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The drivers of West Nile virus human illness in the Chicago, Illinois, USA area : fine scale dynamic effects of weather, mosquito infection, social, and biological conditions

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Full Title:	The drivers of West Nile virus human illness in the Chicago, Illinois, USA area : fine scale dynamic effects of weather, mosquito infection, social, and biological conditions
Short Title:	Fine scale drivers of West Nile virus human illness in Chicago
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Abstract:	West Nile virus (WNV) has consistently been reported to be associated with human cases of illness in the region near Chicago, Illinois. However, the number of reported cases of human illness varies across years, with intermittent outbreaks. Several dynamic factors, including temperature, rainfall, and infection status of vector mosquito populations, are responsible for much of these observed variations. However, local landscape structure and human demographic characteristics also play a key role. The geographic and temporal scales used to analyze such complex data affect the observed associations. Here, we used spatial and statistical modeling approaches to investigate the factors that drive the outcome of WNV human illness on fine temporal and spatial scales. Our approach included multi-level modeling of long-term weekly data from 2005 to 2016, with weekly measures of mosquito infection, human illness and weather combined with more stable landscape and demographic factors on the geographical scale of 1000m hexagons. We found that hot weather conditions, warm winters, and higher MIR in earlier weeks increased the probability of an area of having a WNV human case. Higher population and the proportion of urban light intensity in an area also increased the probability of observing a WNV human case. A higher proportion of open water sources, percentage of grass land, deciduous forests, and housing built post 1990 decreased the probability of having a WNV case. Additionally, we found that cumulative positive mosquito pools up to 31 weeks can strongly predict the total annual human WNV cases in the Chicago region. This study helped us to improve our understanding of the fine-scale drivers of spatiotemporal variability of human WNV cases.
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Opposed Reviewers:	
Response to Reviewers:	Reviewer #1: Peer review report on PLOS ONE manuscript " The drivers of West Nile virus human illness: fine scale dynamic effects of weather, mosquito infection, social, and biological conditions", (Manuscript number PONE-D-19-34216). Recommendation: Minor Revision Comments to Authors: This manuscript analyzes the available long-term data of mosquito infection rates, West Nile virus human cases and weather variables from 2005 to 2016 combined with landscape and demographic characteristics of two Illinois counties of the Chicago

region in order to evaluate relationships between the factors on fine temporal and spatial scale and identify the drivers that potentially affect the presence of human WNV illness and may act as early warning predictors.
The paper is well written with a well-organized text, the data were analyzed using multi-level statistical modeling approaches and the findings are sufficiently documented and the results are valuable for a better understanding of the fine-scale drivers of spatiotemporal variability of WNV human case prevalence in an urban environment such as in the study area.
Although numerous published studies that have shed light on factors that affect WNV transmission in an area, the knowledge regarding the influence of climatic variables in correlation with the data from the entomological surveillance and the number of WNV human cases, is still limited.
For that reason, the paper makes a substantial contribution to the literature and is therefore recommended for publication in PLOS-ONE after minor revision taking into account the following general or specific comments.
•Thank you for your comments and your feedback!

General comments

The study uses and analyzes the 10-year data (2005 to 2014) from Cook and DuPage counties in the Chicago, Illinois region and the accuracy of the predictions of the developed model tested with the data of the same specific area.
However, according to the literature, it is well known that models predicting the WNV transmission and human WNV infections do not always have the same accuracy when applied to other areas with different mosquito fauna, weather conditions and/or geomorphological and demographic characteristics. Therefore, we consider that the study area should also be mentioned in the title.
•Thank you for the suggestion, we have made that change

Please comment and, if necessary, provide an adequate justification in the manuscript, for the reason that in this work were note included data from passive or active monitoring of WNV presence in birds and equids, which are considered by several authors as important prediction factors of the presence and spread of WNV virus in an area.
•We have added a statement (145-147) that the avian and equid surveillance programs were not consistent across the time period, and added a discussion section (467-474) about the point.

Specific comments

Line 170 of the manuscript: If available, please provide information on the species of Culex mosquitoes that have been tested for WNV presence as the vectorial competence of different species may vary significantly for WNV transmission to humans.
•We agree that is an important point; we have added some information as to common species in the region.

Line 179 of the manuscript: Please add a bibliographical reference in the reference section for the MIR estimation tool by Biggerstaff, 2006.
•Thank you, corrected

Line 188 of the manuscript: Please provide a definition and some additional information about the category of "probable cases of WNV" that were also included in the study along with the "confirmed cases" because the symptoms of infection by the West Nile vary in severity, with the mild forms can be easily confused with flu symptoms and usually go unreported.
•We have added the information. The difference between probable and confirmed cases is confirmatory testing by either IDPH or CDC; all cases had positive diagnostic results and clinical signs during the likely transmission season.

	Lines 578-580 of the manuscript: Please, correct Reference no 39 by adding the name of the journal, volume number and pages numbers. Messina JP, Brown W, Amore G, Kitron UD, Ruiz MO. West Nile Virus in the Greater Chicago Area: A Geographic Examination of Human Illness and Risk from 2002 to 2006. URISA Journal 2011;23: 5-18. •Corrected Reviewer #2: Dear authors, This is a well written paper that deals with the determination of factors affecting the spatiotemporal variability of WNV cases in humans through identification of the fine scale drivers of WNV transmission in an urban area with a repeated history of WNV outbreaks. The findings are very interesting since they include multi-level modeling of weekly data from over a decade and they extend our knowledge in the correlation of variables related to temperature, precipitation, mosquito infection, land cover, and demographic characteristics with the probability of an area having a WNV case or not. •Thank you Further down please consider some comments of minor importance that may benefit the manuscript. It seems that the infection status of avian population, as primary reservoirs of WNV, and equids, as dead-end hosts, were not included among the tested variables for modeling structure. Please note that these are critical factors implicated in the WNV transmission in order to develop predictive models. As mentioned in the introduction, public health surveillance for WNV involves collection and testing of dead birds suspected to have died of WNV, testing of sentinel chickens or of wild birds captured for this purpose and reporting of cases of equine illness. Could you please justify this data gap in the model structuring? Is there any surveillance system for infected avian and equids population in the study area? In the “Introduction” you may add any relevant literature data where bird and/or equine infection rate were used for development of models predicting WNV transmission in humans. Also, in lines 440-459 of the manuscript, you could mention the fact that avian and equids infection status was not considered as a factor for prediction of WNV cases in humans in the study area. •We have added a statement as to the inconsistent application of avian and equid surveillance in this region (145-147), and given more information about that surveillance in the discussion (467-474), including references to models using these data types. According to the best multivariable model that was used, the proportion of open water was negatively associated with the probability of WNV cases. Also, as mentioned in the discussion, a negative association of precipitation and WNV cases was observed and this indicates that dry and hot weather conditions would increase the probability of an area being positive for a WNV case. Instead, it is supposed that high rainfall and high percentage of water bodies in an area may favor mosquito population by increasing their breeding sites, and therefore may lead to increased WNV cases in humans. Hence, a positive correlation between precipitation and water bodies with WNV cases in humans is anticipated. Please comment. •Open water is classified as areas in which any aquatic vegetation is submerged, as opposed to woody or herbaceous wetlands. This is not likely to be stagnant water of the type used by Culex mosquitoes for breeding. Therefore, the negative association between proportion of open water and WNV cases is most likely due to the fact that open water, as defined, does not favor the mosquito population. We have noted this in the discussion (434-438).
Additional Information:	
Question	**Response**

Financial Disclosure Enter a financial disclosure statement that describes the sources of funding for the work included in this submission. Review the submission guidelines for detailed requirements. View published research articles from *PLOS ONE* for specific examples. This statement is required for submission and **will appear in the published article** if the submission is accepted. Please make sure it is accurate. **Unfunded studies** Enter: *The author(s) received no specific funding for this work.* **Funded studies** Enter a statement with the following details: • Initials of the authors who received each award • Grant numbers awarded to each author • The full name of each funder • URL of each funder website • Did the sponsors or funders play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript? • **NO** - Include this sentence at the end of your statement: *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.* • **YES** - Specify the role(s) played. * typeset	This publication was supported by Cooperative Agreement #U01 CK000505, funded by the Centers for Disease Control and Prevention (RLS). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Competing Interests Use the instructions below to enter a competing interest statement for this submission. On behalf of all authors, disclose any competing interests that could be perceived to bias this work—acknowledging all financial support and any other relevant financial or non-financial competing interests. This statement **will appear in the published article** if the submission is accepted. Please make sure it is	The authors have declared that no competing interests exist.

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Ethics Statement Enter an ethics statement for this submission. This statement is required if the study involved: • Human participants • Human specimens or tissue • Vertebrate animals or cephalopods • Vertebrate embryos or tissues • Field research Write "N/A" if the submission does not require an ethics statement. General guidance is provided below. Consult the submission guidelines for detailed instructions. **Make sure that all information entered here is included in the Methods section of the manuscript.**	This project was approved by the Institutional Review Boards of the University of Illinois Urbana-Champaign (#08686) and the Illinois Department of Public Health (#0950). Consent was not obtained because data were analyzed anonymously.

Format for specific study types **Human Subject Research (involving human participants and/or tissue)** • Give the name of the institutional review board or ethics committee that approved the study • Include the approval number and/or a statement indicating approval of this research • Indicate the form of consent obtained (written/oral) or the reason that consent was not obtained (e.g. the data were analyzed anonymously) **Animal Research (involving vertebrate animals, embryos or tissues)** • Provide the name of the Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board that reviewed the study protocol, and indicate whether they approved this research or granted a formal waiver of ethical approval • Include an approval number if one was obtained • If the study involved *non-human primates*, add *additional details* about animal welfare and steps taken to ameliorate suffering • If anesthesia, euthanasia, or any kind of animal sacrifice is part of the study, include briefly which substances and/or methods were applied **Field Research** Include the following details if this study involves the collection of plant, animal, or other materials from a natural setting: • Field permit number • Name of the institution or relevant body that granted permission	
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A Data Availability Statement describing where the data can be found is required at submission. Your answers to this question constitute the Data Availability Statement and **will be published in the article**, if accepted. **Important:** Stating 'data available on request from the author' is not sufficient. If your data are only available upon request, select 'No' for the first question and explain your exceptional situation in the text box. Do the authors confirm that all data underlying the findings described in their manuscript are fully available without restriction?	
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and contact information or URL). • This text is appropriate if the data are owned by a third party and authors do not have permission to share the data. * typeset	
Additional data availability information:	

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To the editor:

Please consider our revised manuscript, "**The drivers of West Nile virus human illness in the Chicago, Illinois, USA area: fine scale dynamic effects of weather, mosquito infection, social, and biological conditions**", for publication in *PLoS One*. This manuscript describes original research involving the modeling of human cases of West Nile Virus by using fine scale measures that may affect human risk. This work should appeal to a broad audience, as it both identifies information of importance to public health and describes relationships between spatial factors and human risk of infection that can inform future studies into human exposure.

We are unable to share human illness data as they are provided under a data use agreement with the Illinois Department of Public Health due to identifiability of cases at this spatial resolution. Requests for data may be sent to the Illinois Department of Public Health, Infectious Diseases.

Thank you,

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The drivers of West Nile virus human illness in the Chicago, Illinois, USA area: fine scale dynamic effects of weather, mosquito infection, social, and biological conditions

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Short title: Fine scale drivers of West Nile virus human illness

Abstract

West Nile virus (WNV) has consistently been reported to be associated with human cases of illness in the region near Chicago, Illinois. However, the number of reported cases of human illness varies across years, with intermittent outbreaks. Several dynamic factors, including temperature, rainfall, and infection status of vector mosquito populations, are responsible for much of these observed variations. However, local landscape structure and human demographic characteristics also play a key role. The geographic and temporal scales used to analyze such complex data affect the observed associations. Here, we used spatial and statistical modeling approaches to investigate the factors that drive the outcome of WNV human illness on fine temporal and spatial scales. Our approach included multi-level modeling of long-term weekly data from 2005 to 2016, with weekly measures of mosquito infection, human illness and weather combined with more stable landscape and demographic factors on the geographical scale of 1000m hexagons. We found that hot weather conditions, warm winters, and higher MIR in earlier weeks increased the probability of an area of having a WNV human case. Higher population and the proportion of urban light intensity in an area also increased the probability of observing a WNV human case. A higher proportion of open water sources, percentage of grass land, deciduous forests, and housing built post 1990 decreased the probability of having a WNV case. Additionally, we found that cumulative positive mosquito pools up to 31 weeks can strongly predict the total annual human WNV cases in the Chicago region. This study helped us to improve our understanding of the fine-scale drivers of spatiotemporal variability of human WNV cases.

Introduction

West Nile virus (WNV), a mosquito-borne zoonotic disease, was first identified in the United States in the summer of 1999 in New York City [1]. The mosquitoes of several *Culex* species are the primary enzootic and bridge vectors for the transmission of WNV, and several bird species are known to contribute in the amplification of the virus [2–4]. Since its first successful invasion in New York, WNV quickly adapted to the local populations of *Culex* vector mosquitoes and avian populations and rapidly spread throughout the conterminous United States [5,6]. The first major WNV outbreak in the United States was observed in 2002, when more than 4,150 human cases and 284 deaths attributable to WNV infection were reported to the CDC from 40 states compared to only 149 cases and 19 deaths from 10 states cumulatively during the three years from 1999 to 2001 [7]. This stirred a prompt public health response from federal, state, and local public health agencies and led to the establishment of a more robust surveillance of mosquitoes and birds to monitor and control the spread of WNV [8].

Public health surveillance for West Nile virus (WNV) involves collection and testing of *Culex* vector mosquitoes, collection and testing of dead birds suspected to have died of WNV, testing of sentinel chickens or of wild birds captured for this purpose, and reporting of cases of human and equine illness [9]. The ultimate goal of these surveillance data is to target mosquito control, and thereby reduce illness through the reduction of the number of infected vector mosquitoes, and to target educational messages to warn citizens to reduce individual exposure. One additional advantage of having a strong surveillance system in place is that the long-term data generated can be integrated with publicly available weather, landscape, and socioeconomic data and can be used effectively to identify the important drivers of WNV transmission and to develop predictive models [10,11].

Several earlier studies have identified some of the important drivers of WNV transmission in humans. These factors include prior weather conditions and landscape structure that affect the mosquito’s biological responses, the abundance and infection status of the vector mosquitoes, demographic and social characteristic of population, individual human behavior, and the level of public awareness [10–17]. For example, an analysis of 12 years of mosquito testing and human illness data in Ontario, Canada showed that, while the mosquito infection rate of one week earlier was the strongest temporal predictor of human risk of WNV, an epidemic threshold based on the cumulative positive *Culex* pools up to mid-August (week 34) can be successfully used to predict human WNV epidemics [16]. In Long Island, New York, more than 65% of forecast models based on past mosquito infection and human illness correctly predicted seasonal total human WNV cases up to 9 weeks before the first reported cases [18]. Similarly, the vector index, based on a combination of vector infection and abundance was found to be highly correlated with human WNV cases in studies conducted in Larimer County, Colorado (Fauver et al., 2015), and Dallas, Texas [19].

Weather factors are important drivers of WNV transmission due to their direct effect in mosquito biology. When compared with human WNV cases, higher than normal average annual temperatures are associated with an increased likelihood of higher WNV disease incidence, nationally and in most regions in the United States [17]. This relationship was true in Europe, too, where abnormally high July temperature was associated with higher incidence of human WNV cases [20]. The role of precipitation is often controversial and varies by study regions. For example, higher than normal precipitation was positively associated with higher human WNV cases in the eastern region of the United States, but this relationship was reversed for the western region [21]. Another study identified drought as an important driver of WNV epidemics in the United States [22]. Local landscape structures have also been associated with human WNV incidence. The important land cover variables associated with increased risks of human WNV include proximity to wetlands [23,24], higher tree density [24], irrigated and agricultural rural areas [25], urban areas characterized by higher impervious surfaces and storm sewer systems [26], and inner suburbs characterized by older houses, moderate vegetation and moderate population [27].

Apart from extrinsic factors, population structure, demographic characteristics, and individual variation also play roles in WNV epidemics [28]. As people age, especially when they have a history of hypertension and immunosuppression, their risk of WNV disease increases [29,30]. Community characteristics such as income level, the age of housing, management of sewer and drainage system, mosquito abatement practices, and public health infrastructure also determines the risk of WNV human infections [12,26].

Different spatial scales have been used in geographical analyses to identify the drivers of human risk from WNV infections. The most commonly used spatial scale in the United States is counties [17,22,31], census tracts or Zip Code Tabulation Areas (ZCTA) [12,32], census block groups [33], and buffers of varying sizes around trap locations or human cases [24]. Each of these spatial scales has its own inherent biases, as these political boundaries do not necessarily correspond to the ecological processes of the disease in question [34]. Alternatively, dividing the area into equal spaces, such as rectangular bins or hexagons, has been used to reduce some of these biases (e.g. [35]). Hexagonal grids have an additional advantage in that they reduce the edge effects, better fit curved surfaces, and have identical neighbors [36,37].

In Illinois, WNV human infections have been endemic since 2002, with annual variability in the number of cases [38]. The majority of the human WNV cases have been reported from the northeastern region, where the largest number of people in the state is congregated. A census tract level analysis in this region using human WNV occurrence data from the 2002 outbreak year identified that census tracts with lower population density, relatively close WNV positive dead bird specimens, a higher percentage of older white residents, and housing built between 1950 and 1959 were more likely to be associated with spatial clusters of WNV cases [12]. A follow up expanded this study to look at annual incidence of WNV human illness in northeastern Illinois from 2002 to 2006, with additional variables to assess the effects of rainfall, temperature and the WNV mosquito infection rate [39]. This analysis determined that white populations and housing from the 1950s were associated with increased illness in some years, but this was not consistent. Interestingly, census tracts with lower rainfall had higher rates of WNV illness, but the mosquito infection rate was not an important variable in any of the models [39].

Despite the identification of some of these potential risk factors, accurate prediction of human illness cases from WNV remains elusive at the local scale, especially as it is related to dynamic weather and mosquito infection status. Using long-term data on human WNV illness and intensive mosquito surveillance for the Chicago region, we can identify the fine scale drivers of spatiotemporal variability of human WNV epidemic in an urban environment. The overall goal of this study is to determine factors affecting the spatiotemporal variability of clinical WNV incidence in people through identification of the fine scale drivers of WNV transmission in an urban area with a repeated history of WNV outbreaks. These potential drivers include dynamic mosquito infection and weather. Our specific objectives in this study are to (i) describe the fine-scale temporal and spatial patterns of human WNV illness in the Chicago region, (ii) evaluate the temporal relationships between mosquito infection and human WNV illness, and (iii) determine the fine-scale dynamic effects of weather, land cover, mosquito infection, and demographic factors on the presence of human West Nile virus illness across time and space.

Materials and methods

This project was approved by the Institutional Review Boards of the University of Illinois Urbana-Champaign and the Illinois Department of Public Health.

The two Illinois counties of Cook and DuPage, comprising Chicago and its suburbs, were included in this study. The total area covered by these two counties is nearly 5,100 square kilometers, and the total population in 2010 was 6.1 million. These areas were selected because of the relatively high incidence of human West Nile virus illness reported from these two counties and the long-term intensive mosquito surveillance data available for this region. The temporal window included in this study was the 24-week time period from late May to late October (weeks 22 to 45), which corresponds to the timing of mosquito activity and human WNV illness, with data for the years from 2005 to 2016. The years from 2002 to 2004, during which Illinois had its first invasion from WNV, were excluded in this analysis because of the absence of mosquito testing data. Data on avian and equid surveillance were not included as these programs were not consistently applied across the time period.

We chose to summarize all variables into hexagons to provide a neutral spatial unit of consistent size and shape, which is not possible with political boundaries. For this, we overlaid hexagons measuring 1000 m in diameter on the outlines of Cook and DuPage counties to create a grid of 5,345 hexagons for the study area. Out of these, 328 were excluded after a comparison with fine scale population data from the 2010 U.S. Census indicated that there were no households on record within those hexagons. Thus, 5,017 hexagons were included in the analysis. All independent variables related to weather, land cover, mosquito infection and demography were calculated for each hexagon, as described below.

Mosquito data

Mosquito testing data from 2005 to 2016 were obtained from the Illinois Department of Public Health (IDPH) through a user agreement. The IDPH collates the data from local public health agencies and mosquito abatement districts across Illinois and maintains a statewide database for the results from WNV mosquito testing. The IDPH developed a mosquito surveillance protocol that local health and mosquito abatement districts are expected to follow in order to standardize the mosquito collection and testing across the state. In general, the local agencies collect vector mosquitoes with gravid traps, identify the sex and species of the mosquitoes, and make pools of up to 50 mosquitoes of a single species from those captured in each trap to test for the presence of WNV infection. When fewer then 50 mosquitoes are captured, a pool will consist of fewer than 50 mosquitoes. During the study period, the common tests used to identify WNV in mosquitoes included antigen assays, VecTest or the Rapid Analyte Measurement Platform (RAMP) test. Some pools were also tested by Real Time reverse transcriptase polymerase chain reaction (RT-PCR). In instances when a pool was tested using more than one type of test, only the RT-PCR results were used in the analysis. Our analysis used only the test results from pools of female *Culex* mosquitoes. Not all mosquitoes were identified to species prior to testing; however, the majority of *Culex* collected in this region belong to the species *Cx. pipiens* or *Cx. restuans* [3].

To determine the location of the mosquito traps, we used the existing latitude and longitude recorded in the IDPH database. In cases where the spatial data were missing, we geocoded the trap locations based on the address provided. Our analysis used all the trap locations recorded from 2005 to 2016 from Cook and DuPage counties in addition to any traps located within a 10 km radius from their boundaries (located within Lake, McHenry, Kane, Kendall, and Will counties). For each trap, the mosquito infection rate (MIR) was calculated by week and by year using the formula

$$1000 * \frac{\text{number of positive pools}}{\text{total number of mosquitos in pools tested}} \text{ [40].}$$

Using MIR calculations from all traps, we developed continuous surface maps for MIR for each week and year using the inverse distance weighting (IDW) interpolation technique in ArcGIS 10.1. From this interpolated surface map for each year and week, the average, minimum, and maximum MIR for each hexagon was calculated using the zonal statistics as table function in ArcGIS 10.1. A model builder platform using iteration features in ArcGIS 10.1 was used to run these processes.

Human illness data

Records of human WNV cases in Illinois were obtained from the IDPH through a user agreement. All confirmed and probable cases of WNV reported to the IDPH by medical and public health personnel for the study area were included in this study; the state of Illinois mandates reporting of WNV to local public health departments, which then report all cases to IDPH. Probable cases are those that meet clinical criteria during the season when transmission is likely to occur and meet laboratory criteria for West Nile virus by serology (IgM capture ELISA) or polymerase chain reaction, while confirmed cases are those with confirmatory test results from the IDPH or the Centers for Disease Control and Prevention. All the human WNV cases in Cook and DuPage counties reported from 2005 to 2016 were geocoded and aggregated by hexagons for each week and year. The data were converted into the binary form of presence or absence of a WNV case in a given hexagon and week.

Demographic data

The demographic variables included were total population, racial composition, housing age, and income level. The total population and racial composition included the number of White, African American, Asian, and Hispanic people at the census block level, as reported in the 2010 U.S. Census. The racial population data was converted to the percentage of White, African American, Asian, and Hispanic people in each hexagon. The income data for the block group level were obtained from the 2015 American Community Survey. Housing age was included as the proportions of housing built in different time periods, which was obtained at the block group level from the 2015 American Community Survey. We divided housing age into four different time-periods: pre-World War II houses (built before

1939), post-World War II houses (built between 1940 and 1969), houses built between 1970 and 1989, and houses built after 1990. These demographic data were processed in ArcGIS using the intersection tool to calculate a parameter for each hexagon.

Landcover data

Landcover data for the entire United States was obtained from the national landcover database (NLCD) for the years 2006 and 2011. The NLCD database is a Landsat based landcover data available at a 30 m resolution (www.mrlc.gov). The landcover raster was clipped for Cook and DuPage counties, including a surrounding 1 km buffer. From this clipped raster, the total number of pixels for each land category within each hexagon was calculated using the tabulate as area tool in ArcGIS 10.1. The proportion of each land cover category for each hexagon was then calculated by dividing the number of pixels for that category by the total number of pixels for all categories. In Cook and DuPage counties, 15 different types of landcover were available: urban areas (developed open space, developed low intensity, developed medium intensity, developed high intensity), forests (deciduous, evergreen and mixed), barren land, shrubs, grassland, pasture, cultivated crops, woody wetlands, herbaceous wetlands, and open water. The land cover data from 2006 was used to analyze the WNV cases for the years from 2006 to 2010, while the land cover data from 2011 was used for 2011 to 2016.

Weather data

Spatial weather data on daily mean temperature and precipitation from 2005 to 2016 were obtained from the PRISM Climate Group (PRISM Climate Group, Oregon State University, http://prism.oregonstate.edu). The PRISM daily data are available as spatial grids of 4 km resolution, which are calculated through interpolation and statistical techniques using point data from weather monitoring networks across the country combined with topographic data. These daily data were used to calculate the weekly temperature and precipitation. For our analysis, the weekly mean temperature was calculated by taking the average of the seven daily averages for that week, and the weekly precipitation was calculated as a sum of the daily precipitation for that week. Finally, the weekly temperature and precipitation for each year and week for each hexagon was calculated by using the zonal statistics as table function in ArcGIS 10.1. We also calculated average January temperature for each hexagon for each year from the daily data as a proxy for the winter temperature.

Statistical methods

To assess the temporal relationship between human illness and MIR, we calculated the Spearman rank correlation between the weekly MIR of 1-6 weeks lag and human cases. We repeated this analysis on the subsets of years with high numbers of WNV cases (more than 100 human cases; 2005, 2006, 2012 and 2016) and those with low numbers of WNV cases (less than 100 cases; 2007 - 2009, 2010, 2011, 2013 - 2015) to examine if the relationship between MIR and human cases varies in high and low years. We further examined the ability of the early summer (weeks 22- 27) and mid-summer (weeks 28- 33) average MIR to explain and predict the seasonal annual total WNV cases by using linear regression analysis. In addition, we assessed the ability of the cumulative positive mosquito pools up to week 28 and thereafter, added to each week's data, to find a threshold that could best explain the annual total human WNV cases. In both of these calculations, data from 2005 to 2014 were used to create a regression equation, and data from 2015 and 2016 was used to test the model.

To visualize the spatial patterns of human illness over time, we first developed choropleth maps of WNV cases. Then, we used local Moran's I method using an inclusive second order queen contiguity weight matrix in the spatial analysis software GeoDa to further identify the spatial clusters of cumulative human WNV cases from 2005 to 2016. We also examined differences in results using neighboring cells and rook contiguity weight matrix, but the results did not vary.

For the spatiotemporal statistical model, the outcome variable was the presence/ absence of a human WNV case in each hexagon for each year and week. The predictors included 32 variables related to weather, land cover, mosquito infection and demography (Table 1). The weather variables consisted of mean weekly temperature and precipitation with lags of one to four weeks. The land cover variables include 15 categories, the proportion for each hexagon of: developed open space; developed low, medium, and high intensity urban areas; deciduous, evergreen, and mixed forests; barren land; shrubs; grassland; pasture; cultivated crops; woody wetlands; herbaceous wetlands; and open water. The mosquito infection data included the average MIR with lags of one to four weeks for each hexagon for each year and week. Demographic variables for each hexagon included the proportion of White, African American, Asian, and Hispanic population and the average median household income. In total, there were 1.44 million rows of data (5017 hexagons * 12 years * 24 weeks). A correlation matrix among all variables was created to evaluate multicollinearity before running the model. As our response variable was binary (presence or absence of WNV human cases), we used mixed effects multiple logistic regression with stepwise selection for the statistical analysis, with hexagons as a random variable. We used the PROC GLIMMIX procedure in the SAS statistical software. An Akaike information criterion (AIC) was used to choose the best model [41]. A receiver operating characteristics (ROC) curve was calculated using model predictions for 2015 and 2016 to evaluate model performance. All the statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary).

Table 1. List of explanatory variables.

Variables	Notation
Land cover	
Proportion of developed open space	dospct
Proportion of developed low intensity	dlipct
Proportion of developed medium intensity	dmipct
Proportion of developed high intensity	dhipct
Proportion of deciduous forests	dfpct
Proportion of evergreen forests	efpct
Proportion of mixed forests	mfpct
Proportion of barren land	blpct
Proportion of shrubs	shrubspct
Proportion of grassland	glandpct
Proportion of pasture	pasturepct
Proportion of cultivated land	clpct
Proportion of woody wetlands	wwpct
Proportion of herbaceous wetlands	hwpct
Proportion of open water	owpct
Mosquito infection rate	
Mosquito infection of one week before	mirlag1
Mosquito infection of two weeks before	mirlag2
Mosquito infection of three weeks before	mirlag3
Mosquito infection of four weeks before	mirlag4
Weather	
Temperature	
Average temperature of one week before	templag1
Average temperature of two weeks before	templag2
Average temperature of three weeks before	templag3
Average temperature of four weeks before	templag4
Precipitation	
Average precipitation of one week before	precilag1
Average precipitation of two weeks before	precilag2
Average precipitation of three weeks before	precilag3
Average precipitation of four weeks before	precilag4
Demographic factors	
Percentage of White population	whitepct
Percentage of African American	blackpct
Percentage of Asian population	asianpct
Percentage of Hispanic	hispanicpct
Median household income	income

Results

There were 1,371 total human WNV cases reported in Illinois from 2005 to 2016. Out of these total reported cases, 906 cases (66%) were from the Chicago region (Cook and

DuPage Counties). The number of human WNV cases in the study region varied annually, with the year 2012 reporting the highest number of cases (229) and the lowest number of cases (1) reported in 2009 (Table 2). The average annual MIR during the mosquito season was also highest in 2012 (7.34), with 31.3% of tested pools positive for WNV (Table 2). The number of mosquito pools tested annually ranged from about 6,000 pools in 2016 to over 12,000 pools in 2007.

Table 2. Annual human WNV cases, average seasonal mosquito infection rate (MIR), and mosquito testing from 2005 to 2016 in Cook and DuPage counties.

Year	Number of human cases	Average MIR	Number of pools tested	Number of positive pools	Total number of mosquitoes tested
2005	181	5.33	7,165	1,939	271,235
2006	129	5.35	9,428	1,984	318,386
2007	43	2.65	12,131	1,259	375,520
2008	10	1.91	9,024	587	298,995
2009	1	1.14	9,450	298	311,220
2010	47	5.19	11,491	2,086	393,279
2011	24	3.10	8,911	939	287,774
2012	229	7.35	10,162	3,182	323,497
2013	66	4.26	11,078	1,967	407,326
2014	31	2.97	9,273	990	333,489
2015	36	3.57	7,725	1,046	314,363
2016	108	6.34	6,144	1,687	219,909

MIR= Mosquito infection rate; WNV= West Nile virus

We found a strong temporal relationship between the MIR of previous weeks and human WNV cases in the study region (Table 3, Fig 1). The strongest correlation (r= 0.837) was with MIR at a one-week lag (Table 3). The strength of the correlation was stronger (r= 0.884) in the subset of high infection years (2005, 2006, 2012, and 2016) and relatively lower (r= 0.737) in low years (Table 3). When evaluated for only 2012, when case counts were highest, the correlation between MIR and human WNV cases was also the highest (r= 0.899).

In both high and low years, the strength of the correlation gradually declined with the number of weeks lagged and there was almost no correlation with MIR after lags of four weeks.

Table 3. Spearman correlation of weekly cumulative human WNV cases and lagged MIR for all years and selected subsets of years from 2005- 2016 in Cook and DuPage Counties.

		Years with Human WNV cases		
MIR	All years	>100	<100	229 (Year 2012)
Same week	0.776	0.775	0.671	0.818
One week before	0.837	0.884	0.737	0.899
Two weeks before	0.765	0.766	0.698	0.875
Three weeks before	0.601	0.574	0.556	0.727
Four weeks before	0.429	0.354	0.394	0.501
Five weeks before	0.289	0.147	0.286	0.283
Six weeks before	0.142	0.001	0.120	0.038

MIR= Mosquito infection rate; WNV= West Nile virus

Fig 1. Cumulative weekly human WNV cases (red bars) and mosquito infection rate (blue line) from 2005- 2016 in Cook and DuPage Counties, Illinois.

We found that the MIR of mid-summer (weeks 28-33) was able to explain 93% of the variability in total annual human cases (Table 4, Fig 2). The model predicted 44.8 human cases for 2015, compared to 35 actual cases, and 142.7 human cases for 2016 compared to 108 actual cases. Likewise, the cumulative number of positive pools also strongly explained and predicted the total annual human cases (Table 4, Fig 3); the cumulative number of positive mosquito pools by week 31 explained 93% of the variability in total annual human cases, similar to that explained by mid-summer MIR (Table 4). The model using cumulative positive pools by week 31 predicted 35.1 human cases (vs. 35 actual cases) for 2015 and 102.8 human cases (vs. 108 actual cases) for 2016. The cumulative mosquito positive pools by week 31 thus better predicted the annual human cases than the mid-summer MIR.

Table 4. The regression equations of the relationship between a cumulative number of WNV positive pools, mosquito infection rate in a six-week period early and mid-summer and human West Nile virus illnesses for the year for Cook and DuPage Counties from 2004-2014.

Week	Regression equation	R-square
28	30.1 + 0.445 * Number of positive pools	0.721
29	21.2 + 0.278 * Number of positive pools	0.825
30	11.8 + 0.194 * Number of positive pools	0.895
31	2.33 + 0.144 * Number of positive pools	0.931
32	- 6.0 + 0.118 * Number of positive pools	0.917
33	- 16.5 + 0.103 * Number of positive pools	0.901
34	- 23.7 + 0.0938 * Number of positive pools	0.863
35	- 29.5 + 0.0861 * Number of positive pools	0.813
Early summer (22- 27)	13.7 + 162 * average MIR of week 22- 27	0.833
Mid-summer (28- 33)	- 16.7 + 14.7 * average MIR of week 28- 33	0.936

Fig 2. The relationship between annual human WNV infections and mid-summer mosquito infection rate from 2005- 2014 in Cook and DuPage Counties, Illinois.

Fig 3. The relationship between annual human WNV infections and a cumulative number of WNV positive mosquito pools from 2005- 2014 in Cook and DuPage Counties, Illinois.

The spatial pattern of human WNV cases in Cook and DuPage counties showed that cases were distributed throughout most areas of the study region at some point during the study period, with some pockets of higher numbers of cases (Fig 4). Out of the total 5,345 hexagons in the study area, 750 hexagons had experienced at least one case of human WNV case during the years 2005 to 2016. Cumulatively, 123 hexagons had more than one human WNV case, with the maximum number of cases in a hexagon being five (Fig 4). The local Moran's I identified some spatial clusters of human WNV cases in Cook and DuPage counties (Fig 5): 92 hexagons with higher numbers of cases were also near to others with higher numbers of cases.

Fig 4. The spatial distribution of the cumulative number of human WNV infections from 2005- 2016 in Cook and DuPage Counties, Illinois.

Fig 5. The local Moran's I result showing the spatial clustering of cumulative human WNV infections from 2005- 2016 in Cook and DuPage Counties, Illinois.

The results of the mixed-effects regression analysis showed that temperature, precipitation, land cover, mosquito infection, and demographic characteristics are all associated with the probability of an area having a case of WNV human illness. The AIC criteria used to compare the 10 best competing models showed that a model consisting of 15 variables that included temperature, MIR, land cover, and demographic characteristics was the best model (Table 5). The final multivariable model indicated that higher temperatures two, three, and four weeks earlier and warmer average January temperature were associated with a higher probability of a hexagon being positive for human WNV case (Table 6). The lagged mosquito infection rates of one to four weeks earlier were also positively associated with the outcome variable (Table 6). Among the land cover variables, the proportion of open water, grassland, and deciduous forests were negatively associated with the probability of a WNV case while the proportion of low intensity developed areas was positively associated (Table 6). Among the demographic variable, total population was found to be positively associated with the probability of a WNV case, while the proportion of housing built after 1990 was negatively associated (Table 6). The area under the ROC curve was 0.948, which indicates that model performance was excellent (Fig 6).

Table 5. Candidate models for predicting the probability of human WNV occurrence using weather, land cover, mosquito infection, and demographic factors in Chicago region.

Model	Variables included	K	-2 log likelihoods	AIC	ΔAIC
1	Yr + templag2- 4 + precilag2 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	14	12480.5	12530.5	0
2	Yr + templag2- 4 + precilag2 and 4 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	15	12484.1	12536.1	5.6
3	Yr + templag2- 4 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	13	12489.3	12537.3	6.8
4	Yr + templag2- 4 + precilag2 + mirlag1- 4 + whitepct + dmipct + dhipct	13	12490.8	12538.8	8.3
5	Yr + templag2- 4 + precilag2 and 4 + mirlag1- 4 + whitepct + income + owpct + dmipct + dhipct	16	12488.7	12542.7	12.2
6	Yr + templag1- 4 + precilag2 and 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct	17	12503.5	12559.5	29
7	Yr + templag1- 4 + precilag1-2 and 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct	18	12502.6	12560.6	30.1
8	Yr + templag1- 4 + precilag1- 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct + mfpct + glandpct + wwpct	22	12502.6	12560.6	30.1
9	Global model (all predictor variable included)	33	12476.47	12566.5	36
10	Null model	1	14210.7	14214.7	1684.2

Table 6. Model parameters for the best model using weather, land cover, mosquito infection, and demographic factors to predict the occurrence of WNV human cases in Chicago region.

Variable	Parameter estimate	F-value	P-Value	Odds ratio (95% CI)
Fixed effects				
Year	-	17.33	<0.001	-
Temperature of two weeks before	0.06963	22.36	<0.001	1.08 (1.049 -1.112)
Temperature of three weeks before	0.1085	42.99	<0.001	1.128 (1.092- 1.165)
Temperature of four weeks before	0.1628	116.47	<0.001	1.197 (1.162- 1.234)
Average January temperature	0.3613	16.65	<0.001	
Mosquito infection rate of one week before	0.003199	21.53	<0.001	1.003 (1.002- 1.004)
Mosquito infection rate of two weeks before	0.003938	38.79	<0.001	1.004 (1.002- 1.005)
Mosquito infection rate of three weeks before	0.004003	37.83	<0.001	1.004 (1.002- 1.005)
Mosquito infection rate of four weeks before	0.003958	34.63	<0.001	1.004 (1.002- 1.005)
Total population	0.000225	Infinity	<0.001	1.009 (1.006- 1.012)
Open water percentage	-0.05527	9.58	0.002	0.954 (0.921- 0.988)
Developed light intensity percentage	0.01848	80.65	<0.001	0.990 (0.985- 0.994)
Deciduous forest percentage	-0.02401	4.66	0.0309	0.985 (0.980- 0.991)
Grassland percentage	-0.04603	3.14	0.0763	
Post 1990 built housing percentage	-0.00546	4.28	0.0386	
Random effect				
Subject	Estimate	Standard error	Z-value	P-value
Hexagon ID	1.1769	0.1636	7.19	<0.0001

Fig 6. The receiver operating characteristics (ROC) curve for the final model.

Discussion

We identified important fine-scale drivers of spatiotemporal variability in the human WNV cases in Chicago region, Illinois, an area of ongoing WNV transmission. Our analysis used long-term data on human illness, mosquito surveillance, weather, landscape, and demographic data. We found significant spatial clusters of human WNV cases within this urban environment. We also found a strong correlation between the weekly MIR of earlier weeks and weekly human WNV cases, and further developed predictive temporal models using mid-summer average MIR and cumulative positive mosquito pools which can be used to estimate the total annual human WNV cases.

The temporal variation in the weekly human WNV cases was strongly correlated with MIR of one to four weeks earlier, with a correlation of one week earlier being the strongest. This finding was similar to our earlier model based on Illinois climate divisions, in which Division 2 includes our current study area [42]. The similarity in the correlation may be due to the fact that the data for Climate Division 2 were dominated by the data from Cook and DuPage, as these counties have more intensive surveillance compared to other Illinois counties. However, similar observations were also found in Ontario, Canada, where MIR of one week earlier was most strongly correlated with the weekly variation in human WNV cases [16]. In our study, we also found that the correlations between weekly MIR and human cases increased in high WNV years, which was also observed in a study conducted in Long Island, New York [18]. This is understandable, as stochastic variability decreases with increased numbers of cases, allowing for more precise estimation.

The temporal models we developed using mid-summer average MIR and cumulative mosquito positive pools were both able to explain more than 90% of the variability in the annual number of human cases. This similarity of the results was not surprising, as positive mosquito pools are used to calculate the MIR. However, the cumulative positive pools up to week 31 better predicted the annual human cases compared to mid-summer average MIR for

2015 and 2016. The difference observed between the two approaches may reflect the variability of the MIR calculation depending on the mosquito pool size [43,44]. Taking the most extreme possibility, when there was only one mosquito in a pool and it tested positive, this would yield a MIR of 1000 in contrast to MIR of 20 when a pool with 50 mosquitoes was tested positive. In Ontario, Canada, the cumulative number of positive mosquito pools up to week 34 was suggested as an action threshold potential to estimate the total annual human cases [16]. In Chicago, we obtained this signal three weeks earlier, which can be crucial to the ability to intervene in the upcoming potential human WNV outbreak.

We found spatial clustering of human WNV cases within the study area, indicating that some areas were more likely than others to have a WNV human case. A spatial clustering pattern of human WNV cases in Chicago area was also observed in the 2002 WNV outbreak year [12]. Several factors might play a role in the observed spatial clustering pattern, including differences in the fine-scale variation in the local landscape structure that affects mosquito population, fine-scale weather variation, demographic characteristics, access of people to health care system, and spatially variable mosquito abatement practices [12,39,45,46].

In this study, through multilevel modeling, we identified several dynamic factors that are possibly driving the fine scale spatiotemporal variation in the human WNV cases occurrence in the Chicago region. We found that the higher temperature in the previous weeks increases the probability of an area being positive for a WNV case. The association between higher temperature and WNV human illness has also been observed in other studies conducted at different spatial scales [15,17,20]. This is possibly due to the dynamic effect of higher temperature on mosquito breeding and virus replication [35,47–49]. The unique feature of our study is that by considering the dynamic nature of weather, we allowed the temperature and precipitation to vary both temporally and spatially to capture the better role of weather in the spatiotemporal variability of human WNV cases. The precipitation of earlier weeks was not as important as the temperature of the preceding weeks but still was moderately important. The negative association of precipitation observed indicated that dry and hot weather conditions would increase the probability of an area being positive for a WNV case. Some other studies have also indicated that hot dry weather conditions are conducive for WNV transmission [50,51]. While it may seem counter-intuitive that the proportion of open water was negatively correlated with WNV cases, given *Culex* populations would increase with an increase in breeding sites, the definition of open water (areas in which any aquatic vegetation is submerged) is such that it is unlikely to provide good breeding habitat for *Culex*.

We also found increased MIR up to four weeks earlier will increase the probability of an area being positive for a WNV human case. The temporal association between lagged MIR and human WNV cases is relatively well established [10,16,52]. However, it was interesting to find the positive association of MIR when spatiotemporal variabilities of human cases were considered. In our current analysis, we found that areas with a higher percentage of white population had a higher probability of being positive for WNV, which has also been observed in a previous study of this [12]. This may be a function of access to the health care system and likelihood of seeking medical treatment and testing [12,27], or may simply be due to high proportions of white population in areas of the study region where environmental conditions are also conducive to increased mosquito activity.

This study also found that the probability of a hexagon being a positive for WNV case decreased in developed medium and high-intensity urban areas and increased in developed low-intensity urban areas, indicating that the suburban areas of Chicago are more at risk than the highly developed urban centers. The lack of mosquito breeding grounds and bird activity in the high-intensity urban areas might be responsible for this. Previous studies conducted in the same area have also indicated that sub-urban region in Chicago is at more risk from the WNV [12,27]. This is probably due to the poor sanitation system in the older houses compared to new houses.

In this study, we did not consider prior seasonal differences in the weather conditions, which we recommend be incorporated in future studies. In addition, the calculation of MIR for hexagons may be biased as the IDW interpolation technique used to develop continuous surface maps is affected by the uneven distribution of mosquito traps across the study area. Alternatively, other interpolation methods such as kriging might be used to develop continuous surface maps for MIR, as this method takes into account spatial autocorrelation and also creates an error map. In this study, we did not distinguish between neuroinvasive and non-neuroinvasive WNV cases. Separate analysis for only neuroinvasive cases might help us to identify what conditions drive the occurrence of the severe form of WNV infection and should also help to reduce diagnostic bias. Also, in future studies, we might consider using different spatial scales to identify if the geographic scale has affected the results. We were also unable to use data from avian or equid surveillance in this study, despite its usefulness in other modeling approaches [53–55], due to the lack of consistent data across the time period. Bird surveillance in Illinois is limited to passive surveillance of a small number of dead birds tested in each county per year, and is generally suspended after WNV is known to be circulating in the area, while equid surveillance is based entirely on passive self-reporting [56]. This lack of consistent data on avian mortality has been noticed by others [10], and remains an issue for the use of data on the primary host in WNV forecasting.

In conclusion, our analysis helped to better understand the fine-scale dynamic drivers of WNV transmission in an urban environment. The dynamic interplay between temperature and precipitation, mosquito infection, land cover, and demographic characteristics determine the probability of an area having a WNV case or not. Additionally, we established an important temporal relationship between cumulative mosquito positive pools and mid-summer average MIR with the total annual human WNV cases. This information can be used as a guideline to develop a threshold for public health intervention.

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Figure 1

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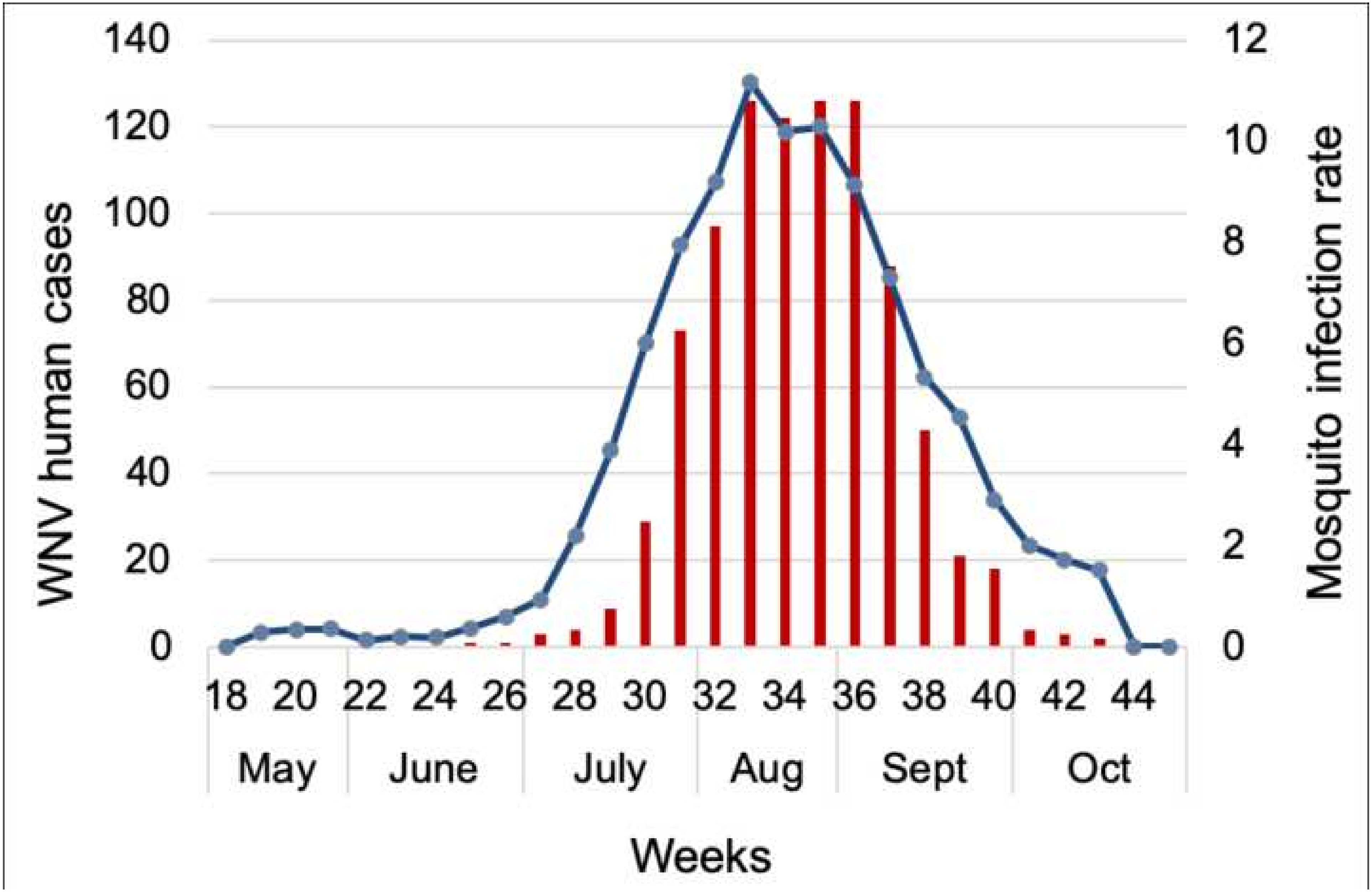

Figure 2

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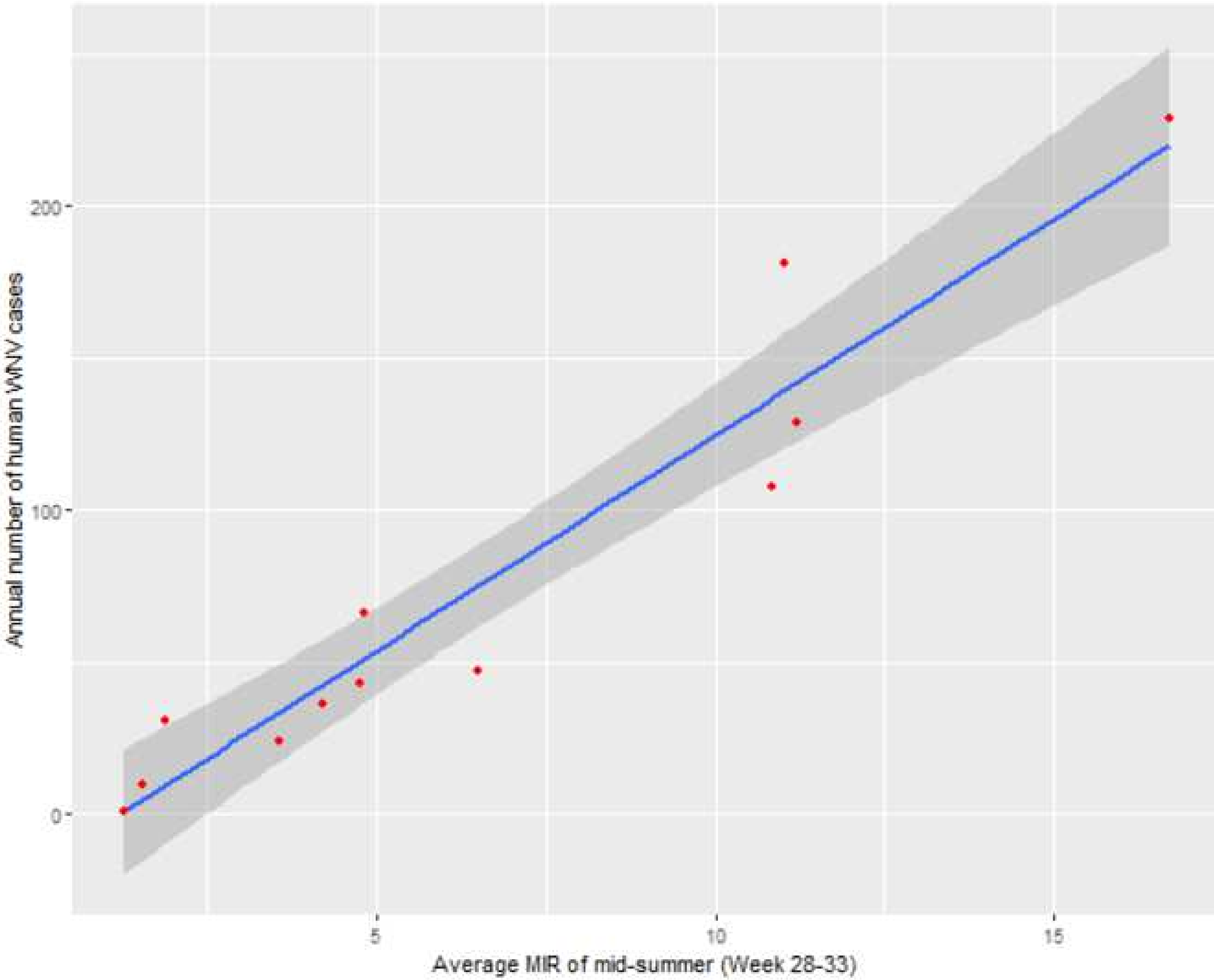

Figure 3

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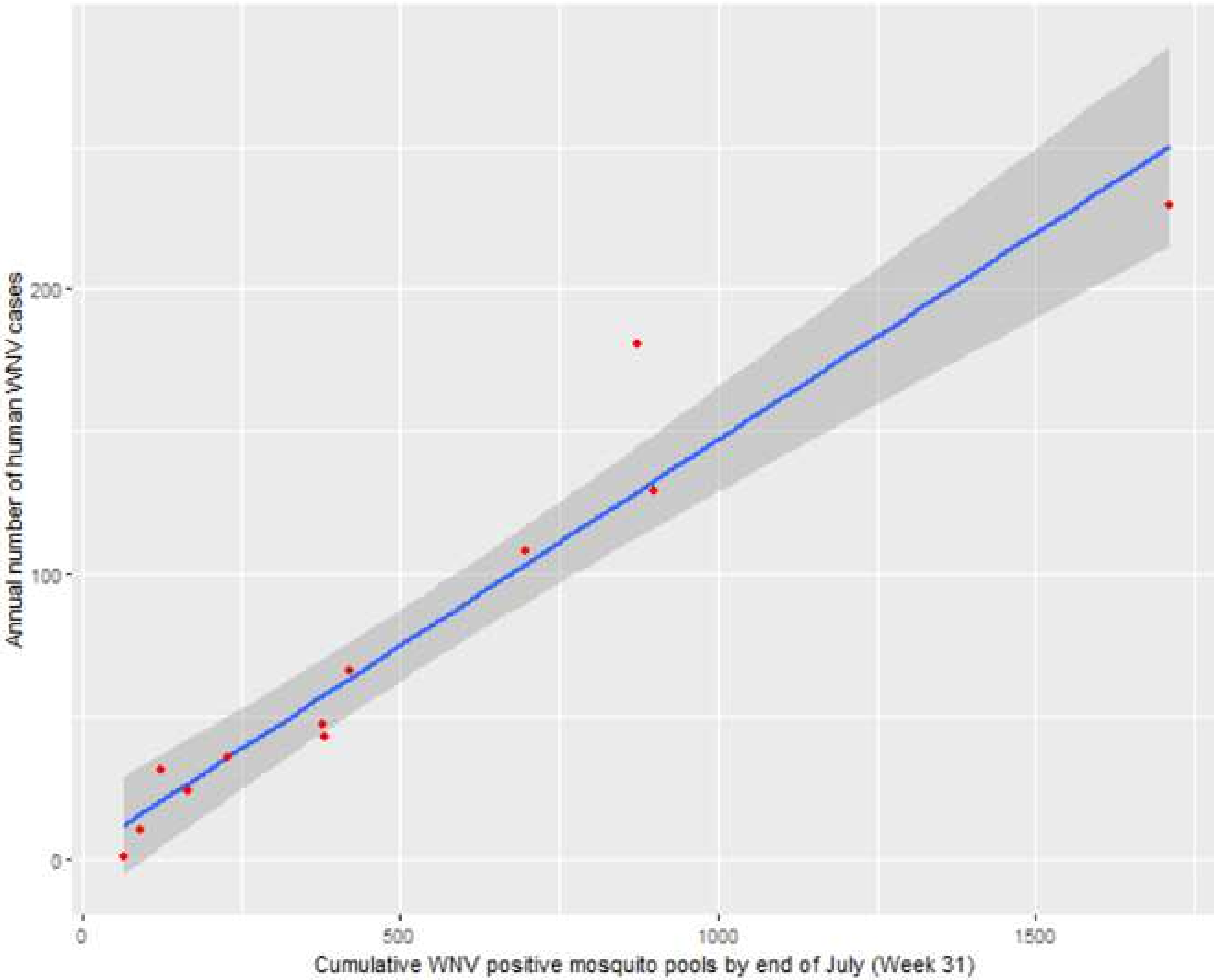

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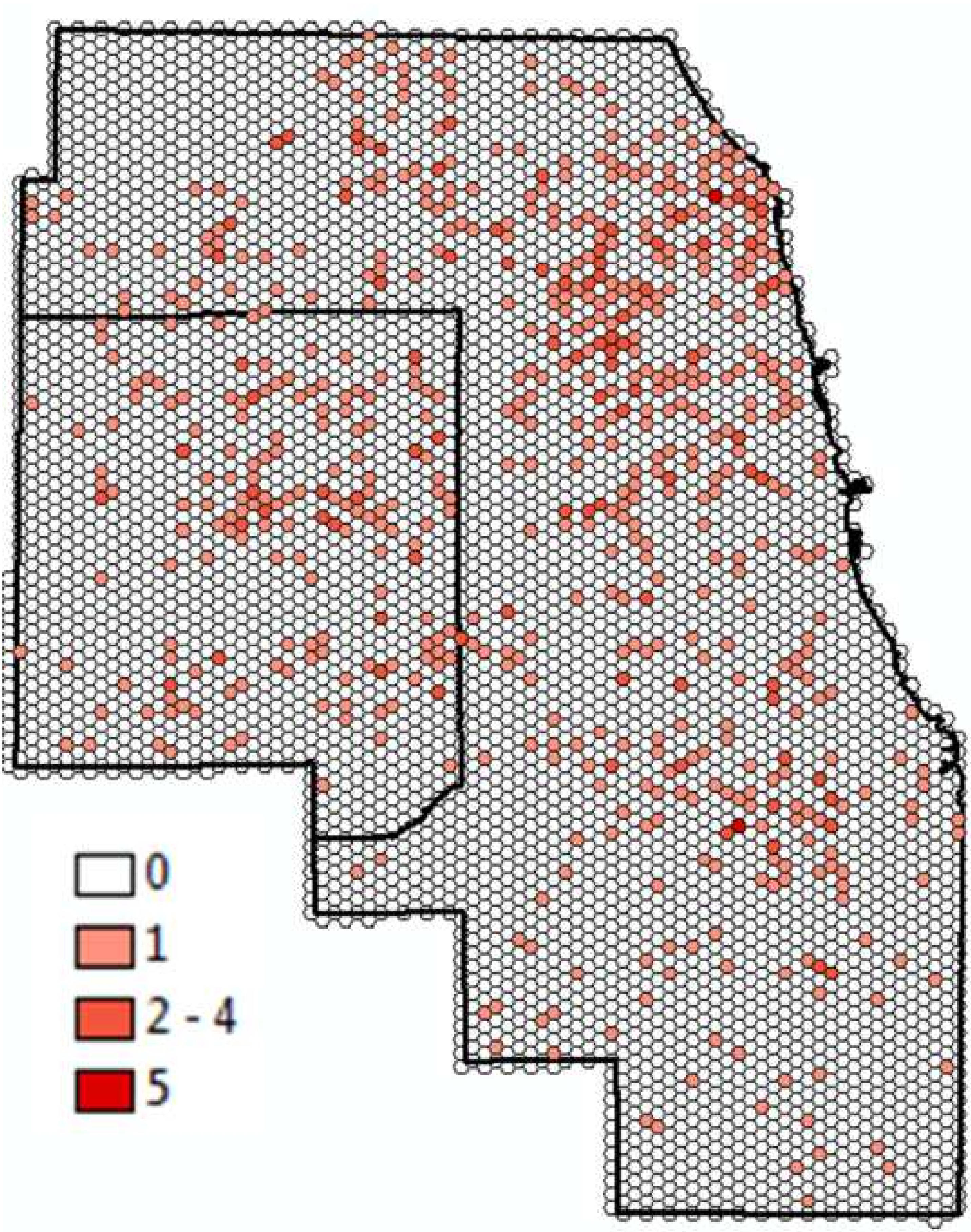

Figure 5

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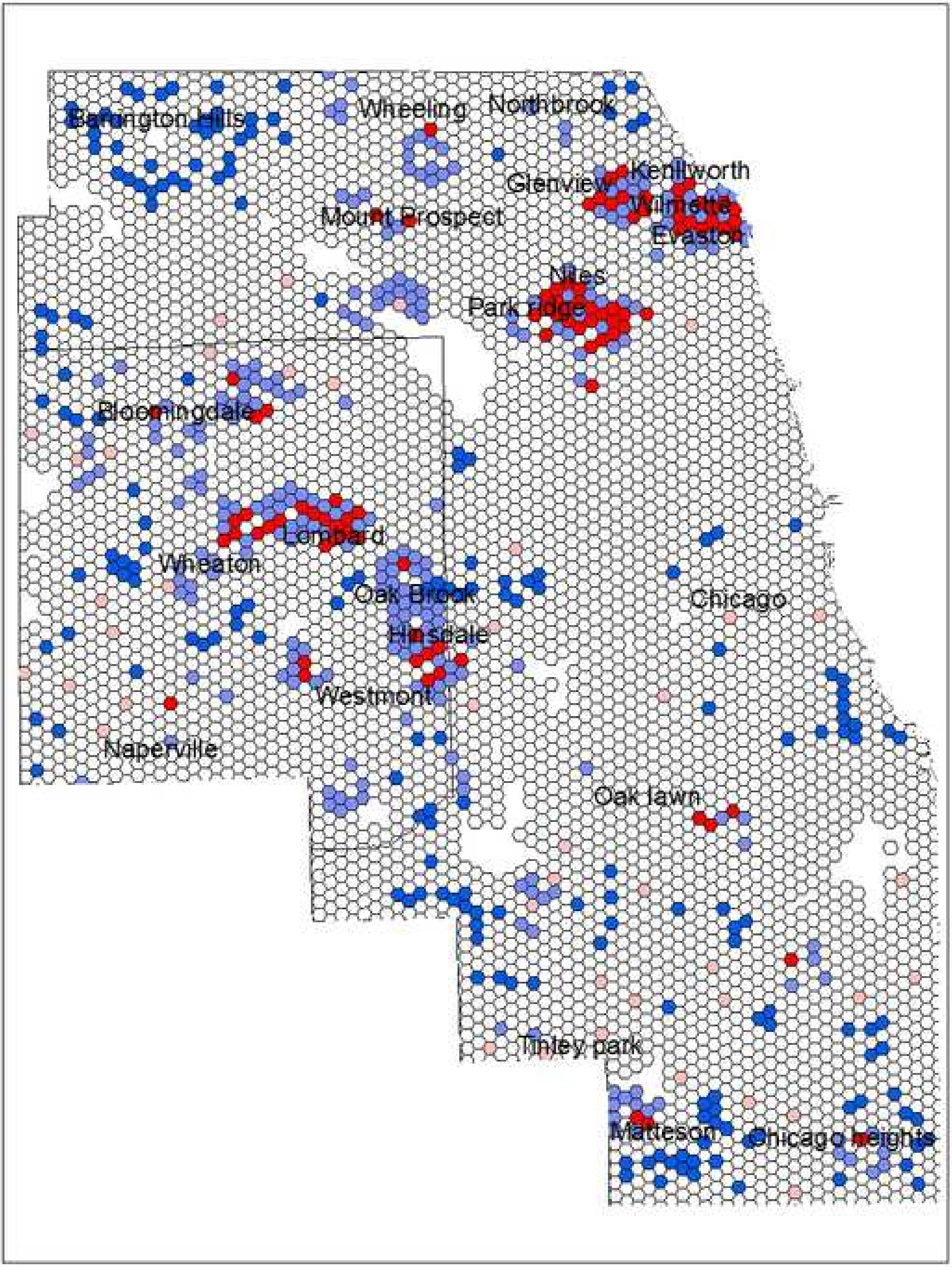
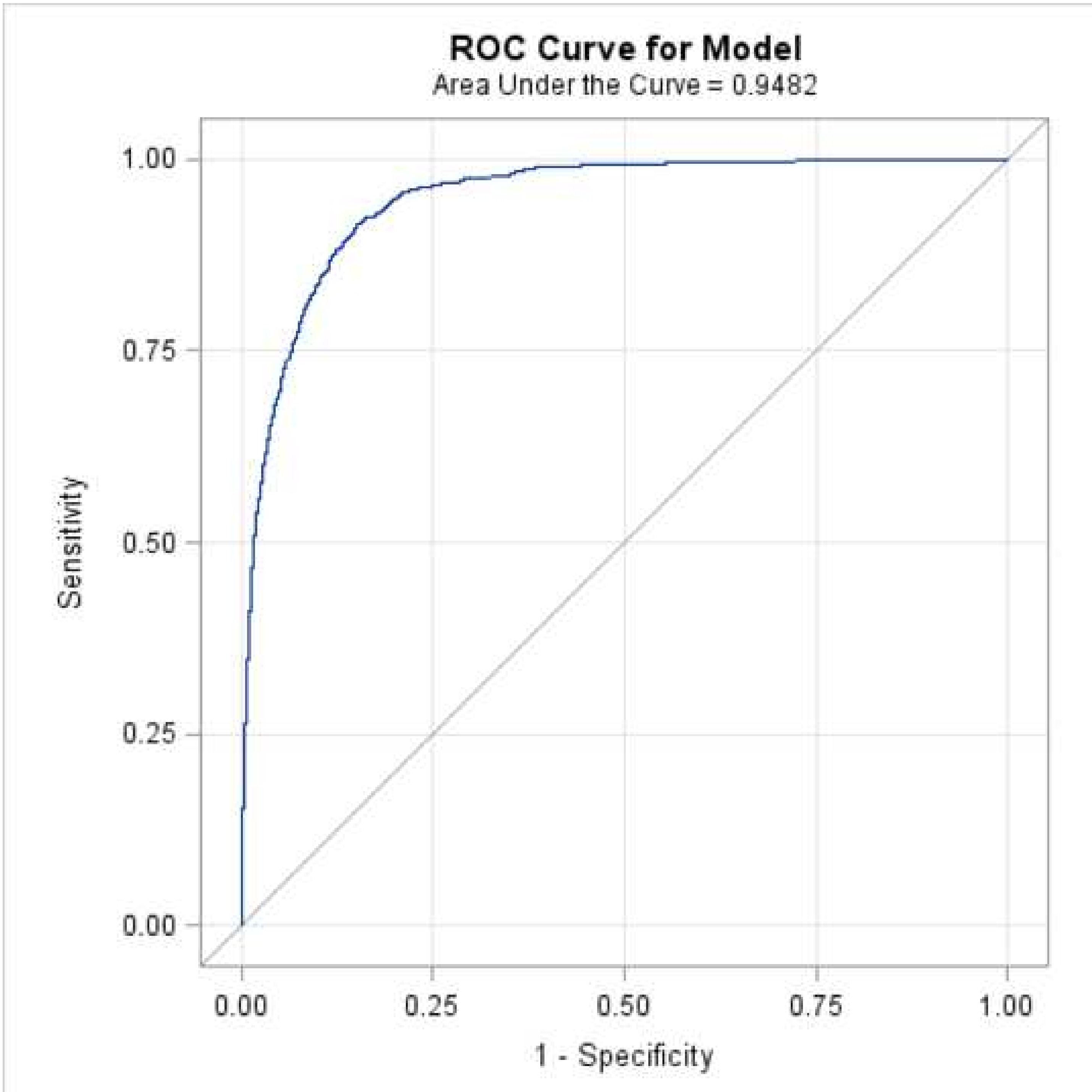


Figure 6


ROC Curve for Model
Area Under the Curve = 0.9482
Sensitivity
1.00
0.75
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1.00
1 - Specificity

The drivers of West Nile virus human illness in the Chicago, Illinois, USA area: fine scale dynamic effects of weather, mosquito infection, social, and biological conditions

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Short title: Fine scale drivers of West Nile virus human illness

Abstract

West Nile virus (WNV) has consistently been reported to be associated with human cases of illness in the region near Chicago, Illinois. However, the number of reported cases of human illness varies across years, with intermittent outbreaks. Several dynamic factors, including temperature, rainfall, and infection status of vector mosquito populations, are responsible for much of these observed variations. However, local landscape structure and human demographic characteristics also play a key role. The geographic and temporal scales used to analyze such complex data affect the observed associations. Here, we used spatial and statistical modeling approaches to investigate the factors that drive the outcome of WNV human illness on fine temporal and spatial scales. Our approach included multi-level modeling of long-term weekly data from 2005 to 2016, with weekly measures of mosquito infection, human illness and weather combined with more stable landscape and demographic factors on the geographical scale of 1000m hexagons. We found that hot weather conditions, warm winters, and higher MIR in earlier weeks increased the probability of an area of having a WNV human case. Higher population and the proportion of urban light intensity in an area also increased the probability of observing a WNV human case. A higher proportion of open water sources, percentage of grass land, deciduous forests, and housing built post 1990 decreased the probability of having a WNV case. Additionally, we found that cumulative positive mosquito pools up to 31 weeks can strongly predict the total annual human WNV cases in the Chicago region. This study helped us to improve our understanding of the fine-scale drivers of spatiotemporal variability of human WNV cases.

Introduction

West Nile virus (WNV), a mosquito-borne zoonotic disease, was first identified in the United States in the summer of 1999 in New York City [1]. The mosquitoes of several *Culex* species are the primary enzootic and bridge vectors for the transmission of WNV, and several bird species are known to contribute in the amplification of the virus [2–4]. Since its first successful invasion in New York, WNV quickly adapted to the local populations of *Culex* vector mosquitoes and avian populations and rapidly spread throughout the conterminous United States [5,6]. The first major WNV outbreak in the United States was observed in 2002, when more than 4,150 human cases and 284 deaths attributable to WNV infection were reported to the CDC from 40 states compared to only 149 cases and 19 deaths from 10 states cumulatively during the three years from 1999 to 2001 [7]. This stirred a prompt public health response from federal, state, and local public health agencies and led to the establishment of a more robust surveillance of mosquitoes and birds to monitor and control the spread of WNV [8].

Public health surveillance for West Nile virus (WNV) involves collection and testing of *Culex* vector mosquitoes, collection and testing of dead birds suspected to have died of WNV, testing of sentinel chickens or of wild birds captured for this purpose, and reporting of cases of human and equine illness [9]. The ultimate goal of these surveillance data is to target mosquito control, and thereby reduce illness through the reduction of the number of infected vector mosquitoes, and to target educational messages to warn citizens to reduce individual exposure. One additional advantage of having a strong surveillance system in place is that the long-term data generated can be integrated with publicly available weather, landscape, and socioeconomic data and can be used effectively to identify the important drivers of WNV transmission and to develop predictive models [10,11].

Several earlier studies have identified some of the important drivers of WNV transmission in humans. These factors include prior weather conditions and landscape structure that affect the mosquito’s biological responses, the abundance and infection status of the vector mosquitoes, demographic and social characteristic of population, individual human behavior, and the level of public awareness [10–17]. For example, an analysis of 12 years of mosquito testing and human illness data in Ontario, Canada showed that, while the mosquito infection rate of one week earlier was the strongest temporal predictor of human risk of WNV, an epidemic threshold based on the cumulative positive *Culex* pools up to mid-August (week 34) can be successfully used to predict human WNV epidemics [16]. In Long Island, New York, more than 65% of forecast models based on past mosquito infection and human illness correctly predicted seasonal total human WNV cases up to 9 weeks before the first reported cases [18]. Similarly, the vector index, based on a combination of vector infection and abundance was found to be highly correlated with human WNV cases in studies conducted in Larimer County, Colorado (Fauver et al., 2015), and Dallas, Texas [19].

Weather factors are important drivers of WNV transmission due to their direct effect in mosquito biology. When compared with human WNV cases, higher than normal average annual temperatures are associated with an increased likelihood of higher WNV disease incidence, nationally and in most regions in the United States [17]. This relationship was true in Europe, too, where abnormally high July temperature was associated with higher incidence of human WNV cases [20]. The role of precipitation is often controversial and varies by study regions. For example, higher than normal precipitation was positively associated with higher human WNV cases in the eastern region of the United States, but this relationship was reversed for the western region [21]. Another study identified drought as an important driver of WNV epidemics in the United States [22]. Local landscape structures have also been associated with human WNV incidence. The important land cover variables associated with increased risks of human WNV include proximity to wetlands [23,24], higher tree density [24], irrigated and agricultural rural areas [25], urban areas characterized by higher impervious surfaces and storm sewer systems [26], and inner suburbs characterized by older houses, moderate vegetation and moderate population [27].

Apart from extrinsic factors, population structure, demographic characteristics, and individual variation also play roles in WNV epidemics [28]. As people age, especially when they have a history of hypertension and immunosuppression, their risk of WNV disease increases [29,30]. Community characteristics such as income level, the age of housing, management of sewer and drainage system, mosquito abatement practices, and public health infrastructure also determines the risk of WNV human infections [12,26].

Different spatial scales have been used in geographical analyses to identify the drivers of human risk from WNV infections. The most commonly used spatial scale in the United States is counties [17,22,31], census tracts or Zip Code Tabulation Areas (ZCTA) [12,32], census block groups [33], and buffers of varying sizes around trap locations or human cases [24]. Each of these spatial scales has its own inherent biases, as these political boundaries do not necessarily correspond to the ecological processes of the disease in question [34]. Alternatively, dividing the area into equal spaces, such as rectangular bins or hexagons, has been used to reduce some of these biases (e.g. [35]). Hexagonal grids have an additional advantage in that they reduce the edge effects, better fit curved surfaces, and have identical neighbors [36,37].

In Illinois, WNV human infections have been endemic since 2002, with annual variability in the number of cases [38]. The majority of the human WNV cases have been reported from the northeastern region, where the largest number of people in the state is congregated. A census tract level analysis in this region using human WNV occurrence data from the 2002 outbreak year identified that census tracts with lower population density, relatively close WNV positive dead bird specimens, a higher percentage of older white residents, and housing built between 1950 and 1959 were more likely to be associated with spatial clusters of WNV cases [12]. A follow up expanded this study to look at annual incidence of WNV human illness in northeastern Illinois from 2002 to 2006, with additional variables to assess the effects of rainfall, temperature and the WNV mosquito infection rate [39]. This analysis determined that white populations and housing from the 1950s were associated with increased illness in some years, but this was not consistent. Interestingly, census tracts with lower rainfall had higher rates of WNV illness, but the mosquito infection rate was not an important variable in any of the models [39].

Despite the identification of some of these potential risk factors, accurate prediction of human illness cases from WNV remains elusive at the local scale, especially as it is related to dynamic weather and mosquito infection status. Using long-term data on human WNV illness and intensive mosquito surveillance for the Chicago region, we can identify the fine scale drivers of spatiotemporal variability of human WNV epidemic in an urban environment. The overall goal of this study is to determine factors affecting the spatiotemporal variability of clinical WNV incidence in people through identification of the fine scale drivers of WNV transmission in an urban area with a repeated history of WNV outbreaks. These potential drivers include dynamic mosquito infection and weather. Our specific objectives in this study are to (i) describe the fine-scale temporal and spatial patterns of human WNV illness in the Chicago region, (ii) evaluate the temporal relationships between mosquito infection and human WNV illness, and (iii) determine the fine-scale dynamic effects of weather, land cover, mosquito infection, and demographic factors on the presence of human West Nile virus illness across time and space.

Materials and methods

This project was approved by the Institutional Review Boards of the University of Illinois Urbana-Champaign and the Illinois Department of Public Health.

The two Illinois counties of Cook and DuPage, comprising Chicago and its suburbs, were included in this study. The total area covered by these two counties is nearly 5,100 square kilometers, and the total population in 2010 was 6.1 million. These areas were selected because of the relatively high incidence of human West Nile virus illness reported from these two counties and the long-term intensive mosquito surveillance data available for this region. The temporal window included in this study was the 24-week time period from late May to late October (weeks 22 to 45), which corresponds to the timing of mosquito activity and human WNV illness, with data for the years from 2005 to 2016. The years from 2002 to 2004, during which Illinois had its first invasion from WNV, were excluded in this analysis because of the absence of mosquito testing data. Data on avian and equid surveillance were not included as these programs were not consistently applied across the time period.

We chose to summarize all variables into hexagons to provide a neutral spatial unit of consistent size and shape, which is not possible with political boundaries. For this, we overlaid hexagons measuring 1000 m in diameter on the outlines of Cook and DuPage counties to create a grid of 5,345 hexagons for the study area. Out of these, 328 were excluded after a comparison with fine scale population data from the 2010 U.S. Census indicated that there were no households on record within those hexagons. Thus, 5,017 hexagons were included in the analysis. All independent variables related to weather, land cover, mosquito infection and demography were calculated for each hexagon, as described below.

Mosquito data

Mosquito testing data from 2005 to 2016 were obtained from the Illinois Department of Public Health (IDPH) through a user agreement. The IDPH collates the data from local public health agencies and mosquito abatement districts across Illinois and maintains a statewide database for the results from WNV mosquito testing. The IDPH developed a mosquito surveillance protocol that local health and mosquito abatement districts are expected to follow in order to standardize the mosquito collection and testing across the state. In general, the local agencies collect vector mosquitoes with gravid traps, identify the sex and species of the mosquitoes, and make pools of up to 50 mosquitoes of a single species from those captured in each trap to test for the presence of WNV infection. When fewer then 50 mosquitoes are captured, a pool will consist of fewer than 50 mosquitoes. During the study period, the common tests used to identify WNV in mosquitoes included antigen assays, VecTest or the Rapid Analyte Measurement Platform (RAMP) test. Some pools were also tested by Real Time reverse transcriptase polymerase chain reaction (RT-PCR). In instances when a pool was tested using more than one type of test, only the RT-PCR results were used in the analysis. Our analysis used only the test results from pools of female *Culex* mosquitoes. Not all mosquitoes were identified to species prior to testing; however, the majority of *Culex* collected in this region belong to the species *Cx. pipiens* or *Cx. restuans* [3].

To determine the location of the mosquito traps, we used the existing latitude and longitude recorded in the IDPH database. In cases where the spatial data were missing, we geocoded the trap locations based on the address provided. Our analysis used all the trap locations recorded from 2005 to 2016 from Cook and DuPage counties in addition to any traps located within a 10 km radius from their boundaries (located within Lake, McHenry, Kane, Kendall, and Will counties). For each trap, the mosquito infection rate (MIR) was calculated by week and by year using the formula

$$1000 * \frac{\text{number of positive pools}}{\text{total number of mosquitos in pools tested}}$$ [40]~~(Biggerstaff, 2006)~~.

Using MIR calculations from all traps, we developed continuous surface maps for MIR for each week and year using the inverse distance weighting (IDW) interpolation technique in ArcGIS 10.1. From this interpolated surface map for each year and week, the average, minimum, and maximum MIR for each hexagon was calculated using the zonal statistics as table function in ArcGIS 10.1. A model builder platform using iteration features in ArcGIS 10.1 was used to run these processes.

Human illness data

Records of human WNV cases in Illinois were obtained from the IDPH through a user agreement. All confirmed and probable cases of WNV reported to the IDPH by medical and public health personnel for the study area were included in this study; the state of Illinois mandates reporting of WNV to local public health departments, which then report all cases to IDPH. Probable cases are those that meet clinical criteria during the season when transmission is likely to occur and meet laboratory criteria for West Nile virus by serology (IgM capture ELISA) or polymerase chain reaction, while confirmed cases are those with confirmatory test results from the IDPH or the Centers for Disease Control and Prevention. All the human WNV cases in Cook and DuPage counties reported from 2005 to 2016 were geocoded and aggregated by hexagons for each week and year. The data were converted into the binary form of presence or absence of a WNV case in a given hexagon and week.

Demographic data

The demographic variables included were total population, racial composition, housing age, and income level. The total population and racial composition included the number of White, African American, Asian, and Hispanic people at the census block level, as reported in the 2010 U.S. Census. The racial population data was converted to the percentage of White, African American, Asian, and Hispanic people in each hexagon. The income data for the block group level were obtained from the 2015 American Community Survey. Housing age was included as the proportions of housing built in different time periods, which was obtained at the block group level from the 2015 American Community Survey. We divided housing age into four different time-periods: pre-World War II houses (built before

1939), post-World War II houses (built between 1940 and 1969), houses built between 1970 and 1989, and houses built after 1990. These demographic data were processed in ArcGIS using the intersection tool to calculate a parameter for each hexagon.

Landcover data

Landcover data for the entire United States was obtained from the national landcover database (NLCD) for the years 2006 and 2011. The NLCD database is a Landsat based landcover data available at a 30 m resolution (www.mrlc.gov). The landcover raster was clipped for Cook and DuPage counties, including a surrounding 1 km buffer. From this clipped raster, the total number of pixels for each land category within each hexagon was calculated using the tabulate as area tool in ArcGIS 10.1. The proportion of each land cover category for each hexagon was then calculated by dividing the number of pixels for that category by the total number of pixels for all categories. In Cook and DuPage counties, 15 different types of landcover were available: urban areas (developed open space, developed low intensity, developed medium intensity, developed high intensity), forests (deciduous, evergreen and mixed), barren land, shrubs, grassland, pasture, cultivated crops, woody wetlands, herbaceous wetlands, and open water. The land cover data from 2006 was used to analyze the WNV cases for the years from 2006 to 2010, while the land cover data from 2011 was used for 2011 to 2016.

Weather data

Spatial weather data on daily mean temperature and precipitation from 2005 to 2016 were obtained from the PRISM Climate Group (PRISM Climate Group, Oregon State University, http://prism.oregonstate.edu). The PRISM daily data are available as spatial grids of 4 km resolution, which are calculated through interpolation and statistical techniques using point data from weather monitoring networks across the country combined with topographic data. These daily data were used to calculate the weekly temperature and precipitation. For our analysis, the weekly mean temperature was calculated by taking the average of the seven daily averages for that week, and the weekly precipitation was calculated as a sum of the daily precipitation for that week. Finally, the weekly temperature and precipitation for each year and week for each hexagon was calculated by using the zonal statistics as table function in ArcGIS 10.1. We also calculated average January temperature for each hexagon for each year from the daily data as a proxy for the winter temperature.

Statistical methods

To assess the temporal relationship between human illness and MIR, we calculated the Spearman rank correlation between the weekly MIR of 1-6 weeks lag and human cases. We repeated this analysis on the subsets of years with high numbers of WNV cases (more than 100 human cases; 2005, 2006, 2012 and 2016) and those with low numbers of WNV cases (less than 100 cases; 2007 - 2009, 2010, 2011, 2013 - 2015) to examine if the relationship between MIR and human cases varies in high and low years. We further examined the ability of the early summer (weeks 22- 27) and mid-summer (weeks 28- 33) average MIR to explain and predict the seasonal annual total WNV cases by using linear regression analysis. In addition, we assessed the ability of the cumulative positive mosquito pools up to week 28 and thereafter, added to each week's data, to find a threshold that could best explain the annual total human WNV cases. In both of these calculations, data from 2005 to 2014 were used to create a regression equation, and data from 2015 and 2016 was used to test the model.

To visualize the spatial patterns of human illness over time, we first developed choropleth maps of WNV cases. Then, we used local Moran's I method using an inclusive second order queen contiguity weight matrix in the spatial analysis software GeoDa to further identify the spatial clusters of cumulative human WNV cases from 2005 to 2016. We also examined differences in results using neighboring cells and rook contiguity weight matrix, but the results did not vary.

For the spatiotemporal statistical model, the outcome variable was the presence/ absence of a human WNV case in each hexagon for each year and week. The predictors included 32 variables related to weather, land cover, mosquito infection and demography (Table 1). The weather variables consisted of mean weekly temperature and precipitation with lags of one to four weeks. The land cover variables include 15 categories, the proportion for each hexagon of: developed open space; developed low, medium, and high intensity urban areas; deciduous, evergreen, and mixed forests; barren land; shrubs; grassland; pasture; cultivated crops; woody wetlands; herbaceous wetlands; and open water. The mosquito infection data included the average MIR with lags of one to four weeks for each hexagon for each year and week. Demographic variables for each hexagon included the proportion of White, African American, Asian, and Hispanic population and the average median household income. In total, there were 1.44 million rows of data (5017 hexagons * 12 years * 24 weeks). A correlation matrix among all variables was created to evaluate multicollinearity before running the model. As our response variable was binary (presence or absence of WNV human cases), we used mixed effects multiple logistic regression with stepwise selection for the statistical analysis, with hexagons as a random variable. We used the PROC GLIMMIX procedure in the SAS statistical software. An Akaike information criterion (AIC) was used to choose the best model [41]. A receiver operating characteristics (ROC) curve was calculated using model predictions for 2015 and 2016 to evaluate model performance. All the statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary).

Table 1. List of explanatory variables.

Variables	Notation
Land cover	
Proportion of developed open space	dospct
Proportion of developed low intensity	dlipct
Proportion of developed medium intensity	dmipct
Proportion of developed high intensity	dhipct
Proportion of deciduous forests	dfpct
Proportion of evergreen forests	efpct
Proportion of mixed forests	mfpct
Proportion of barren land	blpct
Proportion of shrubs	shrubspct
Proportion of grassland	glandpct
Proportion of pasture	pasturepct
Proportion of cultivated land	clpct
Proportion of woody wetlands	wwpct
Proportion of herbaceous wetlands	hwpct
Proportion of open water	owpct
Mosquito infection rate	
Mosquito infection of one week before	mirlag1
Mosquito infection of two weeks before	mirlag2
Mosquito infection of three weeks before	mirlag3
Mosquito infection of four weeks before	mirlag4
Weather	
Temperature	
Average temperature of one week before	templag1
Average temperature of two weeks before	templag2
Average temperature of three weeks before	templag3
Average temperature of four weeks before	templag4
Precipitation	
Average precipitation of one week before	precilag1
Average precipitation of two weeks before	precilag2
Average precipitation of three weeks before	precilag3
Average precipitation of four weeks before	precilag4
Demographic factors	
Percentage of White population	whitepct
Percentage of African American	blackpct
Percentage of Asian population	asianpct
Percentage of Hispanic	hispanicpct
Median household income	income

Results

There were 1,371 total human WNV cases reported in Illinois from 2005 to 2016. Out of these total reported cases, 906 cases (66%) were from the Chicago region (Cook and

DuPage Counties). The number of human WNV cases in the study region varied annually, with the year 2012 reporting the highest number of cases (229) and the lowest number of cases (1) reported in 2009 (Table 2). The average annual MIR during the mosquito season was also highest in 2012 (7.34), with 31.3% of tested pools positive for WNV (Table 2). The number of mosquito pools tested annually ranged from about 6,000 pools in 2016 to over 12,000 pools in 2007.

Table 2. Annual human WNV cases, average seasonal mosquito infection rate (MIR), and mosquito testing from 2005 to 2016 in Cook and DuPage counties.

Year	Number of human cases	Average MIR	Number of pools tested	Number of positive pools	Total number of mosquitoes tested
2005	181	5.33	7,165	1,939	271,235
2006	129	5.35	9,428	1,984	318,386
2007	43	2.65	12,131	1,259	375,520
2008	10	1.91	9,024	587	298,995
2009	1	1.14	9,450	298	311,220
2010	47	5.19	11,491	2,086	393,279
2011	24	3.10	8,911	939	287,774
2012	229	7.35	10,162	3,182	323,497
2013	66	4.26	11,078	1,967	407,326
2014	31	2.97	9,273	990	333,489
2015	36	3.57	7,725	1,046	314,363
2016	108	6.34	6,144	1,687	219,909

MIR= Mosquito infection rate; WNV= West Nile virus

We found a strong temporal relationship between the MIR of previous weeks and human WNV cases in the study region (Table 3, Fig 1). The strongest correlation (r= 0.837) was with MIR at a one-week lag (Table 3). The strength of the correlation was stronger (r= 0.884) in the subset of high infection years (2005, 2006, 2012, and 2016) and relatively lower (r= 0.737) in low years (Table 3). When evaluated for only 2012, when case counts were highest, the correlation between MIR and human WNV cases was also the highest (r= 0.899).

In both high and low years, the strength of the correlation gradually declined with the number of weeks lagged and there was almost no correlation with MIR after lags of four weeks.

Table 3. Spearman correlation of weekly cumulative human WNV cases and lagged MIR for all years and selected subsets of years from 2005- 2016 in Cook and DuPage Counties.

		Years with Human WNV cases		
MIR	All years	>100	<100	229 (Year 2012)
Same week	0.776	0.775	0.671	0.818
One week before	0.837	0.884	0.737	0.899
Two weeks before	0.765	0.766	0.698	0.875
Three weeks before	0.601	0.574	0.556	0.727
Four weeks before	0.429	0.354	0.394	0.501
Five weeks before	0.289	0.147	0.286	0.283
Six weeks before	0.142	0.001	0.120	0.038

MIR= Mosquito infection rate; WNV= West Nile virus

Fig 1. Cumulative weekly human WNV cases (red bars) and mosquito infection rate (blue line) from 2005- 2016 in Cook and DuPage Counties, Illinois.

We found that the MIR of mid-summer (weeks 28-33) was able to explain 93% of the variability in total annual human cases (Table 4, Fig 2). The model predicted 44.8 human cases for 2015, compared to 35 actual cases, and 142.7 human cases for 2016 compared to 108 actual cases. Likewise, the cumulative number of positive pools also strongly explained and predicted the total annual human cases (Table 4, Fig 3); the cumulative number of positive mosquito pools by week 31 explained 93% of the variability in total annual human cases, similar to that explained by mid-summer MIR (Table 4). The model using cumulative positive pools by week 31 predicted 35.1 human cases (vs. 35 actual cases) for 2015 and 102.8 human cases (vs. 108 actual cases) for 2016. The cumulative mosquito positive pools by week 31 thus better predicted the annual human cases than the mid-summer MIR.

Table 4. The regression equations of the relationship between a cumulative number of WNV positive pools, mosquito infection rate in a six-week period early and mid-summer and human West Nile virus illnesses for the year for Cook and DuPage Counties from 2004-2014.

Week	Regression equation	R-square
28	30.1 + 0.445 * Number of positive pools	0.721
29	21.2 + 0.278 * Number of positive pools	0.825
30	11.8 + 0.194 * Number of positive pools	0.895
31	2.33 + 0.144 * Number of positive pools	0.931
32	- 6.0 + 0.118 * Number of positive pools	0.917
33	- 16.5 + 0.103 * Number of positive pools	0.901
34	- 23.7 + 0.0938 * Number of positive pools	0.863
35	- 29.5 + 0.0861 * Number of positive pools	0.813
Early summer (22- 27)	13.7 + 162 * average MIR of week 22- 27	0.833
Mid-summer (28- 33)	- 16.7 + 14.7 * average MIR of week 28- 33	0.936

Fig 2. The relationship between annual human WNV infections and mid-summer mosquito infection rate from 2005- 2014 in Cook and DuPage Counties, Illinois.

Fig 3. The relationship between annual human WNV infections and a cumulative number of WNV positive mosquito pools from 2005- 2014 in Cook and DuPage Counties, Illinois.

The spatial pattern of human WNV cases in Cook and DuPage counties showed that cases were distributed throughout most areas of the study region at some point during the study period, with some pockets of higher numbers of cases (Fig 4). Out of the total 5,345 hexagons in the study area, 750 hexagons had experienced at least one case of human WNV case during the years 2005 to 2016. Cumulatively, 123 hexagons had more than one human WNV case, with the maximum number of cases in a hexagon being five (Fig 4). The local Moran’s I identified some spatial clusters of human WNV cases in Cook and DuPage counties (Fig 5): 92 hexagons with higher numbers of cases were also near to others with higher numbers of cases.

Fig 4. The spatial distribution of the cumulative number of human WNV infections from 2005- 2016 in Cook and DuPage Counties, Illinois.

Fig 5. The local Moran's I result showing the spatial clustering of cumulative human WNV infections from 2005- 2016 in Cook and DuPage Counties, Illinois.

The results of the mixed-effects regression analysis showed that temperature, precipitation, land cover, mosquito infection, and demographic characteristics are all associated with the probability of an area having a case of WNV human illness. The AIC criteria used to compare the 10 best competing models showed that a model consisting of 15 variables that included temperature, MIR, land cover, and demographic characteristics was the best model (Table 5). The final multivariable model indicated that higher temperatures two, three, and four weeks earlier and warmer average January temperature were associated with a higher probability of a hexagon being positive for human WNV case (Table 6). The lagged mosquito infection rates of one to four weeks earlier were also positively associated with the outcome variable (Table 6). Among the land cover variables, the proportion of open water, grassland, and deciduous forests were negatively associated with the probability of a WNV case while the proportion of low intensity developed areas was positively associated (Table 6). Among the demographic variable, total population was found to be positively associated with the probability of a WNV case, while the proportion of housing built after 1990 was negatively associated (Table 6). The area under the ROC curve was 0.948, which indicates that model performance was excellent (Fig 6).

Table 5. Candidate models for predicting the probability of human WNV occurrence using weather, land cover, mosquito infection, and demographic factors in Chicago region.

Model	Variables included	K	-2 log likelihoods	AIC	ΔAIC
1	Yr + templag2- 4 + precilag2 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	14	12480.5	12530.5	0
2	Yr + templag2- 4 + precilag2 and 4 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	15	12484.1	12536.1	5.6
3	Yr + templag2- 4 + mirlag1- 4 + whitepct + owpct + dmipct + dhipct	13	12489.3	12537.3	6.8
4	Yr + templag2- 4 + precilag2 + mirlag1- 4 + whitepct + dmipct + dhipct	13	12490.8	12538.8	8.3
5	Yr + templag2- 4 + precilag2 and 4 + mirlag1- 4 + whitepct + income + owpct + dmipct + dhipct	16	12488.7	12542.7	12.2
6	Yr + templag1- 4 + precilag2 and 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct	17	12503.5	12559.5	29
7	Yr + templag1- 4 + precilag1-2 and 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct	18	12502.6	12560.6	30.1
8	Yr + templag1- 4 + precilag1- 4 + mirlag1- 4 + income + whitepct + owpct + dmipct + dhipct + mfpct + glandpct + wwpct	22	12502.6	12560.6	30.1
9	Global model (all predictor variable included)	33	12476.47	12566.5	36
10	Null model	1	14210.7	14214.7	1684.2

Table 6. Model parameters for the best model using weather, land cover, mosquito infection, and demographic factors to predict the occurrence of WNV human cases in Chicago region.

Variable	Parameter estimate	F-value	P-Value	Odds ratio (95% CI)
Fixed effects				
Year	-	17.33	<0.001	-
Temperature of two weeks before	0.06963	22.36	<0.001	1.08 (1.049 -1.112)
Temperature of three weeks before	0.1085	42.99	<0.001	1.128 (1.092- 1.165)
Temperature of four weeks before	0.1628	116.47	<0.001	1.197 (1.162- 1.234)
Average January temperature	0.3613	16.65	<0.001	
Mosquito infection rate of one week before	0.003199	21.53	<0.001	1.003 (1.002- 1.004)
Mosquito infection rate of two weeks before	0.003938	38.79	<0.001	1.004 (1.002- 1.005)
Mosquito infection rate of three weeks before	0.004003	37.83	<0.001	1.004 (1.002- 1.005)
Mosquito infection rate of four weeks before	0.003958	34.63	<0.001	1.004 (1.002- 1.005)
Total population	0.000225	Infinity	<0.001	1.009 (1.006- 1.012)
Open water percentage	-0.05527	9.58	0.002	0.954 (0.921- 0.988)
Developed light intensity percentage	0.01848	80.65	<0.001	0.990 (0.985- 0.994)
Deciduous forest percentage	-0.02401	4.66	0.0309	0.985 (0.980- 0.991)
Grassland percentage	-0.04603	3.14	0.0763	
Post 1990 built housing percentage	-0.00546	4.28	0.0386	
Random effect				
Subject	Estimate	Standard error	Z-value	P-value
Hexagon ID	1.1769	0.1636	7.19	<0.0001

Fig 6. The receiver operating characteristics (ROC) curve for the final model.

Discussion

We identified important fine-scale drivers of spatiotemporal variability in the human WNV cases in Chicago region, Illinois, an area of ongoing WNV transmission. Our analysis used long-term data on human illness, mosquito surveillance, weather, landscape, and demographic data. We found significant spatial clusters of human WNV cases within this urban environment. We also found a strong correlation between the weekly MIR of earlier weeks and weekly human WNV cases, and further developed predictive temporal models using mid-summer average MIR and cumulative positive mosquito pools which can be used to estimate the total annual human WNV cases.

The temporal variation in the weekly human WNV cases was strongly correlated with MIR of one to four weeks earlier, with a correlation of one week earlier being the strongest. This finding was similar to our earlier model based on Illinois climate divisions, in which Division 2 includes our current study area [42]. The similarity in the correlation may be due to the fact that the data for Climate Division 2 were dominated by the data from Cook and DuPage, as these counties have more intensive surveillance compared to other Illinois counties. However, similar observations were also found in Ontario, Canada, where MIR of one week earlier was most strongly correlated with the weekly variation in human WNV cases [16]. In our study, we also found that the correlations between weekly MIR and human cases increased in high WNV years, which was also observed in a study conducted in Long Island, New York [18]. This is understandable, as stochastic variability decreases with increased numbers of cases, allowing for more precise estimation.

The temporal models we developed using mid-summer average MIR and cumulative mosquito positive pools were both able to explain more than 90% of the variability in the annual number of human cases. This similarity of the results was not surprising, as positive mosquito pools are used to calculate the MIR. However, the cumulative positive pools up to week 31 better predicted the annual human cases compared to mid-summer average MIR for

2015 and 2016. The difference observed between the two approaches may reflect the variability of the MIR calculation depending on the mosquito pool size [43,44]. Taking the most extreme possibility, when there was only one mosquito in a pool and it tested positive, this would yield a MIR of 1000 in contrast to MIR of 20 when a pool with 50 mosquitoes was tested positive. In Ontario, Canada, the cumulative number of positive mosquito pools up to week 34 was suggested as an action threshold potential to estimate the total annual human cases [16]. In Chicago, we obtained this signal three weeks earlier, which can be crucial to the ability to intervene in the upcoming potential human WNV outbreak.

We found spatial clustering of human WNV cases within the study area, indicating that some areas were more likely than others to have a WNV human case. A spatial clustering pattern of human WNV cases in Chicago area was also observed in the 2002 WNV outbreak year [12]. Several factors might play a role in the observed spatial clustering pattern, including differences in the fine-scale variation in the local landscape structure that affects mosquito population, fine-scale weather variation, demographic characteristics, access of people to health care system, and spatially variable mosquito abatement practices [12,39,45,46].

In this study, through multilevel modeling, we identified several dynamic factors that are possibly driving the fine scale spatiotemporal variation in the human WNV cases occurrence in the Chicago region. We found that the higher temperature in the previous weeks increases the probability of an area being positive for a WNV case. The association between higher temperature and WNV human illness has also been observed in other studies conducted at different spatial scales [15,17,20]. This is possibly due to the dynamic effect of higher temperature on mosquito breeding and virus replication [35,47–49]. The unique feature of our study is that by considering the dynamic nature of weather, we allowed the temperature and precipitation to vary both temporally and spatially to capture the better role of weather in the spatiotemporal variability of human WNV cases. The precipitation of earlier weeks was not as important as the temperature of the preceding weeks but still was moderately important. The negative association of precipitation observed indicated that dry and hot weather conditions would increase the probability of an area being positive for a WNV case. Some other studies have also indicated that hot dry weather conditions are conducive for WNV transmission [50,51]. While it may seem counter-intuitive that the proportion of open water was negatively correlated with WNV cases, given *Culex* populations would increase with an increase in breeding sites, the definition of open water (areas in which any aquatic vegetation is submerged) is such that it is unlikely to provide good breeding habitat for *Culex*.

We also found increased MIR up to four weeks earlier will increase the probability of an area being positive for a WNV human case. The temporal association between lagged MIR and human WNV cases is relatively well established [10,16,52]. However, it was interesting to find the positive association of MIR when spatiotemporal variabilities of human cases were considered. In our current analysis, we found that areas with a higher percentage of white population had a higher probability of being positive for WNV, which has also been observed in a previous study of this [12]. This may be a function of access to the health care system and likelihood of seeking medical treatment and testing [12,27], or may simply be due to high proportions of white population in areas of the study region where environmental conditions are also conducive to increased mosquito activity.

This study also found that the probability of a hexagon being a positive for WNV case decreased in developed medium and high-intensity urban areas and increased in developed low-intensity urban areas, indicating that the suburban areas of Chicago are more at risk than the highly developed urban centers. The lack of mosquito breeding grounds and bird activity in the high-intensity urban areas might be responsible for this. Previous studies conducted in the same area have also indicated that sub-urban region in Chicago is at more risk from the WNV [12,27]. This is probably due to the poor sanitation system in the older houses compared to new houses.

In this study, we did not consider prior seasonal differences in the weather conditions, which we recommend be incorporated in future studies. In addition, the calculation of MIR for hexagons may be biased as the IDW interpolation technique used to develop continuous surface maps is affected by the uneven distribution of mosquito traps across the study area. Alternatively, other interpolation methods such as kriging might be used to develop continuous surface maps for MIR, as this method takes into account spatial autocorrelation and also creates an error map. In this study, we did not distinguish between neuroinvasive and non-neuroinvasive WNV cases. Separate analysis for only neuroinvasive cases might help us to identify what conditions drive the occurrence of the severe form of WNV infection and should also help to reduce diagnostic bias. Also, in future studies, we might consider using different spatial scales to identify if the geographic scale has affected the results. We were also unable to use data from avian or equid surveillance in this study, despite its usefulness in other modeling approaches [53–55], due to the lack of consistent data across the time period. Bird surveillance in Illinois is limited to passive surveillance of a small number of dead birds tested in each county per year, and is generally suspended after WNV is known to be circulating in the area, while equid surveillance is based entirely on passive self-reporting [56]. This lack of consistent data on avian mortality has been noticed by others [10], and remains an issue for the use of data on the primary host in WNV forecasting.

In conclusion, our analysis helped to better understand the fine-scale dynamic drivers of WNV transmission in an urban environment. The dynamic interplay between temperature and precipitation, mosquito infection, land cover, and demographic characteristics determine the probability of an area having a WNV case or not. Additionally, we established an important temporal relationship between cumulative mosquito positive pools and mid-summer average MIR with the total annual human WNV cases. This information can be used as a guideline to develop a threshold for public health intervention.

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Reviewer #1: Peer review report on PLOS ONE manuscript " The drivers of West Nile virus human illness: fine scale dynamic effects of weather, mosquito infection, social, and biological conditions", (Manuscript number PONE-D-19-34216).

Recommendation: Minor Revision

Comments to Authors:

This manuscript analyzes the available long-term data of mosquito infection rates, West Nile virus human cases and weather variables from 2005 to 2016 combined with landscape and demographic characteristics of two Illinois counties of the Chicago region in order to evaluate relationships between the factors on fine temporal and spatial scale and identify the drivers that potentially affect the presence of human WNV illness and may act as early warning predictors.
The paper is well written with a well-organized text, the data were analyzed using multi-level statistical modeling approaches and the findings are sufficiently documented and the results are valuable for a better understanding of the fine-scale drivers of spatiotemporal variability of WNV human case prevalence in an urban environment such as in the study area.
Although numerous published studies that have shed light on factors that affect WNV transmission in an area, the knowledge regarding the influence of climatic variables in correlation with the data from the entomological surveillance and the number of WNV human cases, is still limited.
For that reason, the paper makes a substantial contribution to the literature and is therefore recommended for publication in PLOS-ONE after minor revision taking into account the following general or specific comments.

- Thank you for your comments and your feedback!

General comments

The study uses and analyzes the 10-year data (2005 to 2014) from Cook and DuPage counties in the Chicago, Illinois region and the accuracy of the predictions of the developed model tested with the data of the same specific area.
However, according to the literature, it is well known that models predicting the WNV transmission and human WNV infections do not always have the same accuracy when applied to other areas with different mosquito fauna, weather conditions and/or geomorphological and demographic characteristics. Therefore, we consider that the study area should also be mentioned in the title.

- Thank you for the suggestion, we have made that change

Please comment and, if necessary, provide an adequate justification in the manuscript, for the reason that in this work were note included data from passive or active monitoring of WNV presence in birds and equids, which are considered by several authors as important prediction factors of the presence and spread of WNV virus in an area.

- We have added a statement (145-147) that the avian and equid surveillance programs were not consistent across the time period, and added a discussion section (467-474) about the point.

Specific comments

Line 170 of the manuscript: If available, please provide information on the species of Culex mosquitoes that have been tested for WNV presence as the vectorial competence of different species may vary significantly for WNV transmission to humans.

- We agree that is an important point; we have added some information as to common species in the region.

Line 179 of the manuscript: Please add a bibliographical reference in the reference section for the MIR estimation tool by Biggerstaff, 2006.

- Thank you, corrected

Line 188 of the manuscript: Please provide a definition and some additional information about the category of "probable cases of WNV" that were also included in the study along with the "confirmed cases" because the symptoms of infection by the West Nile vary in severity, with the mild forms can be easily confused with flu symptoms and usually go unreported.

- We have added the information. The difference between probable and confirmed cases is confirmatory testing by either IDPH or CDC; all cases had positive diagnostic results and clinical signs during the likely transmission season.

Lines 578-580 of the manuscript: Please, correct Reference no 39 by adding the name of the journal, volume number and pages numbers.
Messina JP, Brown W, Amore G, Kitron UD, Ruiz MO. West Nile Virus in the Greater Chicago Area : A Geographic Examination of Human Illness and Risk from 2002 to 2006. URISA Journal 2011;23: 5-18.

- Corrected

Reviewer #2: Dear authors,

This is a well written paper that deals with the determination of factors affecting the spatiotemporal variability of WNV cases in humans through identification of the fine scale drivers of WNV transmission in an urban area with a repeated history of WNV outbreaks. The findings are very interesting since they include multi-level modeling of weekly data from over a decade and they extend our knowledge in the correlation of variables related to temperature, precipitation, mosquito infection, land cover, and demographic characteristics with the probability of an area having a WNV case or not.

- Thank you

Further down please consider some comments of minor importance that may benefit the manuscript.

It seems that the infection status of avian population, as primary reservoirs of WNV, and equids, as dead-end hosts, were not included among the tested variables for modeling structure. Please note that these are critical factors implicated in the WNV transmission in order to develop predictive models.
As mentioned in the introduction, public health surveillance for WNV involves collection and testing of dead birds suspected to have died of WNV, testing of sentinel chickens or of wild birds captured for this purpose and reporting of cases of equine illness.
Could you please justify this data gap in the model structuring? Is there any surveillance system for infected avian and equids population in the study area?
In the "Introduction" you may add any relevant literature data where bird and/or equine infection rate were used for development of models predicting WNV transmission in humans. Also, in lines 440-459 of the manuscript, you could mention the fact that avian and equids infection status was not considered as a factor for prediction of WNV cases in humans in the study area.

- We have added a statement as to the inconsistent application of avian and equid surveillance in this region (145-147), and given more information about that surveillance in the discussion (467-474), including references to models using these data types.

According to the best multivariable model that was used, the proportion of open water was negatively associated with the probability of WNV cases. Also, as mentioned in the discussion, a negative association of precipitation and WNV cases was observed and this indicates that dry and hot weather conditions would increase the probability of an area being positive for a WNV case.
Instead, it is supposed that high rainfall and high percentage of water bodies in an area may favor mosquito population by increasing their breeding sites, and therefore may lead to increased WNV cases in humans. Hence, a positive correlation between precipitation and water bodies with WNV cases in humans is anticipated. Please comment.

- Open water is classified as areas in which any aquatic vegetation is submerged, as opposed to woody or herbaceous wetlands. This is not likely to be stagnant water of the type used by *Culex* mosquitoes for breeding. Therefore, the negative association between proportion of open water and WNV cases is most likely due to the fact that open water, as defined, does not favor the mosquito population. We have noted this in the discussion (434-438).