Author’s response to reviews

Title: The global threat of Zika virus to pregnancy: epidemiology, clinical perspectives, mechanisms, and impact

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Response to Reviewers’ reports

REVIEWER #1

Major comments:

1) There is no mention of animal models of disease. There have been several recent major advances in this field, and a section in the review covering this would be useful.

   RESPONSE: We have updated the section on animal models (lines 143-152) and included more details on how they support a causal link between ZIKV infection and microcephaly.

2) There is only a single sentence reporting the association of ZIKV and Guillain-Barre syndrome, which is not referenced. Although dedication of an entire section to ZIKV and GBS may be excessive for this report, certainly more than 1 sentence is merited to relay
the current clinical and epidemiologic evidence surrounding this high morbidity condition.

RESPONSE: We have expanded this section (lines 89-95) to describe Guillain-Barré syndrome and its link with ZIKV infection. However, as noted, the focus of the review is on microcephaly and other fetal complications and abnormalities.

3) References are not included for the potential for ZIKV transmission by oral and anal sex, nor is there mention of asymptomatic sexual transmission. All should be added to the "Zika virus identification and epidemiology" section of the manuscript.

RESPONSE: These references have now been added (lines 51 and 52).

4) Lines 73-74: the authors incorrectly define primary and secondary microcephaly as intrauterine and post-natal development of microcephaly, respectively. Primary microcephaly is the result of genetic or maternal medical history leading to abnormal brain development. Secondary microcephaly is the result of infection or vascular disruption resulting in the arrest or destruction of normally forming brain. The authors should make this correction and reference the relevant texts or reviews of microcephaly.

RESPONSE: We agree that there was error in the text. This has now been corrected (lines 66 to 70).

5) Lines 96-98: Although the authors refer to the currently 'front-running' theory regarding risk of ZIKV infection being most likely to result in microcephaly or other birth defects if infection occurs during the first trimester, there is data from Rio de Janeiro (Brasil et al., NEJM, 2016) demonstrating that severe birth defects occur if ZIKV infection occurs at any point during pregnancy. To present a balanced and complete perspective on the risks of ZIKV infection during pregnancy, this manuscript and its findings should be mentioned in this section.

RESPONSE: We have now included this reference and noted that central nervous system abnormalities have been reported for fetuses infected as late as 27 weeks of gestation (lines 136 and 137).
6) Lines 240-242: the authors make no mention of non-infectious causes of microcephaly or conditions associated with it (e.g., genetic predisposition, alcoholism, unmanaged diabetes, history of pregnancy losses). As the differential diagnosis for causes of microcephaly can be broad, a sentence describing these additional causes is needed.

RESPONSE: We have now added a sentence acknowledging these additional causes (lines 309 to 311).

Minor issues:

1) Though generally well-written, there are a handful of editorial aspects that merit revision. Careful proofreading should be sufficient to identify and correct such typographical, grammatical, or structural errors.

RESPONSE: We have proofread the manuscript for any errors.

2) The authors frequently refer to "Zika" as either an illness or a pathogen throughout the manuscript. Both are incorrect. 'Zika virus' is the transmissible agent responsible for infection and (in some cases) disease. 'Zika virus disease' (e.g., rash, fever, body pain) is the illness that results from infection with Zika virus. The authors should be careful to appropriately refer to both the pathogen and the disease throughout the manuscript.

RESPONSE: We have now standardized the terminology we use in the manuscript and checked the use of “ZIKV” and “Zika” throughout the manuscript for relevance.

3) Lines 282-284: the two halves of this sentence are both accurate. However, the authors attempt to extend findings from ZIKV infection in skin cells to observations seen in placental cells. These are two entirely different cell types, and findings from one may not be able to be extended to the other. The authors should soften this statement.

RESPONSE: We have now modified this part of the manuscript to clarify for readers that this statement referred to skin fibroblasts.
1) Data or figures are linked to the time, and this is not indicated there.

RESPONSE: Data and figures are correct at the time of submission, which will be indicated in the accepted manuscript.

2) 4 million cases in 2016? up to? source?

RESPONSE: As stated in lines 163 and 164, the Lancet publication dated 6th of Feb 2016 that we cite reported that WHO estimates up to 4 million cases of Zika infection (including asymptomatic cases) will occur in the Americas in 2016.

3) The Shepard's Criteria and the Bradford-Hill criteria have been clearly addressed in the recent NEJM report of the CDC about it.

RESPONSE: We agree with the reviewer and had cited this report in our manuscript (ref 24).

4) "Therefore there is a strong justification for testing for asymptomatic at-risk pregnant women." This comment is not clear enough, not supported and not discussed as should be according to its potential importance.

RESPONSE: We further detailed what was meant by “at-risk pregnant women”. Our comment was referring to CDC guidelines (MMWR Morb Mortal Wkly Rep. 2016 Apr 1;65(12):315-22). This has been made clearer in lines 266 to 272.

5) "Potential mechanisms linking ZIKV and microcephaly" section is very limited, and being the center of this review lacks of many aspects and relevant references that should be included.

RESPONSE: We are not aware of major works that should be included in this review that we have not already cited. However, we have now included mention of findings from recently published animal models and preclinical vaccine trials. We note that our review
is not primarily focused on the mechanisms linking ZIKV infection and microcephaly; instead we have aimed to give a broader picture of the epidemiology, clinical aspects, mechanisms and impact of ZIKV in pregnancy. We therefore tried to balance all the sections equally.

6) If extended, from that section, a figure explaining the reported mechanisms should be included.

RESPONSE: We have now included a new figure to address this point (Figure 2).

7) Conclusion repeats most of the paper but not really indicated where are we going now with the research on this topic.

RESPONSE: Throughout the review, we do reflect on key issues and priorities in different sections. We have avoided repetition of these points in the concluding paragraph. We have drawn a broader conclusion that “a strong and rapid global public health and research response to the virus is essential to limit and prevent the major health, social, and economic impact of the virus, and to advance the development of therapeutics, vaccines, and improved diagnostics.”