Characterizing Areas with Increased Burden of West Nile Virus Disease in California, 2009–2018

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Abstract

West Nile virus (WNV) is a mosquito-borne flavivirus that can cause severe neurological disease in humans, for which there is no treatment or vaccine. From 2009 to 2018, California has reported more human disease cases than any other state in the United States. We sought to identify smaller geographic areas within the 10 California counties with the highest number of WNV cases that accounted for disproportionately large numbers of human cases from 2009 to 2018. Eleven areas, consisting of groups of high-burden ZIP codes, were identified in nine counties within southern California and California's Central Valley. Despite containing only 2% of California's area and 17% of the state's population, these high-burden ZIP codes accounted for 44% of WNV cases reported and had a mean annual incidence that was 2.4 times the annual state incidence. Focusing mosquito control and public education efforts in these areas would lower WNV disease burden.

Keywords: West Nile virus, California, arbovirus, epidemiology, public health

Introduction

WEST NILE VIRUS (WNV) is the leading cause of mosquito-borne disease in the contiguous United States (Rosenberg et al. 2018, McDonald et al. 2019). WNV is maintained in an enzootic cycle between birds and mosquitoes and is transmitted tangentially to humans primarily by *Culex* mosquitoes (Petersen et al. 2013, Reisen 2013, Rochlin et al. 2019). This complex ecology results in high spatiotemporal variability in disease incidence, with seasonal summer peaks that vary in size and location (Lindsey et al. 2010, CDC 2020). Although most areas have only sporadic cases or periodic outbreaks, some have a consistently higher burden of WNV disease.

Most WNV infections are asymptomatic (Mostashari et al. 2001, Sejvar and Marfin 2006, Petersen et al. 2013). Approximately 20–30% of infections result in an acute systemic febrile illness and <1% lead to neuroinvasive disease (*e.g.*, meningitis, encephalitis, or myelitis), with a higher incidence among older populations. Among patients with neuroinvasive disease, the case fatality rate is close to 10% (Sejvar 2007). Due to its severe clinical features, diagnosis and reporting of neuroinvasive disease are more consistent and re-

complete than non-neuroinvasive disease (Lindsey et al. 2008, 2010). From 2009 to 2018, a total of 21,869 WNV disease cases were reported in the United States, including 12,835 (58.7%) cases of neuroinvasive disease and 1199 (5.5%) deaths (CDC 2020). California reported more cases of WNV disease than any other state, accounting for 4035 (18%) of all cases nationwide from 2009 to 2018 (California Department of Public Health 2019, Snyder et al. 2020a).

Since WNV was introduced in North America, there have been a number of studies exploring demographic, ecological, environmental, and community determinants of WNV disease. In Orange County, California, increased WNV incidence was associated with low income and high housing density from 2004 to 2008 (Harrigan et al. 2010). In Kern County, there was an association between human WNV cases and delinquent mortgages and neglected swimming pools (Reisen et al. 2008). A 2019 study in San Joaquin County, California, analyzing data from 2011 to 2015, indicated that WNV incidence was higher in communities with a high number of housing foreclosures, a higher proportion of non-White residents, and a higher proportion of the population over 50 years of age (Hernandez et al. 2019). In addition,

although nationwide disease incidence is generally higher in rural areas compared with cities, most cases are reported from large metropolitan areas (Petersen 2019). Although temperature and humidity have been shown to be closely related to increased WNV transmission (Epstein 2001, Epstein and Defilippo 2001, Hernandez et al. 2019), the relationships between WNV disease and other environmental parameters are not as well described, but increased amounts of vegetation have been associated with WNV risk (Brownstein et al. 2002, Ruiz et al. 2007).

No WNV vaccine or specific treatment is currently available for use in humans (Beasley 2011, Kaiser and Barrett 2019). Reducing mosquito exposure through vector control, public education, and personal protective behaviors are the primary forms of prevention (Petersen et al. 2013). States report disease cases to the CDC by county of residence (CDC 2020), and California has already identified that >95% of all cases occur in southern California or Central Valley counties (Snyder et al. 2020b). However, California's counties are large, with 47 of the 58 having areas greater than 2000 km^2, including San Bernardino County, the largest in the continental United States, covering 51,947 km^2. Identifying subcounty areas with increased burden of WNV disease could help optimize interventions and resource allocation. In this descriptive retrospective study, we identified and characterized California counties and ZIP codes with disproportionately high numbers of WNV disease cases to direct further evaluation and prevention efforts.

Methods

Geographic area

California has a population of 39.6 million people and a cumulative area of 423,971 km^2 (U.S. Census Bureau 2017). The state has 58 counties and 2597 ZIP codes.

Case identification and reporting

WNV disease is a nationally notifiable condition (NNDSS 2020). Cases that meet the national surveillance case definition, developed by the Council of State and Territorial Epidemiologists (CSTE 2015), and occur among California residents are reported to the California Department of Public Health (CDPH) by health care providers and diagnostic laboratories. WNV disease cases with symptom onset from January 1, 2009, to December 31, 2018, were extracted from CDPH records. Asymptomatic infections do not fulfill the case definition and therefore were excluded from analyses. The collection and analysis of human surveillance data are routine public health activities and are exempt from Institutional Review Board review and approval Project 2020-072-CDPH.

Defining high-burden counties and ZIP codes

We defined the 10 California counties with the most reported WNV infections from 2009 to 2018 as high-burden counties. Within each high-burden county, we divided ZIP codes into categories based on the cumulative number of WNV cases per ZIP code. Five categories were created using natural (Jenks) breaks, rounded to the nearest five (0, 1–5, 6–10, 11–20, and ≥21) to visualize the data. In each high-burden county, we identified one or more groups of adjacent ZIP codes with >21 cases, which collectively had a higher

incidence than the entire county. If another ZIP code with less WNV disease (≤21) was geographically contained within the group of highest burden ZIP codes and was in the same county, it was also included to provide a contiguous area for analysis. All ZIP codes within these groups were defined as high burden, whereas all other ZIP codes within the county were defined as low burden, even those with >21 cases.

Comparing characteristics of high- and low-burden ZIP codes

Community-level demographic data for each ZIP code were excerpted from the U.S. Census Bureau 2017 American Community Survey, 5-year estimates (U.S. Census Bureau 2017). Potential risk factors for elevated WNV incidence included population, median age, proportion of population aged ≥60 years, proportion of the population that was White non-Hispanic, median household income, and proportion of the population with health insurance. Population density was estimated using the population size and the area of each ZIP code in square kilometers.

Mean elevations of each ZIP code, in meters, were estimated from the USGS 100-meter resolution raster file of the contiguous United States (U.S. Geological Survey 2012). To estimate land cover, we used the USGS GAP/LANDFIRE National Terrestrial Ecosystems raster file (U.S. Geological Survey Gap Analysis Program 2011). We extracted all raster points classified as low, moderate, or high intensity developed land cover, combined them into a single polygon, and calculated the proportion of each ZIP code that was covered by any of these land cover groups. We also identified which ZIP codes were within the jurisdictional boundaries of a local vector control agency (MVCAC 2017).

Data analyses

Average annual incidence per 100,000 residents was calculated by dividing the total number of cases in that time period within a geographic unit by the 2017 population estimate for that geographic area, multiplying by 100,000, and then dividing by 10. Continuous demographic and environmental characteristics of high- and low-burden ZIP codes were compared with two-sample t-tests. The only noncontinuous characteristic, presence or absence of a vector control agency in a ZIP code, was compared by chi-square analysis or by Fisher's exact test if an expected cell value was less than five. Due to making 10 comparisons, we applied a Bonferroni correction, reducing the threshold for statistical significance to $p \leq 0.005$. Statistical analyses were conducted using SAS software, v.9.4 (SAS Institute 2016, Cary, NC), while all mapping and spatial calculations were conducted using ArcGIS Pro 2.3.15769 (Esri, Inc., 2018, Redlands, CA).

Results

A total of 4123 WNV disease cases were reported in California from 2009 to 2018, with an average statewide annual incidence of 1.1 cases per 100,000 population. The median number of cases each year was 425 (range, 112–843 cases). There were 2735 (66%) cases with symptom onset from July to September. The median age of case-patients was 59 years (interquartile range, 47–69 years), with 1978 (48%) cases aged ≥60 years; 2561 (62%) cases were male. Of the 4123 cases, 2899 (70%) were reported as neuroinvasive disease cases.

High-burden counties

Each of the 10 (17%) counties in California with the highest number of WNV cases had >100 total cases reported from 2009 to 2018 (Fig. 1A). All 10 counties were located in southern California (Los Angeles, Orange, Riverside, and San Bernardino) or California's Central Valley (Stanislaus, Kern, Fresno, Butte, Sacramento, and Tulare). Combined, these 10 counties accounted for 3338 (81%) of the WNV disease cases reported in the state during this time frame (Table 1). Los Angeles County accounted for 1414 (34%) of all cases reported statewide. The median number of annual cases in these high-burden counties during the 10-year period ranged from 11 in Butte, San Bernardino, and Tulare to 151 in Los Angeles. Eight of the counties had an average annual incidence ≥1.1 per 100,000 residents.

High-burden ZIP codes

Of the 2597 ZIP codes in California, 30 (1.2%) had >20 WNV disease cases (maximum: 43) and 94 (3.6%) had 11–20 cases reported from 2009 to 2018; 1766 (68.0%) ZIP codes had no WNV disease cases reported during the 10-year period (Fig. 1B). Within the 10 counties with the most cases, we identified 11 geographical groupings of ZIP codes with a higher incidence of WNV disease than the county as a whole, including two high-burden ZIP code clusters each in Los Angeles and Orange counties and one cluster each in Riverside, San Bernardino, Stanislaus, Kern, Fresno, Butte, and Tulare counties (Fig. 2 and Table 2). These 11 ZIP code

clusters included 151 (5.8%) of the 2597 ZIP codes in California, contained 6.5 million (16.6%) of the state's 39.1 million population, and covered 3444 miles^2 (2.3%) of the state's total area, but accounted for 1710 (44.3%) of the state's WNV disease cases reported from 2009 to 2018. Combined, the 11 clusters had an average annual incidence of 2.6 cases per 100,000 persons per year, almost 2.5 times the state's average annual incidence.

The largest cluster comprised 40 adjacent ZIP codes in western Los Angeles County, which contained 3.8% of the state's population and 0.1% of the state's total area, but accounted for 10.8% of the reported WNV disease cases. Two clusters that straddled the border between southeastern Los Angeles County and northwestern Orange County (*i.e.,* Los Angeles County—east, and Orange County—north) included a total of 31 ZIP codes, containing 3.4% of the state's population and covering 0.2% of the state's total area, but accounting for 8.1% of the state's WNV disease cases. In the northern Central Valley, the only high-burden cluster was identified in Butte County. Although Sacramento County had 124 reported cases from 2009 to 2018, they were relatively evenly distributed throughout the county with no high-burden ZIP codes identified.

Characteristics of high-burden ZIP codes

When aggregated, the 151 ZIP codes in the 11 high-burden clusters had a higher mean population, higher population density, younger median age, and a smaller proportion of the population aged 60 years and older than the 2446 low-burden
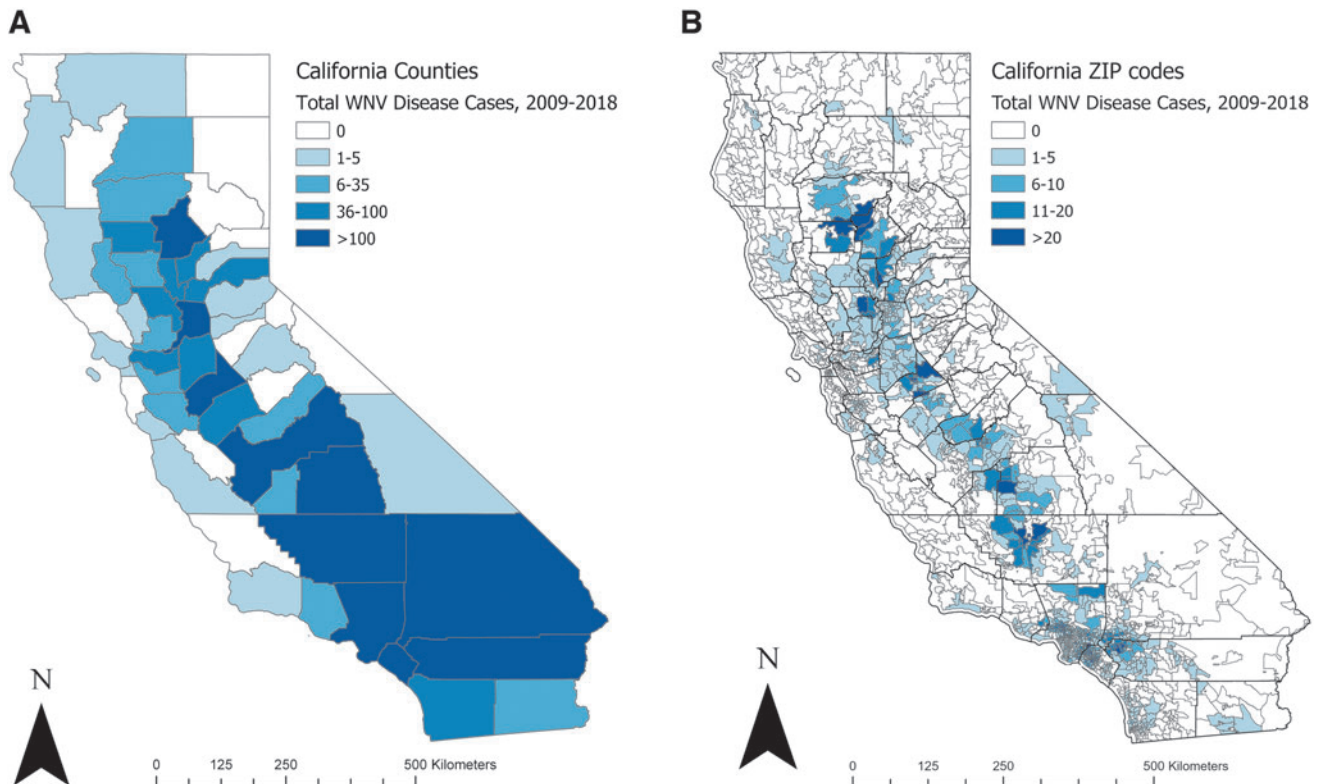

FIG. 1. WNV disease cases by county **(A)** and ZIP code **(B)** of residence—California, 2009–2018 (n = 4123 cases). Detailed regional maps of ZIP code-level data are shown in Fig. 2. **(B)** Includes 3864 (94%) cases with known ZIP code of residence. WNV, West Nile virus.

TABLE 1. CALIFORNIA COUNTIES WITH THE MOST REPORTED WEST NILE VIRUS DISEASE CASES, 2009–2018

County	Region	Cumulative cases [N=4123] n (%)	Annual cases Median, (IQR)	Average annual incidence Per 100,000 population[a]
Los Angeles	Southern California	1414 (34)	151 (37–263)	1.4
Orange	Southern California	502 (12)	22 (4–35)	1.6
Riverside	Southern California	271 (7)	16 (6–33)	1.1
San Bernardino	Southern California	206 (5)	11 (5–38)	1.0
Stanislaus	Central Valley	206 (5)	18 (14–27)	3.8
Kern	Central Valley	186 (5)	18 (13–25)	2.1
Fresno	Central Valley	169 (4)	14 (9–23)	1.7
Butte	Central Valley	155 (4)	11 (3–24)	6.8
Sacramento	Central Valley	124 (3)	13 (5–18)	0.8
Tulare	Central Valley	105 (3)	11 (7–12)	2.3

Ten (17%) of California's 58 counties accounted for 3338 (81%) of the 4123 cases reported from 2009 to 2018.
[a]Incidence calculated using the 2017 Census-estimated population.
IQR, interquartile range.

ZIP codes in the same nine counties (Table 3). The higher burden ZIP codes were also lower in elevation, more developed, and more likely to be within the service area of a local vector control agency. These trends were relatively consistent across counties. However, unlike the high-burden ZIP codes in rest of the nine counties, high-burden ZIP codes in Los Angeles County had a similar number of residents and population density compared with low-burden ZIP codes in the county.

Discussion

California has the highest WNV disease burden in the United States, but that burden is not uniformly distributed in the state. From 2009 to 2018, the 10 counties with the highest WNV disease burden in California were all in southern California or the Central Valley. Among these 10 counties, there were clusters of ZIP codes with a disproportionately higher burden of human WNV disease. These 11 high-burden groups of ZIP codes collectively contained 17% of California's population and covered 2% of its area, but accounted for 44% of the state's WNV disease cases reported during the 10-year study period. In Los Angeles County alone, two of these high-burden ZIP code clusters accounted for 14.3% of all cases reported in the state despite being home to 5.4% of the population and comprising 0.2% of state's area.

By identifying contiguous ZIP codes within already high-burden California counties with elevated burden of WNV disease, we have potentially found areas that could benefit the most from targeted public education campaigns, where vector control agencies should focus mosquito control efforts, particularly when resources, such as time and staffing, are limited. Not only is there no effective treatment for patients with WNV disease but also medical care, particularly for those with neuroinvasive disease, is expensive. National estimates found an average annual cost of $56 million in medical expenses due to WNV disease from 1999 to 2016 (Ronca et al. 2019). In Sacramento County in 2005, an epidemic year of WNV disease and environmental activity, it was estimated to cost ~$33,000 to treat each patient with WNV neuroinvasive disease and >$700,000 to provide emergency vector control to treat the county's 2570-km^2 area (Barber et al. 2010). If vector control efforts prevented just 15

WNV neuroinvasive disease cases, it became more cost-effective than providing medical care (Barber et al. 2010). A more recent study in California found that from 2004 to 2017, there was a median charge of $142,321 per patient with WNV disease; an average of almost $60 million in charges per year (Snyder et al. 2020a). Based on these latter estimates, vector control efforts are even more cost-effective. By treating these smaller, densely populated high-disease burden areas, resources would be used most efficiently to reduce the current disease burden.

We also described the common demographic and environmental characteristics of these high-burden ZIP codes. When compared with the rest of the county, they tended to have higher populations and population densities than other parts of the same county. Residents in high-burden ZIP codes were, on average, younger than residents of lower burden ZIP codes. They also tended to have a higher proportion of White non-Hispanic residents, although that difference was not significant ($p > 0.005$). These clusters of high-burden ZIP codes were at a lower elevation, had more of their land area classified as developed, and were more likely to be within the service area of a vector control agency.

There were several differences between the population at risk of WNV and the demographic characteristics of these high-burden ZIP code groups. It is well established that older persons are more at risk of severe WNV disease (O'Leary et al. 2004, Hayes et al. 2005, Martinez et al. 2017, McDonald et al. 2019, Petersen 2019), and in at least one part of California's Central Valley, incidence was reported to be higher in areas where the population was older (Hernandez et al. 2019). However, we focused on the raw number of cases, which has previously been observed to be higher in metropolitan areas (Petersen 2019) where populations tend to be younger (Parker et al. 2018). The WNV incidence in these areas is not the highest in California (Snyder et al. 2020b), but by sheer numbers and density of people, there were more cases.

The environmental characteristics of higher burden groups of ZIP codes were largely consistent across high-burden counties. The primary vectors of WNV in California, *Culex tarsalis*, *Culex pipiens*, and *Culex quinquefasciatus* (Goddard et al. 2002), are found at lower elevations in the state (Bohart and Washino 1978) where most of the cases were reported. Metropolitan areas, which have higher populations and
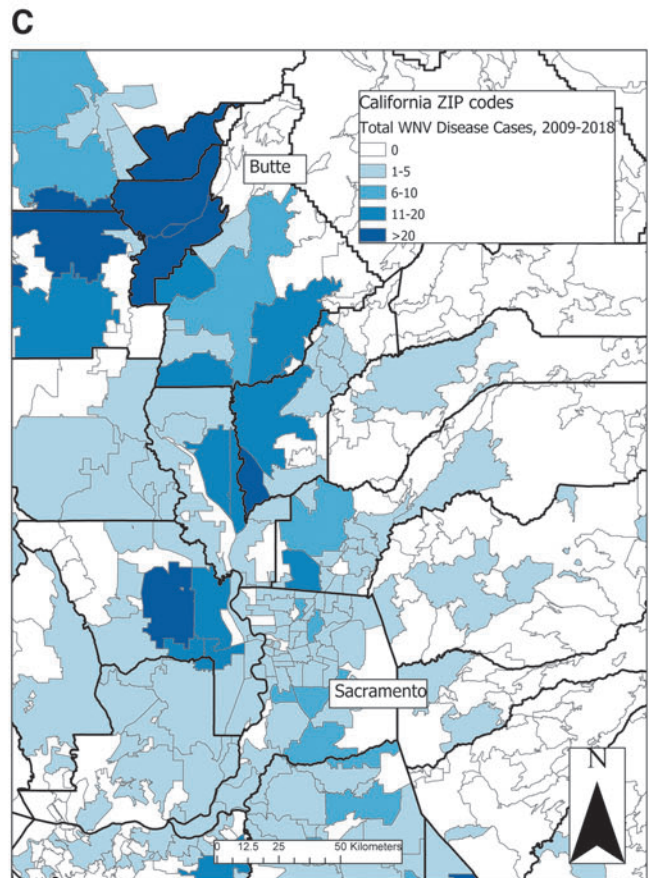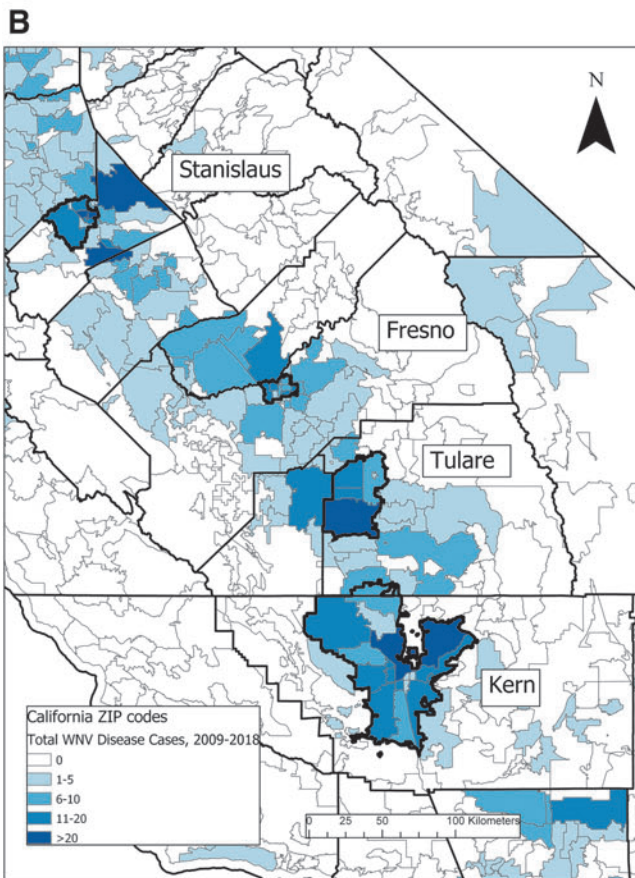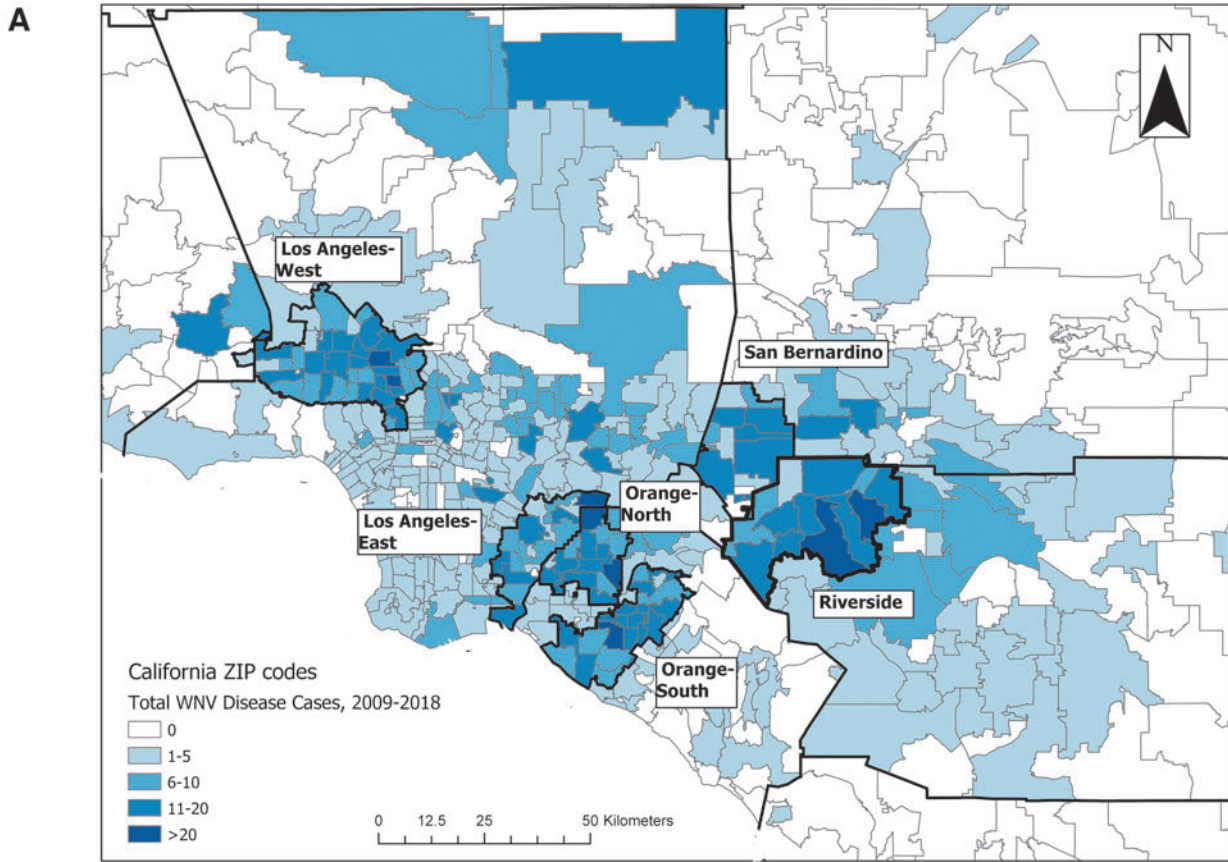
FIG. 2. WNV disease cases by ZIP code in (A) southern California; (B) southern Central Valley; and (C) northern Central Valley—California, 2009–2018.

TABLE 2. CHARACTERISTICS OF CALIFORNIA ZIP CODE CLUSTERS
WITH HIGH BURDEN OF WEST NILE VIRUS DISEASE, 2009–2018

ZIP code clusters	ZIP codes; [N = 2597] n (%)	Population; [N = 39,071,323] n (%)	Area (km²); [N = 423,971 km²] n (%)	Cumulative cases; [N = 3864] n (%)	Average annual incidence (1.1) Per 100,000 population
Los Angeles—West	40 (1.5)	1,489,910 (3.8)	523 (0.1)	417 (10.8)	3.0
Los Angeles—East	17 (0.7)	628,593 (1.6)	218 (0.1)	134 (3.5)	2.1
Orange—North	14 (0.5)	682,856 (1.8)	218 (0.1)	178 (4.6)	2.6
Orange—South	18 (0.7)	880,417 (2.3)	293 (0.1)	214 (5.5)	2.4
Riverside	12 (0.5)	652,435 (1.7)	593 (0.1)	170 (4.4)	2.6
San Bernardino	10 (0.4)	493,390 (1.3)	329 (0.1)	99 (2.6)	2.0
Stanislaus	8 (0.3)	278,486 (0.7)	566 (0.1)	116 (3.0)	4.2
Fresno	9 (0.3)	349,781 (0.9)	199 (<0.1)	77 (2.0)	2.2
Tulare	5 (0.2)	226,646 (0.6)	668 (0.2)	55 (1.4)	2.4
Kern	15 (0.6)	674,425 (1.7)	4128 (1.0)	164 (4.2)	2.4
Butte	3 (0.1)	111,302 (0.3)	1186 (0.3)	86 (2.2)	7.7
All ZIP code clusters	151 (5.8)	6,468,241 (16.6)	8921 (2.1)	1710 (44.3)	2.6

Percentages calculated as proportion of California's total reported cases.

subsequently higher population densities, tend to have more area covered with low to high developed land cover, defined as 20–100% of the area covered with impervious surfaces (MRLCC 2011). In the northeastern United States, WNV incidence was higher in urban counties than those with more forest cover (Brown et al. 2008). Although several prior studies focused on vegetation abundance, as opposed to coverage by impervious surfaces, they only looked at a single year of disease in New York City, Chicago, and Detroit (Brownstein et al. 2002, Ruiz et al. 2007). However, our study covered a period of 10 years, including 2012–2016, when California experienced a drought of historic severity (USGS 2020). To simplify the variation in vegetation during a prolonged time period, we chose to focus on impervious land cover.

There were several limitations to this study. Available surveillance data included only reported cases. However, <5% of WNV non-neuroinvasive disease cases are likely to be diagnosed and reported (Lindsey et al. 2010, McDonald

et al. 2019). Reported cases could differ from unreported cases in their geographic distribution or key demographic characteristics that would have biased these results. For example, low-burden ZIP codes tended to be lower income areas, although we did not observe a significant difference ($p > 0.005$) in income, where residents often have limited access to medical care, resulting in fewer reported cases (Shi et al. 2010). This may have been due to the ecological nature of our analysis or the inadequacy of using a measure such as median household income to describe poverty. Furthermore, this study was based on the residential address of reported cases, but this may have been different than the location where infection occurred. We visualized the geographic distribution of cases to identify high-burden areas instead of more robust methods such as geographically weighted regression or hot spot analysis, using Getis-Ord G. A previous exploration of those methods consistently identified Los Angeles County as a high-burden area (unpublished data),

TABLE 3. CHARACTERISTICS OF ZIP CODES IN CONTIGUOUS GROUPS WITH HIGH BURDEN OF REPORTED WEST NILE
VIRUS DISEASE CASES COMPARED WITH ALL OTHER ZIP CODES IN NINE CALIFORNIA COUNTIES (LOS ANGELES,
ORANGE, RIVERSIDE, SAN BERNARDINO, STANISLAUS, KERN, FRESNO, BUTTE, AND TULARE)

Characteristic	High-burden ZIP codes (IQR) [N = 151]		Low-burden ZIP codes (IQR) [N = 607]		p[a]
Total population	6,468,241		14,818,550		
Mean population	42,836	27,233–55,869	25,245	3962–38,304	**<0.001**
Population density per km²	2369	1140–3379	1756	43–2725	**0.004**
Median age in years	36 years	32–39	39 years	32–43	**<0.001**
Proportion aged ≥60 years	18%	14–20	21%	14–25	**<0.001**
Average elevation	160 meters	39–249	421 meters	65–583	**<0.001**
Proportion of developed land cover	71%	56–95	43%	38–88	**<0.001**
Proportion with vector control agency	99%		88%		**<0.001**
Proportion of White non-Hispanic residents	37%	20–51	42%	16–66	0.01
Median household income	$67,436	51,961–84,714	$63,558	41,276–80,230	0.08
Proportion of medically insured people	89%	86–92	88%	85–94	0.61

Bold text indicates statistical significance.
[a]Due to making 10 comparisons, the Bonferroni adjustment was applied, resulting in statistical significance at $p \leq 0.005$.

which is not surprising given that Los Angeles County reports more cases than any other county and has a population of >10 million people, 25% of the state's total (U.S. Census Bureau 2017). However, we sought to explore the potential for high-burden areas in other parts of the state. There is also the risk that ZIP codes in the high-burden groups were similar to each other simply due to spatial proximity. Autocorrelation is likely in any geospatial analysis and methods to address it tend to reduce statistical power. However, we set a very high threshold for statistical significance ($p \leq 0.005$) so as to reduce the potential impact of autocorrelation.

All 10 counties that reported the most WNV cases had at least one vector control agency that services most or all of the county's area. As a result, 99% of our high-burden ZIP codes fell within the service area of a vector control agency. Those agencies collect environmental data, such as mosquito abundance and infection rates, to estimate risk of human WNV transmission (Snyder 2020b). We hope to quantify how those environmental indicators were associated with the number and timing of human cases in a given area. In response to surveillance results, the vector control agencies routinely conduct mosquito control, including the application of pesticides to reduce mosquito abundance (Barber et al. 2010). It is feasible that their ongoing mosquito control activities have already substantially reduced WNV transmission in California, particularly in lower burden areas.

Conclusion

There is no vaccine to prevent or specific therapy to treat WNV disease (Beasley 2011, Kaiser and Barrett 2019). Comprehensive mosquito control, public education, and personal protective behaviors remain the primary tools for prevention and control. Targeting enhanced efforts to a limited number of areas that account for a disproportionate number of cases could provide substantial reductions in disease burden and lead to a more efficient and effective deployment of public health resources.

Authors' Contributions

All authors met the definition of authorship, as defined by the International Committee of Medical Journal Editors.

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Author Disclosure Statement

The authors report no real or perceived conflicts of interest.

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