Reviewer's report

Title: Seroprevalence and risk factors of herpes simplex virus type-2 infection among pregnant women in Northeast India.

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Reviewer: Joshua Schiffer

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This paper is a cross-sectional seroprevalence survey in NE India. The authors correctly point out that HSV-2 is good marker of sexual risk, and may be an independent risk factor for HIV-1 acquisition and transmission. The paper is important because NE India is the current site of an important HIV epidemic. Behavioral surveys do a poor job of estimating sexual risk. Therefore, an HSV-2 serosurvey can be a valuable tool to measure HIV-1 epidemic potential. Indeed, this survey identifies that there is some degree of risk in this population. However, there are several major issues:

Major compulsory revisions:

First, there is no limitations section describing the many limitations of deriving odds ratios from a cross-sectional survey in which cases are not matched with controls. It should be emphasized in the discussion that the study’s findings are hypothesis generating only. This paper would be considerably stronger if the authors performed a case-control analysis to better define risk factors for HSV-2. At minimum, a reasonable justification for not doing so should be included.

Second, a major point of the paper that should be emphasized is the lack of a typical age-cohort effect where the oldest members of the population have highest seroprevalence. This is somewhat of a rare and interesting finding for a chronic infectious disease and imply that HSV-2 is a relatively recent addition to the population. It also means that the current seroprevalence of HSV-2 may be a great measure for HIV-1 risk in this community, and that HSV-2 incidence (which is more difficult to measure and probably a better measure of risk), may actually be high.

Third, the authors need to speculate on the following: why is reported genital ulcer disease so low? Potential reasons include cultural stigma of reporting genital ulcers, genetic factors that limit severity of disease, or an inadequate questionnaire / interview. A clinical point of the paper may be that patients nd clinicians under recognize herpes lesions: this has been widely observed in other populations.

Fourth, is there an obvious difference to explain the striking differences in HSV-2 prevalence across Indian states? This interesting finding survives multi-variate analysis. Are there data on sexual networks in different provinces that may explain this? Please speculate.

Fifth, what is a joint family, and why is this group at lower risk than members of a
nuclear family?
Finally, there are several grammatical errors that are listed below, though some may have been missed.

Minor revisions:

In the background:

- The statement that HSV-2 facilitates spread of HIV-1 among low-risk populations needs at least one, and preferably multiple citations.

* Despite a very nice list of cofactors in Table 1, the reader does not emerge with a general feel for the population demographics in the region. This would help frame the paper. For example, is there a mobile or static labor force? What proportion of the HIV-1 epidemic is thought to be related to IDU behaviors? Is female sex work common? Are there broad cultural differences between provinces? Are there well-defined sexual networks? Is it common for younger women to engage in sexual debut with older men? A one paragraph overview of these points would strengthen the paper. Several papers by Laith Abu-Raddad have taken a similar approach in the Middle East: these descriptives are vital for the reader who is unfamiliar with the region.

In the methods:

- It should be explained why women under 18 were excluded, as adolescents may be a key population to study. If seroprevalence were high among this group, this would be a critical finding.

- Under data collection, “etc.” should be removed. All demographic data that were queried should be listed. If the authors selected possible risk factors a priori, then this lends more credibility to the analysis. This should also be stated in the methods.

- The study should be classified specifically as a cross-sectional study. Odds ratios derived from cross-sectional studies are more tenuous than those from case-control studies.

In the results:

- The seroprevalence should show numerator and denominator for each of the 5 states.

- The seroprevalence should be listed for all 3 trimesters with numerators and denominators.

- The seroprevalence should be listed for those with and without GUD with numerators and denominators.

- Comparisons of prevalences between groups should include p-values.

- The very low number of study participants who reported history of genital ulcers (19/1640) is fascinating given the moderate HSV-2 seroprevalence. Is data available from gynecological exam on the date of this visit? It would be interesting to see what % of pts had GUD on the day of the exam. Typically, recognition of GUD by patients increases with focused clinician education:
however, this is an intensive process that is quite rarely done in most clinics.

In the discussion:

• The authors appear to misinterpret the meaning of peak seroprevalence at age 22-25: this in fact contrasts with most other studies of HSV-2. Typically, during a stable epidemic as in Africa, Europe and the US, seroprevalence increases linearly with age. This is not surprising as people accrue infection over time. However, this study shows a peak (albeit a blunted peak) within a relatively young age cohort (22-25). The implications are that HSV-2 is reasonably new in the young population, and the epidemic is in an expansion phase in NE India. The authors should speculate on why this is the case. The probable explanation is changing sexual habits and network structure among the younger generation.

• In regards to the above, a key unreported measure of local HSV-2 epidemiology is incidence rather than prevalence. It can be a devilish task to identify the true incidence as this is a non-linear measure requiring multiple serial data point. Yet, the lack of an age-cohort effect may imply high incidence among young women, and early epidemic stage despite seemingly low HSV-2 prevalence. A follow up seroprevalence survey, as well as a partnership with mathematical modelers, would be useful to confirm this expansion. This concept should be included in the discussion.

• The high seroprevalence cited in ref 30 (33.2%) needs to be explained in reference to the lower prevalence reported throughout India. Is this due to inclusion of other countries, including SE Asia?

The paper also had several grammatical errors, some of which are listed below. It will need closer inspection prior to publication.

Abstract:

Last sentence in background should read “located in NE region of India. Due to lack of ….from this part of the country, there is a need….”

Last sentence in methods should read: “…analyses were performed…”

2nd sentence in Results should read: “Higher seroprevalence was observed…”

Background:

1st sentence should be “…infection is almost always sexually transmitted and is…..”

Methods:

In “Specimen collection” section, it should read “Plasma samples were subjected to…”

Results:

Should read “The majority of subjects were house wives…., belonged to the nuclear family, and from…..”
Discussion

Should be… “…seroprevalence found in this study has also been observed in earlier studies.”

Should be: “inner-city communities”

Should be: “was reported to be 33.2%”

Should be “higher coitarchal age was associated with a lower chance…”

Should be “higher seroprevalence was found among Christians versus Muslims, condom non-users versus users etc…”

Should be “Modifiable risk factors included low coitararchal age, low condom usage, multiple sex partners, and alcohol use…”

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests