Author's response to reviews

Title: Airport sentinel surveillance and entry quarantine for dengue infection following fever screening program in Taiwan

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Author's response to reviews: see over
Dear reviewers and editors,

We greatly appreciate your very helpful review of our manuscript. Without your many precious critiques and essential comments, we could not program to make many improvements on this study. We are continuing to be inspired very much by your advices and comments. According to the respected reviewers’ comments, we have made the major and specific revisions suggested (please see the appendix I-III).

Again, we express our deep gratitude for your help and for allowing us to revise this manuscript as well as giving us a valuable opportunity to improve it.

With best wishes,

Mei-Mei Kuan

Feng-Yee Chang

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According to the reviewers’ comments and advices, we have made each revision as possible as we can. Please see the following checking listing
Appendix I (reviewed by Dr Dounia Bitar)

I. Minor essential revisions

Background
- 1st sentence "dengue is the most common arboviral infection worldwide" : please give a reference. → It is revised and cited, according to the reviewer’s advices
- 4th sentence: is "uncontrolled" urbanization the factor for increasing breeding-sites, or is it just "urbanization" → It is revised as just “urbanization” according to the reviewer’s comments
– in last paragraph (non contact thermometers) :
  (a) references 10-13 refer to "the threat of pandemic influenza" as this was a future event : this might need an update → It is already updated according to the reviewer’s comments
  (b) authors mention that "the extension of cameras for a public health application has not been assessed" : this sentence (largely extracted from reference 10) was true some years ago but things have evolved = references could be updated; see for instance Hewlett & al, 2011 → It is already updated the references in background and added the reference of Hewlett & al, 2011 in discussions, according to the reviewer’s comments.

Method
- Page 6, 3rd line : "6 inspection operations i.e. 4 or 1 entry gates" : not clear → There seems to be a bias in evaluating the efficacy of airport screening. True positive cases and false positive cases are compared with the total number of imported dengue cases. Are there other entry routes for potentially infected cases, e.g. by boat? How far these cases, who did not pass through an airport, would influence calculations? → The 3rd line is revised as "10 inspection operations i.e. 4 or 1 entry gates..." and is adjusted the calculation by enrolling the data of by other entry routes.

Results
- First sentence is not clear. I guess we should read "fever prevalence detected by NCIT ranged between 0.46 and 2.58% of all passengers, and etc." → Base on the reviewer’s direction, It is corrected as “fever prevalence is detected by NCIT and double checked by ear thermometer ranged between 0.09 and 0.1 % of all passengers, and etc."
- Results should refer to table 2 instead of table 1. Table 1 is not useful and confusing. Table 2 needs clarifications; add a sum (or average) in order to be coherent with text.
  → 1) According to the reviewer’s suggestion: 1) the order of table 2 and table 1 is exchanged each other. 2) The renewed table 2 is edited into a concise form. Considering it regarding presenting the geographic heterogeneous distribution of domestic cases, thus we intend to keep it.
- Were "febrile passengers" (Table 2, col.3) detected by NCIT alone, or by NCIT followed by ear thermometer?
  → We have added the related annotations into the renewed Table 1 according to the reviewer’s comments.
- How can the authors explain the difference between febrile passengers (col.3) and those who underwent a laboratory sample (col.5)?
  → 1) confirmed febrile passengers defined as NCIT detected positive followed by ear temperature with abnormal temperature e.g. more than 37.8°C, 2) If the confirmed febrile arrivers is coming from dengue affected area e.g. Southeastern Asia… etc. would be taken specimens for diagnostics.
- What is the difference between "total imported dengue cases" (Y axis, figure 1B) and "dengue importations detected in the community" (Y axis, Fig 1C)? (the same comment applies in the text).
  → The number of total imported dengue cases is aggregated amount of importations detected in borders screening plus those of detected in community (We have revised it to add an annotation in corresponding sites)
- Figure 1A is not useful, results mentioned in text are sufficient.
  → Figure 1A is deleted according to the reviewer’s suggestion
Discussion
- Page 11 Sensitivity result for 2007 is 40.2% and not 40.5% (72/179)
  → We have revised it.
- Page 11, line 14: editing "which could partially curb the domestic transmission"… .
  → It has been revised according to the reviewer’s suggestion
- See comment in method as regard to efficacy of airport screening vs. other routes of introduction of cases: How far these cases would influence the evaluation?
  → We have add the data of by other routes i.e. those data of port screening in method section
- Page 11, lines 3&4: "the proportion of cases detected increased yearly": this increase is not significant using a Poisson regression.
Since we didn’t claim this increasing is statistic significantly, we have revised it into a clearer sentence, according reviewer’s comment.
- Page 13, the discussion opposes NCIT vs. PCR. Where do the ear thermometers stand? There are two triage steps for fever, for different thresholds, before blood sample is taken. These steps are not clearly discussed in terms of feasibility, time constraints, costs.
- The procedure of triages was conducting mass screening by NCIT, double confirmed by tympanic temperature readings. Then the confirmed febrile cases were taken specimens for dengue diagnostics.
- Page 13, References 10 to 19. The authors seem to imply that all these references suggested that entry screening was effective for SARS. I am not sure that the respective author’s suggestions were as clear. If so, a short summary of their conclusions for the different germs would be helpful.
- We have revised it according to the reviewer’s suggestion.

- Also, at bottom of page 13, is reference 16 appropriate?
- No, it is not appropriate. Instead I replaced it with a proper one, according to the reviewer’s suggestion.

**Quality of written English:** Needs some language corrections before being published
- We have improved the English as could as possible.

- acknowledgement section:
- We would also like to have your allow to be addressed your contribution in acknowledgement section.
Appendix II (reviewed by Dr Benjamin M. Althouse)

I. Major Compulsory Revisions

Here is a list of major problems still needing to be addressed:

- It is still not clear to me the case definitions. My impression from the manuscript is that “domestic” and “imported” cases are identified from national databases as cases who have not and have traveled within 2 weeks of developing symptoms (Figure 2). I am still unclear however about figure 1 and the calculation of PPV, NPV, etc. How are those cases identified? Are they described here (pg 6): “For effective surveillance, both passive surveillance mechanisms, such as hospital-based reporting systems, and active surveillance methods, such as health statements from inbound passengers, self-reports, expanded screening for contacts of confirmed cases, patients with fever of unknown origin and school-based reporting, and community screenings, were established in central and local health departments.”? What is “effective” surveillance? Please make the distinction in the “Case definitions” section, as the formulation of this effects the calculation of PPV, NPV, sensitivity and specificity.

We have made several revisions in methods section. 1) the calculation of PPV, NPV is utilized the national database  2)The “effective” surveillance is to describe the comprehensive coverage of our national databases which is integrated, constructed by several notification systems, enrolled data of various populations. And our data is relied on this national database. Also, we have renewed the related issues according to the comments.

- The calculations of PPV, NPV, sensitivity and specificity are suspect to me. I do not know what exactly is being calculated. Is “total dengue importations” the total number of cases, reported in the national database who have traveled out of the country 2 weeks before symptom onset? Or is it the number of cases identified for the “effective surveillance”? Either way, then the low PPV could be due to either: 1) infections arriving by methods other than plane, 2) infections which are actually secondary but in people who have coincidentally traveled recently, or 3) cases who are not yet symptomatic when screened in the airport (as stated by the authors). These are biases and limitations that should be mentioned in the manuscript.

We have made several revisions in methods section. The calculations of PPV, NPV, sensitivity and specificity are presented by formulations listed plus definition of each items. The PPV range of fever screening in this study is 1.28-3.22% and is consistent with several other studies varied from 1-68%. This variation is influenced by the different triage procedures among various studies. Since there is no golden
standard for its inspiration by difference purposes, thus the results is depended. The related information is added into discussion, according to the comments.

- Additionally, the use of ecological data to calculate these numbers is open to many biases. How confident are the authors that the national database captures all the cases? What about those cases who do not report seek medical care? Are there any individual-level data gathered at the surveillance sites? Also, a few sentences on the airports in Taiwan would be helpful – are many cases being imported through other airports?

→ Indeed, the strategy of this study is limited by lacking individual-level data. The underestimation caused by mild infections or 10-90% asymptomatic infections had reported by several others studies, we have underlined to add these issues in discussions. There were 0-3 dengue importations respectively introduced by boats during study period. We have added the related data and information into the text, according to the reviewer’s comment.

- There are still numbers in the paper that do not appear in tables (pg 7: “between 0.46 and 2.58% and between 31.5 and 50.9% (3706-5656/11,121-12,553) of the incoming febrile travelers”, pg 11: “cases increased yearly (e.g., 40.5% (72/179) in 2007, 44.7% (101/226) in 2008, 53.9% (110/204) in 2009 and 42.2% (129/304) in 2010)” and pg 12: “imported versus domestic cases varied widely (i.e., 2.98–22.5”)”).

→ We have revised the related information (p.g. 7, pg11 and p.g 12) according to the reviewer’s directions.

- The conclusion (p g 11): “Moreover, we revealed that the number of reported imported dengue cases peaked earlier than the reported domestic dengue cases by 2–4 months”. No data has been presented on the no-lag (t=0) case. Even though lags of 2 months or 4 months are statistically significantly associated with domestic cases, how do we know these lags are better? The trend in r^2 appears to be decreasing with increasing lag. Also, what is the justification of the choice of two months? The generation time of dengue is only two weeks.

→We have revised it according the comments. Add the data of no-lag (t=0) status. “The monthly fluctuations in the numbers of total imported dengue cases (X) with a 2 month lead-time (t: month) were paralleled with those of the domestic dengue cases (Y) based on the consecutive 4-year surveillance by a Pearson’s rank test (n = 48, RX(t-0):Y =0.24, RX(t-1) :Y =0.47, RX(t-2):RX(t-2):Y = 0.55, RX(t-3):Y = 0.45, RX(t-4):Y = 0.22). Alternatively, by regression test with a lead-time 2 months, a significantly paralleled pattern was shown between the monthly cumulative number of imported dengue cases
(X) versus domestic dengue cases (Y) with $R^2_{X;Y} = 0.31$, $P_{slop} < 0.00001$ ($R^2_{X(t-0);Y} = 0.06$, $R^2_{X(t-1);Y} = 0.22$, $R^2_{X(t-2);Y} = 0.31$, $R^2_{X(t-3);Y} = 0.20$, $R^2_{X(t-4);Y} = 0.05$).

• the conclusion (pg 12): “Most of all, the distinct impact of dengue importations on community dengue epidemics was due to the ecological heterogeneity.” This is not supported by the data presented. First of all, the numbers for the slopes (“2.98–22.5”) are no longer presented in the manuscript (I had to return to the previous draft), and secondly, are not directly comparable as presented. The slope for (t=2) is the number of domestic cases two months in the future for one imported case now, the slope for (t=3) is the number of domestic cases three months in the future for one imported case now. For a proper comparison to be made, they must be the same lag.

→ There might be multiple factors in ecology which influences the activity of mosquitos’ transmission dengue virus thus caused the lag time of starting and peaking in the local epidemics. Thus, fluctuating pattern of the monthly numbers of dengue importations with 0-3 months paralleled with domestic cases. The related discussion is added according to the reviewer’s comments

• The authors misuse the term “asymptomatic”. Asymptomatic cases are those that are infected but never develop symptoms. The authors state (pg 12): “the low PPV of our results with respect to border control utilizing NCITs for reducing the risk of introducing infectious etiological agents into a country is primarily limited by the asymptomatic (afebrile) viremic passengers who bypass the temperature threshold of the NCITs”. This is a valid limitation (but not the only one, see above): they are referring to individuals who have not yet developed symptoms, but will be identified and counted later by physicians. Those who are truly asymptomatic will never develop fever and be missed (presumably) by the national surveillance system. I would rephrase the language to enhance clarity.

→ I appreciate the reviewer’s advices on the concept of “asymptom”. Based on it, I have revised the related issues in the context.

• Along the same lines (pg 14): “According to 3 studies, the proportion of symptomatic dengue patients vs. asymptomatic patients is 1:0.75, 1:1.8 or 1:3 [18]. Therefore, only 25%-57% of imported dengue cases appear with symptoms. Half of those symptomatic dengue cases can be detected by airport quarantine, but half of the cases are latent and can only be discovered after symptoms have appeared and patients seek medical attention.” It should be made clear that the “half of the cases [that] can only be discovered after symptoms have appeared and patients seek
medical attention” are not asymptomatic, but not-yet-symptomatic. I would rephrase this sentence to clearly delineate between those that are not-yet infectious and those that are truly asymptomatic. Also, where does the “half” in “half of the cases are latent” come from? I would say “some of the symptomatic dengue cases” and “the other cases are latent”, or something similar.

→ Yes. Actually our meaning is consistent with viewer’s comment. According to the reviewer’s comments, we have revised the related data into a clear sentence. Since “18, 1: 0.75 to 1: 3 “ could transformed into ” 25%-57%”, we complied them. We further added other references for citation “ a lot of dengue infection were not reported” in discussion. Actually, according to our results, approximately 45 % of symptomatic dengue importations could be screened in the airports (table 1).

- Minor Essential Revisions
There are still grammatical errors throughout the manuscript.

→ We have improved the English editing as could as possible.

-I’m not sure what the authors are referring to when they say a “robot vector” (pg 12 and 16).

→We have replaced “robot vector” with “principle vector”

- Discretionary Revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being Published

→We have improved the English as could as possible.

- acknowledgement section:

→We would also like to have your allow to be addressed your contribution in acknowledgement section.
Appendix III (reviewed by Dr Lasse Vinner)
Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

Materials and methods:
The case definition of a confirmed Dengue case requires detection of RNA, antigen or antibody titre increase in sequential samples. In the materials and method section it remains unclear if cases were in fact confirmed as the authors write that antibodies “and/or” RTPCR was used to confirm infections.
- Appreciate this comment. We have revised the text according to the advices

Results:
The first sentence of the result section does not make sense unless there is a reference to table 2.

➔ We have revised to add the referenced Table in the corresponding sentences, according to the reviewer’ comments

-Secondly it contains inconsistent numbers: “By implementing airport fever screening, fever prevalence detected by NCIT ranged between 0.46 and 2.58% (TABLE 2) and between 31.5 and 50.9% (3706-5656/11,121-12,553) of the incoming febrile travelers, who underwent blood sampling for laboratory confirmation (i.e.; only categories of febrile passengers returning from southeastern or southern Asia endemic countries were detected for dengue infection); of these, ranged from 1.3 to 3.3% (72-129/3706-5654) were confirmed as dengue infection, 2007-2010 (Table 1, Fig 1A).” As the first manuscript was compromised by inconsistent or even missing numbers in several figures/tables it is problematic that the numbers in the text are still apparently inconsistent: In one parenthesis the range is 3706-5656 in the next it is given as 3706-5654! Maybe a simple mistake, but re-checking the calculated prevalence I get a different result in 2 cases compared to the authors 3706/12553 =29.5% NOT 31.5% and 129/3706=3.5% not 3.3%. Why are the fever prevalence given with 2 decimals whereas others are with only 1 decimal?

➔ Appreciate the reviewer’s approvals and corrections. We have corrected the related data and revised the contents according to the reviewer’s instructions. Additionally, the Table are revised into a simplified form with summary data.

-In my opinion Figure 1 lacks the quality required to communicate the data.
(E.g. (1) Colors; light blue is picked for the very two lines that are closest together. (2) No logic in what axis is to be used, (3) title on axis almost covers the scale (4) Figure legend fails entirely in describing what is shown on the figure and (5) even a spelling mistake (trvelers)). Ironically the figure appears twice, although this may be related to the uploading system and may have nothing to do with the authors.

Because the Figure 1 A was deleted, suggested by one of the reviewers, so the related data were instead presented in Table or text.

It appears confusing that panels 2A, 2B and 2C are not presented as a single figure instead of one with separate panels. Figure 2A: The figure is not communicating the data. (e.g. (1) Numbers on X-axis is not visible. (2) the blue dotted line is probably the total (?) number of imported cases (3) how does the figure show “the positive relationship RX(t-2):Y = 0.56 or RX(t-3):Y = 0.46 “ as indicated in the legend.)

1) 2A, 2B and 2C being presented as separate panels is according to the policies of Journal. 2) Numbers on X-axis in Figure 2A is revised according to the comments. 3) the blue dotted line is added to revised as “the number of imported cases” in Fig 2A according to the reviewer’s directions. 4) the positive relations presented by R values, instead described in legend is moved to text.

Discussion

-It is not clear what relevance the calculate linear relationship in Figure 2B has.

We have added the related explanation in the discussion. This is a trial to present the analysis results of the potential relations of the number of imported cases on domestic cases.

-Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct) In figures: Either provide the n, R2 and P values in the legend OR on the figure. Not both places. In the text carefully consider if all values must be mentioned.

We have revised it according to the reviewer’s comments.

acknowledgement section:
We would also like to have your allow to be addressed your contribution in acknowledgement section.