Author's response to reviews

Title: Five-year trends in epidemiology and prevention of mother-to-child HIV transmission, St. Petersburg, Russia: results from perinatal HIV surveillance

Authors:

Dmitry M Kissin (DKissin@cdc.gov)
Michele G Mandel (MMandel@cdc.gov)
Natalia Akatova (Akatova_Natasha@hotmail.com)
Nikolay A Belyakov (Akatova_Natasha@hotmail.com)
Aza G Rakhmanova (Rakhmanova@peterlink.ru)
Evgeny E Voronin (EVoronin1@rambler.ru)
Galina V Volkova (Akatova_Natasha@hotmail.com)
Alexey A Yakovlev (Akatova_Natasha@hotmail.com)
Denise J Jamieson (DJamieson@cdc.gov)
Charles Vitek (CVitek@cdc.gov)
Joanna Robinson (Joanna@pedaids.org)
William C Miller (Bill_Miller@unc.edu)
Susan Hillis (SHillis@cdc.gov)

Version: 2 Date: 19 August 2011

Author's response to reviews: see over
August 19, 2011

Dr. Francesco Maria Fusco  
Editor, BioMed Central  
Floor 6, 236 Gray's Inn Road  
London WC1X 8HB  
United Kingdom

RE: Manuscript 4102829535413171

Dear Dr. Fusco:

Thank you very much for your review of our paper entitled “Five-year trends in epidemiology and prevention of mother-to-child HIV transmission, St. Petersburg, Russia: results from perinatal HIV surveillance”. We have revised the manuscript after careful consideration of your valuable suggestions and comments; we feel that the changes recommended are important and that they significantly strengthen the manuscript. A summary of the revisions is attached. All authors of the original manuscript have read and approved the revised version of the paper. Please do not hesitate to contact us if you have any questions or comments. We look forward to hearing from you soon.

Sincerely,

Dmitry Kissin, MD, MPH  
Division of Reproductive Health  
Centers for Disease Control and Prevention  
4770 Buford Highway NE, MS K-34  
Atlanta, Georgia 30341-3724, U.S.A.  
Phone: (770) 488-6408  
Fax: (770) 488-6391  
E-mail: DKissin@cdc.gov
Referee 1:

1. Is the question posed by the authors well defined? The authors clearly stated that they were assessing trends in HIV seroprevalence, trends in birth rates among HIV-infected women, and trends in uptake of several interventions to prevent mother-to-child transmission.

2. Are the methods appropriate and well described? The methods are appropriate for the questions and are well described.

3. Are the data sound? The data are sound in their ability to detect trends. One issue, which does not detract from that fact, regards their estimate of birth rate among HIV-infected women, and that is that the good ascertainment of cases in their Enhanced Perinatal Surveillance (their numerator) and the underestimation of the number of cases (their denominator) would tend to exaggerate the rate in general. I do think that this effect is likely to be consistent over the study period, and will thus not affect their ability to detect a trend.

First actual suggestion; that this issue be addressed is considered a major compulsory suggestion (according to the editor's classification of suggestions). It is a little unusual to show no significant decline in annual rates when each year is considered separately, but then to combine the first pair and second pair of years in order to get a P<0.05. I discussed this issue with a biostatistician, and, together, we developed two alternative ways of looking at the transmission rates. It would be more honest to acknowledge the spike that occurs in 2005 and then to test for a decline from then through 2007. Second, one could combine the IDU and non-IDU data and perform a regression with a linear term for year and an indicator variable for IDU status. Irrespective of which alternative is selected, we do suggest dropping the present depiction of Fig 4, substituting a new figure that shows the curves for the annual transmission rates for the IDU and non-IDU groups, including, perhaps, confidence bounds. Since this suggestion is deemed a major compulsory revision, it means that I needed to check "unable to decide" below, which overstates the case a little.

Response: We originally combined years 1-2 and 3-4 due to the small numbers of perinatally-infected infants. However, we agree with the reviewer that it is more appropriate to test the trend of perinatal HIV transmission from 2005 through 2007. We did additional analyses and made the changes in each section of the paper: Abstract (p. 3), Methods (p. 10), Results (p. 13), Discussion (p. 15,16).

Second suggestion, considered a minor essential revision: The other data in Fig 4—use of ARV relative to EGA—should be in a Figure separate from the Transmission rates, and if this is done, two separate clearly labeled curves should be shown WITHOUT the shading between the curves.

Response: We removed shading of the curves, as suggested by the reviewer. However, we retained graphs on the same figure, as we believe that, from ecologic perspective, it is important to consider trends of perinatal transmission in relationship with timing and completeness of antiretroviral prophylaxis.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? It does.

5. Are the discussion and conclusions well balanced and adequately supported by the data? The discussion and conclusions are clearly written and supported by the data, as is the Background section.

6. Are limitations of the work clearly stated? Yes
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? Yes
9. Is the writing acceptable? The writing is clear.

A few minor revisions:
Method,
1) second to last line: “low risk”, the words can be hyphenated

Response: Corrections were made on page 6.

2) Variable and definition section, last long paragraph, explanation of CDC Case definition: in items a-d, the modifiers for the term ‘HIV-infected’ would possibly be more appropriately expressed as adverbs, e.g., ‘definitively HIV-infected’; in items c-d, the ‘not HIV-infected’ could be stated, e.g., as ‘definitively HIV-uninfected’.

Response: Corrections were made on page 9.

Results
1) 4th paragraph: In the sentence beginning, “The proportion of women without prenatal care…”, the numbers given in parentheses are ranges, unlike in every other instance in the Results, where the parenthetical numbers are those from 2004 and 2008. This could be explained.

Response: When there was a trend, we showed the change from 2004 to 2008. When the proportions were stable (as with proportion of women without prenatal care), we showed the range. We clarified this on page 12.

Discussion
1) 3rd paragraph, last sentence: “…the increasing trend of injection drug use during pregnancy…” does not appear to be mentioned in the Results.

Response: The increasing trend of injection drug use during pregnancy is mentioned in the last sentence of the second paragraph in the Results section (p. 11).

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: 'I declare that I have no competing interests'
Referee 2:

This is a well thought out and written paper, which provides evidence that targeted and comprehensive HIV prevention measures are effective. In addition, this report demonstrates the vital role of enhanced perinatal surveillance in driving programmatic improvements. The questions posed by the authors is well defined and the method of using the perinatal surveillance system and HIV reporting is unique, appropriate and well described. The data is based on actual population level data which gives it strength and the manuscript does adhere to the relevant standards for reporting and data deposition. The discussion is adequate but would have benefitted from some mention of the cost of setting up the system and potential role for scaling up in other parts of Russia. The limitations of the work are clearly stated. The title and abstracts do convey the content of the paper.
* No Major or minor revisions.

Discretionary Revisions:
Authors kindly consider including some discussion about (a) the cost of setting up the systems and is it scaleable. Also are findings generalizable to other parts of the country. (b) Because most of MTCT of HIV now occurs in developing countries, this article will benefit from discussing the potential role for introducing and/ or scaling up such a system in developing countries.

Response: We added information on cost of enhanced perinatal surveillance, as well as discussion on scalability of such system in Russia and generalizability of our findings to other countries (p. 16-18).

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests.
Referee 3:

Five-year trends in epidemiology and prevention of mother-to-child HIV transmission, St. Petersburg, Russia: results from perinatal HIV surveillance

This study provides information on the trends in the epidemiology and prevention of mother-to-child HIV transmission in St. Petersburg based on an enhanced perinatal surveillance system. This has enabled the authors to describe the trends in social, perinatal, and clinical factors influencing mother-to-child HIV transmission stratified by history of injection drug. The historical driving force of the HIV epidemic in males in Russia has been male injection drug users, though now the epidemic is evident in increasing numbers in other groups, particularly females of reproductive age. This has led to the stratification based on the women’s injection drug use history, an important aspect though not one that necessitates to be reflected in the title. An important strength of the study is that the enhanced perinatal surveillance system, on which the trend analysis is based, captures information in over 90% of HIV infected women giving birth in St Petersburg. However, those women non-captured (i.e. delivering in low-risk maternity hospitals) are implied to be women with not as high an HIV prevalence as the others (and if infected, not with manifest HIV disease). Universal HIV testing of pregnant women (or of documented status) would address that concern. The authors state that: ‘nearly all women in St. Petersburg and Russia deliver in medical facilities, and there has been high coverage with antenatal and natal HIV screening …’, the reader is accordingly supposed to infer a virtual universal coverage regarding women knowing their HIV status. The sustained strategy for opt-out is then to maintain such a high coverage and also capture, with rapid testing in labor, any of those that are missed through non-use of prenatal services.

The authors acknowledge that standard HIV case reporting underestimates the HIV prevalence in women of reproductive-aged women, but that birth data are more comprehensive. This has implications on the indicator related to HIV-infected women giving birth. The authors suggest that the decreasing birth rate in HIV-infected women may be due to decreased fecundity as a result of decreased fertility desires and/or improved family planning services. A personal communication is cited to state that there was no increase in abortions amongst HIV-infected users. Although pregnancy intendedness had decreased in both IDU and non-IDU women giving birth, at the end of the reporting period (2008) there were still 30.2% and 46% respectively with an unintended pregnancy giving birth, reflecting an as yet substantial unmet need.

The surveillance system shows that though an increasing proportion of HIV-infected women are on some form of antiretroviral drugs (ARVs either as prophylaxis or for their own need), by the last reporting year (2008) there were still 12.1% non-IDU and 29.5% IDU women that had no prenatal care and hence no ARVs (presumably up to the time of labour).

The perinatal transmission rates show a trend in reduction in both IDU and non-IDU groups but infant HIV follow-up is by no means comprehensive (about 60% overall for 4 years of surveillance).

From a program perspective, the study has highlighted important areas that need strengthening and which include increasing family planning uptake, earlier use of ARVs and increased infant follow-up. The women with no prenatal care, in both groups, points to efforts required to ensure that HIV-infected women enter the formal health system to enable specific PMTCT interventions to be effected. It more importantly points to the value of the surveillance system in program management which not only requires population, facility, and health systems indicators but also in the ability to capture and analyse individual level characteristics to better inform program. An important value of the paper is in this aspect – for the surveillance system to be able to assess and modulate program strategies in reducing PMTCT.
Major Compulsory Revisions/Clarifications
1. In the discussion and conclusions the authors should frame the value of the enhanced perinatal surveillance system regarding its assessment of trends in perinatal transmission on the fact that about 60% of the infants were followed up. Do the authors have any reason to suggest that the trends would not show such an effect had there been a wider coverage of infant follow-up? For example, are there any important differences between the populations that have infant follow-up as opposed to those that do not? At the very least, the authors should mention in the discussion whether this was the case or not.

Response: We acknowledged that large proportion of HIV-exposed infants had undetermined HIV status as a limitation in the Discussion section. We also included data on the characteristics of women whose infants had undetermined HIV status and potential impact on HIV transmission rates (p. 18-19).

2. Similarly, since the data are available, the authors could report on any difference(s) in characteristics between women that are IDU and non-IDU. This could be on pooled data over all years, or taking the last surveillance year. If the authors feel that Table 1 cannot accommodate yet another column for this, any important findings could be narrated instead of tabulated.

Response: We included the paragraph comparing characteristics of women that are IDUs and non-IDUs in the Results section (p. 13-14).

3. The authors have described how data is obtained for the enhanced perinatal surveillance system (medical abstraction and through interview for self-report of injection drug use, pregnancy intendedness and other factors). Do they feel that any others characteristics could be added? (Partner’s IDU history, if relevant). The authors should mention in the discussion how feasible it would be to duplicate the system in other cities? Would resources be available to administer such a system?

Response: Enhanced perinatal surveillance system has been adapted to be locally relevant and useful. National and local experts should determine what characteristics need to be included in enhanced perinatal surveillance. We added information on cost of enhanced perinatal surveillance, as well as discussion on scalability of such system in Russia and generalizability of our findings to other countries (p. 16-18).

4. Is the enhanced perinatal surveillance system linked to any other registration system? Can it be? Or is it only linked to the maternity hospital records? Is there any infant registration or other systems that could be linked to the mother?

Response: Enhanced perinatal surveillance system is not currently linked to other systems. However, it can potentially be linked to maternal and infant records at the City AIDS Center, where both HIV-infected mother and her child(ren) receive treatment, care and support. We added a sentence about potential linkage to the Discussion section (p. 16).

Minor Essential Revisions
Minor issues not for publication
1. Email addresse: Akatova_Natasha@hotmail.com appears to be the common email address for NA, NAB, GVV, and AAY. Unless this is intentional, correct change to the correct address for NAB, GVV, and AAY.
Response: This was intentional. Since some coauthors are not using e-mail on a regular basis, we provided e-mail of the project coordinator for more efficient communication.

2. WCM. Check whether Bill_Mmiller@unc.edu is correct. Are there supposed to be two ‘m’s?

Response: E-mail address for Dr. Miller has been corrected.

3. Background; Para 2; instead of
- Many barriers to effective perinatal prevention relate to either behavioral characteristics of HIV-infected women themselves (e.g., use of family planning, initiation of prenatal care)....
State:
Many barriers to effective perinatal prevention relate to either behavioral characteristics of HIV-infected women themselves (e.g., suboptimal/inadequate use of family planning, late initiation of prenatal care)....

Response: The abovementioned sentence on pages 4 and 5 has been changed.

4. Methods; Para 1;
Instead of: Therefore, the number of HIV cases in the general population are severely underestimated [3]. Suggest Therefore, the number of HIV cases in the general population is severely underestimated [3].

Response: The abovementioned sentence on page 6 has been changed.

5. Results; Para 7
The overall rate of perinatal HIV transmission during that period was 4.0% (CI 2.7%-5.8%) and 7.0% (CI 5.5%-9.0%) among non-IDUs and IDUs, respectively. Since this is a new paragraph continuing on from results of the 4-year period (2004-2007) in the previous paragraph, suggest: The overall rate of perinatal HIV transmission during the 4-year surveillance period (2004-2007) was 4.0% (CI 2.7%-5.8%) and 7.0% (CI 5.5%-9.0%) among non-IDUs and IDUs, respectively.

Response: The abovementioned sentence on page 13 has been changed.

6. Acknowledgements and Funding; first sentence ‘The enhanced perinatal surveillance system in St. Petersburg was established and supported by the Elizabeth Glaser Pediatric AIDS Foundation, the St. Petersburg City AIDS Center, USAID/Moscow, and CDC.’... This is repeated at the end of the section. Suggest remove the latter repetition.

Response: Duplicate sentence has been removed.

7. Figure 4.
Spelling of prophilaxis should be prophylaxis

Response: Spelling has been corrected.

8. References
#9 - Year of article missing (it is 2010)
Response: Publication year has been added.

Discretionary Revisions/clarifications
1. The system focuses on perinatal transmission and its determinants. Within the current context in Russia, prevention of mother to child transmission may depend predominantly on perinatal transmission as opposed to those infected subsequently (e.g. though breastfeeding or other means). Accordingly, it is assumed that on remote follow-up of infants born to HIV-infected mothers, HIV status (if infected) would be a reflection of perinatal transmission. The authors may want to comment on this.

Response: The sentence explaining that HIV-infected women in Russia are not usually breastfeeding has been added to Methods section on page 9.

2. The authors may wish to comment whether any specific programmatic adjustments (to increase HIV testing in pregnancy or labour, increased ARV uptake, increased family planning uptake) have occurred over the years based on the enhanced perinatal surveillance system.

Response: We included discussion on programmatic changes implemented in St. Petersburg during the assessment period and provided references of publications that describe these changes in more detail (p.17): “In St. Petersburg, enhanced perinatal surveillance was critical in identifying areas needing improvement, such as limited use of effective family planning [21], low infant follow-up [10], and delayed and less effective antiretroviral prophylaxis [9]. Immediate, focused attention by the local public health leadership made it possible to address each of these issues in a timely fashion through program and policy improvements. As a result, we observed fewer unintended pregnancies, improved infant follow-up, earlier and more effective antiretroviral prophylaxis, and, subsequently, fewer HIV-infected infants.”

3. Can the trend in a higher proportion of those over 30 years of age (IDU and non-IDU) be explained by better coverage of those in that age group, increasing (and/or) more recent HIV infection in that demographic or that they were not tested in previous pregnancies in the past?

Response: As the coverage of all age groups in antenatal HIV testing has been very high, it is unlikely that either better coverage or previously not being tested are contributing to increasing proportion of older HIV-infected women giving birth. Although there is probably some component of increased transmission in older women as the HIV-infected male IDUs age, a fourth explanation may be a larger contributor to this trend. Routine surveillance suggests fewer new cases among young women in Russia. As the prevalent cases age, this will lead to an increased proportion of HIV-infected women who are older and they will represent a larger proportion of delivering mothers.

4. Noted that age category of <21 years is used. Is there any reason for this preference as opposed to <20 as used in general demographic categorizations? (Noted that numbers are small, but how may this have affected the trend?)

Response: We don’t believe that using age category of “<21” instead of “<20” could have affected the trend.

5. It is interesting to note that there is a trend of a slight of increase in the proportion of injection drug use during pregnancy (Table 1) despite a decreasing proportion of such women over the surveillance period. Does this mean less HIV-infected women with a history of ever use of injection drugs are giving birth, but those that do are more prone to report current pregnancy injection drug use?
Response: The reason for increasing use of injection drugs during pregnancy among women with a history of injection drug use is not clear. It is possible that ascertainment of injection drug use status improved over time.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: This reviewer previously worked with one of the co-authors (Densie J Jamieson) over 2 years ago, but not on any work related to this paper.