PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	SAFETY, EFFICACY AND IMMUNOGENICITY OF THERAPEUTIC VACCINES IN THE TREATMENT OF PATIENTS WITH HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA ASSOCIATED WITH HUMAN PAPILLOMAVIRUS: A SYSTEMATIC REVIEW PROTOCOL
AUTHORS	Gonçalves, Caroline Amélia; LOPES-JÚNIOR, LUÍS CARLOS; Nampo, Fernando Kenji; Zilly, Adriana; Mayer, Paulo César Morales; Pereira-da-Silva, Gabriela

VERSION 1 - REVIEW

REVIEWER	Thomas Harder Robert Koch Institute, Germany
REVIEW RETURNED	18-Oct-2018

GENERAL COMMENTS	This systematic review protocol is sound and well-written. I have only a few comments aiming to improve some aspects of the protocol: 1) To my opinion, if the authors apply the Cochrane risk of bias tool, it is not necessary to use Jadad scale in addition. Rather, to assess the evidence quality beyond risk of bias in single studies, I suggest to use GRADE. 2) The authors should assess the possibility of publication bias if enough studies per outcome are identified. 3) In the PICO table, it would be useful to specify the outcomes (i.e., CIN2/3) rather than writing "efficacy". 4) During data extraction, It would be useful also to extract information on conflict of interest and study sponsorship from the included studies.

REVIEWER	Ricardo Rosales VIROLAB S DE RL DE CV
REVIEW RETURNED	04-Dec-2018

GENERAL COMMENTS	THE PAPER IS CLEAR AN WELL WRITTEN. IN ADDITION COVERS THE OBJETVES OF THE RESEARCH

REVIEWER	Dr Stacey Bryan Institute for Women's Health University College London
REVIEW RETURNED	20-Apr-2019

GENERAL COMMENTS	This is a systematic review protocol in which the authors have outlined clearly the aims of the paper. I think it should be made clearer how immunogenicity will be evaluated across the various studies. The limitations of the study have been outlined well, however there have been other studies looking into therapeutic vaccines (Current research into novel therapeutic vaccines against cervical cancer. Cordeiro MN, 2018) how will this study be different to the others.

VERSION 1 – AUTHOR RESPONSE

 Reviewer Reports:

- Reviewer 1:

Reviewer Name: Thomas Harder

Institution and Country: Robert Koch Institute, Germany

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below:

This systematic review protocol is sound and well-written. I have only a few comments aiming to improve some aspects of the protocol:

Response: Thank you so much!

1) To my opinion, if the authors apply the Cochrane risk of bias tool, it is not necessary to use Jadad scale in addition. Rather, to assess the evidence quality beyond risk of bias in single studies, I suggest to use GRADE.

Response: Absolutely! Does make sense. Thanks for this suggestion!

So, we will use only the Cochrane's Risk-of-Bias Tool as recommended instead of Jadad Scale. Moreover, in order to assess the evidence quality of the risk of bias in single studies, we have added the GRADE in our protocol as suggested.

2) The authors should assess the possibility of publication bias if enough studies per outcome are identified.

Response: Sure! This is very relevant aspect to be considered. Thanks for this suggestion!

We have make some editions in the main document. "We will assess the possibility of publication bias if enough studies per outcome are identified".

3) In the PICO table, it would be useful to specify the outcomes (i.e., CIN2/3) rather than writing "efficacy".

Response: OK! Done! Thanks.

4) During data extraction, it would be useful also to extract information on conflict of interest and study sponsorship from the included studies.

Response: OK! Done! We really appreciate it! Thanks for this recommendation. We have added these aspects into extraction form.

- Reviewer 2:

Reviewer Name: Ricardo Rosales

Institution and Country: VIROLAB S DE RL DE CV

Please state any competing interests or state ‘None declared’: NONE DECLARED

Please leave your comments for the authors below:

THE PAPER IS CLEAR AN WELL WRITTEN. IN ADDITION, COVERS THE OBJETIVES OF THE RESEARCH

Response: Thank you so much!

- Reviewer 3:

Reviewer Name: Dr Stacey Bryan

Institution and Country: Institute for Women's Health, University College London

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below:

1. This is a systematic review protocol in which the authors have outlined clearly the aims of the paper.

Response: Thank you so much!

2. I think it should be made clearer how immunogenicity will be evaluated across the various studies.

Response: OK. Done! We added this note in Table 2. Please, check out the editions. “Immunogenicity will be evaluated across the various studies in exploratory way in the blood and in the target tissue (including immune response to vaccine antigen, e.g. systemic T-cell response measured by γ IFN enzyme-linked immunospot assay (Elispot); assessment of HPV-specific CD8 and CD4 immune response; or also, via systemic induction of HPV E6- and E7- specific T-cell immune responses measured by IFNg ELISPOT, and changes of involved lesions and HPV infection status at the uterine cervix)”; among other parameters (e.g. generation of antibodies and release of cytokines).

3. The limitations of the study have been outlined well, however there have been other studies looking into therapeutic vaccines (Current research into novel therapeutic vaccines against cervical cancer. Cordeiro MN, 2018) how will this study be different to the others.

Response: First, our study differs from the proposal of Cordeiro et al., 2018 because it is a systematic review guided by Cochrane Collaboration and not a review of the literature. Second, our study evaluates variables such as immunogenicity, safety, and efficacy of therapeutic vaccines for the treatment of cervical intraepithelial neoplasia (CIN), which are not addressed in an in-depth way in the article by Cordeiro et al., 2018, since the authors focused on target epitopes for the development of vaccines, adjuvants and routes of administration.

Third, because our study addresses high-grade cervical intraepithelial neoplasia (CIN 2/3), which are precursor lesions of cervical cancer, and represents a relevant period (approximately 20 years) between the time of infection and the development of cervical cancer, demonstrating urgency in therapies for this purpose. Since in developing countries there is a high prevalence and incidence of these viruses due to the low adhesion of the prophylactic vaccines, therefore, the treatment before cervical cancer is necessary. As the authors Cordeiro et al., 2018 have stated: "late diagnosis is commonly associated with a poor prognosis". In addition, the "best immunogenicity in terms of CD4 + and CD8 + T cell responses and clinical responses was seen in patients with premalignant diseases such as cervical intraepithelial neoplasia (CIN)", especially when related to patients with recurrent cervical cancer, since systemic alterations and sites associated with cancer appear to be related to deleterious effects on immunocompetent T cells. Thus, cervical cancer has a worse prognosis, greater damage to the organism due to its association with conventional treatments, lower immunogenicity, lower clinical response and besides being associated with high mortality rates.

Finally, Cordeiro et al., 2018, highlights in their work the immunotherapy of DNA vaccines, which also differs from the proposal of our study that is not limited to the type of vaccine but an overview of the therapeutic vaccines used for CIN 2/3 that evaluated safety, immunogenicity as well as efficacy. Overall, we can say that they differ in the study proposal, type of pathology evaluated, as well as outcomes assessed. Furthermore, the authors did not evaluate the methodological quality of ongoing clinical trials. Thus, these aspects pointed out above explains why our review is necessary.

VERSION 2 – REVIEW

REVIEWER	Dr Stacey Bryan University College London Hospital
REVIEW RETURNED	08-May-2019

GENERAL COMMENTS	The authors have addressed my initial comments