Author’s response to reviews

Title: The Changing Epidemiology of Dengue in China, 1990-2014: a descriptive analysis of 25 years of Nationwide Surveillance Data

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Author’s response to reviews: see over
To: Dr. Claire Barnard, Deputy Editor, BMC Medicine  
Re: Revision of manuscript 1643447191157616

Dear Dr. Barnard,

Thank you for the opportunity to revise our manuscript “The Changing Epidemiology of Dengue in China, 1990-2014: a descriptive analysis of 25 years of Nationwide Surveillance Data”. We have read through the reviewers’ comments and have addressed each issue below. You will find a point-by-point response to each comment in blue, with a highlighted reference to the page and paragraph where changes have been made in the manuscript. We thank the reviewers for their insightful comments and feel the manuscript is much stronger after taking these into account. We look forward to hearing from you and your team.

Warmest regards,

Hongjie Yu, MD, MPH, PhD
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Point-by-point response

Referee 1:
There is not much information about dengue in China, so this well-written report provides an important overview and is very timely given the 2014 outbreaks of dengue in Guangzhou.

Major compulsory revisions:
It is very unusual to ask a traveler to remember whether he/she remembers being bitten by mosquitoes in the past 2 weeks, and also not being bitten in its home country. The bite of Aedes mosquitoes is known to be imperceptible. So to include a 'memory' of being bitten as part of the criteria for an imported cases is not only not justified, but plain wrong. This is however not the mistake of the authors. But if the definition of an imported cases was travel to a dengue affected area AND indeed s history of mosquito bites, this would explain the very low proportion of 3.7% of imported cases versus 95.3%. The authors should highlight that imported cases are probably underestimated based on the definition used. In light of the other statements by the authors that the local outbreaks in those provinces are most likely due to imported cases rather than indigenous transmission, one would expect a higher proportion of imported cases.

Response: We accept this suggestion and discuss it on Page16, Paragraph 2.

Three editions of the criteria/guidelines for dengue diagnosis and case classification (probable and confirmed cases) issued by the Chinese Ministry of Health were successively used from 1990 to 2014 (see the new Additional file 2):
2. 2001: Diagnostic criteria and principle of management of dengue fever.
3. 2008: Diagnostic criteria for dengue fever.

In the 2001 edition, the history of “mosquito bite” was firstly taken as one part of epidemiologic linkages in the diagnosis criteria. According to the 2001 edition, the “mosquitoes bite” criterion was used in the definition for identifying imported and indigenous cases in a guideline beginning in 2005 issued by the Chinese Ministry of Health. For the reasons similar to those mentioned by the reviewer, and following the 2008 edition which excluded the “mosquitoes bite” from the diagnostic criteria, a new guidelines was issued by the China CDC in October 2014 and implements in 2015, which omits “mosquitoes bite” from the definition of an imported case.
Minor essential revisions:
Dengue IgM positive is only a probably diagnosis, not a confirmed diagnosis.

Response: IgM positive was used as a confirmed diagnosis in the 2001 edition of diagnosis criteria before September 1, 2008, and then it was used as a probable diagnosis in the 2008 edition. We clarify this in the Methods section on Page 8, Paragraph 2.

Referee 2:
This manuscript by Lai and colleagues reports the trend of dengue incidence in China from 1990 to 2014. Using data obtained from passive surveillance through mandated notification of both clinically diagnosed and laboratory confirmed dengue, the authors show that the incidence of dengue is increasing in many parts of China, especially in the southern provinces. They also suggest that the indigenous transmission is fuelled by importation of virus through viremic travellers and pose the question of whether dengue has established endemicity in southern China. The findings in this manuscript is important as not only does China have the population in the world, southern China also has several cities with high human population density. Both factors may contribute to the overall increasing burden of dengue globally. There are, however, a number of areas in the manuscript that needs to be clarified. These are:

Major compulsory revisions
1. The case definition of dengue needs to be carefully defined. The authors report here that clinically diagnosed cases using the WHO 2009 dengue classification scheme without laboratory confirmation were considered probable dengue. This is not plausible as the study period started in 1990. The authors should provide detailed case definition that was issued to medical practitioners to guide disease notification. It may well be likely that the case definition evolved over time, especially since WHO issued two dengue case classification schemes during the study period; one in 1997 and another in 2009. Perhaps the authors would consider describing the case definitions that were applied during the different periods between 1990 and 2014?

Response: We accept the reviewer’s suggestion - and provide a summary of diagnosis criteria and cases definition from 1990 to 2014 in the new Additional file 2 and mentioned this in the Methods section on Page 8, Paragraph 2. Three editions of the criteria/guidelines for dengue diagnosis and case classification
issued by the Chinese Ministry of Health were successively used from 1990 to 2014:

2. 2001: Diagnostic criteria and principle of management of dengue fever.
3. 2008: Diagnostic criteria for dengue fever.

We compared these three guidelines and found that there are no significant changes on epidemiologic linkage and clinical manifestations for dengue diagnosis, but the laboratory tests for diagnosis have some obvious changes during the study period (see next section).

2. More details on the laboratory methods for diagnosis should also be described. Again, that this study covered a 24-year period presents challenges that the authors need to carefully consider. What methods were used to detect a four-fold or greater rise in antibody titer in paired serum samples? What methods were used to isolate dengue virus? When was RT-PCR introduced as a diagnostic test for dengue in China? These descriptions are important as the introduction of more sensitive tests could result in increased number of reported cases without increased transmission.

   **Response:** A summary of diagnosis criteria and case classification during the study period is now described in the new Additional file 2 with the information about laboratory tests. We also now discuss on **Page 15, Paragraph 2** about how the number of reported cases may be influenced by the introduction of more sensitive and fast laboratory tests.

   Compared to the 1988 edition, the main change in laboratory tests in the 2001 edition was the introduction of enzyme-linked immunosorbent assay (ELISA), immunofluorescence method (FA/IFA), and dengue blot (DB) for serologic tests, detecting nucleic acid by RT-PCR, and detection of antigen by monoclonal antibodies immunofluorescence (mbAb-FIA). Compared to the 2001 edition, the main change in laboratory tests in the 2008 edition was that IgM positive changed from a confirmed test to a probable test, as well as the introduction of mac-ELISA for serologic tests and real-time fluorescence quantitative PCR for detecting nucleic acid.

3. Following on from both comments #1 and #2, changes to the case definition used for probable dengue surveillance and laboratory tests used to confirm dengue could result in major shifts in the incidence of dengue. The authors should provide a discussion on how changes in both case definition and
introduction of new laboratory tests might have impacted the observed dengue incidence.

**Response:** According to the comments #1 to #3, we have discussed the changes of case definition and laboratory tests, and their potential impacts on the reported dengue incidence on *Page 15, Paragraph 2.*

4. The definition of an imported case is problematic. To classify a dengue case as imported instead of indigenous, the authors applied three criteria: a recent travel history, recall of having been bitten by mosquitoes within the past 15 days and no recollection of being bitten by mosquitoes domestically. This case definition introduces major problems with recall bias. In fact, most people are unable to recall being bitten by day-biting *Aedes* mosquitoes and tend to remember nigh-biting mosquitoes as the latter would disrupt their sleep. Perhaps there may be some confusion when translated from Chinese but this case definition would provide very misleading results on the proportion of imported and indigenous cases.

**Response:** As our response to the comments of Referee #1, we have clarified the case definition in the Methods section on *Page 9, Paragraph 1* and discussed it on *Page 16, Paragraph 2.* The “mosquitoes bite” criterion was used in the definition to identify imported cases in a guideline issued by the China CDC from 2005 to 2014, but it was impractical and recently a new version of the guideline has been issued in October 2014 and implements in 2015, which excludes “mosquitoes bite” in the definition of an imported case for similar reasons to those mentioned by the reviewer.

**Minor compulsory revisions**

1. 1st paragraph of introduction: the authors attributed the observation that sequential dengue infection increases the risk of severe dengue to the work of Sabin reported in 1952. This is inaccurate. Please cite the relevant papers to support this statement.

**Response:** Three relevant papers were cited in the 1st paragraph of introduction:


2. The authors suggested that preventing exposure to mosquito bite is the most effective method to reducing dengue incidence, in the last sentence of the 1st paragraph of introduction. This is erroneous. The only instances where dengue incidence was successfully reduced for significant span of time were the Pan American Aedes eradication program and the vector control efforts in Cuba and Singapore. All of which relied on suppressing vector population. Furthermore, there is no evidence to show that methods that could reduce exposure to mosquito bites, such as the type of clothing or the use of mosquito repellants, were able to reduce significantly the incidence of dengue. Please correct this statement.

Response: Done. We have modified the sentence and put suppressing vector population as the main method for dengue prevention on the 1st paragraph of introduction.

3. „Seasonal“ on the 2nd y-axis has been misspelt.

Response: Done. We have corrected it on the heatmap.

Discretionary revisions
1. The description on the vector surveillance and control program in China is currently rather cursory and even vague. Given the increasing trend of dengue and the call made by the authors for better preventive measures, perhaps the authors would consider providing a more detailed description of the current vector control program and suggestions on the improvements that could be made.

Response: In this study, we didn’t include data on vector surveillance. According to the reviewer’s suggestion, we added a description of the China national vector surveillance program in the discussion on Page 17, Paragraph 2. Previously, China has not implemented a national vector control program for dengue, but some provinces or cities will conduct vector control during the dengue epidemic season.

2. The reported demographic of dengue cases show that a high proportion of cases are adults. This trend suggests a predominance of peri-domestic transmission, which would be consistent with the authors’ suggestion that virus
transmission is driven mostly by Aedes albopictus. Perhaps the authors could consider making this link in the discussion?

**Response:** The high proportion of adults in cases most likely owes to the fact that the population in China has very low seroprevalence of dengue antibodies, and is therefore broadly susceptible to dengue infection, whereas the population in dengue endemic countries has higher rates of immunity, especially in adults and the elderly, which has been discussed on Page 16, Paragraph 2. However, we could not reason out why the adults would be more likely to be exposed peri-domestically virus transmission driven by *Aedes albopictus*, explained by the differences in the entomology and ecology of *Aedes albopictus* and *Aedes aegypti*.

**Referee 3:**

While there is nothing in this Report that surprises, the authors have methodically quantified what, until now, has been only qualitative information. It is likely that a report like this would be highly cited. Some of the Figures may not be essential but placing them as Additional Files is appropriate.

**Response:** We would like to keep the current places of figures in the manuscript, but if the editor requires us to move some figures into Additional files, we are also happy to do that.

**Minor Essential Revisions**

1. While the authors have distinguished "reported" from "laboratory confirmed" cases of dengue, they have not discussed the magnitude of the error likely to exist in the number of "reported cases" and what this might mean for their conclusions. There is an extensive literature from Thailand, Myanmar and Malaysia, dating back to the 1960s, which identifies the difference between dengue cases diagnosed clinically, often by very experienced clinicians, and the number of these diagnoses that can be confirmed by laboratory testing. It has been our experience that between 30 and 90 per cent of "reported" cases of dengue in south east Asia do not have a dengue infection.

**Response:** For the change of case definition and laboratory methods during the study period, we have provided more details in the new Additional file 2 and Methods section on Page 8, Paragraph 2, and also discussed on Page 15, Paragraph 2. The varying criteria/guidelines for case definitions were also added in the Additional files.
2. The authors might discuss, in greater detail, the issue of whether all dengue outbreaks in China are due to imported viruses or whether dengue virus transmission is endemic. Could one or two imported cases have initiated some of the huge outbreaks reported in China recently. What insights might be available in the dengue modelling literature?

Response: In this study, we didn’t have the data on all outbreaks, but we have discussed the relationship between imported cases and local outbreaks on Page 19, Paragraph 1. It seems as though the dengue outbreaks were initially sparked by imported cases, and then the virus spread locally because indigenous cases were mainly reported from July to November, especially for the 2014 huge outbreak. In addition, on Page 21, Paragraph 3, we also suggested future research directions on the drivers of these outbreaks and how this should be conducted through modeling and mapping to explore the relative roles of importation and local transmission.

Editorial comments:

There are also a small number of editorial changes that should be made at this stage:

1. Authors’ contributions: please list the full contributions of each author in the preparation of this manuscript; some of these are incomplete at present (e.g "YL, DM and QC assisted in data analysis"). More information can be found at: http://www.biomedcentral.com/bmcmed/authors/instructions/researcharticle#formatting-contributions

Response: Done.

2. Please confirm whether all the figures were made exclusively for this manuscript, or whether permission was obtained from the copyright holder to reproduce them from elsewhere.

Response: We confirm that all the figures were produced by ourselves and have not been published elsewhere.

3. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

Response: Done.