Reviewer’s report

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

Version: 0 Date: 11 Jun 2016

Reviewer: Tyler Sharp

Reviewer's report:

This is a comprehensive review of Zika with a focus on risks to pregnant women. The review is generally complete, although due to the rapidly evolving nature of the field there are several recent advances that were not included in the manuscript.

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.

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.

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.

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.

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.

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.

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.

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.

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.

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below.
If your reply is yes to any, please give details below.

None.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal