Author's response to reviews

Title: Effectiveness of a prevention of mother-to-child HIV transmission programme in Guangdong province from 2007 to 2010

Authors:

Li Bing (pumpli587@yahoo.com.cn)
Zhao Qing guo (zggfrost@126.com)
Zhang Xiao zhuang (zxz53@126.com)
Wu li (447390763@qq.com)
Chen Ting ting (37501207@qq.com)
Liang Zhi jiang (183558283@qq.com)
Xu Long chang (651906818@qq.com)
Yu Shou yi (522276188@qq.com)

Version: 5 Date: 4 April 2013

Author's response to reviews: see over
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Authors:

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Liang Zhi-jiang (183558283@qq.com)
Xu Long-chang (651906818@qq.com)
Yu Shou-yi (522276188@qq.com)

Version: 2 Date: 27 January 2013

Author’s response to reviews: see over
We very much appreciate the careful reading of our manuscript and valuable suggestions. We have carefully considered the comments and have revised the manuscript accordingly. We have highlighted the changes with blue color in the new manuscript.

Reviewer's report
Title: Effectiveness of a prevention of mother-to-child HIV transmission programme in Guangdong province from 2007 to 2010
Version: 2 Date: 27 January 2013
Reviewer: Joseph Kagaayi
Reviewer's report:
It is not indicated if there was IRB review for this study
Level of interest: An article of limited interest
Quality of written English: Not suitable for publication unless extensively edited

The entire paper was revised by the authors, and the whole manuscript was reviewed by a professor. We hope that we have satisfactorily your constructive suggestions.

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
'I declare that I have no competing interests

Reviewer's report
Title: Effectiveness of a prevention of mother-to-child HIV transmission programme in Guangdong province from 2007 to 2010
Version: 2 Date: 1 February 2013
Reviewer: Wilson Sadoh
Reviewer's report:
Reviewer’s comments on manuscript titled ‘Effectiveness of a prevention of mother to child HIV transmission programme in Guangdong province from 2007 to 2010’

Major compulsory revisions:

1. The authors set out to conduct a case control study, after recruiting the HIV negative mothers and their infants; nothing was heard of them subsequently. It appears that the study was a retrospective review of PMTCT activities in the province. The authors need to clarify this.

We agreed the reviewers’ advices and revised our Study design as following: The retrospective cross-section analysis was conducted using the data of reported case
cards of HIV positive mothers and their infants from 2007 to 2010 in Guangdong province of China. The case cards of HIV positive mothers were reported in five days after their HIV infected status were confirmed, and then the case cards of all infants born to HIV positive mothers were reported in five days after their HIV infected status were tested in the follow up period of 18 months. The mother’s HIV infected status was confirmed by the Western blot after her HIV antibody was positive. The infant’s HIV infected status was confirmed by the Western blot after the HIV antibody was positive at age 12 months and 18 months. If the condition was available, the infant’s HIV infected status was confirmed by HIV DAN polymerase chain reaction (PCR) tests through transported dry blood spots (DBS) at age 6 weeks to 3 months. During the follow up period, there were no death of infants, and only four infants became AIDS patients.

2. In the methods, the authors should clearly state what protocol obtains in the province with respect to ARVs for HIV positive mothers and HIV exposed infants at different entry points into the programme. For example if diagnosis is made antenatally, intrapartum and post partum for mother and baby.

   With the consideration of availability of ARV drugs and existed evidences, and reference of regimen recommend by WHO since 2004, the PMTCT program of Guangdong from 2007 to 2010 used the ARV prophylaxis protocol of zidovudine (AZT) started in late pregnancy, combined with lamivudine (3TC) and single-dose nevirapine (sdNVP) during labour, and stopped in one week after delivery. And women with a CD4 count below 200 cells/mm³ were given antiretroviral treatment. Due to any unexpected reasons, if the HIV positive mothers couldn’t take the ARVs before parturient, the mothers would be offered sdNVP intrapartum as soon as possible.

   The protocol with respect to ARVs was added in the methods.

3. What were the indications for the elective caesarian deliveries was it offered to those whose HIV diagnosis was made intrapatum?

   The indication for the elective caesarian deliveries was if the HIV infected status
confirmed antemataally and the service condition was safe, the pregnancy women were planed to elective caesarian delivery. Those whose HIV diagnosis was made intrapatatum would be offered emergency caesarian or vaginal delivery according clinical needs.

In addition, the recommended safe elective caesarian delivery of PMTCT program in Guangdong from 2007 to 2010 was refer to the trial implement protocol of PMTCT program issued by Health Department of China since 2005. But with the consideration of availability of ARV drugs and new evidences, and the guidelines of PMTCT of WHO in 2010, Health Department of China updated the protocol of PMTCT program in 2010 and didn’t recommend elective caesarian delivery of HIV positive mother, so in the new protocol of PMTCT program in Guangdong since 2011 has no longer recommended elective caesarian and just advised safe delivery, and HIV infected not the indication of elective caesarian for PMTCT anymore, and the delivery mode of HIV positive mother only determined by clinic indications.

Minor essential revision
1. The entire manuscript has numerous grammatical errors; it is certainly not suitable for publication unless extensively edited. I believe this will improve on the level of interest which I currently consider as an article of interest its field. It will also improve the understanding of the manuscript.

The entire paper was revised by the authors, and the whole manuscript was reviewed by a professor. We hope that we have satisfactorily your constructive suggestions.

2. The abstract is rather lengthy, it should be cut down.

We have already cut down our abstract as following: Background: To achieve the goal of United Nations of elimination of new HIV infections, a program of prevention of mother-to-child transmission (PMTCT) was launched in Guangdong province. The objective of this study is to evaluate the effectiveness of the PMTCT program. Methods: The retrospective cross-section analysis was conducted using the data of
case reported cards of HIV positive mothers and their infants from 2007 to 2010 in Guangdong province, and 108 pairs of eligible subjects were obtained. We described the data and compared the rates of MTCT by various PMTCT interventions respectively.

Results: The overall rate of HIV MTCT was 13.89% (15) among 108 pairs of HIV positive mothers and their infants; 60.19% (65) of the mothers ever received ARVs, 80.56% (87) of infants born to HIV positive mothers ever received ARVs, but 16.67% (18) of the mothers and infants neither received ARVs. Among all the mothers and infants, who both received ARVs, received triple ARVs, mother received ARVs during pregnancy, and both received ARVs and formula feeding showed the lower rates of HIV MTCT, and the rates were 8.06%, 2.50%, 5.77%, and 6.67% respectively. In infants born to HIV positive mother, who received mixed feeding had a higher HIV MTCT up to 60.00%. Delivery mode might not relative to HIV MTCT.

Conclusions: The interventions of PMTCT program in Guangdong could effectively reduce the rate of HIV MTCT, but the effectiveness of the PMTCT program were heavily cut down by the lower availability of the PMTCT interventions.

Keywords: HIV/AIDS, Mother to children transmission (MTCT), Anti-retroviral (ARV), Effectiveness of PMTCT
Reviewer #3:
The objective of this study was evaluate an PMTCT program with respect to rates of MTCT by various PMTCT interventions and determine the factors influencing MTCT rates.

**Major Compulsory Revisions**

**General:** The manuscript requires lots of grammatical edits

The entire paper was revised by the authors, and the whole manuscript was reviewed by a professor.

**Methods**

1) About 45 percent of the potential participants did not meet eligibility criteria. The study population is potentially highly selected and results may not be generalizable. The authors note that the biggest reason for non-eligibility was loss to follow-up. The authors do not give information about the possible losses to follow-up. Authors would have to rule-out competing risks such as death of infants (especially if they were HIV–infected). This study therefore has the potential to under-estimate the MTCT rates.

We have already added the information about the possible losses to follow-up in our discussion as following: All of the excluded objects were due to loss to follow-up the HIV infectious status of infants, which mostly because of population flowing and the parent was afraid of impact to the life of their child after the HIV infectious status was exposed. According to the information of mothers’ reported cards, in 88 subjects who lost to follow up, the mean age of mother was 28.78±5.28 years, which was higher than the mean age of targeted subject (t=2.13, p=0.03); But the distributions of marital status, education level, occupation, and the rate of ARV prophylaxis were no significant difference respectively between lost follow up mothers and targeted mothers (p>0.05). And 67.05% (59/88) of mothers and 79.55% (70/88) of their infants ever received ARVs among 88 subjects who lost to follow up. According to these data, it was suppose that the estimation of MTCT rates in this study was acceptable.

Therefore, we think that although maybe we under-estimate the MTCT rates, because of the general statuses of the subjects lost to follow-up were comparable with that of the targeted subjects, this under-estimate the MTCT rates will minimum or be disregard.
2) Authors report that they did a case-control analysis. The implication of this is that the study was a casecontrol study. Clearly this is not a case-control study. The study looks at cumulative HIV infection by 18 months as the outcome and predictors of infection ascertained from medical records. This analysis is more of cross-section than case-control.

We have already revised our method to cross-section analysis. The details as following: The retrospective cross-section analysis was conducted using the data of reported case cards of HIV positive mothers and their infants from 2007 to 2010 in Guangdong province of China. The case cards of HIV positive mothers were reported in five days after their HIV infected status were confirmed, and then the case cards of all infants born to HIV positive mothers were reported in five days after their HIV infected status were tested in the follow up period of 18 months.

3) The authors report results on timing of infant HIV infection but they do describe how and when infant HIV testing was done. Was it done at birth, 6 weeks etc? was is done using DNA PCR, RNA PCR, or ELISA tests at 18 months. This is important for assessing the validity of HIV tests reported by time of infection.

We tested HIV of mothers and infants of the PMTCT program as following: The mother’s HIV infected status was confirmed by the Western blot after her HIV antibody was positive. The infant’s HIV infected status was confirmed by the Western blot after the HIV antibody was positive at age 12 months and 18 months. If the condition was available, the infant’s HIV infected status was confirmed by HIV DAN polymerase chain reaction (PCR) tests through transported dry blood spots (DBS) at age 6 weeks to 3 months. During the follow up period, there were no death of infants, and only four infants became AIDS patients.

We have already added these contents in our method of the manuscript.

4) Since the was interested in determining factors influencing MTCT rates, multivariable analyses are necessary appropriate.
Thanks for this suggestion. We have already done multivariable logistic regression analysis. However, due to the number of the HIV positive infants was too small, the results were unsatisfied. And the main objective of our study is to evaluate the effectiveness of the PMTCT program by comparing the rates of MTCT by various PMTCT interventions respectively, so we did the mono-variable analyses. And we have already revised the purpose of the study accordingly.

In addition, we think that the influencing factors of influencing MTCT rates need to further analyses and study, so we have cut down the try to analyses the influencing factors in our revised manuscript. Because the influencing factors of MTCT rates are complicated and multiple, maybe includes the accessible of PMTCT intervention such as HIV test, the ARV drugs, safe delivery, eligible feeding, and the capability of the providers and system of health care, the convenience and integrated of PMTCT service, the social-economy influencing factors, the knowledge, attitude, behavior of MTCT of individual, the individual variation of physiology and genetics, the resource and policy of PMTCT, and so on.

Results
It is difficult to follow a number of percentages in the manuscript. Some do not add-up to 100. Consider this section for example “Among 108 HIV positive puerperants and their infants, 16.67% (18/108) of them did not received ARVs, 2.78% (3/108) of them only mothers received ARVs, 23.15% (25/108) of them only infants received ARVs, 57.41% (62/108) of them both mothers and infants received ARVs, and 37.04% (40/108) of puerperants received triple ARVs regimen”
Also consider this “…..only 60.19% (65/108) of them received ARVs prophylaxis during perinatal period…” and compare it to “….Only 55.56% (60/108) received ARVs prophylaxis during labor….Only 51.85% (56/108) received ARVs prophylaxis postnatal”
In the statement “…..As to the confirmed period of HIV infected status of 108 puerperants, 5.56% (6) were before pregnancy, 53.70% (58) were during pregnancy, 18.52% (20) were in the intrapartum period, 22.22% (24) were in the postpartum
period" It is difficult to understand what the authors mean by infection before pregnancy in the MTCT context. The authors use this is other places in the manuscript.

We are sorry that we couldn’t present our results clearly, and (1) the 40 puerperants received triple ARVs regimen were another category and different to who received ARVs, (2) the optimal ARV prophylaxis protocol of the PMTCT program was zidovudine (AZT) started in late pregnancy, combined with lamivudine (3TC) and single-dose nevirapine (sdNVP) during labour, and stopped in one week after delivery. Because of bad available or clinic advice effect of ARVs, the HIV positive mothers might receive the ARVs on one period of during pregnancy, intrapartum and postpartum, therefore, the percentages of when received ARVs were the person-time percentages, and might add up to more than 100. (3) The before pregnancy means before the present pregnancy, includes marital medical examination, during the other health care service like induced abortion, physical examination, visit besides pregnancy, and so on. We have already revised these problems as following:

In all of 108 HIV positive mothers, only 60.19% (65) of them ever received ARVs prophylaxis from 28 weeks to one week of postpartum, but only 37.04% (40) of mothers received triple ARVs regimen.

In the 52 (48.15%, 52/108) mothers who received ARVs prophylaxis antenatally, 59.62% (31) received AZT, 26.92% (14) received sdNVP+3TC+AZT, 3.85% (2) received 3TC+AZT.

In the 60 (55.56%, 60/108) mothers who received ARVs prophylaxis intrapartum, 66.67% (40) received sdNVP+3TC+AZT, 15.00% (9) received sdNVP+AZT, 10.00%(6) received AZT, 8.33% (5) received 3TC+AZT.

In the 56 (51.85%, 56/108) mothers who received ARVs prophylaxis postnatal, 48.21% (27) were 3TC+AZT, 30.36% (17) were sdNVP+3TC+AZT, 17.86% (10) were AZT, 1.79% (1) were sdNVP+AZT, 1.79% (1) were 3TC.

There were 80.56% (87/108) of infants born to HIV positive mothers received ARVs prophylaxis, and in these 87 infants, 77.01% (67) of them received sdNVP+AZT, 10.34% (9) received AZT, 8.05% (7/87) received sdNVP, 3.45% (3) received
3TC+AZT, 1.15% (1) received 3TC+sdNVP+AZT.

As to the confirmed period of HIV infected status of 108 mothers, 5.56% (6) were before the present pregnancy, 53.70% (58) were antenatal of this pregnancy, 18.52% (20) were in the intrapartum of this pregnancy, 22.22% (24) were in the postpartum of this pregnancy.

**Minor Essential Revisions**

I guess by puerperants the authors mean mothers. Could they use mother instead

We have already used mothers instead puerperants.
Reviewer #4:

Reviewer’s comments on manuscript titled ‘Effectiveness of a prevention of mother to child HIV transmission programme in Guangdong province from 2007 to 2010’

Major compulsory revisions:

1. The authors set out to conduct a case control study, after recruiting the HIV negative mothers and their infants; nothing was heard of them subsequently. It appears that the study was a retrospective review of PMTCT activities in the province. The authors need to clarify this.

   We have already changed to use retrospective cross-section analysis, and revised our Study design as following: The retrospective cross-section analysis was conducted using the data of reported case cards of HIV positive mothers and their infants from 2007 to 2010 in Guangdong province of China. The case cards of HIV positive mothers were reported in five days after their HIV infected status were confirmed, and then the case cards of all infants born to HIV positive mothers were reported in five days after their HIV infected status were tested in the follow up period of 18 months. The mother’s HIV infected status was confirmed by the Western blot after her HIV antibody was positive. The infant’s HIV infected status was confirmed by the Western blot after the HIV antibody was positive at age 12 months and 18 months. If the condition was available, the infant’s HIV infected status was confirmed by HIV DAN polymerase chain reaction (PCR) tests through transported dry blood spots (DBS) at age 6 weeks to 3 months. During the follow up period, there were no death of infants, and only four infants became AIDS patients.

2. In the methods, the authors should clearly state what protocol obtains in the province with respect to ARVs for HIV positive mothers and HIV exposed infants at different entry points into the programme. For example if diagnosis is made antenatally, intrapartum and post partum for mother and baby.

   Thanks for this suggestion. The protocol with respect to ARVs was added in the methods. The added protocol as following: With the consideration of availability of ARV drugs and existed evidences, and reference of regimen recommend by WHO
since 2004, the PMTCT program of Guangdong from 2007 to 2010 used the ARV prophylaxis protocol of zidovudine (AZT) started in late pregnancy, combined with lamivudine (3TC) and single-dose nevirapine (sdNVP) during labour, and stopped in one week after delivery. And women with a CD4 count below 200 cells/mm$^3$ were given antiretroviral treatment. Due to any unexpected reasons, if the HIV positive mothers couldn’t take the ARVs before parturient, the mothers would be offered sdNVP intrapartum as soon as possible.

3 What were the indications for the elective caesarian deliveries was it offered to those whose HIV diagnosis was made intrapatum?

The indication for the elective caesarian deliveries was if the HIV infected status confirmed antematially and the service condition was safe, the pregnancy women were planed to elective caesarian delivery. Those whose HIV diagnosis was made intrapatum would be offered emergency caesarian or vaginal delivery according clinical needs.

In addition, the recommended safe elective caesarian delivery of PMTCT program in Guangdong from 2007 to 2010 was refer to the trial implement protocol of PMTCT program issued by Health Department of China since 2005. But with the consideration of availability of ARV drugs and new evidences, and the guidelines of PMTCT of WHO in 2010, Health Department of China updated the protocol of PMTCT program in 2010 and didn’t recommend elective caesarian delivery of HIV positive mother, so in the new protocol of PMTCT program in Guangdong since 2011 has no longer recommended elective caesarian and just advised safe delivery, and HIV infected not the indication of elective caesarian for PMTCT anymore, and the delivery mode of HIV positive mother only determined by clinic indications.

Minor essential revision
1. The entire manuscript has numerous grammatical errors; it is certainly not suitable for publication unless extensively edited. I believe this will improve on the level of interest which I currently consider as an article of interest its field. It will also improve
the understanding of the manuscript.

The entire paper was revised by the authors, and the whole manuscript was reviewed by a professor. We hope that we have satisfactorily your constructive suggestions.

2. The abstract is rather lengthy, it should be cut down. Declaration of competing interests: None declared Assessment: There are previous works on the impact of PMTCT, the difficulty with reading and understanding the authors of the current work makes it difficult to do a fair assessment. I am unable to reject or accept the manuscript until the major revisions have being sorted out.

We have already cut down our abstract as following: Background: To achieve the goal of United Nations of elimination of new HIV infections, a program of prevention of mother-to-child transmission (PMTCT) was launched in Guangdong province. The objective of this study is to evaluate the effectiveness of the PMTCT program.

Methods: The retrospective cross-section analysis was conducted using the data of case reported cards of HIV positive mothers and their infants from 2007 to 2010 in Guangdong province, and 108 pairs of eligible subjects were obtained. We described the data and compared the rates of MTCT by various PMTCT interventions respectively.

Results: The overall rate of HIV MTCT was 13.89% (15) among 108 pairs of HIV positive mothers and their infants; 60.19% (65) of the mothers ever received ARVs, 80.56% (87) of infants born to HIV positive mothers ever received ARVs, but 16.67% (18) of the mothers and infants neither received ARVs. Among all the mothers and infants, who both received ARVs, received triple ARVs, mother received ARVs during pregnancy, and both received ARVs and formula feeding showed the lower rates of HIV MTCT, and the rates were 8.06%, 2.50%, 5.77%, and 6.67% respectively. In infants born to HIV positive mother, who received mixed feeding had a higher HIV MTCT up to 60.00%. Delivery mode might not relative to HIV MTCT.

Conclusions: The interventions of PMTCT program in Guangdong could effectively reduce the rate of HIV MTCT, but the effectiveness of the PMTCT program were
heavily cut down by the lower availability of the PMTCT interventions.

Keywords: HIV/AIDS, Mother to children transmission (MTCT), Anti-retroviral (ARV), Effectiveness of PMTCT

Declaration of competing interests: None declared

Assessment: There are previous works on the impact of PMTCT, the difficulty with reading and understanding the authors of the current work makes it difficult to do a fair assessment. I am unable to reject or accept the manuscript until the major revisions have being sorted out.