Spatio-temporal and neighborhood characteristics of two dengue outbreaks in two arid cities of Mexico

Pablo A. Reyes-Castro[a,*], Robin B. Harris[a], Heidi E. Brown[a], Gary L. Christopherson[b], and Kacey C. Ernst, PhD [a]

[a] Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona, USA

[b] School of Geography and Development, University of Arizona, Tucson, Arizona, USA

*__Corresponding author__: Permanent address: Center for Studies on Health and Society, El Colegio de Sonora, Ave. Obregón 54, Hermosillo, Sonora, MX, 83000; email address: preyes@colson.edu.mx

Abstract

Little is currently known about the spatial-temporal dynamics of dengue epidemics in arid areas. This study assesses dengue outbreaks that occurred in two arid cities of Mexico, Hermosillo and Navojoa, located in northern state of Sonora. Laboratory confirmed dengue cases from Hermosillo (N=2,730) and Navojoa (N=493) were geocoded by residence and assigned neighborhood-level characteristics from the 2010 Mexican census. Kernel density and Space-time cluster analysis was performed to detect high density areas and space-time clusters of dengue. Ordinary Least Square regression was used to assess the changing socioeconomic characteristics of cases over the course of the outbreaks. Both cities exhibited contiguous patterns of space-time clustering. Initial areas of dissemination were characterized in both cities by high population density, high percentage of occupied houses, and lack of healthcare. Future research and control efforts in these regions should consider these space-time and socioeconomic patterns.

Keywords: dengue outbreak; space-time clustering; socioeconomic factors

1. Introduction

Dengue fever is a vector borne disease transmitted by the *Aedes* genus of mosquito. The number of dengue fever cases reported by the Member States in three WHO regions increased from 2.2 million in 2010 to 3.2 million in 2015 (WHO, 2016). This increase is likely a combination of real transmission increases and improved surveillance. Mathematical modelling approaches that attempt to account for the significant underreporting of dengue disease (Silva et al., 2016) estimate the global incidence at about 50 million – 100 million symptomatic cases per year (Stanaway et al., 2016). The principal vector, the *Ae. aegypti* mosquito, is well adapted to human environments (WHO, 2009). Once a female *Aedes* mosquito becomes infected with one of the four serotypes (DEN-1 to DEN-4) and survives past the extrinsic incubation period (EIP), it remains infectious for life (Barbazan et al., 2010).

Dengue virus transmission clusters in both space and time (Getis et al., 2003; Mammen et al., 2008), and multiple factors influence spatio-temporal dynamics of dengue virus transmission. Warmer temperature increase the frequency of blood feeding and viral development rate, and shortens the EIP (Brunkard et al., 2008; Chan and Johansson, 2012; Watts et al., 1987). These relationships partially drive the observed seasonal pattern of higher incidence during the warm season (Carbajo et al., 2012). Spatial patterns are generally associated with areas of overlapping proximity of and interaction between the vector and potential hosts. Most female *Ae. aegypti* mosquitos spend their lifetime in or close to the place where they became adults (Harrington et al., 2005). Therefore, a limited flight range plus human interactions within neighborhoods and human mobility across a community can determine the spatial patterns of the transmission (Harrington et al., 2005; Maciel-de-Freitas and Lourenço-de-Oliveira, 2009; Stoddard et al., 2013, 2009).

Modeling approaches demonstrate that dengue epidemics vary spatially on a local scale due to the nature of the human population structure (Favier et al., 2005; Halstead, 2008). Socioeconomic characteristics of households related to uncontrolled urbanization, migration, deficiencies in water supply and garbage disposal, and vector control activities can play a significant role in the spatio-temporal distribution of dengue virus transmission (Caprara et al., 2009; Gómez-Dantés et al., 2011; Gómez-Dantés and Ramsey, 2009; Martín et al., 2010).

Determining the underlying patterns of space-time clustering (Morrison et al., 1998; Sharma et al., 2014) provides an opportunity to identify dengue transmission foci and gain a better understanding of the disease spread (Sharma et al., 2014). Ascertaining predictive factors for these foci and the times with higher risk of spread should facilitate more efficient disease surveillance and control (WHO, 2009).

An analysis of the spatial-temporal dynamics of two dengue outbreaks in Hermosillo, Sonora (SON) and Navojoa, SON, two arid cities of northern Mexico, was conducted in order to determine 1) spatio-temporal clustering patterns of reported dengue cases, 2) whether the socio-demographic patterns of reported dengue cases change as the outbreaks progress, and 3) whether these patterns are similar across the two outbreaks.

2. Methods

2.1 Study areas

Both cities are located in the arid State of Sonora, MX, and are approximately 50 km from the Sea of Cortez. Hermosillo is a medium-sized city of 800,000 inhabitants located at 29°05’ N latitude and 110°57’ W longitude with an average altitude of 216 meters above sea level. Further south of the State, the city of Navojoa, population 150,000 inhabitants, is located at 27°04’ N latitude and 109°26’ W longitude, at an altitude of 40 meters above sea level (INEGI, 2016). Both cities have average annual temperatures around 25°C with daily maximum temperatures above 43°C from May to August (SMN, 2016). Approximately 100 mm of precipitation occurs annually and is predominantly accumulated during the rainy season which occurs during the months of July and August, overlapping the warmest months. Given the low levels of precipitation both cities experience water scarcity though as an urban center water shortages are more severe in Hermosillo (Pineda-Pablos, 2007).

Dengue epidemiology and vector ecology: Dengue fever reemerged in the south of Sonora in 1982 (Macías-Duarte et al., 2009). Currently, the state has areas of endemic dengue virus transmission and experiences focused outbreaks of dengue disease. Despite their arid conditions, dengue shows an endemic-epidemic pattern in the localities of study which is likely a result of fluctuating levels of immunity to specific dengue serotypes. Since 2006, Hermosillo has shown annual cumulative incidences within the range of 1.0 to 29.9 per 100,000 inhabitants; however, periodic outbreaks have resulted in much higher incidence in 2010 (397.6 per 100,000), 2014 (227.0 per 100,000) and 2015 (120.7 per 100,000). Navojoa has presented with a similar pattern. There are years with low incidence from 0 to 32.5 per 100,000, and years when the incidence is very high with outbreaks in 2008 (466.6 per 100,000) and 2009 (157.6 to 466.6 per 100,000). The highest transmission years were selected for Navojoa, 2008, and Hermosillo, 2010. Until 2011, only serotype DENV-1 was identified as circulating in both cities, but currently, DENV-2 also circulates in the State. Given the limited sero-typing of cases, it is unclear when and where DENV-2 began circulating in Sonora. Dengue cases start to increase after the onset of the rainy season in late August-beginning of September, then they peak in mid-October and generally decline in late November but sometimes transmission goes into late December.

Ae. aegypti are well established throughout urban areas in Sonora. However, there have been no detections of *Ae. albopictus* by the Health Department or by trapping activities conducted by this research team. Adult *Ae. aegypti* populations in Hermosillo, have been shown to remain low until September/October, coinciding with peak transmission (Ernst et al., 2016).

Surveillance and control measures: Surveillance for both dengue cases and *Ae. aegypti* presence are conducted throughout the state of Sonora. *Ae. aegypti* surveillance is actively conducted through a network of ovitraps that are placed throughout both localities. Entomological indicators include positivity per trap. Passive surveillance for dengue cases is conducted by physicians and hospitals throughout the state. Reports of both probable and laboratory confirmed cases are submitted to the state and municipal health departments. A multi-faceted approach is taken to prevent and control transmission including; educational campaigns, indoor and outdoor spraying of insecticides, source reduction for *Aedes aegypti*, and distribution and application of larvicides.

2.2. Data sources and variables

Surveillance information: 2,843 and 511 laboratory confirmed cases of dengue were reported in the urban cities of Hermosillo (in year 2010) and Navojoa, (in year 2008) SON, Mexico. Case information was obtained from the surveillance system of the Health Ministry of the State of Sonora. The state laboratory performed diagnostic confirmation of probable dengue patients depending on timing of specimen collection during clinical disease period of evolution of the infection by using immunosorbent assay (ELISA) for detection of viral antigen NS1≥1 unit, IgM≥11 units, or high levels of IgG≥22 units as indicator of a recent and active reinfection (Vázquez-Pichardo et al., 2011; Watthanaworawit et al., 2010). Confirmed cases were those with a positive result in one of the three tests. About 96% of the cases (n=2,730 and n=493) were successfully geocoded by residence in ArcGIS 10.1. Limited demographic and clinical variables were also available related to sex, age, day of symptoms onset, presence of hemorrhagic fever (DHF), and fatalities. Comparisons of the demographics of dengue incidence are made between the two cities; including age, sex distributions, and manifestation of DHF.

Neighborhood characteristics: Socioeconomic characteristics of the neighborhoods of residence were assigned to cases by overlaying the case maps of both cities with census unit level data from the 2010 Mexican census (INEGI, 2010). The urban areas are comprised of 391 census units in Hermosillo and 69 in Navojoa. Neighborhood characteristics included: median age as an indicator of susceptibility, unemployment status (%) as an indicator of socio-economic standing, population with no health care (%) as a modifier of being detected and reported as a dengue case, migrant population in the last 5 years (%) as an indicator of mobility of the population and potential viral introduction, and houses with no piped water (%) as a proxy for water storage which may provide larval habitat and overall infrastructure that may influence vector-human contact (Padmanabha et al., 2010; Schmidt et al., 2011). Three additional variables; persons per house, occupied houses (%) and population density (persons per hectare) were used as indicators of proximity between individuals which can influence *Ae. aegypti* dynamics and the transmission patterns among residents (Rodrigues et al., 2015; Schmidt et al., 2011). Census data were available for 2010 which coincided with the outbreak in Hermosillo but was two years after the 2008 outbreak in Navojoa. Population growth was registered as 1.9% for Navojoa which would result in a difference of 4000 inhabitants. This was the best approximation available as the other census data available were from 2000, eight years prior.

2.3. Statistical analysis

Space-time analysis: Date of symptom onset was used to assess temporal patterns. Both cities show similar temporal patterns with peak during week 42. For each city's outbreak, cases were grouped into sequential 4-week periods to represent five time periods during the epidemics, early, mid-early, middle, mid-late and late, corresponding to weeks 36 and lower, 37-40, 41-44, 45-48, and 49-52. Kernel density estimation in ArcGIS 10.1 was used to demonstrate the geographical progression of the outbreaks across the five sequential 4-week periods. A search radius of 500 m was used which represents the 90th percentile of vector flight distance in urban areas reported by Maciel-de-Freitas and Lourenco-de-Oliveira (2009).

High density zones of dengue incidence for the 4-week periods were defined as those areas with ≥10 cases per 0.8 km^2. This cut-off point was defined using the Natural Breaks Jenks method found for the first 4-week period in Hermosillo. It was kept constant for the other 4-weeks groups in both cities to visualize and compare the progression of the outbreaks between periods and cities. These same criteria for estimation were used for each 4-week period to compare between periods and cities.

Space-time retrospective cluster analysis was performed in SaTScan v9.3 in order to detect high-risk clusters of dengue. The analysis was based on a Poisson probability model. In addition to the case file, the model used a population file as background which allowed adjustment for uneven population distribution across the study area. As census units are very irregular in shape and size within and between study areas (Hermosillo: range=0.2 to 140 hectares; Navojoa: range=3.6 to 180 hectares) census block data were used to create uniform polygons for space-time cluster detection as follows. Population values were obtained from census data for each census block (INEGI, 2010). A shapefile of a regular grid of 250m cells (6.3 hectares each) was created and overlaid with the map of blocks with population values from 2010 census. The centroid of each census block was calculated and assigned the population size. All the population of each block centroid that fell within each grid cell was summed to get an estimation of the population size by grid cell. This newly created grid with population values was used for further analyses. The space-time scan statistic uses a cylindrical window which moves across space and time to detect possible clusters. The maximum cluster size was fixed at a radius of 500m for the circular spatial window and a maximum temporal window of 50% of the time period to create a standard for comparing clusters between cities that would comprise the maximum length of the transmission period. Significant clusters were tested using a p-value <0.05 after running 999 Monte Carlo simulations (Kulldorff, 2014).

Socioeconomic pattern analysis: Cumulative incidence (C.I.) was calculated as cases per 10,000 inhabitants and descriptive statistics of individual characteristics of cases were calculated. Mean values of case neighborhood characteristics were estimated for each of the 4-week periods. Ordinary Least Square (OLS) simple linear regressions were used to assess trends individually for each the socioeconomic characteristic of cases (dependent variable) across weeks (independent variable). Cases from both cities were merged into a single database. Effect modification by city was assessed by creating interaction terms between week and city in order to determine those associations modified by the city. Because there was significant interaction (*p*-value <0.1) for several of the socioeconomic variables, the OLS regression analysis was stratified by city to assess trends. Significant trends in which the slopes were the same direction in both cities were plotted in overlaying graphs with the epidemic curves. Significant associations were assessed using a *p*-value <0.05. Statistical analysis was performed with the software package STATA 13.1. Maps were created in ArcGIS 10.1.

3. Results

The 2010 outbreak in Hermosillo represented 2,843 laboratory confirmed cases of dengue with incidence rate of 397.6 cases per 100,000 inhabitants. Navojoa identified 511 cases in 2008 for an incidence of 466.6 cases per 100,000. The distribution of cases by epidemiologic week was similar for both cities (Fig. 1). Sporadic cases occurred from week 1 to 34. The onset of the outbreaks started on week 35 (early September) and peaked in week 42 (mid-October) with declining number of cases until late December.

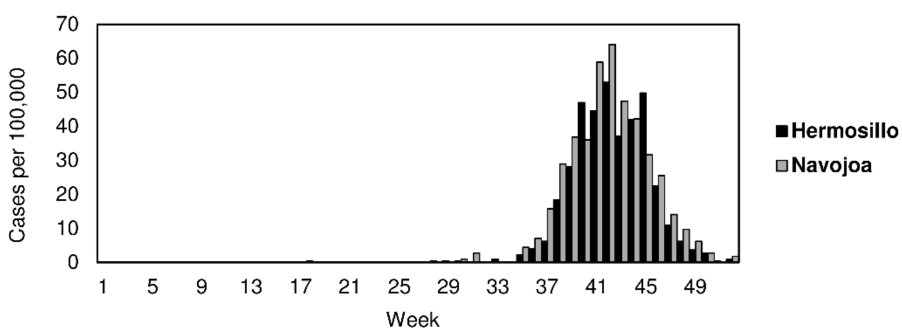

Fig. 1. Epidemic curves for dengue; Navojoa 2008, Hermosillo 2010

In both cities, women accounted for a higher proportion of cases (Hermosillo=57.5%, Navojoa=59.5%; *p*-value=0.42). Females were reported as confirmed dengue cases at an incidence rate 1.4 times higher than males in both cities (Hermosillo: 45.8 vs 33.8 cases per 10,000; Navojoa: 51.5 vs 37.8

cases per 10,000) (Table 1). In Hermosillo there was a relatively equal distribution by age group in both sexes, except for the 0-9 age group which presented with the lowest incidence (males: 10.0; females: 13.9 per 10,000). In contrast, Navojoa showed lower incidence rate for males in the age groups 30-39 (17.1 per 10,000) and 40-49 (16.6 per 10,000). More severe manifestations of dengue were identified in Hermosillo, 405 DHF cases which resulted in a DF: DHF ratio of 6.0, this was much lower than the 169.3 ratio of DF:DHF in Navojoa. In Hermosillo, males were more affected by DHF (males: 5.1 vs females: 7.0 incidence rate ratio), especially in the age groups 10-19, 40-49, and 60 and older. Laboratory results indicate that 48 (9.4%) Navojoa cases and 64 (2.3%) Hermosillo cases had previously been infected with dengue.

Table 1. Distribution of dengue cases by sex, age, and severity

	FD		FHD		Total		Incidence rate ratio (DF/DHF)
	Cases	Incidence rate	Cases	Incidence rate	Cases	Incidence rate	
Hermosillo	2,443	34.2	405	5.7	2,848	39.8	6.0
Male	1,004	28.2	198	5.6	1,202	33.8	5.1
0-9	59	8.8	8	1.2	67	10.0	7.4
10-19	295	43.4	64	9.4	359	52.8	4.6
20-29	227	36.4	31	5.0	258	41.4	7.3
30-39	137	24.1	29	5.1	166	29.2	4.7
40-49	123	28.3	28	6.4	151	34.8	4.4
50-59	88	30.2	14	4.8	102	35.1	6.3
60-69	39	25.9	12	8.0	51	33.8	3.3
70 and more	30	30.6	10	10.2	40	40.7	3.0
Missing	6		2		8		
Female	1,439	40.1	207	5.8	1,646	45.8	7.0
0-9	76	11.8	13	2.0	89	13.9	5.8
10-19	287	44.1	46	7.1	333	51.1	6.2
20-29	315	51.0	44	7.1	359	58.1	7.2
30-39	218	38.0	25	4.4	243	42.4	8.7
40-49	235	51.8	28	6.2	263	57.9	8.4
50-59	161	51.9	21	6.8	182	58.6	7.7
60-69	90	52.7	17	10.0	107	62.7	5.3
70 and more	46	35.6	11	8.5	57	44.1	4.2
Missing	11		2		13		
Navojoa	508	44.6	3	0.3	511	44.9	169.3
Male	209	37.6	2	0.4	211	38.0	104.5
0-9	28	26.4	0	0.0	28	26.4	------
10-19	64	59.1	0	0.0	64	59.1	------
20-29	48	55.4	1	1.2	49	56.5	48.0
30-39	14	17.1	0	0.0	14	17.1	------
40-49	11	16.6	0	0.0	11	16.6	------
50-59	13	26.2	1	2.0	14	28.2	13.0
60-69	16	54.5	0	0.0	16	54.5	------
70 and more	13	58.5	0	0.0	13	58.5	------
Missing	2				2		
Female	299	51.3	0	0.0	299	51.3	------
0-9	33	32.0	0	0.0	33	32.0	------
10-19	74	68.3	1	0.9	75	69.3	74.0
20-29	52	57.7	0	0.0	52	57.7	------
30-39	42	48.4	0	0.0	42	48.4	------
40-49	32	43.9	0	0.0	32	43.9	------
50-59	43	78.2	0	0.0	43	78.2	------
60-69	15	45.0	0	0.0	15	45.0	------
70 and more	8	29.1	0	0.0	8	29.1	------

Incidence per 10,000 inhabitants

3.1. High density areas of dengue

In Hermosillo, high density areas started in the northern side of the city (Fig. 2). This area covered 1.4% of the total area of the city (weeks 33-36). During the next period (weeks 37-40), high density areas increased to 10.4% of the geographic city area and expanded towards the southeast. Over the next period (weeks 41-44) the high density areas covered almost 30% of the city. After this period, the outbreak started to recede to 16.9% of the geographic city area (weeks 45-48), and during the last period (weeks 49-52) receded to a very small area (0.1%) with high density of dengue. Comparatively, the geographic coverage of the outbreak of Navojoa followed a similar progression at the beginning of the outbreak but receded more quickly in geographic size (Fig. 2). As in Hermosillo, small areas of high density initiated the outbreak in the west and south side of the city during week 36 and earlier (1.4% vs. 1.0%, $p = 0.06$). From weeks 37-40, the areas of high incidence had a similar increase as Hermosillo and were focused in the southwest side of the city (9.4% vs. 10.4%, $p = 0.11$). During the third period of the outbreak (weeks 41-44), the high density area covered less than that of Hermosillo (22.2% vs. 29%, $p <0.001$). The geographic area of the fourth period remained smaller in Navojoa than in Hermosillo during week 45-48 (8.6% vs. 16.9%, $p < 0.001$).

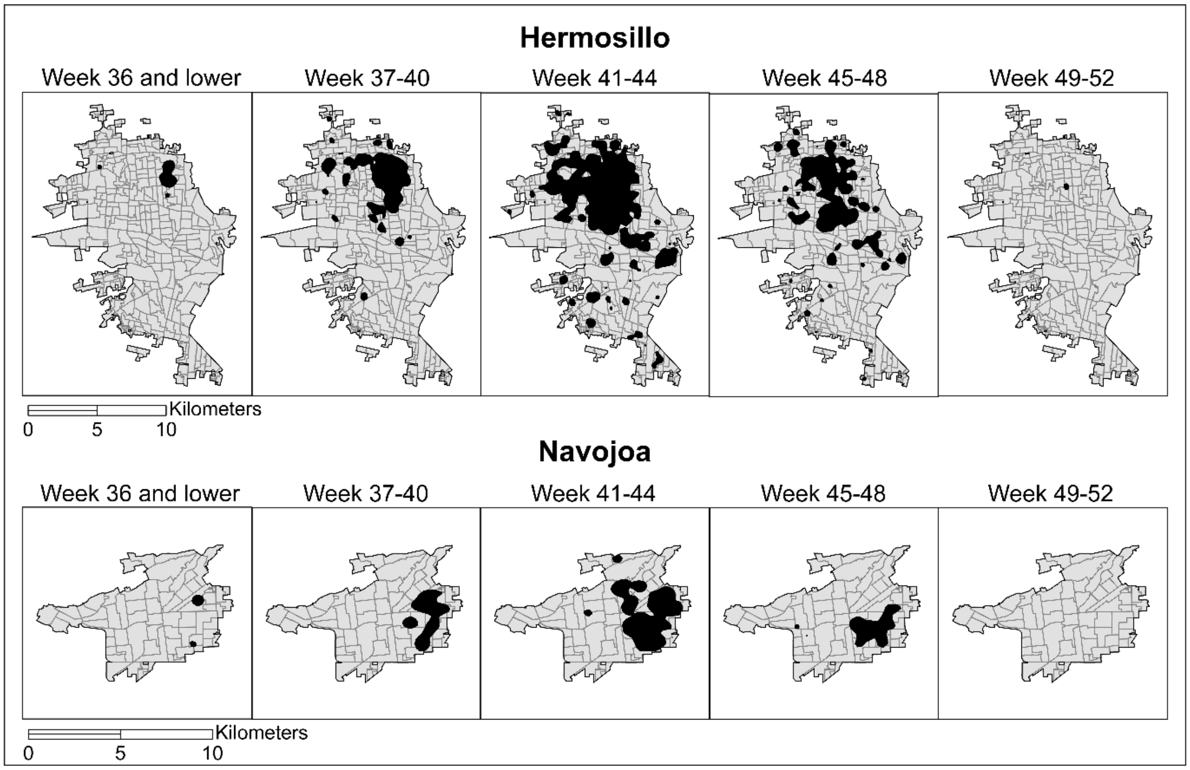

Fig. 2. Spread of high density areas of dengue cases (≥10 cases per 0.8 km^2) by period of time and city-outbreak in Sonora, Mexico

3.2. Space-time clustering

Space-time clustering was observed in both cities (Fig. 3). The red circles represent the first space-time clusters in early September in Hermosillo and late August in Navojoa. In Hermosillo, the clusters show the point of origin being in the northwest side of the city and moving to contiguous neighborhoods from west to the east and to the center of the city during the months of October and November. There was also a space-time cluster in the northwest side of the city on Sep 11-Nov 8 with lower dissemination to neighboring areas. In temporal terms, the map also shows that in Hermosillo the transmission within the initial clusters began in September/early October and transmission within the cluster was sustained approximately for two months. In Navojoa, the first space-time cluster occurred in the west side of the city and the disease clusters moved to the east. Geographical progress westward stopped in October but transmission in some clusters was sustained for longer periods, almost three months. This is consistent with what was demonstrated in the period analysis from the previous section.

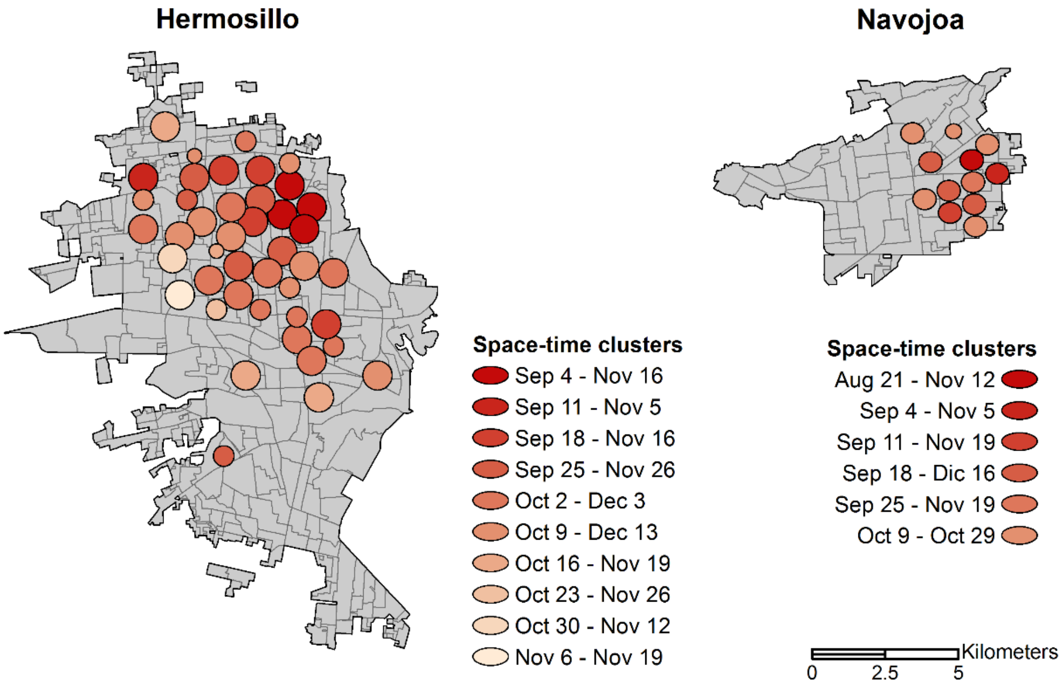

Fig. 3. Space-time clusters of dengue cases (500m window) in city-outbreaks

3.3. Case Neighborhood characteristics across time

Demographic characteristics of the neighborhoods in which dengue cases resided changed over time. The progression of the outbreak through neighborhoods with different demographics was modified by the city-site for median age (*p*-value= 0.015), no basic education (*p*-value=0.017), and population density (*p*-value =0.005). To examine the changes in neighborhood demographics, models for each city were created (Table 2). In both cities, as the outbreak progressed, the neighborhood characteristics in which cases resided shifted from neighborhoods with higher percent of people with no health services to lower percentages (Hermosillo: β=-0.212, *p*-value<0.001; Navojoa: β= -0.133, *p*-value<0.01). Similarly, case neighborhoods at the beginning of the outbreak had a higher percent of occupied houses as compared to neighborhoods at the end of the outbreak (Hermosillo: β=-0.039, *p*-value<0.01; Navojoa: β=-0.056, *p*-value<0.01). Regression analysis confirmed the shifting population density in neighborhoods where dengue cases resided. While both cities had a significant decrease in case neighborhood population density, the decline was greater in Hermosillo compared to Navojoa (Hermosillo: β= -1.9, p-value<0.001 Vs Navojoa: β= -0.687, p-value<0.05). These trends were visually detectable when plotting the distribution of these three significantly changing neighborhood characteristics with the epidemiologic curve (Fig. 4) where the epidemiologic curve overlaid on the distribution of the three significant neighborhood characteristics in both cities shows the association between the epidemiologic weeks and urbanization and health care.

Table 2. Mean values of neighborhood characteristics of dengue cases by 4-week periods by city-outbreaks and bivariate association between neighborhood characteristics of cases and epidemiologic week (OLS regression) by city-outbreaks

	Weeks 36 and lower	Weeks 37-40	Weeks 41-44	Weeks 45-48	Weeks 49-52	Total	OLS regressions β
Navojoa	n=17	n=134	n=242	n=92	n=12	n=497	
Median age (years)	28.5	27.5	27.3	28.0	27.1	27.5	0.022
Unemployment (%)	5.5	5.2	5.4	5.6	5.2	5.3	0.028
No health care (%)	18.4	17.9	17.7	17.0	16.3	17.6	-0.133**
No basic education (%)	26.6	27.3	30.2	29.0	27.5	29.0	0.184
Migration (%)	2.3	2.2	1.9	2.1	2.0	2.0	-0.016
Occupied houses (%)	99.1	99.0	98.8	98.6	98.4	98.8	-0.056**
Persons per house	3.8	3.9	3.9	3.9	4.0	3.9	0.071
No piped water (%)	3.5	3.0	3.8	3.5	4.4	3.5	0.067
Population density (persons/ha)	54.4	53.1	47.0	47.8	47.7	49.1	-0.687*
Hermosillo	n=66	n=711	n=1,262	n=638	n=53	n=2,730	
Median age (years)	25.7	27.6	29.5	29.5	28.1	28.9	0.238***
Unemployment (%)	4.7	5.5	5.9	6.0	5.9	5.8	0.066***
No health care (%)	24.6	24.6	22.7	22.5	23.2	23.2	-0.212***
No basic education (%)	24.2	25.8	24.4	24.4	25.3	24.8	-0.105*
Migration (%)	2.2	2.0	2.0	2.0	2.0	2.0	-0.000
Occupied houses (%)	98.9	98.9	98.7	98.6	98.6	98.7	-0.039**
Persons per house	3.8	3.7	3.6	3.6	3.7	3.7	-0.014***
No piped water (%)	1.2	1.3	1.3	1.9	1.8	1.4	0.079*
Population density (persons/ha)	99.2	86.9	74.8	73.1	69.3	78.0	-1.900***

Each neighborhood characteristic is treated as dependent variable. β coefficients represent the mean change in the neighborhood characteristic of cases per 1 week increment.
*** *p*-value<0.001, ** *p*-value<0.01, * *p*-value<0.05

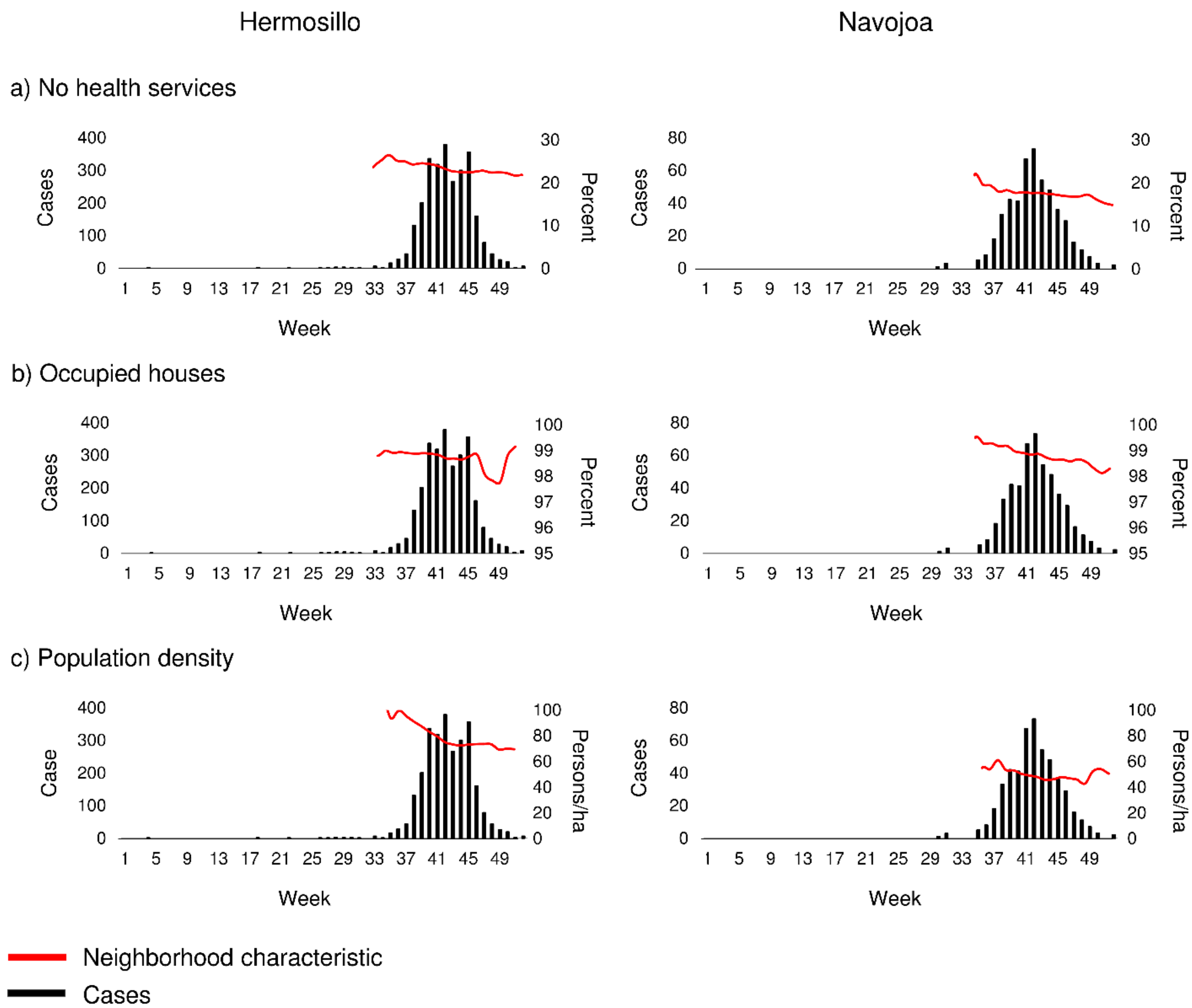

Fig. 4. Significant association between neighborhood characteristics of dengue cases and week of occurrence by city-outbreaks

4. Discussion

Comparisons between the two outbreaks in the state of Sonora, Mexico demonstrate several significant similarities in temporal distribution, space-time progression across contiguous neighborhoods, and shifting socio-demographic and socio-economic patterns of neighborhoods reported cases reside in over the course of the outbreaks. These similarities have significant implications for both the monitoring and prevention of dengue in these communities, and perhaps more broadly in other communities of Mexico, especially communities in arid regions.

In these outbreaks, almost all of the cases occurred between September and December in both cities, with the peak of the outbreaks occurring in mid-October. This temporal distribution fits with the traditional distribution of epidemics in the arid region of the Sonoran desert. In this region, outbreaks arise during and after the summer monsoon season and disappear with the introduction of the winter season when lower temperatures suppress vector populations (Macías-Duarte et al., 2009; Ray et al., 2007).

Kernel density analysis and space-time scan statistics revealed similar patterns of geographic expansion in the two cities at the beginning of the outbreak. However, differences were observed at the peak of the outbreak with a higher proportion of geographic area in Hermosillo experiencing high dengue transmission. Despite this difference, the infection was progressively disseminated beyond the initial foci of case households in both cities with spatio-temporal clusters maintained during several months. This is consistent with the space-time pattern of transmission in a city of Puerto Rico where they reported significant clusters of dengue cases within the same households over periods of three or less days; however, dengue cases were spread across the locality over longer periods of several weeks (Morrison et al., 1998).

A second pattern identified in each city was the contiguity of dissemination. Kan et al. (2008) found two different spatial patterns of dengue: contiguous and relocation. In this current study, the transmission in both cities started in a specific neighborhood and showed a contiguous pattern of dispersion with the geographical progression of disease moving into progressively into adjacent neighborhoods. Considering human mobility is a major factor for transmission within a community (Benedictis et al., 2003; Harrington et al., 2005; Vanwambeke et al., 2006; WHO, 2009), a predominant contiguous spatial pattern of transmission across time suggests the predominance of human and/or in the case of dengue, vector mobility occurring within a close range, possibly related to residential activities within the neighborhood and, to a lesser extent, the mobility of persons to further distances within the community (Kan et al., 2008).

These results support the use of targeted control efforts, particularly at the beginning of an outbreak. These initial foci served as a sustained source of infection to contiguous areas and targeting them early could reduce spread across the city (Harrington et al., 2005). Due to higher levels of uncertainty in reporting, particularly at the beginning of an outbreak, both confirmed and probable case clusters should be investigated. The delays in waiting for confirmation can be significant. A study in Brazil reported a two-month delay in the identification of a dengue outbreak using passive surveillance information, although dengue-like cases were detected clinically almost immediately (Pontes et al., 2000). Improvements to passive surveillance systems to identify early onset of dengue outbreaks is urgently needed (Wilder-Smith et al., 2012). In the current study, the initial space-time clusters in both Hermosillo and Navojoa were sustained two and three months, respectively, and progressed to neighboring areas. Therefore, a combination of passive and active surveillance activities and syndromic surveillance, by using dengue-like reported cases, could help to improve the early detection of outbreaks. It might also inform the implementation of opportune peri-focal vector control measures (Pontes et al., 2000).

Over the course of the outbreak case neighborhood characteristics shifted from areas with higher to lower 1) proportions of people with no health services, 2) population densities, and 3) percent of occupied houses. The steeper slope of Hermosillo related to population density could be explained in two ways. First, by the difference in the underlying characteristics of the two cities. Hermosillo is the capital of the state of Sonora and it has a greater average population density (52.8 persons/ha) compared to Navojoa (33.4 persons/ha) (INEGI, 2010). A study in an urban locality of Taiwan (Chan et al., 2015) found a significant influence of high population density on dengue incidence only during the peak of the epidemic. The authors concluded that population density may have significant influence on transmission only when the number of infected cases is large enough (Chan et al., 2015). Secondly, differences in human mobility might also provide an explanation to the differing density patterns. A study of the spatio-temporal dynamics of dengue transmission in a city of Taiwan found that high population density was a significant factor only for commuter cases where residence was different from working places (Wen et al., 2012). The current study did not have information about commuting activities of the cases, however as a larger urban area with greater infrastructure and public transportation it is possible that Hermosillo may have commuter patterns that differ from Navojoa. Future studies should include information about the mobility of cases during their daily activities to determine if routine mobility influences the dissemination of the disease across neighborhoods.

An important contrast between outbreaks was the difference in DHF occurrence with a minimum incidence in Navojoa and a remarkable 1 in 6 DHF cases in Hermosillo. Additionally, a high proportion of cases in Navojoa had evidence of a previous dengue infection. While this suggests the circulation of two or more serotypes, the official report of the Laboratory of the Health Ministry indicates that only DENV-1 was circulating in the localities during the outbreaks (Dirección General de Epidemiología, 2014). This discrepancy between severity of disease manifestation and circulating serotypes should be explored in detailed follow-up studies. There is a need for population-based serological surveys and an assessment of internal migration and mobility to better understand the potential role of new serotypes introduced into these localities.

Availability of piped water was not different in case neighborhoods over the course of the epidemic. This variable may not be the best indicator of water disruption and resultant water storage behaviors which are important factors for the creation of vector breeding sites (Caprara et al., 2009). Both cities have a high coverage of piped water above 95% (INEGI, 2010); however, there are significant problems of water supply and distribution particularly in Hermosillo (Pineda-Pablos, 2007; Salazar-Adams and Pineda-Pablos, 2010).

One limitation of this study was that the clusters obtained in the spatio-temporal analysis were based on the residence of cases and other criteria for geocoding could lead to a different distribution. This is a common issue in most geographic studies of dengue, and still provides useful information given that people are often at home during the peak biting periods of the *Ae. aegypti*, the only vector in these two cities, early morning and before dusk (WHO, 2012). In addition, the analysis was limited by the data available. Key factors that would improve the analysis are the immunological status of the population, vector density, and vector control activities during the outbreaks as they could influence the spatio-temporal results. The analysis was restricted to laboratory confirmed cases which may lead to underestimate the real proportions and rates of disease however, a previous assessment (Reyes-Castro, 2015) of the case distribution pattern in Hermosillo did not demonstrate any difference between suspect and confirmed cases.

5. Conclusions

In summary, the spatio-temporal pattern of dengue transmission during two urban outbreaks in Sonora, MX were similar in overall seasonal distribution of cases and progression of the outbreaks. For both, the focus of transmission started in neighborhoods with high population density, and low access to healthcare and was maintained over a period of 2-3 months in these foci. Transmission disseminated to areas adjacent to these foci in both cities. These results support the strategy of early identification and targeting of intervention efforts in these areas to reduce subsequent transmission across a wider geographic area. Given that the neighborhood characteristics were similar for these initial foci between the outbreaks, further research should be conducted to provide a more in depth profile of high risk neighborhoods that can be more closely monitored for dengue and other arboviral activity. The results of this study can be used by the local health authorities to enhance the surveillance in specific high risk areas to identify initial increases in transmission. Future investigations should explore whether these same patterns are replicated using all reported case data, not just the laboratory confirmed cases. Similar results would support the use of syndromic surveillance, which is more sensitive but less specific. Given the time delays and increased labor involved in confirmatory testing, the use of syndromic cases could lead to earlier detection of an outbreak and facilitate prompt focal control that could reduce subsequent spread.

Funding: This work was supported by the National Institutes of Health - NIAID [R01-AI091843].

Competing interest: No conflict of interest exists

Acknowledgements

This research was made possible with surveillance data provided by the Health Ministry of the State of Sonora. We would like to thank Dr. Gerardo Alvarez-Hernandez for his valuable support during the data acquisition process.

References

Barbazan, P., Guiserix, M., Boonyuan, W., Tuntaprasart, W., Pointer, D., Gonzalez, J.-P., 2010. Modelling the effect of temperature on transmission of dengue. Med. Vet. Entomol. 24, 66–73.

Benedictis, J.D., Chow-Shaffer, E., Costero, A., Clark, G.G., Edman, J.D., Scott, T.W., 2003. Identification of the People from Whom Engorged Aedes Aegypti Took Blood Meals in Florida, Puerto Rico, Using Polymerase Chain Reaction-Based Dna Profiling. Am. J. Trop. Med. Hyg. 68, 437–446.

Brunkard, J.M., Cifuentes, E., Rothenberg, S.J., 2008. Assessing the roles of temperature, precipitation, and ENSO in dengue re-emergence on the Texas-Mexico border region. Salud Pública México 50, 227–234.

Caprara, A., Lima, J.W. de O., Marinho, A.C.P., Calvasina, P.G., Landim, L.P., Sommerfeld, J., 2009. Irregular water supply, household usage and dengue: a bio-social study in the Brazilian Northeast. Cad. Saúde Pública 25 Suppl 1, S125-136.

Carbajo, A.E., Cardo, M.V., Vezzani, D., 2012. Is temperature the main cause of dengue rise in non-endemic countries? The case of Argentina. Int. J. Health Geogr. 11, 26. doi:10.1186/1476-072X-11-26

Chan, M., Johansson, M.A., 2012. The Incubation Periods of Dengue Viruses. PLoS ONE 7, e50972. doi:10.1371/journal.pone.0050972

Chan, T.-C., Hu, T.-H., Hwang, J.-S., 2015. Daily forecast of dengue fever incidents for urban villages in a city. Int. J. Health Geogr. 14, 9. doi:10.1186/1476-072X-14-9

Dirección General de Epidemiología, 2014. Panorama Epidemiológico del Dengue. Secretaría de Salud.

Ernst, K.C., Walker, K.R., Reyes-Castro, P., Joy, T.K., Castro-Luque, A.L., Diaz-Caravantes, R.E., Gameros, M., Haenchen, S., Hayden, M.H., Monaghan, A., Jeffrey-Guttierez, E., Carrière, Y., Riehle, M.R., 2016. Aedes aegypti (Diptera: Culicidae) Longevity and Differential Emergence of Dengue Fever in Two Cities in Sonora, Mexico. J. Med. Entomol. doi:10.1093/jme/tjw141

Favier, C., Schmit, D., Müller-Graf, C.D.., Cazelles, B., Degallier, N., Mondet, B., Dubois, M.A., 2005. Influence of spatial heterogeneity on an emerging infectious disease: the case of dengue epidemics. Proc. R. Soc. B Biol. Sci. 272, 1171–1177. doi:10.1098/rspb.2004.3020

Getis, A., Morrison, A.C., Gray, K., Scott, T.W., 2003. Characteristics of the Spatial Pattern of the Dengue Vector, Aedes Aegypti, in Iquitos, Peru. Am. J. Trop. Med. Hyg. 69, 494–505.

Gómez-Dantés, H., Martín, J.L.S., Danis-Lozano, R., Manrique-Saide, P., 2011. Integrated prevention and control strategy for dengue in Mesoamerica. Salud Pública México 53, s349–s357.

Gómez-Dantés, H., Ramsey, J., 2009. Dengue in the Americas: challenges for prevention and control. Cad Saúde Pública 25, s19–s31.

Halstead, S.B., 2008. Dengue Virus–Mosquito Interactions. Annu. Rev. Entomol. 53, 273–291. doi:10.1146/annurev.ento.53.103106.093326

Harrington, L.C., Scott, T.W., Lerdthusnee, K., Coleman, R.C., Costero, A., Clark, G.G., Jones, J.J., Kitthawee, S., Kittayapong, P., Sithiprasasna, R., Edman, J.D., 2005. Dispersal of the Dengue Vector Aedes Aegypti Within and Between Rural Communities. Am. J. Trop. Med. Hyg. 72, 209–220.

INEGI, 2016. Instituto Nacional de Estadística y Geografía (INEGI) [WWW Document]. INEGI. URL http://www.inegi.org.mx/ (accessed 7.9.14).

INEGI, 2010. Censo de Población y Vivienda 2010 [WWW Document]. Inst. Nac. Estad. Geogr. URL http://www.inegi.org.mx/est/contenidos/proyectos/ccpv/cpv2010/Default.aspx (accessed 7.9.14).

Kan, C.-C., Lee, P.-F., Wen, T.-H., Chao, D.-Y., Wu, M.-H., Lin, N.H., Huang, S.Y.-J., Shang, C.-S., Fan, I.-C., Shu, P.-Y., Huang, J.-H., King, C.-C., Pai, L., 2008. Two clustering diffusion patterns identified from the 2001-2003 dengue epidemic, Kaohsiung, Taiwan. Am. J. Trop. Med. Hyg. 79, 344–352.

Kulldorff, M., 2014. SaTScan User Guide for version 9.3.

Macías-Duarte, A., Alvarado-Castro, J.A., Dórame-Navarro, M.E., Félix-Torres, A.A., 2009. Dispersal and oviposition of laboratory-reared gravid females of Toxorhynchites moctezuma in an arid urban area of Sonora, Mexico. J. Am. Mosq. Control Assoc. 25, 417–424.
Maciel-de-Freitas, R., Lourenço-de-Oliveira, R., 2009. Presumed unconstrained dispersal of Aedes aegypti in the city of Rio de Janeiro, Brazil. Rev. Saúde Pública 43, 8–12.
Mammen, M.P., Jr., Pimgate, C., Koenraadt, C.J.M., Rothman, A.L., Aldstadt, J., Nisalak, A., Jarman, R.G., Jones, J.W., Srikiatkhachorn, A., Ypil-Butac, C.A., Getis, A., Thammapalo, S., Morrison, A.C., Libraty, D.H., Green, S., Scott, T.W., 2008. Spatial and Temporal Clustering of Dengue Virus Transmission in Thai Villages. PLoS Med 5, e205. doi:10.1371/journal.pmed.0050205
Martín, J.L.S., Brathwaite, O., Zambrano, B., Solórzano, J.O., Bouckenooghe, A., Dayan, G.H., Guzmán, M.G., 2010. The Epidemiology of Dengue in the Americas Over the Last Three Decades: A Worrisome Reality. Am. J. Trop. Med. Hyg. 82, 128–135. doi:10.4269/ajtmh.2010.09-0346
Morrison, A.C., Getis, A., Santiago, M., Rigau-Perez, J.G., Reiter, P., 1998. Exploratory space-time analysis of reported dengue cases during an outbreak in Florida, Puerto Rico, 1991-1992. Am. J. Trop. Med. Hyg. 58, 287–298.
Padmanabha, H., Soto, E., Mosquera, M., Lord, C.C., Lounibos, L.P., 2010. Ecological Links Between Water Storage Behaviors and Aedes aegypti Production: Implications for Dengue Vector Control in Variable Climates. EcoHealth 7, 78–90. doi:10.1007/s10393-010-0301-6
Pineda-Pablos, N., 2007. Construcciones y demoliciones. Participación social y deliberación pública en los proyectos del acueducto de El Novillo y de la planta desaladora de Hermosillo, 1994-2001. Región Soc. 19, 89–115.
Pontes, R.J., Freeman, J., Oliveira-Lima, J.W., Hodgson, J.C., Spielman, A., 2000. Vector densities that potentiate dengue outbreaks in a Brazilian city. Am. J. Trop. Med. Hyg. 62, 378–383.
Ray, A.J., Garfin, G.M., Wilder, M., Vásquez-León, M., Lenart, M., Comrie, A.C., 2007. Applications of Monsoon Research: Opportunities to Inform Decision Making and Reduce Regional Vulnerability. J. Clim. 20, 1608–1627. doi:10.1175/JCLI4098.1
Reyes-Castro, P., 2015. Dynamics of Dengue Transmission in the Arid Region of Sonora, Mexico. University of Arizona, Tucson, AZ.
Rodrigues, M. de M., Marques, G.R.A.M., Serpa, L.L.N., Arduino, M. de B., Voltolini, J.C., Barbosa, G.L., Andrade, V.R., de Lima, V.L.C., 2015. Density of Aedes aegypti and Aedes albopictus and its association with number of residents and meteorological variables in the home environment of dengue endemic area, São Paulo, Brazil. Parasit. Vectors 8, 115. doi:10.1186/s13071-015-0703-y
Salazar-Adams, A., Pineda-Pablos, N., 2010. Escenarios de demanda y políticas para la administración del agua potable en México: el caso de Hermosillo, Sonora. Región Soc. 22, 105–122.
Schmidt, W.-P., Suzuki, M., Dinh Thiem, V., White, R.G., Tsuzuki, A., Yoshida, L.-M., Yanai, H., Haque, U., Huu Tho, L., Anh, D.D., Ariyoshi, K., 2011. Population Density, Water Supply, and the Risk of Dengue Fever in Vietnam: Cohort Study and Spatial Analysis. PLoS Med 8, e1001082. doi:10.1371/journal.pmed.1001082
Sharma, K.D., Mahabir, R.S., Curtin, K.M., Sutherland, J.M., Agard, J.B., Chadee, D.D., 2014. Exploratory space-time analysis of dengue incidence in Trinidad: a retrospective study using travel hubs as dispersal points, 1998–2004. Parasit. Vectors 7, 1–11. doi:10.1186/1756-3305-7-341
Silva, M.M.O., Rodrigues, M.S., Paploski, I.A.D., Kikuti, M., Kasper, A.M., Cruz, J.S., Queiroz, T.L., Tavares, A.S., Santana, P.M., Araújo, J.M.G., Ko, A.I., Reis, M.G., Ribeiro, G.S., 2016. Accuracy of Dengue Reporting by National Surveillance System, Brazil. Emerg. Infect. Dis. 22, 336–339. doi:10.3201/eid2202.150495
SMN, 2016. Información climatológica [WWW Document]. Serv. Meteorológico Nac. Com. Nac. Agua. URL http://smn.cna.gob.mx/es/component/content/article?id=42 (accessed 11.3.16).
Stanaway, J.D., Shepard, D.S., Undurraga, E.A., Halasa, Y.A., Coffeng, L.E., Brady, O.J., Hay, S.I., Bedi, N., Bensenor, I.M., Castañeda-Orjuela, C.A., Chuang, T.-W., Gibney, K.B., Memish, Z.A., Rafay, A., Ukwaja, K.N., Yonemoto, N., Murray, C.J.L., 2016. The global burden of dengue: an

analysis from the Global Burden of Disease Study 2013. Lancet Infect. Dis. 16, 712–723. doi:10.1016/S1473-3099(16)00026-8
Stoddard, S.T., Forshey, B.M., Morrison, A.C., Paz-Soldan, V.A., Vazquez-Prokopec, G.M., Astete, H., Reiner, R.C., Vilcarromero, S., Elder, J.P., Halsey, E.S., Kochel, T.J., Kitron, U., Scott, T.W., 2013. House-to-house human movement drives dengue virus transmission. Proc. Natl. Acad. Sci. 110, 994–999. doi:10.1073/pnas.1213349110
Stoddard, S.T., Morrison, A.C., Vazquez-Prokopec, G.M., Soldan, V.P., Kochel, T.J., Kitron, U., Elder, J.P., Scott, T.W., 2009. The Role of Human Movement in the Transmission of Vector-Borne Pathogens. PLoS Negl. Trop. Dis. 3, e481. doi:10.1371/journal.pntd.0000481
Vanwambeke, S.O., van Benthem, B.H., Khantikul, N., Burghoorn-Maas, C., Panart, K., Oskam, L., Lambin, E.F., Somboon, P., 2006. Multi-level analyses of spatial and temporal determinants for dengue infection. Int. J. Health Geogr. 5, 5. doi:10.1186/1476-072X-5-5
Vázquez-Pichardo, M., Rosales-Jiménez, C., Núñez-León, A., Rivera-Osorio, P., Cruz-Hernández, S.D.L., Ruiz-López, A., González-Mateos, S., López-Martínez, I., Rodríguez-Martínez, J.C., López-Gatell, H., Alpuche-Aranda, C., 2011. Serotipos de dengue en México durante 2009 y 2010. Bol. Méd. Hosp. Infant. México 68, 103–110.
Watthanaworawit, W., Turner, P., Turner, C.L., Tanganuchitcharnchai, A., Jarman, R.G., Blacksell, S.D., Nosten, F.H., 2010. A prospective evaluation of diagnostic methodologies for the acute diagnosis of dengue virus infection on the Thailand-Myanmar border. ResearchGate 105, 32–7. doi:10.1016/j.trstmh.2010.09.007
Watts, D.M., Burke, D.S., Harrison, B.A., Whitmire, R.E., Nisalak, A., 1987. Effect of Temperature on the Vector Efficiency of Aedes aegypti for Dengue 2 Virus. Am. J. Trop. Med. Hyg. 36, 143–152.
Wen, T.-H., Lin, M.-H., Fang, C.-T., 2012. Population Movement and Vector-Borne Disease Transmission: Differentiating Spatial–Temporal Diffusion Patterns of Commuting and Noncommuting Dengue Cases. Ann. Assoc. Am. Geogr. 102, 1026–1037. doi:10.1080/00045608.2012.671130
WHO, 2016. Dengue and severe dengue [WWW Document]. URL http://www.who.int/mediacentre/factsheets/fs117/en/ (accessed 11.14.16).
WHO, 2012. Global Strategy for Dengue Prevention and Control 2012-2020. World Health Organization, Geneva.
WHO, 2009. Dengue guidelines for diagnosis, treatment, prevention, and control. TDR : World Health Organization, Geneva.
Wilder-Smith, A., Renhorn, K.-E., Tissera, H., Abu Bakar, S., Alphey, L., Kittayapong, P., Lindsay, S., Logan, J., Hatz, C., Reiter, P., Rocklöv, J., Byass, P., Louis, V.R., Tozan, Y., Massad, E., Tenorio, A., Lagneau, C., L'Ambert, G., Brooks, D., Wegerdt, J., Gubler, D., 2012. DengueTools: innovative tools and strategies for the surveillance and control of dengue. Glob. Health Action 5. doi:10.3402/gha.v5i0.17273