Reviewer's report

Title: The case for a universal hepatitis C vaccine to achieve hepatitis C elimination

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Reviewer: Marian E. Major

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This study uses a mathematical model to examine the potential impact of a hepatitis C vaccine on the feasibility and cost of achieving the WHO elimination goal of an 80% reduction in HCV incidence by 2030. The method was calibrated to 167 countries and studied high-risk populations, i.e. people who inject drugs (PWID), and the general community.

The group found that with a vaccine available, the optimal strategy was to include vaccination within test and treat programs, in addition to vaccinating adolescents in settings with high levels of community transmission. Of the 167 countries modelled, between 0 and 46 could achieve an 80% reduction in incidence without a vaccine. This increased to 17-110 countries if a 75% efficacious vaccine with a 10-year duration of protection were available. Vaccination would also reduce the costs of elimination substantially.

This is a highly relevant study and important to the field of HCV vaccine development. It is a very comprehensive model, including 167 countries, high and low-risk populations. Given the challenges in performing clinical trials in at-risk populations, namely PWID, studies such as these are pivotal in continuing to advance HCV vaccine strategies.

Main Comments:

1. The study includes a great deal of data, most of which is included in supplemental files. It would be beneficial to the reader if data were referred to more specifically for the supplemental tables.

2. When considering vaccine efficacy, it was unclear if the vaccine considered was a 1, 2 or 3 dose vaccine. The vaccine currently in Phase II trials is a two-dose vaccine. The number of doses in a vaccine is an important consideration for time to protective responses, compliance, and in considering the possibility of high-risk individuals becoming infected between doses. Using a one-dose vaccine in this model provides a best case scenario in terms of compliance and outcome.

3. Lines 247-250: 0 to 46 countries achieving an 80% reduction in incidence with testing and treatment alone is a big range. The authors state that this depended on coverage range but more explanation would help the reader understand such a substantial difference.
Where 80% was not met what was the % reduction? The WHO goal is shifting as the challenges of meeting the 80% reduction become clearer, therefore, such data may become relevant.

4. In general, I would find it more useful to see figures showing the final % reduction rather than the figures showing whether or not the target was met.

5. There are several statements in the Discussion that are either not directly supported by the findings or where figures or data are not referenced. Specifically:

i. Lines 340 to 342: The authors state that if a vaccine were available to reduce reinfection in treated individuals, testing requirements among PWID were reduced to either two-yearly for 109 (65%) of the 167 countries, or annually 38 (23%) of the 167 countries. Where is this data shown? The consideration of reinfection in treated individuals is important and could have a significant impact on the long-term prevalence of HCV (e.g. over the course of 30 years) if only treatment programs remain in use.

ii. Lines 367 to 370: The authors state that for settings with high rates of transmission in the general community, the model suggests that introduction of a vaccination program for adolescents would provide additional benefit. How is this shown from the data? It is unclear where adult only vaccination outcomes were compared with vaccination strategies that included adolescents.

6. The authors make an important point regarding adolescents as they may not be included in a first-generation vaccine population. The current vaccine in the phase II trial is for adults (aged 18-45). It would have been helpful to see a model consider adults with the addition of adolescents or provide data that support the importance of extending any vaccine licensed for use in adults to adolescents. If this data is contained within the submission it is not clear.

Minor comment:

Lines 130 to 133 describe the classification of people in the model. This would be clearer if the groups were number or labelled (a, b, c etc).
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
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Not applicable

Are the conclusions drawn adequately supported by the data shown?
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