UNIVERSITY OF GEORGIA
Odum School of Ecology

August 4, 2018

Re: Resubmission of *Spatio-temporal spillover risk of yellow fever in Brazil* PARV-D-18-00420R1

Dear Editor,

Please find enclosed with this letter our revised manuscript "Spatio-temporal spillover risk of yellow fever in Brazil" which we resubmit for publication as a research article in *BMC Parasites & Vectors*.

Our manuscript presents a statistical model which predicts the spatio-temporal spillover risk of yellow fever (YF) in each Brazilian municipality by month based on environmental and demographic covariates. Previous methods mapping YF spillover risk have failed to incorporate the temporal dynamics and ecological context of the disease, and are therefore unable to predict seasonality in spatial risk across Brazil. Here, we present a temporally explicit statistical model to predict the propensity of yellow fever spillover across Brazil. We also further divide our model into a regional model consisting of two areas as determined by non-human primate reservoir richness, to better contextualize the spillover process. Taking this approach, we observe that the seasonality of peak spillover risk differs across the country, giving rise to higher yellow fever spillover risk in densely populated, coastal cities than the remote Amazonian municipalities (coinciding with yellow fever's historical range) at certain times of the year. This counter-intuitive conclusion is particularly timely given that the most recent outbreak occurred within the coastal region, which has previously been thought to be low risk and was only recently included in the recommended vaccination area.

We thank the reviewers for identifying areas of weakness or confusion in the original manuscript. The comments have been carefully considered. We have addressed specific comments below:

Specific replies

Reviewer #1:

This revised manuscript represents a substantially improved version of the original manuscript. My original review comments and edits were addressed. The text is now much easier understand. Below are a few comments that I hope will strengthen the manuscript even further.

Consistently spell Amazon River as Amazon River, not Amazon river Consistently spell Yellow Fever (YF), Yellow Fever Virus (YFV), etc. (e.g., WNV, LRR, HRR), and make sure the acronyms are introduced upon first use and then used consistently instead of the full expressions; avoid introducing acronyms repeatedly

> *Thank you for your keen eye. All capitalizations should be consistent. Acronyms are introduced in the abstract, main text, and figure captions for readability.*

Data = plural

> *Verbs following "data" have been changed to the plural form.*

Check tenses: e.g., l. 383 should be "we were able", not "we are able"

The sentence now reads "By modeling regional spillover risk separately in high and low NHP richness regions, we identified different seasonal patterns between regions." (line 378). The remainder of the text has been proof read for tense.

Punctuation needs checking

The manuscript has been proofed by the authors.

Please clarify further the meanings of National Model and Regional Model in the Introduction

The last paragraph of the Introduction has been edited to include more details of the National and Regional model. The final paragraph now reads:
Past spatial mapping of YF risk in Brazil has assumed a temporally constant risk or similar environmental drivers of YF spillover across all regions of Brazil, regardless of their NHP species richness [14, 15, 21, 22]. Here, we first present a statistical model (National model) that incorporates monthly variation in covariates to predict the propensity of YF spillover across municipalities (sub-state administrative units) of Brazil. Secondly, we better contextualize the spillover process by fitting models to two contiguous regions determined by NHP reservoir richness. The composite of these models are presented as the Regional model. Finally, we present the models? predictions of the spatio-temporal risk of YF transmission by month across Brazil from 2001 to 2013 for the National and Regional model.

l. 153: text suggests variables were cube root transformed or not transformed at all; comments to reviewers suggests different or no transformations were applied; which is it?

The manuscript accurately reflects our transformation methods. All variables were visually inspected for normality. NDVI, mean temperature, mosquito occurrence were not transformed. Population density was log_{10} transformed. The remaining variables (rainfall, fire density, non-human primate species richness, and NHP-agriculture overlap) are cube root transformed. The cube root transformation was able to minimize skewness in the data and handle zero values. This additional information has been included in the manuscript methods in text and in Table 1.
The text reads:
"All variables were visually inspected for normality and cube root transformed if needed, except for population density, which was log_{10} transformed (Table 1). " (line 159).

l. 197: Why were only maxima considered? Minima are extreme events also and once would think that extreme aridity, very low temperatures, or very low NDVI may result in low spillover risk.

It is possible that environmental minima may result in low spillover risk, but was not explicitly included in the model. The additional set of minima scaled variables would be highly correlated with the maxima scaled variables. Given that our method does not use model selection, we made the a priori decision to only include maxima scaled variables. Scaling by the maxima was chosen over the minima because we wanted to explore the possibility of environmental triggers leading to a rare event- spillover.

ll. 252/253: unclear what numbers in parentheses refer to ($> 5, < 5$). Richness? Units of measurement?

Units, NHP reservoir species, have been included in the text (line 255).

l. 291: I was unable to play the movie on my Mac or PC this time.

We have verified the movie file opens properly.

ll. 504/505: Why is it doubtful that urban transmission occurred during the study?

> *The last reported case of urban transmission in Brazil occurred in 1942. We have included a citation to support this claim (line 464). Additionally, we are confident making this claim because of the relative infrequent reporting of multiple cases per a month in a municipality. Further, a majority of municipalities do not report cases in consecutive months, suggesting sustained urban transmission is rare. See the supplement for summary of case, and municipality-month data.*

ll. 510/511: remotely sensed data are always spatially explicit, just perhaps not at the desired spatial resolution

> *This was poor expression. The sentence now reads "Further, remotely sensed environmental data is often at spatial resolutions that are coarser than the disease data, or are averaged over time. "(line 485)*

l. 836: "Spatial data was not explicitly incorporated into the model." This is misleading: the models were based on data derived from spatial datasets; the model outputs include maps, which represent spatial data. Did you intend to say that "spatial dependence was not considered in the models", etc.?

> *Yes. Thank you for the suggested alternative wording. The sentence now reads "Spatial dependence was not considered in the model." (line 726)*

Will the scripts be made available, either in a place like GitHub or as a supplemental material? I think it would be great if you did so and included specifics in the manuscript.

> *Yes. Following the journal guidelines we have included a link to the Figshare repository under the "Availability of data and material" section.*

Reviewer #2: The authors have addressed my comments in detail with new analyses that satisfied all of my remaining queries to what is already good paper. I remain a little disappointed about the lack of use of vaccination data, but realise that this would require significant new work and is maybe outside the scope of this existing analysis. I have no outstanding issues with this paper.

> *Thank you for your comments.*

These results are original and not under consideration for publication elsewhere. All authors have approved the attached manuscript for submission.

I can be reached by email (reni@uga.edu), phone (706-583-5538) or post (Odum School of Ecology, University of Georgia, Athens, GA 30602). Thank you for your consideration.

Sincerely,
RajReni Kaul