

Liang-Sheng Ma, Science Editor
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May 12th, 2021

Dear Dr. Ma,

Subject: Submission of revised paper, Manuscript NO: 65350

Thank you for your email dated May 2nd 2021 enclosing the reviewers' comments. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point-by-point manner below. Changes made to the original manuscript are shown using track changes.

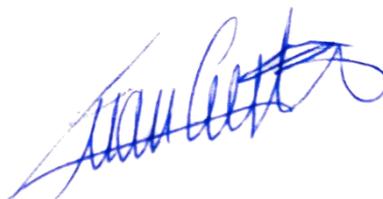
We are very grateful to you and the reviewers for the valuable comments and suggestions which have improved our work.

Please note that the total number of references has increased to 313 since due to the revisions, new publications have been incorporated, and additionally clinical trials have also been added as references, following the references guidelines.

On the other hand, we would like to let you know that figures cannot be provided in editable forms since they were created using Biorender. However, there are PDF files which allow editing of texts, and in case they are needed, we can send them as well. We provide original figures in .png format as well as embedded in a power point presentation.

We hope the revised version is now suitable for publication in World Journal of Hepatology and look forward to hearing from you soon.

Sincerely,



Juan Cristina, PhD
Full Professor
Laboratorio de Virología Molecular
Facultad de Ciencias, Universidad de la República, Uruguay

Response to Reviewer 04417620:

Thank you for your kind review of our manuscript. We appreciate your suggestion and believe it has improved our paper since we have now incorporated information that was not mentioned in the original draft:

Reviewer comment: Discussion on the role of computational vaccine design strategies to design a highly conserved and effective HCV vaccine candidate will improve the manuscript.

We have followed the reviewer's suggestion and subsequently added a paragraph discussing the importance of computational design of vaccine epitopes. This new information is now found within the "APPROACHES TO DESIGN VACCINE CANDIDATES FOR HCV" section, under the subheading "Recombinant subunits and synthetic peptides".

The paragraph addition looks as follows:

"Of interest, computational identification of B and T cell epitopes has been explored as an alternative for the rational design of effective vaccine candidates. By means of different immune-bioinformatic and population dynamics simulation approaches, many predicted epitopes in E2, NS3/4A, NS5A and NS5B have been identified[209–212]. These approaches provided valuable information and in silico screening methods for highly conserved immunogen candidates with the putative ability to block escape mutations (for a detailed review please see[213]). These computational designs can help speeding up vaccine development at the experimental stages by rationally selecting the most promising epitopes for subunit vaccine in vitro and ex vivo evaluation."

Response to Reviewer 03475479:

Thank you for your review of our manuscript. We understand your concerns regarding the widespread use of DAAs making vaccine protection in not endemic areas less effective, reason why we have tried to emphasize the motives behind the need for an HCV vaccine.

Reviewer comment: But, as authors mentioned, DAAs for HCV has been developed and widely used. Vaccines in less-endemic status has smaller values for effective protection.

In the "INTRODUCTION" section, under the subheading "Hepatitis C virus infection and the need for a vaccine", paragraph 3, we had already introduced the issue of DAA-based treatments and how despite exhibiting high curing rates, not only is access to those therapies uneven in different countries, but also the possibility of reinfection and of developing hepatocellular carcinoma still remains. In our opinion, all these issues highlight the need for a vaccine. However, in order to stress the importance of a future HCV vaccine, and considering the facts mentioned before, we have added, at the end of the same paragraph the following:

“Vaccination against HCV infection would reduce public healthcare resources by avoiding expensive DAA-based regimens or medical treatments for any liver or metabolic complications derived from long-term infections[15–17], especially in low- or middle-income countries, where HCV prevalence is still moderate-high and access to diagnosis and treatment uneven and costly[18].”

In addition, at the end of paragraph 6 of the same section we have included information on modelling studies which indicate that HCV eradication seems unlikely by the sole use of antiviral therapy:

“Modelling studies have indicated that, even with the introduction of new DAA treatments, only a quasi-eradication of HCV would be possible[26,27], highlighting the need for a vaccine against HCV.”

While we understand that protection derived from immunization in low prevalence areas might not be as effective as that which might occur in regions of high HCV prevalence, as mentioned in the manuscript, there are high-risk groups such as people who inject drugs, where reinfections are common and therefore, a prophylactic vaccine, even one with low efficacy, can be extremely useful (see paragraph 2 of subheading “Prophylactic versus therapeutic vaccines” under the INTRODUCTION section).

Reviewer comment: Authors should also discuss economic significance in HCV vaccine.

We appreciate the reviewer’s concern regarding this particular topic. We agree that the economic significance is one of the challenges for the development of a successful vaccine, and as such, we had already included a sub-section (“Lack of economic incentive”) under the “CHALLENGES FOR DEVELOPING ANTI-HCV VACCINES” section. Nevertheless, we decided to add a paragraph with our own view based on information available for other vaccines and diseases:

“From an economic perspective, though, there is well-reported evidence that vaccines are, in the long run, the most cost-effective public health measure after access to clean water[93,94], and a vaccine to fight HCV will, most likely, not be an exception.”

Additionally, we thought that the end of the “CONCLUSIONS AND PERSPECTIVES” section would benefit from stressing out the importance of allocating new funds to HCV vaccine research:

“This renewed interest in funding HCV vaccines might be what is needed to achieve HCV global eradication, as has been proposed by the WHO a few years ago. Allocating funds for this purpose boosts the research area that has been left behind in terms of breakthroughs that can be effectively translated to public health benefits.”

Despite being our belief that an HCV vaccine is necessary to eradicate HCV and finally tackle the health burden associated to HCV infections, it is beyond the

scope of our review to perform a cost-benefit analysis of HCV vaccination. In order to do an economic analysis a vast number of variables inside and outside healthcare should be taken into consideration, such as productivity, disease control, reallocation of health resources, fiscal revenues, amount of money spend in treatments versus in vaccinations, manufacturing costs (of vaccines versus drugs), and many others, which would account for a different review topic than the initially selected. For this reason, we have not discussed the economic significance of HCV vaccination more thoroughly.