Author’s response to reviews

Title: Zika vaccines and therapeutics: landscape analysis and challenges ahead

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Version: 1 Date: 02 Mar 2018

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Reviewer #1:

Minor comments/suggestions:

"yellow fever (YF), Japanese encephalitis (JE), and Tick-borne Encephalitis (TBE)" should be "yellow fever (YFV), Japanese encephalitis (JEV), and Tick-borne encephalitis (TBEV)".
Change throughout the manuscript.

Response: amended accordingly.

When possible identify the full strain name utilized for either the therapeutic or vaccine candidate: Example: Instead of "ZIKV Puerto Rico strain" state "ZIKV Puerto Rico strain PRVABC59"
Table 1. "Immunogen" column. Should "prME" be "PrM/E"?

Table 2. Improve consistency in terms and style. See examples below.

"Platform" column. "non VLP" should be "non-VLP"; "Live Attenuated Recombinant Virus" should be Live, attenuated recombinant virus; "inactivated virus + aluminum adjuvant" should be "Inactivated virus + aluminum adjuvant"; "peptide" should be "Peptide".

"Antigen" column. Different terms are used for the same antigen (whole virus, zika virus, full genome, whole virion) - choose a single term. "PrM/E protein and PrM/E/NS1" should be "PrM/E and PrM/E/NS1"; "PrME+NS1" should be "PrM/E+NS1"; "prME" should be "PrM/E"; Zika structural proteins?; "prM-E" should be PrM/E; "ZIKA virus PreM and Envelope proteins" should be "PrM and E"; "ZIKV, YF, and CHIKV surface antigens" should be "ZIKV, YFV, and CHIKV surface antigens". Precede all antigen information with "ZIKV" (e.g. ZIKV PrM/E proteins).

"Adjuvant" column. Choose either "Alum" or "Aluminum", consider using Aluminum.

Table 3. "Description" column. Bulleted points either start with a capital letter or without, be consistent throughout.

Response: we have amended the manuscript and in particular the tables taking all the above into account.
Author discretionary comments/suggestions:

Use of "The" preceding "WHO" throughout the manuscript (e.g. The WHO…)

Response: although in verbal communication, "the" is used before WHO, WHO has strict specifications that "the" should not be used before WHO. It should be used when WHO is written out as "the World Health Organization": Hence we did not do this suggested change.

Improve consistency utilizing ZIKV structural protein names throughout the manuscript/tables.

Response: done accordingly.

Page numbers and continuous line numbering are not utilized.

Response: not sure whether we need to do this?

"spread of the ZIKV on 18 November 2016, the long-term needs for a ZIKV vaccine" consider "…the long-term need for a ZIKV vaccine…"

Response: thank you. Corrected.
"Under the Blueprint Plan of Action, WHO has led a series of initiatives to maintain" consider "…led a series of initiatives to maintain…"

Response: amended.

Reviewer #2:

Well-written organized, and comprehensive synthesis of the current considerations and landscape for Zika vaccine development from a number of existing WHO reports available on the WHO and clinicaltrials.gov websites by a group of eminent authors who appear to have been involved in the series of WHO meetings that led to the source documents. As WHO should be a main driver in coordination of the many Zika vaccine efforts worthwhile, exposing thoughts and the landscape widely may be worthwhile.

Response: thank you

The review largely overlaps a series of similar and slightly more expansive articles just published in a supplement to J Inf Dis in December 2017.

The important hurdles posed by the limitations of current diagnostics are underplayed here, just a brief statement without elaboration in an ending paragraph. If laboratory endpoints in clinical trials are to be paramount as suggested by the authors, this warrants more discussion.

Response: We have expanded the text to elaborate further on the complexities of Zika diagnostics.
The history of flavivirus vaccine development is much in the news these days with the challenges of dengue vaccine becoming more apparent. This needs a full and separate section for discussion.

Response: we would like to point out that the recent problems of the tetravalent vaccine where the problem lies in the interaction between the four serotypes cannot be extrapolated to a single serotype vaccine as for Zika or yellow fever. Nevertheless, we have expanded the text to address this issue.

More is now known of biology and impact of infection in pregnant women (CZS) and populations (GBS). A numerical impact ballpark that would drive vaccine development strongly or not might be stated. Any adverse effects of live virus vaccines might then be put in context of levels of sexual transmission and levels of CZS in future epidemics.

Response: good suggestion and we have added this to the manuscript. Kindly note that no ballpark number has been identified by WHO that would drive vaccine development or introduction.

Should the discussion of the possible vaccine platforms be re-ordered in order of likelihood of success? Seems unusual to lead with nucleic acid vaccines, a platform that has yet to see success for any infectious disease.

Response: The rationale for starting with the nucleic acid vaccines was that they are furthest ahead in development. We have added this information.
The non-vaccine therapeutics and prophylaxis seem the least promising, do they need so much coverage or do they belong in another paper?

Response: As this reviewer points out, there have been various reviews on Zika vaccine development already. The novelty of this manuscript is the fact that we are addressing both therapeutics and preventive measures and their commonalities in terms of feasibility issues for clinical trial designs at a time when the global case numbers are declining. The role of therapeutics may take on more relevance in case the low incidence does not warrant widespread use of vaccines. We need additional interventions to mitigate congenital Zika syndrome. We are now facing a serious challenge that we may never be able to license any intervention (be it vaccines or therapeutics) before the next outbreak happens. Therefore the discussion on immune correlates is very important.

There is too little discussion on sample size of necessary clinical trials, period of follow-up (given the antibody-dependent enhancement issues with flaviviruses), need for multiple trials in multiple regions, and cost.

Response: we have expanded the manuscript to address these issues.

Fatigue by industry for development of vaccines for newly emerging viruses has been evident recently and needs discussion.

Response: good suggestion and we have added a section on donor and industry fatigue.