Author’s response to reviews

Title: Knowledge and attitude towards pregnancy-related issues of Zika virus infection among general practitioners in Indonesia

Authors:

Harapan Harapan (harapan@unsyiah.ac.id)
Yogambigai Rajamoorthy (yogambigai@utar.edu.my)
Prattama Utomo (prattamasantoso@gmail.com)
Samsul Anwar (s4m_seupeng@yahoo.co.id)
Abdul Setiawan (drmaliq@gmail.com)
Alma Alleta (alma@unsyiah.ac.id)
Alfredo Bambang (alfredoibc2012@gmail.com)
Muhammad Ramadana (rizki.mpawill@gmail.com)
Ikram Ikram (ikramkeren@yahoo.co.id)
Nur Wahyuniati (nur.wahyuniati@unsyiah.ac.id)
Reza Maulana (rezamaulana@unsyiah.ac.id)
Ichsan Ichsan (ichsanmd_aceh@unsyiah.ac.id)
Rosaria Indah (rosariaindah1974@gmail.com)
Abram Wagner (awag@umich.edu)
Ulrich Kuch (kuch@med.uni-frankfurt.de)
Alfonso Rodríguez-Morales (ajrodriguezmmmd@gmail.com)
David Groneberg (arbozmed@uni-frankfurt.de)
Mohd Andalas (andalas@unsyiah.ac.id)
Ruth Müller (ruth.mueller@med.uni-frankfurt.de)
Mudatsir Mudatsir (mudatsir@unsyiah.ac.id)
Robin L. Cassady-Cain, PhD
BMC Infectious Diseases

Re: Your submission to BMC Infectious Diseases - INFD-D-18-01045

Thank you very much for your email from 13 January 2019 and for the comments on our manuscript. We have carefully revised the manuscript in response to the extensive and insightful comments we received from the reviewers.

In particular, the reviewers provided constructive comments and some corrections. In the revised version of manuscript, all the suggested corrections are made and explanations related to reviewer concerns are provided. Appended below is the list of all reviewers’ comments along with our responses to each point.
We have revised our Tables (added the abbreviation list under the tables and marked the P-values that are significant).

We also added new affiliation for Dr. Ruth Muller because she is currently working in the two affiliations.

We hope that this revised version will be suitable for publication in BMC Infectious Diseases.

Sincerely yours,

Corresponding authors

Harapan Harapan, MD
Mudatsir Mudatsir, PhD

RESPONSES TO REVIEWERS

Reviewer 1

Moritz Kraemer (Reviewer 1): This work presents an assessment of the attitudes and knowledge towards pregnancy related issues of Zika virus among general practitioners using online surveys. This study was well conducted and an important contribution to the growing field of qualitative epidemiology. I am not familiar with surveys so cannot speak to the validity or reliability of that part of the study.

Authors’ Responses:

Thank you for your insightful comments.

Major comment: Despite the importance of knowledge and attitudes towards Zika related infections and potential congenital syndromes the epidemiological importance of such information should be stated more clearly. Similarly, a question that is obvious is whether
Indonesia has had Zika virus outbreaks or current reports of infections? This would provide more context to the importance of such a study.

Authors’ Responses:

Thank you for your suggestions. We have added information into the introduction based on the reviewer’s comments about: a). The importance and epidemiology of microcephaly-associated ZIKV and b). The Epidemiology of Zika in Indonesia. We also added about the global risk fork ZIKV infection.

Revised manuscript: P6, L13-60 – P7, L1-13

Since then, ZIKV has continued to spread and has been reported in 86 countries in the Americas, Africa, and southeast Asia [5]. Globally, it is predicted that over 2.17 billion people live in areas that are environmentally suitable for ZIKV transmission, and 1.42 billion of them live in Asia [6]. Asia is susceptible to epidemic ZIKV transmission because of widespread distribution of the mosquito vectors for ZIKV, the large amount of travel to and from Zika-affected areas, conducive conditions for ZIKV transmission, and limited health resources [7-10].

In Indonesia, although there has not been any Zika outbreak, there is evidence of ZIKV transmission in this country. Seroprevalence studies in Central Java and Lombok identified anti-ZIKV antibodies during 1978 and 1983 using haemagglutination inhibition test [11, 12], although these antibodies might be cross-reactive with Dengue virus. A recent study found that among 662 serum samples collected from children aged 1-4 years in 2014, 9.1% of them were ZIKV seropositive using a plaque reduction neutralization test [13]. Around the same time, two Australian travelers were reported to have acquired ZIKV infection after visiting Indonesia in 2013 and 2014 [14, 15]. In 2015, ZIKV was isolated for the first time in Indonesia, from an acute febrile patient in Jambi with no history of travelling abroad [16]. No other cases have been reported since. However, there is potential of underestimation of Zika cases in Indonesia [17]. Firstly, there is a potential of misclassification between Zika and Dengue due to similar clinical presentations and the lack of a widely available Zika diagnostic tests throughout Indonesia. In addition, currently Zika is reported based on case-based surveillance in which is often biased based on whether testing is done and which tests are used [18]. In fact, a recent modeling study ranked Indonesia as the third country most at risk for ZIKV exposure due to the monthly volume of airline travelers [8]. These evidence suggest Zika is potentially as a major health problem in Indonesia.

Revised manuscript: P7, L30-52
There is a strong association between congenital Zika virus infection and microcephaly; one study estimates the odds of microcephaly to be 73.1 times higher among those with ZIKV infection [22]. Multiple outbreaks of microcephaly-associated with Zika cases have been reported since reemerge [23-27]. In Brazil for example, during two Zika outbreaks in 2015 and 2016, more than 1.6 million cases were reported and during this period, 1950 cases of ZIKV infection-related microcephaly were confirmed [27]. This devastating complication was one factor that led the WHO to declare ZIKV infection as a Public Health Emergency of International Concern (PHEIC) and as an ongoing challenge in 2016 [28]. Microcephaly associated with ZIKV infection has been also reported in Asian countries [29-31].

Statistical analysis: From table 1 it appears that none of the predictors are statistically significant. That is interesting and should point towards new directions of education. What would help the reader is a map of collection sites (locations) and how they are distributed among urban and rural doctors. That could provide some indication where the gaps are highest and which GPs should be targeted. Including this information would make the study more interesting and potentially relevant for a wider audience (i.e., if there is spatial heterogeneity governments could target their programs better).

Authors’ Responses:

Thank you for your comments. This study was an online-based study. Unfortunately, we did not collect the exact location of the respondents making it not possible to create a map as recommended. We have included this as one of limitation of our study (See Discussion P19, L13-25). Nevertheless, during the study, we collected three measures as an indicator of place: (a) The province (Aceh province OR other provinces); (b) Location of workplace (District, Regency OR Province) and; (c) Type of workplace (Community health centre, Private clinic or hospital OR Government hospital) – See Table 1. District, Regency and Community health centre indicate a rural or sub-urban area while others (i.e. Province, Private clinic or hospital OR Government hospital) indicate an urban area. Therefore, using those measures as an indicator, we are able to show the distribution of GPs in urban vs rural areas. We have added more detail information about this in the Results Section (P13, L38-43). In addition we also analyzed our data based on type of workplace which is one of the most important heterogeneous variables related to medical setting.

Our study indicates that urbanicity (urban (province) vs rural or sub-urban (district and regency)) is also not associated with the knowledge and attitude domains. We have explained the possible reason for the homogeneity of knowledge and attitude related pregnancy-related Zika among GPs in this study and we have given a recommendation to the government on how to deal with these study findings (See Discussion P16, L2-50 and P18, L25-57). Our further recommendation
to include Zika material in Medical curricula in Indonesia have been published elsewhere (Harapan et al., CEGH, In press, https://doi.org/10.1016/j.cegh.2018.12.006).

Revised manuscript: P19, L12-25

Third, we did not collect the exact location of the respondents making it not possible to create a map showing spatial heterogeneity. However, our study is still able to show the distribution of the respondents between rural (district) and urban (regency) areas. In addition, we also analyzed respondents based on type of workplace, which is one of the most important heterogeneity analysis in medical setting because it reflects facility characteristics.

Revised manuscript: P13, L38-43

The majority (70.3%) of the GPs enrolled in this survey were working in a health centre located in the rural (district) or sub-urban (regency) areas, and about 30% of them were working in the urban areas (provincial level).

Reviewer 2

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

Authors’ Responses:

No response

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate
Authors’ Responses:
No response

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
Yes - experiments and analyses were performed appropriately
Authors’ Responses:
No response

Statistics - Is the use of statistics in the manuscript appropriate?
Yes - appropriate statistical analyses have been used in the study
Authors’ Responses:
No response

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
No - there are minor issues
Authors’ Responses:
All issues raised by Reviewer #2 have been addressed individually (see below for more details).

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Probably - with minor revisions
Authors’ Responses:
All issues raised by Reviewer #2 have been addressed individually (see below for more details).
INTRODUCTION

Though with over two pages, one may adjudge it as lengthy depending on the journal's preference. However, it could go for a reasonably written introduction.

Authors’ Responses:

There is no word limitation for BMC Infectious Diseases and therefore the length of our Introduction is acceptable by the journal rules and policies. In the revised version, we have added more information about the epidemiological importance of congenital syndromes and information of Zika in Indonesia as requested by Reviewer #1.

METHODS

a. They the authors mentioned that they assessed the validity and reliability of the study instrument (questionnaire) but did not mention the outcome of that assessment. What was the Cronbach's alpha of this questionnaire?

Authors’ Responses:

Thank you for your comments. We have provided the Cronbach's alpha score of questionnaire for both knowledge and attitude domain. We include this information after we discuss the pilot study (and not in the Results section) because we want to give a clear idea of our methods to readers within the methods section, and these results are not part of the full study mentioned in the results.

Revised manuscript: P10, L10-15
The Cronbach's alpha score was 0.78 and 0.70 for knowledge and attitude domain, respectively, indicating good internal consistency of the items in the scale.

RESULTS

a. Page 11, line 45-50: If 850 responses were received and 311 responses were excluded what is then the response rate? Does subtracting 311 from 850 give 457 or 539? Please clarify the number of responses that were analyzed.

Authors’ Responses:

Author would like to thank Reviewer #2 for raising this issue. There was a typo on the number of responses. The correct number is 393 not 311. We confirm that there were 457 respondents included in the final analysis. We have revised the manuscript accordingly.

Revised manuscript: P12, L13-18

Among these, 393 responses had to be excluded due to incomplete information, leaving a total of 457 (53.7%) participants with complete responses.

b. Page 12, line 44-54: the authors appeared to be discussing the result, (a finding that 73.9% of respondents mentioned that ZIKV could be passed through breast milk). This should be done under the Discussion section.

Authors’ Responses:

Thank you for your suggestion. We have moved that part to Discussion.

Revised manuscript: P15, L52-59 - P16, L1-3

For example, 73.9% of respondents mentioned that ZIKV could be passed through breastfeeding. In fact, there are no reports to suggest that a ventricular septal defect was associated with ZIKV infection, and the U.S. CDC stated that there are no reports of infants getting ZIKV through breastfeeding, and mothers are encouraged to breastfeed even in areas with risk of Zika [67].
CONCLUSION

With the statement "This study reveals that knowledge about pregnancy-related problems with ZIKV infection is poor and homogenous among GPs across the most populous regions of Indonesia." there appear to be a contradiction here if the authors had mentioned in the results (page 12, line 26) that 60.5% of respondents had good knowledge of ZIKV infection. This section may need to be improved upon to reflect what is in the results.

Authors’ Responses:

Thank you for your correction. This was a misstatement in the original manuscript and we have revised the sentence.

Revised manuscript: P19, L45-50

This study reveals that the knowledge about pregnancy-related problems with ZIKV infection is relatively high and homogenous among GPs across the most populous regions of Indonesia.

REQUESTED REVISIONS:

ADDITIONAL REQUESTS/SUGGESTIONS:

None

Authors’ Responses:

No response

------------------------

Journal Requirements:

------------------------

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and
our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

Author Responses:

None of the reviewers asked for English corrections (and we had a native English language review revisions to the manuscript). All of the errors and typos that have been pointed by reviewers have already been revised.

--------------------

Editorial Policies

--------------------

Please read the following information and revise your manuscript as necessary. If your manuscript does not adhere to our editorial requirements, this may cause a delay while this is addressed. Failure to adhere to our policies may result in rejection of your manuscript.

In accordance with BioMed Central editorial policies and formatting guidelines, all manuscript submissions to BMC Infectious Diseases must contain a Declarations section which includes the mandatory sub-sections listed below. Please refer to the journal's Submission Guidelines web page for information regarding the criteria for each sub-section (https://bmcinfectdis.biomedcentral.com/).

Where a mandatory Declarations section is not relevant to your study design or article type, please write "Not applicable" in these sections.

For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must confirm this under this sub-heading and also provide their reasons. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page (see links below).

Declarations

- Ethics approval and consent to participate
- Consent to publish

- Availability of data and materials

- Competing interests

- Funding

- Authors' Contributions

- Acknowledgements

Author Responses:

We had included all items of the Declarations Section in our previous manuscript and therefore no revision is required.

End