BLOOD IN THE WATER: WETLANDS, WET SPELLS, AND DROUGHT REGULATE MOSQUITO-BORNE DISEASE TRANSMISSION AT MULTIPLE SCALES

By

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ABSTRACT

BLOOD IN THE WATER: WETLANDS, WET SPELLS, AND DROUGHT REGULATE MOSQUITO-BORNE DISEASE TRANSMISSION AT MULTIPLE SCALES

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Outbreaks of mosquito-borne diseases pose a significant global public health challenge and are difficult to predict over space and time. In the United States, two of the most important mosquito-borne pathogens, West Nile virus (WNV) and Eastern equine encephalitis virus (EEEV), have irregular outbreak patterns that are potentially linked to variation in climate and land cover. In particular, spatial heterogeneity in WNV and EEEV transmission may be associated with wetlands because they provide suitable habitat for mosquito vectors and avian hosts. Additionally, drought and wet spells may affect multiple aspects of these disease systems, including their arthropod vectors and pathogen hosts. However, wetlands are not homogeneous and the effects of wetlands on WNV and EEEV transmission may vary due to vegetation, connectivity, size, and inundation characteristics. Also, drought and wet spells can lead to increases in disease transmission in some contexts and decreases in others. Finally, wetland characteristics and climate conditions likely interact in complex ways resulting in both spatial and temporal heterogeneity in disease transmission.

In this dissertation, I address the influence of wetlands and climate on WNV and EEEV transmission at a range of temporal and spatial scales. In Chapter 1, I examined the effects of drought conditions and several wetland characteristics on county-level human WNV incidence in the northeastern and midwestern USA. I found that drought and wetland characteristics had regionally variable effects: counties west of the Mississippi River with small wetlands and counties undergoing drought with high levels of semi-permanent wetlands had 100% and 300%

higher human WNV incidence, respectively, and counties east of the Mississippi River with high levels of connected wetlands had 50% higher human WNV incidence than counties without these wetland characteristics. In Chapter 2, I investigated the influence of wetland characteristics and drought and wet spells on EEEV vector infection rates and abundance in Connecticut, USA. I found that evergreen and deciduous forested wetlands were associated with high EEEV vector abundance and that emergent and shrub wetlands were associated with low vector abundance, but that the effects of wetlands on EEEV vector infection rates were weak. Wet conditions during the transmission season and during the fall/winter preceding the transmission season were also favorable for EEEV transmission. In Chapter 3, I examined the influence of drought and wet spells on WNV vector infection rates and abundance in Chicago, Illinois; Ft. Collins, Colorado; and Coachella Valley, California. I detected significant regional differences in the influence of drought and wet spells, likely due to variation in regional aridity and WNV ecology. I also detected local-scale dissimilarities in the influence of drought and wet spells, which were likely caused by surrounding cover of wetlands, impervious surfaces, croplands and forest. These findings demonstrate that the effects of wetland and climate on WNV and EEEV transmission are context dependent, and likely mediated by regional aridity, vector natural history, and wetland characteristics. This underscores the importance of avoiding sweeping generalizations about the influence of wetlands or climate on mosquito-borne disease transmission in the United States.

This dissertation is dedicated to my mom, Anna Drallios, for her inspiring writing and political activism while I myopically focused on my research; to my dad, Jon Skaff, for raising two kids while writing a dissertation, which I find incomprehensible; to my sister, Sophia Skaff, for her inspiring wanderlust; and to my girlfriend, Mary Flegler, for not being complacent in the search for a meaningful job and life.

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PREFACE

The three chapters in this dissertation have been written as stand-alone manuscripts with coauthors. Chapter 1 was written with Dr. Kendra Cheruvelil and published in Landscape Ecology in February 2016; Chapter 2 was written with Dr. Kendra Cheruvelil, Dr. Theodore Andreadis, and Dr. Philip Armstrong and published in Parasites and Vectors in October 2017; Chapter 3 was written with Dr. Kendra Cheruvelil and Dr. Zofia Taranu and will be submitted for peer review in 2018. Below are the associated citations:

Skaff, N. K., and K. S. Cheruvelil. 2016. Fine-scale wetland features mediate vector and climate-dependent macroscale patterns in human West Nile virus incidence. Landscape Ecology **31**:1615-1628.

Skaff, N. K., P. M. Armstrong, T. G. Andreadis, and K. S. Cheruvelil. 2017. Wetland characteristics linked to broad-scale patterns in Culiseta melanura abundance and eastern equine encephalitis virus infection. Parasites & vectors **10**:1-16.

Skaff NK, Taranu Z, Cheruvelil KS. Regional climate and local land cover alter the effects of drought and wet spells on West Nile virus transmission. *In prep.*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Climate and land cover changes in the coming century are expected to trigger profound shifts in the distribution and severity of disease (Gage et al. 2008, Patz et al. 2008, Lafferty 2009). Mosquito-borne pathogens may be exceptionally susceptible to these changes because mosquito vectors and hosts are highly responsive to environmental perturbations (Reiter 2001, Reiter 2008). In particular, drought and wet spells can influence several aspects of mosquito-borne disease transmission, and are expected to change in frequency and severity in the future (Strzepek et al. 2010, Dai 2013, Brown et al. 2014). Also, wetland land cover can facilitate transmission because it supplies aquatic habitat for larval mosquitoes and a suitable environment for multiple aspects of the host life cycle (Carpenter and La Casse 1965, Tiner Jr 1984, Laderman et al. 1989). By further examining how these factors influence transmission, it is possible to more effectively predict outbreaks of these pathogens.

Two important mosquito-borne pathogens in the United States, West Nile virus (WNV; *Flaviviridae*; *Flavivirus*) and Eastern equine encephalitis virus (EEEV; *Togaviridae*, *Alphavirus*), have transmission cycles that may be susceptible to the effects of drought and wet spells and wetland land cover. WNV is geographically pervasive and the most prevalent mosquito-borne pathogen in the US (Reimann et al. 2008). The primary WNV vector species differ across US regions. *Culex pipiens* and *Culex restuans* proliferate in northern latitudes in container habitats or other stagnant pools; *Culex quinquefasciatus* is primarily found in southern states with mild winter temperatures; and *Culex tarsalis* is often found in wetlands west of the Mississippi River (Pratt et al. 1963, Goddard et al. 2002, Kilpatrick et al. 2005). The primary EEEV vector is *Culiseta melanura*, which overwinters in the larval stage and prefers cool, acidic larval habitats (Weaver 2005, Armstrong and Andreadis 2010). Outbreaks of EEEV have been expanding regionally in the US since 2000, although the reasons for the expansion are not clear (Armstrong and Andreadis 2013). WNV and EEEV circulate among passerine birds and ornithophilic vectors and may cause severe illness in humans that are incidentally infected (Scott and Weaver 1989, Reimann et al. 2008, Reisen 2013). Transmission of both pathogens is usually most intense during the summer months, but environmental conditions throughout the year can influence transmission (Weaver 2005, Reisen 2013).

Previous studies suggest that WNV and EEEV transmission may be closely associated with the occurrence of drought and wet spells. These climate conditions can alter either vector abundance or vector infection rates, both of which affect the risks of outbreak in humans (Bolling et al. 2009, Kilpatrick and Pape 2013). Drought can reduce vector abundance by limiting available aquatic larval habitat (Reisen et al. 1992), or may increase vector abundance by increasing organic content in larval habitats (Andreadis et al. 2004, Johnson and Sukhdeo 2013). In contrast, wet conditions can increase vector abundance by creating larval habitats (Reisen et al. 1992) or reduce vector abundance by decreasing larval habitat stability and organic content due to frequent flushing (Shaman et al. 2002, Andreadis et al. 2004, Koenraadt and Harrington 2008). Drought can also increase WNV rates in vectors by restricting aquatic habitat availability, thus facilitating contact between vectors and susceptible hosts in remaining refugia (Shaman et al. 2005, Johnson and Sukhdeo 2013). In contrast, wet spells can increase infection prevalence by supporting larger populations of susceptible passerine species, including the hatch year birds (Rotenberry and Wiens 1989, Sæther et al. 2004) that are important for WNV amplification (Hamer et al. 2008b). However, it is not clear whether the effects of drought and wet spells differ across regions with different ecological characteristics, at local scales due to land cover differences, or if the timing of climate events plays a role. This information will help to determine when, where, and how the effects of climate conditions manifest in WNV and EEEV transmission.

Wetlands may also play a key role in transmission, because they can provide habitat for larval mosquitoes and attract susceptible hosts (Carpenter and La Casse 1965, Tiner Jr 1984, Laderman et al. 1989). Certain wetland characteristics have been shown to be particularly important. For example, wetland vegetation imposes important constraints on the suitability of wetland habitats for larval development and on the locations where contact between vectors and susceptible avian hosts occurs (Rey et al. 2012). Connectivity of wetlands to other aquatic habitats may influence mosquito abundance via changes in mosquito predator dispersal, while wetland size can influence the composition of host communities (Chase and Shulman 2009, Johnson et al. 2012). Climate conditions, including drought and wet spells, can interact with specific wetland characteristics to influence transmission. Wetlands with semi-permanent inundation regimes can be highly favorable for vectors after drought periods (Chase and Knight 2003), and drought can eliminate temporary wetlands forcing vectors and avian hosts onto a few remaining permanent refuges leading to vector-host contact (Shaman et al. 2005). Finally, climate-driven increases in groundwater levels can inundate some wetlands resulting in larger vector populations (Howard et al. 1988). Despite the apparent importance of wetland characteristics, studies at broad spatial scales have typically failed to account for how differences among wetland habitats can influence disease transmission (e.g. Gibbs et al. 2006, Ezenwa et al. 2007, Bowden et al. 2011, DeGroote and Sugumaran 2012). Therefore, research is needed to determine whether specific wetland characteristics have an epidemiologically-relevant influence on EEEV and WNV transmission over broad areas.

The following chapters examine how climate conditions and wetland characteristics influence human WNV incidence, and WNV and EEEV vector abundance and infection rates. Chapter 1 focuses on the effects of drought conditions and three fine-scale wetland characteristics—wetland size, connectivity, and inundation regime—on broad-scale human WNV incidence in the northeastern and midwestern United States. Chapter 2 examines the effects of several wetland characteristics and drought and wet spells on EEEV transmission at multiple spatial scales and temporal periods in Connecticut, USA. Finally, Chapter 3 addresses the influence of drought and wet spells on WNV vector abundance and infection rates in Chicago, Illinois; Ft. Collins, Colorado; and Coachella Valley, California. By determining how climate, wetlands and interactions between the two influence EEEV and WNV transmission it is possible to better predict the location and timing of mosquito-borne disease outbreaks. With this information, future climate and land cover changes will have easier to anticipate effects on the severity and geographical distribution of mosquito-borne pathogens.

CHAPTER 1: Fine-scale wetland features mediate vector and climate-dependent macroscale patterns in human West Nile virus incidence

We take a spatially explicit GIS-based approach to determine whether fine-scale wetland characteristics influence annual county-level human West Nile virus incidence across the northeastern and midwestern US. Our results indicate that the effects of wetland characteristics are regionally dependent and may be mediated by other factors such as vector species-specific traits and climate. For a full text of this work go to: https://www.researchgate.net/publication/295085677_Fine-scale_wetland_features_mediate_vector_and_climate-dependent_macroscale_patterns_in_human_West_Nile_virus_incidence

CHAPTER 2: Wetland characteristics linked to broad-scale patterns in *Culiseta melanura* abundance and Eastern equine encephalitis virus infection

We examined the effects of wetland characteristics and climate conditions on *Cs. melanura* abundance and infection with Eastern equine encephalitis virus (EEEV) at multiple spatial scales in Connecticut, USA. Our results suggest that wetland vegetation is an important determinant of *Cs. melanura* abundance and that wet conditions during the summer and winter are linked to increased risks of EEEV transmission. For a full text of this work go to: https://parasitesandvectors.biomedcentral.com/articles/10.1186/s13071-017-2482-0

CHAPTER 3: Regional climate and local land cover alter the effects of drought and wet spells on West Nile virus transmission

Abstract

Climate change is expected to cause regional shifts in the severity and frequency of drought and wet spells, both of which influence components of mosquito-borne disease transmission. However, responses to these climate conditions can be complex and may increase disease transmission in some contexts, but reduce it in others. This is particularly true for West Nile virus (WNV), the most prevalent mosquito-borne pathogen in the United States, because its continental range spans a huge variety of ecosystems, resulting in regional variation in vectors, hosts, and their environmental preferences. Therefore, we evaluated the influence of drought and wet spells on WNV vector abundance and vector infection rates in Chicago, Illinois; Ft. Collins, Colorado; and Coachella Valley, California. These locations span major gradients of climate, land cover, and vector species, offering insight into WNV transmission across a large part of the WNV range. We found that the influence of drought and wet spells was vastly different among the three locations, and that local-scale land cover, particularly wetlands, mediated effects on vector abundance and infection rates. These results point to the importance of multi-scale studies of disease transmission and underscore the complex and sometimes contradictory responses of pathogens to climate patterns.

Introduction

Changes in the severity and frequency of drought and wet spells are predicted in the coming century. Severe drought is projected to increase substantially over a wide area of the globe, including most regions of the United States (US; Karl 2009, Strzepek et al. 2010, Dai 2013). However, some US regions may experience fewer months of drought and wetter conditions (Karl 2009, Strzepek et al. 2010). These changes are likely to have important, regionally-specific implications for disease transmission, particularly transmission of mosquito-borne pathogens. Drought and wet spells have been shown to affect multiple components of mosquito-borne disease systems, including vectors, pathogens, and pathogen hosts (Githeko et al. 2000, Brown et al. 2014). However, responses to these climate conditions can be complex, leading to increases in disease transmission in some contexts, but decreases in others (Landesman et al. 2007, Brown et al. 2014, Skaff and Cheruvelil 2016). Therefore, it is essential to understand the spatial and temporal factors that determine specific responses.

West Nile virus (WNV; *Flaviviridae*; *Flavivirus*is) one of the most significant vector-borne threats to human health in the US (Reimann et al. 2008). This pathogen circulates primarily among passerine birds and ornithophilic *Culex* mosquitoes, with human infection resulting from spillover transmission (Reimann et al. 2008, Reisen 2013). In the US, the primary vector species differ across geographic gradients. *Culex pipiens* and *Culex restuans* proliferate in northern latitudes in container habitats or small pools; *Culex quinquefasciatus* has similar habitat preferences, but is not cold tolerant and is primarily found in southern states with mild winters; and *Culex tarsalis* is often found in wetlands and agricultural settings west of the Mississippi River (Pratt et al. 1963). Viral transmission can occur between the spring and fall, although it is most intense in the mid to late summer (Reisen 2013).

Previous studies indicate that WNV transmission is closely associated with drought and wet spells. Summer Palmer Drought Severity Index (PDSI) was found to be significantly associated with annual human WNV cases in half the states in the continental US (Paull et al. 2017). Drought and wet spells proceeding the transmission season were also associated with human WNV incidence, with drought linked to higher WNV incidence in the western USA and wet conditions linked with higher WNV incidence in the eastern US (Landesman et al. 2007). In contrast, above average rainfall had a positive effect on human WNV infection in the western US and a negative effect in the eastern US (Hahn et al. 2015). The effects of climate appear to be geographically pervasive and may act on multiple aspects of WNV transmission.

Drought and wet spells can influence WNV transmission via changes in either vector abundance or vector infection prevalence, both of which increase the likelihood that WNV-infected mosquitoes blood-feed on humans (Bolling et al. 2009, Kilpatrick and Pape 2013). Drought can reduce vector abundance by limiting available aquatic larval habitat (Reisen et al. 1992), or may increase vector abundance by increasing organic content in larval habitats (Andreadis et al. 2004, Johnson and Sukhdeo 2013), or by eradicating mosquito predators (Chase and Knight 2003). In contrast, wet conditions can increase vector abundance by creating larval habitats (Reisen et al. 1992) or reduce vector abundance by decreasing larval habitat stability and organic content due to frequent flushing (Shaman et al. 2002, Andreadis et al. 2004, Koenraadt and Harrington 2008). Drought can increase WNV prevalence in vectors by reducing available aquatic habitat, thus facilitating contact between vectors and susceptible hosts in remaining refugia (Shaman et al. 2005, Johnson and Sukhdeo 2013). In contrast, wet spells can increase WNV infection prevalence by supporting larger populations of susceptible passerine species, including the hatch year birds (Rotenberry and Wiens 1989, Sæther et al. 2004) that are important for WNV amplification (Hamer et al. 2008b).

Given the wide variation in the effects of drought and wet spells on WNV transmission, it is important to understand the spatial context determining when and where these divergent relationships are observed. These relationships may differ based on regional WNV ecology, multi-scaled landscape cover and use, or the timing of the drought or wet spell. For instance, drought may have different effects depending on the regional vector species (Landesman et al. 2007, Skaff and Cheruvelil 2016), wetlands and croplands can mediate relationships between drought and mosquito abundance or infection (Shaman et al. 2005, Shaman et al. 2010, Skaff et al. 2017), and the timing of drought and wet spells (i.e., prior to or during the transmission season) can determine how vector populations respond (Chase and Knight 2003, Shaman et al. 2005, Skaff et al. 2017). However, there are few studies comparing the effects of these climate conditions on vector abundance and WNV infection rates across regions and through time, nor are there systematic analyses of how these effects may differ depending on local-scale land cover.

We evaluated how drought and wet spells influence vector abundance and vector minimum infection rate (MIR) at multiple scales using mosquito surveillance datasets from Chicago, IL; Ft. Collins, CO; and Coachella Valley, CA. These locations have dissimilar climates, land cover patterns, and vector species, which provided an opportunity to better understand links between climate and WNV transmission in different parts of the WNV range. We addressed three main questions: 1.) How do the effects of drought and wet spells on abundance and MIR differ among these three locations?; 2.) How does the timing of drought and wet spells mediate these relationships?; 3.) What local-scale land cover characteristics are associated with differences in the effects of drought and wet spells on vector abundance and MIR?

Methods

Study locations, mosquito sampling, and data sources

Chicago: This US city with a population of 2.7 million (2010 US census) and an area of 600 km^2 borders the southwestern edge of Lake Michigan in the north central US. It has a temperate climate, with four distinct seasons including cold snowy winters and warm humid summers (Peel et al. 2007). The city receives an average of 99.3 cm of precipitation per year (Midway Airport station; https://www.ncdc.noaa.gov/cdo-web/datatools/normals). The most important WNV vector is *Cx. pipiens*, which blood-feeds on both avian and mammalian hosts (Hamer et al. 2008a). Another species, *Cx. restuans*, has similar blood-feeding preferences and may also play a role in WNV transmission in this region (Hamer et al. 2008a). We grouped these two species in our analysis, because they are morphologically similar and were often not distinguished during sample collection and processing.

Mosquito surveillance data were acquired from the Chicago Department of Public Health (CDPH). Gravid traps baited with a grass infusion and BG-sentinel traps (https://www.bg-sentinel.com) baited with CO_2 and a BG-lure were typically operated twice per week between late May and early October from 2004–2016. All collected *Cx. pipiens* and *Cx. restuans* were pooled in groups of up to 50 and tested for WNV weekly using RT-PCR. Further details on data collection and virus detection protocols have been previously reported (Jones et al. 2011). Traps that were operated, but failed to capture mosquitoes were not recorded in the available dataset and therefore were not included in our analyses. Sampling sites were located in a range of habitat types and were generally surrounded by large amounts of impervious cover (Table 1). The exact locations of traps were not provided by CDPH, but were listed within city blocks (~0.02 km^2). We used ggmap package in R version 3.3.3 to geocode city blocks to approximate geographic coordinates.

Fort Collins: This US city with a population of 145,000 (2010 US census) and an area of 148 km^2 is located in the foothills of the Rocky Mountains in the west central US. It has a semi-arid climate with four distinct seasons, and minimal precipitation (average of 40.9 cm per year) that typically occurs in the spring and summer (https://www.ncdc.noaa.gov/cdo-web/datatools/normals; Peel et al. 2007). *Cx. tarsalis* and *Cx. pipiens* transmit WNV in this region, although *Cx. tarsalis* is the primary enzootic and epizootic vector (Bolling et al. 2009). Here we focus only on *Cx. tarsalis*.

Mosquito surveillance data were acquired from Vector Disease Control International, a company specializing in Integrated Mosquito Management (http://www.vdci.net). CDC Miniature Light Traps with a CO_2 attractant and gravid traps baited with an alfalfa and MicrobeLift (https://www.microbelift.com) infusion were operated weekly from late May through mid-September 2006–2012. Collected *Cx. tarsalis* were combined in pools of up to 50 and tested for WNV virus using RT-PCR. Traps that were operated, but failed to capture mosquitoes were not recorded in the available dataset and therefore were not included in our analyses. Sampling sites were located in a range of wetland, impervious and cropland cover but generally had little forest (Table 1).

Coachella Valley: The Coachella Valley is located in southern California on the northern shore of the Salton Sea, an inland waterbody. The valley has an area of ~1,728 km^2 and is bounded by several mountain ranges. It consists of nine cities with a total population of 346,518 and several small, heavily-agricultural communities. The climate is extremely arid with mild winters and extremely hot summers. Most precipitation occurs during the winter, with a yearly average of 8.1 cm (Mecca Station, https://www.ncdc.noaa.gov/cdo-web/datatools/normals). The valley is dominated by resorts and residential areas in the north, transitioning to irrigated cropland moving south toward the Salton Sea. Areas around the Salton Sea consist of managed wetlands used for bird conservation and duck hunting (http://ca.audubon.org/conservation/roadmap-protecting-bird-habitat-salton-sea; Reisen et al. 2008). *Cx. tarsalis* and *Cx. quinquefasciatus* are the primary vectors in this region, although *Cx. tarsalis* plays a key role in enzootic transmission (Reisen et al. 2008). We focus only on *Cx. tarsalis*.

Mosquito surveillance data were acquired from the Coachella Valley Mosquito and Vector Control District. CDC light traps with a CO_2 attractant, gravid traps baited with an alfalfa infusion, and a small number of BG-sentinel traps were operated for one night every week or two weeks from January through December, 2006-2016. Collected *Cx. tarsalis* were combined in pools of up to 50 and tested for WNV virus using RT-PCR. We did not include data from traps that failed to capture mosquitoes in order to remain consistent with the surveillance datasets from Chicago and Ft. Collins. Unlike in Chicago and Ft. Collins, sampling occurred year-round due to the mild conditions, and *Cx. tarsalis* abundance was relatively high during all months. WNV was detected in mosquitoes in all months, although it was generally highest in July and August. Sampling sites were located in areas with a range of wetland and cropland cover, but generally had little forest and impervious cover (Table 1).

Land Cover

We quantified the land cover characteristics within buffers of 100 m, 500 m, 1000 m, and 5000 m around each sampling site in Chicago, Ft. Collins, and Coachella Valley. The characteristics included were: 1) the percent of impervious surfaces, 2) the percent of cultivated land cover, 3) the area of irrigated cropland, 4) the percent of forest cover, 5) the area of all wetlands, and 6) the area of wetlands with specific vegetative, system and inundation classifications (details below). Impervious surface data were acquired from the 2006 National Land Cover Database Percent Developed Imperviousness layer (https://www.mrlc.gov/nlcd06_data.php) and the percent impervious surface was calculated by determining the mean pixel value within each buffer. Cultivated land cover data were also acquired from the 2006 National Land Cover Database (https://www.mrlc.gov/nlcd06_data.php) and the percent of cultivated land was determined by calculating the percent of pixels within each buffer with a value of 82 (NLCD code for cultivated land). In order to also assess the influence of irrigated croplands, we included data from the Moderate Resolution Imaging Spectroradiometer (MODIS) Irrigated Agriculture Dataset for the United States (MIrAD-US; https://earlywarning.usgs.gov/USirrigation). We calculated the percent cover of irrigated cropland by calculating the proportion of pixels within each buffer that contained irrigated cropland. Forest cover was acquired from the United States Geological Survey (USGS) 2010 Global Tree Canopy Cover dataset (https://landcover.usgs.gov/glc/TreeCoverDescriptionAndDownloads.php). The mean value of each pixel representing the percent of tree canopy cover was calculated within each buffer. Finally, we used the National Wetlands Inventory to determine the total wetland area and area of wetlands with three vegetation types, four different system classifications and four different water inundation regimes (https://www.fws.gov/wetlands/). Wetland vegetation types included: 1) emergent, 2) forest, and 3) scrub/shrub wetlands; wetland system classifications included: 1) palustrine, 2) riverine, 3) pond, and 4) farmed wetlands; wetland inundation regimes included 1) temporarily flooded, 2) seasonally flooded, 3) semi-permanently flooded and 4) permanently flooded wetlands. We calculated the total area of polygons of each wetland type within buffer areas. We used the raster, rgeos and sp packages in R version 3.3.3 to calculate land cover around sampling sites.

Analytical methods

Our analyses consisted of four steps: 1) we calculated response variables (vector abundance and MIR) annually for each individual sampling site; 2) we calculated Pearson correlations between each response variable and monthly PDSI for each sampling site; 3) we determined whether similar sampling sites had significant correlations with monthly PDSI across months; and 4) we identified the land cover variables associated with significantly and non-significantly correlated sampling sites during each month. Step 2 allowed us to determine how the effects of drought and wet spells on abundance and MIR differed between regions; steps 2 and 3 allowed us to determine how the timing of drought and wet spells mediated these regional relationships; and steps 2 and 4 determined whether local-scale land cover characteristics were associated with differences in the effects of drought and wet spells at sampling sites.

1) Quantifying vector abundance and MIR: We calculated mean annual MIR and mean annual vector abundance per trap night for each sampling site. MIR was determined by calculating the annual average weekly MIR ((# positive pools in week/total weekly capture)*1000). Annual abundance per trap night was calculated by determining the total number of mosquitoes captured at each site per year, then dividing by the total number of trap nights. In order to ensure an adequate sample size to detect correlations between PDSI and MIR/vector abundance, sampling sites were only included in our analyses if they had at least four years with detections of WNV for MIR analysis, and at least four years of sampling for vector abundance analyses.

2) Correlation Analysis: In order to assess the impacts of drought and wet spells at each sampling site, we calculated Pearson correlations between monthly PDSI and a) annual vector abundance per trap night and b) mean annual MIR. For each site, we calculated mean PDSI for each month from the June of the previous year through the last month of sampling in the focal year (year mosquito surveillance data were collected). This information was derived using rasterized data from the Wild West Drought Tracker (https://wrcc.dri.edu/wwdt/about.php) and was calculated by determining the mean pixel value within a 500 m buffer of each site (Abatzoglou et al. 2017). Pearson correlations were considered significant at $p < 0.1$ in order to include sites with obvious correlations that had a small sample size. We were willing to accept an elevated probability of falsely rejecting the null hypothesis (type I error), because findings hinged on overall monthly and regional patterns across multiple sites rather than the correlations at individual sites.

3) Similarity of sampling sites: We determined whether similar sampling sites had significant correlations between PDSI and a) vector abundance and b) mean annual MIR in different months. Bray-Curtis similarity indices were generated using the vegan package in R version 3.3.3.

4) Land cover drivers of correlations: Classification trees (rpart package in R version 3.3.3) were used to identify potential land cover drivers of significant correlations between monthly PDSI and a) annual vector abundance per trap night, and b) mean annual MIR. Land cover variables associated with a higher or lower likelihood of a significant correlation at a site during each month (previous June – focal October) were selected using the Gini index as the splitting criteria. We limited overfitting of trees by setting the minimum bucket size to half the sample size of the minority binary outcome, setting complexity parameter to 0.01, and by only growing trees for months where at least 15% of sites had a significant correlation. Due to low sample sizes, there was instability in 10-fold cross validation outcomes, so these results were not used to limit tree size. However, trees generally had fewer than three splits due to other efforts to limit overfitting.

All figures were generated using the ggplot2 package in R version 3.3.3.

Results

Question 1: Regional differences in the effects of drought and wet spells

We detected differences in the influence of drought and wet spells among our three study locations. In Chicago, PDSI was consistently and negatively correlated with both MIR and vector abundance, while it changed through time and differed by response variable in the other locations (Figure 1a,b; Figure 2a,b). In Fort Collins, negative correlations between MIR and PDSI dominated from May to September of the focal transmission season (Figure 1c). During other time periods, few sampling sites had significant correlations between MIR and PDSI (Figure 1c). During June through November of the previous year, significant correlations between PDSI and vector abundance were exclusively negative (Figure 1d). There was a subsequent period of transition from December to April when there were few to no sites with significant correlations, then from May to September, significant correlations between PDSI and abundance were exclusively positive (Figure 1d).

In Coachella Valley, few sites had correlations between PDSI and MIR from June through December of the previous year, but from January through December of the focal year, positive correlations were common and were observed in approximately a quarter of the sampling sites (Figure 1e; Figure 2a). Vector abundance was more tightly linked with PDSI than was MIR. During an extended period from January to December of the focal year, vector abundance was consistently and positively correlated with PDSI in Coachella Valley (Figure 1f; Figure 2b). Overall, our results show that dry conditions increased MIR and abundance in Chicago, dry and wet conditions increased MIR and abundance in Ft. Collins depending on the timing and response variable, and wet conditions consistently increased MIR and abundance in Coachella Valley.

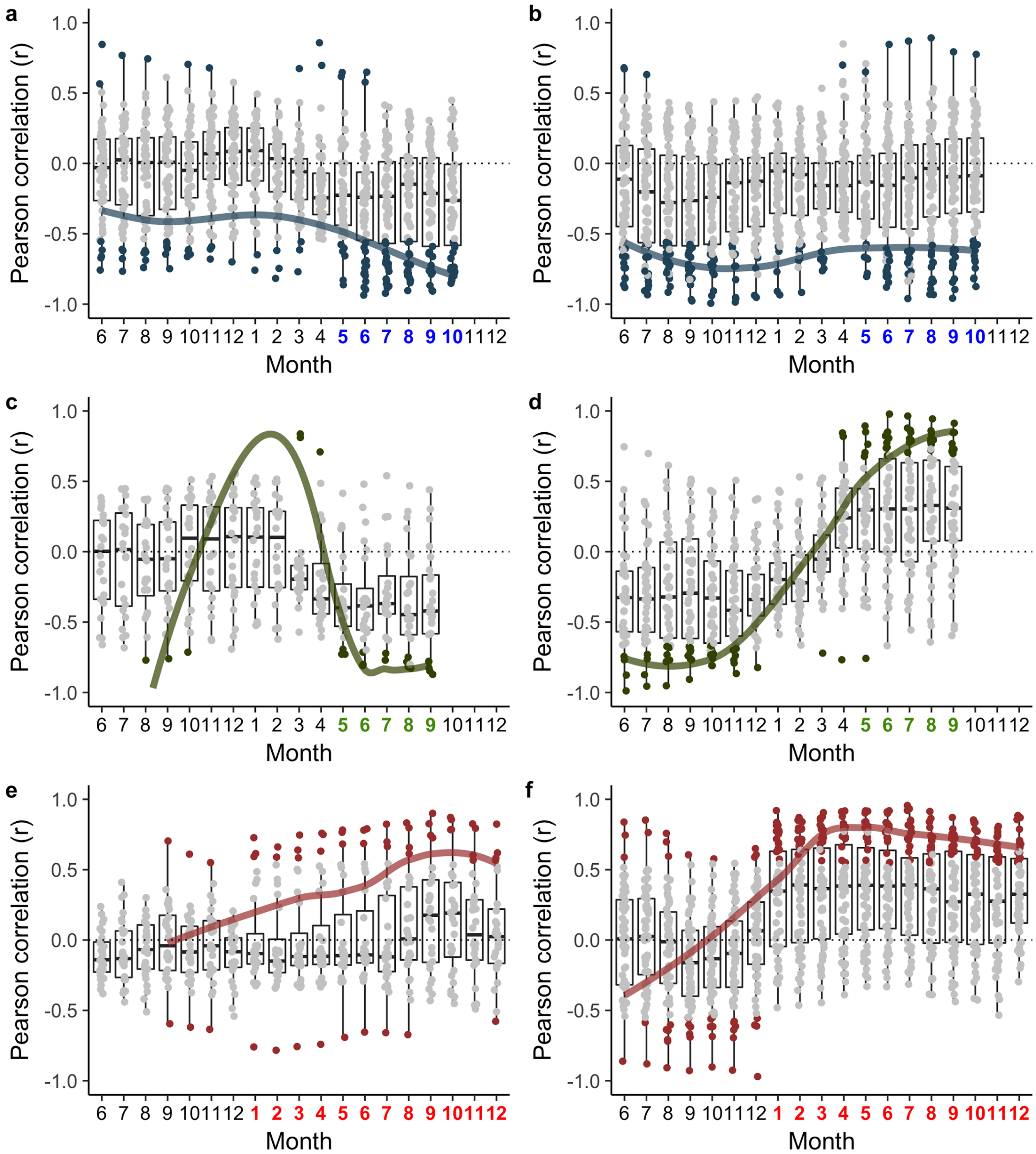

Figure 1. Pearson correlations between monthly Palmer Drought Severity Index (PDSI; June previous year through December focal year) and annual mean minimum infection rate (MIR; left panels; a,c,e); and monthly PDSI and total vector abundance (right panels; b,d,f) at each sampling site. Plots depict correlations in Chicago (top two panels with blue color scheme; a,b); Ft. Collins (middle two panels with green color scheme; c,d); and Coachella Valley (bottom two panels with red color scheme; e,f). Sampling sites with statistically significant correlations ($p<0.1$) are depicted with colored (dark) points; sites with non-statistically significant correlations are grey (light). Lowess curves are fitted through the points with statistically significant correlations to reflect overall patterns in the effects of drought and wet spells across

months. Months during the focal year when mosquito sampling occurred are labeled with a bolded and colored font.

Question 2: The importance of drought and wet spell timing

We found that the timing of drought and wet spells (i.e. the month of PDSI measurement) had two distinct consequences for observed correlations with MIR and vector abundance. First, timing determined whether significant correlations were observed and the direction of observed correlations at a site. Henceforth, we refer to this as a ‘directional effect’. Second, timing determined which sampling sites were significantly correlated with PDSI – we refer to these as ‘site-level effects’. Site-level effects were identified by determining the similarity of the sampling sites with significant correlations in different months. In Chicago, the directional effects of timing were minimal given that significant correlations were overwhelmingly negative during all months for both MIR and vector abundance (Figure 1a,b; Figure 2a,b). However, site-level effects of timing were prevalent. We found that the sampling sites where MIR and vector abundance were significantly correlated with PDSI differed depending on the month, even though the directional effects were consistently negative through time (Figure 3a, b). For MIR, the sampling sites negatively correlated with PDSI between June and October of the focal year were very different from the sampling sites with significant negative correlations between the previous August and the previous December (<11% similarity; Figure 3a). A similar but weaker pattern was observed for vector abundance in Chicago (Figure 3b).

Both directional and site-level effects of the timing of drought and wet spells were identified in Ft. Collins and Coachella Valley. In these locations, the directional effects tended to change between the transmission season and the months preceding the transmission season (Figure 1c-f). Also, our analysis of site-level effects indicates that sampling sites in Ft. Collins with significant positive correlations between PDSI and vector abundance from May to September of the focal year were very different from the negatively correlated sites during July through December of the preceding year (0% similarity; Figure 3d). In Coachella Valley, sampling sites with significant positive correlations between PDSI and vector abundance from January through December were markedly different from the sites where significant correlations were observed from June to December of the previous year (<25% similarity; Figure 3e,f). In Ft. Collins and Coachella Valley, there were very few significant correlations between PDSI and MIR prior to the transmission season, so site-level effects of timing could not be evaluated (Figure 3c,e). These results indicate that the month when drought and wet spells occur heavily influences the site-level effects in Chicago, and both the directional and site-level effects in Ft. Collins and Coachella Valley.

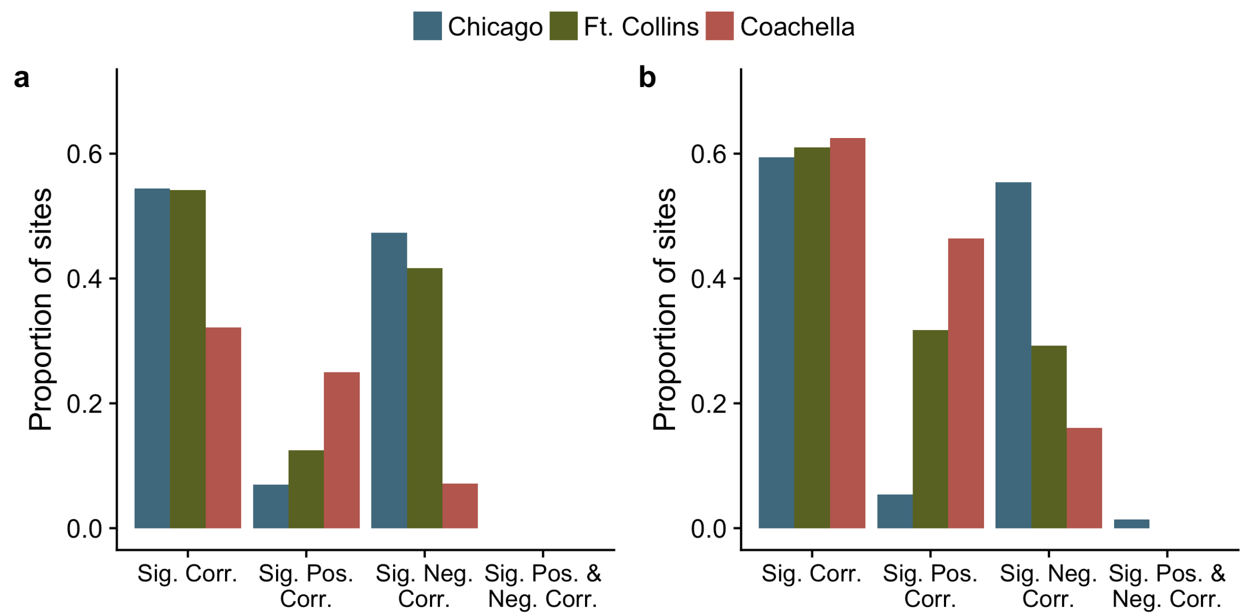

Figure 2. The proportion of sampling sites in Chicago (left, blue), Ft. Collins (middle, green), and Coachella Valley (right, red) with statistically significant Pearson correlations (p<0.1), statistically significant positive Pearson correlations, statistically significant negative Pearson correlations, and both positive and negative significant correlations between Palmer Drought Severity Index (PDSI) and minimum infection rate(MIR) (a), and PDSI and vector abundance (b)

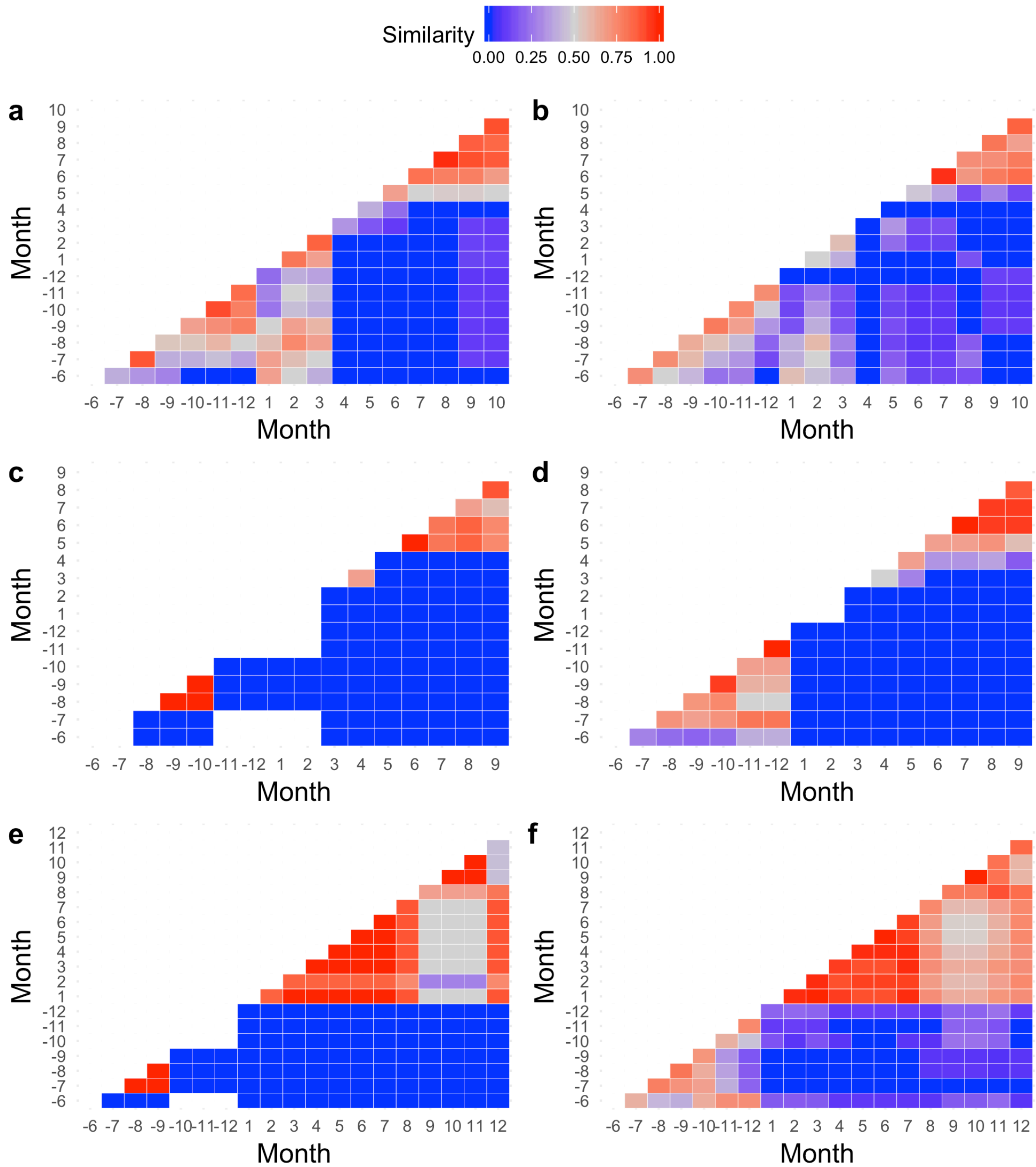

Figure 3. Comparing the Bray-Curtis similarity indices for the sampling sites with significant Pearson correlations ($p<0.1$) between Palmer Drought Severity Index (PDSI) and minimum infection rate (MIR; left panels, a,c,e) and PDSI and vector abundance (right panels, b,d,f) for each month in Chicago (top panels; a,b), Ft. Collins (middle panels; c,d), and Coachella Valley (bottom panels; e,f). Higher similarity values (red) indicate that the months compared have similar sampling sites with significant correlations; low similarity values (blue) indicate that the months compared have different sampling sites with significant correlations. If both months compared have no sampling sites with significant correlations, than no similarity value is calculated. Months labeled with a negative sign represent the previous year (e.g. previous June), rather than the focal year (e.g. current June)

Question 3: Local land cover regulation of drought and wet spell effects

Although we observed distinct regional patterns, many sampling sites within each region did not conform to the dominant paradigm. Therefore, we examined whether observed differences among sampling sites in the same region were related to a site's surrounding land cover context.

We found that the local land cover variables associated with significant correlations differed among locations and by response variable. In Chicago, forest cover and impervious surfaces increased the likelihood that a site had a significant negative correlation with MIR (Figure 4a), but wetlands and impervious surfaces were most important in determining the likelihood of a significant correlation with vector abundance (Figure 4b). In Ft. Collins, wetland area consistently affected the likelihood of a significant correlation for both MIR and vector abundance (Figure 4c,d). In Coachella Valley, the total wetland area was important in determining the likelihood of significant correlations for MIR, but wetlands, forests, and croplands were all important for vector abundance. (Figure 4 e,f). In all, we found that a wide variety of land cover variables were important and that multiple land cover variables could concurrently mediate the effects drought and wet spells on the response variables.

We also found that local land cover variables could either increase or decrease the likelihood of detecting a significant correlation at a sampling site. In Chicago, land cover variables generally increased the likelihood of detecting a significant negative correlation (Figure 4a,b), but in Ft. Collins land cover could increase or decrease the likelihood (Figure 4c,d). For example, wetlands increased the likelihood of detecting a significant negative correlation, but decreased the likelihood of detecting a significant positive correlation at sampling sites in Ft. Collins (Figure 4c,d). In Coachella Valley, wetlands increased the likelihood of a significant positive correlation with MIR, but decreased the likelihood of a significant correlation with vector abundance. Croplands also increased the likelihood of detecting a significant positive correlation with vector abundance (Figure 4e,f). Overall, local land cover had a pervasive influence on the importance of drought and wet spells that could either increase or decrease the likelihood of a significant correlation at a sampling site.

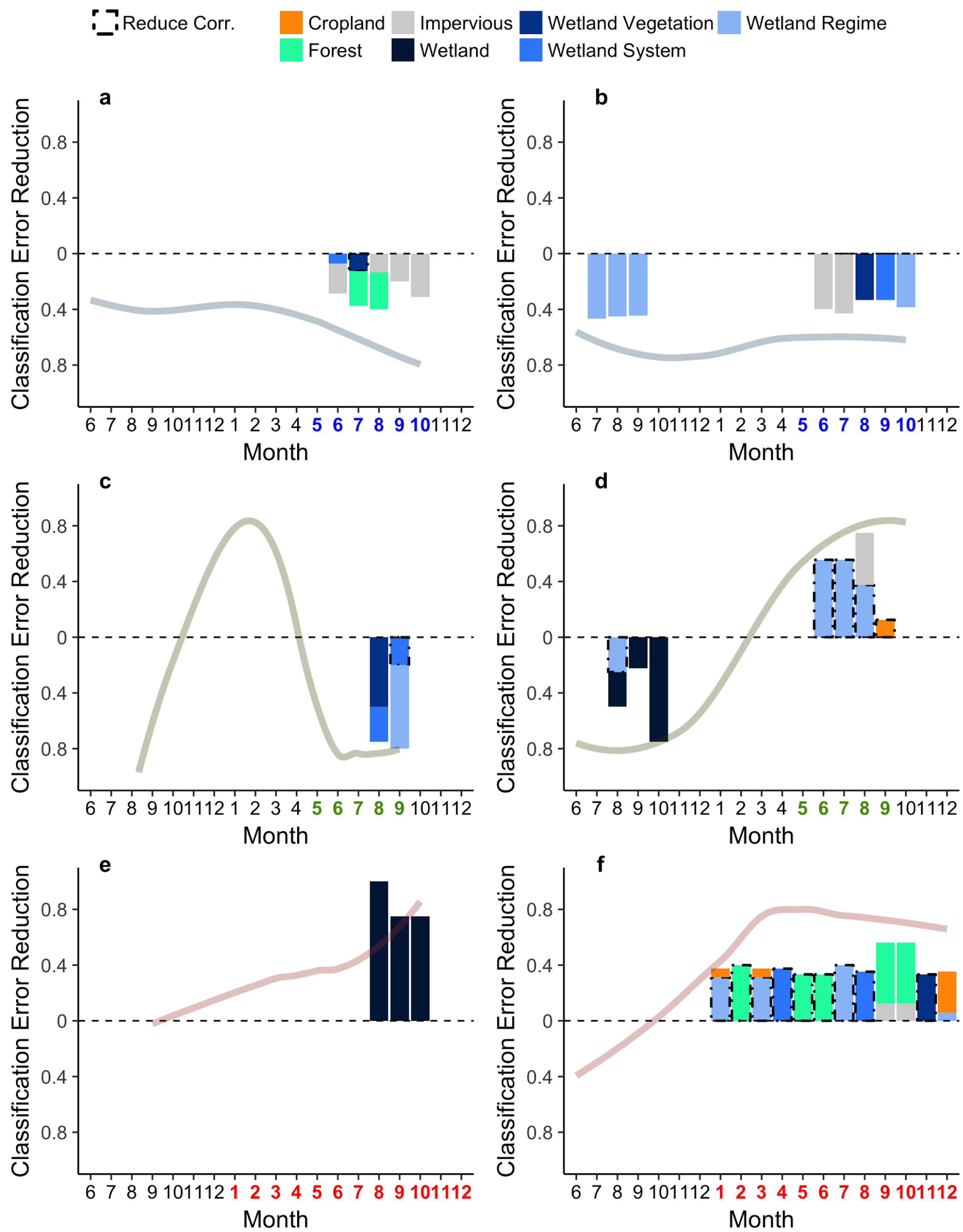

Figure 4. Land cover variables identified in classification trees that increase or decrease the likelihood that a sampling site has a statistically significant positive or negative correlation between Palmer Drought Severity Index (PDSI) and minimum infection rate (MIR; left panels; a,c,e) and PDSI and vector abundance (right panels; b,d,f) in each month in Chicago (top panels; a,b), Ft. Collins (middle panels; c,d), and Coachella Valley (bottom panels; e,f). The y-axis represents the percent of sites that the land cover variable helps to correctly classify and can be interpreted similarly to the proportion of variance explained by the variable (R2). Land cover variables associated with significant negative correlations are represented by bars pointing down, and those associated with significant positive correlations are represented by upwards pointing

Figure 4 (cont'd)
bars. Variables that reduce the likelihood a site has a significant correlation (rather than increase the likelihood) are represented by bars outlined with a dashed line. Lowess curves from Figure 1 are overlaid to show patterns of significant correlations across months. Months during the focal year when mosquito sampling occurred are labeled with a bolded and colored font. Wetland refers to the total area of all wetland types around a sampling site; wetland vegetation refers to the area of either emergent, forest, or shrub wetland; wetland system refers to the area of wetlands with either a palustrine, riverine, pond or farmed classification; wetland regime refers to the area of wetlands with either a temporarily flooded, seasonally flooded, semi-permanently flooded, or permanently flooded inundation pattern

Discussion

We found that WNV vector abundance and infection rates had complex and contradictory responses to drought and wet spells – conditions that were favorable for disease transmission in some circumstances were unfavorable or had no effect in others. Our findings help to identify the specific context and spatial scales at which these differing outcomes occur. We found that the influence of drought and wet spells varied significantly across regions, that the timing of drought and wet spells had a strong influence on corresponding changes in vector abundance and infection rates, and that differences in local-scale land cover altered these relationships.

Regional climate and biota alter the effects of drought and wet spells

We detected regional differences in relationships between PDSI and our response variables that appear to be mediated by a combination of climate differences and vector habitat preferences. In Chicago, which receives plentiful annual rainfall and has poorly drained soils, we found that drier conditions during any part of the previous or focal transmission season were associated with both higher vector abundance and MIR. This suggests that dry weather in this area, at nearly any time of year, could lead to increased risks of transmission to humans.

This result is consistent with the current understanding of WNV transmission in Chicago and other areas of the Northeast US. The primary vectors, *Culex pipiens* and *Culex restuans*, generally prefer stagnant water sources with high organic content for larval development (Pratt et al. 1963, Gardner et al. 2012). Dry conditions promote these characteristics because they reduce habitat flushing and support the accumulation of organic matter (Munstermann and Craig Jr 1976, Gardner et al. 2012). Catch-basins, built in Chicago to ameliorate backyard and basement flooding, may exacerbate the issue by creating plentiful habitat for local vectors during dry periods (Ruiz et al. 2004). Rainfall events of just 3.5 cm were found to flush larva from catch-basins in Chicago (Gardner et al. 2012), so even moderate droughts that reduce the likelihood of heavy precipitation may lead to substantial increases in vector populations. Associations between drought and high vector infection rates are likely tied to drought-driven changes in vector-host contact due to increases in vector abundance, abundance of key hosts, or greater overlap in the spatial distribution of vectors and hosts (Kilpatrick et al. 2005, Shaman et al. 2005, Hamer et al. 2009, Johnson and Sukhdeo 2013).

Locations in drier climates responded differently; wet conditions were more likely to be associated with high vector abundance and high MIR. The driest study location, Coachella Valley, receives ~8.1 cm of precipitation per year. We found that wet conditions in this location were associated with greater vector abundance and MIR, particularly around the transmission season. This result indicates that in more arid climates, the availability of larval habitats may constrain abundance and that increases in water availability may be an important driver of WNV transmission. Previous research in Coachella Valley supports this idea; aquatic larval habitats suitable for the primary vector, *Culex tarsalis*, are generally in short supply and dry, hot periods can reduce water sources even in wetlands and agricultural areas (Reisen et al. 1995). Available water in Coachella Valley, especially associated with wetlands in the nearby Salton Sea, may also increase the attractiveness of the location to bird populations (Patten et al. 2003), which could increase the pool of susceptible hosts. Therefore, wet spells may have important implications for both WNV vector abundance and infection rates in other similar arid environments.

Responses to drought and wet spells in Ft. Collins had characteristics reminiscent of the other two locations. This is not surprising since Ft. Collins has an intermediate climate; it is semi-arid and receives less than half the precipitation of Chicago but ~30 cm more precipitation per year than Coachella Valley. Wet spells may fill ephemeral larval habitats in Ft. Collins, like depressions and retention ponds (Schurich et al. 2014), leading to increases in vector abundance. However, as in Chicago, dry conditions may reduce predator populations and enable vector proliferation (Chase and Knight 2003) or restrict vectors and hosts to persistent aquatic habitats (particularly riparian and agricultural zones), facilitating vector-host contact and viral amplification (Shaman et al. 2005, Shaman et al. 2010).

Regionally divergent responses may also be a reflection of biological differences between the primary vector species in each location, rather than purely a reflection of variation in environmental aridity. In Ft. Collins and Coachella Valley, *Cx. tarsalis* utilizes clean, natural larval habitats in vegetated margins around waterbodies (Zou et al. 2006) and thus may benefit from water-induced flooding rather than the drought-related stagnation favored by *Cx. pipiens/Cx. restuans* in Chicago. The overall influence of drought and wet spells is likely a complex reflection of biology and climate that ultimately determines transmission dynamics and human infection risks.

<u>Local land cover regulates the effects of drought and wet spells</u>

Although an influence of drought and wet spells was detected in all three locations, the effects were not uniform across sampling sites. Only ~60% of sampling sites had a significant correlation with PDSI (Figure 2). In any individual month, a third or fewer sampling sites had statistically significant correlations. We also observed a large degree of dissimilarity in the sites with significant correlations, depending on the timing of the drought and wet spell. These differences were associated with local-scale land cover characteristics and the important land cover variables reflected the regional WNV transmission ecology. For example, forest cover and impervious surfaces increased the likelihood of a negative correlations between PDSI and MIR in Chicago, likely because damp and cool urban green spaces provide a favorable setting for vector-host contact. In Ft. Collins and Coachella Valley, wetlands decreased the likelihood of significant correlations between PDSI and vector abundance potentially because, in more arid regions, wetlands act as supplemental sources of water, thus limiting the sensitivity of vector population to fluctuations in PDSI. This effect may be especially prominent in Coachella Valley, because many of the wetland habitats are artificially inundated (https://www.fws.gov/refuge/Sonny_Bono_Salton_Sea/wildlife_and_habitat/index.html) and therefore less dependent on rainfall or ground water for inundation.

Land cover either increased or decreased the likelihood of significant correlations between PDSI and the response variables, meaning that it coupled or decoupled relationships between WNV transmission and climate conditions. This has important implications for how the risks of WNV transmission are distributed across the landscape. Local land cover can create pockets that have persistently high or low risks regardless of climate conditions, or with risks that fluctuate significantly with the occurrence of drought and wet spells. Although we were unable to acquire sufficiently detailed data on vector control efforts, these management activities likely decouple relationships between climate and WNV transmission. Management efforts in the three locations varied across sampling sites and through time depending on perceived risks of transmission by local specialists, perhaps creating pockets of reduced risk on the landscape. Future studies should attempt to account for these activities in order reduce unexplained spatial variation in local responses to drought and wet spells.

Conclusion

The observed regional differences in WNV transmission underscore the complex and sometimes contradictory responses of pathogens to climate patterns. Our findings warn against over-generalizing disease responses to climate change, as the effects may differ depending on context. For instance, based on our findings, an increased frequency of drought could increase WNV transmission in Chicago, decrease it in Coachella Valley and have uncertain effects in Ft. Collins. Regional biotic differences, such as vector species habitat preferences, and climate differences, like environmental aridity, may help to explain divergent regional responses. However, the relative importance of climate and biology are difficult to disentangle, because regional biology is a reflection of evolutionary adaptation to climate conditions. Future studies should assess the influence of drought and wetness among different vectors in the same location, to help distinguish these effects.

These findings also highlight the multi-scale nature of disease risks. Although our results indicate that drought and wet spells had consistent effects at broad scales, we did not detect these effects at individual sampling sites in many land cover contexts. Although local-scale processes are commonly obscured by regional aggregations of environmental heterogeneity (Huston 1999), this idea has been under-emphasized in a disease context, particularly in studies of WNV transmission. Future studies should consider the heterogeneous impacts of climate conditions at local scales when developing models of disease risk.

Table 1. Mean climate and land cover characteristics (within 500 m of sampling sites) of Chicago, Ft. Collins, and Coachella Valley.

			Annual PDSI		Total Wetland, 500m		Forest, 500m		Impervious, 500m		Cropland, 500m	
	Mean Annual Temp. (°C)	Mean Annual Precip. (cm)	Mean	Range	Mean (%)	Range	Mean (%)	Range	Mean (%)	Range	Mean (%)	Range
Chicago	10.8 (51.4 °F)	99.3	2.9	-3.8-7.3	3.2%	0-46.1%	3.4%	0.03-42.5%	58.7%	25-86.6%	0.0%	0-0%
Ft. Collins	10.2 (50.3 °F)	40.9	-0.9	-6.6-5.1	9.0%	0-43.9%	1.4%	0-5.7%	24.1%	2.8-46.5%	10.3%	0-71.3%
Coachella Valley	23.1 (73.5°F)	8.1	-2.0	-5.1-4.6	15.8%	0-60%	0.4%	0-6.9%	4.2%	0.5-17.6%	30.8%	0-85.7%

Table 2. Summary of vector surveillance data included in analysis for Chicago, Ft. Collins, and Coachella Valley. Values for MIR (minimum infection rate) and abundance represent monthly mean across all sampling years.

	# Sites						May		June		July		August		September		October	
	MIR	Abund.	Months Sampled	Years Sampled	Vector Species	Total Captured	MIR	Abund.	MIR	Abund.	MIR	Abund.	MIR	Abund.	MIR	Abund.	MIR	Abund.
Chicago	57	74	May – Oct.	2004-2016	*Culex pipiens/restuans*	136,361	0	3.05	0.27	10.13	6.09	16.43	13.99	15.23	9.59	8.91	2.22	6.34
Ft. Collins	24	41	May – Sept.	2006-2012	*Culex tarsalis*	103,649	0	5.65	1.97	14.87	1.55	43.94	14.8	22.98	12.63	3.84	–	–
Coachella Valley	28	56	Jan. – Dec.	2007-2016	*Culex tarsalis*	748,226	0.15	82.9	0.94	64.03	3.61	41.15	5.05	42.28	1.54	63.45	0.08	97.37

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CONCLUSION

Unpredictability in the location and timing of mosquito-borne disease outbreaks is a significant public health issue and a major challenge for researchers (Reiter 1988, Brown et al. 2008). My dissertation addresses this issue by identifying where and when outbreaks of WNV and EEEV are likely to occur as a result of favorable climate conditions and land cover characteristics. Given expectations of extreme changes in climate and land cover in the coming century (Pielke 2005, Karl 2009), these results may have important implications for predicting the future geographical distribution and timing of mosquito-borne disease outbreaks.

We established that land cover characteristics, particularly wetlands with specific vegetative and inundation features, were likely important drivers of WNV and EEEV outbreaks. Further, we found that these land cover types could either increase or decrease the likelihood of pathogen transmission, and that their effects influence areas several kilometers away. These findings address a significant gap in the literature, because they show that land cover features, including wetlands with very specific characteristics, can have far-reaching implications on landscape-scale disease transmission. This knowledge will allow health and mosquito control specialists to more efficiently identify and target habitats that broadly increase disease risks to humans. Further research should be conducted to identify the potential mechanisms linking wetlands with vector infection rates and abundance.

I also determined that the occurrence of drought and wet spells may influence the timing of WNV and EEEV outbreaks. Wet periods were associated with increased risks of EEEV transmission and both drought and wet spells were associated with increased risks of WNV transmission depending on geographical region and timing of the climate conditions. We also found that the influence of these climate conditions could vary depending on local-scale wetland characteristics and other land cover features. Therefore, our findings warn against over-generalizing pathogen responses to climate change, as the effects may differ depending on the regional and local context. Although previous work has determined that climate conditions play a role in WNV and EEEV transmission, we expand on this by specifying how the effects of drought and wet spells are modified by local land cover and by the timing of these climate conditions. Future work is needed to determine the mechanisms by which drought and wet spells affect vector and host populations, and more specifically how these conditions alter vector abundance, and contact between vectors and hosts.

This research identifies specific environmental characteristics that favor WNV and EEEV transmission and thus helps to reduce the uncertainty in when and where outbreaks of these pathogens occur. As a result, interventions and resources aimed at reducing transmission, like educational outreach and mosquito control, can be allocated more effectively at times and in locations with the greatest need. Decision-making informed by this research should help to lessen the serious human health burden of these pathogens.

APPENDIX

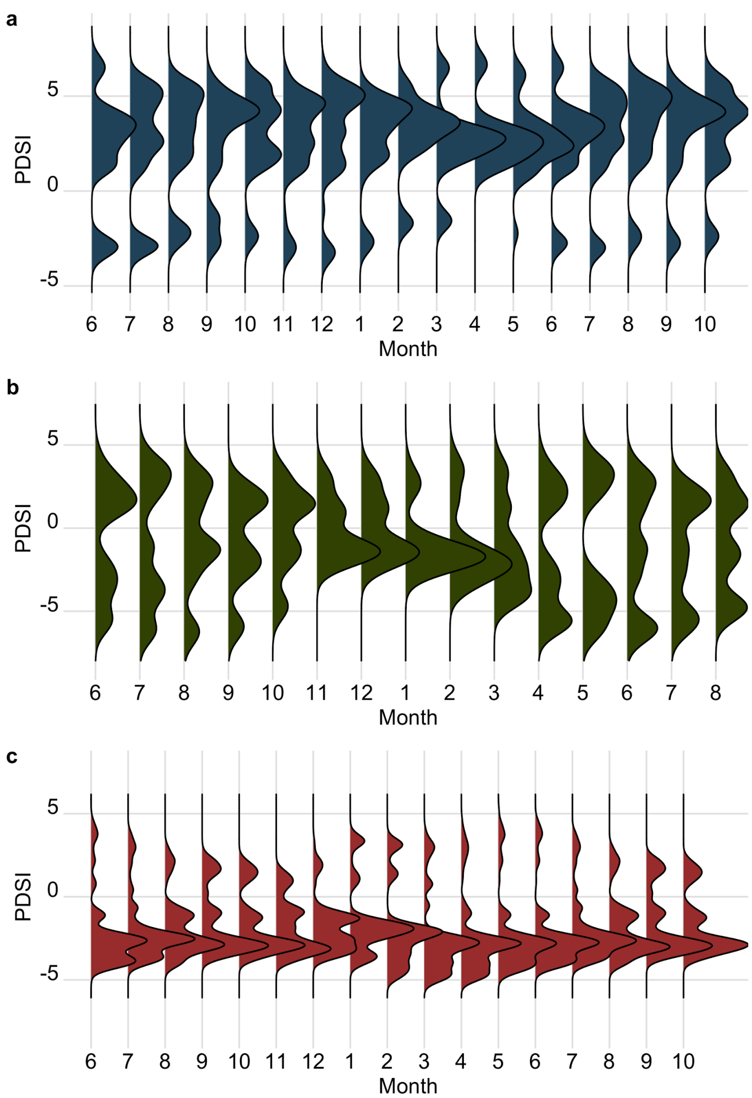

Figure S1. Frequency distribution of PDSI values for each month for a) Chicago, b) Ft. Collins, and c) Coachella Valley.

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