PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Female sex work interventions and changes in HIV and syphilis infection risks from 2003 to 2008 in India.
AUTHORS	Arora, Paul; Nagelkerke, Nico; Moineddin, Rahim; Bhattacharya, Madhulekha; Jha, Prabhat

VERSION 1 - REVIEW

REVIEWER	Paul Feldblum, PhD Senior Epidemiologist FHI 360 Research Triangle Park, NC, USA I declare no competing or conflicting interest relevant to this manuscript.
REVIEW RETURNED	25-Feb-2013

THE STUDY	If the authors wish to associate syphilis rates with numbers of infections treated, could they not use syphilis treatments as the independent variable, instead of treatements for all STIs? How are STIs generally diagnosed? How accurate are those diagnoses? Do clinics rely on syndromic diagnosis?
RESULTS & CONCLUSIONS	My main quarrel with the ms is that the authors attribute changes in the infections to the interventions. These are statistical associations and should be described as such, i.e. more cautiously. The associations may or may not be causal, but the language used consistently implies causality: "leads to", "contributes to", "treatment has reduced." Also, alternative explanations get short shrift. Web Figure 1 indicates that overall HIV incidence was diminishing substantially between 1998 and 2004, the start of the period covered in this analysis. What else was occurring in these states during the study period? Is there evidence of behavior change from other data sources? What was the HIV treatment picture? I do not disagree with the authors; I simply think that this modeling work calls for more modesty. One additional point: the authors' findings seem to differ from those of Kumar et al (ref 14). Can they say something about that?

REVIEWER	Damien de Walque Senior Economist Development Research Group The World Bank
REVIEW RETURNED	05-Mar-2013

GENERAL COMMENTS	This is a very interesting article which presents important results and

	is well written. Here are my main comments for improving the manuscript: 1) The authors are careful to stress that the placement of the intervention districts was not random. In effect, they are using dose-response version of a difference-in-difference strategy, looking at differences in the evolution over time between districts with larger interventions and those with less interventions. This identification strategy is appropriate under the hypothesis of parallel trends, i.e. that districts with more interventions and districts with less interventions experienced parallel trends in HIV and syphilis infections before the start of the intervention. In other words, the authors need to show that there were no convergent or divergent trends before the start of the intervention. In the current manuscript, this is not shown or discussed. They account for possible regression to the mean by including an interaction term between baseline prevalence and year, but what they would really need to do is present some evidence from before the start of the intervention. If that data is not available, the authors should discuss this as a limitation of their analysis. 2) Related to the issue of non-random placement of the intervention, for the part of the analysis that compares the NACO and the Avahan intervention districts, the authors should elaborate on the criteria used for the placement of the Avahan intervention. And was NACO filling the void where Avahan was not implemented or where they using other criteria. Again, the comparison between Avahan and NACO is valid only if there were no pre-existing convergent or divergent trends before the two types of districts. 3) I think the authors should discuss more extensively the contrast between their results which suggest that STI treatment is an important channel in reducing HIV infections and the results from randomized control trials in Africa. Currently the authors have only a short sentence about this p. 15. 4) I also found that the authors could be more detailed about the representativeness of a sample of pregnant women being tested for HIV and syphilis. What is the percentage of women in those Indian states who deliver in health facilities and/or receive ante-natal care? How do these women compare to those who do not attend health facilities? Minor comments: - P. 11, first paragraph: "A similar gradient from STIs treated, FSWs reached and condoms distributed was observed…". The gradient actually seems positive, if close to zero and insignificant, for FSWs reached. - P. 15, 5th line, replace "while less in known" by "while less is known".

REVIEWER	Laura Packel, PhD MPH Clinical Sciences Program Officer California HIV/AIDS Research Program University of California, Office of the President USA I certify that I have no competing interests with this submission.
REVIEW RETURNED	13-Mar-2013

RESULTS & CONCLUSIONS	All of the FSW interventions are lumped together (separating out STI treatment). I'm not sure how helpful this approach is in determining

	what is working to bring down HIV prevalence - it's certainly an interesting ecologic analysis but I think leaves something to be desired in terms of where do we go from here as we cannot get a sense of the specifics of these interventions and if there are categories of interventions that might have been more effective than others.
GENERAL COMMENTS	I chose minor revision because I think it would be helpful to have some more detail about the interventions. I know there were many of them so not detail on each, but perhaps categorizing the interventions with some more specific detail rather than lumping them into FSW reached and condoms distributed. Also, are there any existing estimates of the HIV or syphilis prevalence in the FSW population in the Indian States discussed in the paper?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Paul Feldblum, PhD

Senior Epidemiologist
FHI 360,Research Triangle Park, NC, USA

I declare no competing or conflicting interest relevant to this manuscript.

1. If the authors wish to associate syphilis rates with numbers of infections treated, could they not use syphilis treatments as the independent variable, instead of treatments for all STIs?

This would have been ideal but, unfortunately, was not possible. The NACO TI dataset did not contain data on numbers of treatments or referrals for specific STIs. Therefore it was not possible to explore and compare the impact of specific STI treatments on risk of HIV. In the discussion section we have included a call for revisiting opportunities to integrate rapid diagnostic technologies, currently being piloted in India (and elsewhere), into surveillance to provide this additional information (pg 18).

2. How are STIs generally diagnosed? How accurate are those diagnoses? Do clinics rely on syndromic diagnosis?

For the purposes of the NACO TI data, STIs are diagnosed syndromically and projects would either provide treatment or refer the subject to a preferred STI clinic both of which should be following the WHO/NACO STI syndromic treatment guidelines. In India, NACO guidelines for STI treatment, which both NGOs and STI clinics follow, differentiate between herpetic- and non-herpetic ulcer only be the presence of vesicles. The choice of treatment follows a decision tree and, given the lack of specificity inherent in syndromic management, treatment is broad with antibiotics in addition to acyclovir in the case where vesicles are suspected. Syndromic management of STIs are well documented, but we have added a brief explanation on page 6.

3. My main quarrel with the ms is that the authors attribute changes in the infections to the interventions. These are statistical associations and should be described as such, i.e. more cautiously. The associations may or may not be causal, but the language used consistently implies causality: "leads to", "contributes to", "treatment has reduced."

We have reworded our manuscript to be more cautious in interpretation using more conservative language (highlighting association instead of causation). Further we have included the point in our discussion on page 16 on the limitation of non-randomized designs highlighting the fact that these findings are statistical associations and those other unknown or unmeasured factors may be contributing to any associations that we observed.

4. Also, alternative explanations get short shrift. Web Figure 1 indicates that overall HIV incidence was diminishing substantially between 1998 and 2004, the start of the period covered in this analysis. What else was occurring in these states during the study period? Is there evidence of behavior change from other data sources? What was the HIV treatment picture? I do not disagree with the authors; I simply think that this modeling work calls for more modesty.

While many factors may have an influence on the outcome, the objective of this analysis was to assess whether the sex work interventions were among them. We have now included on page 17 a brief comment of the results of our examination of district-level data on changes in behavior and HIV awareness in general populations. These were not related to either spending/or condom use, STI treated or FSWs reached and were not related to HIV or syphilis risk. We include a note that the results of state-level sexual behavioural surveys suggest a changing population in terms of condom use with increases reported from 2001 to 2006 and that the prevalence of STIs in high-risk groups declined during the same time period according to biological surveys. We have also discussed the limited role played by expansion of HIV treatment during the study time period.

5. One additional point: the authors' findings seem to differ from those of Kumar et al (ref 14). Can they say something about that?

Three important differences between our study and the one by Kumar et al were the use of a different exposure measure, time periods and statistical model. We have now noted these differences in the discussion on page 17.

Briefly, in their 2011 study of the impact of interventions on the risk of HIV, Kumar et al used an indirect measure of intervention (an “intensity” measure) based on the number of condoms distributed to each district as a proportion of the estimated number of sex acts between FSWs and clients. We used two direct measures of the number of STIs treated and FSWs reached per capita in each district. Secondly, Kumar et al examined trends in HIV among ANC attendees from 2000 to 2008, we examined trends from 2003 to 2008 as surveillance coverage for south India were only complete from 2003 onwards. Finally, that study used a statistical model that did not account for the variation in baseline HIV prevalence (either with a random intercept at the district level or with an explicit baseline prevalence term). This would have been of critical importance as interventions were not randomly assigned.

Reviewer #2: Damien de Walque
Senior Economist
Development Research Group
The World Bank

This is a very interesting article which presents important results and is well written.
Here are my main comments for improving the manuscript:

1) The authors are careful to stress that the placement of the intervention districts was not random. In effect, they are using dose-response version of a difference-in-difference strategy, looking at differences in the evolution over time between districts with larger interventions and those with less interventions. This identification strategy is appropriate under the hypothesis of parallel trends, i.e. that districts with more interventions and districts with less interventions experienced parallel trends in HIV and syphilis infections before the start of the intervention. In other words, the authors need to show that there were no convergent or divergent trends before the start of the intervention. In the current manuscript, this is not shown or discussed. They account for possible regression to the mean

by including an interaction term between baseline prevalence and year, but what they would really need to do is present some evidence from before the start of the intervention. If that data is not available, the authors should discuss this as a limitation of their analysis.

Agreed. Unfortunately the data are unable to test this assumption. In principle, it would be possible to explore this assumption empirically by looking at the pre-2003 evolution of prevalence in intervention and non-intervention districts with the same prevalence in 2003. Pre-2003 surveillance data in south India were incomplete and limited to a subset of districts. Further, data on syphilis were only available from 2002 onwards. We have now acknowledged this issue in our methods section on page 8 and further discussed this as a limitation on page 16.

2) Related to the issue of non-random placement of the intervention, for the part of the analysis that compares the NACO and the Avahan intervention districts, the authors should elaborate on the criteria used for the placement of the Avahan intervention. And was NACO filling the void where Avahan was not implemented or where they using other criteria. Again, the comparison between Avahan and NACO is valid only if there were no pre-existing convergent or divergent trends before the two types of districts.

Agreed. Avahan interventions in south India were selectively placed in 70 districts with the highest HIV prevalence among young pregnant women attending public prenatal clinics. In one state, Karnataka, there was a decision made between Avahan and NACO to divide the districts such that they were mutually exclusive in their operations. In the other states of south India, this was not the case and districts that were “Avahan” districts may have also had NACO-funded interventions running in them. We have added a section to describe this process in the methods section on page 6 and discussed the limitation on page 16/17.

3) I think the authors should discuss more extensively the contrast between their results which suggest that STI treatment is an important channel in reducing HIV infections and the results from randomized control trials in Africa. Currently the authors have only a short sentence about this p. 15.

Agreed. We have expanded on this in the discussion section (p 15) noting the results of an expert review of all nine RCTs on the effect of STI treatment or prevention on HIV incidence. We note that our results are in contrast to these findings however our duration of follow up was much longer and many of the published trials were powered to detect a large decrease in HIV incidence, based on expectations of the first successful trial, but that the effect of STI treatment is likely more modest.

4) I also found that the authors could be more detailed about the representativeness of a sample of pregnant women being tested for HIV and syphilis. What is the percentage of women in those Indian states who deliver in health facilities and/or receive ante-natal care? How do these women compare to those who do not attend health facilities?

We disagree somewhat with the reviewer on the importance of representativeness. Indeed, WHO devised ANC surveillance (pregnant women at publically funded clinics who are tested for HIV in anonymous and unlinked fashion – but are provided with syphilis results and counseled to be tested for HIV, usually at an attached clinic) to monitor changes and not absolute levels of HIV in the population. We have earlier published (Lancet. 2006; 367: 1164-1172.) that women in India who attend public clinics are not representative of the population. If the characteristics of the women who attend are relatively stable, trends in HIV prevalence in young women are recommended for use as a proxy of trends in incidence in the general population.

In 2006, among women who had one live birth in the past five years, 89% to 99% of women in the four large south Indian states reported at least one antenatal care visit. Limited information is collected about them in the data aside from age, literacy status and urban/rural locality and these characteristics have not changed significantly from 2003 to 2008. We have now added this prevalence of ANC use and note that stable demographics of young ANC attendees in the methods section (p 7).

Minor comments:
- P. 11, first paragraph: “A similar gradient from STIs treated, FSWs reached and condoms distributed was observed…”. The gradient actually seems positive, if close to zero and insignificant, for FSWs reached.
We agree with the reviewer and have re-written this comment as:
“Similarly, the largest association between intervention and HIV risk was with STIs treated. FSWs reached and condoms distributed were not significantly associated with HIV risk”.

- P. 15, 5th line, replace “while less in known” by “while less is known”.
Done. Corrected.

Reviewer #3: Laura Packel, PhD MPH
Clinical Sciences Program Officer
California HIV/AIDS Research Program
University of California, Office of the President

I certify that I have no competing interests with this submission.

1. All of the FSW interventions are lumped together (separating out STI treatment). I'm not sure how helpful this approach is in determining what is working to bring down HIV prevalence - it's certainly an interesting ecologic analysis but I think leaves something to be desired in terms of where do we go from here as we cannot get a sense of the specifics of these interventions and if there are categories of interventions that might have been more effective than others. I chose minor revision because I think it would be helpful to have some more detail about the interventions. I know there were many of them so not detail on each, but perhaps categorizing the interventions with some more specific detail rather than lumping them into FSW reached and condoms distributed.

The NACO TI evaluation data, there was limited information on each specific project. Data available were project duration, numbers of target groups reached, name of funding organization and other limited descriptive information. Data on specific activities of the interventions that reached FSWs were also not available. The broad target group of each project was available and the reported number of FSWs reached, STIs treated or condoms distributed and so we had a way, albeit crude, to compare different types of interventions.

We have expanded the methods section on page 6 to describe the activities of these different types of interventions based on guidelines for community-based organizations and Avahan reports. Further we have added a few words in the discussion on page 16 to describe this limitation in generalizing our results to prevention efforts in India.

2. Also, are there any existing estimates of the HIV or syphilis prevalence in the FSW population in the Indian States discussed in the paper?

See reply to reviewer 1, point 4. We believe this comment is similar to Reviewer #1’s fourth comment calling for additional background information on other STI and behaviour data from these four states. Web Table 1 has details of testing in STI clinics suggesting a significant decline in HIV prevalence among male and female VCTC attendees in the high-burden southern states and significant declines in syphilis prevalence among male STI clinic attendees in some of these states. We have expanded on this point in the discussion on page 17 by referring to behaviour and biological surveys in high risk groups and the general population of these states.

VERSION 2 – REVIEW

REVIEWER	Paul Feldblum, PhD Senior Epidemiologist FHI 360 Research Triangle Park, NC 27709 USA I have no competing interest.
REVIEW RETURNED	09-Apr-2013

GENERAL COMMENTS	I think the authors have adequately addressed all of the reviewers' comments.

REVIEWER	Damien de Walque Senior Economist Development Research Group The World Bank United States
REVIEW RETURNED	27-Apr-2013

GENERAL COMMENTS	The authors carefully addressed my initial comments and suggestions - as well as those raised by other reviewers - and I think this is a very interesting paper. I am looking forward to its publication.