Author’s response to reviews

Title: Syndemics of syphilis, HCV infection, and methamphetamine use along the east coast of China

Authors:

   meizhen liao (liaomz161@126.com)
   dianmin kang (hivjiance@126.com)
   xiaorun tao (hivjiance@126.com)
   yuesheng qian (hivjiance@126.com)
   guoyong wang (hivjiance@126.com)
   cui yang (cyang@jhsp.h.edu)
   xiaoyan zhu (hivjiance@126.com)
   na zhang (hivjiance@126.com)
   zhenqiang bi (bzg63@163.com)
   yujiang jia (jiayj@aol.com)
   Catherine Cox (katiecakesc@gmail.com)

Version: 5 Date: 8 January 2014

Author’s response to reviews: see over
January 8, 2014

RE: BMC Public Health- Manuscript ID-1765436590851401: Syndemics of Syphilis, HCV Infection, and Methamphetamine Use along the East Coast of China

Dear Editor,

Many thanks for the revision and improvement opportunities. Although this is the fourth revisions, all authors have worked together in providing point-by-point responses to the issues raised by the reviewers. All major revisions are highlighted in RED in the manuscript.

**Previous comments not adequately addressed.**

*Point 9 How did the recruitment took place? How many participants were recruited through which recruitment strategy? A flow chart could be informative to present recruitment. It is still not clear how many participants were recruited through which recruitment strategy.*

Thanks for the reviewer’s comments. Here are some details about the recruitment process. Prior to the recruitment of the participants, we conducted informative research including in-depth interviews with key informants to gather the background information among drug users, e.g., the venues to access them, selection of the candidates of the first group for interview, and sampling frame. All potential participants were invited for an eligibility assessment. Recruitment criteria required that participants be willing to complete the study, and self-report having used drugs in the past year. Participants were approached from drug user gathering venues, such as bars, night clubs, bathhouses, saunas, public parks, outdoor cruising areas, and HIV testing sites. After these initial participants were approached and interviewed after an eligibility assessment, we asked the participants to refer their peers to attend the study. A mixed recruitment method, including community outreach, venue-based recruitment, and peer referrals, was applied in the study. Structured questionnaire based interviews were conducted by trained health professionals in a carefully selected clinic in each city. Voluntary participation, anonymity, and confidentiality were ensured for all participants. Some of the participants did not want to visit the clinic, so the trained interviewer conducted their interviews within the community or venues such as hotels or bars. The revisions were made in the Methods Section and highlighted in red.

We also recognized the limitation of the study that non-response or refusal information of the participation was not collected during the recruitment process that could reduce to the representativeness of the study participants, which is acknowledged in the Discussion Section on page 13. Therefore, we are not able to provide a flow chart that could be informative to present recruitment. It is not clear how many participants were recruited through which recruitment strategy.

*Point 10 Recruitment criterium: participants should be willing to complete the study.*
This leads to a selection bias, and should be mentioned in the discussion. How many people were recruited/asked and how many agreed to participate in the study? It is still not clear how many people were recruited/asked and how many agreed to participate in the study. The sentence ‘It could be another limitation that non-response or refusal of the participation was not collected.’ is unclear and grammatically incorrect. Information on study participation is an important measure of the quality of the study. For example, if 50 drug users were recruited and only 1 participated versus 50 recruited and 40 participated. If this information is missing, this should be acknowledged. Please rephrase into; ‘Second, information on study participation was lacking. Non-response could be substantial in this study because drug use is illegal in China. Moreover, the recruitment criterion to complete the study could have led to a selection bias. Therefore the results of this study are not fully generalizable to drug users in other settings or countries.’

Many thanks for the reviewer’s suggestions. We have incorporated those suggestions in lines 5-8 on page 13 in the Discussion Section.

Point 14 Did you test for confounding and effect modification? Details on effect modification are missing.

Thanks for the reviewer’s comment. More details were added in the Statistical Analyses, “The prevalence rates were calculated by demographic characteristics, drug use and sexual behaviors, and utilization of HIV-related prevention services.” in line 4 in the “Statistical Analyses” of Result Section. All potential co-linearity, potential confounding, and effect modification were examined and taken into consideration in the final models.

Results

Point 18 Generally, syphilis is a problem in a specific risk group for STDs; men who have sex with men. Do you have any information regarding sexual preference of the participants? Otherwise, this should be mentioned as a limitation in the Discussion.

We did not collect all participants’ sexual preference in this study. We added it as the limitation of the study in line 1 of the last paragraph on page 13 in Discussion Section.

Discussion

Major compulsory revisions

Point 22 Drugs were not associated with syphilis infection. Only injecting drug use was independently associated with HCV infection, although it is not clear which type injected drug, probably heroin. This is a main result of the study and should be stated more clearly. ‘All participants are drug users, therefore, this study could not conclude whether or not the drugs were associated with syphilis infection. However, all syphilis cases (77) are methamphetamine users with 2 of them also ketamine and amphetamine users. Drug use is strongly associated with syphilis. This explanation seems contradictory. Indeed this study can not conclude whether drug use is associated with syphilis. However, syphilis
prevalence in this study can be compared with syphilis prevalence in the general population or other risk groups to highlight the syndemics of drug use. Please add this in the discussion to make a better statement. Can you distinguish between which type injected drug was associated with syphilis infection, in addition to comment #9.

Of all participants in this study, 11.4% (n=92) reported having ever injected drugs, among which 68.5% reported having ever injected club drugs, 16.3% injected traditional drugs and 15.2% injected traditional /club drugs.Injecting drug wasn’t associated with syphilis infection. The HCV prevalence was 9.78% among injection drug users and 2.94% among non-injection drug users. Injection drug use was associated with HCV infection. We added this content in the first paragraph on page 12 in Discussion section. We also added the syphilis prevalence among FSW, MSM, pregnant women and unpaid blood donors in the same year to highlight the syndemics of drug use. The revision was made in lines 2-4 of the second paragraph on page 10 in the Discussion Section.

Point 23 Independent risk factors for syphilis were female sex, having commercial sex in the past 12 months, with less regular sex partners and co infection with HCV. No conclusions are made to target syphilis prevention in female sex workers, although this is the most vulnerable group for possible syphilis infection according to your results. ‘Our previous report (Liao et al. Sexually Transmitted Diseases, 2011) revealed an alarmingly high prevalence of methamphetamine use among FSWs. Methamphetamine users were more likely to be single, younger, inconsistent condom users, and have syphilis.’ This is the conclusion of another study, my question was about syphilis prevention which seems warranted regarding the results of this study.

Of all participants in this study, 17.8% (n=143) were female, among which 65.0% (n=93) reported having commercial sex. The syphilis prevalence was significantly higher among those females who have ever had commercial sex than those females who have never had commercial sex (22.5% VS. 8.0%). Our previous report also showed methamphetamine use among FSWs was independently associated with unprotected sex and syphilis (Liao et al. Sexually Transmitted Diseases, 2011). More explanation was made in lines 1-7 of the second paragraph on page 11 in the Discussion Section.

Point 24 Independent risk factors for HCV were injecting drug users and co-infection with syphilis. No recommendations for information/prevention programs were made. According to this study, needle sharing of injecting drug users could be a reasonable cause of the HCV infections.

Thanks for the reviewer’s excellent suggestions. We included the following in the Discussion Section (lines 1-4 of the first paragraph on page 12), “Independent risk factors for HCV were injection drug users and co-infection with syphilis. According to this study, needle sharing of injection drug users could be a reasonable cause of the HCV infections. The findings underscore that harm reduction clear needle should be emphasized.”

Point 25 The sentences ‘China has seen…of Shandong Province’ (China has seen an upsurge in club drug use in recent years, especially methamphetamine, quickly replacing
heroin to become the widespread illicit drugs in the nation. However, research on HIV/other STDS/HCV and club drugs remains scarce in China; both the extent of the epidemic and club drug abuse behaviors and social consequences of club drug use are not yet to be fully recognized. This study contributes to understanding the emergent role of club drug abuse on the HIV/STD epidemic and its association with risky sexual behavior in the 2 cities of Shandong Province.) are well written and should be moved to the Introduction. It represents your study objective more concise than current sentences in the Introduction. Please indicate if the sentences have been deleted or rephrased.

We moved the sentence to the Introduction. We divided the sentence into two parts, the former part “China has seen… across the nation” was moved to the lines 3-5 in the first paragraph on page 5, and the second part “However, the research…of Shandong Province” had some revisions made to it and moved to the lines 2-8 in the second paragraph of the Introduction Section.

Point 30 ‘Despite these limitations and possible biases, we feel the data highlight a prevention opportunity that cannot be ignored.’ Think about which prevention opportunities are supported by the results of this study and which prevention opportunities are supported by literature. ‘The current intervention efforts for substance abuse in China is still concentrated on heroin, which played an important role in China’s HIV/AIDS epidemic in the past decades, but so far no efforts have been made to tackle the new emerging challenge of club drug use. However, unprotected heterosexual contacts has been increasing proportionally in contribution of HIV transmission in China, and the club drug abuse could potentially fuel this trend in the nation without better-targeted, effective intervention efforts taking place in a timely fashion.’ This was still missing in the manuscript.

The results of this study showed new types of drugs, especially MA, have become the predominant source of drug abuse in these two cities in China. More sex and drug-related intervention efforts should be made to target syphilis prevention in female sex workers, especially those drug using female sex workers. The revision was made in the lines 6-8 of the second paragraph on page 12 in Discussion Section.

Additional comments

Introduction

However, in recent years, China has seen an upsurge in club drug use in recent years, especially methamphetamine, which is quickly replacing heroin to become the most widespread illicit drug across the nation.

Statistical analyses

Point 1 ‘The prevalence rates were calculated using demographic characteristics, drug use and sexual behaviors, and utilization of HIV-related prevention services’

The sentence was revised as “The prevalence rates of syphilis, HCV and unprotected sex were calculated by demographic characteristics, drug use and sexual behaviors, and
utilization of HIV-related prevention services”.

**Point 2 What kind of univariate and multivariable analyses was performed; logistic of lineair.**

The univariate involving only one variable was applied for analysis, the multivariable logistic regression analysis was performed, not linear regression analysis.

**Point 3 What procedure was used for the multivariable model (e.g. backward stepwise).**

The backward stepwise procedure was applied.

**Results**

**Point 4 ‘Of 805 eligible participants, 82.8% were male; 28.0% single, 70.2% currently married or cohabitating;’ Did you exclude participants who did not completed the survey (how many?)?**

We only analyzed those eligible participants, we didn’t collect the number of non-response or refusal of participation, and it is not clear how many participants were recruited through which recruitment strategy.

**Point 5 ‘about 66.8% correctly answered at least 6 out of 8 questions on HIV transmission,’ Delete the word ‘about’ .**

The revision was made on page 9 in the Result Section.

**Point 6 ‘only 16.1% received HIV-related intervention in the past 12 months;’ Delete the word ‘only’. Results should be interpreted in the discussion.**

The revision was made on page 8 in the Result Section. The low proportion of HIV-related prevention services reflected the low intervention efforts. We made interpretation in lines 14-16 of the second paragraph on page 11 in the Discussion Section.

**Point 7 ‘while only 52.6% knew their HIV test result (Table 1).’ Delete the word ‘only’. Results should be interpreted in the discussion.**

The revision was made on page 9 in the Result Section. This study showed only 4.7% had a test for HIV in the past 12 months while 52.6% knew their HIV test result. Drug use is illegal in China, most drug users don’t come back to get their HIV test result or change their contact phone number. This highlighted the great need to improve VCT accessibility targeted drug users. Interpretation was showed in lines 15-16 of the second paragraph on page 11 in the Discussion Section.

**Point 8 ‘Of the participants, 96.6% (778) were methamphetamine users, 6.3% (51) ketamine users, 4.5% (36) MAMD users, 4.0% (32) amphetamine users and 3.2% (26) heroin users.’ Please add n=, for example (n=778) in the manuscript.**
The revision was made in the Results Section.

**Point 9** What is the difference between heroine use and injecting drugs? This is not clear in the manuscript. Which drugs are injected? This is important for HIV, HCV and syphilis infection.

Of all participants, 11.4% (n=92) reported having ever injected drugs with 15 traditional drug users, 63 club drug users and 14 traditional/club drug users.

**Point 10** ‘Of the participants, 98.8% reported ever having sex with regular sex partners,’ In addition to reviewer #1, the definition of regular sex partner is still missing. It seems likely to me that a person can only have 1 regular sex partner.

The regular sex partner refers to their spouse if married or the sex partners that are not married but live together. The revision was made in the Measures Section on page 7.

**Point 11** ‘Of the participants, 0.2% were infected with HIV, 9.6% with syphilis and 3.7% with HCV. 1.4% (11) were infected with both syphilis and HCV. Please add n=, for example (n=778) in the manuscript.

The revision was made in the Results Section.

**Point 12** In the introduction the focus of the paper is on HIV/STD transmission. However, a multivariable model for HIV correlates was lacking. This should be added.

Only 2 HIV positives were found in this study, because the number of HIV positives were limited, a multivariable model for HIV correlates was lacking in this study.

**Point 13** Move ‘unprotected sex’ to drug use and sexual behaviors.

The revision was made in the Results Section on page 9.

**Point 14** Combine prevalence and correlates of HIV, syphilis and HCV into one paragraph.

The revision was made in the Results Section on page 10.

**Point 15** Use the same sequence of variables in methods, results and discussion. For example in the discussion HIV was mentioned first and the next sentence starts with MA use. ‘This is the first to report on the assessment of the syndemics of HIV, syphilis, HCV, and MA use among drug users in China. This study found alarmingly high rates of MA use (96.6%), syphilis (9.6%), and HCV infection (3.7%) among drug users in the two cities along the east coast of China with historically low HIV prevalence.’
Thanks for the excellent suggestions. We have revised the sequence of variables in the methods, results and discussion.

Point 16 Add HIV prevalence to the above sentences.

It was revised as:
‘This is the first to report on the assessment of the syndemics of HIV, syphilis, HCV, and MA use among drug users in China. This study found alarmingly high rates of syphilis (9.6%), HCV infection (3.7%), and MA use (96.6%) among drug users in the two cities along the east coast of China with historically low HIV prevalence.’ We did not include HIV prevalence since it is low at this moment.

Point 17 Shortly describe the other predictors besides ‘Syphilis and HCV infection predicted each other.’

The revision was made in line 5 of the first paragraph in the Discussion Section on page 10.

Point 18 This sentence belongs in the introduction. ‘MA use quickly replaced heroin as the most widespread abused drug in China [8]. However, research on club drugs and its impact on HIV/other STDs including syphilis and HCV remains scarce in China.’

Thanks for the reviewer’s comments. We deleted this sentence in the Discussion Section since we have a similar description in the Introduction Section.

Point 19 Move this section to the introduction after ‘across the nation’... ‘In recent years, Shandong is one of the provinces confronting the rapid emerging club drug use. One of the cities along the east coast has been named the “ice city”, for its common use of club drugs, especially among young people. MA and other club drugs are often used in entertainment venue settings, such as hotels, Bars, KTV and tea houses. Club drugs were perceived as a pastime, an entertainment additive without any stigma attached to it, rather than the highly stigmatized traditional substance abuse. Methamphetamine can be smoked, snorted, injected or orally ingested. These drugs meet the psychological characteristics of young people, e.g., curiosity, wonder, and excitement [19, 20].’

This section was moved to lines 5-13 in the Introduction Section on page 5 according to the reviewer’s suggestion.

Point 20 This is not a conclusion of this study: ‘There is a general lack of knowledge about the harmful impact of club drugs, as shown by a study in which 44.3% of the respondents considered club drug use as being of little or no harm at all [12]. Most young people in Thailand perceived MA as controllable and does not cause negative consequences [21]; therefore, the misperception toward club drugs could also fuel the epidemic of club drug abuse.’ Start with discussing the results of this study.

Many thanks for the reviewer’s suggestion, we deleted the sentences “There is a general
lack……..could also fuel the epidemic of club drug abuse”, and added content discussing
the results of this study in lines 1-7 of the second paragraph of the Discussion Section on
page 11.

Point 21 What STD, please be clear you only tested for HIV, syphilis and HCV.
‘It is even more worrisome that club drug users will take a potential role in the
epidemiologic bridge of HIV/STD transmission to their regular sex partners [23].’

“STD” was revised as “syphilis” in this sentence.

Point 22 Do not repeat results in the discussion; interpret the results. For example:’ This
study showed that 98.8% reported ever having sex with regular sex partners, with 74.7%
never using condoms in the past 12 months and 92.7% not using a condom in the last
sexual encounter.’

We made revisions to not repeat results in the Discussion Section, revisions were made in
lines 5-7 of the first paragraph on page 11.

Point 23 ‘and the prevention infrastructure has not been strategized to tackle the newly
emerging challenge of club drug abuse.’ What kind of prevention do the authors
recommend? This is missing in the discussion.

This study showed low VCT and intervention accessibility and less intervention efforts
targeted to this group. The current intervention efforts are less focused on club drug users.
Condom promotion effect is not good among club drug users, and more efforts should be
focused on health promotion and behavioral intervention in the community and the
establishment of syphilis referral mechanism with treatment as prevention, et al.

Point 24 Move the limitations to the end of the discussion.

The revisions were made according to reviewer’s suggestion.

Point 25 ‘Further research is needed’ is a vague statement. Be more specific; what kind
of research, which important information is still missing?

Thanks for the reviewer’s suggestion. We added additional research suggestions, “……
and further research is needed to better understand the causal pathway of the syndemics,
the driven forces for high prevalence of syphilis, HCV, and MA use.

Point 26 Table 1 ‘Subtotals do not add up to 100% for some variables because of
missing values’ Response to reviewer #1; ‘Because the variables “types of drugs” and
“injected drug use” were multi-choice variables, the percentages will not add up to
100%.’ This should also be added to the table, or described in methods.

We added it to Table 1.
Point 27 Table 2. OR and 95% CI are described in table 2, therefore remove OR and 95% CI from text in results and refer to table 2.

Thanks for the reviewer’s excellent comments. The revisions were made in the Conclusion of the abstract.

Again, we are grateful for the revision and improvement opportunities. We look forward to you reviewing our revised manuscript. If you have any questions, please feel free to contact Meizhen at liaomz161@126.com/+86-186-1528-1775 (Beijing Time) or Yujiang at jiayj@aol.com/+1-615-482-1512 (Eastern Time, as in Washington DC, USA).

Sincerely,

Meizhen Liao, MD, PhD
Shandong Center for Disease Control and Prevention

Yujiang Jia, MD, DrPH
Vanderbilt University School of Medicine