Author's response to reviews

Title: Prevalence of HIV, Herpes Simplex Virus-2, and Syphilis in Male Sex Partners of Pregnant Women in Peru

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Author's response to reviews: see over
To the Editor,

Thank you for the opportunity to present our revised manuscript, “Prevalence of HIV, HSV-2, and Syphilis in Male Sex Partners of Pregnant Women in Peru” (Manuscript # 2811671171617362) for continued consideration for publication in *BMC Public Health*. We have incorporated the reviewer’s recommendations for modifications and include a point-by-point response to their comments below.

Thank you for your consideration. We look forward to your reply.

Sincerely,

Jesse Clark
Reviewer's report 1

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The methods section should describe in more detail how the men were approached. Doing a study on male partners of pregnant women may be difficult because men may be difficult to approach and may be reluctant to participate in such study.

Response: Men accompanying pregnant women at one of the specified recruitment sites were invited by the attending obstetrician to participate in the study. To supplement the information on participant identification and recruitment present in the Methods section of the manuscript we have added the following statement: “Potential participants were informed of the study by the obstetrician caring for the man’s pregnant partner.”

2. The methods section should also be explicit on how the research team dealt with men who were found to have syphilis (were they treated?) and men who were found to be HIV infected (were they informed about their HIV status? did they have access to ART?).

Response: The following information has been added to the Methods section: “Participants were instructed to return to the study site 10 days after sample collection for post-test counseling and provision of test results. Men with serologic evidence of syphilis infection were treated according to Peruvian Ministry of Health guidelines with 2.4 million units penzathine Penicillin G intramuscularly once and then monitored for response to treatment by repeated serologic testing at 3, 6, and 9 months. Those participants diagnosed with HIV infection were referred to local facilities designated by the Ministry of Health for ongoing management of HIV infection, including antiretroviral therapy for appropriate candidates. Participants diagnosed with HSV-2 infection by serology received no antiviral therapy unless they reported evidence of an active herpes outbreak, in which case they were provided with Acyclovir 200 mg orally 5 times daily for a period of 10 days. All participants diagnosed with an STI were advised of the importance of partner notification.”

3. Again in the methods section, please provide more details on the testing for HIV. What was done in case of discordant results? What was done if the WB was inconclusive?

Response: The description of HIV testing methods has been modified to read as follows: “Two HIV ELISAs were used for screening (Vironostika, bioMérieux; Marcy l’Étoile, France; Genetic Systems, Biorad; Hercules, CA, USA) and samples positive by one or both ELISA-positive samples were confirmed by Western Blot (Genetic Systems, Biorad; Hercules, CA, USA). Inconclusive results on the Western Blot assay were interpreted as negative.”

4. I am not clear about the enrollment (first paragraph of the results section). How many pregnant women were "index" women? For how many pregnant
women was there no male partner? How any male partners were approached and how many consented to be in the study?

Response: We agree with the reviewer's wish for more information. However, specific data on the number of pregnant women treated during the study period, the exact number of men approached for participation, and the exact refusal rate of men approached for participation was not recorded.

5. Third paragraph of the results section: please give the numbers of HIV infections (x number out of y number tested). Do the same for syphilis and HSV-2.

Response: The absolute number of infections in the population tested (n/N) has been included in the manuscript as requested.

6. Fourth paragraph of the results section, second sentence. How did the 5.9% of pregnant women whose partner denied intercourse in the month before conception, become pregnant? Did they have an extramarital partner?

Response: As a condition of study enrollment, all participants reported sexual contact with the pregnant woman during the past year. 5.9% of participants denied unprotected intercourse in the month prior to conception. The language of the manuscript has been modified to clarify this point.

7. Please provide more details on condom use.

Response: We agree with the reviewer's wish for more detailed information on condom use by study participants such as frequency of use with their pregnant partner and with any additional sex partners. However, beyond information concerning any unprotected intercourse with their pregnant partner prior to conception, and any unprotected intercourse with female sex workers and/or with other men in the preceding 12 months, no additional data on condom use was recorded.

8. In the tables please provide all the data not only the OR. I would like to see prevalence of syphilis by age categories, by categories of numbers of partners etc.

Response: The requested information has been provided as Table 2.

9. I suggest not to include in the multivariate analysis "genital ulcers" and history of STD as these are likely consequences of HSV-2 and not risk factors as such.

Response: We agree and have revised the multivariate analysis to remove these variables.

10. The discussion section focuses on recent high risk behaviour of men. But men could have been infected with HIV or syphilis or HSV-2 years before the study and still pose a risk for their female partner. I am afraid I do not agree that
the past risk behaviour of the men is played down so much.

Response: We agree with the Reviewer's concerns. Due to the complexity of discussing recent vs. past behavior and behavioral vs. biological risk factors for HIV and STI acquisition and transmission to current sex partners, particularly with the limited data available, we have removed the paragraph in the discussion that addresses this point.

Reviewer's report 2
General
The title suggests epidemiological results rather than the actual question posed by the paper, i.e. could the male sex partners of pregnant women serve as a bridge between core risk groups (female sex workers and men who have sex with men) and the general population for HIV transmission?

Response: We agree with the Reviewer's concerns about drawing conclusions about the possibility of epidemiologic “bridging” with the available data. Although the issue is an important question to be addressed, and though our data do not provide evidence supporting the definition of male partners of pregnant women in Peru as a “bridging” population, we agree that no definitive conclusions can be reached from the existing data. Accordingly, we have revised the manuscript to remove any emphasis on the issue of bridging and have focused more closely on the epidemiology of HIV/STIs and associated risk behaviors in this population. We have also added the following passage to the discussion section to address the issues of using male sex partners of pregnant women as a surveillance population: "Further, modifications in sexual practices that often occur as a result of a woman’s pregnancy may also have substantially altered the risk behavior of one or both members of the partnership during the year preceding evaluation, significantly influencing the recent risk behaviors assessed in our study. As public health authorities consider the appropriateness of monitoring seroprevalence among pregnant women as a marker for disease prevalence in the general population, it may also be important to take steps to define an appropriate, corresponding male population for epidemiologic surveillance."

Enrolment of 1,835 male sex partners of pregnant women in approximately 5
weeks shows a good acceptance of the survey. I do share, however, the authors’ concern about the limitations in having the questionnaires administered by the female partner’s obstetrician instead of by skilled interviewers. This methodological error may have led to underdeclaration of outside partners during the previous 12 months as it is to be feared that future fathers, who are expected to behave in a responsible way, may have adjusted their answers accordingly.

Response: We agree with the Reviewer’s concerns, and address this limitation in the Discussion section.

I would recommend that the authors concentrate on the epidemiological results, as the investigation methodology does not allow them to conclude that the risk of a bridge between core risk groups and the general population for HIV transmission is low.

Response: We agree with the Reviewer’s criticism and have revised the manuscript as described above.

Discretionary Revisions (which the author can choose to ignore)
The fact that 37.1% of male partners declaring sex with female sex workers and 11% with other men in lifetime drop down to 8.9% and 1.7% respectively during the 12 months prior to interview could mean that these types of sex are part of youth’s experiences that exit with age. Although the low rate of outside unprotected sex is very encouraging, the sanitary risks should not be minimized, all the more so as the HSV-2 prevalence, long known to be a risk factor for HIV transmission, is high among the male sex partners.

Response: We agree and have removed the paragraph minimizing the impact of past risk behavior on current risk for STI transmission, as described above.

It would be worthwhile to investigate the possible consequences of sexual behavior of bisexual men and of men who have sex with female sex workers on the spreading of STIs and HIV in the Peruvian population.

Response: We agree with the Reviewer and note that our group has previously addressed the issue of male clients of female sex workers as a possible “bridging” population (Miller et al., “Clients of female sex workers in Lima, Peru: a bridge population for sexually transmitted disease/HIV transmission?” STD 31: 337-342; 2004). In addition, our group is actively investigating the issue of bisexual behavior among men as a risk factor for dissemination of the HIV epidemic to the general population (cf. Konda et al., “High rates of sex with men among high-risk, heterosexually-identified men in low-income, coastal Peru,” AIDS and Behavior, In Press).

Reviewer’s report 3

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. In the abstract it is reported that this study is based on 1835 male partners of
the pregnant women. Yet when you look at table 1, the total number of participants is less than 1835 and it is not explained. E.g. Education (N=1795), City (N=1796), Employment (N=1797), Relation with pregnant women (N=1783). All the calculations of prevalence of sexual behaviour characteristics, report of GUD, drug use etc were based on N=1795 and not on the reported N=1835. Can the authors explain the discrepancy?

Response: A total of 1835 participants were enrolled, but a small number of participants did not respond to all of the survey questions, and were not included in the analyses of these questions, or in the multivariate analyses that included any of these questions. The following footnote has been added to Table 1 to explain this discrepancy: “* Complete survey response data not available for some participants.”

2. Can the authors give both the number (N) and percentages of the STIs in the result section, paragraph 3

Response: The requested data has been provided.

3. Pg 7, line 22 and Table 1. The mean number of life time partners is reported as 9.9 with a SD of 35.1. For number of yrs with the pregnant woman, Mean 3.9 and SD 4.6. It portrays a pregnant woman with a negative number of lifetime partners!!! It will be better if the authors use the median and the range to describe the population, rather than the mean.

Response: We agree and have modified the presentation of the data as requested.

4. Pg 7, last paragraph. The 31 participants reporting sexual contact……51.6% said they had unprotected intercourse with men. But in previous sentence it is reported that 0.9% described unprotected sex with men during that time. Can you clarify what does 0.9% refers to, is lifetime or last year unprotected sex.

Response: Of the 31 men who reported sexual contact with another man in the past year, 51.6% reported unprotected intercourse during these contacts. However, within the entire sample of 1835 participants, only 0.9% reported unprotected sex with another man within the past year. The language of the manuscript has been modified to clarify these statements.

5. Pg 10, paragraph 1. A further complication is the fact that only 30%.......That sentence is not very clear. Did the authors meant that some of the subjects were recruited at a subsequent visits to the hospital, and not as described in the methodology or?? Can it be re-written in a clearer way.

Response: As stated in the Methods section, the majority of participants (70%) were recruited and enrolled at the time of the hospital visit. However, 30% of participants were recruited during prenatal home visits and had to present to the hospital study site for enrollment. The additional burden that had to be surpassed by participants recruited during home visits may have led to bias in the sample population. To clarify this fact, the section cited has been rephrased.
as follows: “A further complication is the fact that the majority of study participants (70%) were enrolled at hospital recruitment sites, with only 30% enrolled during prenatal home visits. This discrepancy in recruitment is probably due to the fact that participants recruited during home visits were obligated to attend an additional enrollment visit at the hospital study site in order to participate.”

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. In table 2, HSV-2 column, regarding sexual active years. The unadjusted and adjusted OR and confidence intervals are exactly the same, was there a typo error?

Response: There was not a typo in presentation of these results. The similarity in results reflects the small variation in reporting the number of sexually active years.

2. Can the authors define in the methods section what do they mean by “recent contact” in terms of time.

Response: The following statement has been added to the Methods section: “For the purposes of data collection, “recent” sexual contact was defined as sexual contact within the preceding 12 months.”

3. Pg. 7, last paragraph. The subjects recent contact with MSM is given at 1.7% in line 27 and appears to be given at 1.0% in line 30. If this is a typographical error, please correct.

Response: We thank the reviewer for noticing this typo. The prevalence of recent contact was 1.7% and has been corrected.

Discretionary Revisions (which the author can choose to ignore)
1. Pg 3, line 16. I suggest; Among……., 26.7% of their HIV infected male partners…..

Response: We agree and have made the recommend modification.

2. Pg 5, line 5. You said the study was conducted in the 3 cities with higher HIV prevalence than in other places/general population. Can you add what is the prevalence of HIV in the general Peru population vs. range of HIV prevalence in the 3 cities so that the reader can get understand a bit about the local situation in Peru.

Response: We agree and have revised and amended the manuscript as follows: “The study was performed in the coastal cities of Lima, Ica, Trujillo, and Chiclayo, capital cities of provinces reporting some of the highest numbers of HIV infections in Peru [3]. Of the 16,888 cases of HIV infection diagnosed in Peru between 1983 and 2004, 73.1% were reported in the provinces of Lima/Callao, 3.1% in Ica, 2.3% in La Libertad (Trujillo), and 1.59% in Lambayeque (Chiclayo). Other individual
provinces contributed between 0.2% and 2.6% of the total number of diagnosed HIV infections in Peru [15].”

3. Can you add a sentence describing when and where the test results and counselling were given, and how you dealt with HSV-2 positive cases?

Response: The following information has been added to the Methods section: “Participants were instructed to return to the study site 10 days after sample collection for post-test counseling and provision of test results.”

4. Pg 9, par 3. Your meaning will be clear to readers dealing with these issues but would be more clear if you perhaps reversed the first 2 sentences in order. You want the readers understanding to be “to the extent that HSV-2 and other genital ulcerative diseases increase risk of HIV infection” the prevalence of HSV-2 in this …………..

Response: We appreciate the Reviewer’s suggestion and have revised the syntax accordingly.

5. Pg 9, par 4, line 6. Typo error, …..only 1.7% and 8.8% . Change to 8.9% to match previous percentages.

Response: We thank the Reviewer for noticing the typo. The line cited has been removed from the manuscript.

6. Pg 10, line 12. Typo; amongpregnant, two words.

Response: We thank the Reviewer for noticing the error.

7. There is a need to check the way the journals have been quoted e.g. Aids instead of AIDS in ref no 8, 10 etc.

Response: We have attempted to correct misprints in the journal citations, but are unable to alter modifications introduced by the EndNote bibliographic system (e.g., Aids instead of AIDS).

8. Pg 2 (abstract) and pg. 9, 1st & 4th paragraphs. The idea that a majority of the subjects were at less risk because although they had a history of contact with MSM & FSW, they had not had contact within the past year (recent?), needs further attention or presentation in another manner. Although infectiousness varies at different stages of the an STD, we are never-the-less dealing with 2 lifetime diseases (HIV and HSV-2) and a third that responds to treatment (syphilis). In this context, “recent” and “risk” may not relate as clearly as implied ???.

Response: We agree and have removed the discussion of past risk behavior and current risk for infectious transmission, as discussed above.