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Statistical and visual analysis of human West Nile virus infection in the United States, 1999–2008

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ABSTRACT

Human cases of West Nile virus (WNV) infection have spread across the continental United States since the disease's first appearance in the United States in 1999. However, most WNV spatial studies to date have focused on relatively small scale urban areas. This study examines spatial autocorrelation and clustering of WNV cases from 1999 to 2008 throughout the continental United States. The data, collected by the Centers for Disease Control and Prevention (CDC) at the county level, were normalized by population, then a global Moran's I test for spatial autocorrelation was performed on both the non-normalized and normalized datasets for each year during the study period. Both datasets exhibited strong positive spatial autocorrelation for every year ($p < 0.01$). There was also a geographic pattern of high-value clustering in the northern Midwest that was unexpected. These results indicate significant clustering of human WNV cases throughout the United States, as well as an interesting unexplained regional pattern in the northern Midwest that deserves further investigation.

Introduction

Since its first appearance in the United States in 1999 (Petersen & Roehrig, 2001), West Nile virus (WNV) has spread across the continent and is approaching endemic levels, infecting over 29,000 people in less than a decade. Primarily transmitted by mosquitoes, WNV infection in humans can be deadly. Though the mortality rate is low (approximately 4.5% for neuroinvasive cases in the US, and less than 1% for all infections) over 1130 people have died in the US from WNV since 1999 (Staples, 2009). It is also believed that vector-borne diseases, such as WNV, may become more widespread in the future as suitable vector habitats spread in response to climate change (Luber & Hess, 2007). In reaction to WNV's introduction into the US and subsequent diffusion, ArboNET was created by the Centers for Disease Control and Prevention (CDC) to monitor and track WNV cases and other human arboviral diseases within the US.

Along with several other well-known viruses, such as Western Equine virus and St. Louis virus, West Nile virus is an arbovirus (arthropod-bourne virus) which involves the "transmission between vertebrate host organisms by bloodfeeding arthropod vectors such as mosquitos, ticks, sand flies, and midges" (Last, 2001; p. 92). WNV is transmitted by mosquito vectors, which bite and infect other animals, primarily birds (Herrington, 2003; Rappole, Derrickson, & Hubálek, 2000). Birds act as amplifying hosts, developing sufficient viral levels to transmit the infection to other biting mosquitoes which go on to transmit the virus to other birds and humans (Komar et al., 2001).

West Nile virus, like all viruses, is an obligate parasite and depends on the cells it infects for replication (Campbell, Marfin, Lanciotti, & Gubler, 2002; Oldstone, 1998). In mammals the virus does not multiply well, and it has been demonstrated that mosquitoes biting infected mammals do not ingest sufficient virus to become infected, making mammals dead-end infections (Hayes et al., 2005). With the possible exceptions of mother-to-child transmission and the exceptionally rare contaminated blood transfusion, human-to-human transmission is not a factor in WNV infections. This is good for infected individuals, as quarantines are not a necessary part of treatment, and it is also good for epidemiologists, as there is one less transmission variable to consider when identifying distribution patterns (Ciota et al., 2008).

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Conceptual framework

West Nile virus

Culex restuans and *Culex pipiens* (the northern house mosquito), two of the four main WNV mosquito vectors, are predominantly urban mosquitos (Ghosh, 2011). It is further believed that urban *C. pipiens* mainly bite humans while rural *C. pipiens* primarily feed on birds (Crans, 2010). Partially for these reasons, most spatial studies of West Nile virus to date have focused on relatively small scale urban areas. For example, outbreaks in the Chicago and Detroit areas were studied, and positive correlation between infection and socioeconomic factors was found (Ruiz, Walker, Foster, Haramis, & Kitron, 2007). Vector mosquito abundance was found to be spatially correlated in New York, although autocorrelation of infection rates were not examined (Trawinski & Mackay, 2008).

Strong correlation was found between human land-use and WNV infection rates among American crows in the northeastern United States (LaDeau, Calder, Doran, & Marra, 2010). Further, Rappole et al. (2000) studied the impact of migratory birds, which can act as introductory and/or amplifying hosts, on West Nile virus infections by examining migratory paths in the western hemisphere as potential paths of infection. They found various potential bird hosts that nest in the New York City area (where the first infections in the western hemisphere occurred) migrate to practically all regions of the western hemisphere at different times of the year. Rappole et al. (2000) predicted widespread WNV infection throughout North America in just a few short years. Their prediction was proven correct as WNV infection has occurred throughout North America in a manner consistent with migratory bird transport (Rappole & Hubalek, 2003).

Several studies have examined the impacts of temperature and precipitation patterns on the distribution of vector-borne diseases, finding strong relationships between weather/climate and vector habitats, especially for mosquito-borne diseases (Frumkin, Hess, Luber, Malilay, & McGeehin, 2008; Houghton, Prudent, ScottWade, & Luber, 2012). Researchers working in Indian River County in Florida found positive correlations between hydrology models and WNV infection, concluding that further study could potentially lead to successful forecast models on a national scale to predict WNV risk (Shaman, 2009). Hongoh, Berrang-Ford, Scott, and Lindsay (2012) examined *C. pipiens* (primary mosquito vector) distribution in Canada according to landscape and climate factors. Their habitat suitability models generally agreed with known occurrences, suggesting climate is a key factor in *C. pipiens* distribution. One national scale study found a potential correlation between decreased WNV infection rates and below average summer temperatures (Reisen, 2009), though it did not address spatial autocorrelation of human infections. Another study hypothesized that increasing water flow in catch basins would positively impact breeding conditions for Culex mosquitos, and alternately drought years would negatively impact mosquito populations. These impacts would in turn affect infection rates (Ghosh, 2011).

West Nile virus occurs in one of two forms: neuroinvasive and non-neuroinvasive. Neuroinvasive WNV is a potentially life-threatening class of diseases including West Nile meningitis, West Nile encephalitis, and acute flaccid paralysis. The latter (non-neuroinvasive) is a less-serious form of infection often referred to as West Nile fever, which is generally accompanied by very mild symptoms. Non-neuroinvasive symptoms are so mild that many cases are likely misdiagnosed and unreported every year (Sejvar et al., 2003).

Spatial autocorrelation

Spatial autocorrelation analysis helps determine the relationship of a variable through space. Specifically, spatial autocorrelation is a geostatistical measure that "refers to the correlation of a variable with itself through space" (Burt & Barber, 1996; p. 411). Strong spatial autocorrelation signifies that adjacent or near values of a variable are strongly related (Ebdon, 1986). An example of positive spatial autocorrelation is typically found in housing values where higher priced homes tend to be clustered or near other higher priced homes (Burt & Barber, 1996). Spatial autocorrelation was used in this study to determine if human WNV cases are spatially related throughout the United States.

Much time and effort has gone into determining which methods of detecting spatial autocorrelation are most sensitive and most accurate (Goovaerts, 2010; Haining, Kerry, & Oliver, 2010). While no one method or test has been identified as superior for every purpose or study, important limitations and considerations have been identified for common existing tests. One of the most common and widely accepted spatial statistical tests, the Moran's coefficient or Moran's I, was the test chosen for use in this study. Gaudart et al. (2007) compared various spatial statistical tests for identification of high risk zones without point source location. Both global and local variations of Moran's I were tested along with Tango's statistic, the scan statistic, and the oblique regression tree. The global Moran's I revealed only very low clustering, but the local Moran's I was the most sensitive of the three local methods tested. Methods of adjusting the Moran's I statistical test to account for population-density have also been outlined (Assuncao & Reis, 1999; Oden, 1995), however this study used a standard Moran's I test and adjusted for population-density manually as discussed below. Many of these tests have also been used for studying spatial patterns of disease (Huang, Pickle, & Das, 2008; Marshall, 1991), and the effectiveness of these methods for disease cluster identification have been positively shown.

Hypothesis and objectives

West Nile virus is a continuing problem in the United States, however, little research has been done to examine the spatial extent and relationship of WNV throughout the United States. This study seeks to contribute to this discussion by examining the spatial dynamics of WNV in the conterminous United States. Specifically, this study examines the hypothesis that human cases of WNV within the United States are spatially autocorrelated. Many studies to date have focused on WNV infection in highly urbanized areas with large populations, such as the New York City and Chicago regions (Brown, Duik-Wasser, Andreadis, & Fish, 2008; Nash et al., 2001; Ruiz et al., 2007; Shaman, 2009). Given the high population densities of such urban centers, higher infection rates are expected (Oldstone, 1998). Infections are also considered more common in densely populated urban areas primarily because they are reported by people, and in general infection rates are observed/believed to decrease with increasing distance from urban cores (Ghosh, 2011). Until now, however, it has been unclear how significant WNV infection has been in less populated regions of the country, and whether or not human cases are spatially autocorrelated across the entire continental United States.

This study had the following objectives: first, to visualize the rates of WNV infection throughout the United States, and second, to examine spatial autocorrelation of WNV across the United States at the county level from 1999 through 2008.

Materials and methods

Data

Population data were obtained from the US Census Bureau (US Census; www.census.gov). The Census Bureau makes yearly