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Title: Mucosal COVID-19 vaccines - risks, benefits and control of the pandemic

Running title: Mucosal COVID-19 vaccines

Manuscript Type: Minireviews

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience.

Dear Editor,

Dear reviewers,

Thank you for your time to review our Manuscript ID: 76337, Authors: Dimitrina Miteva, Monika Peshevska-Sekulovska, Violeta Snegarova, Hristiana Batselova, Radostina Alexandrova, Tsvetelina Veselinova Velikova.

We have incorporated most of the suggestions made by the reviewers. Those changes are highlighted in green within the manuscript. Please see below, in blue, for a point-by-point response to the reviewers' comments. All page numbers refer to the revised manuscript file.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear authors. It has been a pleasure to review your manuscript. The topic discussed interest me greatly and I found the article informative. I hope my comments would be useful to your team to improve the manuscript for publication.

- Thank you for the suggestions and constructive critic. Your evaluation of the manuscript is of a great importance to us. Thus, we are grateful for your time and overall positive assessment of the manuscript. We believe that in such a way we improved the paper significantly.

Abstract - IN is not a common abbreviation for intranasal even in current literature. Suggest to spell it out

- Thank you for the note. We agree that this is not standard abbreviation. We spell it out within the manuscript.

- Additional illness-> Did you mean side /adverse effects?

- Thank you for the note. We can see that there is a misunderstanding, thus, we changed it with preventable.

- “IN vaccines based on the previously successfully used IN vaccines in mankind's history” – what are you trying to convey with this sentence?

- Thank you for the note. We mean that there were effective vaccines, such as against flu. We change the wording to improve clarity.

Core tip - Multiple sentence structure errors and improper usage of words (e.g. “....regions with unavailable healthcare...”)(....give hope for preventing infections additional to reduced transmission....)

- We agree completely with the referee for these issues. We have corrected them.

Manuscript body - General language much improved.

Only few errors (e.g. They examined the incidence of children (incidence of infection among children?) due to infectious diseases depending on whether the last vaccine they received.)

➤ Thank you for noticing us this mistake. We have corrected.

Please correct spelling errors and remove errors from past editing (e.g. noted). placed before the sentence in page 12 second last paragraph, some brackets not removed –males but not in females [82]. (). Several other studies.....)

➤ Thank you for your valuable comments. We did not notice these mistakes during the submission. We have corrected them all.

Standardization of font styles throughout manuscript is required -> pg 16-17 font is clearly different

➤ We have corrected this issuer43.

- Several repetitions in points (e.g. needle use in vaccination) which could be put together instead of mentioning again.

➤ We completely agree with the referee. We did our best to put them together.

- More discussion and references on benefits of intranasal vaccination would help to increase the scientific value of this paper (e.g. the point on oral vaccines being cost effective through bypassing antigen purification was intriguing. Expanding this point would be interesting)

➤ Thank you for the valuable suggestion. We searched again the published data and added new references on the topic. We completely agree that is crucial in our manuscript.

- Several sentences were long-winded and could be shortened considerably to reduce the word count of the manuscript and improve readability

➤ Thank you for the note. We took it seriously and revised all the text. We tried to improve the manuscript to be more clear and concise.

References - Needs substantial correction. Format issues and improper references (e.g. 9. Clinical trials website??, to name a few)

- Thank you, we have corrected the references as per journal requirements.

*overall, the article was pulled down mainly by the language quality. Although it is acceptable once the necessary corrections are made, it would be better if it was passed to an English editor involved in our field of research as offered by most publishing companies. Thank you.

- We agree with the referee that the language and style were not perfect; therefore, we revised it carefully, and once again gave it to the colleague of us, who is proficient in English,

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting and well documenting as well as discussing the mucosal SARS-CoV-2 vaccine, such as one targeting the nasal or oral mucosa, would be ideal if it could also be demonstrated to be safe. It is also fascinating to see if IN administration of SARS-CoV-2 mRNA vaccines may induce resident memory T cells and B cells and protect the lungs and gut. Recent and ongoing studies highlight the importance of understanding local immune responses to SARS-CoV-2 and suggest that research on mucosal, natural, and vaccine-mediated immunity to SARS-CoV-2 is of tremendous translational and therapeutic value.

- Thank you for the suggestions and constructive critic. Your evaluation of the manuscript is of a great importance to us. Thus, we are grateful for your time and overall positive assessment of the manuscript. We believe that in such a way we improved the paper significantly.

Albeit, this current review provide update knowledge in coronavirus pandemics related fields. I still have some minor suggestions.

1, The paper is written in a professional style, and it was a pleasure to read it. Very interesting! However, it would be much better if the authors can provide some tables for this review paper so that the reader can easily catch the concept. Meanwhile, Figure 1 is also highly professional, but

the authors should guide the readers to the meaning of the images appropriately; otherwise, it is likely to cause misunderstandings. Therefore, I suggest that the author consider revising these figure legends again.

- Thank you for the valuable evaluation of our figure. We have extended the explanation of the figure to clarify the mechanisms.

2, Mucosal vaccines against SARS-CoV-2 are incredibly challenging to develop and confirm their safety. However, they will offer the ability to trigger stable, protective immune responses at the sites of pathogenic infection. In addition to SARS-CoV-2, it would be much better if the author can also discuss mucosal vaccines for other types of coronavirus including MERS, and SARS-CoV...etc. (PMID: 15660214, 33918958, 34176764, 32615317, PMID: 35215783).

- Thank you for the great suggestions. We have discussed these vaccines and we believe that your recommendations significantly improved the quality of the paper.

3, The author needs to follow the “Guidelines For Authors” and edit the format of the references for the manuscript (<https://www.wjgnet.com/bpg/gerinfo/204>). For example, Reference No 53, ...in Denmark: nationwide retrospective cohort study. Open Forum Infect Dis 2016; 3:XXX–XX. Please correct XXX during revision.

- We completely agree with this note. We have format all the references as per both reviewers suggested

6 EDITORIAL OFFICE’S COMMENTS

Authors must revise the manuscript according to the Editorial Office’s comments and suggestions, which are listed below:

(1) Science editor:

This manuscript explored mucosal SARS-CoV-2 vaccines. It is suggested to add tables explaining the subject of this manuscript and mucosal vaccines for other types of coronaviruses, including MERS and SARS-CoV, etc.; please further revise the language of this manuscript; in addition, please revise the citations of references according to the journal format requirements.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

- Thank you for the overall evaluation of our paper as good. We did our best to improve the quality of the paper that will meet the rigorous criteria of the journal.
- We add a table that summarizes the findings for the existing mucosal vaccines in the paper, additional figure on the existing mucosal vaccines against COVID-19 (Figure 2), we revised the language and style thoroughly, and we format the references as per journal style and requirements.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Virology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-

alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

- Thank you for the great suggestions. We have prepared figures according to the requirements. We want to declare that all of them are original figures, crafted by our team.