PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidemiology of dengue and the effect of seasonal climate variation on its dynamics: a spatio-temporal descriptive analysis in the Chao-Shan area, on China's southeastern coast
AUTHORS	Zhang, Qin; Chen, Yuliang; Fu, Yu; Liu, Tao; Zhang, Qingying; Guo, Pi; Ma, Wenjun

VERSION 1 - REVIEW

REVIEWER	Scott Halstead Uniformed Services University of the Health Sciences, USA
REVIEW RETURNED	27-Jul-2018

GENERAL COMMENTS	This is an analysis of the temporal epidemic dynamics with a specific periodicity related to climatic drivers using a wavelet analysis of dengue "cases" in the Chao-Shan area of Guangdong Province, China. Whether any of these cases were caused by dengue viruses is unknown as no laboratory test results were reported. Most of the interesting and important epidemiological features of the outbreak were not studied. For example, what dengue virus or viruses were being transmitted during the period of study? What was the age-specific dengue antibody prevalence in the population studied? What was the rate of dengue disease in each age group? Age specific attack rates of clinically overt dengue infections in human vary greatly according to the type of virus being circulated and whether the infectioned hosts are experiencing primary or secondary infections (secondary infection occurs in individuals with immunity to a dengue type other than the one circulating during the period of study). Even more important, there is no mention of the distribution of potential vector mosquitoes nor were the mosquito vectors of these outbreaks specifically identified during the period of the study. Dengue virus outbreaks in northern and southern temperate areas of the world have been described in the published literature for more than 300 years. The bionomics and ecology of Aedes aegypti-borne viral diseases have been studied for generations and reported extensively in the literature and in standard textbooks. Where are the citations to this literature? The references cited are mainly of recent dengue activity in China and that appear to ignore the described biology of dengue in other temperate countries. Mosquito longevity and biting activity are greatly influenced by temperature and humidity. The incubation period of dengue viruses in mosquito vectors is under temperature control, the higher the temperature the shorter the extrinsic incubation period

	permitting a higher fraction of dengue-infected mosquitoes to successfully obtain the two blood meals required for transmission.

REVIEWER	Alessio Andronico Institut Pasteur, France
REVIEW RETURNED	30-Jul-2018

GENERAL COMMENTS	This paper presents an analysis of dengue case data from a densely populated region in southern China and spanning a four-year period (2014-2017). The main focus is on studying seasonal effects on dengue incidence. Like previously published studies, the authors find an association between climatic variables – in particular temperature – and incidence. They also estimate a higher risk of dengue transmission for temperatures around 25 C. The authors have collated a nice dataset and, overall, the paper is interesting, technically sound, and - for the most part - clearly written. I have only few minor comments included hereafter. 1. The authors should indicate the type of mosquitoes that are present in the study area. Are Aedes Albopictus and Aegypti equally present in the three locations they considered? 2. Similar to the previous point: if the information was available, please indicate the dengue serotype/serotypes. Was there only one serotype circulating during the entire study period? 3. The authors find that Chaozhou accounts for 78% of the total number of dengue cases reported from 2014 to 2017. It would be useful to indicate if there are any differences in terms of population or climatic variables between the three cities they considered. 4. Figure 5: please add the units (presumably weeks) to the y axes of the heat maps. 5. The third quartile is missing on page 2 line 33, page 8 line 26 (and following two lines), and page 10 line 15. 6. Page 2 line 39: Consider rephrasing the sentence "We detected an annual attack activity…" 7. Page 2 line 44 and page 3 line 13: Rephrase the sentence "… the risk of transmission is most when the temperature is reached to around…" 8. Page 4 line 20: "… a succession of epidemic fluctuation of dengue occurred…" Please clarify. 9. Page 5 line 27: Please rephrase the sentence "…highlights gaps in our knowledge to the current status of dengue epidemic…" 10. Page 5 line 42: Please rephrase the sentence "All information on individual privacy of patients…" Typos: Page 2 line 15: replace "assess" with "assessed" Page 8 line 39: replace "the patients was" with "the patients were" Page 11 line51: replace "expect" with "except" Discretionary: Figure 3: it would be useful to clarify how dengue cases were spatially aggregated. The text mentions streets in Chaozhou, but how were the coordinates of the circles in Figure 3 assigned? Figure 4: the scale of the three time series in panel B is not the same. I would advise the authors to use the same scale or to explicitly warn the reader in the legend.

REVIEWER	James Valcour
	Memorial University of Newfoundland, Canada
REVIEW RETURNED	21-Oct-2018

GENERAL COMMENTS	Overall
	The paper presents and interesting and important topic on the impact of climate on Dengue infections in Southeast China. The topic and objectives were clearly outlined, but a discussion of the Dengue virus (and Dengue Fever) would improve the article. Some detail in the methods section of the paper is lacking (see below). Results from the study are clearly explained for the most part (see below). The discussion of the results was well presented with supporting evidence. Except for the Discussion section, there were several awkward sentences and typos.
	A statistical review of the methods and results is warranted given the advanced techniques presented in the article.
	No information on approval of ethics was provided, but this might not be necessary given that the study used secondary data. At my institution, ethics approval is also necessary for secondary data analysis.
	With minor revisions and clarification of the methods, the paper should be acceptable for publication.
	Minor issues
	Introduction
	The Introduction would benefit from an expanded explanation of what dengue is, how it manifests, and how it might be linked to climate (i.e. that it is viral and mosquito-borne and the symptoms of infection).
	Page 4; line 9: "is a" should be "has been".
	Page 4; line 55: "However, the impact …" would be better to drop 'however' (e.g. "The impact …").
	Page 5; line 7: "square kilometers, but a very" would be better as "square kilometers, with a very".
	Page 5, line 9-11: I am not sure of the relevance of this statement.
	Page 5, line 14-18: This sentence is awkward. Please reword.
	Page 5, line 24-29: Break into two sentences. In it's current form the last part makes no sense.
	Page 5, line 33-35: Date format should be consistent with the rest of the document (i.e. change to "month day, year").
	Material and Methods
	The methods for a number of the analyses needs to be better explained.
	1) How were climatic variables aggregated? The time scale is stated (weekly) but was the mean or the median estimated? Did it use the daily average values, or maximum, or minimum values? Was a simple arithmetic mean calculated? The information must be included. (Section "Climate Surveillance Data")
	2) Statistical Analysis Section
	a. How the probability density distributions were estimated should be explained.
	b. How the map of cases was created should be explained in further detail. Residential address was used, but how cases were aggregated is not stated. The analysis was not conducted at the address level, nor is it at the level earlier stated of the 3 cities. This explanation should also include what software was used for data aggregation and mapping (the methods state R was used for analysis, if was done for the map, it would be helpful to state which package was used for mapping, if not, what GIS package was used).

Page 5; line 57: What exactly are "special climatic conditions"? This was also mentioned in the introduction and should be more clearly stated.

Page 6; line 3: "communions" this word typically refers to a spiritual connection. Replace with a more suitable word.

Page 7, line 3: "reaction ability" please define what this means or reword.

Page 7, line 3-9: The sentence is awkward. Please consider revising.

Results

The graphs present look great in color, but if printed in black and white are un-interpretable. Attention should be paid to both figures 1 and 2.d to make them interpretable for those who would print the article in black and white.

Table 1: Please include a "Total" column for all three cities since total values are also referred to in the Results section.

Figure 2.d: Consider using dashed / dotted lines to indicate the different areas. This is uninterpretable in black and white.

Figure 3: uses a dot map to describe the spatial distribution of Dengue cases in Chao-Shan. Some aggregation has occurred (see comment in methods), but it is unclear to what level aggregation has been applied. The overlapping circles on the map makes interpretation very difficult, particularly in more highly populated areas. Incidence cases (this should also be stated in the methods) are used to determine the radius of the 'dot' on map and this is not made clear in the interpretation of the results. This map would be stronger if the incidence risk of the cases is presented. It is difficult to ascertain whether the pattern observed is a function of population or an actual higher incidence in these areas. Given the large number of points for the map, an alternative method such as kernel smoothing might provide a more robust picture of the incidence count.

Figure 5: The units for the "Time" axis should be stated. The x-axis would benefit from either having markings at yearly or seasonal intervals.

Page 8, line 39: change "most of the patients was male patients," to "most of the patients were male," (delete the second "patients").

Page 8, line 40-42: Change "irrespectively" to "irrespective". The rest of this sentence does not make sense, please revise.

Page 9, line 3-5: This is impossible to tell from the map presented in Figure 3. Was a separate analysis done that examined incidence? Was this just by a visual inspection of the numbers? Or was a more sophisticated cluster analysis performed?

Discussion

Overall, very well written. My only revisions would be for a sentence on Page 11, line 51-55, the sentence is awkwardly formed, and Page 11, line 57, add "observed" to the sentence so it reads "… dynamics of dengue observed in our study …"

REVIEWER	Mark Janko
	Duke University, USA
REVIEW RETURNED	01-Dec-2018

| GENERAL COMMENTS | The authors set out to understand the relationship between environmental conditions such as mean temperature on incidence of Dengue (or probably Dengue) virus incidence in a region of China. The authors present a sophisticated analysis on a challenging subject, and are to be commended. I have a number |

of comments, both major and minor that I feel would improve the manuscript.

Major Comments:
While the study uses aggregated data, the authors should probably note what agency/institution, if any, granted ethical approval to conduct the study.

Can the authors share data and code in a supplement?

Can the authors include a STROBE statement/complete a checklist in a supplement? This appears to be required for the journal (from the reviewer checklist, at least)

Much of the discussion is spent justifying the use of the GAMLSS. This should be done in the methods section. They discuss fitting 70 different models, but do not explain how they arrived at 70. This should be done. For example, something like: 'we considered temperature and precipitation separately, then with both in model, then with both plus interaction, yielding 4 models."

Additionally, the authors should describe what 'local powers' are and how to interpret them/what they mean, since this seems key. In other words, it would be helpful if the authors described why they fit the 70 models they did, and then how to interpret the results.

Figure 5 is nearly impossible to interpret. Time should be relabeled (into calendar time, such as month of year, or week). Additionally, the 4 decimal places in the local power axis makes it hard to read (i.e. no decimals are needed, in my opinion). It's also unclear what local power means, since, in statistical terminology, power is a probability, whereas the figure reports powers ranging from 0 to 38000.

Figure 6. The authors note that the effect of temp on dengue is greatest around 25 degrees. It looks more like 27 degrees based on the plot. i.e. the curve definitely continues to go up after 25 degrees. So perhaps give a range (25-28 C)? That said, it's hard to interpret, since it's unclear what scale the y-axis is on. Are these partial effects log relative risks? Also, what are the blue dots? Are they log incidences?

Minor Comments:
Page 6, line 54 (Statistical Analysis). I would avoid saying that you computed the probability density distribution. It's a plot of the proportion of cases by time (onset to diagnosis).

The sentence (page 7, 2nd paragraph), "A stat significance test was performed to test the null that a period was irrelevant..." needs to be re-written. A null hypothesis significance test can either reject the null or fail to reject the null. So the authors should define what the null is numerically, rather than say it's testing 'relevancy.' i.e. what is relevant?

All percentages should be reported to, at most, 1 decimal.

The authors report two different versions of IQR. For example, median age (31 years) vs time from onset to diagnosis (2.75-8). The former is technically correct (statistically), but conveys less

	information than the latter. I would recommend reporting all IQRs using the latter format. Figure 2d. The Y axis should not be labeled probability density function. It should be labeled proportion. Figure 3. The caption says that you're reporting incidence, but the figure only shows number of cases. What is the person-time exposed here? Figure 6. I'd pick different colors for the dots. The hollow, light blue dots are very hard to see. Also, I don't know what all gray lines are. These should be described, or removed.

VERSION 1 – AUTHOR RESPONSE

To reviewer #1:

Dear professor, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "This is an analysis of the temporal epidemic dynamics with a specific periodicity related to climatic drivers using a wavelet analysis of dengue "cases" in the Chao-Shan area of Guangdong Province, China. Whether any of these cases were caused by dengue viruses is unknown as no laboratory test results were reported. Most of the interesting and important epidemiological features of the outbreak were not studied. For example, what dengue virus or viruses were being transmitted during the period of study? What was the age-specific dengue antibody prevalence in the population studied? What was the rate of dengue disease in each age group? Age specific attack rates of clinically overt dengue infections in human vary greatly according to the type of virus being circulated and whether the infected hosts are experiencing primary or secondary infections (secondary infection occurs in individuals with immunity to a dengue type other than the one circulating during the period of study). Even more important, there is no mention of the distribution of potential vector mosquitoes nor were the mosquito vectors of these outbreaks specifically identified during the period of the study. Dengue virus outbreaks in northern and southern temperate areas of the world have been described in the published literature for more than 300 years. The bionomics and ecology of Aedes aegypti-borne viral diseases have been studied for generations and reported extensively in the literature and in standard textbooks. Where are the citations to this literature? The references cited are mainly of recent dengue activity in China and that appear to ignore the described biology of dengue in other temperate countries. Mosquito longevity and biting activity are greatly influenced by temperature and humidity. The incubation period of dengue viruses in mosquito vectors is under temperature control, the higher the temperature the shorter the extrinsic incubation period permitting a higher fraction of dengue-infected mosquitoes to successfully obtain the two blood meals required for transmission."

Response: Dear Professor, we really thank you for your important suggestions. We really cherish this opportunity for explaining some issues to you here. Our responses are arranged as follows: 1) for your comments that "Whether any of these cases were caused by dengue viruses is unknown as no laboratory test results were reported?", "what dengue virus or viruses were being transmitted during the period of study?", and "What was the age-specific dengue antibody prevalence in the population studied?", we feel that these comments are very accurate and intelligent. However, at present, we can't obtain the data on laboratory test results for different kinds of dengue viruses. Therefore, we can't study the epidemical features of dengue cases caused by different viruses as well as the age-specific dengue antibody prevalence in the population at present. We find your opinion very important.

So, we spent some time and learned that there are but not many sentinel surveillance hospitals (around 3~4 hospitals) located in the study areas, which are monitoring the dengue cases by viruses. It means that we can obtain more detailed information about the dengue cases in the study areas. However, these sentinel hospitals are supervised by the government. We are now contacting potential collaborators to get relevant surveillance data to achieve the analysis goal you mentioned. But it beyond the scope of this present study because we mainly focused on the effect of seasonal climate variation on the dynamics of dengue epidemic in southeastern China. We really thank you for your suggestion. We feel that we should acknowledge them as limitations. Therefore, continuous studies should be performed to investigate the issues in future. Likewise the distribution of potential vector mosquitoes and the mosquito vectors identified themselves we are not able to obtain at present because the related dengue virus surveillance system is very weak in the study areas, the Chao-Shan area, on China's southeastern coast. We plan to investigate the issues with future studies. We really thank you for the insightful comments. We have acknowledged these issues as limitation in the last paragraph, the Discussion part. Please check them; 2) for your comment that this present study should cite relevant literature about the biology of dengue in other temperate countries, we have added relevant literature ([1] Scott B. Halstead, E. J. O'ROURKE. Antibody-enhanced dengue virus infection in primate leukocytes. Nautre 1977; [2] Maria G. Guzman, Duane J. Gubler, Alienys Izquierdo, Eric Martinez, Scott B. Halstead. Dengue infection. Nature Reviews Disease Primers 2016; [3] Guzman MG, Harris E. Dengue. Lancet 2015; [4] Cory WM, Andrew CC, and Kacey E. Climate and Dengue Transmission: Evidence and Implications. Environmental health perspectives 2013) according to your suggestion. Please check them in the 1st paragraph, the Introduction part. Thank you.

To reviewer #2:

Dear professor, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "This paper presents an analysis of dengue case data from a densely populated region in southern China and spanning a four-year period (2014-2017). The main focus is on studying seasonal effects on dengue incidence. Like previously published studies, the authors find an association between climatic variables - in particular temperature - and incidence. They also estimate a higher risk of dengue transmission for temperatures around 25oC. The authors have collated a nice dataset and, overall, the paper is interesting, technically sound, and - for the most part - clearly written. I have only few minor comments included hereafter."

Response: Dear Professor, we thank you for your encouragement. We really cherish this opportunity for revising our manuscript.

2) Comment: "The authors should indicate the type of mosquitoes that are present in the study area. Are Aedes Albopictus and Aegypti equally present in the three locations they considered?"

Response: Dear Professor, we thank you for your comments and encouragement. We have added relevant descriptions about the type of mosquitoes that are present in the study area. Please check it in the last sentence of the 3rd paragraph, the Introduction part. Thank you.

3) Comment: "Similar to the previous point: if the information was available, please indicate the dengue serotype/serotypes. Was there only one serotype circulating during the entire study period?"

Response: Dear Professor, we thank you for your important comments. However, at present, we can't obtain the data on laboratory test results for various kinds of dengue viruses. Therefore, we can't study the epidemical features of dengue cases caused by different viruses in the population at present. We are now contacting potential collaborators to get relevant surveillance data for dengue

serotype/serotypes. We really thank you for your suggestion and acknowledge that continuous studies should be performed to investigate the issues in future. We have acknowledged it as a limitation. Please check it in the last paragraph, the Discussion part.

4) Comment: "The authors find that Chaozhou accounts for 78% of the total number of dengue cases reported from 2014 to 2017. It would be useful to indicate if there are any differences in terms of population or climatic variables between the three cities they considered."

Response: Dear Professor, we feel that this comment is very accurate and insightful. We have discussed the reasons according to your comment. Please check them in the 2nd paragraph, the Discussion part.

5) Comment: "Figure 5: please add the units (presumably weeks) to the y axes of the heat maps."

Response: Dear Professor, we thank you for your comments. We have added the units (weeks) to the y axes of the heat maps. Please check it in Figure 5. Thank you.

6) Comment: "The third quartile is missing on page 2 line 33, page 8 line 26 (and following two lines), and page 10 line 15."

Response: Dear Professor, we thank you for your comments. The original expressions have been revised. Please check them in the manuscript. Thank you.

7) Comment: "Page 2 line 39: Consider rephrasing the sentence "We detected an annual attack activity…""

Response: Dear Professor, we thank you for your comments. We have rephrased the sentence as "We found an annual peak incidence occurred in autumn…" based on your suggestion. Please check it.

8) Comment: "Page 2 line 44 and page 3 line 13: Rephrase the sentence "… the risk of transmission is most when the temperature is reached to around…""

Response: Dear Professor, we thank you for your comments. Based on the comments you and Reviewer #4 raised, we have rephrased the sentence as "…the risk of transmission is highest when the temperature is between…". Please check it. Thank you very much.

9) Comment: "Page 4 line 20: "… a succession of epidemic fluctuation of dengue occurred…" Please clarify."

Response: Dear Professor, we thank you for this smart comment. We feel very sorry for the poor expression in the unrevised version of the manuscript. We have revised it as "In particular, an extensive outbreak of dengue hit China in 2014, and high risk areas for dengue outbreaks were concentrated in neighboring provinces including Guangdong, Guangxi and Yunnan of southern China". We really thank you for this important comment.

10) Comment: "Page 5 line 27: Please rephrase the sentence "…highlights gaps in our knowledge to the current status of dengue epidemic…""

Response: Dear Professor, we thank you for your comments. We have rephrased the sentence as "…There is an urgent need to understand the association between dengue epidemics and seasonal climatic conditions in order to take corresponding protective measures" according to your comment. Thank you.

11) Comment: "Page 5 line 42: Please rephrase the sentence "All information on individual privacy of patients…""

Response: Dear Professor, we thank you for your comments. We have rephrased this sentence as "All private information on cases diagnosed as dengue is kept confidential in this study". Please check it. Thank you very much.

12) Comment: "

Typos:

Page 2 line 15: replace "assess" with "assessed"

Page 8 line 39: replace "the patients was" with "the patients were"

Page 11 line51: replace "expect" with "except" "

Response: Dear Professor, we have revised the typos you pointed out. Please check them. Thank you very much.

13) Comment: "

Discretionary:

Figure 3: it would be useful to clarify how dengue cases were spatially aggregated. The text mentions streets in Chaozhou, but how were the coordinates of the circles in Figure 3 assigned?

Figure 4: the scale of the three time series in panel B is not the same. I would advise the authors to use the same scale or to explicitly warn the reader in the legend."

Response: Dear Professor, we thank you for your comments. 1) According to your suggestions, relevant descriptions about how dengue cases were spatially aggregated as well as how the coordinates of the dengue cases have been added in the 3rd paragraph, the Results part. In addition, Reviewer #3 also suggests us to produce a kernel density estimate map instead of a dot map to describe the spatial distribution of dengue cases. We have adopted his suggestion, and revised Figure 3 as a kernel density estimate map. Please check it. Relevant descriptions have been added in the 1st paragraph in the Statistical Analysis section of the Material and Methods part, and the 3rd paragraph in the Results part. We very much hope you understand this. Thank you a lot; 2) for your comment that "the scale of the three time series in panel B is different in Figure 4", in fact, we have tried to re-scale the y axis in panel B according to your suggestion. However, we find that the generated plot is very unclear because the obvious dispersion in the number of dengue cases among the three cities during the period. So, we have kept the plot as it was. We really thank you for the advice, and very much hope that you can understand this situation. Thank you.

To reviewer #3:

Dear professor, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "Overall

The paper presents and interesting and important topic on the impact of climate on Dengue infections in Southeast China. The topic and objectives were clearly outlined, but a discussion of the Dengue virus (and Dengue Fever) would improve the article. Some detail in the methods section of the paper is lacking (see below). Results from the study are clearly explained for the most part (see below). The discussion of the results was well presented with supporting evidence. Except for the Discussion section, there were several awkward sentences and typos. A statistical review of the methods and

results is warranted given the advanced techniques presented in the article. No information on approval of ethics was provided, but this might not be necessary given that the study used secondary data. At my institution, ethics approval is also necessary for secondary data analysis. With minor revisions and clarification of the methods, the paper should be acceptable for publication."

Response: Dear Professor, we really thank you for your energizing comments. We have carefully revised the manuscript based on your important comments. Thank you.

2) Comment: "Minor issues

Introduction

The Introduction would benefit from an expanded explanation of what dengue is, how it manifests, and how it might be linked to climate (i.e. that it is viral and mosquito-borne and the symptoms of infection).

Page 4; line 9: "is a" should be "has been".

Page 4; line 55: "However, the impact …" would be better to drop 'however' (e.g. "The impact …").

Page 5; line 7: "square kilometers, but a very" would be better as "square kilometers, with a very".

Page 5, line 9-11: I am not sure of the relevance of this statement.

Page 5, line 14-18: This sentence is awkward. Please reword.

Page 5, line 24-29: Break into two sentences. In its current form the last part makes no sense.

Page 5, line 33-35: Date format should be consistent with the rest of the document (i.e. change to "month day, year")."

Response: Dear Professor, we thank you for your comments. For the comment "The Introduction would benefit from an expanded explanation of what dengue is, how it manifests, and how it might be linked to climate", corresponding content has been added in the 1st paragraph, the Introduction part. The grammatical errors have been revised according to your comment. The relevance of the statement in lines 9-11 in page 5 referred to the Wikipedia and has been added. The sentence in lines 14-18 in page 5 has been reworded. The sentence in lines 24-29 in page 5 has been broken into two sentences. The date format in lines 33-35 in page 5 has been revised. Please check the revisions based on your suggestion. Thank you very much.

3) Comment: "Minor issues

Material and Methods

The methods for a number of the analyses needs to be better explained.

1) How were climatic variables aggregated? The time scale is stated (weekly) but was the mean or the median estimated? Did it use the daily average values, or maximum, or minimum values? Was a simple arithmetic mean calculated? The information must be included. (Section "Climate Surveillance Data"). "

Response: Dear Professor, we thank you for your comments. In fact, the daily average values of climatic variables were used. The issues you mentioned above have been clarified in the Climate Surveillance Data section, the Material and Methods part. Thank you very much.

4) Comment: "Minor issues

Material and Methods

2) Statistical Analysis Section

a. How the probability density distributions were estimated should be explained.

b. How the map of cases was created should be explained in further detail. Residential address was used, but how cases were aggregated is not stated. The analysis was not conducted at the address level, nor is it at the level earlier stated of the 3 cities. This explanation should also include what software was used for data aggregation and mapping (the methods state R was used for analysis, if was done for the map, it would be helpful to state which package was used for mapping, if not, what GIS package was used)."

Response: Dear Professor, we thank you for your comments. First, more explanations have been added to clarify the probability density distributions used. Please check them in the 1st, 2nd and 3rd sentences in the 1st paragraph, the Statistical Analysis section, Material and Methods part. Second, more explanations about the questions how the map of cases was created and how dengue cases were aggregated are added. Please check them from the 4th to 7th sentences in the 1st paragraph, the Statistical Analysis section, Material and Methods part. In fact, maps were generated using ArcGIS 10.2 software, and R software (version 3.4.3) was used for the statistical analyses including Morlet wavelet transform, GAMLSS models and so on. We have revised the sentences according to your suggestions. Please check them in the Statistical Analysis section, Material and Methods part.

5) Comment: "Minor issues

Material and Methods

Page 5; line 57: What exactly are "special climatic conditions"? This was also mentioned in the introduction and should be more clearly stated."

Response: Dear Professor, we thank you for your comments. Corresponding content has been revised in the Introduction part, and the Material and Methods part, respectively.

6) Comment: "Minor issues

Material and Methods

Page 6; line 3: "communions" this word typically refers to a spiritual connection. Replace with a more suitable word."

Response: Dear Professor, we really thank you for this accurate comment. We have revised the word based on your suggestion. Please check it.

7) Comment: "Minor issues

Material and Methods

Page 7, line 3: "reaction ability" please define what this means or reword."

Response: Dear Professor, we thank you. We feel that the previous statement "reaction ability" is not appropriate. So the sentence has been revised in order to make it more understandable. Please check it in the 1st paragraph, the Statistical Analysis section, Material and Methods part.

8) Comment: "Minor issues

Material and Methods

Page 7, line 3-9: The sentence is awkward. Please consider revising."

Response: Dear Professor, we thank you for your comments. The sentence has been revised according to your suggestion. Please check it.

9) Comment: "Results

The graphs present look great in color, but if printed in black and white are un-interpretable. Attention should be paid to both figures 1 and 2.d to make them interpretable for those who would print the article in black and white.

Table 1: Please include a "Total" column for all three cities since total values are also referred to in the Results section."

Response: Dear Professor, we thank you for your comments. According to your suggestion, a "Total" column for all three cities has been included. Please check it in Table 1. In addition, for the color graphs in both figures 1 and 2.d, we will prefer to publish them in color even if this charges some fees, if there is a chance to publish our article. We will coordinate with the journal. Thank you very much for your warm reminder.

10) Comment: "Results

Figure 2.d: Consider using dashed / dotted lines to indicate the different areas. This is uninterpretable in black and white."

Response: Dear Professor, we thank you for your comment. As we mentioned above, we will prefer to publish them in color because the visualization of color pictures at its current status is the better option. We hope you can understand this. We prefer to publish the figure in color even if this charges some fees. We will coordinate with the journal if there is a chance to publish our article. We really thank you for this valuable comment.

11) Comment: "Results

Figure 3: uses a dot map to describe the spatial distribution of Dengue cases in Chao-Shan. Some aggregation has occurred (see comment in methods), but it is unclear to what level aggregation has been applied. The overlapping circles on the map makes interpretation very difficult, particularly in more highly populated areas. Incidence cases (this should also be stated in the methods) are used to determine the radius of the 'dot' on map and this is not made clear in the interpretation of the results. This map would be stronger if the incidence risk of the cases is presented. It is difficult to ascertain whether the pattern observed is a function of population or an actual higher incidence in these areas. Given the large number of points for the map, an alternative method such as kernel smoothing might provide a more robust picture of the incidence count. "

Response: Dear Professor, thank you very much for your important comment. We have adopted your suggestion by using a kernel smoothing method (please refer to: Silverman, BW. Density Estimation for Statistics and Data Analysis. New York: Chapman and Hall, 1986) to produce a more robust picture of the incidence count. Please check it in Figure 3. In addition, relevant descriptions have been added in the 1st paragraph in the Statistical Analysis section of the Material and Methods part, and the 3rd paragraph in the Results part. Please check them. Thank you.

12) Comment: "Results

Figure 5: The units for the "Time" axis should be stated. The x-axis would benefit from either having markings at yearly or seasonal intervals. "

Response: Dear Professor, we thank you for your comments. The unit (week) for the "Time" axis in Figure 5 has been stated. Please check it. We would like to explain to you that the figure assessed the periodicity of the time series of the variables by a time-dependent wavelet analysis. We prefer to maintain the original form of the x-axis, because the x-axis and the y-axis should be maintained the same dimension and representation, which is easy for potential readers to observe and compare. We appreciate your understanding.

13) Comment: "Results

Page 8, line 39: change "most of the patients was male patients," to "most of the patients were male," (delete the second "patients")."

Response: Dear Professor, thank you for your comment. This sentence has been revised according to your suggestion. Please check it.

14) Comment: "Results

Page 8, line 40-42: Change "irrespectively" to "irrespective". The rest of this sentence does not make sense, please revise."

Response: Dear Professor, we thank you for your comments. The word "irrespectively" has been changed to "irrespective". The rest of this sentence has also been revised to make it clearer. Please check it.

15) Comment: "Results

Page 9, line 3-5: This is impossible to tell from the map presented in Figure 3. Was a separate analysis done that examined incidence? Was this just by a visual inspection of the numbers? Or was a more sophisticated cluster analysis performed?"

Response: Dear Professor, we really thank you for this accurate comment. We have modified the sentence to express our meaning more accurately. In fact, we just depicted the areas which have the greatest number of dengue cases. Therefore, the previous expression "spatially aggregated" has been removed in this revised manuscript based on your comment. The whole sentence has been revised to make it more accurately. In addition, as responding to the above comment #11, we have adopted your suggestion by using a kernel smoothing method to produce a new plot to the spatial distributions of dengue cases. Please check it in Figure 3. In addition, relevant descriptions have been added in the 1st paragraph in the Statistical Analysis section of the Material and Methods part, and the 3rd paragraph in the Results part. Thank you.

16) Comment: "Discussion

Overall, very well written. My only revisions would be for a sentence on Page 11, line 51-55, the sentence is awkwardly formed, and Page 11, line 57, add "observed" to the sentence so it reads "…dynamics of dengue observed in our study …""

Response: Dear Professor, we thank you for your comments. This sentence in line 51-55 on Page 11 has been revised to make it clearer. Also, the word "observed" has been added to the sentence as "…dynamics of dengue observed in our study …" based on your suggestion. Please check it. Thank you for these important comments.

To reviewer #4:

Dear professor, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "The authors set out to understand the relationship between environmental conditions such as mean temperature on incidence of Dengue (or probably Dengue) virus incidence in a region of China. The authors present a sophisticated analysis on a challenging subject, and are to be commended. I have a number of comments, both major and minor that I feel would improve the manuscript."

Response: Dear Professor, we really thank you for your encouragement and important comments. We have carefully revised the manuscript based on your important comments. Thank you.

Major Comments:

2) Comment: "While the study uses aggregated data, the authors should probably note what agency/institution, if any, granted ethical approval to conduct the study."

Response: Dear Professor, we really thank you for the comment. We are very grateful for the opportunity to explain the issue for you. In fact, your comment "the study uses aggregated data" is correct. We actually obtained the surveillance data of dengue in the study sites and only used the count data. Therefore, no ethics committee approval is required to obtain the data since the count data is presented. No personal information is revealed in this word, thereby maintaining confidentiality. This can be seen in a lot of relevant literature that has been previously published. We really appreciate your understanding.

3) Comment: "Can the authors share data and code in a supplement?"

Response: Dear Professor, we thank you for your comments. So far, we can't share this surveillance data of dengue publicly because of personal privacy and legal issues. We very much hope that you will understand this situation. For the code used in this study, we want to point out that the analysis models established here is actually ready for use. For example, the gamlss package within R software was used to establish the generalized additive model for location, scale and shape (GAMLSS) model. Potential readers can learn the principles of the model and build the model directly from relevant guide files released by R software (https://www.r-project.org/). According to your suggestion, we have added relevant content to depict it more clearly. Please check them in the 2nd and 4th paragraphs in the Statistical Analysis section, Material and Methods part. Thank you.

4) Comment: "Can the authors include a STROBE statement/complete a checklist in a supplement? This appears to be required for the journal (from the reviewer checklist, at least)"

Response: Dear Professor, we thank you for this comment. According to your suggestion, a STROBE statement has been included in a supplement. Please check it in the Supplementary File (Table S2).

5) Comment: "Much of the discussion is spent justifying the use of the GAMLSS. This should be done in the methods section. They discuss fitting 70 different models, but do not explain how they arrived at 70. This should be done. For example, something like: 'we considered temperature and precipitation separately, then with both in model, then with both plus interaction, yielding 4 models.'"

Response: Dear Professor, we really thank you for this important comments. We have revised the manuscript to make it clearer. Relevant content has been added in the 4th paragraph in the Statistical Analysis section, Material and Methods part. Please check them. Thank you.

6) Comment: "Additionally, the authors should describe what 'local powers' are and how to interpret them/what they mean, since this seems key. In other words, it would be helpful if the authors described why they fit the 70 models they did, and then how to interpret the results."

Response: Dear Professor, we thank you for your comments. First, the expression 'local powers' is actually short for the expression 'local wavelet power spectrum'. Our time series data of climatic factors were analyzed by wavelet analysis, and then the wavelet decomposition results were used to calculate power spectrum. By decomposing the time series into the time-frequency domain, wavelet analysis can obtain the significant fluctuation pattern of the time series, that is, the periodic change dynamics and the periodic dynamic time pattern. Therefore, we can detect the temporal periodicity in a time series by inspecting the plot of 'local wavelet power spectrum'. Based on your suggestion, relevant content has been added in the 2nd paragraph in the Statistical Analysis section, Material and Methods part. Second, for the comment "it would be helpful if the authors described why they fit the 70 models they did", we have revised the manuscript by adding relevant content to make it clearer. Please check it in the above response. We really thank you for the important comments.

7) Comment: "Figure 5 is nearly impossible to interpret. Time should be relabeled (into calendar time, such as month of year, or week). Additionally, the 4 decimal places in the local power axis makes it hard to read (i.e. no decimals are needed, in my opinion). It's also unclear what local power means, since, in statistical terminology, power is a probability, whereas the figure reports powers ranging from 0 to 38000."

Response: Dear Professor, we thank you for your comments. As responding to you in the above comment #6, we have fully explained the meaning of the 'local powers' which is actually short for the expression 'local wavelet power spectrum'. The wavelet analysis model was performed in our study to assess our time series data of climatic factors and dengue cases. Specifically, by using the wavelet analysis model, we obtained the wavelet decomposition results, and then used them to calculate power spectrum. By decomposing the time series into the time-frequency domain, the wavelet analysis can let us observe the significant fluctuation pattern of the time series, that is, the periodic change dynamics and the periodic dynamic time pattern. Therefore, we can detect the temporal periodicity in a time series by inspecting the plot of 'local wavelet power spectrum'. Necessary illustrations about the methodology have been added in the 2nd paragraph, the Statistical Analysis section, Material and Methods part. Please check them. Additionally, we agree with you that "the 4 decimal places in the local power axis makes it hard to read (i.e. no decimals are needed, in my opinion)". We have adopted your suggestion and reduce the number of decimal places. However, the 1 decimal place in the axis should be reserved because we have to keep the consistent gradient between the numbers and colors for the 'power' in the plot. We have revised the figure according to your suggestion. Please check it. We thank you for understanding this situation.

8) Comment: "Figure 6. The authors note that the effect of temp on dengue is greatest around 25 degrees. It looks more like 27 degrees based on the plot. i.e. the curve definitely continues to go up after 25 degrees. So perhaps give a range (25-28 C)? That said, it's hard to interpret, since it's unclear what scale the y-axis is on. Are these partial effects log relative risks? Also, what are the blue dots? Are they log incidences?"

Response: Dear Professor, thank you for your comments. First, we accept your suggestion and think it more appropriate to depict it as a range (25°C - 28 °C). We have revised it in the 5th paragraph, the Results part. Second, the y-axis represents the value of partial effect function from a smoothing effect term in a GAMLSS model. By 'partial effect' function we mean how x (temperature in our study) is influence the parameter of interest given that the rest of explanatory terms for this paramerer are on specified values (Please refer to: Stasinopoulos D. M. Rigby R.A. (2007) Generalized additive models for location scale and shape (GAMLSS) in R. Journal of Statistical Software, 2007). In fact, by plotting the value of smoothing effect term against their predictors, we can identify the nonlinear relationship between the dependent variable and the independent variables from this plot. In addition, the lightblue

dots are partial residuals of the model. The partial residuals of the model were also drawn and added in the figure because we can see how the model fits in the data. It is a widely used strategy in previous studies. According to you suggestion, relevant content has been added in the 4th paragraph in the Statistical Analysis section, Material and Methods part. Necessary descriptions have also been added in the caption of Figure 6. Please check them. We really thank you for the important comments.

Minor Comments:

9) Comment: "Page 6, line 54 (Statistical Analysis). I would avoid saying that you computed the probability density distribution. It's a plot of the proportion of cases by time (onset to diagnosis)."

Response: Dear Professor, thank you very much. In fact, in the section of Statistical Analysis you mentioned above, we really calculated the probability density distribution of duration from case onset to case diagnosis. It is not a simple proportional indicator, but what it's going to say is basically consistent with what a proportional indicator is going to say. Actually, we have referred to a previous study and adopted this method of data calculation and presentation (Please refer to: WJ Xing, et al. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study. The Lancet Infectious Diseases, 2014). We really thank you for this opportunity, and very much hope that the issue has been explained clearly by us.

10) Comment: "The sentence (page 7, 2nd paragraph), "A stat significance test was performed to test the null that a period was irrelevant..." needs to be re-written. A null hypothesis significance test can either reject the null or fail to reject the null. So the authors should define what the null is numerically, rather than say it's testing 'relevancy.' i.e. what is relevant?"

Response: Dear Professor, we really thank you for your comments. Based on your suggestion, we have revised the sentence as "a statistical significance test was performed to test the null hypothesis that the signal in a wavelet plot is generated by a stable process of a given background power spectrum (usually white noise) at a certain time with significance level of 95%" to make the explanation clearer. Please check it in the 2nd paragraph in the Statistical Analysis section, Material and Methods part. Thank you very much.

11) Comment: "All percentages should be reported to, at most, 1 decimal."

Response: Dear Professor, thank you. We have revised the manuscript according to your suggestion. Please check them.

12) Comment: "The authors report two different versions of IQR. For example, median age (31 years) vs time from onset to diagnosis (2.75-8). The former is technically correct (statistically), but conveys less information than the latter. I would recommend reporting all IQRs using the latter format."

Response: Dear Professor, thank you very much. We have adopted your suggestion by reporting all IQRs using the latter format. Please check them in the manuscript.

13) Comment: "Figure 2d. The Y axis should not be labeled probability density function. It should be labeled proportion."

Response: Dear Professor, we really thank you for your comments. As we have responded to your comment # 9 in the above section, we really calculated the probability density distribution of duration from case onset to case diagnosis. It is not a simple proportional indicator, but what it's going to say is basically consistent with what a proportional indicator is going to say. Actually, we have referred to a previous study and adopted this method of data calculation and presentation (Please refer to: WJ Xing, et al. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study. The Lancet

Infectious Diseases, 2014). We really thank you for this opportunity, and very much hope that this issue has been explained clearly.

14) Comment: "Figure 3. The caption says that you're reporting incidence, but the figure only shows number of cases. What is the person-time exposed here?"

Response: Dear Professor, thank you. It is a mistake. Our original intention is to express it as "number of dengue cases". We have revised the caption of Figure 3 by removing the word "incidence" and expressing it as "number of cases". In addition, Reviewer #3 also suggests us to produce a kernel density estimate map instead of a dot map to describe the spatial distribution of dengue cases. We have adopted his suggestion, and revised Figure 3 as a kernel density estimate map. Relevant descriptions have been added in the 1st paragraph in the Statistical Analysis section of the Material and Methods part, and the 3rd paragraph in the Results part. We very much hope you understand this. Thank you a lot.

15) Comment: "Figure 6. I'd pick different colors for the dots. The hollow, light blue dots are very hard to see. Also, I don't know what all gray lines are. These should be described, or removed."

Response: Dear Professor, we really thank you for your comments. As we have responded to your comment # 8 in the above section, the lightblue dots are partial residuals of the model. The partial residuals of the model were also drawn and added in the figure because we can see how the model fits in the data. It is a widely used strategy in previous studies. We have explained it in the above section. Necessary descriptions have also been added in the caption of Figure 6. In addition, based on your suggestion, the gray lines have been removed from the figure. We really thank you for the important comments.

VERSION 2 – REVIEW

REVIEWER	Alessio Andronico Institut Pasteur
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	The authors have addressed all the comments raised during the review, so I recommend this article for publication.

REVIEWER	James Valcour Memorial University of Newfoundland, Canada
REVIEW RETURNED	13-Mar-2019

GENERAL COMMENTS	The authors have done a very good job addressing the my concerns / comments, as well as those of other reviewers. I am happy with the paper as presented, although I still contend that providing graphs that would allow for interpretation when printed grey scale would enhance the paper. I concede that it is the authors prerogative to stick with the figures as presented, since there is nothing inherently incorrect with them. Minor Corrections (language edits from me are in between asterisks (i.e. *like this*):

| | Table 1, Total Column: The first value doesn't need the "%" sign as you stated that in your row label.

Results, paragraph 3, sentence 2: ... hotspots *suggesting* that ... period were *around* Xixin ... |
|---|---|

| REVIEWER | Mark Janko
Duke University, USA |
|---|---|
| REVIEW RETURNED | 13-Mar-2019 |

| GENERAL COMMENTS | The authors present a revised manuscript on Dengue case counts and related climate variables. They use a number of sophisticated modeling techniques (time series analysis and GAMs).

1) The authors need an explicit statement about whether or not they received ethical approval for the study, or if no approval was needed.

2) I believe the authors should share their code. The reviewer checklist indicates that reproducability should be a criterion for evaluating the article. The authors point to the R packages that they use, and state that readers can reference the documentation to reproduce the results. This is not entirely true. While it is true that the software documentation would allow readers to familiarize themselves with the methods, it does not provide a step-by-step guide that would allow a reader to reproduce the results. For example, the software documentation will not help readers with the data management and modeling decisions specific to the data and research question. Sharing code in a supplement would be an easy initial step to aid in reproduceability.

The authors undertake a large model-selection exercise, but report that they fit either 63 or 70 models. This needs to be corrected.

The authors state: "Unlike traditional linear regression, the approach enables to find a nonlinear relationship between the dependent variable and a set of independent variables by specifying an appropriate smooth function term that describes the relationship [27]." This sentence is not true. It is quite trivial to identify non-linear relationships from linear regression. For example: $y= b0 + x1*b1 + x1^2*b2$ captures a non-linear relationship between y and x1, and can be done using linear regression. The authors should instead indicate that there is more flexibility in identifying those non-linearities using a GAM-based approach. |
|---|---|

VERSION 2 – AUTHOR RESPONSE

To reviewer #2:

Dear professor, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "The authors have addressed all the comments raised during the review, so I recommend this article for publication."

Response: Dear Professor, we really thank you for your important suggestions which have greatly improved our manuscript.

To reviewer #3:

Dear professor, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "The authors have done a very good job addressing the my concerns / comments, as well as those of other reviewers. I am happy with the paper as presented, although I still contend that providing graphs that would allow for interpretation when printed grey scale would enhance the paper. I concede that it is the authors prerogative to stick with the figures as presented, since there is nothing inherently incorrect with them."

Response: Dear Professor, we thank you very much for your valuable comments. We will keep in touch with the editorial department on how to further improve the quality of figures before the publication of the manuscript.

2) Comment: "Minor Corrections (language edits from me are in between asterisks (i.e. *like this*): Table 1, Total Column: The first value doesn't need the "%" sign as you stated that in your row label. Results, paragraph 3, sentence 2: ... hotspots *suggesting* that ... period were *around* Xixin ..."

Response: Dear Professor, thank you very much for your comments. The "%" sign for the Total Column in Table 1 has been removed. Also, we have edited the language as you mentioned in the sentence 2, paragraph 3, Results. Please check them.

To reviewer #4:

Dear professor, thank you very much for these constructive comments, which have greatly improved our manuscript. Our responses to the comments are listed one by one as follows. Please check them.

1) Comment: "The authors present a revised manuscript on Dengue case counts and related climate variables. They use a number of sophisticated modeling techniques (time series analysis and GAMs)."

Response: Dear Professor, we really thank you for your energizing comments.

2) Comment: "The authors need an explicit statement about whether or not they received ethical approval for the study, or if no approval was needed."

Response: Dear Professor, thank you very much. We have added an explicit statement about the ethical approval for the study. Please check it in the section of Patient and Public Involvement, the Material and methods part. Thank you again.

3) Comment: "I believe the authors should share their code. The reviewer checklist indicates that reproducability should be a criterion for evaluating the article. The authors point to the R packages that they use, and state that readers can reference the documentation to reproduce the results. This is not entirely true. While it is true that the software documentation would allow readers to familiarize themselves with the methods, it does not provide a step-by-step guide that would allow a reader to

reproduce the results. For example, the software documentation will not help readers with the data management and modeling decisions specific to the data and research question. Sharing code in a supplement would be an easy initial step to aid in reproducibility."

Response: Dear Professor, thank you very much. We feel your suggestion is understandable, and really agree with your suggestion. Therefore, we have shared the R codes in a supplement. R codes were provided to show how to employ the time-dependent wavelet analysis to assess the periodicity of the time series, and GAMLSS model to study the association between seasonal characteristics of dengue and climatic variables (see Supplementary Material, "R codes"). According to your suggestion, relevant statements have been added in the last paragraph in the Statistical Analysis section, the Material and methods part. Please check them.

4) Comment: "The authors undertake a large model-selection exercise, but report that they fit either 63 or 70 models. This needs to be corrected."

Response: Dear Professor, thank you very much. We have revised the content to make it clearer. Please check it in the 4th paragraph of the Statistical Analysis section, the Material and methods part. Thank you again.

5) Comment: "The authors state: "Unlike traditional linear regression, the approach enables to find a nonlinear relationship between the dependent variable and a set of independent variables by specifying an appropriate smooth function term that describes the relationship [27]." This sentence is not true. It is quite trivial to identify non-linear relationships from linear regression. For example: $y = b_0 + x_1 * b_1 + x_1^2 * b_2$ captures a non-linear relationship between y and x1, and can be done using linear regression. The authors should instead indicate that there is more flexibility in identifying those non-linearities using a GAM-based approach."

Response: Dear Professor, we thank you for your comments. We have adopted your suggestion by indicating that there is more flexibility in identifying those non-linearities using a GAM-based approach. Please check it in the 3rd paragraph, the Discussion part. Thank you again.