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Delineating West Nile Virus Transmission Cycles at Various Scales: The Nearest Neighbor Distance–Time Model

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Abstract

Various approaches are used to identify West Nile virus (WNV) exposure areas, including unusual sightings of infected dead birds, mosquito pools or human cases both prospectively and retrospectively. A significant and largely unmet need in WNV research is to incorporate the temporal characterization of virus spread and locational information of the three components of transmission cycle—i.e., birds (reservoir), mosquitoes (vector), and humans (host)—on a localized scale. Exposure areas containing all three components of the WNV cycle in close proximity have higher potential to amplify an outbreak as compared to exposure areas delineated by a single component. In this paper, we introduce a novel approach, termed ‘Nearest Neighbor Distance Time’ or NNDT, to identify and retrospectively monitor WNV transmission cycles on various scales in the Twin Cities Metropolitan area of Minnesota. The NNDT model was implemented in a geographic information system using data from the period 2002 to 2006. The results indicated that 2002 and 2003 had three such WNV cycles, followed by one, two, and four respectively in 2004, 2005, and 2006. The NNDT method can be useful in locating chronically exposed areas and generating hypotheses about the transmission of WNV.

Keywords

West Nile virus; space-time model; exposure areas; spider diagrams

Introduction

Background

West Nile Virus (WNV) is a vector-borne infectious disease spreading rapidly throughout the United States and exacting a high toll in terms of human and animal lives. It is transmitted to humans and other mammals by mosquitoes which acquire the virus by feeding on infected birds (CDC 1999; Rappole et al. 2000; CDC 2002; MDH 2003). Most people infected with WNV are asymptomatic or experience only a flu-like illness. In others, the virus causes West Nile fever (CDC 1999) and in some of these cases, the infected people develop West Nile encephalitis (inflammation of the brain) or meningitis (inflammation of the lining of the brain and spinal cord), both of which can be fatal (CDC 1999; Hayes et al. 2005; Grinev et al. 2006; Hayes 2007). The geographic distribution of WNV has expanded since its discovery in Uganda in 1937 and now includes all continents save for Australia and

Antarctica (Hayes 2007). In the United States, the virus first appeared in the Bronx borough of New York in 1999 (CDC 1999) and since then, it has spread rapidly west and south, causing seasonal epidemics.

It is challenging to predict and explain the spread of WNV because it propagates via complex interrelationships between human, avian, and mosquito habitat systems, which can further be influenced by environmental, built-environment, and anthropogenic risk factors (Brownstein et al. 2002; Ruiz et al. 2004; Gibbs et al. 2006). This complexity has prompted both prospective and retrospective techniques to identify WNV exposure areas (Brownstein et al. 2002; Mostashari et al. 2003b; Theophilides et al. 2003; Ruiz et al. 2004; Bowman et al. 2005; Eidson et al. 2005; Cooke et al. 2006; Corrigan et al. 2006; Diuk-Wasser et al. 2006; Gibbs et al. 2006; Johnson et al. 2006; Tachiiri et al. 2006; Theophilides et al. 2006; David et al. 2007; Lian et al. 2007).

The prospective techniques are mainly early warning approaches based on information on a single component of the WNV transmission cycle, i.e., either infected birds or human cases. In the retrospective group, the most common approach to delineate WNV exposure areas is the use of mathematical or statistical models, relating the incidence cases of either infected dead birds or human cases to a range of risk factors. Even though the existing methods significantly advanced, our understanding of the virus transmission needs to incorporate the spatio-temporal information of the three components of the transmission cycle affecting virus spread—birds (reservoir), mosquitoes (vector), and humans (host)—in the model.

The aim of our study is to use Geographic Information Science (GIS) techniques and ecological knowledge of WNV transmission to develop an approach identifying exposure areas and transmission cycles retrospectively in their entirety (birds, mosquitoes, and humans) on various scales. We situated this research in the Twin Cities Metropolitan Area (TCMA) of Minnesota, U.S.A. (Figure 1). The virus first reached Minnesota in 2002, creating epidemiological hotspots of WNV infections in 2003 (MDH 2003), and 2007 saw one of the most severe incidences of WNV in Minnesota. The increasing occurrence of warmer and wetter falls in Minnesota suggests that mosquito lifespan may be increasing, leading to increased incidence of WNV infections in the future (MDH 2005).

The paper is organized as follows. The remaining part of this section critically reviews the existing methodologies for delineating WNV exposure areas and introduces the Nearest Neighbor Distance–Time (NNDT) method as an effective alternative. The following section describes the datasets used in this study. Then the terminology and methodology used are described. In the next two sections, respectively, we report the results and describe the computational controls used to determine the sensitivity of the technique in various scenarios. We conclude with a discussion of the implications of the results for the mosquito abatement policies in the Twin Cities, and future lines of investigation.

Existing Methodologies

The initial and the most widely used methodologies to delineate WNV exposure areas appear with the measurement of densities of WNV infected dead birds and number of dead birds per unit area (Eidson et al. 2001a; Eidson et al. 2001b; Mostashari et al. 2003a; Eidson et al. 2005). Density estimation results in a smoothed surface showing the spatial variation of local densities of points (in this case location of WNV-infected dead birds) for a user-specified search radius. Typically, regions with higher dead bird density are regarded as high-risk areas and vice versa. In a similar approach, dead crow density (DCD) is calculated from real-time surveillance data for an areal unit, such as counties, and monitored at static time slices over a specific period of time (Eidson et al. 2005). Even though these approaches

produce quick and simple maps for identifying areas of high WNV incidences, they have a number of limitations.

First, density estimation algorithms select an arbitrary cut-off radius to estimate density and identify exposure areas which have no association with the actual transmission of the virus. Second, density measurement is sensitive to the surveillance of infected dead birds reported by humans, which in turn are dependent on the confounding effects of population density and the varying level of interest of different communities to report number of dead birds. Third, the assumption of a uniform distribution of infected dead birds for density calculation does not hold for spatial units varying in size and shape, resulting in the aggregation issues of a modifiable areal unit problem (MAUP) (Fotheringham and Wong 1991). Fourth, DCD calculated for large spatial units such as counties neglects the local variation of risk. Fifth, density maps created using kernel functions show inaccuracies of results near the boundaries due to edge effects (Theophilides et al. 2003). Sixth, the density measures are only spatial methods, meaning that the temporal characterization of virus transmission is ignored. Studies using density algorithms only express time as static slices over a period. Seventh, they also do not consider the ecology of the WNV transmission cycle.

Another approach to identify WNV exposure areas for humans is to use incidence cases—either infected dead birds (Theophilides et al. 2003; Johnson et al. 2006; Theophilides et al. 2006), positive mosquito pools (Tachiiri et al. 2006), or equine cases (Corrigan et al. 2006)—as proxies for human incidence. Even though these studies advance our understanding of how to delineate WNV exposure areas, they are based on only one component (dead birds or mosquito abundance or equine cases) of the transmission cycle. For example Theophilides et al. (2003) developed a Dynamic Continuous-Area Space–Time model (DYCAST) using the nonrandom spatio-temporal interaction of dead birds only as an early warning for amplification of WNV cycles. However, the efficiency of the DYCAST model can be increased further by incorporating the space–time interaction of mosquito pools as an added parameter along with infected bird cases.

Typically, retrospective exposure models specify the incidence cases (infected birds or human cases) as the response variable, which is regressed by a set of predictor or WNV risk factors. Linear, logistic, or Poisson link functions are used to identify statistically significant relationships between the predictors and the response variable; and exposure areas are delineated based on the spatial distribution of selected predictors. Though mathematical and statistical modeling attempts to overcome some of the limitations of density estimation approach, they also have shortcomings. First, linear or logistic models assume *a priori* distribution between the WNV incidences of birds, mosquitoes, or human cases and the predictor variables which do explain the complex interactions among the components of the transmission cycle coupled with a myriad of risk factors mentioned above. Second, similar to the density-based approaches, these techniques typically center on a single host to identify WNV exposure areas, likely missing exposure areas involving all three components of the transmission cycle which have a higher potential to amplify a WNV outbreak. Third, these regression-based techniques do not incorporate the temporal characterization of virus transmission; they are only spatial models.

The literature on methodologies which take into account the spatial as well as the temporal nature of virus transmission and incorporate multi-host ecological information of WNV to identify exposure areas retrospectively is rather scant. Orme-Zavaleta et al. (2006) applied a Bayesian probabilistic relational technique to generate spatio-temporal models from heterogeneous data sources including location and dates of dead birds, positive mosquito pools, and human cases in order to investigate the nature of WNV transmission dynamics in Maryland (Orme-Zavaleta et al. 2006). The development of the NNDT model adds to the

limited number of methodologies which consider the spatio-temporal information of all three components of the WNV transmission cycle.

Materials and Methods

Data

The study used three datasets for the years 2002 to 2006. The Metropolitan Mosquito Control District (MMCD) provided the location and the date of WNV-infected dead birds (crow and blue jay) reported by the public. The raw data were later geocoded at the street level, verified, and cleaned with occasional field validation by MMCD staff.

The MMCD also provided the location of WNV-positive mosquito pools or traps designed for weekly sampling of mosquitoes of different species for viral analysis (MMCD 2004). The MMCD has three types of collection traps for mosquitoes, which are evenly distributed, in the Twin Cities Metropolitan area. The trap types are CO₂, gravid, and sweep traps. The CO₂ traps are elevated in the tree canopy and are used for collecting female mosquito samples in their host-seeking phase. Located on the ground, the gravid traps are designed to attract female mosquitoes seeking oviposition sites (i.e., places to lay eggs).

The location and the onset date of infected human cases by U.S. census zip code was provided by the Minnesota Department of Health (MDH). The WNV-infected human cases were aggregated by zip code in order to comply with the confidentiality of human health-related data and the guidelines of the University of Minnesota's Institutional Review Board (IRB). Table 1 lists these data. The IRB determined that this study (reference number 0611E96307) is exempted from the review under federal guidelines 45 CFR Part 46.101(b) category #4 including existing data, records review, and pathological specimens.

Methodology

The execution of the Nearest Neighbor-Distance-Time (NNDT) model involved the following steps: 1) calculating Euclidian distances to the nearest dead bird or mosquito pool location; 2) creating spider diagrams for these nearest neighbors centered on zip codes with human cases; 3) choosing spider webs connected to both the birds and the mosquito pools; 4) applying the temporal rule of virus transmission from one component to another; and 5) selecting spider webs for delineating transmission cycles. The following paragraphs describe each of these steps in more detail.

We calculated Euclidean distances from the centroid of zip codes with at least one WNV-infected human case to the nearest location of a dead bird and a positive mosquito pool (Table 2). The maximum, minimum, and the mean distances from the centroid of zip codes to the nearest location of a dead bird were highest in 2002 (Table 2). In Minnesota, WNV cases first appeared in 2002, and there were 102 reports of infected dead birds. This probably was an undercount because 2002 was the first year that WNV was detected in Minnesota and there was lack of general knowledge or awareness of the virus early in the year. When the number of incidences peaked in 2003, the distances dropped significantly.

The minimum and mean distances of the location of infected dead birds from the centroid of zip codes were 0.1 and 1.2 miles, respectively. Thus there was an apparent negative relationship between distance and the number of dead bird reports. For example, in 2005, there were only 60 locations of dead birds and the mean distance from the centroid of a zip code to a nearest location of a dead bird was as high as 4.7 miles. However, with the increase of dead birds reports in 2006 (479 cases), the mean distance decreased significantly to 1.8 miles. This is somewhat expected given that, all other things being equal, an increase in incidence also increases the likelihood that a human case will have a bird case nearby.

The surveillance of *Culex pipiens*, *Culex restuans*, and *Culex tarsalis* mosquito species, the main vectors of WNV transmission in Minnesota, increased from 2002 onward. Given that the traps are inspected weekly, not daily, temporal analysis of WNV-positive mosquito pools is likely to be biased. Nevertheless, the temporal resolution of a week can still be used to delineate WNV exposure areas.

In the second step, for each year, the mean distances from the centroid of zip codes to the nearest location of infected dead bird and mosquito pools were used as the cut-off distances for *spider* diagrams. A spider diagram joins a single source feature to a set of nearest similar destination features (points, lines, and polygons) based on a user-specified distance threshold. Here the centers were the centroids of zip codes with at least one WNV human case, and destination features were locations of dead birds and positive mosquito pools. Figure 2 shows an example of a spider diagram for the year 2006. Based on the mean distances, the center of the spider diagram connected six locations of dead birds and two mosquito pools by *spider legs*. The formation of a network including destination features, spider legs, and a center or centroid is called a *spider web*. Similar spider diagrams were generated for all zip codes with at least one human case from 2002 to 2006. It is also important to note that since the distances calculated by the NNDT technique were “local” they were sensitive to sub-regional variations in WNV incidence.

In the third step, the spider diagrams were categorized into three groups: spider diagrams connected to both the locations of dead birds and mosquito pools, to the locations of either birds or mosquito pools, and to neither. Only the first category of spider diagrams (those with both dead birds and pools) were selected for the next step.

In step four, the selected spider webs, centered on the centroids of zip codes, were further classified by the temporal thresholds of virus transmission from birds to mosquitoes, and then from mosquitoes to humans. Spider diagrams were only selected when they satisfied the temporal sequence of actual WNV transmission and when the reporting dates of the dead birds within the reach of a spider diagram (or “web”) were 10–15 days prior, and the testing dates of mosquito pools were 5–7 days before the onset date of human cases found in that zip code. These temporal thresholds are well documented components of the WNV disease cycle (Theophilides et al. 2003; Orme-Zavaleta et al. 2006; Theophilides et al. 2006). The WNV research groups at the MMCD and the MDH confirmed that these temporal windows are appropriate for capturing bird-mosquito-human dynamics because infected birds generally tend to live 10 to 14 days after being infected by the virus. Mosquitoes are capable of transmitting the virus to another animal or humans within a week after feeding on infected bird (MMCD 2002; MDH 2005).

Finally, in step five, WNV transmission cycles were delineated by drawing circles centered on the zip codes of selected spider diagrams with a radius equivalent to the distance between the furthest destination feature (birds or mosquito pools) in that particular spider web. Figure 3 shows the steps involved in the NNDT method.

Results

The NNDT method retrospectively identified WNV transmission cycles with an area ranging from 5 to 150 sq miles. To recap, NNDT calculated distance to the nearest dead bird or pool location, created spider diagrams for these nearest neighbors, and selected spider diagrams centered on zip codes, which satisfy the spatial and temporal rules used to delineate WNV transmission cycle. The years 2002 and 2003 had three WNV cycles each, followed by one and two in 2004 and 2005 respectively, and five cycles in 2006 (Table 3). We plotted all the cycles on a single map to highlight the temporal trends (Figure 4).

For the year 2002, we identified three WNV transmission cycles, all within 3 to 7 miles from the centroid of zip codes with positive human cases, and covering an aggregate area of about 255 sq miles. Per Figure 4, these cycles were located in the southwestern part of the metro area (Maple Plain, Minnetrista, Chaska, and Eden Prairie). WNV peaked in the year 2003 along with increased dead bird surveillance and testing of mosquito pools. Three local WNV cycles were delineated within 1 to 3 miles from the zip codes with human cases. Compared to 2002, the 2003 cycles were much more intense and localized, given that there were 44 dead birds, 381 positive mosquitoes, and 7 human cases within an area of approximately 90 sq miles. They were also centered on the densely populated areas of Minneapolis, South St. Paul, Golden Valley, and Edina).

There were no spatial overlaps of transmission cycles in 2002 and 2003 because WNV activities shifted from the less populated suburban areas to the more densely populated urban areas. There were two possible reasons for this spatial shift. The first reason could be attributed to the habitat characteristics of different mosquito species. According to the MMCD pool inspection reports there was a significant increase in *Culex tarsalis* mosquitoes in 2002, which were typically found in the open prairie grasslands and dry short grasses common in the rural and suburban southwest metro. This increased vector population likely led to the formation of WNV transmission cycles in the area. Conversely, in 2003, there were more *Culex restuans* species, which were predominantly found in urban areas. This led to the delineation of WNV transmission cycles in the urban areas of Minneapolis and St. Paul. Therefore the increase of abundance of *Culex restuans* over *Culex tarsalis* resulted in the spatial shift of the transmission cycles. The second reason lies with the surveillance system. By 2003, public awareness of WNV in Minnesota was widespread, in part due to the news in the local media along with advertisements and precautionary measures issued by MDH. Greater awareness could create a higher rate of reporting of dead birds, which could increase the number of dead bird locations in areas of greater population (i.e., urban areas). In addition, MMCD increased the frequency of testing of mosquito-breeding sites for WNV infection between 2002 and 2003.

Only one WNV transmission cycle was observed in 2004 in North Saint Paul. This particular cycle differed from the previous cycles. It affected an area of 5 sq miles only, and the virus was transmitted from infected birds (8) to mosquitoes (25) and finally to humans (2) (Location A in Figure 4). The Euclidean distances from the human case (centroid of the zip code) to the nearest dead bird was approximately 0.35 miles and 1 mile to the WNV positive mosquito pool. Identification of a transmission cycle in such a small area could be useful in investigating the potential causal factors of WNV infection and the social and environmental characteristics determining WNV incidence, such as land use, population characteristics, presence of stagnant water features, and catch basins.

The WNV cycles identified in 2005 and 2006 shared similarities with those of 2003. The two 2005 cycles were similar in that they were in urban areas; 17 dead birds, 35 infected mosquitoes and 4 human cases were found. In 2006, five WNV transmission cycles had a total area of about 130 sq miles and were similar to the 2003 cycles in that they were smaller and more intense than in other years. The Euclidean distances of dead birds and positive mosquito pools from the human cases at the centroid of the zip codes were all within 1 to 3 miles and had a total of 102 infected dead birds, 1129 infected mosquitoes, and 8 human cases. Like those of 2003, the 2006 cycles were in the urban areas of Brooklyn Park, Minneapolis, Richfield, and South Saint Paul.

Trend analysis of the WNV transmission cycles from 2002 to 2006 indicated that in spatial terms, after 2002, the location of the cycles shifted from the suburban western and southwestern TCMA to the densely populated areas near the core cities of Minneapolis and

Saint Paul. The South Saint Paul region was identified as an exposure area for three years (2003, 2005, and 2006) (Location B in Figure 4), and thus it is an important location for further investigation.

In terms of temporal dynamics, reporting of dead birds after the onset of a human case dropped significantly; on average the number of dead birds reports declined from 12 cases before to one or no cases after the human onset date. This was likely because of a localized reduction in bird population due to either bird die-offs or migration, leaving mosquitoes to feed on dead-end hosts such as humans and other mammals, especially horses. There was also evidence that the WNV cycle reached its peak 10-15 days prior to the onset of human illness, and by the time humans developed WNV symptoms, the transmission of virus was disrupted in that area due to a lack of a substantial number of infected birds.

Sensitivity Analyses

The preceding discussion highlighted the methodology and the interpretation of results obtained from the Nearest-Neighbor-Distance-Time (NNDT) model in the study area. We performed a series of computational controls to investigate the behavior of the NNDT technique in different scenarios, focusing on randomization tests and an examination of the assumptions as a form of model validation.

Randomization Test

We conducted randomization tests by shuffling the locations and the reporting dates of WNV infected dead birds, positive mosquito pools, and human cases. For both the processes of time and place shuffling, we expect to lose any kind of spatial pattern and correlation in the distribution of each of the components, relation between the proximity of one component to another, and the temporal sequence in the reporting of WNV infected dead birds, mosquitoes, and humans. Given that NNDT primarily considers the non-random spatial and temporal distribution of the three main components, it should not identify any WNV transmission cycles from the random data.

In our test, we randomized the locations of dead birds, mosquitoes, and human cases but kept their reporting dates the same. We generated a data-set by randomly choosing the locations for each of the components while keeping the number of incidences the same for a particular year. For example, the generated dataset for the year 2003 had random locations of 285 dead birds, 4 WNV positive mosquito pools, and 26 infected human cases. Figure 5 presents a comparison of the application of NNDT to a real and a random dataset for 2003. Part A represents the results of NNDT on the real data, with three WNV transmission cycles. Part B shows the results obtained from the noisy data. The NNDT methodology halted at step 3, where the spider diagrams centered on centroids of zip codes with at least one human case did not connect to the locations of dead birds and the mosquito pools based on the distance thresholds computed in step 1. Hence no transmission cycles were identified for this particular dataset.

Similar results were obtained from other datasets for the years 2002, 2004, 2005, and 2006. The NNDT failed at step 3 or 4, where temporal rules were applied to the selected centroids joining both the locations of birds and the mosquito pools. The selection of zip codes were refined further if, in a particular spider web, the reporting dates of dead birds were 10-15 days prior and the mosquito pools were 5-7 days earlier than the reporting dates of human cases assigned to the centroid of zip codes. Comparing the results of the random to the real datasets, it appeared that chance played little part in identifying WNV transmission cycles by the NNDT technique.

We next tested the temporal aspect of the NNDT model by randomizing the reporting dates of dead birds, infected mosquito pools, and human cases while keeping their spatial locations the same. As expected, the NNDT will not detect any WNV transmission cycles from the scrambled datasets because the temporal sequence of virus transmission from birds to mosquitoes and then to humans will be lost. Figure 6 shows the outcome of NNDT when applied to a real and a randomized data-set for 2002. Based on the spatial rules only, the NNDT technique identified three spider centers or centroids of zip codes connecting to the destination features of dead birds and mosquito pools for both the real (Part A) and the scrambled (Part B) dataset. As shown in Part A, all three centroids fulfilled the temporal rules, and we can delineate WNV transmission cycles centered on those centroids. However, Part B shows that even when we have same centroids selected, the failure to satisfy the temporal rules did not allow the formation of any WNV transmission cycles.

Finally, we randomized the locations of birds, mosquito pools, and human cases, as well as their reporting dates for the years 2002 to 2006. The NNDT approach did not find any transmission cycles. The methodology either did not find any centroids of zip codes connecting the locations of dead birds and mosquito pools or did not satisfy the temporal rules. These tests indicate that the NNDT methodology is robust, and the delineation of transmission cycles based on spatial and temporal rules did not arise by chance in the case examined here.

Modification of the Assumptions

There are two key assumptions of the NNDT model. To calculate the distance between the locations of a human case to the nearest location of an infected dead bird, we assumed that the human cases were reported at the centroid of the zip codes. This was meant to satisfy the human health data confidentiality requirement. Then, to compute the cut-off distances to draw the spider diagrams, we also assumed that the *mean* of the distances between the zip codes and the nearest location of dead birds and mosquito pools was an appropriate distance indicator. The following sections describe scenarios for which these assumptions were modified.

Varying the Locations of Human Cases—To investigate the sensitivity of NNDT method, we repeated the calculations with human cases reported at several random locations within a particular zip code. This was carried out by running the NNDT technique ten times for each year from 2002 to 2006.

We calculated the average distances to the nearest location of infected dead birds and mosquito pools from the location of human cases aggregated at random points in the zip codes. We then used these distances to draw spider diagrams for birds and mosquito pools from the respective random points. The results of distance calculations are summarized in Table 4. Except for 2005, the mean distances to the nearest location of dead birds and mosquito pools computed from the random locations of human cases located in the reported zip codes were within 1 mile. The averages computed for 2006 had the smallest range of 0.62 miles and 0.63 miles to the locations of dead bird and mosquito pools, respectively.

Figure 7 depicts the error plot of the distances computed from the ten random location of human cases and the nearest location of a dead bird and a mosquito pool in 2006. Each vertical line shown represents one nearest neighbor distance calculation with maximum (top cap), mean (solid dot), and minimum (bottom cap) values. The solid and dashed horizontal lines are the average, maximum, and minimum values of distances calculated from the centroid of the zip code. For all the runs with random locations, the mean distances were very similar to the value calculated from the centroid of zip codes. This was true for the bird as well as mosquito pool locations. The small changes in the averages calculated from

random points are likely to have little or no effect on the size of spider diagrams and, hence, the delineation of transmission cycles.

As shown in Table 4, the range of average distances to the nearest location of infected dead birds in 2005 was 2.8 miles and to mosquito pools 2.2 miles. Figure 8 shows two error bar plots for the distances calculated from 10 random locations of human cases to dead birds and mosquito pool locations in 2005. For the dead birds, only two out of the 10 averages were within a mile from the average distance calculated from the centroid of zip codes. For the mosquito pools, six averages were within a mile from the actual average distance. Such variation in the average distances calculated from the random points will likely influence the size and location of spider diagrams and, eventually, the delineation of WNV transmission cycles. Comparing the results of 2005 to other years, we found two plausible reasons for such wide variation. First, there were far fewer WNV incidences in 2005 as compared to other years. Second, the zip codes reported with at least one WNV infected human case in 2005 covered a bigger area than did the zip codes with reported human cases in other years. Hence we can conclude that the NNDT methodology is sensitive to the number and density of infected cases. The technique will also have better results if the aggregating units for the human cases are smaller in size.

Varying the Distance Indicator—We also analyzed the results of NNDT when maximum and minimum distances were used between the centroid of zip codes and the location of infected dead birds and positive mosquito pools. The findings were compared to those obtained with mean distances.

The NNDT identified zero transmission cycles when the distance between the location of infected dead birds, positive mosquito pools, and human cases at the centroid of the reported zip codes was minimum. This result was consistent across all years in that none of the centroids or spider diagram centers connected both the destination features (birds and mosquitoes) and hence halted the NNDT methodology at step two.

Using the maximum distance as the cut-off to draw spider diagrams increased almost all the delineated WNV transmission cycle in size. This was true for the years 2004, 2005, and 2006, while in 2002 and 2003, the areas of two transmission cycles remained the same. The length of the spider legs for the bird and mosquito spider diagram increased too, connecting more dead birds and mosquito pools located further away from the centroid of the zip code with at least one infected human case. This did not necessarily result in either more transmission cycles or larger areas of transmission, primarily because the reporting dates for dead birds and mosquito pools did not satisfy the temporal conditions; they fell outside the 10 to 15 days for dead birds and 5 to 7 days for mosquito pools. Thus, if we exclude the destination features which did not satisfy the temporal rules, the structure of the spider diagrams and the resulting WNV transmission cycle resembled those delineated using the mean distances.

Using the maximum distance as a threshold resulted in more centroids of zip codes fulfilling the spatial rule of NNDT by connecting to both the locations of infected dead birds and positive mosquito pools in 2004, 2005, and 2006. However, these new centroids did not meet the temporal criteria for reporting dates.

To sum up, using minimum distance threshold did not identify any transmission cycles. Using maximum distance did result in more spider webs with both dead birds and mosquito pools but it did not satisfy the temporal criteria of the NNDT model.

Conclusion

We demonstrated the use of NNDT as a new approach to delineate WNV exposure areas. The Nearest-Neighbor-Distance-Time model uses geographic information techniques and the ecology of the virus to retrospectively delineate transmission cycles as exposure areas in their entirety, including dead birds, mosquito pools, and human cases. The NNDT methodology takes into account the distance–time interaction and the sequence of virus transmissions from one component to another. As such, this approach improves upon the use of arbitrary “critical” density measures, goes beyond the use of clusters of a single component of the WNV transmission cycle, addresses in part the Modifiable Areal Unit Problem (MAUP) problem, and provides more flexibility in some respects than statistical models based on *a priori* relationships (although it does not address multivariate causality in the way statistical models do). More broadly, NNDT demonstrates how examining distances among the locations of infected dead birds, positive mosquito pools, and infected human cases infuses a “local” dimension to the “global” knowledge of the time required for the virus to be transmitted from one component to another in the cycle.

The results obtained with NNDT provide evidence that dead bird reports are an essential part of the delineation of WNV cycles on a localized scale. In the Twin Cities Metropolitan area, the cycle peaked 10–15 days prior to the onset of human illness, a period which was consistent with the epidemiology of the virus transmission from bird to mosquito and then to human. Temporal analysis of the delineated cycles at local scales also showed evidence of substantial reduction in the reporting of dead birds after the 10-to-15-day window, due to a localized reduction in bird population or a migration or both. This indicated a reduction in amplification activities due to a lack of an abundant reservoir (bird population) and cessation of virus proliferation with the onset of human illness.

These findings can influence remediation and control strategies. For example, preventive strategies such as insecticide spraying may be best concentrated during the temporal window of 10–15 days after WNV-infected dead birds have been reported, because by the time humans develop WNV symptoms in an given area, the risk of further amplification of WNV disease may have subsided and widespread spraying of insecticide will have little or no effect at that time. This will also lead to more efficient allocation of resources. Further, measured use of insecticides and pesticides will balance the need for mosquito eradication with the desire to limit the negative environmental impacts from insecticide usage.

Delineation of WNV cycles at local scales can also be used to develop hypotheses related to the disease spread and thus advance our understanding of the complexity of avian-mosquito-human environmental systems on a micro scale. The NNDT methodology, for example, found that the WNV transmission cycle in North Saint Paul in 2004 remained active for 12–16 days prior to the date of human illness and then subsided with a substantial decrease in dead bird reporting. These dynamics point to the need to investigate the feeding behavior of mosquitoes and their habitat systems. The delineation of WNV cycles and their components at a local scale helps such localized investigations by prompting questions such as “Why did a WNV cycle occur here?” or “What environmental and neighborhood characteristics catalyze the formation of WNV transmission cycles?”

Despite the success of the NNDT methodology, certain issues require further research and are worthy of a mention here. The NNDT technique is sensitive to the number of incidences, as noted above for the year 2005. It performs efficiently with a higher number of infected dead birds or mosquito pools or human cases and, as such, it is dependent upon the efforts of surveillance programs. Also, the technique will have better results if the human cases are obtained at much finer spatial resolution than zip codes.

This paper mainly concentrated on developing a novel technique to retrospectively visualize and delineate WNV transmission cycles in its entirety at various scale. A critical future research direction includes investigation of the complex avian-mosquito-human and environmental interrelationships which contribute to WNV high-risk exposure areas. We also need to improve our understanding of the extent to which NNDT can be applied to other WNV-prone areas in the world, given that the characteristics of transmission cycle and surveillance programs vary significantly from one region to another.

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Figure 1.
The study area.

Figure 2.
Example of a spider diagram, 2006.

Figure 3.
Schematic diagram of the Nearest-Neighbor-Distance-Time (NNDT) methodology.

Figure 4.
Location of WNV transmission cycles delineated at local scales, Twin Cities Metropolitan Area of Minnesota, 2002-2006.

Figure 5.
Comparison of results obtained with the NNDT applied to a real and a randomized dataset (2003).

Figure 6.
Comparison of NNDT when applied to a real vs. a temporally randomized data set (2002).

Figure 7. Error plot of the distances computed from the 10 random locations of human cases and the nearest location of a dead bird and a mosquito pool (2006).

Figure 8.

Error bar plots for the distances calculated from 10 random locations of human cases to dead bird and mosquito pool locations (2005).

Table 1

Description of the data.

Year/Component	2002	2003	2004	2005	2006	Resolution	Temporal Scale, Resolution	Attributes
Dead birds	102	285	125	60	479	Point	2002-2006, Day	X/Y, Date reported
No. of Mosquitoes (No. of Pools)	1101 (5)	1388 (17)	26 (2)	161 (14)	1549 (90)	Point	2002-2006, Day	X/Y, Collection date, Trap type, Species, No. of mosquitoes
Human Cases	13	26	6	7	15	Zip Code	2002-2006, Day	Onset date

Table 2

Nearest-neighbor Euclidean distances from the centroid of zip codes with at least one WNV-infected human case (in miles).

Year	Distance to Nearest Dead Birds			Distance to Nearest Positive Mosquito Pool		
	Maximum	Minimum	Mean	Maximum	Minimum	Mean
2002	14.9	0.93	4.35	21.4	1.5	11.8
2003	6.2	0.1	1.2	24.9	1.2	8.1
2004	6.2	0.4	3.1	23.6	1.0	13.7
2005	8.1	0.7	4.7	16.2	5.6	10.3
2006	11.8	0.9	1.8	11.2	1.1	3.7

Table 3

West Nile Virus incidences at a micro-scale, 2002-2006.

Year	No. of Cycles	No. of infected dead birds	No. of positive Mosquitoes	No. of positive Human Cases	Range of Cycle area in sq miles
2002	3	5	1705	5	50 to 150
2003	3	44	381	7	5 to 50
2004	1	8	25	2	5
2005	2	17	35	4	50 to 150
2006	5	102	1129	8	7 to 35

Table 4

Comparison of statistics of mean distance thresholds computed from random locations of human cases and centroids of zip codes to the locations of infected dead birds (Bird) and positive mosquito pools (Mosq).

Run	2002		2003		2004		2005		2006	
	Bird	Mosq	Bird	Mosq	Bird	Mosq	Bird	Mosq	Bird	Mosq
R1	4.35	11.18	1.86	8.70	3.42	13.67	4.97	10.56	2.49	4.35
R2	4.35	11.18	1.24	8.08	3.42	14.91	4.97	10.56	1.86	4.35
R3	3.73	11.81	1.24	8.08	2.49	13.67	4.35	11.18	2.49	3.73
R4	3.73	11.81	1.86	8.39	2.49	13.05	5.59	10.56	2.49	3.73
R5	4.35	11.18	1.24	8.08	3.11	14.29	6.21	9.94	2.49	4.04
R6	4.97	11.81	1.55	8.08	3.73	14.29	4.66	11.18	1.86	3.73
R7	4.35	11.81	1.86	8.08	3.42	14.91	4.97	9.01	2.17	3.73
R8	4.35	11.81	1.24	8.08	3.42	13.67	3.42	9.94	1.86	3.73
R9	4.97	11.18	1.55	7.46	3.11	13.05	4.35	9.32	1.86	3.73
R10	4.35	11.81	1.55	8.39	2.49	13.67	4.97	10.56	2.17	4.04
Centroid	4.35	11.81	1.24	8.08	3.11	13.67	4.66	10.25	1.86	3.73
Range	1.24	0.62	0.62	1.24	1.24	1.86	2.80	2.17	0.62	0.63