PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling Analysis
AUTHORS	Jiang, Y; Ni, Weiyi; Wu, Jing

VERSION 1 – REVIEW

REVIEWER	Yingyao Chen Fudan University School of Public Health Key Lab of Health Technology Assessment, National Health Commission Shanghai，China
REVIEW RETURNED	10-Jun-2019

GENERAL COMMENTS	The authors provided a comprehensive cost-effectiveness analysis of the 9-valent HPV vaccine in China and clearly answered other reviewers' comments, yet this manuscript would be improved if the authors could address the following issues: 1. The number of girls included for cost effectiveness analysis was not clearly stated in the main text or tables. Since some girls at the target age groups do not have independent income to afford HPV vaccines, especially the high-priced 9-valent HPV vaccine, could the authors elaborate more on the assumptions being made about the target population uptake of HPV vaccines? 2. Although HPV vaccine efficacy maybe close to 100%, it would be better to see how efficacy varies between vaccines (bivalent, quadrivalent & 9-valent) and HPV types. 3. Vaccine administration costs were assumed to be $18 using the model default value with inflation. Costs are usually highly context-based, so it may not be appropriate to use the model default value. It was not clear what types of costs were included in the vaccine administration costs. Also it was not clear who afford the administration costs, which could be an issue because it should be consistent with the perspective of this analysis.

REVIEWER	Jason Ong Monash University, Australia London School of Hygiene and Tropical Medicine, United Kingdom
REVIEW RETURNED	29-Jun-2019

GENERAL COMMENTS	Thank you for the opportunity to review your interesting and important research. - could you give more information about why China chose 16 years old as the lower cut-off age for the nonavalent vaccine?

	- conclusion of abstract needs reframing - as it stands, it is a very general statement - can you relate your conclusion more to the results of your study? - line 54 - is "value-based pricing" the correct term to be used here? I understand this term to refer to a consumer's willingness-to-pay but you don't really measure that in your study. consider rephrasing. - line 76 - can you give more details of what prices were used in these studies? - line 89 - can you expand on what the controversies are regarding the cost-effectiveness of the HPV vaccines in China? why is it still under dispute? A statement of how your paper contributes to this dispute would also be helpful to frame the justification for publishing your research. - line 99 - I don't understand this sentence and what it means to be "satisfactory" vs. "unsatisfactory" - you use the 1-3X GDP thresholds ... does China have a more accurate threshold (either implicitly or explicitly)? - Table 1 - what cost components are going into "vaccine administration costs" - personnel time? consumables? facility costs? - please clarify - your perspective is "private sector purchaser" - can you clarify if the costs for cancer treatment (in Table 1) is out of pocket costs for patients? are these economic costs? - your sensitivity analyses seems to be missing evaluating the impact of varying discount rate and disutility weights - will be important to see the effect of these in your tornado plot - can you add your 5 year survival, all-cause mortality, cervical cancer incidence into your Table 1 so this can be more transparent to see the estimates you are using in your model? - can you be more explicit about your time-horizon? - consider creating a second table and moving the section of "Base case and exploratory results" into your results section - the prices for the nonvalent vaccine at $680 and $220 are stated to be cost-effective and highly cost-effective, but there is no mention of the affordability of these vaccines at this price point for people living in China. please discuss. - there is a lack of comparison of your findings with other similar CEA papers in your discussion - please add further discussion about papers that also report the ICERs of the bivalent, quadrivalent and nonavalent vaccines from other countries. - I don't agree with your paragraph explaining the use of average CERs over incremental CERs - the conclusion from your results should be based on ICERs not ACERs, as ACERs can misrepresent the cost-effectiveness of interventions - limitation section needs to be strengthened - could you mention the likely impact of your stated limitations on your results.... related to this is your comment regarding lack of accounting for herd immunity and cervical screening programs - these are two big ommissions that detract from the realism of your model - Appendix 1 - can you report your kappa results? - Appendix 3 - I don't understand why you need to discount the cost of your vaccines - isn't this a once-off cost at the start of your model? - for your cohorts starting at a higher starting age - did you adjust the effectiveness of the vaccine downwards to account for the likelihood of an older woman already having less benefit from the vaccination.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Yingyao Chen
Institution and Country:
Fudan University School of Public Health
Key Lab of Health Technology Assessment, National Health Commission
Shanghai, China
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The authors provided a comprehensive cost-effectiveness analysis of the 9-valent HPV vaccine in China and clearly answered other reviewers' comments, yet this manuscript would be improved if the authors could address the following issues:

1. The number of girls included for cost effectiveness analysis was not clearly stated in the main text or tables. Since some girls at the target age groups do not have independent income to afford HPV vaccines, especially the high-priced 9-valent HPV vaccine, could the authors elaborate more on the assumptions being made about the target population uptake of HPV vaccines?
We agree that the vaccine coverage rate should be made more explicit in the text. The vaccine uptake rate (or coverage rate as in the PRIME model terms) is 100%. This is mandated by our study objective, which is to evaluate the cost-effectiveness of the vaccines for a recipient whose characteristics follow the average profile of the target population. This is obtained by taking the mean ICER result of the cohort. If the vaccine uptake rate is not 100%, then the mean ICER result of the cohort is not applicable to an average individual.
We have made the uptake rate more explicit in the text.

2. Although HPV vaccine efficacy maybe close to 100%, it would be better to see how efficacy varies between vaccines (bivalent, quadrivalent & 9-valent) and HPV types.
As far as carcinogenic HPV types are concerned, the bivalent and quadrivalent vaccines target at types 16/18 and the 9-valent vaccine targets at types 16/18/31/33/45/52/58. Thus, the efficacy of the different vaccines is reflected by the HPV types they cover and the proportion of cervical cancer each of the types accounts for. The proportion of cervical cancer that was attributable to types 16/18/31/33/45/52/58 was 92% and the proportion that was attributable to types 16/18 was 69.1%. These were described in Table 1 and were based on the International Agency for Research on Cancer (IARC) estimates for China.

3. Vaccine administration costs were assumed to be $18 using the model default value with inflation. Costs are usually highly context-based, so it may not be appropriate to use the model default value. It was not clear what types of costs were included in the vaccine administration costs. Also it was not clear who afford the administration costs, which could be an issue because it should be consistent with the perspective of this analysis.

The administration costs of $15 in the original model (inflated to $18 in our study) was based on the assumption that the delivery costs of three doses in low-, middle, and high-income countries were $5, $15, and $15 dollars, respectively. China was (and still is) considered a middle-income country. However, we agree the costs varies across settings even within middle-income countries. Whereas six dollars may not be the exact number of injection administration costs in many areas of China, it should be within a reasonable neighborhood of the actual values. For example, a cost-effectiveness analysis conducted in the Chinese setting published in 2019 used an input value of $4.5/injection for the administration costs (Xu et al. Cost-effectiveness of Teriflunomide Compared to Interferon Beta-

1b for Relapsing Multiple Sclerosis Patients in China. Clinical drug investigation 39.3 (2019): 331-340).

Reviewer: 2
Reviewer Name: Jason Ong
Institution and Country:
Monash University, Australia
London School of Hygiene and Tropical Medicine, United Kingdom
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Thank you for the opportunity to review your interesting and important research.

- could you give more information about why China chose 16 years old as the lower cut-off age for the nonavalent vaccine?

This would be a helpful piece of additional information to the context. However, we conducted search in both Chinese and English and did not find official information regarding why the age limit was set as it is in China. Hence, we are not able to provide this information.

- conclusion of abstract needs reframing - as it stands, it is a very general statement - can you relate your conclusion more to the results of your study?
Thanks for spotting this. We have revised the conclusion in the abstract to focus it on the results of the present study.

- line 54 - is "value-based pricing" the correct term to be used here? I understand this term to refer to a consumer's willingness-to-pay but you don't really measure that in your study. consider rephrasing.

We agree value-based pricing is related to the willingness-to-pay threshold which is involved in the determination of the cost-effectiveness of the product at certain price levels. However, it is not necessarily directly related to measuring willingness-to-pay. Value-based pricing refers to “price of a drug set on the magnitude of its benefit” and an example is Regeneron setting the price of dupilumab according to the cost-effectiveness analysis conducted by Institute for Clinical and Economic Review. There are also other examples of HTA entities and Institute for Clinical and Economic Review in the US calculating value-based prices using cost-effectiveness analysis. As such, we reserve our use of the term.

references:
Kaltenboeck, Anna, and Peter B. Bach. "Value-based pricing for drugs: theme and variations." Jama 319.21 (2018): 2165-2166.
Robinson, James C., Scott Howell, and Steven D. Pearson. "Value-based pricing and patient access for specialty drugs." Jama 319.21 (2018): 2169-2170.

- line 76 - can you give more details of what prices were used in these studies?

Thanks for reminding. We have clarified on the price used in the previous analyses.

- line 89 - can you expand on what the controversies are regarding the cost-effectiveness of the HPV vaccines in China? why is it still under dispute? A statement of how your paper contributes to this dispute would also be helpful to frame the justification for publishing your research.

Thanks for the important comment. Given that the effectiveness part is fixed, the controversy of the cost-effectiveness pertains to the acquisition costs. We have rephrased the sentence to reflect this. Since our study focuses on the 9-valent vaccine, we refrain from expanding the analyses to and making conclusions on the other vaccine types per se to avoid overstatement.

- line 99 - I don't understand this sentence and what it means to be "satisfactory" vs. "unsatisfactory"
When WHO developed the PRIME model, the original developers rated the parameters of the model used for each country such as cancer incidence, cancer mortality and HPV distribution. The assessment was based on whether country-specific data were available and the quality of methods. We have expanded the sentence.

- you use the 1-3X GDP thresholds ... does China have a more accurate threshold (either implicitly or explicitly)?

Unfortunately, there isn't a more accurate threshold either explicitly or implicitly reported or used by the National Health Commission, the State Medical Insurance Administration, or the expert panel that compose the Chinese guidelines of pharmacoeconomic evaluation.

- Table 1 - what cost components are going into "vaccine administration costs" - personnel time? consumables? facility costs? - please clarify
The administration costs of $15 in the original model (inflated to $18 in our study) was based on the assumption that the delivery costs of three doses in low-, middle, and high-income countries were $5, $15, and $15 dollars, respectively. China was (and still is) considered a middle-income country. However, we agree the costs varies across settings even within middle-income countries. Whereas six dollars may not be the exact number of injection administration costs in many areas of China, it should be within a reasonable neighborhood of the actual values. For example, a cost-effectiveness analysis conducted in the Chinese setting published in 2019 used an input value of $4.5/injection for the administration costs (Xu et al. Cost-effectiveness of Teriflunomide Compared to Interferon Beta-1b for Relapsing Multiple Sclerosis Patients in China. Clinical drug investigation 39.3 (2019): 331-340).

- your perspective is "private sector purchaser" - can you clarify if the costs for cancer treatment (in Table 1) is out of pocket costs for patients? are these economic costs?

The costs are direct medical costs and the number in the table represents the total amount. The costs may or may not be out-of-pocket (OOP) depending on the insurance status. It is noteworthy that the medical insurance pays only a small portion of healthcare expenditure in China (median reimbursement rate of 33% for inpatient costs and 0% for outpatient costs). We cannot accurately adjust the costs to reflect the out-of-pocket burden. To test the robustness of the results to this data deficiency, we conducted a sensitivity analysis of changing the cancer treatment costs and this input variable had the least impact among all. Therefore, using OOP costs, if available, will not likely impact the conclusions to the extent that the inference is changed.

Reference: Zhang, Chuanchuan, et al. "Health insurance and health care among the mid-aged and older Chinese: Evidence from the national baseline survey of CHARLS." Health economics 26.4 (2017): 431-449.

- your sensitivity analyses seems to be missing evaluating the impact of varying discount rate and disutility weights - will be important to see the effect of these in your tornado plot
Thanks for the suggestion. We have added these two analyses to the tornado graph. Using alternative discount rates had substantial impacts on the results.

- can you add your 5 year survival, all-cause mortality, cervical cancer incidence into your Table 1 so this can be more transparent to see the estimates you are using in your model?
The cervical cancer incidence, cervical cancer mortality, and the all-cause mortality data vary by age. Therefore, it is challenging and arguably infeasible to put all of them into Table 1. However, these input data are available in the model at http://primetool.org/about-hpv/ and the website of GLOBOCAN at http://gco.iarc.fr/databases.php. We notice that the previous studies that utilized the PRIME tool were not able to list the input data in tables as well, perhaps due to lack of space. We therefore added statements about the location of these data in the “data sharing statement”.

References:
Jit M , Brisson M , Portnoy A , et al. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study[J]. The Lancet Global Health, 2014, 2(7):e406-e414.
Minh H V , My N T T , Jit M . Cervical cancer treatment costs and cost-effectiveness analysis of human papillomavirus vaccination in Vietnam: A PRIME modeling study[J]. BMC Health Services Research, 2017, 17(1):353.

- can you be more explicit about your time-horizon?
Thanks for catching this. The time horizon is from the age of vaccination to 100 years old. We have added this to the text.

- consider creating a second table and moving the section of "Base case and exploratory results" into your results section

Thanks for the suggestion. We have separated the second panel of the table to a second table which is now “Table 2”.

- the prices for the nonvalent vaccine at $680 and $220 are stated to be cost-effective and highly cost-effective, but there is no mention of the affordability of these vaccines at this price point for people living in China. please discuss.
With the focus now given to the comparison with the quadrivalent vaccine, these prices no longer appear to be sitting on the efficiency frontier.
Indeed, some literature narratively described the situation that the incremental cost-effectiveness ratio being under the cut-off but the budget impact being substantial as “cost-effective but unaffordable”. However, a couple of International Society for Pharmacoeconomics and Outcomes Research Special Task Force Reports have noted that this phenomenon is actually caused by the cut-off in CEA being unaligned with the implicit cut-off such that the cut-off used in the CEA fails to reflect the opportunity costs incurred given the magnitude of the impact on healthcare expenditure. We used alternative cut-offs in the present analysis.
In addition, the term “affordability” is not well-defined in economics and is often considered equivocal due to lack of basis in economic theory. Some would even argue “affordability is essentially a sentiment”. To avoid ambiguity in defining and using the term in our analysis, we did not touch on affordability.

References:
Lomas, James, et al. "Resolving the “cost-effective but unaffordable” paradox: estimating the health opportunity costs of nonmarginal budget impacts." Value in Health 21.3 (2018): 266-275.
Phelps, Charles E., et al. "Approaches to aggregation and decision making—a health economics approach: an ISPOR Special Task Force report [5]." Value in Health 21.2 (2018): 146-154.
Janet Weiner and Aaron Glickman. “WHAT IS “AFFORDABLE” HEALTH CARE? A review of concepts to guide policymakers”.
https://ldi.upenn.edu/sites/default/files/pdf/Penn%20LDI%20and%20USofC%20Affordability%20Issue%20Brief_Final.pdf

Niëns, L. M., et al. "Practical measurement of affordability: an application to medicines." Bulletin of the World Health Organization 90 (2012): 219-227.

- there is a lack of comparison of your findings with other similar CEA papers in your discussion - please add further discussion about papers that also report the ICERs of the bivalent, quadrivalent and nonavalent vaccines from other countries.
We have added a paragraph comparing the results for Chinese and the results in several other countries in the discussion section.

- I don't agree with your paragraph explaining the use of average CERs over incremental CERs - the conclusion from your results should be based on ICERs not ACERs, as ACERs can misrepresent the cost-effectiveness of interventions

Thanks for this important catch. We have re-organized our presentation of results and rephrased our discussion such that the comparison with the quadrivalent vaccines is of primary interest.

- limitation section needs to be strengthened - could you mention the likely impact of your stated limitations on your results.... related to this is your comment regarding lack of accounting for herd immunity and cervical screening programs - these are two big ommissions that detract from the realism of your model

We have expanded our discussion of the limitations and tried to explain the potential impacts of them.

- Appendix 1 - can you report your kappa results?

We have added the Kappa number.

- Appendix 3 - I don't understand why you need to discount the cost of your vaccines - isn't this a once-off cost at the start of your model?
The reviewer's interpretation was correct. The vaccine costs only happened once at the vaccination age which was the beginning of the time horizon. This part of the costs was the same whether discounted or not.

- for your cohorts starting at a higher starting age - did you adjust the effectiveness of the vaccine downwards to account for the likelihood of an older woman already having less benefit from the vaccination.

The protective efficacy was not adjusted as the vaccinated individuals age. This was added to the limitations section.

VERSION 2 – REVIEW

REVIEWER	Yingyao Chen Key Lab of Health Technology Assessment, NHC Fudan University School of Public Health
REVIEW RETURNED	24-Sep-2019

GENERAL COMMENTS	The authors answered previous questions in a detailed manner. The manuscript has been much improved after their careful revision, however there are some issues remaining to be clarified.

	1. This study is based on the comparison with no vaccination at all, however some other CEA literatures regarding HPV vaccine used cervical cancer screening program and/or screening plus vaccination program as the comparison group. Could you please clarify why you use blank comparison group in your study? 2. Even though the model default for vaccine efficacy is 100%, it is usually not the case in real-world setting. Many literatures in this field also did not use the 100% efficacy assumption. Inclusion of vaccine efficacy into sensitivity analysis may partially solve this problem, but it is still better to cite literatures regarding the safety and efficacy of HPV vaccine, especially among Chinese or Asian populations, to support your decision. 3. Adverse events following immunization (AEFIs) are not taken into account in your study. How would this impact your analysis results? 4. Since the time horizon of this study is from the age of vaccination to 100 years old, the duration of protection from HPV vaccine is an important issue to be taken into account. Given the high price of HPV vaccine, whether HPV vaccine provides lifelong protection may impact your analysis results and conclusion. Is there any literature regarding the persistence of protection from HPV vaccine?

REVIEWER	Jason Ong Monash University, Australia London School of Hygiene and Tropical Medicine, United Kingdom
REVIEW RETURNED	08-Sep-2019

GENERAL COMMENTS	Thank you for responding to my comments. I just had one lingering concern re: could you give more information about why China chose 16 years old as the lower cut-off age for the nonavalent vaccine? Your answer: This would be a helpful piece of additional information to the context. However, we conducted search in both Chinese and English and did not find official information regarding why the age limit was set as it is in China. Hence, we are not able to provide this information. My response: Thank you for looking. You need to then justify why only people 16 and above are included in your model. As you know, the current understanding of HPV vaccines is that its maximal effectiveness is achieved when you vaccinate someone before their sexual debut. In most countries, this means vaccination at 10-11 years old. Can you please provide further justification in your manuscript to verify this point?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Jason Ong

Institution and Country:

Monash University, Australia

London School of Hygiene and Tropical Medicine, United Kingdom

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Thank you for responding to my comments. I just had one lingering concern

re: could you give more information about why China chose 16 years old as the lower cut-off age for the nonavalent vaccine?

Your answer: This would be a helpful piece of additional information to the context. However, we conducted search in both Chinese and English and did not find official information regarding why the age limit was set as it is in China. Hence, we are not able to provide this information.

My response: Thank you for looking. You need to then justify why only people 16 and above are included in your model. As you know, the current understanding of HPV vaccines is that its maximal effectiveness is achieved when you vaccinate someone before their sexual debut. In most countries, this means vaccination at 10-11 years old. Can you please provide further justification in your manuscript to verify this point?

Thanks for reiterating the importance of vaccination age in the model. We fully agree that vaccination before sexual debut is the best practice. However, using a younger age still doesn’t guarantee that the target population is 100% sexually inactive.

That said, the vast majority of the 16 years old female in China did not have sexual debut. According to a study by Zhao et el., only 6.9% of females in the age group of 15-19 years old were sexually active in 2012. This number is expected to be even lower among girls aged 16 years since it is closer to the lower bound of the age group. Another study in the same year by Guo et al. confirmed that sexual debut before age 18 was rare in China.

Granted, even 7% is not necessarily a negligible proportion. However, we toggled the age from 16 to 13 in our sensitivity analyses, and the inference of cost-effectiveness did not change in any of the comparison using either the cost-effective threshold or the highly cost-effective threshold.

The appendix contained relatively extensive text to describe the reasons of using the age of 16.

Zhao, Fang-Hui et al. "A multi-center survey of age of sexual debut and sexual behavior in Chinese women: suggestions for optimal age of human papillomavirus vaccination in China." Cancer epidemiology 36.4 (2012): 384-390.

Guo, Wei et al. "The timing of sexual debut among Chinese youth." International perspectives on sexual and reproductive health (2012): 196-204.

Reviewer: 1

Reviewer Name: Yingyao Chen

Institution and Country:

Key Lab of Health Technology Assessment, NHC

Fudan University School of Public Health

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The authors answered previous questions in a detailed manner. The manuscript has been much improved after their careful revision, however there are some issues remaining to be clarified.

1. This study is based on the comparison with no vaccination at all, however some other CEA literatures regarding HPV vaccine used cervical cancer screening program and/or screening plus vaccination program as the comparison group. Could you please clarify why you use blank comparison group in your study?

Thanks for the suggestion. In the current version of the manuscript, the 9-valent vaccine is compared to the quadrivalent vaccine in the base case.

The focus of the present study is comparing among different types of vaccines and no vaccination. Whereas screening is important (not just cancer screening but also HPV test), including screening creates numerous combinations of screening strategies and types of vaccine. This is an important topic in its own right but may obscure the concentration of the present study. In addition, combining the screening programs which are likely provided by the government and the vaccination which are likely purchased out-of-pocket may create confusion of the decision perspective.

We have added such explanation in the discussion section.

2. Even though the model default for vaccine efficacy is 100%, it is usually not the case in real-world setting. Many literatures in this field also did not use the 100% efficacy assumption. Inclusion of vaccine efficacy into sensitivity analysis may partially solve this problem, but it is still better to cite literatures regarding the safety and efficacy of HPV vaccine, especially among Chinese or Asian populations, to support your decision.

Thanks for the important suggestion. In the pivotal clinical trial based on which the quadrivalent HPV vaccine was approved by the Chinese regulatory body, the efficacy against cervical intraepithelial neoplasia (CIN) grades 1+ & 2+ related to HPV16/18 was 100%. It was the same for that of HPV 6/11/16/18 at the 12th month. Also, the efficacy against cervical persistent infection was consistently above 90%. As such, we conducted a sensitivity analysis changing the efficacy to 90%. The tornado graphs were updated accordingly. The inference of cost-effectiveness was not changed in any comparison using either threshold.

Reference

Wei L, Xie X, Liu J, et al. Efficacy of quadrivalent human papillomavirus vaccine against persistent infection and genital disease in Chinese women: A randomized, placebo-controlled trial with 78-month follow-up. Vaccine. 2019; 37: 3617-24.

3. Adverse events following immunization (AEFIs) are not taken into account in your study. How would this impact your analysis results?

Incorporating adverse events of HPV vaccine is challenging because evidence in literature does not necessarily support elevated risk of adverse events as a result of HPV vaccination. For example, a WHO report systematically reviewed clinical trials of HPV vaccines and found no difference in the rates of severe adverse events among those who received HPV vaccines and those received placebo (https://www.who.int/vaccine_safety/HPV_vaccination_safety_report_AHTA_dec17.pdf). In fact, the same document among several others suggested good tolerance of HPV vaccines. Hence, the submitted work did not include adverse events.

4. Since the time horizon of this study is from the age of vaccination to 100 years old, the duration of protection from HPV vaccine is an important issue to be taken into account. Given the high price of HPV vaccine, whether HPV vaccine provides lifelong protection may impact your analysis results and conclusion. Is there any literature regarding the persistence of protection from HPV vaccine?

Whereas HPV vaccine has not come into being for a long enough follow-up to evaluate lifetime efficacy, the current evidence does not support drop in its efficacy after five years.

Reference

Deleré Y, Wichmann O, Klug SJ, et al. The efficacy and duration of vaccine protection against human papillomavirus: a systematic review and meta-analysis. Dtsch Arztebl Int. 2014; 111: 584-91.

VERSION 3 – REVIEW

REVIEWER	Yingyao Chen Key Lab of Health Technology Assessment, NHC Fudan University School of Public Health
REVIEW RETURNED	28-Oct-2019

GENERAL COMMENTS	The authors responded to my comments properly. I have no more concern regarding this manuscript. This version of manuscript is qualified for acceptance.

REVIEWER	Jason Ong Monash University, Australia
REVIEW RETURNED	30-Oct-2019

GENERAL COMMENTS	Thank you for addressing my previous concern. I have no further edits to suggest and wish you the very best in your ongoing important research in this area.