; 7: 410–19.). I feel strongly that trends in numbers of reports probably reflect trends in testing – this is certainly the case for the UK and may well be more general.

Response:

Unsettled by your comment, we checked the latest online version of the Health for all database (http://data.euro.who.int/hfadb/ updated July 2008) for hepatitis C incidence data once more. Selecting the parameter “2023 Hepatitis C incidence per 100000” yields an empty table. However, the parameter “2022 Number of new hepatitis C cases” provides the data, we have used for our report. Meanwhile data are available up to 2006. According to the database definition, new cases are meant to represent acute cases (ICD-10: B17.1). We certainly share your concerns that not all national authorities
always reported only acute infections to WHO, which may explain some of the temporal and geographic variation in the data. However, as we cannot prove this, we would prefer to stick with the statement that currently European incidence data are not comparable and need to be standardised. Another argument, why we don’t want to exaggerate this point is that even countries, which in the past assessed newly detected cases within their surveillance, recently restricted surveillance to acute cases. As a consequence most European countries nowadays can only report acute cases.

3. The third issue refers to the use of attributable fractions where specific data is not available. Although the authors discuss this and mention that it does not allow inter-country comparisons, they do then make conclusions about trends across Europe using these fractions. I cannot see that it is internally consistent to compare prevalence between countries and then use a broad regional AF to compare burden in the same countries – this makes the discussion of trends across the continent rather self-fulfilling. Surely burden must vary according to past and current prevalence and a more appropriate analysis might have been to estimate attributable fraction from a constant relative risk and the prevalence of infection. If the data does not support this more valid approach I would suggest that discussion of inter-country comparisons is limited and interpretation simplified to estimate overall burden.

Response:

As indicated by the second paragraph of our discussion we fully agree with your comment. Because deriving country-specific HCV attributable fractions for cirrhosis and liver cancer in deed would be a major research project of its own, especially in view of the questionable validity of the current prevalence data, we followed your suggestion to even more restrict our interpretation to overall and regional burden of disease estimation and refrain from inter-country comparisons. Specifically, in the revised version of the manuscript, we completely avoided to interpret results for individual countries. Furthermore we deleted all references to individual countries in the result section, which originally were only meant to describe the data but might be over-interpreted by the reader. In addition, we extended the second paragraph of the discussion in order to explain why, despite the limited inter-country comparability, we presented country-specific burden of disease estimates in our tables.
Reviewer #2 (Gary Davis):

This is an important contribution, though its observations and conclusions are largely based on absent, clearly inaccurate, or questionable data, as the authors readily acknowledge. Nonetheless, the authors have done a reasonable job in examining inconsistencies in the data and recognizing gaps.

I have a few minor suggestions:

1. Pg 9. Incidence reporting in inherently inaccurate for the clinical reasons cited as well as reluctance to report. Some earlier studies also estimated incidence based on prevalence and estimated chronicity rates; this is similar to your duration calculation method. Is there a way to correlate the sophistication of the public health or overall health reporting system in various countries to reported incidence? What does the last sentence in the second paragraph mean, i.e. fluctuations appear to be undirected?

   Response:

   Thank you very much for acknowledging the importance of our contribution and your very specific comments. We think that theoretically it would be possible to correlate the sophistication of the surveillance system to the reported incidence. However, the result would be highly speculative. Firstly, because the completeness and sensitivity of surveillance data is influenced by many factors, which are difficult to measure and to quantify. Secondly and maybe even more important in the case of hepatitis C, is that you can only report what has been diagnosed first. We think that the completeness of HCV surveillance data depends more on whether a country has implemented some sort of screening programme or not. Nevertheless, standardising HCV surveillance in Europe is an important issue.

   The unclear last sentence of the second paragraph of the incidence section in the results was modified as follows: "In some countries incidence appears to rise and fall without a trend."

2. Pg 10, Prevalence. What does "population representativeness" mean? How were the WHO prevalence data and those reported in publications obtained (methodology)? Are the national prevalence data from national health authorities that are referred to in the 3rd paragraph subjective estimates?
Response:

We replaced "population representativeness" by “representativeness for the general population”.

WHO prevalence data have either been reported by the country or selected from published prevalence studies (see prevalence section in the results). Prevalence estimates from national sources are not subjective, however, the underlying empirical evidence used is often not available to the public. Reasons why national estimates might differ from WHO data are discussed in the prevalence section of the discussion. In our opinion a main reason is that national prevalence estimates may be based on a variety of study results and modelling assumptions, especially, when representative population surveys are lacking or correction for selection bias is needed. As national health institutions do not have to adhere to scientific documentation standards or publish the result in scientific media the underlying evidence or assumptions are often hard to assess.

3. Pg 11, Mortality (and same comment for quality of life section): I am not sure that I understand how death from hepatitis C occurs without either cirrhosis or liver cancer being present. Please explain.

Response:

Deaths may occur in the acute phase due to fulminant hepatitic failure which is rare but a very severe condition. An Italian study, published in 2003 by Bianco et al., reported 2 fatalities (0.1%) due to fulminant hepatitis among 1536 cases of acute hepatitis C.

Besides the mortality risk, studies have shown that HCV infection diminishes health-related quality of life even in the absence of advanced liver disease. This issue is addressed in the quality of life section of our discussion including references.

4. Discussion: Many of the deficiencies in the data have already been described in the results section and do not require repeating. I would suggest that the discussion be shortened and focus on specific deficiencies and how they might be addressed by physicians, hospitals, national public health authorities, and the WHO. Clearly, the authors are presenting this data to serve as a foundation for moving public health and patient care forward. That cannot be
accomplished without better data and awareness. Congratulations on tackling a very difficult project.

Response:

We would like to thank you for supporting our goal to increase the awareness for hepatitis C and speed up public health activities in that area. In response to your comment we have removed some redundancy from the discussion. However, we did not substantially shorten the discussion. Given the weakness of available data, there is a high risk that our results might be over-interpreted by less informed readers. Therefore we think it is essential to discuss the limitations of our results very carefully and in depth. We very much liked your statement regarding the broader goal of our work. As it is spot on, we included the essentials of your comment in our discussion and conclusion.
Reviewer #3 (Sheng-Nan Lu):

The authors tried to estimate the HCV-related burden in Europe. Using available data, they estimated its incidence, prevalence, mortality (hepatitis, cirrhosis and HCC), quality of life (DALY and LYD) and liver transplantation. This is a well-writing manuscript. In Introduction, the authors pointed out the significant of study. In the Materials and Methods, they planned to collect comprehensive data with systematic review. In Discussion, they analyzed the limitations of this study in details. However, this manuscript is submitted as an “original articles”. Their own results should be most important part. In this study, the information collected, including incidence, prevalence and mortality, might not be representative and accurate enough. Using such quality of data, the authors should hardly convince readers of their results and deductions.

Response:

We would like to thank you for reviewing our manuscript. There is no doubt that our manuscript is rather a review than an original article and that the data presented in our work are weak. However, let us point out that our objective was not to come up with perfectly valid burden of disease data for the whole of Europe but to summarise presently available data and to identify areas where better data are needed. Despite weaknesses in the data, our review shows that hepatitis C must be considered as a major public health problem, that requires public awareness and concerted actions. In fact, by revealing the paucity of available information, our study indicates that hepatitis C is still a neglected disease in many countries and might prompt necessary actions. Therefore we think that our study is relevant. However, we might have failed to appropriately explain the relevance. To be more clear, we modified the first two paragraphs of the discussion in the revised manuscript. As we know from presenting preliminary results to different audiences (including physicians, public health representatives, members of the European parliament, and members of patient organisations) there is considerable interest in our topic.