Am. J. Trop. Med. Hyg., 84(2), 2011, pp. 234–238
doi:10.4269/ajtmh.2011.10-0134

Regional Differences in the Association Between Land Cover and West Nile Virus Disease Incidence in Humans in the United States

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Abstract. West Nile virus (WNV) is generally considered to be an urban pathogen in the United States, but studies associating land cover and disease incidence, seroprevalence, or infection rate in humans, birds, domesticated and wild mammals, and mosquitoes report varying and sometimes contradictory results at an array of spatial extents. Human infection can provide insight about basic transmission activity; therefore, we analyzed data on the incidence of WNV disease in humans to obtain a comprehensive picture of how human disease and land cover type are associated across the United States. Human WNV disease incidence in Northeastern regions was positively associated with urban land covers, whereas incidence in the Western United States was positively associated with agricultural land covers. We suggest that these regional associations are explained by the geographic distributions of prominent WNV vectors: *Culex pipiens* complex (including *Cx. pipiens* and *Cx. quinquefasciatus*) in the Northeast and *Cx. tarsalis* in the Western United States.

INTRODUCTION

West Nile virus (WNV) is the most widespread arbovirus in the world, occurring on every continent except Antarctica.[1] WNV has been found in 59 mosquito species (the majority of mosquito infections in North America are *Culex* spp.) and 284 bird species, which suggests that it is an ecological generalist compared with other arboviruses, an important factor in explaining its broad geographic distribution.[1] Since its introduction to New York City in 1999, over 29,000 human WNV disease cases have been reported in the United States, over 1,100 of which have resulted in death.[2] Accordingly, management and control of vector populations have become urgent public health activities in many areas. Environmental and demographic factors such as temperature, rainfall, land use, and human population density could be used by many agencies to identify areas of increased risk of WNV disease infection in humans to target control efforts more effectively. The importance of these factors changes from place to place, however, depending on the vector and host species present and the geographic extent or region under consideration. Identifying predictive covariates of WNV transmission should, therefore, be considered a key part of pathogen management. Numerous studies have reported associations between different land cover types and WNV disease incidence in humans,[3–6] seroprevalence or infection rates in birds[7] and wild and domesticated mammals,[8–10] and infection rates in mosquitoes.[11,12] However, the strength and direction of these correlations have varied considerably. For instance, both positive[6] and negative[9] associations with crop land cover were reported in the South Central state of Texas. Furthermore, although it is often assumed that human disease attributed to WNV (including WN fever and meningitis/encephalitis) is an urban disease in the United States, this idea has not been well-tested, and support for this generalization is mixed.[13] After reviewing the current literature, it is not clear how land cover associates with human WNV disease incidence in different regions of the country as well as in the United States as a whole. We sought to clarify this relationship by analyzing the strength and direction of the association between human WNV disease incidence and land cover at two spatial extents in the continental United States.

MATERIALS

Geographic and case reporting data were obtained from public sources. Specifically, human population size for each county in the United States was obtained from the US Census Bureau.[14] Land cover data were downloaded from the 2001 National Land Cover Database (NLCD), which partitions land cover into 16 classes: open water, perennial ice or snow, developed open space (less than 20% impervious surface), developed low intensity (20–49% impervious surface), developed medium intensity (50–75% impervious surface), developed high intensity (80–100% impervious surface), barren land, deciduous forest, evergreen forest, mixed forest, shrub, grassland, pasture, crops, woody wetlands, and herbaceous wetlands.[15] We calculated the proportion of each land cover type (excluding open water and perennial ice or snow) within each county using a geographic information system.[16] We recognize that there are compositional differences in land cover and human population between counties, but our data and that of other researchers in the field indicate that aggregating these data at a county resolution is a viable method for these analyses.[3,9,17–19]

Human disease case data (2002–2008) with a county resolution, including meningitis/encephalitis, WN fever, and other clinical/unspecified cases as defined by the Centers for Disease Control and Prevention (CDC),[20] were collated from the US Geological Survey Disease Maps webpage.[21] Alaska and Hawaii were excluded because human WNV disease cases have not been reported from these states. The average annual incidence (number of reported cases per 100,000 people) was calculated for each county over the study period. WNV meningitis and encephalitis cases (2002–2008) with a state resolution were retrieved from the CDC West Nile Statistics webpage.[2] The average annual WNV meningitis and encephalitis incidence in each state was estimated as the average annual number of cases per 100,000 individuals.

METHODS

WNV disease incidence analysis with county resolution. Correlations between the percent of each land cover type

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and average WNV disease incidence between 2002 and 2008 were calculated at national and regional spatial extents. At both extents, analysis was first performed using every land cover type independently and then repeated after combining the four developed land cover types into a single urban land cover category. We used Pearson's and Spearman's correlation coefficients as alternative measures of the association of human WNV disease incidence with different land cover types. Pearson's correlation is more precise in the case where observations are normally distributed and the correlation is approximately linear, whereas Spearman's performs better in the presence of outliers or as we observed in many of our analyses, when the distribution of observations is strongly skewed and the association is only monotonic. We used $\alpha = 0.01$ to test for the significance of the associations that we found. Support for an association between incidence and land cover type was considered to be strong if either the Pearson's or Spearman's test was significant and the other test did not disagree (i.e., was significant in the same direction or was not significant).

Because the westward spread of WNV could have caused human disease incidence to peak earlier in the Eastern United States than in Western states, we also analyzed land cover correlations based on the year in which each county reached its highest human disease incidence. We assigned each county to a peak year; however, if the same peak number occurred in more than 1 year, the peak year was considered to be the earliest year that the peak occurred. All counties in which no human WNV disease cases were reported were discarded only for this analysis on the basis that a peak year cannot be assigned to a county in which no human disease cases have been reported. Statistical analysis and determination of significance were done as in previous analyses.

Analysis of correlation between total reported WNV disease cases and WNV meningitis and encephalitis cases. Because human WNV disease cases are severely underreported, we were concerned that detected associations might result from patterns in reporting bias rather than underlying disease transmission intensity.[22,23] To address this possibility, we investigated the correlation between the WN fever cases reported in each state and WNV meningitis and encephalitis disease cases in each state for each year in the study period as well as all years in the study period combined. Such neuroinvasive disease cases are considered to be much less subject to underreporting and therefore, are a more reliable indicator of disease trends, although less precise because the number of neuroinvasive cases is relatively small.[22,23] A strong correlation between total reported WNV disease cases and neuroinvasive cases would justify the use of total case reports as a sensitive, albeit biased, indicator of changes in true incidence.

WNV meningitis and encephalitis incidence analysis with state resolution. To further reinforce our findings from the preceding analyses, we also analyzed correlations between neuroinvasive disease incidence and land cover type at both national and regional extents, aggregating cases within states. Because of the smaller sample size of the data at the state resolution, we relaxed the threshold of significance from $\alpha = 0.01$ to $\alpha = 0.05$. Significance was determined in the same way as the previous analyses.

Generalized additive model. To assess the potential confounding effects of spatial autocorrelation, we fit county-level human disease incidence data to data on land cover[15] and vector mosquito presence[24] using two different geoadditive models.[25] A geoadditive model is a generalized additive model (GAM) in which effects are assumed to vary smoothly in space. Geoadditive models have been shown to perform well in comparative analyses with simulated data[26] and can be quite robust to variation in model specification.

TABLE 1

Correlation values between human WNV disease incidence and the proportion of each land cover at a county resolution at the national extent

Land cover type	Pearson	*P* value	Spearman	*P* value
Developed, open space	−0.21	$< 2.20 \times 10^{-16}$	−0.11	1.43×10^{-9}
Developed, low intensity	−0.25	$< 2.20 \times 10^{-16}$	−0.11	5.39×10^{-10}
Developed, medium intensity	−0.18	$< 2.20 \times 10^{-16}$	−0.09	1.96×10^{-7}
Developed, high intensity	−0.12	1.40×10^{-11}	−0.04	0.034
Barren land	−0.05	0.008	−0.06	5.50×10^{-4}
Deciduous forest	−0.51	$< 2.20 \times 10^{-16}$	−0.46	$< 2.20 \times 10^{-16}$
Evergreen forest	−0.29	$< 2.20 \times 10^{-16}$	−0.32	$< 2.20 \times 10^{-16}$
Mixed forest	−0.32	$< 2.20 \times 10^{-16}$	−0.36	$< 2.20 \times 10^{-16}$
Shrub	0.03	0.06	−0.04	0.012
Grassland	0.46	$< 2.20 \times 10^{-16}$	0.27	$< 2.20 \times 10^{-16}$
Pasture	−0.28	$< 2.20 \times 10^{-16}$	−0.22	$< 2.20 \times 10^{-16}$
Crops	0.3	$< 2.20 \times 10^{-16}$	0.35	$< 2.20 \times 10^{-16}$
Woody wetland	−0.19	$< 2.20 \times 10^{-16}$	−0.11	8.69×10^{-10}
Herbaceous wetland	0.1	5.01×10^{-9}	0.14	1.01×10^{-14}

Land cover types in bold font are statistically significant.

RESULTS

Correlation values from the total WNV disease incidence analysis with county resolution at the national extent are presented in Table 1. We found human WNV disease incidence to be positively associated with crop and grassland cover, whereas it was negatively associated with all developed land cover types at this extent. Results from the peak year analysis (Table 2) agreed with these values, showing that averaging human disease incidence over the study period was not affected by the

TABLE 2

Results from peak year analysis

Land cover	2002	2003	2004	2005	2006	2007	2008	All years	Total US
Developed, open space	−	−	−	−	−	−	−	−	−
Developed, low intensity	−	−	−	−	−	−	−	−	−
Developed, medium intensity	−	−	−	−	−	−	−	−	−
Developed, high intensity	−	−	−	−	−	−	−	−	−
Barren land	−	−						−	−
Deciduous forest	−	−			−	−		−	−
Evergreen forest	−	−					−	−	−
Mixed forest		−		−	−	−		−	−
Shrub	+				+			+	
Grassland		+	+		+	+	+	+	+
Pasture	−	−	−		−	−		−	−
Crops	+	+		+		+	+	+	+
Woody wetland		−	−		−			−	−
Herbaceous wetland	−	+	−						+

All years refers to all peak year data, which excluded counties that had no reported WNV human disease cases. Total US refers to the results from the first analysis at the national extent, which did not exclude counties that had no reported WNV human disease cases. Cells marked with a minus sign are significantly negatively associated with the indicated land cover for that year. Cells marked with a plus sign are significantly positively associated with the indicated land cover for that year. Empty cells are not significantly associated with a land cover in either direction. Significance was determined if one test was significant and the other test did not disagree (i.e., was significant with the same sign or was not significant).

East to West spread of this disease. Aggregating all developed land cover types did not alter the strength or direction of the correlations found (Supplemental Table S1). We also found the number of WN fever cases and WNV meningitis and encephalitis cases to be highly correlated in all years in the study period (Supplemental Table S2). Results from the meningitis/encephalitis incidence analyses (Supplemental Tables S3–S5) agreed with the total WNV disease incidence analyses, although the correlations and *P* values were not as strong because of a decrease in sample size (county versus state resolution).

Results from the county resolution analysis at the regional extent are presented in Table 3. In the Eastern regions (Mid-South, Mid-Atlantic, New England, and Great Lakes), we found a positive association between human WNV disease incidence and developed land cover (Supplemental Figure S1), whereas in the Western regions (Upper Plains, Northwest, Southwest, and South Central), we found a positive association between human WNV disease incidence and crop or grassland cover. The GAMs (Supplemental Tables S6 and S7) explained 80.4% (with land cover) and 80.1% (without land cover) of the variation in our data.

DISCUSSION

For both WNV meningitis and encephalitis incidence rates and total WNV disease incidence rates, we found regional differences in the associations between the proportion of specific land cover types and human WNV disease incidence. In contrast to the Northeast, where we found the proportion of developed land cover to be positively associated with human WNV disease incidence, in the Western part of the country, human WNV disease incidence was positively associated with the proportion of grassland and crop land cover. Associations at the national extent were disproportionately affected by associations in the Western part of the country; this is shown by similarities in the associations in the Western regions and the national extent in contrast with the Eastern regions and the national extent.

Disease vectors are often associated with landscape because the abundance and distribution of vectors are determined by the environment.[27] In this study, we used 14 land cover classes[15] to characterize the landscape in different regions of the United States. West of the Mississippi River, the main mosquito vector of WNV is *Cx. tarsalis*, which breeds in standing water that receives ample sunlight, such as in savannas or grasslands.[28–30] The prominent WNV vector that is abundant on the East coast is *Cx. pipiens*, which is found more commonly in suburban to urban areas, mostly because it breeds in artificial containers that are often polluted or eutrophic. This species can reproduce in storm sewers and sewage treatment plants as well as in ditches and other drainage facilities that are nutrient-heavy.[28–30] *Cx. pipiens* is also found in Western urban areas; however, the majority of infections in the Western United States are in predominantly rural counties.

When we compared the preferred habitat of these mosquito species with the WNV disease-promoting land cover types in the regions in which the species are located, we found striking similarities: *Cx. pipiens* prefers urban polluted habitats and is located in regions that showed positive associations between human WNV disease incidence and urban land cover, whereas *Cx. tarsalis* prefers natural ground pools and is located in regions that showed positive associations between incidence and agricultural land cover. Because of the similarities between vector habitat and WNV disease-promoting land covers in these regions, we speculated that a regional difference in the abundance of these species is the determining factor behind the associations that we found. This conjecture was confirmed by the results of our GAMs, which show only a 0.03% difference in the deviance explained between the two models. When we included both land cover type and mosquito species presence as predictors, the model explained 80.4% of the variation in our data. However, when we include only mosquito species presence as a predictor, the model still explains 80.1% of our data, indicating that the effect of land cover type on human disease risk is primarily mediated by its effect on the vector community.

TABLE 3
Associations between human WNV disease incidence and land cover at the regional extent

Land cover	Positive	Negative
Developed, open space	Mid-South, Great Lakes, New England, Mid-Atlantic	Upper Plains, Northwest
Developed, low intensity	Mid-South, Great Lakes, New England, Mid-Atlantic	Upper Plains, Northwest, South Central
Developed, medium intensity	Mid-South, Great Lakes, New England, Mid-Atlantic	Upper Plains, Northwest
Developed, high intensity	Mid-South, Great Lakes, New England, Mid-Atlantic, South Central	Upper Plains, Northwest
Barren land	Mid-Atlantic	Deep South, Great Lakes, Southwest
Deciduous forest	None	Upper Plains, Deep South, Mid-South, Great Lakes, Mid-Atlantic, Northwest, South Central
Evergreen forest	None	Upper Plains, Deep South, Mid-South, Great Lakes, New England, Northwest, South Central, Southwest
Mixed forest	None	Upper Plains, Mid-South, Great Lakes, New England, Northwest, South Central, Southwest
Shrub	Deep South	Mid-South, Great Lakes, New England, Southwest
Grassland	Upper Plains, Northwest, South-Central, Southwest	Deep South, Great Lakes, Mid-Atlantic
Pasture	None	Upper Plains, South Central
Crops	Deep South, Mid-South, Great Lakes, Mid-Atlantic, Northwest, South Central, Southwest	Upper Plains
Woody wetland	Deep South, Mid-Atlantic	Upper Plains, Great Lakes, South Central
Herbaceous wetland	Mid-Atlantic, Southwest	Great Lakes

Regions are listed by significant positive or negative associations with specific land cover types.

To our knowledge, no previous studies have considered land cover correlations with WNV disease incidence between regions. However, some studies that looked at specific cities or regions have yielded results similar to ours. For instance, a positive association with agricultural land and negative associations with wetlands, forests, and developed land have been found previously in the Upper Plains.[5] When looking at equine WNV, deciduous forest was found to reduce the predicted infection rate in horses in the South Central region, and an increased human disease incidence and risk of death attributed to WNV was found to be associated with crop land cover in the same region.[6,9] A study in the Great Lakes region also found negative associations with agricultural land, wetland, and forest cover and a positive association with fractionated habitat, which would be comparable with our developed land cover classifications.[4] In the Mid-South, a model identified the ideal conditions for WNV vector mosquitoes to be at a Normalized Difference Vegetation Index (NDVI) value > 0.30 (indicating moderate vegetation cover).[31] This supports the positive correlation between crop land cover and human WNV disease incidence that we found in the same region, because WNV vector mosquitoes are projected to be found in the same land cover type. A study in New England also reported a positive association between urban land cover and human WNV disease incidence and a negative association between forested land cover and human disease incidence.[3] In the Mid-Atlantic, it was found that WNV antibodies in several mammal species increased as urbanization increased, consistent with the positive correlation that we report between WNV incidence and urban land cover in this region.[8] In addition to findings concerning the association between WNV incidence and land cover, many studies also report the presence or abundance of *Cx. pipiens* in Eastern regions or *Cx. tarsalis* in Western regions.[5,6,10,11,31–38] Supplemental Figure S2 has a range map of these species.[24]

A few studies have reported results that were contradictory to our findings. In the Northwest, a study found that the abundance of potential WNV vector species increased with increasing urbanization.[36] This study concentrated on the urban center of Seattle, and of the 26 sites sampled, only 4 were not classified as urban or suburban. This uneven distribution of sites along an urban gradient could contribute to the apparent contradiction with our results. In the Southwest, higher infection rates of primary mosquito vectors were found in urban areas.[11] However, high mosquito infection rates do not necessarily lead to high human disease infection rates, especially if high densities of other appealing hosts are also present in urban areas and therefore, mosquitoes are not feeding on humans (the dilution effect).[13] Another possible explanation is that increased mosquito infection rates are masked by even larger increases in the human population. When looking at equine WNV disease, a negative correlation with crops was reported in the South Central region. This study used a different land cover dataset than was used for our analyses, which could have resulted in differences in land cover classifications between the two datasets.[9] In the Deep South, two different studies found increased seroprevalence in birds as urbanization increased.[7,10] These two studies did not use a land cover dataset to classify urban or suburban land use in their respective studies: one used an urban score based on human population density and forest cover,[7] whereas the other used field observations to make land use classifications.[10] Therefore, it is possible that what they classified as urban on a small scale may not have been classified as urban in the NLCD 2001 dataset, which provides uniform land cover classifications across the United States.

In summary, we found strong evidence that human WNV disease associations with land cover differ at the regional extent. Our study shows that urban land cover is positively associated with human WNV disease incidence in Northeastern regions, whereas agricultural land, such as grassland and crops, is positively associated with disease incidence in the Western part of the country. Analyses incorporating peak year of human disease infection, as well as WNV meningitis and encephalitis disease incidence, supported these associations. Because of the different habitats present in these positive associations, we suspect that regional differences in the community of WNV-competent mosquitoes are the probable drivers behind the correlations that we report. Research aimed at succinctly defining the ranges of these mosquito species in the United States would be beneficial in further determining the validity of our speculation.

Our results suggest that the relationship between land cover composition and human WNV disease incidence should not be generalized at the national extent, and they provide supporting evidence for regional vector control programs. In short, WNV disease is not simply urban or suburban but is a disease whose transmission processes are embedded in an ecological–epidemiological system that varies across large-scale environmental gradients.

Received March 1, 2010. Accepted for publication November 1, 2010.

Note: Supplemental materials are available at www.ajtmh.org.

Acknowledgments: The authors thank Bill Reisen and three anonymous reviewers for helpful comments.

Financial support: This project was supported by NSF-EF-0723601.

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