Author’s response to reviews

Title: Seroprevalence and associated factors of HSV-2 infection among general population in Shandong Province, China

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Dear Prof. Jason Ong,

Thank you very much for you to give us an opportunity to revise our manuscript. We have addressed all the comments raised by reviewers. All revisions in the manuscript are highlighted in yellow. Please find our point-to-point reply to the comments below.

Please feel free to contact us if you have any question about the revision and we are looking forward to your good news.

Best wishes,

Very Respectfully,

Pengcheng Huai
Manuscript reference number: INFD-D-18-02304

Title: Seroprevalence and risk factors of HSV-2 infection among general population in Shandong Province, China: a cross-sectional study

Authors: Pengcheng Huai; Furong Li; Zhen Li; Lele Sun; Xi’an Fu; Qing Pan; Gongqi Yu; Zemin Chai; Tongsheng Chu; Zihao Mi; Fangfang Bao; Honglei Wang; Bingni Zhou; Chuan Wang; Yonghu Sun; Guiye Niu; Yuan Zhang; Fanghui Fu; Xiaqiao Lang; Xiaoling Wang; Hui Zhao; Daina Liu; Hong Liu; Dianchang Liu; Jian Liu; Aiqiang Xu; Furen Zhang

Submitted Journal: BMC Infectious Diseases

Editor Comments:

BMC Infectious Diseases operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Response: Thank you very much for your suggestions.

Reviewer reports:

Sileshi Garoma Abeya, Ph.D (Reviewer 1): Reviewers comment

I would like to thank the editorial office for inviting me to review this manuscript. In general the manuscript is good and considered an important and subject area. My comments are indicated below.
1. Title

*The risk factor should be changed to associated factor

*Better to delete a cross-sectional study

Response: Thank you very much for your comments. “Risk facors” has been changed to “associated factors”. “A cross-sentional study” has been deleted from the title.

2. Abstract

*Have a separate sub-section for objective

Response: Thank you for your comment. Objective has been separated as a sub-section.

*Need editorial corrections, e.g. the way P value are written should be corrected according to the standards

Response: Thank you for your comment. The format of P value has been changed to captal italic letter according to the standards.

*Indicate whether it is adjusted or crude OR

Response: Thank you for your comment. We have added adjusted before OR.

*Conclusions: Better to include the prevalence in addition to the associated factors

Response: Thank you very much for your comment. “This study showed a relatively low burden of HSV-2 in Shandong province, China compared with the seroprevalence reported in many other provinces and countries.” We have added this sentence in the text.
3. Background

*Page 5- Line 6- editorial correction (be transmitted)
Response: Thank you for your comment. We have corrected the error.

*Page 6- line 5-8- Should be shifted to methods section
Response: Thank you for your comment. Line 5-8 has been shifted to methods section.

4. Methods

*Page 6- Line 1- Indicate the type of study design
Response: Thank you for your comment. We have added the type of study design at the beginning of this paragraph.

*Page 6- Line 16- 17- better to make clear between probability proportionate to size sampling (PPS) method and proportional allocation to sample size-these have different interpretations
Response: Thank you for your comment. “PPS sampling method is often used in multi-stage complex sampling and the probability of selection for a unit is directly proportional to its size. While in proportional allocation, the probability of selection for a unit is the same for all strata.” We have added these in the manuscript.

*Page 7- Line 1- Better to include exclusion
Response: Thank you very much for your comment. We have included exclusion criteria in the text.
*Page 7- Line 2- "willingness to provide blood" should be in an ethical consideration section
Response: Thank you for your comment. "Willingness to provide blood" has been shifted to ethical consideration section.

*Page 7- Line 17-20- Should be in the operational definition section
Response: Thank you very much for your comment. These contents have been separated in the operational definition section, which following the procedures section.

*Page 8- Line 10- "Beijing Modern Gold Biotech Co., Ltd., Beijing, China"- not important to mention the details
Response: Thank you for your comment. We have deleted the details.

*Page 9- line 2- "0.10 in bivariate analysis" Need to have references
Response: Thank you for your comment. We have added the reference.

5. Results

*Page 10- line 13-17- add Adjusted (AOR)
Response: Thank you for your comment. We have added AOR in the text.
6. Discussion

*Page 11- line 1- "This is the first study with a large sample size"- This should be confined to your level of knowledge.

Response: Thank you for your comment. We have added “to our knowledge” at the beginning of this sentence.

*Page 13- Line 22- As one of the limitation "the results of this study might not be extrapolated to all other provinces in China"- Why as they have similar socio-demographic characteristics?

Response: Thank you for your comment. The results of this study might not be extrapolated to other provinces with different socio-demographic characteristics in China. We have deleted this limitation to avoid dispute.

7. Conclusions

*Page 14- Line 1- "This study showed a relatively low burden of HSV-2 in Shandong province"- Better to indicate the number

Response: Thank you for your comment. We have added the seroprevalence of HSV-2 in this sentence.

8. Abbreviations

*Page 15- Line 1- All are acronyms

Response: Thank you for your comment. The word “abbreviations” was replaced by “acronyms”.
9. Ethics approval and consent to participate

*Page 15- Line 10-11- "The topic of the questionnaires related to sex" - Incomplete sentence
Response: Thank you for your comment. We have corrected the error and added “was” before “related” in this sentence.

10. Tables and Figures

*Page 21- Line 1-6- The title of tables and figure should be written complete sentences. Just add study period
Response: Thank you for your comment. We have added the study period in the title of tables and figure.

*Page 23- 24- Table 2 and 3- a need to have 95% CI for the crude and adjusted OR
Response: Thank you for your comment. We have added 95% CI for the crude and adjusted OR respectively.

Christine Johnston (Reviewer 2): This well-written manuscript describes a cross-sectional seroepidemiology study of HSV-2 infection in Shandong Province, China using a multi-stage complex sampling method. The authors used a type-specific HSV-2 ELISA test to determine seroprevalence, and determined risk factors for HSV-2 seroprevalence. They found quite a low seroprevalence (3.4%) overall, but similar to global epi trends, they found that HSV-2 seroprevalence is higher in women and increases with age.

The major critique of the paper is with the choice of serologic assay and choice of cut-off. The test characteristics of the ELISA test utilized are not described (no reference given regarding the test characteristics of this assay), but it is assumed to be type-specific (authors, please confirm). Other ELISA tests have shown a high rate of false positive tests at low index value (<3.0-3.5), such that the USA 2015 CDC STD Treatment Guidelines recommends that low positive test results (<3.5) with such ELISA tests be tested with a second, confirmatory method. The authors
should address this issue with false positive tests, perhaps even performing a sensitivity analysis of their results with a higher cut-off value.

Response: Thank you so much for your comments. According to the manufacturer instructions, the sensitivity, specificity, false positive rate and false negative rate of the type-specific HSV-2 IgG ELISA test were 97.3%, 98.1%, 1.9% and 2.7% respectively. We have added these characteristics in the text. We have not performed a second, confirmatory test due to low false positive rate.

Cut-off value was 0.15 for this test, which were different from many other ELISA tests. Result was valid only when optical density (OD) value of cut-off control ≥ 0.15, OD value of positive control ≥ 1.00, and OD value of negative control ≤ 0.05 for each test. OD value of sample more than that of cut-off control was deemed positive.

Other minor issues are noted below:

1. Introduction: Third paragraph. Note that it is typically not recommended to serologically screen pregnant women for HSV-2 infection. For instance, the American College of Obstetrics and Gynecology recommends against screening asymptomatic pregnant women for HSV-2. It will be difficult to determine a control program for HSV-2.

Response: Thank you very much for your comments. We have just learned that serologic screening for genital herpes was associated with psychosocial harms among pregnant women. Thus, we have deleted the recommendation of serologic screening pregnant women for HSV-2 infection.

2. A couple of typos/misspellings on Paragraph #2 of Procedures section of methods. See "smoked" and "commercial"

Response: Thank you for your comment. We have corrected the error.
3. Discussion, paragraph 2: This seems to make a lot of assumptions about sexual behavior of migrants without many publications to back up the assertions. Please look at wording and soften or provide further references.

Response: Thank you very much for your comments. We have soften the wording.

4. Discussion, paragraph 3: The statistics from the USA are quite out of date and much higher than current estimates. Please include more up-to-date statistics.

Response: Thank you very much for your comments. We have added more up-to-date statistics in the text. According to a paper published in 2018 (PMID: 29442994), prevalence of HSV-2 infection was 12.1% (95% CI, 9.7-15.0) among adults 14–49 years of age in the USA in 2015-2016.

5. Discussion: Divorced or widowed women-Again, this seems to make a lot of assumptions about practices without a lot of references to back up the claims. Either provide more references or soften the wording.

Response: Thank you very much for your comments. We have soften the wording.

6. Discussion, limitations: Please discuss small sample size of some of groups with large CIs, ie 18-24 year old group is very small, which adds some uncertainty to the estimates.

Response: Thank you very much for your comment. We have added these as a limitation in the Discussion Section.

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.
Response: Thank you very much for your suggestions. The language of our manuscript was revised by International Science Editing.

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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

Response: Thank you very much for your comments. This manuscript adheres to all the above editorial policies and requirements.