Author's response to reviews

Title: Spatiotemporal analysis of indigenous and imported dengue fever cases in Guangdong province, China

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Prof. Frank Mockenhaupt

BMC Infectious Diseases

Dear Prof. Mockenhaupt,

Thank you very much for your letter of the 28\textsuperscript{th} March, 2012 including the referees’ re-

comments on our paper. Please find enclosed a copy of our revision with the following

changes, according to the suggestions/comments

With kind regards.

Yours sincerely,

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\textbf{In response to referee 1 (Mathuros Tipayamongkholgul )}

\textbf{Concern 1.1} The author classified dengue reported cases into imported and indigenous regarding their experience of mosquito biting within the past 15 days. The definition does not sound correct in epidemiologic view point. Dengue virus transmits to human from only Aedes mosquito not any mosquito. Therefore such definition may lead to an over detection of dengue imported case and finally lead to a bias result, because bitten by mosquito in forest or beach area may not relate to dengue fever.

1. As it’s hard to accurately know in practice whether the dengue fever cases were bitten overseas by \textit{Aedes} mosquitoes or other mosquitoes. The history of mosquito bite outside of mainland China is the most feasible epidemiologic evidence to assist in classifying imported and indigenous dengue cases. According to the definition of imported cases, in addition to the overseas travel and mosquito biting history, imported cases are those which present with the clinical manifestations of dengue fever and have no history of mosquito bite in domestic regions.
A little revision on the definition of imported cases was added on page 7.

**Concern 1.2** Moreover, people travelled to dengue free area does not have the same risk of who travelled to endemic area. The author did not mention in methods whether the travel destination had been taken into account.

2. The travel destination (dengue-affected areas) of imported cases was added on page 7.

**Concern 1.3** The authors applied population in year 2005 to calculate dengue incidence. What is the percentage of population growth during the study period in this region? The population between 2005 and 2010 are steady, isn’t it? If not, you may over estimate the incidence in 2010.

3. In our study, the cumulative incidence from 2005-2010 (in figure 3) was calculated by applying the 6-year cumulative cases and the population in 2005, which have not been compared among years. The dengue incidence rate per year from 2005-2010 (in table 1) was calculated by applying the annual cases and the population in the corresponding year, thereby the fluctuation of annual population number have no impact on the incidence comparing by year.

Some description of the annual incidence calculation was added in page 8.

**Concern 1.4** Additionally, the authors may consider to polish the presentation of table 1 and 2, such as in table 1 “cases(% of all cases)”, the authors should remove % from the result cell “6(100%)”. In table 2, the authors may consider to correct the presentation of P-value such as P-value =0.00 changed to P-value <0.01.

4. Done. Thanks.

**Response to the concerns from referee 2 (Benjamin M. Althouse )**

**Concern 2.1:** It might be interesting to look at the precise timing of imported and indigenous cases, ie: do indigenous cases always follow imported cases (as one might expect). Maybe make a mention of this in the discussion.

5. Yes. The relationship between the indigenous cases and the imported cases in Guangdong province needs to be further investigated in future research. This has been added to the discussion in page 13.

**Concern 2.2:** There’s a typo on figure 4: “Ever affected areas”

6. Done. Thanks.
Concern 2.3: It would be easier to read figure 5 if the letters (a, b, c, d) had descriptive labels, i.e.: “a. all cases”, “b. indigenous cases”, “c. imported cases (50%)”, “d. imported cases (10%)”

7. Done. Thanks.

Response to the concerns from referee 4 (Marc Souris)

Major compulsory revision

Concern 4.1: I do not question the quality of the Chinese CDC. By counting the mobile population, we are talking about an incidence of less than 1/100 000 000, which is very low for dengue, given its transmission cycle. A description of the spatial differences in the monitoring system is essential to ensure the validity of the dataset. Furthermore, introduction talk about 650000 dengue cases for 30 years (78-2008) in whole mainland China. Do you think that 1600 cases in Guangdong province for 6 years is realistic, if Guangdong province account for more than 80 % of all cases? Something seems to be wrong.

8. Since dengue fever re-emerged in mainland China in 1978, dengue fever outbreaks in various scales have occurred in China. The most severe outbreaks of dengue fever occurred Hainan province in the 1980s, resulting in > 600,000 cases, while the size of epidemics decreased sharply since 1990s. When entering into the 2000s, the occurrence of dengue fever cases in the whole country remained low (<2000 cases per year), and Guangdong province has had the highest incidence of Dengue fever [1]. Therefore, Guangdong province accounted for more than 80 % of all cases in China only in the last decade.

It is made clearer that the figure of 80% relates to the last decade in page 6.

Concern 4.2: Of course, I do not question the search of clusters. But a study on space-time cluster detection with a limited number of cases (e.g., 6 cases in 2005, 19 in 2009) aggregated in few spatial objects (124) seems not very interesting. With a so low incidence, this search for clusters loses its appeal if done with groups of cases, integrated in geographical objects.

9. The method of SaTScan, employed in our study, is good at detecting space-time clusters with low disease incidence. In this study, several space-time clusters of dengue fever cases in Guangdong province were detected, which could provide valuable information for the local public health departments to identify the areas with a high risk of dengue fever, and more intensive control measures should be implemented in these areas.

Concern 4.3: The study suffers from many defects. The fact of aggregating cases in county is nowhere discussed. The fact of cluster detection on the presence / absence by county is nowhere discussed. Secondary clusters with a single object inside (as shown in table) does not really make sense.
10. We addressed in the methods the fact that we analyzed cases at the county level. Due to the large number of counties in Guangdong province (n=123), and their relatively small and homogeneous size, the county provides sufficient resolution to identify spatial patterns in dengue risk. There is no problem in identifying spatial clusters comprising a single geographical unit. It simply means that the county had a significantly higher than average incidence and wasn’t surrounded by other similarly high-incidence counties.

**Minor essential revisions**

**Concern 4.4:** Abstract. « so as to identify high-risk areas of the province and thereby help plan resource allocation for dengue interventions » This study present observed incidence. High-risk need to be replaced by high incidence all over the paper.

11. Incidence is a measure of the force of infection, and, therefore, disease risk.

**Concern 4.5:** Abstract. « Descriptive spatiotemporal analyses were conducted, including plotting of seasonal distribution of cases » No seasonal mapping was presented. Only incidence by year. Choropleth maps are not a good way to present ratio mapping. A extended literature present how to map diseases data.

12. Figure 2 demonstrates the seasonal distribution of both indigenous cases and imported cases. We do not claim to map seasonal patterns, only show them temporally in the time-series plot presented in Figure 2. We have changed the abstract to say “temporal and spatial”.

**Concern 4.6:** Abstract. « The space-time scan statistic was used to determine space-time clusters of dengue fever cases ». Only spatial analysis by county was presented, not on cases.

13. The results of space and time scan statistic analysis were presented in table 2. We have added “at the county level” to indicate this was the geographical unit of the analysis.

**Concern 4.7:** Abstract. « This study demonstrated that the geographic range of imported and indigenous dengue fever cases has expanded over recent years ». The conclusion is not demonstrated by this study (no expansion analysis).

14. The geographic expansion of imported and indigenous dengue fever cases was visually presented in figure 4.

**Concern 4.8:** p6. 650000 cases for 30 years (78-2008) in whole mainland China. Do you think that 1600 cases in Guangdong province for 5 years is realistic, if Guangdong province account for more than 80 % of all cases? Something seems to be wrong.

15. Refer to item 8 for response to concern 4.1.

**Concern 4.9:** p6. « The mean population per county is about 783,000 people (ranging from 78,800 to 7.1 million) ». Such a difference in density between county represent a very strong problem with statistical analysis and spatial analysis. With such a low incidence as presented
with dengue dataset, counties with low density have a very high variability compared to counties with higher density.

16. We adopted the incidence rate by county to conduct the statistical analysis and spatial analysis, which has taken into account the variability both on the cases and population.

**Concern 4.10:** p8. « The space-time scan statistic was calculated on the imported and indigenous dengue fever cases to test whether the cases were distributed randomly over space and time and, if not, to locate space-time clusters and determine their statistical significance » Cluster detection is different from random distribution analysis. A spatial distribution can be globally randomly distributed and showing significant clusters.

17. The rational of space-time scan statistic was briefly introduced in methods section. This method is popularly used to detect the disease cluster with statistical significance in many published studies. More references and application on this method could be found on this website: [http://www.satscan.org/references.html](http://www.satscan.org/references.html). The null hypothesis of cluster detection statistics is that the distribution is spatially random, hence our use of this terminology.

**Concern 4.11:** No need to describe the method used by SatScan. References only are needed.

18. We have decided to keep the detailed description because other reviewers have asked for more detail and it is useful for the reader to understand the basis of the method.

**Concern 4.12:** p9. « In the SaTScan software, a default maximum spatial cluster size of 50% of the population was used, so as to detect the large clusters that tend to have a small relative risk but a high statistical significance. Furthermore, a maximum spatial cluster size of 10% of the population was further employed to detect possible subclusters with smaller size ». Need to specify that « population » means number of counties in a cluster...

19. 50% of the population means 50% of the whole population in the study area, not the number of geographical units.

A minor revision on it was done in page 9.

**Concern 4.13:** p9. With low number of reported cases, integration in large zones weeks spatial analysis. A better way is to analyse cases using their address, not incidence in geographic entities by integration. This is my principal concern in term of methodology.

20. In this study, the spatial analysis was conducted at county level, which is a common geographic analysis scope. See our response to concern 4.3.

**Concern 4.14:** p10. Temporal analysis must be represented for the whole period (2005-2010) in a graph, giving number of reported cases by month.

21. Table 1 has presented the results on the temporal analysis by year from 2005-2010, and the seasonal distribution of cases was also given in figure 2.
References: