June 3, 2016

Dear Mr. David Accame,

Thank you for the excellent reviews of our manuscript “FLIRT-ing with Zika: A web application to predict the movement of infected travelers validated against the 2016 Zika virus epidemic,” as it served to strengthen and clarify our original submission. We have incorporated and addressed the reviewers’ comments and hope the changes have made our article suitable for publication within *PLoS Currents Outbreaks.* We have summarized our responses on the following pages.

Kind regards,



Andrew G. Huff, Ph.D., M.S.

Associate Professor

College of Veterinary Medicine

Michigan State University

Response to reviewers is in blue:

Once the revisions are complete, please resubmit your revised manuscript online and provide us with a brief rebuttal letter outlining your point-by-point response to the comments raised. You may send the rebuttal letter via email to currents@plos.org.  
  
Reviewer Comments:  
Reviewer 1

Methodology - Is the methodology appropriate and has it been reported in sufficient detail to allow the replication of the work? No   
  
Results and interpretation - Do the results appear reliable? Are the conclusions supported by the results presented? Yes   
  
Quality of the written English - Is the English at an adequate standard for publication? Yes   
  
Data availability - Does the work adhere to community standards for data-sharing and reporting? Yes   
  
Ethical standards - Does the research meet all applicable standards for the ethics of experimentation and research integrity? Yes   
  
Overall suitability for publication - Is the manuscript suitable for publication? Maybe   
  
What issues must be addressed before this work can be reconsidered?   
  
Both the tool presented and the analysis done are interesting. However the description of the work is not clear in many parts. I also find that a statement in the discussion in not well motivated. I thus recommend the following major revisions:   
  
1) Please, describe more in detail the flight dataset. How many airports?   
What is the coverage by country and continent? - Table & reference statement - list the number of airports in line in the document - coverage is sort of a silly term - how about a percentage of passengers in the data per each country, and aggregated by continent, in the table?

We would like to thank the reviewer for the excellent questions and suggestions. We added the statements (see below) to the method’s data section and have provided supplementary data and figures:

At the time of publication, the database contained 54,870,563 flights globally, and tables containing flight counts by region, country, day of the week, and by airport are available in the supplementary materials.

2) Describe more in details the data on imported cases in US and the   
procedure adopted to collect them. Were cases checked manually? Was it   
always possible to distinguish between different cases?

We would like to thank the reviewer for the excellent questions. We added the statements to the methods section:

“Case count data were obtained daily and manually from news reports using Google Alerts and searching the Internet from January 11, 2016 to March 11, 2016 using the search terms: (1) new U.S. Zika case; (2) U.S. Zika cases; (3) Zika Virus U.S., and, (4) searches by each state (e.g., Florida Zika Cases). Information about all confirmed and suspected Zika cases and their location was collected; however, detailed geographic information beyond the state level was not always available in the news reports and distinguishing between cases was not difficult due to the heightened media attention surrounding Zika Cases at that time.

Case count data were obtained daily and manually from news reports using Google Alerts and searching the Internet from January 11, 2016 to March 11, 2016 using the search terms: (1) new U.S. Zika case; (2) U.S. Zika cases; (3) Zika Virus U.S., and, (4) searches by each state (e.g., Florida Zika Cases). Information about all confirmed and suspected Zika cases and their location was collected; however, detailed geographic information beyond the state level was not always available in the news reports and distinguishing between cases was not difficult due to the heightened media attention surrounding Zika Cases at that time. Most news articles reported heavily on the single first case arriving in a previously Zika-free state. As the Zika Virus epidemic progressed, news articles began reporting on several new cases within a single news article, especially in Zika hotspot states (e.g., Florida, Texas, & New York) where several new cases appeared each day. If specific sub-state level geographic information was available for each case, it was recorded. If not, only state level information was recorded for the cases missing this information. Additional manual internet searches were conducted on cases missing this information to collect missing data and cases were de-duplicated. Real-time reporting alerts from Google Alerts helped the authors identify trends in reporting, like spikes in news activity directly following a new U.S. case finding. Observing these reporting trends helped to identify repeated case reports.”

3) Authors consider two time-windows for validation: Jan 11-Mar11 and Feb   
1-Apr 1. Please better explain and motivate the need of using two very   
similar time-windows. In what sense the dataset Jan11-Mar11 contains more   
data?

We would like to thank the reviewer for the excellent questions. We added the statement to the methods section:

“Using FLIRT’s scheduled direct flights mode, individual network maps were generated for each of the five origin airports using counts of seats traveling from selected the origin airports to all possible connected global destinations in each of the three time periods. Then, only the U.S. destination results were extracted and the number of seats from each origin were aggregated to determine the total connectedness between all five origin airports and each possible U.S. destination. Using the passenger simulation, five global simulations were generated for each time range (20,000 passengers per simulation), and each simulation yielded nearly identical results. The results of these five simulations were summed to produce the final simulation results.

To validate FLIRT, FLIRT’s output was compared to the locations of actual U.S. imported Zika cases. Two time ranges were used to assess FLIRT’s ability to predict the rate of imported Zika cases to the U.S during the 2015 Zika Virus epidemic, and one future time range was considered to make future Zika distribution predictions (Table 1). For each time range, direct scheduled flights and passenger simulation results from selected origins to continental U.S. airports, were exported from FLIRT (Table 1). On 02 February 2016, FLIRTpredicted *a priori* which U.S. locations were most at risk of receiving Zika Infected travelers from February 2016 to April 2016, and this prediction was published in The Guardian (Kelkar, 2016). This prediction was validated in this study. The analysis using the *Expanded Data* range used all available case data collected for this study (163 U.S. Zika cases), and compares it against FLIRT’s 11 January 2016 - 11 March 2016 prediction. The purpose of analyzing the *Expanded Dat*a range (a similar time period) was used to further validate FLIRT *post hoc,* and covered the previous time period merely to avoid the *post hoc* fallacy.”

4) Why choosing the airport with highest traffic in the country of origin?   
How many airports in the origin countries are connected with US? How this   
choice impacts the results? -

We would like to thank the reviewer for the excellent questions. We added the statement to the methods section: “Only international airports were evaluated since only international airports are the only nodes in the network capable of sending infected travelers to the United States from locations with sustained local Zika Virus transmission.”

A brief explanation for the reviewer only:

In venezuela, Monseñor Óscar Arnulfo Romero International Airport is busiest international travel hub and holds 90% of international traffic to and from Venezuela. In Brazil, Guarulhos International Airport in Sao Paulo carries 39,573,000 total passengers annually, about 2.2 times that of Presidente Juscelino Kubutschek International, its second largest. In colombia Bogota airport with 20,258,888 passengers was around 5.5 times as much passenger traffic as the next busiest airport[[1]](#footnote-1). In El Salvador- Monseñor Óscar Arnulfo Romero International Airport is the busiest airport in El SAlvador and handles most international passenger traffic. In Honduras- [Ramón Villeda Morales International Airport](https://en.wikipedia.org/wiki/Ram%C3%B3n_Villeda_Morales_International_Airport)m 763,000 Toncontin International airports, 587,000. 1.3 times more. Therefore, the analysis is not sensitive to

The international airport with the most passengers in each selected Zika-affected country was selected as the origin destination, as all origin countries with the exception of Honduras had one main international hub that carried more than 2 times the amount of passengers annually as the second busiest international airport in that country, with the exception of Honduras where the busiest airport still carried 1.2 times the passenger traffic of the second busiest airport. The final airport selections were Guarulhos International Airport (GRU) in Sao Paulo, Brazil; El Dorado International Airport (BOG) in Bogota, Colombia; Monseñor Óscar Arnulfo Romero International Airport (SAL) in San Salvador, El Salvador; Simón Bolívar International Airport (CCS) in Maiquetia, Venezuela; and Ramón Villeda Morales International Airport (SAP) in San Pedro Sula, Honduras.

5) Authors state, “If Zika prevalence varied greatly between different   
airports, such that their number of cases per passenger was vastly   
different, it could alter the distribution of cases. However, it is   
unlikely that this would overwhelm the effects of network structure, given   
the magnitude of difference between cities.” This is not true in general.   
When an outbreak presents an exponential growth of cases, latters vary   
greatly in time, and epidemics in different countries may have occurred in   
different periods, thus presenting a highly heterogeneous prevalence at a   
given moment that may potentially hide the heterogeneity of the network.   
Authors must carefully justify this statement.

We would like to thank the reviewer for their excellent points. We agree with the comments and have clarified the sentence. We have We edited and added this statement to the results section: “The rate of imported cases to specific airports in the U.S., from the origin airports analyzed in this study, is partially dependent on the prevalence of Zika Virus in the source population. If Zika prevalence varied greatly between different airports, such that their number of cases per flight was vastly different, it could alter the distribution of cases in the United States. However, based upon the origin airports and the time periods analyzed in this study, it is unlikely that large differences in prevalence would overwhelm the effects of the network’s structure in this validation of FLIRT since many of the origin airports have similar network structure and passenger volume (see supplementary materials).”

6) The manuscript addresses the role of air-traffic in the risk of

propagation of an emerging disease. The background presented is extremely

poor and authors should cite other related studies. I mention just few of

them, but there are many others:

Thank you. We agree and he have added the articles you referenced in addition to a few other related journals. We are aiming to be concise as possible.

What other improvements might you suggest?   
Minor comment: Page 10, second line after the beginning of the paragraph   
“Generalized linear Models”: correct “number number”

Thank you. Corrected

Additional Technical Requirements:  
7) Please provide the full names and affiliations (Department, Institution, City, State, Country) for all authors as you would like them to appear on the article.

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8) Please structure your abstract with the following heading or similar: Introduction, Methods, Results, Discussion.

Completed. Thank you

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Completed.

11) Please include individual ,jpg files of your images and tables.

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