Author’s response to reviews

Title: Effects on preventing mother-to-child transmission of syphilis and associated adverse pregnant outcomes: a longitudinal study from 2001 to 2015 in Shanghai, China

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Author’s response to reviews:

Dear Editors,

Thank you very much for your reply. We really appreciate the reviewer's comments, which are very informative, suggestive and helpful. Based on these comments, we have done a major revision and the amendments are highlighted in blue in the revised manuscript. We hope that the revision is acceptable, and I look forward to hearing from you soon.

Sincerely yours,

Biao Xu

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Below are our responses to the reviewers.

Reviewer #1

Comment-1: The background information of syphilis in China is not well organized or well evident. For example, the citation of reference 8 is not relevant to sero-prevalence of maternal syphilis and not relevant to increase of syphilis prevalence among pregnant women. Moreover, the reference seems too out-of-date to present the current trend. Also, it seems the figure-related statements of "15,884 pregnant women infected with syphilis" and "406,772 reported cases of syphilis" are not relevant each other.

Response: We acknowledge the reviewer for this helpful comment. The reference 8 showed the rapidly increasing incidence of congenital syphilis since 1990, from which we deduced the rise of prevalence of maternal syphilis. We are very sorry for missing the latest studies with direct evidences. We have now addressed this weakness by re-organizing this part with the new reference, in which we delineated the prevalence of maternal syphilis in 2011-2013 by using the data from the national PMTCT surveillance report on page 3, line 12-13.

Comment-2: It seems not quite appropriate that the return of syphilis in China in 1980s was especially driven by the rural to urban domestic migrants at reproductive ages although the authors cite references 15 and 16.

Response: Thanks for this helpful comment. According to the literatures, China has undergone national economic reform and urbanization since 1980s, along with a large population mobility from rural to urban. In this period, the commercial sexual activities re-emerged, especially among the male domestic migrants at reproductive ages, and further aggravated the epidemics of syphilis and other sexually transmitted diseases. Therefore, we described that syphilis became epidemic again in 1980s, especially among rural-to-urban migrants in the background. We are sorry for this statement has resulted in misunderstanding that return of syphilis in 1980s was driven by migrants. Now we removed this description considering the surveillance data could not directly lead to this explanation, and only described the phenomenon on line 22-24.

“However, syphilis has staged a comeback in China and become epidemic again since 1980s with the rapid urbanization, sexual revolution and re-emerging of commercial sex services.”

Comment-3: It is known from the paper that the nation-wide PMTCT programs of HIV was initiated in China while pilot PMTCT program of syphilis was implemented in some cities including Shanghai in early 2000s. However, the author cited the reference 23 to indicate that for the prevention of maternal-to-child transmission of syphilis, the Shanghai PMTCT program of
HIV, syphilis and HBV was launched in 2001. What is the relationship between the pilot study of syphilis and the municipality initiative to include the three infections?

Response: Sorry for our mistake. Yes, Shanghai PMTCT program of syphilis was launched in 2001, and it has been revised on page 4, line 2.

Comment-4: The methods used for screening and confirmation algorithms ad diagnosis criteria of syphilis among pregnant women should be clearly described. What does "Diagnosis of maternal syphilis is confirmed by double-seropositive" mean? As performance of syphilis tests (including test kits) and quality assurance of the testing are critical for determination of seroprevalence, more information on these aspects are needed.

Response: Thanks for the helpful suggestion. We’ve added a new paragraph started from page 4, line 26 to describe the diagnosis procedure of maternal syphilis.

“Diagnosis of Maternal Syphilis

The serologic-based diagnosis of maternal syphilis uses both non-treponemal and treponemal testing. The non-treponemal test detects the non-specific antibody to reaginic antigen, including the tolulized red unheated serum test (TRUST) and rapid plasma reagin (RPR) test. The treponemal test uses the specific antigen of T. pallidum mainly through T. pallidum particle agglutination assay (TPPA) and Enzyme Linked Immunosorbent Assay (ELISA). Syphilis screening using non-treponemal test or treponemal test should be provided to pregnant women at the time of their first ANC visit. If the screening test shows a positive result, these women should be asked to have the second test for confirmatory diagnosis. Only when both serologic tests of syphilis present a positive result could the pregnant women be diagnosed as maternal syphilis.”

Comment-5: Was the diagnosis of maternal syphilis or determination of seropositivity made by the screening health facilities or the "designated hospital"?

Response: We acknowledge the reviewer for this question. In Shanghai, the non-treponemal tests and treponemal tests of maternal syphilis are provided at the antenatal care visits. Therefore, the diagnosis of maternal syphilis is performed in the hospitals where antenatal care and delivery services were provided. The "designated hospital" is responsible for the specialized treatment for sexually transmitted diseases (STDs) including maternal syphilis. In each district of Shanghai, there is at least one designated hospital for STDs, where the infected cases should be referred for adequate treatment with penicillin and/or other antibiotics immediately.

Comment-6: What is the definition of sero-prevalence used in the study?
Response: Thanks for this question. What we mean in this study is the prevalence of seropositivity. We have replaced the sero-prevalence with prevalence of seropositivity in the revision.

Comment-7: Regarding "Data Collection", it is needed for the authors to indicate the procedure of data collection of the PMTCT programme or the specific data collection for the current study.

Response: Thank you for suggesting. We have clarified the procedure of data collection of the PMTCT program and revised the data collection section as below:

“Data on maternal syphilis screening and treatment in this study were distracted from the municipal and national PMTCT surveillance systems. Once diagnosed with maternal syphilis, information on demographics, history of syphilis infection and the serologic testing results of the infected women should be collected and further recorded into the PMTCT surveillance system by health providers at the ANC hospitals. Additional information about syphilis treatments, pregnant outcomes and health status of newborns should also be reported to the surveillance system.”

Comment-8: There seems no specific data analysis except the application of the WHO developed website-based model for estimation of disease burden of maternal syphilis and adverse pregnancy outcomes. In addition to brief introduction of the estimation model, the authors need to provide the sources of population data used for the estimation, including live-births and stillbirths in Shanghai and out-of-Shanghai and other specific assumptions.

Response: The population data used for APOs estimation, including live-births and stillbirths etc., were collected from Shanghai antenatal care system and Shanghai health statistical yearbooks. We have added this message in data collection on page 5, lines 10-12.

Comment-9: In Figure 1, an indication to determine the seropositivity or seroprevalence is needed in the flowchart.

Response: Thanks a lot. We have marked the infected cases with both sero-positive results in the revised flowchart.

Comment-10: In each of Figure 2, there is too much information. For example, in Figure 2a of Number and proportion of women screened for syphilis by residency, to present resident %, non-resident % and total % is enough to indicate the trend. Same are for others.
Response: Thank you for your helpful comments. We had presented both the percentages and numbers in each of Figure 2 for the purposes of showing both the progress of screening/treatment of the program and the increasing trend of case burdens. There was inconsistency between the trends of the percentages and numbers. For example, in figure 2b, the prevalence of maternal syphilis among non-resident women decreased remarkably from 2007 to 2010 (due to the enlarging denominator), whereas the number of new cases remained rising at the same periods. Another instance could be found in figure 2c. Although the percentage of adequate treatment for maternal syphilis cases was stable during the years of 2003-2010, the total numbers of treated cases increased continuously. Now, we have simplified Figure 2 with total number and categorized percentages on page 14. Meanwhile, the bar graph and line graph were labeled with the annual data for details.

Comment-11: It is not quite clear from the title of "Effects on preventing mother-to-child transmission of syphilis and syphilis associated adverse pregnant outcomes: a longitudinal study from 2001 to 2015 in Shanghai, China", is this study aimed to describe the EFFECTs of the program or ESTIMATIONS of adverse pregnancy outcomes in two specific years. In regard to effects, there were increase of screening coverage but decreases of treatment coverage and increase of maternal sero-prevalence. Actually, the EFFECTs and ESTIMATIONS are linked each other. The authors intend to use the ESTIMATIONS to explain the EFFECTs or use the EFFECTs to support the ESTIMATIONS? It is confused to have them together for the study questions.

Response: Thank you for this very knowledgeable consideration. By using surveillance data on PMTCT program of syphilis, we were able to describe the longitudinal trend of maternal syphilis as well as the progress of syphilis screening and treatment services in Shanghai over 15 years. Together with population data, we further estimated the averted APOs under current PMTCT services and compared the gaps with ECS goals. Through the description and estimation, we could assess the effects of PMTCT on maternal syphilis detection/treatment and the effects on averted APOs.

Comment-12: What are implications of the findings from the study? For example, APOs happened among non-resident maternal syphilis cases accounted for the majority of the APOs in Shanghai varied from 61.4% to 84.8%. Or the proportion of adequate treatment among detected maternal syphilis cases was 96.8% in 2001, reduced to 69.8% in 2011 and rebounded to 83.6% in 2015.

Response: We acknowledge the reviewer for this question. We found that the screening of maternal syphilis has reached a full coverage and large numbers of APOs have been averted attributing to the PMTCT program. However, it was worth noting that the proportion of adequate
treatment among non-resident infected cases were lower, which indicated that health inequity in maternal healthcare utilization is still there. More attentions should be paid to those vulnerable non-resident pregnant women and tailored interventions including health education, PMTCT promotion and point of care should be given to improve their accessibility of maternal healthcare. We have added more detailed discussion on the decreasing proportion of adequate syphilis treatment in 2011-2013 started from page 7 line 33. In this part, we now state:

“In addition, it was observed that proportion of adequate treatment undergone a decrease during the years of 2011-2012 when the national PMTCT program was initially implemented. During the shift and integration of municipal and national PMTCT surveillance systems, some treatment and newborn follow-up information might be missing, which could lead to the underestimation of the proportion of adequate treatment. With the improvement of national PMTCT system, this indicator rebounded to 83.6% in 2015. Even so, there were still gaps with the goal of ECS (90%). To improve the accessibility of syphilis treatment, Shanghai health authority appointed additional thirty-two maternity hospitals as the “designed hospitals” for maternal syphilis medical care in 2016, where infected pregnant women could receive syphilis treatment, specialized antenatal care and safe delivery at the same facility.”

Reviewer #2

Comments: My suggestion of a more appropriate title: I think you can erase (Or DISPENSE) the second presence of the word syphilis It could stay: Effects on preventing MTCT of syphilis and related adverse pregnancy outcomes: a longitudinal study from 2001 to 2015 in Shanghai, China. Well written work, with relevant theme.

The frequency of syphilis and congenital syphilis in pregnancy is a serious problem all over the world, but even more serious in the Americas and Asia, where data are alarming! We know that what has occurred most is not the failure to perform the screening, since the majority of patients who present an adverse result performed prenatal care. What has happened the most is the misinterpretation of serology or non-treatment of sexual partnerships. Intensifying the clarifications for the population of physicians, who attend these women, will help reduce this serious problem. Knowing the epidemiological reality is the first step in defining the most vulnerable populations and focusing efforts on their attention!

Response: Many thanks to the reviewer for this positive feedback, which we appreciate. We acknowledge your excellent suggestion and we have revised the title accordingly.

We agreed that providing syphilis detection and treatment for both infected women and their husband or sexual partner played an important role on preventing the syphilis infection within
the family members, which was also important for the ethical consideration. In fact, the sexual partners of infected women have been integrated into the PMTCT program of syphilis in Shanghai. When the pregnant women were diagnosed with syphilis, the information on syphilis infection of their sexual partners was also investigated during case registration. If the partners were untested, they were further required to receive syphilis screening in the “designed hospitals” where the infected women were referred. Once diagnosed with syphilis, they would receive syphilis treatment together with the pregnant women. The real challenge is whether these partners are willing to participate, or whether the infected women have that partners around.