Author’s response to reviews

Title: Factors associated with Human West Nile Virus Infection in Ontario: A Generalized Linear Mixed Modeling Approach

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Author’s response to reviews:

Dear Editors,

Please find below a response to the editorial and reviewer comments. We have made revisions in the text corresponding to the Editor Comments and Reviewer 4’s Specific Comments.

We have further provided a response to the General Comments provided by Reviewer 4, making efforts to present a detailed explanation given the tone of these remarks.

We hope that you find these revisions acceptable and appreciate your consideration of our manuscript for publication.

Sincerely,

Manisha Kulkarni
Editor Comments:

1. Can you please provide clarification on whether the data was de-identified or not and hence consent was waived? If the need for consent was waived by an IRB or is deemed unnecessary according to national regulations, please clearly state this, including the name of the IRB or a reference to the relevant legislation. If only previously collected data was used in this study, and no participants were involved, please clarify this in the Ethical approval and consent to participate section.

   - Response: This study used previously collected de-identified human disease surveillance data that was obtained from Public Health Ontario, the provincial public health authority. The need for consent was waived in accordance with the TCPS2 policy Article 5.5 for use of secondary data (http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-epic2/chapter5-chapitre5/#toc05-1d). The Ethics approval and consent to participate statement has been revised on page 13.

2. If no funding was obtained for your study we still require this section to be included with the statement “No funding was obtained for this study”.

   - Response: The funding statement has been revised on page 14.

3. Please ensure that all figures/tables and supplementary files are cited within the text. Any items which are not cited may be deleted by our production department upon publication. Currently, Appendix Table 1 is not cited. Please also rename this table as ‘Additional Table 1’ so it is not confused with the other Table 1.

   - Response: The table has been cited in the Methods on page 5, line 116, and renamed as ‘Additional Table 1’ on page 27.

4. There are two minor essential revisions that we request you make prior to final publication. These two revisions are listed in the second reviewer's comments, as stated below. You can make these changes prior to final editing.

   - Response: Please see responses below to the two specific comments made by Reviewer 4.
Unlike Japanese encephalitis virus, no vaccine is currently available to protect humans from the West Nile virus (WNV). Early warning systems to predict severe human WNV season is necessary to reduce WNV related morbidity and mortality.

The authors have conducted a modeling study relating annual WNV incidence in southern Ontario to specific parameters in climate (temperature and rainfall), environment (land cover), human population (age and gender composition), and vectors (proportion of WNV infection in captured mosquitoes). This is a timely study to supplement additional information to existing knowledge about WNV presence in the region. The manuscript is a good try, however, as previous review has pointed out, the flow is a bit disconnected in methods. May the authors further explain why a new, separate model was constructed to investigate association between "early season" climate variables and annual WNV incidence?

- Response: As explained on page 7, line 155-157, and page 9 line 196-199, the early season model included only those variables that would be measurable by public health officials prior to the onset of the WNV season. This effectively excludes mosquito surveillance data from the upcoming year, since mosquito surveillance starts in May.

The authors may aware a very similar study by Giordano et al. (PLoS One. 2017 Aug 22;12(8):e0183568. doi: 10.1371/journal.pone.0183568. eCollection 2017.) which also described seasonal and geographical trends in WNV activity in southern Ontario. Non-Canadian readers may gain useful insights by reading the work by Giordano et al. to understand the background. The authors may consider adding some essential information. For example, there are 36 public health units in the province of Ontario, the reason of grouping Culex pipens and Culex restuans under the group Culex pipens/restuans etc. Also, the authors should consider to include this article in their references since it addressed and investigated the issues alike.

- Response: We are aware of the paper by Giordano et al, which used very similar data sources and was published prior to our study. It should be noted that our study was initially undertaken as part of a Master’s thesis, and preliminary results were presented at the Canadian Society for Epidemiology & Biostatistics (CSEB) annual student conference in June 2016, well in advance of Giordano’s paper (see abstract published in Am J Epidemiol. 2016;184(1):78–80). Nonetheless, despite the similarities between our two studies, our approach differs in notable ways. Importantly, our study explicitly controls for spatial autocorrelation using a mixed effects modelling approach, therefore the estimates of association that we derive are not confounded by spatial effects. Furthermore, we incorporate data on mosquito surveillance and climatic factors in the same model, allowing
us to examine the relative importance of these factors on human WNV incidence across the study area. Importantly, we derived estimates of climatic factors from all of the 28 public health units in southern Ontario, noting that the analysis of climate data in Giordano et al paper was limited to 7 health units where sufficient weather stations were present. We have update the text to make reference to the Giordano et al paper on page 6 line 140.

During the peer review process of the first submission (INFD-D-17-1640), Reviewer 1 has asked the data about frequency of precipitation (days per month). The authors' reply was "Unfortunately, data on the frequency of precipitation were not available." I would like to point out that, the data is openly available from the Government of Canada webpage (address: http://climate.weather.gc.ca/prods_servs/cdn_climate_summary_e.html), recorded in spreadsheets summarizing monthly climatic data. One of the columns is "Number of days with Precipitation 1.0 mm or more (Pd)". Short term but large increase in precipitation may have a negative impact in both larval and adult mosquito survival (Jones et al. J Med Entomol. 2012 May;49(3):467-73.).

Response: While a number of different data sources could have been manipulated to fit in our model, we opted to only include variables that were derived at comparable geographic scales, and for which data was available for all health units in the study area. Our study used human WNV data aggregated at the health unit level, which was necessary due to privacy restrictions. We therefore used climate averages derived from interpolated climate surfaces that had coverage across the study area in order to estimate temperature and precipitation indices at the health unit level, allowing for consistency in our estimates. Point estimates of rainfall amounts from weather stations are limited in their usefulness in this regard, since the number of stations per health unit varies and data from one or two stations may not accurately reflect rainfall patterns across the health unit. Therefore the raw weather station data were not considered as appropriate inputs for our models.

One of the special features of the manuscript is the usage of land cover data. As the authors pointed out that environment have influence on WNV transmission via its effect on ecology. May the authors walk the extra mile to utilize these data? A US group has published a remarkable ecological niche model of the estimated probability of Culex tritaeniorhynchus presence, and thus Japanese encephalitis in Asia (Miller et al. PLoS Negl Trop Dis. 2012;6(6):e1678. doi: 10.1371/journal.pntd.0001678.).

Response: In our study we incorporated land cover estimates that we aggregated at the health unit level to provide a scale comparable with the available human case data, as per the approach we used with all other input variables. As mentioned in the results, these variables were not significant in initial category-specific models and thus were not included
in final multivariable models. An ecological niche model (ENM) of WNV vectors in Ontario would be an interesting study in its own right, and given our familiarity with the use of ENM for disease modelling (see Kulkarni et al. PLoS ONE 2010; 5(2): e9396. doi.org/10.1371/journal.pone.0009396) we agree that this approach is promising for deriving estimates of disease risk across geographic areas. However, the inclusion of an ENM is not within the scope of the present study nor it is not consistent with the study objective, which was to identify readily available indices that could be used in a practical manner by public health officials to predict the risk of a severe WNV season.

The basis to understand WNV transmission is that WNV infection a zoonosis. Transmission of the WNV involves the enzootic cycle with birds as amplifying hosts. The statistical model would be enhanced if avian data is incorporated. The Canadian Wildlife Health Cooperative (CWHC) has the WNV surveillance in dead birds available (2009-present, address: http://www.cwhc-rscf.ca/data_products_wnv.php). The Canadian Cooperative Wildlife Health Centre (CCWHC) (probably the same organization as the CWHC) has published dead bird surveillance reports specific to individual Canadian provinces (for example, the 2005 data can be found in the following address: https://digitalcommons.unl.edu/cgi/viewcontent.cgi?referer=&httpsredir=1&article=1046&context=icwdmccwhcnews). In addition, the authors may mention the role of migratory birds as they may contribute to the long range transport of WNV (Drebot et al. Can J Infect Dis. 2003 Mar;14(2):105-14.). Migratory birds travel across Ontario and bird sanctuaries are located some PHUs. For example, the Jack Miner Migratory Bird Sanctuary in the Windsor-Essex County PHU with the highest incidence.

Response: We have already acknowledged the role of birds in WNV transmission and on page 12 line 275 we have stated “Avian data was not included in the analyses due to paucity of data”. CWHC stopped its WNV dead bird surveillance program in 2009 and has subsequently tested only 300 birds per year across Canada; thus the distribution of these specimens is highly irregular. Therefore, similar to the weather station data that is only available at specific point locations, the available avian surveillance data cannot be considered an appropriate data input for the predictive models we have constructed at the health unit level. Any use of these data would be biased towards areas with tested specimens, which are not sampled in a geographically representative way.

***Specific comments***

Line 105: What is the case definition of both confirmed and probable human WNV infections? Please state or provide reference.
- Response: We have cited the reference for the WNV case definitions on page 5, line 107, and updated the reference list accordingly.

Line 229 to 237: Is there any other biologically plausible explanation for a higher spring temperatures and WNV incidence? Like, quicker thawing may increase flow of water bodies which is unfavourable for larval survival?

- Response: We recognize that there are several plausible mechanisms for the observed associations. We have inserted “or flush Culex breeding sites” on page 10 line 235.