Can local risk of West Nile virus infection be predicted from previous cases? A descriptive study in Quebec, 2011–2016

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Abstract

Objectives This study aimed at (1) describing the local risk of West Nile virus (WNV) infection in humans based on previous case reports and (2) investigating the spatial clustering of cases in the five most affected administrative regions of Quebec, Canada, for the 2011–2016 period.

Methods Human WNV cases declared to the Ministry of Health and Social Services of Quebec (Ministère de la santé et des services sociaux, MSSS) were retrieved. Incidence risk by age and sex was calculated for the study period. The yearly and monthly occurrence of cases in geographical units (GUs) was described and the probability of observing cases in a GU with cases reported in the previous year or month was assessed. Moran's I was used to assess global clustering across the study area. Spatial clusters were identified by the Kulldorff scan statistic.

Results A total of 261 WNV cases were declared to the MSSS between 2011 and 2016 in the study area. Overall, a low percentage of GU with cases reported had additional cases reported over the next month or year. Global spatial clustering was weak but statistically significant ($p < 0.05$) for 2012 and 2015. For these two years, spatial clusters of high-risk GUs were identified.

Conclusion Results underline the challenge of predicting the distribution of WNV incidence risk in Quebec based on previous occurrence of human cases. Ongoing research with high spatial resolution entomological data is still necessary to understand the spatial distribution of risk at a local scale.

Résumé

Objectifs Cette étude visait à (1) décrire le risque local d'infection par le virus du Nil occidental (VNO) chez l'humain à partir des cas rapportés de 2011 à 2016 et (2) estimer le degré d'organisation spatiale de ces cas dans les cinq régions administratives du Québec les plus affectées par le VNO au cours de cette période.

Méthodes Le risque d'incidence de VNO chez l'humain a été calculé, selon l'âge et le sexe des patients, à partir de la liste des cas déclarés au Ministère de la santé et des services sociaux du Québec (MSSS) au cours de la période à l'étude. La distribution annuelle et mensuelle des cas à travers les unités géographiques (UG) à l'étude a été décrite. La probabilité d'observer des nouveaux cas dans une unité géographique où des cas avaient déjà été rapportés au cours de l'année ou du mois précédent a été calculée. Le degré d'agrégation spatiale a été évalué à l'aide du I de Moran. Les agrégats spatiaux ont été identifiés à l'aide du scan de Kulldorff.

Résultats Au total, 261 cas de VNO ont été déclarés au MSSS entre 2011 et 2016 dans la zone d'étude. Un faible pourcentage d'UG ayant eu des cas rapportés à une période donnée ont eu des nouveaux cas au cours du mois suivant ou de l'année suivante. Le degré d'agrégation spatiale des cas était faible dans la zone d'étude mais statistiquement significatif ($p < 0,05$) pour 2012 et 2015. Pour ces deux années, des agrégats spatiaux de cas ont été identifiés.

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Conclusion Il est difficile de prédire la distribution du risque d'incidence du VNO au Québec en se basant sur les cas humains rapportés dans le passé. Des données entomologiques ayant une haute définition spatiale sont requises afin de comprendre la distribution spatiale du risque de VNO à une échelle locale.

Keywords West Nile virus · Risk distribution · Human · Spatiotemporal · Public health

Mots-clés Virus du Nil occidental · Distribution du risque · Humain · Spatiotemporel · Santé publique

Introduction

West Nile virus (WNV) (Flavivirus, *Flaviviridae*) is the primary cause of mosquito-borne encephalitis in North America (Kulkarni et al. 2015). Viremia in humans are low and of short duration. Humans are thus considered dead-end hosts for vector-borne transmission of the virus (Petersen et al. 2013).

Passerine birds and corvids, particularly the American robin (*Turdus migratorius*) and the American crow (*Corvus brachyrhynchos*), are responsible for maintaining and amplifying WNV in nature (Komar 2003; Bergsman et al. 2016; Abdelrazec et al. 2014). *Culex pipiens* is considered to be the main vector of WNV in Northeastern America given its relative abundance, feeding preferences towards birds and competence to transmit WNV, but other less competent and polyvalent mosquito species such as *Aedes vexans* may play a significant role in WNV transmission to mammals (Kilpatrick et al. 2005; Talbot et al. 2019b). Each WNV vector has a relatively specific ecological niche. For example, *C. pipiens* usually breeds in highly organic standing waters, including in human-made water containers, while *A. vexans* larvae develop in various transient freshwater habitats, including flood plains and crop fields (Crans 2004).

Risk of WNV transmission to humans depends on the contact rates between vectors and amplifying hosts, on the infection rates in vectors and on the contact rates between infected competent vectors and humans (Kilpatrick et al. 2005). Various studies reported that geographical, demographical, socio-economical or climatic variables are associated with the vector population dynamics, and some studies reported associations between these variables and the risk of WNV transmission to humans at various geographical scales (Myer and Johnston 2019). The frequently reported associations between environmental factors and risk suggest that, in an area with a diversity of land covers and land use, WNV transmission risk should follow a predictable spatial pattern, with areas where risk is higher than average and areas where risk is lower than average. Moreover, if geographical and demographical variables are relatively constant over a given time period, the observed spatial pattern of relative risk should show some degree of stability over this time period. The recognition of this pattern, if present, may help in identifying high-risk populations and targeting local public health interventions.

However, since the detection of the first human case of WNV in Canada in 2002, available evidence on the viral

activity and outbreaks suggest high heterogeneity of the risk in time and space (Kulkarni et al. 2015). Few epidemiological models have precisely predicted the future spatiotemporal distribution of WNV cases in humans or other incidental hosts in Canada (Berke and Waller 2010; Bouden et al. 2008; Chen et al. 2012; Custer et al. 2009; Epp et al. 2011; Epp et al. 2009; Pan et al. 2008; Wang et al. 2011). Hence, the planning and implementation of surveillance and preventive public health interventions against WNV remain a challenge in Canada.

WNV neurological diseases, West Nile fever and WNV asymptomatic infections (ex. WNV infections identified in blood donors) are mandatory reportable infections in Quebec since 2002 (Chartrand et al. 2018). WNV has been responsible for a few hundred cases in humans in Quebec, Canada, in the last decades, with a major outbreak involving 136 cases in 2012 (National Public Health Institute of Quebec 2013). This study aimed at describing (1) the local risk of WNV infection in humans based on previous case reports and (2) the spatial clustering of cases in the five most affected administrative regions of Quebec, Canada, for the 2011–2016 period, in order to assess if previous case reports could be used to target local surveillance and prevention efforts.

Material and methods

Case data

A database of all cases of WNV infection in humans declared to the Ministry of Health and Social Services of Quebec (Ministère de la santé et des services sociaux, MSSS) during the 2011–2016 period in the five targeted regions was obtained for the current study. All cases had an epidemiological investigation conducted by public health professionals from regional public health agencies. These epidemiological investigations aimed at collecting data including the date of onset of symptoms, various exposure factors and the travel history of patients during the probable exposure period. Cases were defined as a WNV neurological disease, West Nile fever or WNV asymptomatic infection according to the MSSS nosological definitions (Chartrand et al. 2018). The database provided for this study by the MSSS included the age and sex of the patients, the likely year and month of infection according to the onset of symptoms (considering a maximum incubation period of

15 days (Petersen et al. 2013)) and place of residence (municipality and first 3 digits of the postal code) at the time of infection. Only cases that were likely acquired in the province of Quebec according to travel history were included in the study.

Study area

Among the 374 WNV cases reported in Quebec between 2002 and 2016, 334 (89%) were reported from five administrative regions (Montreal, Montérégie, Laval, Lanaudière and Laurentides) (Ministère de la santé et des services sociaux, Québec 2019). The analyses for this study were restricted to these five regions. Given that most municipalities in northern Lanaudière and northern Laurentides were case-free during the study period, the study area was further restricted to areas with reported WNV cases. Hence, within the five selected regions, the study area was defined as a convex polygon connecting the boundaries of the most distal municipalities which had reported at least one case between 2011 and 2016 in the five selected regions. All municipalities included inside the polygon or intersecting the perimeter of this polygon were defined as part of the study area (Fig. 1). All spatial data processing was performed in ArcGIS 10.2.2 (Esri, Redlands, CA).

Geocoding of cases and population data

All patients were geocoded at the centroid of their municipality and of their forward sortation area (FSA) of residence. The

FSA is an area corresponding to the first three digits of the postal code. Administrative geographic boundaries files of 2011 census were obtained from Statistics Canada. The FSA are generally smaller than municipalities in urban areas and the opposite is true in rural areas. However, in any given area, the two types of geographical units share some common boundaries and one can be subdivided by the other. Hence, for any given region across the study area, the smallest geographical unit (GU) available was selected as the epidemiological unit of interest. A geographic boundary file of GUs was created in ArcGIS. Total population was retrieved for each GU from Statistics Canada's 2011 census. Given the small changes in population size of the area over the study period (about a 3% increase), the 2011 population was used as an estimate of the population for years 2011 to 2016 inclusively.

Incidence risk by sex and age

The incidence risk of WNV cases by sex and age categories (using 5-year intervals) was calculated for the entire 2011–2016 period.

Yearly occurrence of cases in local areas based on previous year report

To assess the stability of WNV incidence risk in each GU from one year to the other, the yearly spatial distribution of WNV

Fig. 1 Study area and distribution of the population among geographical units included in the study area, according to Statistics Canada's 2011 census

incidence risk (i.e., cumulative incidence of cases per 100,000 population) from 2011 to 2016 was mapped in ArcGIS. The ability to identify local areas where cases are likely to occur in a year based on case reports from the previous year was assessed by calculating the probability that a positive GU (i.e., with at least one reported WNV case) on a year was positive on the subsequent year, performed for each year. The probability that a negative GU (i.e., with no reported WNV case) on a year was negative on the next year was also calculated.

Monthly occurrence of cases in local areas based on previous month report

The monthly spatial distribution of GUs with reported WNV cases was also mapped for each year under study to descriptively assess the within-year spatiotemporal progression of human infections with WNV. The ability to identify areas where cases are likely to occur over the season based on previously reported cases was assessed by calculating the probability that a positive GU keeps its positive status over two consecutive calendar months. For example, if among the ten GUs that had cases reported in July, five also had cases reported in August, the probability, for a GU, of being positive in August given it was positive in July was deemed to be 50%. The probability that a GU was negative on a given month

among GUs that were negative on the preceding month was also calculated.

Spatial clustering of incidence risk

Moran's I statistic was used to evaluate global spatial autocorrelation in GU incidence risk across the study area using the Poisson constant risk parametric bootstrap described by Bivand et al. (2008), performed separately for each year. Neighbourhood structure (first-order queen contiguity) for this analysis was calculated in GeoDa 1.12.1.131 (Open Source Software under the General Public License, GPL v3.0) and .gal files were exported in R (package "boot" version 1.3-20) to compute Moran's I (Anselin et al. 2006). A Poisson distribution based on the global incidence risk (number of cases divided by the population at risk) in the study area was used for simulating the probable distribution of expected counts of cases in each GU under the constant risk assumption. Moran's I statistic was then computed for each of the 999 Poisson random distributions of risk and observed Moran's I were compared to the 999 randomly simulated Moran's I statistics to obtain an empirical *p* value for the observed statistic.

The presence and location of spatial clusters of GUs with high infection risk were assessed by the Kulldorff scan statistic (SatScan v9.6) (Kulldorff 1997). GUs' centroids were used as point locations for the scan test. The analysis was based on a Poisson model with a maximum cluster size

Fig. 2 Incidence risk (cases per 10,000) in the study area according to sex and age category (2011–2016)

Fig. 3 Risk distribution for West Nile virus cases in humans across the study area, 2011 to 2016, and geographical location of statistically significant spatial clusters. Cut-off for risk categories were defined base on incidence risk quartiles for each year

representing 50% of the total population at risk. Annual counts of cases and total population in each GU were used as cases and population files for the scan analysis, respectively. All statistically significant clusters ($p < 0.05$) were mapped in ArcGIS.

Results

Study area

A total of 354 GUs (small municipalities or FSA) were defined in the study area. These GUs covered the entire study area exhaustively and were mutually exclusive (Fig. 1). The total population included in the study area was 4,471,042 people in 2011.

Incidence risk by sex and age

A total of 261 WNV cases were declared to the MSSS between 2011 and 2016 in the study area. Six of these cases were infected by WNV outside of the province of Quebec and were thus excluded from the analyses. Among the remaining 255 cases, 139 (54.5%) were male and 116 (45.5%) were female. Cases were between 17 and 93 years old. Mean age of cases was 59.5 years old (median 60; interquartile range [49–72]). The distribution of incidence risk per 10,000 according to sex and age category is presented in Fig. 2.

Year to year stability in WNV local incidence risk

The total yearly number of domestic cases reported from 2011 to 2016 within the study area was 36, 125, 25, 6, 38 and 25, respectively. A total of 134 GUs had at least one human WNV case during the 2011–2016 period. The remaining 220 GUs included in the study area reported no cases during this time frame. The maximum number of cases observed in a single GU was 9, with a median of 1 case per positive GU.

The yearly spatial distribution of WNV incidence risk (cases per 10,000 population) is presented in Fig. 3. The yearly count of WNV cases and the incidence risk reported in each GU were highly variable from one year to the other. Table 1 presents the proportion of positive (or negative) GUs that remains positive (or negative) on two consecutive years between 2011 and 2016. The highest proportion of GUs that remained positive on two consecutive years was 44% and was observed for the 2011–2012 period. Only 13 of the 29 GUs that were positive in 2011 were part of the 89 positive GUs during the 2012 outbreak. For the remaining time periods, the proportion of positive GUs that remain positive on the subsequent year ranged between 0% and 20%.

Monthly occurrence of cases in local areas based on previous reports

Figure 4 presents the monthly spatial evolution of WNV cases for each study year. Only a low percentage (ranging from 0% to 50%) of positive GUs in a summer month had cases on the next month (Table 2) during a given year.

Spatial clustering of incidence risk

According to Moran's I statistics, spatial autocorrelation was weak for all years and statistically significant only for years 2012 and 2015 (Table 3). Moreover, statistically significant spatial clusters of GUs with high incidence risk were only detected in 2012 and 2015 (Fig. 3 and Table 3). These clusters were located in suburban areas surrounding the city of Montreal. One corresponded to the city of Laval and the northern suburban areas of the Laurentides region and the other was located in the northeastern part of the region of Montérégie. The risk ratio between intra- and extra-cluster zones was 3.13 for 2012 (Laval cluster, $p < 0.001$) and 10.03 (Laval cluster, $p < 0.01$) and 4.85 (Montérégie cluster, $p = 0.005$) for 2015.

Discussion

Our results suggest a low degree of spatial organization of human cases of WNV infection in Quebec. Statistically significant clusters were detected only for the years 2012 and 2015, which were then located in different areas. Similarly, a weak but statistically significant spatial autocorrelation was only observed for the same two years, which could be secondary to the presence of clusters. Also, the yearly incidence risk in a given geographical unit, relative to the average incidence risk in the study area on the same year, was highly variable from year to year. These results suggest that the spatial distribution of risk is not stable geographically over time. Moreover, our study shows a low ability to predict the occurrence of WNV cases in a given GU based on available early

Table 1 Number and percentage of geographical units that kept their positive or negative status on two consecutive years of the study period

Consecutive years (year 1–year 2)	No. of positive in 2nd year among positive in first year (%)	No. of negative in 2nd year among negative in first year (%)
2011–2012	13/29 (44%)	252/325 (78%)
2012–2013	14/89 (16%)	254/265 (96%)
2013–2014	0/25 (0%)	324/329 (98%)
2014–2015	1/5 (25%)	319/349 (91%)
2015–2016	5/31 (16%)	303/323 (94%)

Fig. 4 Monthly evolution of the spatial distribution of West Nile virus cases during years 2011 to 2016. Blue lines represent areas with cases infected in July of each year according to epidemiological investigations. Green lines represent areas with cases infected in August. Orange lines

represent areas with cases infected in September and red lines represent areas with cases infected in October. Mixed-colour areas represent areas with cases having been infected on different months of a given year

season's data on reported cases, for all years and time periods. Other studies from North America reported a similar spatiotemporal instability for WNV cases in humans (Johnson et al.

2015; Wimberly et al. 2013). The hypothesis proposed by the authors of these studies to explain spatiotemporal instability are (1) shifts in vector populations from one year to the other,

Table 2 Number and percentages of geographical units that kept their positive or negative status on two consecutive months for each year of the study period

Year	August vs. July		September vs. August		October vs. September	
	Positive in August among positives in July (%)	Negative in August among negatives in July (%)	Positive in September among positives in August (%)	Negative in September among negatives in August (%)	Positive in October among positives in September (%)	Negative in October among negatives in September (%)
2011	0/0 (NA)*	341/354 ^{††} (0.96)	5/13 (38%)	331/341 (97%)	0/13 (0%)	340/341 (100%)
2012	2/4 [†] (50%)	309/350 (88%)	9/43 (21%)	269/311 (86%)	0/51 (0%)*	303/303 (100%)
2013	0/1 (0%)	334/353 (95%)	1/19 (5%)	332/335 (99%)	0/4 (0%)	349/350 (100%)
2014	0/1 (0%)	349/353 (99%)	0/4 (0%)	349/350 (100%)	0/1 (0%)*	353/353 (100%)
2015	0/2 (0%)	341/352 (97%)	0/11 (0%)	323/343 (94%)	0/4 (0%)*	350/350 (100%)
2016	0/0 (NA)*		0/4 (0%)	332/350 (95%)	1/18 (6%)	334/336 (99%)

(2) avian herd immunity and population changes and (3) changes in climate and rainfalls. Spatial analyses for these studies were conducted on relatively large geographical units. The current study suggests that similar factors may lead to spatiotemporal instability on a fine geographical scale.

The instability of the yearly and monthly spatial patterns of WNV incidence in humans in Quebec raises several hypotheses about actual WNV risk distribution. First, we may question the assumption that cases in humans consistently reflect the level of WNV enzootic activity in a given GU. In fact, patients may not have been infected in the GUs from where the cases were reported. Thus, cases in humans could provide a different spatiotemporal pattern of risk compared with entomological data. Moreover, as suggested by the low overall incidence rates in Quebec, the contact rate between humans and infected mosquitoes is probably relatively low in Quebec (Rocheleau et al. 2017b), including in areas where WNV enzootic cycle is active, and the multiple interacting factors required for spillover to humans to occur may rarely be combined, possibly making WNV transmission a rare and apparently random event. The association between human case distribution and enzootic cycle distribution may be further obscured by the high proportion (approximately 80%) of asymptomatic infections in humans (Kulkarni et al. 2015). Underreporting of WNV cases may also influence the apparent distribution of risk, mainly if underreporting is unevenly distributed through

the study area. However, it is probable that diagnostic and reporting efforts may be higher in areas where WNV is frequently reported, contributing to clustering of reported cases in these areas (Wimberly et al. 2013).

Our results indicate a low probability of observing cases in a GU of the study area that had cases reported in the previous month. Meanwhile, GUs that had no cases in early summer may have cases in late summer. Moreover, our maps suggest that cases in late summer may appear far away from those reported in early summer. Although this phenomenon has rarely been reported in the literature and may be an artefact caused by a misclassification of exposure geolocation, it may also suggest that multiple and relatively independent foci of WNV risk may appear and disappear in southern Quebec during summer. Multiple foci of arboviral enzootic activity have previously been reported for Eastern equine encephalitis virus, another North American arbovirus amplified by birds, in central New York State (Howard et al. 1996). Various local factors influencing contact rates between vectors and amplifying hosts may explain the emergence and fading of various foci of WNV activity during summer, including heavy rainfalls and strong winds which may wash out vector breeding sites or reduce vectors' questing behaviours (Monath 1988). The interaction between bird and mosquito densities was previously proposed as an important predictor of WNV minimum infection rates (MIR) in mosquitoes in Eastern Canada (Talbot et al. 2019b). The hypothesis of multiple foci of WNV must be considered with caution but could be an important

Table 3 Summary of spatial statistics for human West Nile virus cases, Quebec, 2011–2016

Year	No. of positive geographical units	No. of cases	Incidence risk (per 100,000)	Moran's I statistic (<i>p</i> value)	Number of significant clusters (relative risk/ <i>p</i> value)
2011	29	36	0.81	0.08 (0.09)	None
2012	89	125	2.80	0.18 (0.04)	1 (RR = 3.13/ <i>p</i> < 0.001)
2013	25	25	0.56	0.06 (0.19)	None
2014	5	6	0.13	−0.009 (NA)	None
2015	31	38	0.85	0.13 (0.01)	2 (RR = 10.03/ <i>p</i> = 0.002, RR = 4.85/ <i>p</i> < 0.01)
2016	26	25	0.56	0.08 (0.06)	None

feature of WNV biology that should be further investigated to understand the spatiotemporal risk dynamics. As recommended by several authors, entomological research with high spatial resolution should therefore continue to better understand the biology of WNV and eventually obtain predictive models that are both sensitive and specific and whose impact is significant for public health (Fauver et al. 2016; Myer and Johnston 2019; Talbot et al. 2019a).

Some limitations related to the data and spatial analysis may have had an impact on the study results. The local incidence risks used for mapping may be subject to the modifiable areal unit problem (MAUP) (Waller and Gotway 2004) and very high local risks may result from the occurrence of a single case in a low population area. Moreover, some municipalities have mosquito abatement programs which may vary in time and space and may explain some part of the risk distribution observed here. However, given that few of these programs are targeted towards *Culex pipiens*, the main vector of WNV in Quebec, and given the scarcity of available data on these programs mainly due to the local management of abatement programs, their impact on WNV risk distribution is currently difficult to assess.

The current data also underline the challenge of planning environmental interventions such as the geographically targeted use of larvicides for mosquito control. Given that these interventions must be implemented before competent adult vector populations arise, some degree of prediction about the potential distribution of WNV activity in mosquitoes or amplifying hosts must be obtained to plan the geographical coverage of these interventions. In absence of evidence about the distribution of entomological risk, public health authorities may want to assess risk based on the previous distribution of human cases. However, this could only be accurately done in areas where infection risk is consistent from one year to the other, thus allowing prediction of risk based on previously observed risk.

Despite the low level of spatial organization observed, this study suggests that some restricted geographic areas are more prone to the occurrence of human cases. In southern Quebec, these areas appear to correspond to the northern and southern suburbs of the island of Montreal where there are clusters of geographical units where risk is high. The clusters, which were detected in the two years with the highest case counts, suggest that in some instances environmental conditions may allow for a buildup of WNV activity that allows for increased spillover of the virus to humans in some circumscribed areas. The cluster areas typically consist of suburban neighbourhoods lined with cultivated fields. It is possible, as suggested in a previous study (Rocheleau et al. 2017a), that the interface between suburban and agricultural environments provides particularly favourable conditions for interactions among amplifying hosts, competent vectors and human populations. Targeted information campaigns about protective behaviours against mosquito bites could be

particularly relevant in these high-risk areas. Moreover, some research efforts should be directed at identifying the vector–hosts population dynamics within these areas to better understand the conditions that may favour outbreaks.

Conclusion

In this study, spatiotemporal analysis of human case data has been useful for identifying some high-risk areas, to gain some insights about risk distribution in Quebec and to formulate important hypotheses about the biology of WNV. However, human case data have limitations for assessing the geographical distribution of risk at a fine scale, guiding surveillance and planning interventions. It is still unclear whether or not the distribution of human cases, based on currently available epidemiological data, actually reflects the spatial distribution of risk, i.e., the probability of being infected by a competent mosquito at a given location. This study thus underlines the relevance of ongoing spatial epidemiological research combining entomological data, mosquito infection rates, and precisely georeferenced human infection data to accurately assess and understand the spatiotemporal risk distribution of human WNV diseases.

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Compliance with ethical standards

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Comité d'éthique de la recherche en santé de l'Université de Montréal (protocol 14-135-CERES-D) and with the 1964 Helsinki declaration and its later amendments.

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