Author's response to reviews

Title: Varicella and weather factors in Jinan, eastern China, 2012-2014

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Author's response to reviews:

Dear Editor,

We acknowledge with thanks the receipt of the comments of the reviewers. These comments were highly beneficial in the modification of the manuscript. The manuscript was revised according to all these comments. All modifications and/or corrections are highlighted by using the track changes mode. A point-to-point response to the reviewers’ comments was attached. We appreciate you kindly offer the opportunity to transfer our manuscript.

Best!
Yunqing Yang

Response to the Reviewer 1:

Minor essential revisions
Comment: Language, spelling and grammatical errors are present throughout the article and need attention
Respond: In this revised version of manuscript, we corrected the spelling and grammatical errors. We think this version of manuscript is much clearer than the old one.

Comment: Abbreviations should not be used in the abstract
Respond: As suggestion, we removed the abbreviations from the abstract section.

Comment: Line 50. Morbidity and mortality are very minor findings. They are not mentioned in the results section of the abstract so should not be in the conclusion.
Respond: As suggestion, we removed the expression of morbidity and mortality from conclusion section of abstract.
Comment: Line 56. Introduce shingles as caused by reactivation and the common complication of PHN
Respond: Done as suggestion.

Comment: Line 67. Don’t use “et al” in this context
Respond: We deleted the “et al ” in the context as suggestion.

Comment: Line 72. Indicate what the incidences were in the countries
Respond: We added the incidences of chickenpox form different countries as suggestion.

Comment: Line 73. I think “climate” should replace “weather”
Respond: We replaced the “weather” with “climate” as suggestion.

Comment: Line 74. Reword “fend off”
Respond: We replaced the “fend off” with “prevent” as suggestion.

Comment: Line 112 & 115. Don’t use “etc” in this context
Respond: We removed the “etc” from the context as suggestion.

Comment: Figure 2. I presume the Y-axis should be “per 100,000 inhabitants”.
Respond: The figure 2 indicates the “monthly disturbance of varicella cases”. Actually, every bar of the figure 2 represents total number of the same month from 2012 to 2014. We therefore presented the Y-axis as “reported cases”. If the editor and reviewer think it is better to use “per 100,000 inhabitants”, we would like to comply.

Comment: Line 190-192. Why are there two percentages for humidity, sunshine and rain?
Respond: When preliminary analysis, we found that temperature and atmospheric pressure showed strong negative correlation (r=-0.87). This indicated that the model constructed using contemporaneously both variables suffered from collinearity problems. We therefore conducted two separated models: one included average temperatures but no atmospheric pressure, the other included atmospheric pressure but no average temperature. Both models included additionally relative humidity, wind velocity, rainfall, sunshine and year as independent variables. Therefore, there are two percentages for humidity, sunshine and rain. Those two percentages depended on the temperature or atmospheric pressure in the model. In this revised version, we added more explanations in the method section and results section.

Comment: Lines 84-90. Why the differences between studies. Comment on whether it is or could be due to differences in study structure, different methods of measuring climatic variables, under/over reporting, which might relate to inclusion or not of Lab and/or clinical diagnosis
Respond: These differences are probably due to the difference in weather
pattern of study area and different variables considered in the models. As suggestion, we added these comments in the context.

Comment: Line 124. Measuring from one fixed site station. Is this representative of the whole of Jinan? For examples there is likely to be more rain and less pressure in hilly regions Any comments

Respond: in this study we used the data form meteorological observing station of Jinan which located in the center of Jinan city. This station is also the national meteorological observing station. The reviewer’s concerns are right and important. The weather information obtained from one fixed site station maybe not well representative of the data of whole city. In this revised version, we acknowledged this limitation in the context. Anyway, the change direction of this observation station is consistent with the city. In this study, we focused our analysis results on how much percent increase/decrease in the number of varicella cases correspond to with each one measurement unit rise of weather variables. These suggested that our risk estimates are reliable.

Comment: Figure 3 It is crucial to bring the whole thing together by including a similar plot showing varicella incidence to bring all the findings of the study together and easier for the ready to interpret. Varicella should be at the top with the other graphs beneath in a column format

Respond: Done as suggestion.

Comment: Line 199. “Highly effective”. State the percentages efficacy and/or effectiveness in adults and children

Respond: As suggestion, we added the sentence as “the effectiveness was proved between 80% and 93%”

Comment: Line 200. Who does receive the vaccine? Is it targeted to healthcare workers and adolescents?

Respond: Actually it targeted to adolescents.

Comment: Line 207. Any comments on why incidence is higher in men?

Respond: This is probably due to the fact that male are more active in social activities, therefore more likely to expose to VZV. We added this comment in the context as suggestion.

Comment: Lines 234-254. Where are the possible explanations for temperature, pressure and wind?

Respond: In this study, the wind was not found a significant association with varicella occurrence, we therefore did not discuss this variable in context. As suggestion, we revised and added some explanations for temperature and pressure as following:

We found that temperature was inversely correlated with varicella incidence. This is consistent with those of Garnett GP and colleagues who found few varicella infections occur in tropical regions than in temperate regions in West Indies [16].
In the studies from India, Thailand, Sri Lanka and other countries, varicella incidence has been reported to peak during cooler months [26-28]. A laboratory-based study suggested that VZV seroprevalence rates in tropical climate were markedly lower in all age groups when compared to temperate climates [29]. Furthermore, previous studies have shown that in vitro VZV yield and point of maximum titre were dependent on temperature of incubation [30, 31]. Markus A and his work team revealed that VZV replicates more efficiently at lower temperature [8]. In addition, our study also indicated that high atmospheric pressure presented higher occurrence of varicella infection. This finding is in general agreement with previous findings from Hong Kong [18], which suggested that atmospheric pressure might be considered an important predictor for varicella infection. However, no studies have yet been published revealing the underlying mechanism. A possible explanation might be that high atmospheric pressure is conducive to the spread of the virus particles.

Comment: Line 267. “multifactorial[34, 35]; besides meteorological factors, other environmental and host factors”. Is there any evidence of HLA-type predisposition, ethnic susceptibility?

Respond: The comment is right. there are some evidence indicating that ethnicity(Ayres KL, J Infect. 2010 Sep;61:244-51.) and HLA-type predisposition (Arvin AM, J Infect Dis. 1986 Sep;154:422-9.) also influenced the varicella infection. In this revised version, we added this two factors into the context as suggestion.

Comment: Line 199. “Highly effective”. State the percentages efficacy and/or effectiveness in adults and children

Respond: As suggestion, we added the sentence as “the effectiveness was proved between 80% and 93%”

Discretionary revisions

Comment: Figure 1 is perhaps not necessary

Respond: As suggestion, in this revised version of manuscript we deleted the Figure 1 from context.

Response to the Reviewer 2:

Abstract:

Comment: Line 41: please define hPa upon first use.

Respond: As suggestion, we revised that expression as “hundred pa (hPa)”

Comment: Lines 45-47: the results of two models are given, but the abstract methods fails to describe that two models were utilized. This leaves the readers confused as to what the authors are reporting. I suggest that the authors rewrite the abstract methods to include the two modeling strategies.

Respond: As suggestion, we revised the abstract and added the following sentences:
Given average temperature and atmospheric pressure suffered from collinearity problems, separated models were conducted: one included average temperatures but no atmospheric pressure, the other included atmospheric pressure but no average temperature. Both models included additionally relative humidity, wind velocity, rainfall, sunshine and year as independent variables.

Comment: Line 50-51: The authors state that weather factors affected occurrence and transmission of varicella, but transmission was not explicitly studied in this paper. It would be more prudent to say that weather factors influenced the incidence of varicella.

Respond: Thank you! As suggestion, we revised the conclusion as “Our findings revealed that weather factors had a significant influence on the incidence of varicella, which might be important predictors of varicella infection in Jinan.

Background:
Comment: Lines 58-61. The sentence sounds very anecdotal. Please provide data and a reference on varicella incidence in Jinan.

Respond: As suggestion, we provided the sentences as following:
In 2007, the incidence of varicella was reported of 2841.83 per 100,000 inhabitants [15],

Comment: Lines 73-83: This content seems more appropriate for the discussion section.

Respond: As suggestion, we moved that paragraph to the discussion section

Comment: Lines 113-115: Symptoms that describe varicella were already included in the background. This should be replaced with the case definition as used by the local reportable disease system.

Respond: As suggestion, we replaced the symptoms description with case definition as following:
The case definition includes 1) have fever and characteristic rash; and/or 2) four-fold rise in antibody titer, or antigen detected in blood, or genetic material detected by PCR.

Comment: Lines 143-144: The results of the authors’ tests of collinearity should not be in the methods section. IN fact, they already report these findings in the results section and rationalize how it led them to create two separate models.

Respond: As suggestion, we revised the methods section and some sentence about how to create two separate modes were added as following:
As preliminary analysis, Pearson’s correlation tests were performed to examine the relationship between meteorological variables. If any two variables (e.g. weather factor A and weather factor B) showed strong correction(r>0.85, P<0.01), two separated negative binomial regression models then conducted: one included weather factor A but no weather factor B, the other included weather factor B but no weather factor A. Both models included additionally the
other weather factors as independent variables.

Comment: Line 153: Spell out ln as natural log.
Respond: Done as suggestion.

Comment: Line 156: The authors state that p<0.05 was considered statistically significant in two places (Line 156 and Line 151). Please resolve the redundancy.
Respond: We revised the “the final model included only those variables that reached p<0.05” as “the final model included only those variables that reached statistically significant.” Only one place reserved the stating that “p<0.05 was considered statistically significant”

Results:
Comment: Line 172: Please move the reference to figure 3 to the beginning of the paragraph (this is the first time when figure 3 results are referred to).
Respond: Done as suggestion.

Comment: Line 185: Please move the references to table 2 from line 193 to the beginning of the paragraph (this is the first time when table 2 results are referred to).
Respond: Done as suggestion.

Comment: Line 193: The last sentence should explicitly state that “the models appeared to have good fit (Pearson chi-sq<0.05).”
Respond: Thanks for your good suggestion, the sentence had been revised as “the models appeared to have good fit (Pearson chi-sq<0.05).”

Comment: Table 2 would be clearer if the differences between A and C, and B and D were explained. Are these preliminary and final models?
Respond: Yes these are preliminary and final models. As suggestion, the context was revised as following:
(A) and (C) were respectively preliminary and final models without atmospheric pressure. (B) and (D) were respectively preliminary and final models without average temperature.

Discussion:
Comment: Line 200: It would be better to mention that “vaccination uptake would be better if there were a universal vaccination program.” The point of this sentence seems to want to establish that vaccination uptake was poor.
Respond: Thanks, we replaced the “universal varicella vaccination program has been unavailable to public in previous China” with “vaccination uptake would be better if there were a universal vaccination program.” as suggestion.

Comment: Line 203: Replace “dead cases were reported” with “mortalities
occurred”.
Respond: As suggestion, we replaced “no dead case were reported” with “no mortalities occurred”

Comment: The discussion section might benefit from a conceptual model describing how these meteorological variables are interaction with one another and influencing varicella incidence, using a visual such as a directed acyclic graph. It is difficult for the reader to have a sense of the meaning behind these findings if there is no overall idea on how these variables (together) are influencing varicella incidence.

Respond: many thanks for your good idea! As suggestion, we tried our best to draw a directed acyclic graph but failed. Our study only indicated the relationship between weathers and varicella incidence. On the other hand, the interaction between meteorological variables could not be drawn from our results. Therefore, directed acyclic graph could not develop its function and help readers to catch our finding. Nevertheless, in this revised version, we added more explanations on how weather factors are influencing varicella incidence. Hopefully, this explanation words could be helpful for the readers.

Comment: The authors mention an interesting idea regarding the use of meteorological variables and the prediction of future varicella incidence. It seems that this could have been done with their existing data. Did the authors consider creating models based on the 2012-2013 data and use those estimates to predict the observed data in 2014? It seems that the analysis would be strengthened by this approach.

Respond: Many thanks for your excellent idea and the suggestion coincided with our present work. The analysis method of creating models to predict the observed data is different from what we used in our present manuscript. Because the data from 2012 to 2014 is limited (only about 104 items for analysis), we are now using data from 2012-2014 to predict the observed data in 2015. We hope this work can have it result next year.

Discretionary Revisions:
Comment: Lines 63-64: It does not seem necessary to explain reportable diseases.
Respond: As suggestion, we deleted that sentence about reportable diseases explanation.