Author's response to reviews

Title: Fever screening during the influenza (H1N1-2009) pandemic at Narita International Airport, Japan

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Author's response to reviews: see over
Dear Dr. McVernon,

We would like to submit our revised manuscript entitled “Fever screening during the influenza (H1N1-2009) pandemic at Narita International Airport, Japan” by Hiroshi Nishiura and Kazuko Kamiya for consideration for publication as an Original Article in *BMC Infectious Diseases*.

We appreciate the helpful and constructive comments of the reviewers that have helped us to improve our manuscript. We have revised the manuscript in accordance with the reviewers’ suggestions and our point-by-point responses are attached. We have highlighted the revised text in red in the manuscript.

All the authors have approved the revised manuscript and declare that it is not under consideration for publication elsewhere. The authors have no conflicts of interest to declare.

We hope that our changes are satisfactory and that the revised manuscript will be considered suitable for publication in *BMC Infectious Diseases*.

Yours sincerely,

Hiroshi Nishiura
[RESPONSES TO EDITOR]
The reviewers request some points of clarification on the manuscript, to assist interpretation on the study's findings. Please pay close attention to their comments when preparing your revision.

We found the comments from both reviewers very useful for improving the manuscript and fully followed the suggestions. To improve our English expression, the revised manuscript was edited by a professional English copyediting service prior to this resubmission.

[RESPONSES TO REVIEWER 1: Dr. James McCaw]
The authors have conducted a retrospective analysis of border entry thermal screening at Japan's main international airport, as it pertained to the H1N1 influenza pandemic. Their results provide further support for the limited role such entry screening practices are likely to play in reducing the importation of influenza into the country. I considered the assessment of thermal scanners in the "real-world" environment a strength of the paper. I have no comments on the statistical analysis or interpretation of the results. I have a number minor essential revisions and discretionary revisions, all concerned with expression and communication.

Minor Essential Revisions
1. The phrase "selected and suspected" is used extensively before it is defined and I could not understand its meaning until reading the definition. An alternative expression or full definition needs to be provided at the outset.

We have added an explanation of the phrase “selected and suspected” when it first appears in the main text (page 6, lines 16-17).

2. Background (page 3, lines 23-24, page 4, lines 1-13): With the primary aim of the study to estimate sensitivity, specificity, PPV and NPV, I found the discussion in this part of "Background" to be confusing upon a first reading of the paper. It is not clear
what are "expectations and/or assumptions" and what are "results". e.g. The statement on line 23-24 on high sensitivity and specificity and NPV, if mis-interpreted as a result of the paper is both 1) inconsistent with the actual results and 2) inappropriately placed in Background. The authors need to make clear what is the "status quo or rationale for thermal screening" and what are "new findings" or "challenges to that status quo".

We agree that our original manuscript was missing the expectations and assumptions in published studies as well as relevant challenges for future studies. In the revised manuscript, we have clearly mentioned the assumptions on page 5 (lines 3-6) and emphasized our motivation for conducting our retrospective study in a practical setting on page 5 (lines 17-19).

3. Discussion (page 15, lines 18-21): I did not understand the logic of the sentence beginning "Whereas the sensitivity...". Please address.

We apologize for the confusion, and have rewritten the corresponding sentence (page 17, lines 19-20).

4. Discussion: The discussion is at times repetitious. Please revise to both substantially shorten and help make the key points more accessible.

We have reduced the length of the Discussion. In particular, the third and fourth paragraphs in the original manuscript have been merged and shortened (pages 19-20).

Discretionary Revisions

1. Abstract (lines 13, 17 & 23) and through the main text: The phrase "sensitivity of fever", without the implied "...for detecting H1N1" was difficult to interpret.

We have ensured that the phrase “sensitivity of fever” is consistently followed by “for detecting influenza” (page 2, lines 13, 17 and 24, and throughout the manuscript).

2. Methods (page 5, line 8): Would it be useful to specify that the "portion" is non-random here?

The suggested sentence has been altered accordingly (page 6, line 15).
3. Methods (page 5, line 19): By what device was 38.0°C assessed?

4. Methods (page 6, line 11): Only reflecting my spectacular lack of medical knowledge, but I had to look up the definition of "axillary".

>>> 38.0°C represents the directly measured temperature and the corresponding sentence has been rewritten accordingly (page 7, lines 4-5). We believe that axillary temperature is a common medical term for the readers of *BMC Infectious Diseases*, and adding the earlier correction on page 7 (lines 4-5) did not permit us to reasonably explain the meaning of axillary.

5. I was unsure of what a "satellite" (first used on page 7, line 8) was. The alternative phrase "alliance", also unfamiliar to me, was used for what seemed from the main text to be the same thing, but on examination of figure 1 is different. "Terminal", a far more familiar phrase, was also used. Given the salient point here is not appropriate terminology of the sections of the airport, but rather that the location of scanners can be differentiated within the statistical analysis, perhaps the authors could consider some alternative language to aid in comprehension.

>>> First, a “satellite terminal” is common terminology for referring to the structure/design of airport buildings, and we therefore believe that satellite will not be unfamiliar for readers interested in airport screening. To avoid any confusion for medical readers, we have rewritten the relevant sentence on page 8 (lines 21-23). Second, we used satellite as a variable, because the distances between the scanners and passengers can be best differentiated by the satellites. Moreover, the grouping of the satellites was also differentiated by the terminals. We have noted these points on page 8 line 24 to page 9 line 2.

6. Methods (page 9, lines 13). "..incorporating a demographic variable...": Which demographic variable?

>>> The corresponding sentence has been altered accordingly (page 11, line 5).

7. Results: Fever among confirmed cases. Would it be useful to include "(16)" here in the title to remind the reader of the data set. Furthermore, with just 16 events, the author’s may wish to consider listing the full data set in a new table. Age and temperatures in particular would be interesting to see.

>>>
The information of n=16 has been added to page 11 (line 22). The number of confirmed cases during the very early stage of the 2009 pandemic was as small as 16. To protect the privacy of the limited number of imported cases, only summary statistics of the data are given.

8. Results (page 12, lines 2 and 6): Are the temperatures in brackets standard deviations? Please state explicitly.

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We have ensured that the brackets clearly show the standard deviation (page 12, lines 14 and 16).

9. Results (page 12, line 15): Consider rephrasing "sex-specificity". Further, can the author’s comment on why, when using a cut-off of 37.5, an effect of sex is seen. With this cut-off within the typical temperature range for healthy humans, is this observation to be expected or not based on the physiological differences between (non-fever or only marginal-fever) men and women?

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We have used gender instead of sex throughout the revised manuscript. It may not be valuable to write a possible explanation for the gender difference, but we have at least added an explanation for the similar difference between self-reported cases and other cases (page 14, lines 20-22).

10. Discussion (page 15, lines 17-20) Please reword "not particularly useful"

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The corresponding sentence has been altered accordingly (page 17, line 17).

11. Discussion (page 18, line 17): Consider rewording "..undetected cases were unrecognised". I am not sure what this means.

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We apologize for the confusion, and have rewritten the corresponding sentence (page 20, line 17).

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[RESPONSES TO REVIEWER 2: Dr. Lance Jennings]
The authors have accessed unique international traveller entry screening datasets obtained during the early stages and later stages of Japan’s public health border response to the 2009 pandemic, which has provided an opportunity to investigate fever screening at the border.
Discretionary Revisions

1. A reference for the original Japanese guideline (Page3/Line 13 ) could be included.

> We have included a reference for the original guideline (page 4, line 14).

2. The authors claim that the purpose of the study is to evaluate fever screening as a countermeasure against influenza, (4/21-22) appears very broad.

> The corresponding sentence has been rewritten to more precisely represent the purpose of our study (page 5, lines 4-7).

Minor Essential Revisions

1. It would be helpful if the statement in the Background “the efficacy of entry screening in correctly detecting and diagnosing influenza cases is likely to be small, mainly because of the impossibility of detecting incubating individuals…” be clarified to ensure that there is a clear differentiation between influenza the disease ( the title of the paper is “Fever Screening..”) and influenza infections (of which a proportion will be symptomatic and febrile).

> We agree with the reviewer. We have emphasized the importance of the presence of asymptomatic cases on page 4 (line 12) and page 21 (line 12).

2. Statistical presentations: presentation of sensitivity and specificity calculations consistently as a percentage may be more useful to public health and border and other authorities likely to find this research useful.

> The estimates of diagnostic accuracy are now all expressed as percentages in the main text and Table 1.

Major Compulsory Revisions

1. The clinical examination of passengers (Page 5) requires a little more explanation, as does the criteria for selection of passengers for rapid diagnostic testing. What samples & diagnostic test kits were used? It is recognised that the PPV of rapid antigen detection assays is poor in low influenza prevalence situations (the prevalence of influenza among the passengers is essentially unknown in this study) and that the sensitivity for the H1N1 2009 was generally poor. The PCR methods should also be referenced.
We have described that nasal specimens were used for rapid diagnostic testing. The RT-PCR analysis has been referenced. Since the limited sensitivity of the rapid diagnostic testing is an issue that we did not examine in the present study, we have mentioned this point on page 18 (lines 19-20) as follows: “Of course, a confirmatory diagnosis of influenza is further required to account for the limited sensitivity of the rapid diagnostic testing”.

2. A flowchart should be included to clarify the two datasets and inclusion of the passenger subsets.

3. In the background, the terms used “confirmed cases who were detected and diagnosed...” are confusing and should be clarified. Clearly confirmed cases are those clinically diagnosed cases where ‘laboratory’ testing has been involved and this was only carried out during the collection of data-set 1. In addition, consistency with the correct use of these terms throughout the manuscript is required as later (8/8) “we examined the sensitivity of fever for correctly diagnosing influenza among confirmed cases...” also, (9/16-17) “we also assessed the above-mentioned diagnostic performances” and (13/3) “Diagnostic performances of the infrared thermoscanners” imply (and is also stated at 14/16) that thermal scanning can be used to ‘diagnose’ influenza when these devices are instruments that measures surface temperatures.

4. The discussion focuses on the finding (14/17-) that the “sensitivity of fever (eg 38C) upon arrival was estimated to be as low as 22.2% among confirmed cases...” As the confirmed case sample size is small, a general discussion is required on the proportion of influenza infected individuals whom are likely to have any fever and to what degree medication lowers the temperature. Further, the prevalence of influenza in the study
population is essentially unknown. Thermal scanning generally performs well at
detecting febrile passengers (and this study possibly indicates this with the detection of
73 other febrile passengers; but is not discussed).

First, we agree that it is worth mentioning the published fraction of febrile cases among the total
number of confirmed cases. Although no direct comparison can be made, since the fraction of
febrile influenza cases among international passengers is epidemiologically different from that
among the total influenza cases in a community, the value of 22.2% implies that antipyretics
could have reduced the risk of fever by 76.4%. This point is now addressed on page 18 (lines 1-7).

Second, our study subjects were non-randomly selected. Therefore, we believe that we cannot
state that the study indicates the possible detection of 73 other febrile passengers (and we were
not able to fully follow the logic). We believe that the statement “thermal scanning generally
performs well” should ideally be assessed by the diagnostic performance estimates, and this
point has already been reviewed in the Introduction with appropriate references. To additionally
describe that thermal scanning can detect more febrile passengers, as compared to the absence of
using thermal scanners, we have added a sentence to page 19 (lines 1-2) with an additional
reference to Priest et al. (2011).

5. Following on from (4), the conclusion that “The PPV of the infrared thermoscanners
among the suspected fraction of passengers (n=1,049) was shown to be insufficient to
detect febrile passengers” appears inappropriate. The authors should perhaps limit
their conclusions to their findings on the use of fever screening for the detection of
influenza.

The phrase “detect febrile passengers” has been changed to “detect febrile influenza cases among
passengers” on page 22 (line 6).