Author's response to reviews

Title: Influenza in long-term Dutch travelers in the tropics: symptoms and infections

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Author's response to reviews: see over
Dear Editor,

My co-authors and I would like to thank the reviewers for their time and expertise in critiquing this paper. Please find below a detailed response on a point-by-point basis to each comment. We hope that the reviewers will find that their comments and suggestions are adequately reflected in the changes we have made to the manuscript and that you will continue to consider this paper for publication.

Best regards,
Jane Whelan (corresponding author).

Reviewer: Annelies Wilder-Smith

Reviewer’s report:

Major compulsory Revisions

Abstract: “among 602”—among 602 unvaccinated travelers, I presume? Please add. Of the 602 travelers intending to travel, did not a single one receive the vaccine? Or was recent flu vaccination an exclusion criteria. This is very important information, also for the abstract.

Under the Dutch National Influenza Prevention Programme, influenza vaccine is recommended for high risk groups only and is not covered under mandatory health insurance for healthy young adults. The influenza vaccination status of travelers pre-travel was not confirmed, but the likelihood that travelers were vaccinated pre-travel in the Dutch healthcare system is minimal. We have included this in the method section and also as a limitation in the discussion, and we have deleted ‘unvaccinated’ in the text.

Line 3 (second sentence in introduction): sentence does not have a verb—incomplete sentence

My apologies for this – some text seems to have been lost, in the version originally uploaded. This has been rectified.

Line 5: in one sentence, the authors talk about emerging economies, in the next about tropics and subtropics. What is the link between? Is this study about travel to emerging economies or to the tropics and subtropics? Many emerging economies are now in the tropics and subtropics, so it is important to be precise with the definitions. Is the aim: developing countries as a destination, or emerging countries as a destination, or the tropics and subtropics as a certain “climatically defined zone”?

The study population was indeed travelers to tropical and subtropical zones as defined climatically. I have amended the text to make the distinction clearer.
Methods: nicely detailed. But the inclusion criteria do not specify whether those who received flu vaccine as part of their pre-travel work up were include or excluded. Was flu vaccination an exclusion criterium?

*Flu vaccination was not an exclusion criterion as healthy adults in the Netherlands are not offered influenza vaccination under the Dutch National Influenza Prevention Programme. Vaccinations are paid for through compulsory health insurance in the Netherlands. It is possible that there was some degree of vaccination bought on the private market, but this is very uncommon in the Netherlands and we consider this likelihood minimal.*

Results: Some details are already in Table 1, and hence not all results need to be listed (eg the proportions of influenza antibody levels to the different constellations can be just referred to Table 1 in the text). It would be very important if the authors could add a map with the Influenza Transmission Zones and the 4 regions: South East Asia, Africa, Central and Latin America and “Asia (Other)”; and then draw in the attack rate per region into the map. Even if there are no statistical significant differences, such a map could in the future be cited for an easier overview of attack rates and would convince readers that even travel to Africa poses the same risk as travel to other parts of the world. The information on whether the attack rate for travelers to Africa is the same as the attack rate to Asia is there, but it is somehow hidden. Please highlight the attack rates per transmission zone better, in the text, or as above definitely also in a map, and presented as person-months.

*Thank you for this suggestion. We have added a figure with a world map and the attack rates per region, as recommended.*

The authors set out to examine the differences in the proportion of confirmed influenza infections by sex, age-group, primary influenza transmission zone visited, fever >38.0°C and ILI. Positive predictive value (PPV) for seroconversion was the proportion of symptomatic cases seroconverting for infection. The authors also set out to do logistic regression models. However, the results of all the above are not presented in a table or a version that is more visually palatable than just listing the results in the text. Please add such a table, even if there are no statistical differences.

*As evidenced in Table 1, only age-group was associated with seroconversion for any of the viruses tested. None of the other variables were significantly associated with the outcome at the univariable level and so multivariable logistic regression analyses of baseline characteristics were not conducted. We have added a second table demonstrating the association between seroconversion for individual viruses and ILI.*

Regarding seasonality, we looked at the incidence and seasonal variation of confirmed fever >38 degrees (n=209) and the outcome is below (Figure: Incidence of fever>38 degrees per 100 person-months from Jan to December 2009-2012 by region). In both the total sample and each region, there was no evidence of a seasonal trend in fever onset (numbers for 'Asia, other' are too small to comment and are not significant). Overall, tests for seasonality of fever onset were not very informative (especially as the causes of fever in the tropics are myriad) and for ILI (n=32), numbers by
region are too small to derive any conclusion. We respectfully suggest that the publication of this data will not add to this manuscript which focuses on influenza.

Discussion: in many ways, this is a repetition of the results, and lacks some further in-depth discussion and comparison with the existing literature. Not even the famous study by Margot Muetsch is mentioned! : Influenza virus infection in travelers to tropical and subtropical countries. Mutsch M, Tavernini M, Marx A, Gregory V, Lin YP, Hay AJ, Tschopp A, Steffen R. Clin Infect Dis. 2005 May 1;40(9):1282-7. They enrolled more than 1400 travelers. Among the 211 febrile participants, 27 (12.8%) had seroconversion, 13 (6.2%) with a > or = 4-fold increase; among the 321 afebrile control subjects, 13 (4.0%) had seroconversion, 5 (1.6%) with a > or = 4-fold increase. Twenty-five seroconverters (62.5%; P = .747) acquired influenza outside of the European epidemic season. Sixteen patients (40.0%) sought medical attention either abroad or at home, and 32 (80.0%) were asymptomatic at the time of completion of the survey. Why does the discussion end with such an unfounded conclusion that only high risk groups should receive the vaccine?

This conclusion stands alone, without the context of the previous discussion and needs to be elaborated further. In fact, one could argue that the findings would support recommending flu vaccine for all travelers given the high attack rates? These attack rates are higher than for all over travel-related vaccine preventable diseases including hepatitis A, typhoid fever etc. The rationale for flu vaccination in travelers is not so much preventing severe disease or death (like in flu vaccine programs on a national basis), but more on preventing days of illness on an already very expensive holiday where every single day counts.
In response to the comments of both reviewers, we have rewritten and expanded our discussion. We now compare our results in more depth with other prospective studies, and we also have explained our conclusion why, in the Dutch national guidelines, influenza vaccination is not routinely recommended to travelers and explained with an example why this advice may differ in different countries’ guidelines.

Because there seems to be broad consensus that vaccination is most important for risk groups, we have not changed this conclusion in the abstract.

Reviewer: Ivan FN F.N. Hung

Reviewer’s report:

Major compulsory revisions:

1. Please indicate the travelers' frequency of travel

   Travelers were included in the study if they were planning a single trip of between 12 and 52 weeks’ duration. The median travel duration was 20 weeks (IQR:16-25 weeks).

2. Please include the comorbidity of the recruited subjects and long-term medication that they are taking (for example anti-hypertensives, inhaled steroids/ brochodilators for asthma, oral hypoglycemic agents).

   We did not include this comorbidity in our study because the study aimed to look at conversions and morbidity in an immunocompetent group of travelers that visited our vaccination clinic. Influenza infection was defined as a ≥4-fold rise in antibody titre post-travel from a pre-travel titre of ≥ 10, regardless of vaccination status or comorbidity. Given the fact that this is a cohort of young people who are fit enough to travel long term, mainly for pleasure and who were all seen by our study nurses, we know that there was not much severe comorbidity in the group. Unfortunately, we cannot extract the data on comorbidity from our patient files any more.

3. Please add in the discussion the limitations of the study which include measurement of temperature only if the travelers feel feverish (rather than daily temperature measurement), and no virological data (from nasopharyngeal sampling).

   A limitations section has been added and we now mention specifically that ‘Because virological data from nasopharyngeal sampling was not available for any of the studies, we can not be sure whether the symptoms were caused by influenza or by other infections’. All influenza diagnoses were laboratory confirmed: “Blood samples were taken before and after travel and paired samples were tested
simultaneously post-travel for antibodies against influenza viruses using the hemagglutination-inhibition (HI) assay [5,6].

4. The author should expand the discussion into how the influenza vaccination should be implemented and how to persuade travelers to receive the influenza vaccine.

*We have expanded the discussion, also see our reply to the first reviewer.*