

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	HIV prevalence and factors associated with HIV infection among transgender women in Cambodia: Results from a national integrated biological and behavioral survey
AUTHORS	Chhim, Srean; Ngin, Chanrith; Chhoun, Pheak; Tuot, Sovannary; Ly, Cheaty; Mun, Phalkun; Pal, Dyla; Macom, John; Dousset, Jean-Philippe; Mburu, Gitau; Yi, Siyan

VERSION 1 - REVIEW

REVIEWER	Glenn-Milo Santos Department of Community Health Systems School of Nursing University of California, San Francisco United States of America
REVIEW RETURNED	14-Dec-2016

GENERAL COMMENTS	<p>This is an interesting paper that evaluated the HIV prevalence among transgender women in Cambodia and explored correlates of HIV infection. Transwomen are disproportionately impacted by HIV worldwide, yet they continue to be under-researched. Therefore, this study makes an important contribution to the literature and helps fill in the gaps in our understanding of HIV correlates among transwomen. However, some revisions can further strengthen this manuscript before publication. Below are my specific recommendations for the authors:</p> <p>Introduction</p> <p>1. In the final sentence in the introduction, the authors state that the purpose of the study was also to identify "...ways in which services and policies can be tailored for this [transwomen] population." However, very little information is provided on the level of access to HIV prevention services (condoms and lubricants, HIV and STI testing and treatment, and programs at NGOs). It would be helpful to information on access to these services to address the purpose stated in the introduction. Otherwise, the authors should tweak their introduction to reflect the emphasis on HIV infection only.</p> <p>Methods</p> <p>2. In lines 143-145, the null and alternative hypothesis do not seem to be parallel since the null is framed as cross-sectional, while the alternative is framed in terms of a % decrease. Can the authors clarify? Also, can the authors specify what the % decrease in HIV prevalence is relative to?</p> <p>3. Since authors only looked at the outcome of HIV infection, they should replace multivariate with multivariable throughout the manuscript.</p> <p>4. The study was collected using Respondent Driven Sampling, yet</p>
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	<p>the authors did not seem to conduct any RDS-weighted analyses to account for sampling weights and homophily. This seems like a missed opportunity and doesn't fully leverage the strengths from an RDS-collected dataset. Can the authors clarify why RDS-weighted analyses were not done, especially for the primary multivariable logistic regression model on HIV infection correlates? If there is no compelling reason why it was not done, I highly encourage the authors to conduct this analytic approach.</p> <p>Discussion</p> <p>5. It would be helpful if the authors compare the HIV prevalence rate among transwomen in the study (5.6%) to the most recent prevalence rates in the general adult population in Cambodia (similar to lines 107-110 in the introduction).</p> <p>6. Do authors have a sense of what may explain the increase in HIV prevalence among transwomen in the current study, compared to the 2012 estimates?</p> <p>7. The fourth paragraph (lines 397-411), could use some tweaking in language since some of the points raised are somewhat speculative (e.g., the last two sentences in that paragraph). It would be helpful if the authors use language that acknowledges the uncertainty behind possible explanations (e.g., "it's possible", "this finding may be explained by", etc.)</p> <p>8. In the limitations section, the authors should include the limitation associated with using a backward elimination approach for model building.</p> <p>9. If the authors choose not to revise the analysis to include RDS-weighting, they should also add this as a limitation in their paper.</p>
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REVIEWER	Michele Andrasik Fred Hutchinson Cancer Research Center; University of Washington USA
REVIEW RETURNED	13-Jan-2017

GENERAL COMMENTS	<p>This is an incredibly important topic and one that requires a great deal of attention and research. My initial enthusiasm was damped by the lack of clarity, organization and breadth of the information presented. Although the manuscript is presented as a review it follows none of the required steps to constitute a review. I found the manuscript to be incredibly disjointed and at times difficult to follow. The specific stories are incredibly interesting but the author indicated that they are cases and what is presented does not provide enough detail to satisfy a case study. When reviewing the major models, this also seems like a very superficial overview. There is not an extensive review of the literature or enough depth in the exploration of these models to characterize this as a review. Please consider either presenting a case study or conducting a systematic review of the literature. What you have here is neither and although incredibly interesting this does not meet the necessary standards for publication in a peer-reviewed scientific journal nor does it add to the existing literature.</p>
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REVIEWER	Ellen Weiss Wiewel New York City Department of Health and Mental Hygiene, USA
REVIEW RETURNED	02-Feb-2017

GENERAL COMMENTS	<p>This paper reports the findings of an updated respondent-driven sampling survey of transgender persons in 13 areas of Cambodia. Specifically, it presents HIV prevalence and other characteristics such as sexual behavior and drug use among transgender women. It also investigates factors associated with HIV infection. The authors find an HIV prevalence rate of >5% in this population, with HIV infection associated with residence in an urban area, lower education level, older age, gender expression solely as a woman, and other factors. This paper is focused, comprehensive, and generally very strong. The results section is well-organized. The discussion section methodically reviews each factor associated with HIV infection and interprets the findings.</p> <p>General suggestions are as follows:</p> <ul style="list-style-type: none"> -Throughout the paper, transgender women wearing women's clothes as referred to as "dressing up as a woman." I suggest that this be changed to "dressing as a woman" or "presenting as a woman." "Dressing up" suggests a costume. A person who feels that she is a woman is not wearing a costume if she is wearing clothing that accurately reflects her gender identity. This may just be a language issue; the paper otherwise seems sufficiently sensitive to the study population. -In the methods, results, and/or discussion, it would be helpful to (a) clearly state the type or range of online service referred to, and (b) justify the focus on services that were online and transgender-specific. Was NGO HIV service contact, for example, also entered into the model and just not significant, and is that why it's also not in Table 1? From survey question Q066 and the manuscript tables and text, it's unclear whether "online services developed for people like you (e.g. Facebook, website)" means online dating, health and social services, or is ambiguous. The distinction is important for interpreting the finding. -Perhaps not necessary to address, but please consider: Does self-report / knowledge of positive HIV status influence the findings? First, do the authors think that people who knew they were positive felt comfortable disclosing to the interviewer, or did some of those who tested positive but didn't report being HIV-positive withhold their status? Second, might the relationship between status and the factors investigated look different between those self-reporting a positive status vs. those who did not? Relevant especially because about HIV-positive persons about evenly split between self-reported and not. Might be interesting to add to Table 2 a further breakdown of the positive testers by self-report. Also would be nice to have text in the discussion section exploring the finding that only about half of the positives self-reported – what could it mean? Undetected HIV, HIV stigma...? -The paper is very well-written in general. However, the authors (or a proofreader) should address the missing or wrong words sprinkled throughout. They never interfere with understanding but should be corrected prior. Suggested additions in ** for a few such places: "developed *for* MSM," "with reactive and non-reactive test*s*," "possible that *the* transgender population," etc. <p>Specific suggestions are as follows:</p> <ul style="list-style-type: none"> -Methods: Unclear what is meant by half or all being recruited. Paper states, "Roughly half of the estimated transgender women in all but five sites were successfully recruited. In five study sites where the
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	<p>estimated number of transgender women was smaller than 100, all transgender women were recruited."</p> <p>-Results, Table 2: Under "Role in anal sex with a man (past 12 months)," please change "incentive" to "insertive"</p> <p>-Discussion: At very beginning of first paragraph, may want to restate the overall prevalence of HIV in this population, since that itself was a main finding.</p> <p>-Discussion: Also in the first paragraph or elsewhere, it might be interesting to discuss more the prevalence of HIV prevention behaviors in this population, e.g., condom use.</p> <p>-Conclusions: The paper nicely describes and explains factors associated with prevalence, but it suggests limited action – really just the last sentence. Would be interesting to build up the Conclusions to be more specific. Love the paper's detail elsewhere but something could be trimmed elsewhere if needed to accommodate expanded conclusions.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1 (Glenn-Milo Santos, University of California, San Francisco, USA)

General comments

1. This is an interesting paper that evaluated the HIV prevalence among transgender women in Cambodia and explored correlates of HIV infection. Transwomen are disproportionately impacted by HIV worldwide, yet they continue to be under-researched. Therefore, this study makes an important contribution to the literature and helps fill in the gaps in our understanding of HIV correlates among transwomen. However, some revisions can further strengthen this manuscript before publication.

RESPONSE

Thank you for your supportive comments. We have taken your comments seriously and revised accordingly. We are happy to give you more information as much as possible if our explanations have not yet been clear.

Introduction

2. In the final sentence in the introduction, the authors state that the purpose of the study was also to identify "...ways in which services and policies can be tailored for this [transwomen] population." However, very little information is provided on the level of access to HIV prevention services (condoms and lubricants, HIV and STI testing and treatment, and programs at NGOs). It would be helpful to information on access to these services to address the purpose stated in the introduction. Otherwise, the authors should tweak their introduction to reflect the emphasis on HIV infection only.

RESPONSE

We revised to "to explore HIV prevalence and identify risk factors associated with HIV infection among transgender women in Cambodia. The study findings will help to determine ways in which services and policies can be tailored for this key population. Please see lines 126-128.

Methods

3. In lines 143-145, the null and alternative hypothesis do not seem to be parallel since the null is framed as cross-sectional, while the alternative is framed in terms of a % decrease. Can the authors clarify? Also, can the authors specify what the % decrease in HIV prevalence is relative to?

RESPONSE

As stated in the first sentence of the paragraph, the sample size estimate was determined for the purpose of surveillance to track the change in the epidemic over time. We expected to see a decline in HIV prevalence when compared to the 2012 IBBS results. Therefore, our null hypothesis was that

HIV prevalence remained constant at 4.2% (which was the prevalence found in 2012). Our alternative hypothesis was that HIV prevalence would drop from 4.2% to 3.0%. Please see lines 144-147.

4. Since authors only looked at the outcome of HIV infection, they should replace multivariate with multivariable throughout the manuscript.

RESPONSE

We have replaced the term 'multivariate' with 'multivariable' throughout the manuscript.

5. The study was collected using Respondent Driven Sampling, yet the authors did not seem to conduct any RDS-weighted analyses to account for sampling weights and homophily. This seems like a missed opportunity and doesn't fully leverage the strengths from an RDS-collected dataset. Can the authors clarify why RDS-weighted analyses were not done, especially for the primary multivariable logistic regression model on HIV infection correlates? If there is no compelling reason why it was not done, I highly encourage the authors to conduct this analytic approach.

RESPONSE

We decided not to conduct RDS-weighted analysis for two reasons:

1. One assumption of RDS-weight relies on the accuracy of self-report on their social network. We observed in the field that participants had difficulties to recall number of their peers. We assume that this assumption may not be met. Therefore, we should not adjust our data relying on possibly unrealizable source.
2. Our sample size should be large enough to be meaningful. We took almost 50% of estimated TG women population in each province.

Discussion

6. It would be helpful if the authors compare the HIV prevalence rate among transwomen in the study (5.6%) to the most recent prevalence rates in the general adult population in Cambodia (similar to lines 107-110 in the introduction).

RESPONSE

We have added this information in first paragraph of discussion:

"This study reveals a HIV prevalence of 5.9% among transgender women in Cambodia, which was about 20 times higher than the 0.3% among women attending antenatal care clinics who represent the general adult population aged 15-45, and about 2.5 times higher than the 2.3% among MSM in 2014. This observed prevalence emphasizes that transgender women in Cambodia are at high risk of HIV, and is consistent with global literature regarding high burden of HIV among this transgender populations." Please see lines: 379-384.

7. Do authors have a sense of what may explain the increase in HIV prevalence among transwomen in the current study, compared to the 2012 estimates?

RESPONSE

We added a possible explanation in second paragraph of discussion: "Although statistically non-significant (p -value= 0.13), the prevalence found in this study was higher than the prevalence of 4.2% reported in the smaller ($n= 891$) TGIBBS conducted in 2012 and was therefore contrary to our hypothesized expectations of reduction in HIV prevalence among this population. Recent progress in Cambodia, where 73% of all estimated HIV positive or 93% of those who have been aware positive are in care, had prompted us to hypothesize the lower prevalence. Although we have no concrete evidence regarding the non-significant increase of HIV prevalence, we suggest that it may be related to sampling variation in the two surveys. The previous study recruited participants only from the capital city and five provinces (Phnom Penh, Battambang, Banteay Mean Chhey, Kampong Cham,

Siem Reap and Preah Sihanouk), whereas our study expanded to additional eight provinces.” Please see lines: 385-394.

8. The fourth paragraph (lines 397-411), could use some tweaking in language since some of the points raised are somewhat speculative (e.g., the last two sentences in that paragraph). It would be helpful if the authors use language that acknowledges the uncertainty behind possible explanations (e.g., “it’s possible”, “this finding may be explained by”, etc.)

RESPONSE

We have changed the language as suggested.

9. In the limitations section, the authors should include the limitation associated with using a backward elimination approach for model building.

RESPONSE

We have added this important limitation in the section: “Fifth, we used backward selection in multivariable analysis. By using this method, we possibly dropped one or more variables that would be significant if we keep them until final model.” Please see lines 502-505.

10. If the authors choose not to revise the analysis to include RDS-weighting, they should also add this as a limitation in their paper.

RESPONSE

We used respondent driven sampling, but we did not take into account the RDS-weighting because we believe some of RDS assumptions may not have been met. In this sense, it possibly that selection bias may have occurred. Those who have larger social networks may have more chance to be recruited by their peers. However, we have not known their HIV risks different between TG women with bigger networks, TG women with small networks, and TG women who are isolated. This means that we do not know whether the HIV prevalence is over or under estimated.

Reviewer #2 (Michele Andrasik, University of Washington, USA)

General comments

11. This is an incredibly important topic and one that requires a great deal of attention and research. My initial enthusiasm was damped by the lack of clarity, organization and breadth of the information presented. Although the manuscript is presented as a review it follows none of the required steps to constitute a review. I found the manuscript to be incredibly disjointed and at times difficult to follow. The specific stories are incredibly interesting but the author indicated that they are cases and what is presented does not provide enough detail to satisfy a case study. When reviewing the major models, this also seems like a very superficial overview. There is not an extensive review of the literature or enough depth in the exploration of these models to characterize this as a review. Please consider either presenting a case study or conducting a systematic review of the literature. What you have here is neither and although incredibly interesting this does not meet the necessary standards for publication in a peer-reviewed scientific journal nor does it add to the existing literature.

RESPONSE

We believe these comments came to us by mistakes, since they focus on stories/cases. Our study is an HIV surveillance study. It may be supposed to refer to another systematic review study.

Reviewer #3 (Ellen Weiss Wiewel, New York City Department of Health and Mental Hygiene, USA)

12. This paper reports the findings of an updated respondent-driven sampling survey of transgender persons in 13 areas of Cambodia. Specifically, it presents HIV prevalence and other characteristics such as sexual behavior and drug use among transgender women. It also investigates factors

associated with HIV infection. The authors find an HIV prevalence rate of >5% in this population, with HIV infection associated with residence in an urban area, lower education level, older age, gender expression solely as a woman, and other factors. This paper is focused, comprehensive, and generally very strong. The results section is well-organized. The discussion section methodically reviews each factor associated with HIV infection and interprets the findings.

RESPONSE

Many thanks. We are glad to hear that you find our study useful. We have seriously taken your comments and addressed very carefully.

13. Throughout the paper, transgender women wearing women's clothes as referred to as "dressing up as a woman." I suggest that this be changed to "dressing as a woman" or "presenting as a woman." "Dressing up" suggests a costume. A person who feels that she is a woman is not wearing a costume if she is wearing clothing that accurately reflects her gender identity. This may just be a language issue; the paper otherwise seems sufficiently sensitive to the study population.

RESPONSE

We have changed this terminology throughout the paper.

14. In the methods, results, and/or discussion, it would be helpful to (a) clearly state the type or range of online service referred to, and (b) justify the focus on services that were online and transgender-specific. Was NGO HIV service contact, for example, also entered into the model and just not significant, and is that why it's also not in Table 1? From survey question Q066 and the manuscript tables and text, it's unclear whether "online services developed for people like you (e.g. Facebook, website)" means online dating, health and social services, or is ambiguous. The distinction is important for interpreting the finding.

RESPONSE

We regret that the question was not well defined. The question was asked for program intervention that they want to use online as a mean to reach TG women. Therefore, we do not have more information on this.

15. Perhaps not necessary to address, but please consider: Does self-report / knowledge of positive HIV status influence the findings? First, do the authors think that people who knew they were positive felt comfortable disclosing to the interviewer, or did some of those who tested positive but didn't report being HIV-positive withhold their status? Second, might the relationship between status and the factors investigated look different between those self-reporting a positive status vs. those who did not? Relevant especially because about HIV-positive persons about evenly split between self-reported and not. Might be interesting to add to Table 2 a further breakdown of the positive testers by self-report. Also would be nice to have text in the discussion section exploring the finding that only about half of the positives self-reported – what could it mean? Undetected HIV, HIV stigma...?

RESPONSE

We have concerned about this before we conduct the study; so that we decided to utilize counselors who are all well-trained and from government VCCT center. They all had many-year of experience at VCCT. They know well how to cope with the situation. In the Cambodian context, we believe patients are more likely to trust their counselors.

We did the sub-analysis using simple Chi-square test/Fisher exact test to see whether sexual behaviors differ between those self-reporting a positive status and those who did not. The result shows that the risks among two groups— those self-reporting a positive status and those who did not—were not statistically significant in term of role in anal sex (insertive/receptive), number of sexual

non-commercial sexual partners, number of commercial sexual partners, condom use with non-commercial partners, and condom use with commercial sexual partners.

We have added the results in text in section "Sexual behaviors", but not in table. By so doing, it can simplify the table to have a stand table throughout the paper: "Among participants who had HIV reactive tests, additional analyses were conducted to see if there were differences in sexual behaviors among participants who self-reported a positive status and those who did not. Participants who did not report or unaware of their positive status were significantly less likely to report using a condom at last sexual intercourse (52.4% vs. 79.0%, $p=0.01$). No other significant differences were found." Please see lines 317-322

We have also added a paragraph to discuss the possible explanation for the finding that only about half of the participants who had reactive test self-reported their HIV-positive status: "More than half (52%) of those who had HIV reactive test reported that they never learned about their HIV positive status before participated in the study. We believe that this self-reporting HIV status is realistic. Since we were concerned that those who were already aware of their HIV status may be unwilling to report their status, we decided to use well-trained counselors who all were from government's Voluntary Confidential Counseling and Testing (VCCT) who had many-years of experience in providing VCCT services and are better equipped to cope with difficult situations. In Cambodia, we believe people are more likely to trust their counselors, as opposed to interviewers. However, as in all self-reported measures, the potential for response bias cannot be entirely ruled out." Please see 395-403.

16. The paper is very well-written in general. However, the authors (or a proofreader) should address the missing or wrong words sprinkled throughout. They never interfere with understanding but should be corrected prior. Suggested additions in ** for a few such places: "developed *for* MSM," "with reactive and non-reactive test*s*," "possible that *the* transgender population," etc.

RESPONSE

Another round of proofreading has been performed. We believe the errors/typos has been removed.

17. Methods: Unclear what is meant by half or all being recruited. Paper states, "Roughly half of the estimated transgender women in all but five sites were successfully recruited. In five study sites where the estimated number of transgender women was smaller than 100, all transgender women were recruited."

RESPONSE

This has been revised: "Roughly half of the estimated transgender women in each study site were recruited. However, in five provinces where the estimated number of transgender women was smaller than 100, all transgender women were recruited." Please see lines 160-162.

18. Results, Table 2: Under "Role in anal sex with a man (past 12 months)," please change "incentive" to "insertive"

RESPONSE

We have already corrected it.

19. Discussion: At very beginning of first paragraph, may want to restate the overall prevalence of HIV in this population, since that itself was a main finding.

RESPONSE

To also addressed comments from another reviewer, we have added a paragraph at the beginning of the discussion: "This study reveals that a HIV prevalence of 5.9% among transgender women in

Cambodia. This prevalence was about 20 times higher than the 0.3% among women attending antenatal care clinics in 2014 who represent the general adult population aged 15-45, and about 2.5 times higher than the 2.3% among MSM in 2014. This observed prevalence emphasizes that transgender women in Cambodia are at high risk of HIV, and is consistent with global literature regarding high burden of HIV among this transgender populations.” Please see lines 379-384.

20. Discussion: Also in the first paragraph or elsewhere, it might be interesting to discuss more the prevalence of HIV prevention behaviors in this population, e.g., condom use.

RESPONSE

To also addressed comments from another reviewer, we have added a paragraph to the discussion: “Although the prevalence found in this study was slightly higher than the prevalence of 4.2% reported in the smaller (n= 891) IBBS study of 2012, and was therefore contrary to our hypothesized expectations of reduction in HIV prevalence among this population, this difference was not statistically significant (p-value= 0.13). Recent progress in Cambodia, where 73% of all estimated HIV positive or 93% of those who have been aware positive are in care, had prompted us to hypothesize lower prevalence. Although we have no concrete evidence regarding the slight non-statistically significant increase HIV prevalence, we suggest that it may be related to sampling variation and simply occurred by chance. The previous study recruited participants only from the capital city and five provinces (Phnom Penh, Battambang, Banteay Mean Chhey, Kampong Cham, Siem Reap and Preah Sihanouk), whereas our study expanded to additional 8 provinces.” Please see lines 385-394.

21. Conclusions: The paper nicely describes and explains factors associated with prevalence, but it suggests limited action – really just the last sentence. Would be interesting to build up the Conclusions to be more specific. Love the paper’s detail elsewhere but something could be trimmed elsewhere if needed to accommodate expanded conclusions.

RESPONSE

We have revised the conclusions as suggested. Please see 513-515.

VERSION 2 – REVIEW

REVIEWER	Ellen Wiewel NYC Dept. of Health, USA
REVIEW RETURNED	29-Mar-2017

GENERAL COMMENTS	<p>Thank you for the careful revision after the first round of reviews. I have a few comments following up on your responses to my initial review. They are below and also comments in the attachment.</p> <p>1. "Online services": Please briefly state in the paper that unfortunately you do not have detail about the type of the online services and that it could refer to dating, health and social services, or another type of online service. Could go in the online-related paragraph beginning in line 471 – I don't think this warrants its own entry in the Limitations section.</p> <p>2. "Recruited": This is still confusing. In this and any study where people voluntarily opt in, isn't the entire study population recruited into the study, by design / definition? Or maybe you recruited from a subset of a larger population, like the seeds, or the people that the seeds referred, or the entire underlying transgender population. Needs clarification.</p> <p>3. First paragraph of discussion, added: This paragraph is an</p>
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	excellent addition to the paper. The reviewer also provided a file in addition to these comments. Please contact the publisher for full details.
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VERSION 2 – AUTHOR RESPONSE

Reviewer #3 (Ellen Wiewel, New York City Department of Health and Mental Hygiene, USA)

1. General comments: Thank you for the careful revision after the first round of reviews. I have a few comments following up on your responses to my initial review. They are below and also comments in the attachment.

Response:

Thank you for your support and constructive comments.

2. "Online services": Please briefly state in the paper that unfortunately you do not have detail about the type of the online services and that it could refer to dating, health and social services, or another type of online service. Could go in the online-related paragraph beginning in line 471 – I don't think this warrants its own entry in the Limitations section.

Response:

We have added the statement as suggested: "Unfortunately, in this study, we did not collect the details about the type of the online services, which could refer to dating, health and social services, or another type of online service." Please see lines 482-484.

3. "Recruited": This is still confusing. In this and any study where people voluntarily opt in, isn't the entire study population recruited into the study, by design / definition? Or maybe you recruited from a subset of a larger population, like the seeds, or the people that the seeds referred, or the entire underlying transgender population. Needs clarification.

Response:

For clarification, we have added the following in the Methods section: "Our participants, including the seeds and the people the seeds referred, had to meet the eligibility criteria. These participants were recruited from the entire transgender population in the study sites. However, the initial seeds at each site were recruited through our implementing partners." Please see Lines 168-171.

4. First paragraph of discussion, added: This paragraph is an excellent addition to the paper.

Response:

Thank you.