Author’s response to reviews

Title: Epidemiological analysis of the Kaohsiung city strategy for dengue fever quarantine and epidemic prevention

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Version: 1 Date: 16 Nov 2019

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Dear editors,

We received in early November reviewer comments for our manuscript entitled “Epidemiological analysis of the Kaohsiung city strategy for dengue fever quarantine and epidemic prevention” (Manuscript Number: INFD-D-19-01893).

The authors would like to thank the reviewers for their thorough and expert review of our manuscript, and for their constructive suggestions for improvements. We have edited the manuscript in accordance with these suggestions and below present a point-by-point response to the reviewers’ comments. These edits include new analyses and a more detailed discussion of our conclusions. All edits in response to reviewer comments have been highlighted in the manuscript. And all of the text has been edited by English native speakers for corrected and editing. We believe the review process has significantly strengthened the main conclusions of our manuscript.

Yours sincerely,

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National Health Research Institutes (NHRI).
Reviewer 1 Comments
Reviewer (R) 1: In the section "Database and Case definitions", could you supply more details on the collection of cases. For example, how indigenous cases were collected?
Authors response (A) 1: Follow the reviewer' recommendations, we have added a detailed description on case collection to the “Database and Case Definitions” section. Lines 123-129 now read:
“A standard protocol was adopted by local physicians and epidemiologists to collect individual-level information on each dengue fever case, including the onset of dengue illness, age, gender, clinical manifestations, reporting hospital, diagnosis results and travel history. Dengue case collection and surveillance involved both passive (hospital-based reporting systems) and active (fever screening at airports, self-reporting, expanded screening for contacts of confirmed cases, patients with fever of unknown origin and school-based reporting) detection.”

R2. What are the sensitivity and specificity of the Dengue NS1 Rapid Test? Is it reliable for detecting Dengue information? As we know, arboviruses such as Dengue, Zika have a high-level of cross-reactivity. So is the rapid test good enough to conclude on Dengue infection?

A2: Thank you for highlighting this concern, as we fully agree that highly sensitive and specific tests are essential for accurate laboratory diagnosis of DENV-infected patients.
We evaluated the diagnostic performance of the SD BIOLINE Dengue NS1 rapid test kit (Standard Diagnostics, Inc., Korea); please see references given immediately below. The sensitivity of the Dengue NS1 Ag assay has been shown to be approximately 92%, based on 310 retrospective sera from patients with current dengue infection confirmed by RT-PCR. Specificity was estimated at 98%, based on evaluation of 197 specimens including samples from 147 blood donors, and 50 potentially interfering sera [1-3].
The dengue NS1 antigen was not found in patients with Japanese encephalitis virus or yellow fever virus infections, thereby implying that there was no cross-reaction of the dengue NS1 protein with proteins from other related flaviviruses. We therefore feel this assay kit is sufficiently reliable for the purpose of determining Dengue infection status.
We have included the name of the diagnostic test used to line 147, which now reads:
“specimens were taken for testing with the Dengue NS1 Rapid Test (SD BIOLINE Inc., Korea; sensitivity and specificity estimated at 92% and 98%, respectively) at an airport inspection station”.

References:

R3. In line 226, the reduction in Dengue cases following a major outbreak may also resort from the cross-protection between heterologous serotypes of Dengue.
A3: We agree with the reviewer that this may be possible. Recent studies have indeed shown that different serotypes can affect the severity of the disease and that primary infection with a single serotype of dengue virus elicits short-lived cross-protective immunity against other heterologous serotypes [1-3].

We have therefore changed the manuscript to reflect this possibility. We would like to stress that a deeper understanding this topic is important for improving our knowledge of the epidemiology of dengue, and that using collected serum samples to analyze cross-protection of different serotypes is worthwhile.

Lines 238-242 now read:
“This significant reduction in the number of dengue cases was in part due to a complete reorganization of the dengue quarantine and epidemic preventive network in Kaohsiung in April 2016, though other factors (such as the emergence of cross-protection between heterologous Dengue serotypes following disease outbreaks) may have also contributed to the extent of this reduction.”

References:

R4. In line 230, "in the nation" may be changed to "in Taiwan".

A4: Following the reviewer’s advice, we revised the "in the nation" to "in Taiwan" in line 245.

R5. In the section "Conclusions" (p-15), it is not convincing to claim that imported cases are the reason of local Dengue spread in Kaohsiung. Correlation does not mean causation. Imported cases can be a risk factor but not a reason of local outbreak. For example, the study [1] explores the role of windborne long-distance vector migration.

A5: We fully agree with the reviewer that there may be other factors which influence the prevalence of dengue fever in Kaohsiung, such as vector migration.

We have therefore edited lines 280-283 to reflect this:
Though there may be several factors influencing disease transmission (including vector migration), dengue fever outbreaks in Kaohsiung are the likely the result of imported cases of the disease, in which dengue virus is transported to Kaohsiung via infected individuals and then spread within the community.”

R6: With the case-based surveillance data, the authors may wish to conduct some mathematical modelling studies to sort out the influence of imported cases on local Dengue spread in Kaohsiung. Some useful studies [2], [3] are recommended for their reference.

A6: We agree with the reviewer that mathematical modelling could enable deeper investigation into the influence of imported Dengue cases on local infections. We intend to use surveillance data, coupled with geographical information of Kaohsiung (such as temperature and rainfall), to develop mathematical models in the future.

We will have edited the Discussion section (lines 263 to 266) to reflect the importance of mathematical
modelling and have included the two references suggested by the reviewer: “Furthermore, the use of mathematical modelling, both to predict patterns of future disease outbreaks and to test the origin of disease cases, has becoming increasingly widespread in recent years [27,28]. The wealth of data available as a result of the dengue outbreaks in Kaohsiung could be utilized to develop such models and thus assist in disease control efforts.”

References

Reviewer 2 Comments
R1: Based on the city of Kaohsiung, the authors could put a geographical map showing the distance between the top 5 countries with the most imported cases of dengue (Philippines, Indonesia, Vietnam, Malaysia, and Thailand) and the 5 countries with the least cases (South Africa, Japan, Tuvalu, Marshall Islands and Bangladesh) and discuss the relationship between distance and imported cases.

A1: We feel the reviewers’ suggestion of using a geographical map to show the distance between the top/ bottom 5 countries responsible for Dengue importation and Kaohsiung city would greatly help manuscript readers. Increased levels of air transportation seem to significantly contribute to the spread of dengue, though distance may be less important than the extent of trading links. Recently, several studies of disease have used airline databases and human mobility networks to analyses case importation during outbreaks and estimate potential invasion routes [1~3]. These studies showed that an increase in the number of air passengers, coupled with the incidence rate of dengue fever in the country of departure, had a significant impact on dengue fever transmission in the areas which passengers travelled to.

We therefore consider that the relationship between distance alone and the number of imported cases may not be one of the most essential factors contributing to transmission of dengue fever in Kaohsiung. However, this relationship warrants further investigation in the future in order to confirm its’ relative importance.

We have therefore edited lines 169-170 to reflect this: Supplementary figure 1 shows the top and bottom 5 countries from which dengue was imported, and the distance from these countries to Kaohsiung.

We have included the image as Supplementary Figure 1 within the manuscript with the following legend (lines 288 to 291): Map showing the distance between the top/ bottom 5 countries from which Dengue was imported and Kaohsiung city between 2013 and 2018.

References:
R2: Considering that the detection of circulating viruses, anti-DENV IgM and anti-DENV IgG are related to the stages of infection, in which virus detection occurs in the early days, anti-DENV IgM antibodies are usually detected in the acute phase, whereas Anti-DENV IgG appear in the convalescent phase, I suggest to the authors to evaluate three groups of dengue cases based on the positivity of laboratory tests.

(1) RT-PCR DENV positive / both IgM and IgG anti-DENV negative;
(2) RT-PCR DENV negative / IgM anti-DENV positive / IgG anti-DENV negative;
(3) RT-PCR DENV negative / IgM anti-DENV negative / IgG anti-DENV positive

Analysis of three groups separately may indicate a high risk of transmission, assessing only viremic patients. Or low risk of transmission, as only exposed individuals would be involved. Discuss this hypothesis based on further analysis.

Each group should be analyzed separately, including correlation analysis.

A2: Prior to the Dengue outbreak in Kaohsiung, we tested RT-PCR, IgM and IgG for all samples. After the outbreak however, the number of samples increased significantly and we were able only to conduct NS-1 rapid test screening and RT-PCR detection. Therefore, we unfortunately have incomplete data sets with too few samples to reach any kind of statistical significance for such detailed comparisons. However, although such analyses are not yet available, we intend in the future to conduct an in-depth investigation based on the reviewer’s suggestions. Until then, we could only speculate on the outcomes of these tests.