Author's response to reviews

Title: Emergence of dengue virus 4 genotype II in Guangzhou, China, 2010: Survey and molecular epidemiology of one community outbreak

Authors:

Qin-Long Jing MD (jingqinlong@126.com)
Zhi-Cong Yang MD (gdgzc@163.com)
Lei Luo PHD (llyevy@163.com)
Xin-Cai Xiao PHD (biotin2001@163.com)
Biao Di MD (biao65di@yahoo.com)
Peng He MD (emailhepeng@foxmail.com)
Chuan-Xi Fu PHD (fuchuanxi@gmail.com)
Ming Wang MD (wangming@gzcdc.org.cn)
Jia-Hai Lu PHD (jiahailu@yahoo.com.cn)

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Author's response to reviews: see over
Cover Letter

Dear Editors and Reviewers:

Great thanks for your valuable comments and suggestions.

Our manuscript, **Emergence of dengue virus 4 genotype II in Guangzhou, China, 2010: Survey and molecular epidemiology of one community outbreak**, has been revised carefully according to reviewers’ and editorial comments, with point-by-point responses attached. All changes made to the text are in red color. In addition, we have consulted native English speakers for paper revision before the submission this time. We hope the new manuscript will meet the standard of *BMC Infectious Diseases*.

If you have any question about this paper and changes, please don’t hesitate to let me know. Correspondence about this paper should be directed to Jing Qinlong at the following address, phone and e-mail:
Address: Guangzhou Center for Disease Control and Prevention, No. 1, Qide Road, Baiyun District, Guangzhou City, People’s Republic of China 510440
Tel: 86-20-36055821
Fax: 86-20-36055833
E-mail: jingqinlong@126.com

Thanks again and best regards!

Yours sincerely,
Qin-Long Jing
For your guidance, point-by-point responses are appended below. The original comments are in black, and our responses are in blue.

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Responses to Reviewers
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Reviewer 1: Ng Lee Ching

General:

Reviewer: The manuscript describes briefly a DENV4 outbreak in Guangzhou, China. The amount of information and data should be reduced to a concise case report. Repetitions should be removed. The language needs substantial improvement. Care should be taken in quoting articles, without mis- or over interpretation.

Response: 1. The amount of information and data is reduced to a case report following the instructions for authors of *BMC Infectious diseases*.

   2. Repetitions are removed, especially on phylogenetic analysis.

   3. After consulted native English speakers for paper revision, the language is made substantial improvement.

   4. Care is taken in quoting articles, on mis- and over interpretation. We have checked all the references for accuracy on description.

Specific:

1. Reviewer: Page 2, background of abstract: awkward sentences, suggest to change to: “However, it has not been known to have caused an outbreak in China for the past 20 years”. "The purpose of this study was to elucidate the epidemiology of one local community outbreak caused by DENV-4 in Guangzhou city, China, in 2010; and to
determine the molecular characteristics of the genotype II virus involved.”

**Response:** We modify the two sentences fully in accordance with your suggestions. The new sentences are all placed in Page 2, Para 1, “it has not been known to have caused a local outbreak in china for the past 20 years.” and “The purpose of this study was to elucidate the epidemiology of one local community outbreak caused by DENV-4 in Guangzhou city, China, in 2010; and to determine the molecular characteristics of the genotype II virus involved.”

2. **Reviewer:** Page 2: “imported index case from a tourist from Thailand.”, however later text stated that index was a Guangzhou resident who returned from Thailand.

**Response:** In this outbreak, the imported index case was a Guangzhou resident who travelled back from Thailand. The related sentences are revised in Page 2, Para 2 and Para 3, Page 8, Para 3, and Page 9, Para 4, “a Guangzhou resident who travelled back from Thailand”.

3. **Reviewer:** Page 3, para 1 of background “The total yearly cost of treatment in dengue-endemic areas can reach US $2 billion [3]” The cost is for the 8 countries study, not for all dengue endemic areas.

**Response:** Yes, as you said, we revise the sentence fully according your suggestion in Page 3, Para 1, “The total yearly cost of treatment can reach US $2 billion in five countries in the Americas (Brazil, El Salvador, Guatemala, Panama, and Venezuela) and three countries in Asia (Cambodia, Malaysia, and Thailand)”.
4. Reviewer: Page 3 para 3: “The first detection of DENV-4 was reported in Easter Island, a territory of Chile, in 2009 and was classified to genotype II [8].” This can’t be true.

Response: We read the reference [8] carefully, and revise the sentence in Page 3, Para 3, “The detection of DENV-4 was reported for the first time in Easter Island in 2009, which was placed in genotype II”. We are not very sure whether this modification is your intention, and we hope a further communication.

5. Reviewer: Page 3 para 3: “In addition, DENV-4 has a higher rate of dispersion than other serotypes [12]” please note that this study showed that DENV-4 has higher rate than than DENV2 in the Americas during the study period. Authors should not make a sweeping statement based on the study.

Response: We confirm the original sentence really a sweeping statement, and correct it in Page 3, Para 3, “In addition, DENV-4 has a higher rate of dispersion than DENV-2 in the Americas during the study period [12]”.

6. Reviewer: Page 3, para 3: “and the evolutionary rate may increase following geographical expansion [13].” Not sure how this statement is derived from the article quoted.

9):2279-2284.”, says “Zanotto et al.(1996) postulate that this geographical spread of dengue viruses will result in an increase in virus evolution, which may in turn generate more virulent strains.” in Page 2286 in the magazine.

7. Reviewer: Page 3, para 3 “currently replaced DENV-1 as the primary epidemic strain in the Pacific region [15]. This occurred from 2007-2009. I understand that indeed some islands continues to be hit by DENV-4, however, author is encouraged to give a quote that reflects current situation.

Response: We revised the original sentence upon your suggestion in Page 3, Para 3, “had replaced DENV-1 as the primary epidemic strain in the Pacific region from 2007 to 2009 [16]”.

8. Reviewer: Page 5, para 2: “objecting to recommendations” what does this mean?

Response: “objecting to recommendations” means “meet the case definition of the Diagnostic Criteria for Dengue Fever (WS216-2008) enacted by the Chinese Ministry of Health”. We delete “objecting to recommendations” in the manuscript due to its repetition.

9. Reviewer: It was unclear how 4-fold increase in IgG level was determined. IgG capture kit is meant to detect high level of IgG, typical of secondary infection.

Response: In Guangzhou Center for Disease Control and Prevention, we judge 4-fold increase in IgG level upon an index value or Panbio Units according to the
manufacturer’s instructions, with a parallel test conducted by the Panbio Dengue IgG Capture ELISA between acute phase and convalescent serum samples.

10. Reviewer: Sequencing primers not stated and ref not quoted.

Response: In Page 5, Para 2, “using previously described primers” means Sequencing primers are the same as the three pairs of primers to amplify the entire DENV-4 envelope gene sequence. Details are shown in additional file 1.

11. Reviewer: How extensive was the active searches?

Response: Once a dengue case identified in Guangzhou, active searches must be conducted in a radius of 100 meters around household of each case, every household must be visited by medical professionals in the first three days and every five day until the end of epidemic, including probable case searching, Breteau index survey, and health education. 2 cases were identified from active searches with 18,324 persons visited in this outbreak. The extensive is addressed in Page 6, Para 1, “two cases among 18,324 persons from active searches”.

12. Reviewer: Multiple repetition of results within “results section” (homology and phylotree tell the same story, need to describe only one) and discussion section.

Response: Thanks for your knowledgeable suggestions. Accordingly, we mainly describe the phylogenetic analysis in results section in this manuscript, and delete the same contents in discussion section.
13. **Reviewer:** More info could be given with regard to size of the affected area, and movement of people who got infected.

**Response:** Jingtai Street community, the affected area, covered 11.4 square kilometers, with a population of 32,567 in 2010 in the latest data enacted on October 28 of 2011 by the Baiyun District Bureau of Statistics ([http://stats.by.gov.cn/tjsj/ndsj/201110/13281.html](http://stats.by.gov.cn/tjsj/ndsj/201110/13281.html)). This information is placed in Page 4, Para 4, “In addition, Jingtai Street community, the affected area, covered 11.4 square kilometers with a population of 32,567 in 2010.”

The imported index case visited a friend living on fifth floor on September 2, initiating the first autochthonous case living on third floor in the same building in Jingtai Street. Other autochthonous cases had no obvious gathering activities but all lived in Jingtai Street. These contents are added in Page 6, Para 2, “However, She visited a friend living on fifth floor in Jingtai Street on September 2.”, and page 6, Para 3, “The first autochthonous case who developed illness on September 6 lived on third floor in the same building with the friend visited by the imported index case on September 2. Other autochthonous cases had no obvious gathering activities but all lived in Jingtai Street community.”
Reviewer 2: Kee Tai GOH

Reviewer: I will serve as the second reviewer. I have no further comments to add to what the first reviewer has pointed out. Please advise the authors to revise the manuscript. The revised version should then be sent to the first reviewer for further inputs, if any.

Response: we revise the manuscript as your suggestions. Thanks again for your time and consideration.
Responses to Editor

Additional editorial comments:

1. Editor: It would be very useful to have a figure of cases by date of onset including the imported case, so that reader can better assess the dynamic of spread from the imported case. On this figure, the authors, based on the date of onset, could indicate the duration of infectiousness of the index case. Date of onset that indicated in table 2 should then be deleted.

Response: Thanks for your imaginative suggestion! We add Figure 1 to describe the dynamic of spread from the imported case to 18 autochthonous cases, and delete the Date of onset and Days of interval accordingly in Table 2.

2. Editor: The authors do not mention anything on the proportion of asymptomatic infection. I think that this needs to be discuss since the proportion of asymptomatic infection is high for dengue. They should indicate if a population serosurvey would have been useful or not to assess and better understand how it spread from the imported case.

Response: This is an excellent suggestion. We add the result of population serosurvey from 200 healthy persons in the revised manuscript. The information is added to Page 6, Para 1, “Moreover, 1 (0.50%) serum sample from a healthy person tested positive for IgM in the serosurvey.”
3. Editor: Authors suggest in the discussion that "...early detection of cases and a rapid public health response might prevent such importations leading to outbreaks...". It would be necessary to at least indicate what evidence indicates that such a strategy would be effective, knowing that a large proportion of subject with dengue infection is asymptomatic. What kind of public health response would achieve that.

Response: Thank you for pointing this out. As is known in professionals, early detection of cases and rapid public health response play a vital role in controlling proliferation. We are sorry for careless not tracing the quotation to original source. Now, a new reference is listed in [28], “28. Gubler DJ: Dengue and Dengue Hemorrhagic Fever. Clin Microbiol Rev 1998, 11(3):480-496.”

4. Editor: The authors do not say much on the vector in the region of China where this outbreak occurred. A sentence would be necessary in the background on the type of Aedes involved (A aegypti, A albopictus...) with a statement that indicates if the density of the vector at the time this outbreak occurred was higher than usual or not. In the discussion, the authors indicate "Aedes Alpictus". Don't they mean Aedes albopictus? This needs clarification.

Response: Aedes albopictus is the uppermost vector in the transmission of dengue in Guangzhou. During this outbreak, the average Breteau index (BI) was 8.67 in the first three days after the first autochthonous case was identified on September 13 in 2010, a high density of Aedes albopictus in Guangzhou. This information is addressed concisely in a sentence in Page 4, Para 4, “In this paper, we investigated the DENV-4 outbreak in one community named Jingtai Street with an average Breteau index (BI)
8.67 in the first three days after the first autochthonous case was identified on September 13 in 2010, a high density of Aedes albopictus which was the uppermost vector for dengue in Guangzhou. In addition, it is *Aedes albopictus* not “Aedes Alpictus” which is a miswriting, very sorry for this mistake!
Our additional modification

1. **Data errors in original manuscript:** “the incidence rate of 5.63 per 10,000” is a miscalculation in Page 2, Para 3 and Page 7, Para 2 in the original manuscript.

**Response:** It is a great pity to make this mistake. We revise the data according to the latest data with a population of 32,567 in 2010 in Jingtai Street enacted on October 28 of 2011 by the Baiyun District Bureau of Statistics ([http://stats.by.gov.cn/tjsj/ndsj/201110/13281.html](http://stats.by.gov.cn/tjsj/ndsj/201110/13281.html)) in Page 2, Para 2, “with an incidence rate of 5.53 per 10,000 residents.”, and Page 6, Para 1, “which produced an incidence rate of 5.53 per 10,000 residents.” in revised manuscript.

2. In Page 1, “Laboratory for Tropical Disease Control and Prevention (Key Laboratories of the Ministry of Education of China), Sun Yat-Sen University, Guangzhou 510080, PR China” in original manuscript is corrected to “Key Laboratory of Tropical Disease Control, Sun Yat-sen University, Ministry of Education, Guangzhou 510080, PR China” in this revised manuscript.

3. We add “Grant No 2004D2-D0041” in the Acknowledgements section.

4. We add Consent section and Abbreviations section in this revised manuscript.