DYNAMICS OF DENGUE TRANSMISSION IN THE ARID REGION OF SONORA, MEXICO

by

Pablo Alejandro Reyes Castro

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As members of the Dissertation Committee, we certify that we have read the dissertation prepared by Pablo Alejandro Reyes Castro, titled Dynamics of Dengue Transmission in the Arid Region of Sonora, Mexico, and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

____ Date: (04/17/2015)
Robin B. Harris

____ Date: (04/17/2015)
Kacey C. Ernst

____ Date: (04/17/2015)
Gary Christopherson

____ Date: (04/17/2015)
Heidi Brown

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copies of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

____ Date: (04/17/2015)
Dissertation Director: Robin B. Harris

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SIGNED: Pablo Alejandro Reyes Castro

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ABSTRACT

Most of dengue transmission occurs in tropical and subtropical zones. As a result, studies on the dynamics of dengue transmission are principally focused in these areas. Less is known about the dynamics of dengue transmission and the interplay of social and climatic determinants in arid regions located at the fringe of transmission zones. This dissertation uses surveillance data from the state of Sonora, an arid region in northern Mexico, to examine three specific aims: 1) to assess relationships among social and climatic factors utilizing locality-level dengue incidence data across the state of Sonora, 2) to determine the correlation between the spatial pattern of dengue cases during an outbreak in Hermosillo, a large urban area, and neighborhood-level socio-economic and water supply factors using a novel case-control study design, and 3) to determine how dengue cases disseminated across two arid cities, Hermosillo and Navojoa, and to determine if changing socio-demographic patterns were similar between cities.

Results from the first ecological study indicated that the distribution of dengue across the state was associated most strongly with the climatic gradient and, secondarily, by population size and lack of education. Underreporting in rural areas with lower access to transportation infrastructure was also detected. We demonstrated that a spatially-based case-control study design was useful in identifying associations between dengue transmission and neighborhood-level characteristics related to population density, lack of access to healthcare and water supply restrictions. Finally, the spatio-temporal study identified common patterns between the two cities/outbreaks. Dengue transmission arose and was maintained for 2-3 months in specific foci areas characterized by low access to healthcare and then the disease moved to contiguous areas. Recommendations for

surveillance and control programs based on these results include: 1) in small localities at risk of transmission a combination of active and passive surveillance should be carried out for a period of time to determine if transmission is occurring, 2) monitoring water storage practices during water restrictions and ensuring appropriate messaging about covering storage containers should be made, and 3) spatial monitoring of dengue cases and agency reaction to initial disease occurrence could reduce spread to adjacent areas.

CHAPTER 1. INTRODUCTION

Dengue is one of the most important vector-borne disease worldwide (1). Over 390 million annual cases occur around the world with 96 million symptomatic cases and 24,000 deaths (2,3). The virus of dengue is classified as a *flavivirus* with four different serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) and humans are the primary host. The virus circulates in the blood of infected humans and is transmitted to another host principally by the bite of female *Aedes aegypti* mosquito (1).

Currently, around 2.5 billion people live within areas of dengue transmission (4). The impact of low temperatures on the life-cycle of *Ae. aegypti* mosquito limits the geographical distribution of the vector to the 10°C isotherm limits in January at the north and in July at the south hemisphere (Figure 1). Therefore, dengue transmission is principally located in tropical and subtropical regions (5).

Most dengue research has been conducted in these areas. Less is known about the transmission dynamics of dengue in arid areas on the geographical margins of usual dengue transmission areas (6). The Sonoran desert region stretches from southern Arizona to northern Sonora, Mexico. After a failed intensive *Ae. aegypti* eradication campaign in the Americas region during the 1950's and 1960's (7,8), dengue reemerged in the south of the State of Sonora in 1982 (9). Currently, the state has areas of endemic dengue and experiences focused outbreaks of dengue.

A. Study aims

The overall goal of these projects was to examine the dynamics of dengue transmission in Sonora, Mexico, an arid state in northern Mexico, and to describe the interplay of social and climatic determinants on the occurrence of the disease and how these determinants vary spatially across the region. The study utilized secondary data and geospatial analytic techniques. More specifically, the objectives were:

Aim 1: To assess the association among social and climatic factors with 2006-2011 dengue incidence data and social and climatic factors in the localities in Sonora, Mexico.

Hypothesis 1: Dengue incidence is higher in urban areas closer to the coast where temperature, precipitation and humidity are higher.

Aim 2: To assess the association between dengue fever and neighborhood characteristics related to socioeconomic and water supply factors during the outbreak of dengue that occurred in the urban area of Hermosillo, MX, 2010.

Hypothesis 2: The probability of dengue during the 2010 outbreak in Hermosillo was higher in neighborhoods with lower socio-economic status.

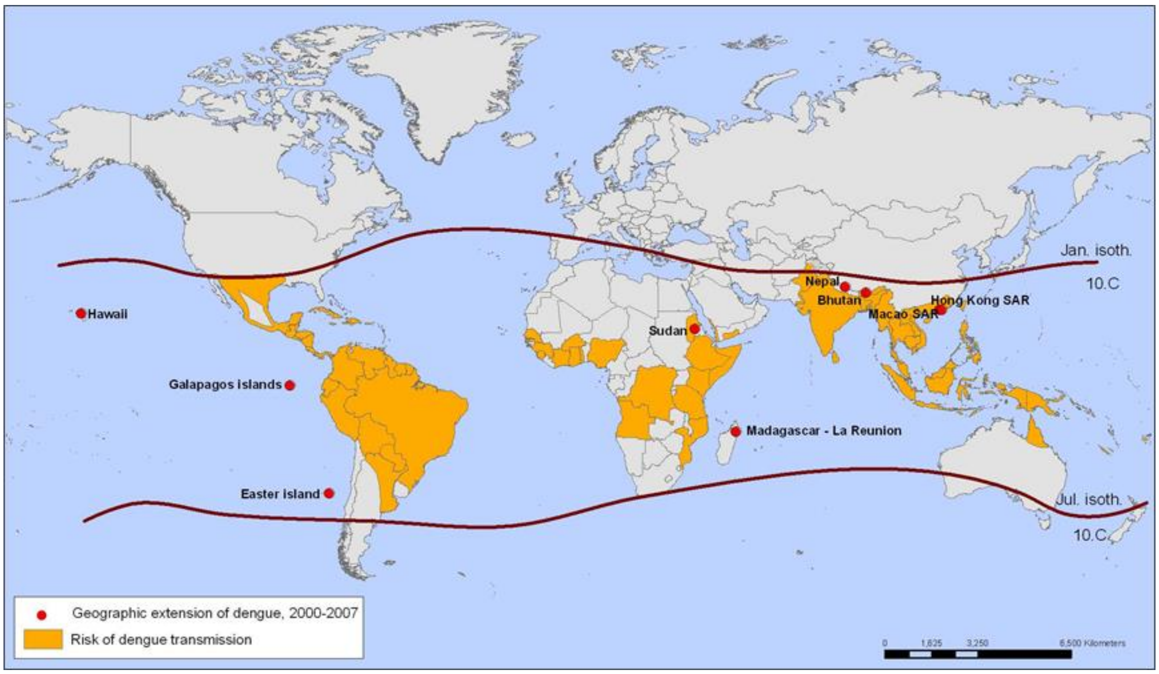
Aim 3: Finally, a spatio-temporal study was conducted for two dengue outbreaks in two arid cities of northern Mexico in order 1) to assess spatio-temporal clustering patterns in the two outbreaks, 2) to determine if there were differences in the socioeconomic patterns of dengue as the outbreaks progressed in each city, and 3) to determine if these patterns were similar between the two cities or outbreaks.

Hypothesis 3: Spatial-temporal clustering will be detected during the 2008 outbreak in Navojoa and the 2010 outbreak in Hermosillo.

Hypothesis 4: Patterns of socio-demographic conditions of neighborhoods affected during the outbreak will initiate in lower socio-economic neighborhoods and expand to contiguous neighborhoods with higher socio-economic characteristics.

Hypothesis 5: Changes in spatio-temporal and socio-economic patterns will be similar between both cities or outbreaks.

Figure 1. Areas at risk of Dengue



Source: World Health Organization, 2006 (10)

B. Dissertation format

The dissertation utilizes the three manuscripts option and consists of three chapters. Manuscripts are included as appendices. Chapter 1 (Introduction) offers an overview of the rationale of the study, the specific aims of the dissertation, and a literature review based on epidemiological data and scientific literature related to dengue. Chapter 2 (Present Study) explains the main characteristics of the surveillance, social and climate data and how they were prepared for analysis. The general methods used to accomplish the three aims and the main results of each of them are also included. Chapter 3 (Conclusions) summarizes the conclusions of each of the aims and discusses future directions for research. Finally, the manuscripts resulting from the three study aims are added as Appendices A, B, and C. Each manuscript is a separate work with its own sections, figures, tables, and references.

The author was responsible for the concept, design, literature review, data preparation, geocoding, statistical analysis, and writing of this dissertation and each of the studies included in the Appendix section. In addition to a literature review for Chapter 1, the author also utilized national public use data to create maps, tables, and graphs to support the arguments presented about dengue in Mexico and the State of Sonora. Digital maps were obtained from the National Institution of Statistics and Geography (INEGI, by its acronym in Spanish) (11). Information of yearly cases and dengue incidence, and dengue serotypes circulation in Mexico was obtained from the Yearbooks of Morbidity (12) and the National System of Epidemiological Surveillance (SINAVE, by its acronym in Spanish) (13) from the National Directorate of Epidemiology of Mexico. The map of the “Percent of Dengue Hemorrhagic Fever Cases by State” (Figure 9) included calculations and mapping conducted by the author. Maps of mean temperature and rainfall were created by the author using information from the Mexico National Weather Service (SMN, by its acronym in Spanish) (14). Correlations between climatic factors and dengue incidence by state were calculated in STATA 13.1 and included as a table. The final version of this dissertation incorporates valuable conceptual, methodological, and editorial comments from members of the dissertation committee.

C. Literature review

This section provides an overview of dengue transmission and factors influencing the dynamics of transmission. General concepts will be contextualized with information about Mexico and specifically to the state of Sonora. State-level data from Mexico are presented in maps and tables by state. This broad scale assessment will provide an overall picture of dengue in Mexico. Finally, the dengue surveillance system in Mexico is described.

1. The study area

The state of Sonora is located in northern Mexico and borders the state of Arizona. To the west, it is delimited by the coast of the Gulf of California and to the east by the Sierra Madre Occidental mountain range. It is an arid and semi-arid state located on the fringe of the winter 10°C isotherm, the geographic constraint of *Ae. aegypti* (1,15–17). According to the 2010 census, Sonora has a total population of 2,662,480 inhabitants (18). The process of development and urbanization during the twentieth century concentrated a large proportion of the population (75%) in urban settlements closer to the coast as well as along the United States-Mexico border (19). The state faces limitations related to the desert environment and water scarcity (20).

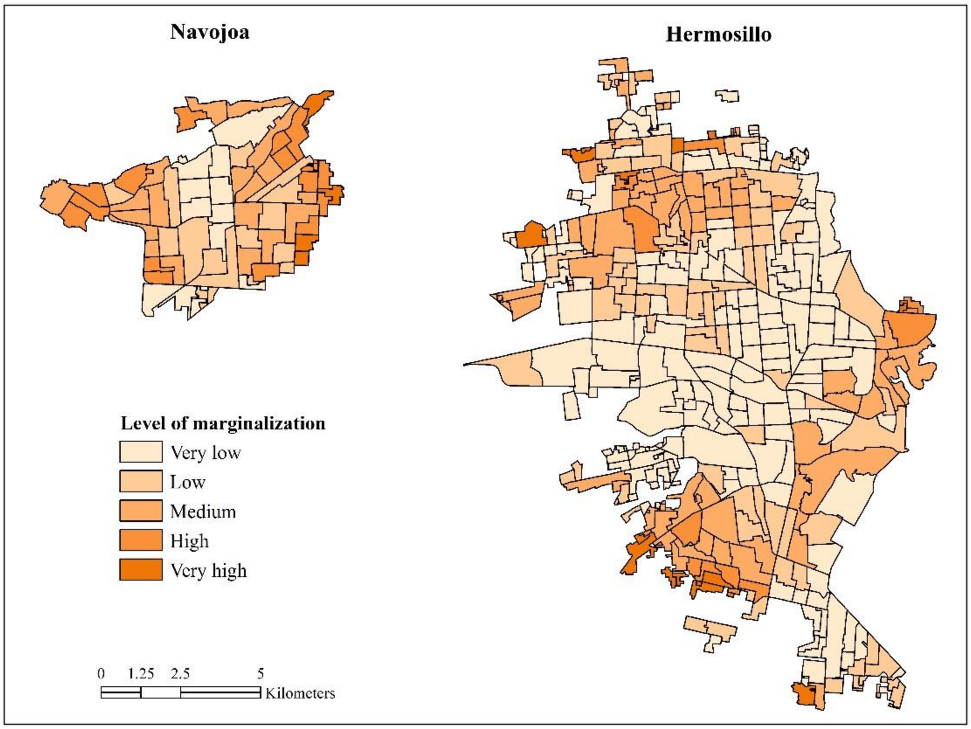
Hermosillo is a middle-size city and the capital of Sonora. It is located at 29°05' N latitude and 110°57' W longitude, with an altitude of 216 meters above sea level (11). According to the 2010 Census, the total population is 715,061 inhabitants (18). Further south, the city of Navojoa, population 113,836 (18) , is located at 27°04' N latitude and 109°26' W longitude, at an altitude of 40 meters above sea level (11) (Figure 2).

According to the Locality Marginalization Index calculated by the National Population Council of Mexico (CONAPO, by its acronym in Spanish) (21), both cities are categorized as having very low marginalization Compared to other cities of Mexico, which means they have a wide coverage of goods and basic infrastructure into households. However, the Urban Marginalization Index estimated by this institution (21) indicates that level of marginalization still varies within the cities (Figure 3).

Figure 2. Study Area

Source: Map created using data from INEGI (11)

Figure 3. Level of urban marginalization of study localities, 2010



Source: Map created using data from CONAPO (21)

2. The virus/vector/host interaction

Different elements interact in the dynamics of dengue transmission. Transmission requires the virus, the mosquito vector, and a susceptible host, all interacting within a suitable environment (22). The dengue virus (DENV) is a *Flavivirus* from the *flaviviradae* family that includes 4 different serotypes (DEN-1, DEN-2, DEN-3, and DEN-4).

Dengue viruses have two different cycles of transmission. The sylvatic cycle involves the transmission between non-human primates of the vectors *Ae. furcifer* and *Ae. luteocephalus* (23). Transmission to humans, however, is mainly focused in urban environments. The urban cycle involves humans and the vector *Ae. aegypti* mosquito, and to a lesser extent *Ae. albopictus*, although *Ae. albopictus* is principally located in Asia

(23–25). The urban cycle of transmission is highly efficient because *Ae. aegypti* is a highly anthropophilic vector (1). In Sonora, *Ae. aegypti* are the only recorded vector of dengue. Female *Ae. aegypti* exploit man-made water containers for oviposition and larval breeding allowing them to live close to humans during every reproductive cycle (26). In fact, most female *Ae. aegypti* spend their lifetime in or close to the same place, within a 100 meters distance, where they became adults (1,27). Infection with DENV occurs when the female mosquito feeds on a viremic human host. After an extrinsic incubation period (EIP)[1] of 7-12 days, the mosquito remains infected the rest of its life and has the potential to transmit during each subsequent blood meal (29).

Humans are the main host and amplifier of the dengue virus. After inoculation with one of the serotypes in a susceptible host, the intrinsic incubation period (IIP)[2] takes around 3 to 10 days (28). A significant proportion of cases (75%) have subclinical manifestations with only mild fever or no symptoms at all, especially infants (2,30). The spectrum of clinical manifestations for symptomatic cases ranges and classically is described as falling into one of three categories depending on the severity of the case (31):

1. Dengue fever (DF): acute febrile illness, frontal headache, retro-ocular pain, muscle and join pain, nausea, vomiting, and rash.
2. Dengue hemorrhagic fever (DHF): acute febrile illness, minor or major bleeding, thrombocytopenia and plasma leaked.

[1] EIP: Period between the time when mosquito takes viraemic bloodmeal from an infected human and the time when the mosquito becomes infectious (28).
[2] IIP: Period of time between the infection and the onset of the symptoms (28).

3. Shock syndrome (DSS): DHF with signs of circulatory failure like narrow pulse pressure, hypotension, or shock[3].

After the recovery phase, the person develops long-term immunity to that specific serotype but not for the other three, making reinfection possible. Reinfection with another serotype has been associated with an increased risk of manifesting severe complications of dengue, including DHF and DSS (33).

3. Epidemiology of dengue

An estimated 390 million annual cases of dengue occur around the world, with 96 million symptomatic cases and 24,000 deaths (2,3). The region of Asia suffers most of the impact of dengue with 70% of the global burden of the disease (271 million of apparent and inapparent cases) occurring there (2) (Figure 4). However, since the 1980s, outbreaks of all four serotypes of DENV has occurred in the Americas (34,35). This follows the collapse of a massive vector control campaign implemented across the Americas during the 1950s and 1960s. In 1972 the *Ae. aegypti* mosquito was near to eradication in 21 countries of the region; (36) however after the program ended, the mosquito re-established widely and dengue transmission resurged.

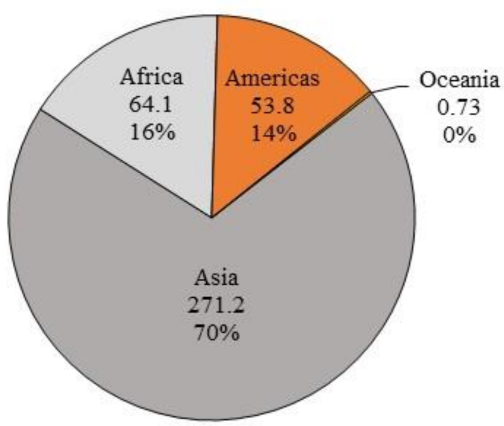
From the 1980s to the 2000s, reported cases in the Americas increased 4.6 and 8.3 times for dengue fever (DF) and dengue hemorrhagic fever (DHF), respectively (34). Currently, the Americas region contributes 14% (53.8 million cases) of the global burden of the disease. More than half of cases occur in two countries, Brazil and Mexico (2).

[3] In 2009, the WHO re-defined the spectrum of dengue cases given the overlap that can occur between the case definitions outlined above. The 2009 classification also has three categories: Dengue without warning signs, dengue with warning signs and severe dengue. As Mexico still uses the classic definition for surveillance purposes, that is the definition we use throughout (32).

This burden means a significant economic impact to the Americas; estimated at US$2.5 billion with 60% of the costs related to loss of productivity for the period 2000-2007 (3).

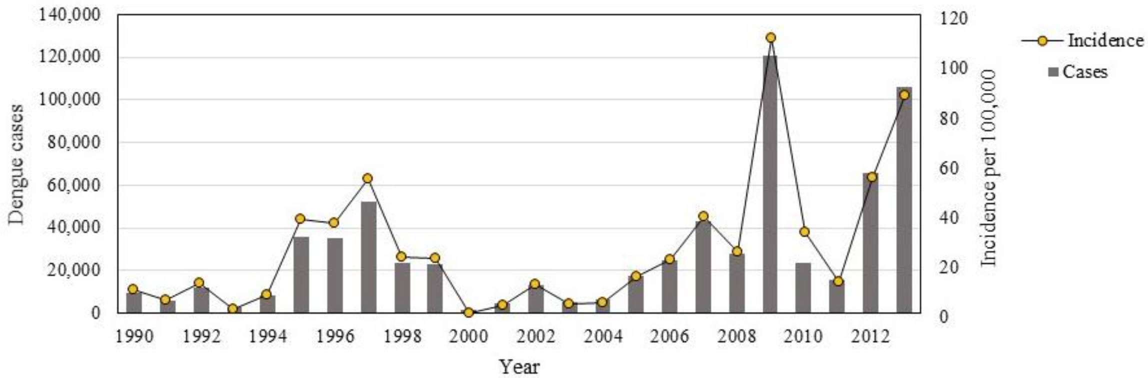
As one of the countries with the highest case burden, dengue ranks as a leading public health concern in Mexico. In 1963, the *Ae. aegypti* mosquito was declared eliminated from the country; however, the mosquito reappeared just two years later and dengue transmission re-emerged with progressive peaks (37). DEN-1 serotype circulated in 1979 and 1980 causing large-scale outbreaks (37). In the mid 1990s another increase in dengue incidence occurred apparently associated with the introduction of serotype DEN-3 (38). From 2000 to 2004, incidence was stable, but reported cases began to rise again (Figure 5). Since that time, reported cases have steadily increased yielding an overall increase from 1.7 cases per 100,000 inhabitants in 2000 to 89.5 cases per 100,000 in 2013 (Figure 5).

Figure 4. Global burden of dengue 2010 by regions
(millions and percent)



Source: Bhat et al. 2013 (2)

Figure 5. Number of dengue cases and Incidence in Mexico, 1990-2013



Source: Figure created using data of national level reported dengue cases from the Mexican Ministry of Health (12)

This situation represents a considerable burden to Mexican society. In 2010, the aggregated adjusted disease burden of dengue was 83.6 DALYs[4] per million population, of which 27% were related to premature fatal episodes (39). As in the rest of the Americas, dengue poses a significant economic burden. In 2010, dengue episodes cost US$247 million; 14% was related to hospitalization, 45% to ambulatory services, 10% to fatalities, and 31% to surveillance and vector control activities (39).

Dengue is not distributed evenly across Mexico. Figure 6 shows the distribution of cumulative incidence of DF and DHF for the period 2000-2013 by state. In general, higher incidence occurs in the coastal states with 436.9 DF cases per 100,000 people per year and 85.3 DHF cases per 100,000 per year in the west and Gulf of Mexico coast. On the opposite end of the spectrum, north and central states have very low or zero incidence. These regions are characterized by higher altitude and greater distance from the coast.

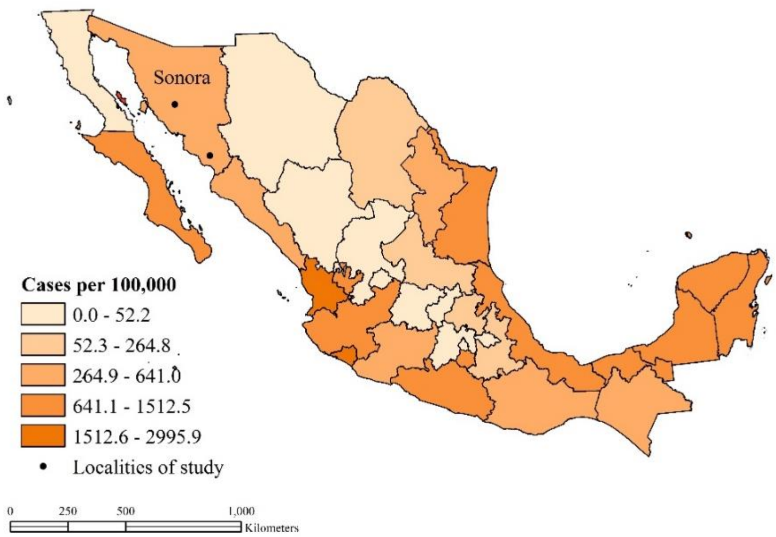
The state of Sonora has a lower incidence compared to national levels (DF=391.1 per 100,000 vs 436.9 and DHF=35.6 per 100,000 vs 85.3). The secular trend in the

[4] Disability adjusted life years

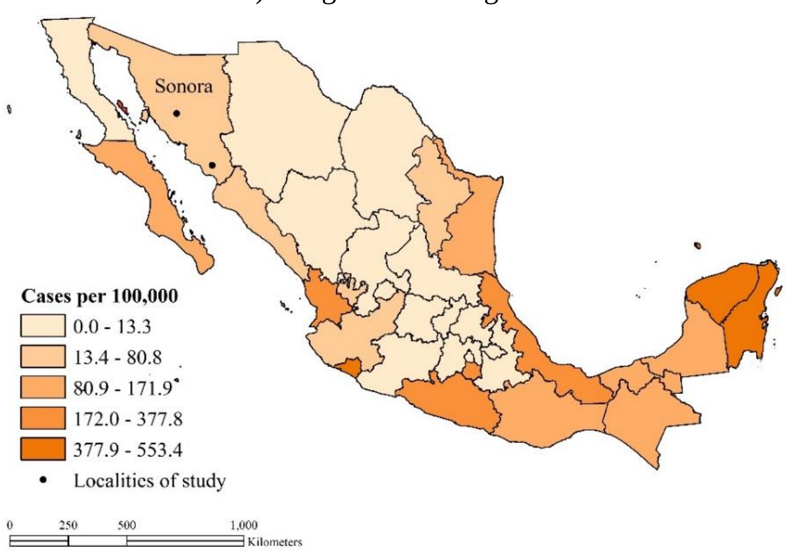
incidence for the 2000-2013 period shows relatively low levels of transmission with a significant peak occurring in 2010 (Figure 7). This trend could be related to specific characteristics related to the arid environment of Sonora.

Figure 6. Cumulative incidence of dengue by State, 2000-2013

a) Dengue fever

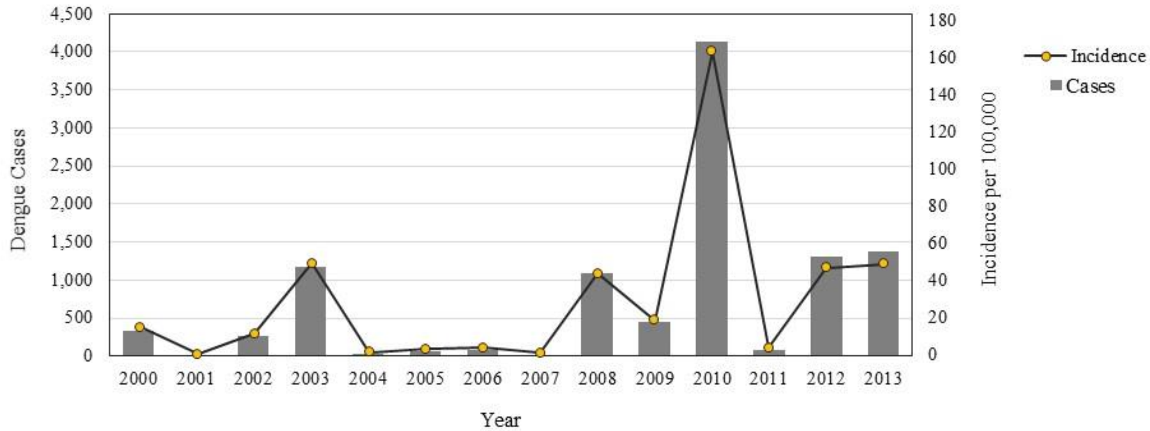


b) Dengue hemorrhagic fever



Source: Maps created using data from the Mexican Ministry of Health (12)

Figure 7. Number of dengue cases and incidence in Sonora, 2000-2013

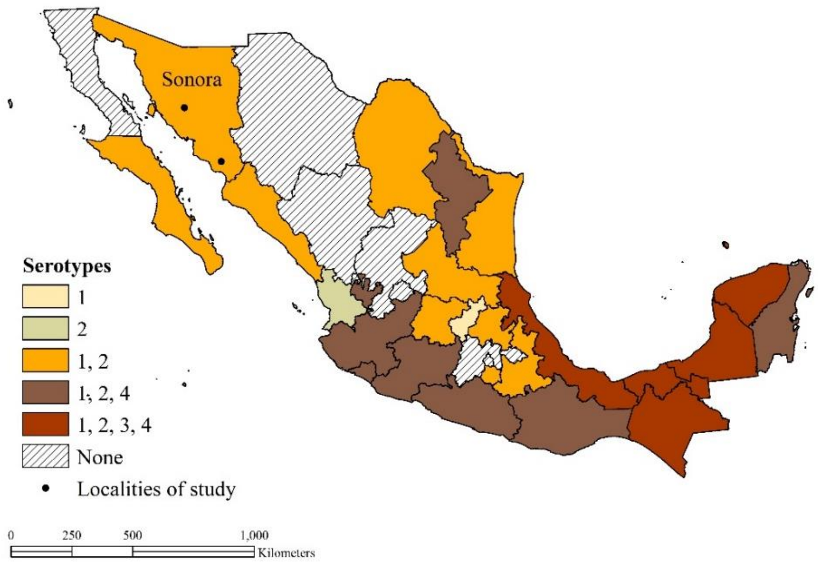


Source: Figure created using data from the Mexican Ministry of Health data (12)

When more than one serotype is circulating in the same geographic area, this increases the possibility of reinfection and may result in greater health impacts (23). Therefore, knowledge of the patterns of serotypes circulating provides a better understanding of the regional patterns of hyperendemicity and dengue severity (40).

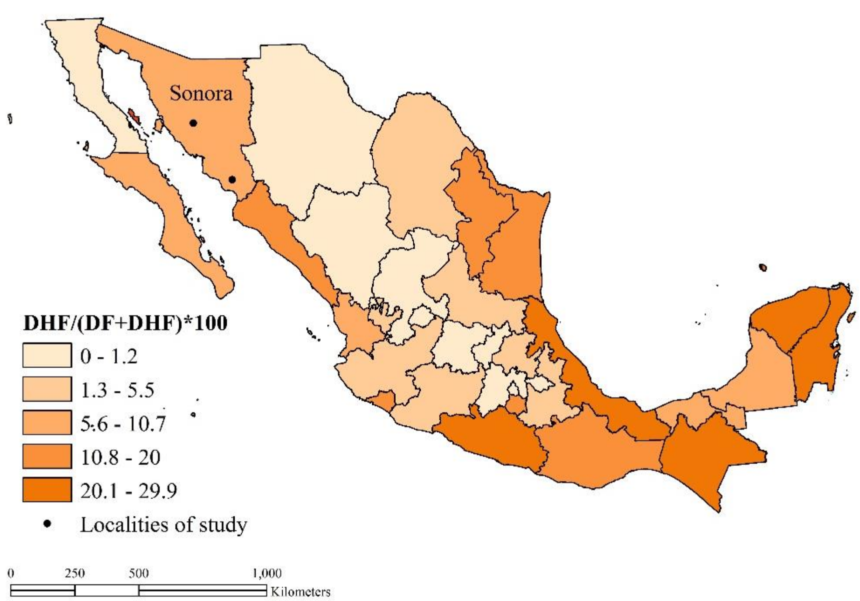
Figure 8 shows the isolated serotypes by state in Mexico in 2013 using data from the Mexico's National Directorate of Epidemiology (13). There were three or four different serotypes circulating in the southeastern region. The co-circulation of multiple strains may explain the disproportionate distribution of DHF observed in the southeastern states (Figure 9) (37). This also could have had some influence on the explosive outbreak observed in Sonora in 2010. While the map indicates the presence of DEN-1 and DEN-2 serotypes in Sonora, previous data from 2010 reported the presence of DEN-1 only (13). Therefore, the outbreak in this arid region with typically low incidence may have been driven by the introduction of DEN-2. Next, different determinants of dengue transmission including climatic and social factors will be described in order to provide a better understanding of the particularities of Sonora in the national context.

Figure 8. Isolated serotypes in Mexico, 2013



Source: Map created using data from Panorama Epidemiológico del Dengue 2013 (13)

Figure 9. Percent of DHF cases by State, 2000-2013



Source: Map created using data from the Mexican Ministry of Health data (12)

4. Climatic factors

Climate and weather influence the dynamics of dengue transmission in multiple ways. Temperature influences virus replication and vector ecology (41). Several studies established that higher temperatures decrease the EIP of the DENV in *Ae. aegypti* (28,29,42)(28,42)(34,42)(33,41). Watts et al. (29) found a reduction in EIP from 12 days at 30°C to 7 days at 32°C and 35°C in *Ae. aegypti*. Similarly, Chad and Johansson (28) found a reduction in EIP from 15 days at 25°C to 6.5 days at 30°C. Similar reductions in EIP were found in *Ae. albopictus* for the DEN-2 virus (43). Fluctuations in temperature may also play a significant role. Rearing *Ae. aegypti* under conditions with a larger diurnal temperature range (DTR) at a low mean temperature (20°C) increased vector competence[5], however rearing them with a smaller DTR and a higher mean temperature (30°C) did not affect vector competence (44).

The life cycle of the vector is also regulated by temperature. A meta-analysis based on 49 studies indicates broadly that temperature increases the development rate of immature stage *Ae. aegypti* (45). The results indicate that the effect of temperature on development rates is not homogeneous and may be affected by factors such as diet, photoperiod, and rearing density. Adult survival is also a critical issue because mosquitoes living beyond the EIP become potential sources of transmission. Laboratory studies indicate temperature thresholds. *Ae. aegypti* mortality increases with temperature exposures >40°C and <0°C (41). A study generated models of survival from published adult *Ae. aegypti* and *Ae. albopictus* laboratory experiments (46). Field survival experiment data were used to adjust predictions of survival for different temperature

[5] Vector competence: Probability of a mosquito becoming infected and subsequently transmitting the virus (44).

conditions in the field. Results indicated that overall *Ae. albopictus* had higher survival in both the lab and the field but tolerance for a wider range of temperatures is better in *Ae. aegypti*.

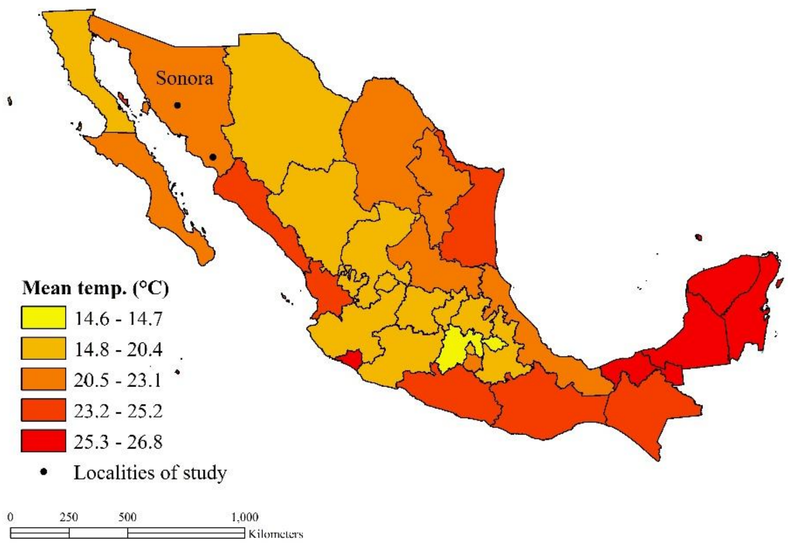
Precipitation also has an impact on vector ecology. Rainfall can generate habitat for the immature stages of *Ae. aegypti* and resulting higher humidity is associated with greater feeding activity, egg development and survival; therefore, increased collections of immature and adult mosquitoes coincide with higher rainfall which may follow regional monsoon patterns (41).

Dengue incidence also shows seasonal variation with higher virus transmission in wet, warm, and humid periods compared to drier, cooler periods (47). Studies show fluctuations in the weekly or monthly incidence depending on the seasonal variations of climate and weather variables in multiple regions (48–59). Factors correlating with dengue incidence include precipitation, minimum and maximum temperature, relative humidity, vegetation indices, and sea surface temperatures associated with El Niño Southern Oscillation (ENSO). While these general associations have been established, a systematic literature review of climate and dengue transmission concludes that the associations between climate, weather, and dengue incidence depend on the local context (41). The seasonal transmission cycles vary geographically; therefore, local variations in weather are more informative than global standardized thresholds (57). Arid and semi-arid regions on the fringe of endemic transmission may be influenced by weather patterns differently than tropical and sub-tropical zones (6). For example, a study in Australia shows that dengue persistent zones located in the wet tropic region are suitable for year-round adult mosquito activity and oviposition, but *Ae. aegypti* is vulnerable to periodic extinction when conditions are too cool or dry for adult activity (58). On the other hand, Patz et al. (5) mention that while temperature may limit dengue transmission in fringe zones lack of immunity of inhabitants may lead to extensive introduction of new dengue infections.

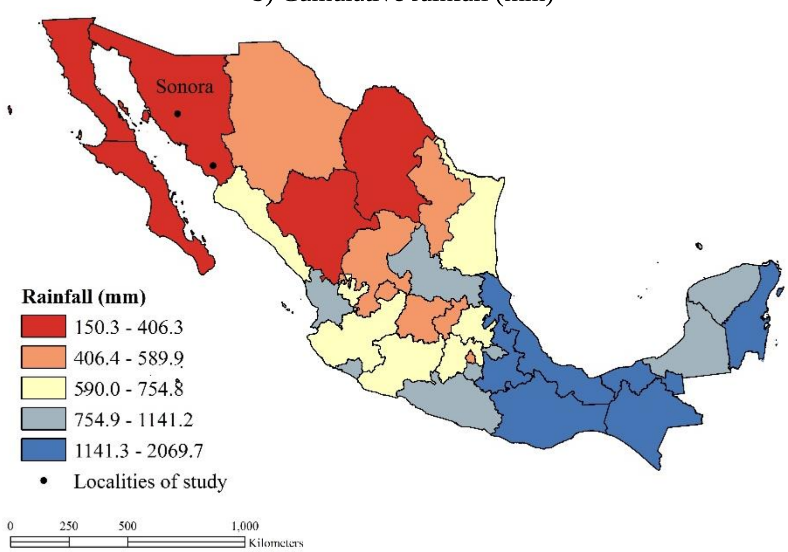
Figure 10 shows a broad overview of mean temperature (°C) and cumulative rainfall (mm) conditions by Mexican state utilizing data from the National Weather Service (SMN, by its acronym in Spanish) (14). Similar patterns can be noted between the map of temperature and the one of dengue incidence (Figure 6). Higher mean temperatures are found in coastal regions and lower temperatures are noted in central and northern states. The pattern of precipitation follows a south-north gradient with higher levels of rainfall in southeastern states and dryer conditions in northwestern states. Table 1 displays the simple Spearman´s correlation based on the DF/DHF incidence and climatic data and show high correlations ($\rho > 0.777$, p-value<0.05) between dengue incidence and temperature variables, and moderate correlations with rainfall (DF $\rho=0.495$, p-value<0.05; DHF $\rho=0.607$, p-value<0.05). While this overall pattern is strong, it cannot explain all variability in dengue transmission. Examining variability across a smaller geographic scale, such as within the state of Sonora, which has much drier conditions and high temperatures, can also be informative.

Figure 10. Temperature and precipitation from SMN by state, 2012

a) Mean temperature (°C)



b) Cumulative rainfall (mm)



Source: Maps created using data from SMN(14)

Table 1. Spearman's correlations between DF and DHF cumulative incidence (2000-2013) with temperature and rainfall from SMN (2012) by state

		1	2	3	4	5	6
1	DF Incidence	1					
2	DHF Incidence	0.941*	1				
3	Annual Mean Temp (C°)	0.816*	0.841*	1			
4	Annual Max Temp (C°)	0.777*	0.789*	0.943*	1		
5	Annual Min Temp (C°)	0.800*	0.851*	0.978*	0.884*	1	
6	Annual Cum Rainfall (mm)	0.495*	0.607*	0.519*	0.372*	0.559*	1

Source: Analyses conducted using data from INEGI (11) and SMN (14)
* *p*-value<0.05

It is well recognized that these conditions are not static. The role of climate change and its potential health effects, including the potential impact on dengue transmission, is an increasing concern to the health of societies. A national study in Mexico, dedicated to predicting the potential effects of climate change on dengue transmission, projects an increase in dengue incidence by 12-18% by 2030, 22-31% by 2050, and 33-42% by 2080 (55). However, there is no information available about the specific effects of climate change on the Sonoran desert. Some information may be drawn from a study by Morin and Comrie (60) about the effect of climate change over the abundance and seasonality of West Nile virus vector (*Culex quinquefasciatus*) in the southern US. According to their projection, the onset of the vector season may be delayed in the southwestern US as a result of extremely dry and hot spring and summer; but the season could also extend because the increment of temperature and fall rains. However, any extrapolation to the dynamics of dengue transmission should be considered with caution because of differences between the ecology of the vector species.

5. Social factors

Social factors have been associated with dengue occurrence; however, there are inconsistences in the literature. In general terms, it is argued that the rapid emergence of dengue is related to population growth, movement of people, uncontrolled urbanization and deficiencies in public health infrastructure and vector control programs (61). Increased population and uncontrolled urbanization have been considered as key factors of the increasing spread of dengue since the 1970s (1). According to one series of estimates, a minimum population size of 10,000 is required to maintain dengue transmission (62). Some evidence suggests that in rural areas, the susceptible population quickly declines below levels of penetrability of the virus (63). In addition, *Ae. aegypti* is primarily an urban mosquito as indicated previously. Therefore, dengue is commonly associated with urban and peri-urban areas. However, there is evidence of expansion from urban to rural settings in the last decade (1).

Associations of dengue with human population density have also shown some contradictory results (64). Overall in the Americas, dengue mortality is associated with higher population density when analyzed by sub-regions (65). However, an urban-level study in Brazil found no association between dengue incidence with neighborhood population density (66). Several studies in Asia also reported contradictory results. For example, a study in an urban locality of Taiwan (67) found a significant influence of high population density on dengue incidence but only during the peak of the epidemic. The authors concluded that high population density might be a significant factor for dengue transmission only with a large number of cases. In contrast, another study from the same region in Taiwan reported an association between higher dengue incidence and lower population density (64). A cohort study from an urban locality in Vietnam reported unexpectedly high incidence rates of dengue in lower population density areas typical of peri-urban areas and villages (68). Thus the controversy remains and may be related to the specific context of an area and the scale of study.

The biology of the vector takes advantage of deficient urban infrastructure for the creation of breeding sites. Dengue transmission has been associated with lack of domestic water supply and sewage systems (69). In Mexico, previous studies found an association between dengue incidence and lack of piped water, further supported by results from an entomological study in a border city of Sonora, MX which determined *Ae. aegypti* presence was associated with a lack of piped water (70). Water supply is crucial to dengue dynamics in arid regions because areas without a consistent water supply may have a corresponding increase in water storage containers (16). Those places where water supply is irregular can promote water storage practices by the community (71,72) which may influence vector dynamics. For example, a study in Australia concludes that the expansion of *Ae. aegypti* could be related to the installation of domestic water tanks as a reaction to climate changes in rainfall patterns (16).

There are also contradictory results regarding the relationships between other socioeconomic factors, such as lack of education (66) and low income (66,69), and dengue incidence. No associations between dengue risk and socio-economic status (SES) were found in several places in Brazil (69,73–76). Moreover, a study in Australia reported higher incidence rates in areas of high SES (77). In the case of Mexico, entomological studies in southern Mexico report high larval breeding risk in household with low socioeconomic status (78); although an entomological study in Ciudad Juarez, an urban city located in a US-Mexico border state, did not find any association between socioeconomic indicators and *Ae. aegypti* distribution (79).

Knowledge and practices of the community are also important influences on dengue transmission. Studies have shown associations between mosquito household infestation and lack of preventive measures, such as no larvicide use in water tanks, use of flower vases, earthen and plastic for water storage (26,80). Dengue transmission has been associated with presence of discarded cans, plastic containers, and tire casings in home environments (81). Unhealthy practices and behaviors can be reinforced by community perceptions. Qualitative research identified misperceptions including confusion of dengue with other febrile diseases, lack of knowledge about the mechanism of transmission, and lack of understanding vector behavior (82).

6. Vector control activities

Different efforts have been made to develop an effective vaccine for dengue. Part of the challenges is to develop a tetravalent vaccine with balanced immunity to the four serotypes because of the risk of DHF/DSS by reinfection of another serotype (61). Although a candidate tetravalent vaccine from a controlled phase 2b trial in Thailand has achieved immunogenicity for the four dengue serotypes, low efficacy is observed for serotype 1, 3 and 4, and more worrisome, a lack of efficacy to serotype 2 (83,84). Despite less than ideal results, several clinical sites for the phase III trial are being held in Mexico (85).

Without an effective tetravalent vaccine or antiviral treatment, vector control is the most used strategy though it is costly and has limited effectiveness (85). Outdoor spraying for adult mosquitos in target areas, distribution of larvicide (abate), and community participation programs focused on elimination of breeding sites into the households are the main vector control activities. The campaign "Patio Limpio" (Clean Backyard) is a community participation program implemented in Mexico designed to train local people to identify, eliminate and monitor breeding sites in households. A study assessment in the Mexican state of Guerrero found approximately 54% of the visited households free of breeding sites as well as a 2.4 times higher probability of developing dengue in non-visited households. However, just 30% of the households in the intervention area were clean after a year (86). A cost-effective analysis of larvicide interventions report a cost ranged from US$40.8 to US$345 per DALY averted (87).

In relation to outdoor/indoor spraying, pyrethroids and, to a lesser extent, organophosphates are the most used chemicals in Mexico; however, resistance to pyrethroids has been reported (88). Studies in Northern Mexico have found evidence of resistance to pyrethroids in Baja California Norte, Baja California Sur and Sonora (89). New chemical products, insecticide-treated curtains, new mosquito traps, genetic modification of male mosquitoes, and other products are being explored as potential strategies to control dengue (61,90).

7. Dengue surveillance in Mexico

Dengue prevention, control activities, evaluation, and research rely on surveillance system information (1). The use of surveillance data has pros and cons and is dependent on how data are collected and the case definitions that are used. The following section provides a description of the main characteristics of the dengue surveillance system in Mexico in order to give information on the contribution and limitations for research.

The activities of vector-borne disease surveillance are based on the Official Norms NOM-032-SSA2-2010 and NOM-017-SSA2-2012 (91) as well as a standardized manual for epidemiological surveillance of vector borne diseases (92). Passive surveillance is the conventional strategy of dengue surveillance in Mexico and cases are assimilated into reports on a weekly basis. Passive surveillance consists of reporting notifiable cases of diseases routinely without active contact by the organization conducting the surveillance (93).

According to the Manual of Standardized Procedures for Weekly Notification of New Disease Cases of Mexico (94), the cases are notified by hospitals and healthcare units as part of their routine clinical activities with persons seeking care. Every hospital and healthcare unit notifies their respective state public health department about new probable cases using a national standard weekly notification form (SUIVE-1). Every Tuesday, the Epidemiology Area of the Sanitary Jurisdictions from the Health Ministry of the State receives all the SUIVE-1 forms from hospitals and healthcare units and enters the information into the Unique System for Automated Epidemiologic Surveillance (SUAVE, by its acronym in Spanish). Every Wednesday, the Office of Epidemiology of the State, validates the collected information reported by the Sanitary Jurisdictions and discusses the results with the Director of Health services and with the personnel of Prevention and Health Promotion services.

All the notifiable (reported) cases are classified as suspicious, probable, or confirmed, based on nationally standardized operational definitions (92):

- Suspicious DF case: every person of any age residing or from a region with dengue transmission with an unspecified fever or compatible viral infection (not recorded by the surveillance system).

- Probable DF case: every suspicious case with fever and two or more symptoms: headache, join pain, skin rash, or retro-orbital pain. For children under 5, only fever is required.

- Confirmed DF case: every probable case with a confirmed recent infection with dengue virus using one or more laboratory testing technique (ELISA, virus culture, PCR). The laboratory of the state performs diagnostic confirmation of probable dengue patients by using immunosorvent assay (ELISA) for detection of viral antigen NS1, IgM or IgG, depending on the timing of seeking care during the clinical period (95).

Additionally, cases can be confirmed by epidemiologic association, which is defined as the situation where one or more symptomatic cases share characteristics related to space, time, as a person with a confirmed case.

There are a significant proportion of cases that do not get laboratory confirmation. The difference, according to national reports, is around 50% between the number of notified and confirmed cases (96).

For practical purposes, the high sensitivity of the probable DF case definition based on symptoms supports early detection of areas of dengue transmission at the local level. This facilitates detection of severe manifestations and determination of serotypes (97). Specificity is gained by laboratory testing confirmation.

The use of notified (probable+confirmed) versus confirmed cases has significant implications directly related to the validity of an epidemiologic study. In this dissertation, confirmed cases were used in order to increase the specificity and reduce misclassification by reducing the number of false-positives (probable non-confirmed cases).

However, there are important limitations related to the use of dengue surveillance data (notified or confirmed). All the notified cases (and those confirmed by lab test later on) are initially detected by physicians based on a set of symptoms. However, according to worldwide estimates, 75% of the cases are asymptomatic (2). Therefore, despite the fact that dengue cases are routinely reported, there are significant problems of underreporting and misclassification of dengue cases as flu or other diseases. According to a cohort study of dengue transmission in two Mexican localities, 61% of cases were asymptomatic and just 18.2% of symptomatic cases were reported to the surveillance system (37). Therefore, epidemiological studies based on surveillance data will have potential problems related to reporting bias (37,72).

The lack of access to health care is another potential limitation. The dengue surveillance information collected by the Health Ministry comes from public and private service providers. However, according to the 2010 census, 25% of the population in Sonora does not have health insurance (18). Therefore, people with no healthcare services, with geographical barriers (especially in rural areas), and/or low economical resources, could be forced to use other medical service providers, such as pharmacies or local healers, and may not be detected by the surveillance system (98).

CHAPTER 2. PRESENT STUDY

The overall goals of the study were to examine the dynamics of dengue transmission in the arid region of the State of Sonora, Mexico, and to describe the interplay of social and climatic determinants on the occurrence of the disease and how these determinants vary by geographic areas within the region. Three studies were performed in order to accomplish the three specific aims of the study. Study #1 provides an overview of the state-level distribution of dengue and associated determinants at a broad scale. Study #2 explores the associations among neighborhood characteristics (socioeconomic and water supply factors) and variability in dengue transmission during a specific dengue outbreak that occurred in the city of Hermosillo in 2010. Finally, the Study #3 compares the space-time patterns and neighborhood characteristics of two outbreaks, the 2010 Hermosillo outbreak and one that occurred in Navojoa in 2008. Commonalities in the socio-demographic patterns of disease progression are assessed in these two urban settings. This chapter presents the summary of the methods used for each of the aims and the main results. The general characteristics of the study are shown in Table 2. The manuscripts appended in the appendix section give more details about the methods, results and discussion of each of the aims.

Table 2. Characteristics of the study of "Dynamics of Dengue Transmission in the Arid Region of Sonora, Mexico"

	Aim 1	*Aim 2*	*Aim 3*
Study	Study #1: Social and climatic factors of dengue fever in the Sonoran desert of Mexico, 2006-2011	Study #2: Socioeconomic and water supply neighborhood factors related to an outbreak of dengue in an arid city of Mexico, 2010	Study #3: Spatio-temporal and socioeconomic characteristics of a dengue outbreak in two arid cities of Mexico
Study area	State of Sonora	Urban area of Hermosillo, Son.	Urban area of Hermosillo and Navojoa, Son.
Unit of analysis	Localities (N=1,158)	Individual cases	Individual cases
Period	2006-2011	2010	2010 (Hermosillo) and 2008 (Navojoa)
Study design	Ecological	Case-control	Cross-sectional (Space-time)
Dependent variable	Cases per 10,000	Binary: Individual dengue cases Vs Random population controls	Individual dengue cases
Independent variables	Social (INEGI): - No health insurance (%) - No basic education (%) - No piped water (%) - Log population size - Distance to highway (km) Climatic (Daymet): - Maximum temperature (°C) - Minimum temperature (°C) - Water vapor pressure (pa) - Cumulative rainfall (in)	Neighborhood characteristics (INEGI): - Median age (years) - Unemployment (%) - No health insurance (%) - No basic education (%) - Migrant population (%) - Occupied houses (%) - Persons per house (persons/house) - No piped water (%) - Population density (persons/ha) - Index of goods Water supply (Agua de Hermosillo): - Water catchment area - Water supply schedule	Neighborhood characteristics (INEGI): - Median age (years) - Unemployment (%) - No health insurance (%) - No basic education (%) - Migrant population (%) - Occupied houses (%) - Persons per house (persons/house) - No piped water (%) - Population density (persons/ha)

A. Data sources

Case data-Surveillance information

All the studies were based on surveillance information provided by the Health Ministry of the State of Sonora. The database contains information on all probable and confirmed cases in Sonora from 2006-2011. Only laboratory confirmed cases were included in the analyses performed. The state laboratory performed confirmation testing using immunosorvent assay (ELISA) for detection of viral antigen NS1, IgM or IgG, depending on the time of specimen collection during the course of clinical disease (95). The variables included in the database were demographic (sex and age), clinical (day of onset, hospitalization, hemorrhage, levels of platelets, and possible death), laboratory information (laboratory results of IgG, IgM, NS1; diagnostic confirmation; and severity of disease in terms of DF or DHF), and geographical (municipality, locality, and address of residence)

The surveillance data were grouped according to the unit of analysis for each specific aim: localities (*Aim 1*) and individual case addresses (*Aims 2* and *3*). Locality-level information for *Aim 1* was joined to the centroid of the inhabited localities. According to the National Institute of Statistics and Geography (INEGI) a locality is defined as every place confined to a municipality or delegation, occupied by one or more houses, which may be inhabited or not (11). Greater than 96% of individual cases for *Aim 2* and *3* were geocoded by address of residence.

Climatic information

Study #1 also utilized climatic information. Gridded multi-year monthly averages of climate variables across Sonora were obtained from version 1 of the Daymet dataset

(99,100). Daymet is a 1 km x 1 km spatial resolution dataset. The multi-year averages were calculated from the five most recent years for which reliable climatic data were present in Daymet over Sonora: 2004, 2005, 2006, 2007 and 2009. Four climate variables were included in the analyses: maximum temperature (C°), minimum temperature (C°), water vapor pressure (pa) as a measure of humidity, and yearly cumulative rainfall (in). Values of climate variables were assigned to the centroids of the localities.

Social information – 2010 Mexican Census

Information related to socioeconomic characteristics of localities or individuals living in localities were obtained from the 2010 Mexican Census collected by the INEGI (18). Included variables were selected based on relevance to dengue dynamics and avoidance of collinearity during the analysis process. Study #1 used a limited number of variables available at locality-level listed in Table 2.

Social information – Index of Goods

For Study #2, an Index of Goods was created as a proxy of wealth for neighborhoods or census units using Principal Component Analysis (PCA), a multivariate statistical technique for variable reduction (101). The variables were obtained from the 2010 Mexican Census (18). The goods included in the index were percentage of houses with refrigerator, laundry machine, car, radio, TV, PC, landline telephone, cellular phone, and internet. Two different factors (or components) were extracted from the PCA using a varimax rotation. Both factors accounted for 84.6% of the total variance. Factor 1 included the goods of internet, PC, landline telephone, laundry machine, car, and radio, which accounted for 52.4% of the variance. Factor 2 included the goods of TV, refrigerator, and cellphone, and accounted for 32.2% of the variance. Factor scores for each neighborhood were calculated by multiplying the census unit standardized score on each variable and its corresponding factor loading obtained in the PCA analysis and these products were summed. Subsequently, a preliminary non-normalized Index of Goods was obtained by using the percentages of explained variance for the two factors as weights following the next formula:

$$No\ normalized = [52.4 * (factor1\ score)] + [32.4 * (factor2\ score)]$$

Finally, the index was normalized by scaling the values between 0-1 following the formula:

$$Index\ of\ Goods = \frac{no\ normalized - Min}{Max - Min}$$

Where:

Index of Goods= new normalized value in the census unit or neighborhood
No normalized= no normalized observed value in the census unit or neighborhood
Min= minimum value
Max= maximum value

Spearman's correlation was used to compare the Index of Goods with the official measure of Urban Marginalization by census unit estimated by the National Population Council of Mexico (21). The analysis showed a high correlation (ρ=0.931, *p*-value<0.001).

Social information – Water supply

Water supply information for Study #2 was provided by Agua de Hermosillo. The municipal water supply schedule during the water restriction program in 2010 and water catchment areas were used to create a new variable based on geographic locations of the water supply zones. Supply schedules were divided into morning (5:00 am – 1:00 pm) and afternoon (2:00 pm – 10:00 pm) water availability. Four water catchment areas were defined by their supply from different wells. A new area classification was created based on the different combinations of supply schedules and water catchment areas. This final classification was included as a categorical variable and used for modeling.

B. Overviews and analysis strategies

1. Study #1 (*Aim 1*)

This study is an ecological analysis performed to assess the association between dengue incidence from 2006-2011 in localities of Sonora, MX (N=1,158 localities) and social and climatic factors. The purpose was to provide a preliminary context of the distribution of dengue cases on a broader scale within the region. Using Geographic Information Systems (GIS) techniques and statistical analysis, the study gives an overview on dengue incidence in the localities of Sonora (2006-2011) and its relationship to socio-demographic and the climatic factors of temperature, precipitation and humidity (Table 2). An additional concern was to control the analysis for the potential problem of underreporting especially in rural localities with lower access to transportation and healthcare infrastructure. A map of localities was provided by INEGI (11). Surveillance, social, and climatic information defined at the locality-level were joined to the map of localities in ArcGIS 10.1. Data for localities were represented by information at their centroids.

Statistical analysis

Descriptive statistics (mean, median, standard deviations (SD), minimum (min). and maximum (max.) values) were estimated for all the variables. Exploratory Spatial Data Analysis (ESDA) was used to examine the data for clustering of dengue cases (102). Incidence rates were calculated considering the number of cases occurred in the locality divided by the total population multiplied by 10,000. Associations between incidence rates and social and climatic determinants were analyzed with zero-inflated negative binomial (ZINB) modelling[6]. The primary binomial model examined the association between the dengue incidence with social (percent of population with no basic education, Log-population size, percent of population with no access to health care, percent of houses with no piped water) and climate (vapor pressure, cumulative rainfall average maximum and minimum temperature). Incidence Rate Ratios (IRR) were reported. Additionally, the zero-inflated component was used to assess whether localities reporting no cases might be associated with factors related to under-reporting (Log-population size and distance (km) to the main highway). Odds ratios (OR) were estimated. Associations were considered statistically significant with *p*-values<0.05 and 95% confidence intervals (C.I.) were generated. Statistical and ESDA analysis were performed with the software packages STATA 13.1 and GeoDa 1.4.6.

2. Study #2 (*Aim 2*)

A retrospective case-control study design was used to assess the association between dengue occurrence and neighborhood factors related to socioeconomic and water supply characteristics in the city of Hermosillo, 2010. During that time, Hermosillo was undergoing water rationing. From an urban scale, this study also used GIS techniques not only to geocode individual cases, but also to create random points that were used as population controls. This allowed comparison of the probabilities of dengue transmission by neighborhood characteristics. A total of 2,730 laboratory-confirmed dengue cases were reported in 2010 and geocoded by residence in ArcGIS 10.1. These cases were then

[6] For more details about ZINB and its application in the study, see Appendix A

paired with 2,793 randomly generated point locations (controls), weighted by population density.. Neighborhood characteristics of cases and controls were assigned by overlaying the case-control map with census data from INEGI and water supply polygons.

Statistical analysis

Cumulative incidence (cases per 10,000 inhabitants) and descriptive statistics of individual characteristics of cases are reported. Means with standard deviations (SD) and proportions (%) of neighborhood variables were estimated for cases and controls. Comparison of neighborhood characteristics between cases and controls were made using *t*-test and x^2 test for continuous and categorical variables, respectively. Unconditional logistic regression was used to assess the association of dengue fever with socioeconomic and water supply factors. Crude and adjusted odds ratios (OR) are reported. A dengue probability map was created by weighting each socioeconomic and water supply variable by its β coefficient. Significant associations were considered for associations with *p*-values<0.05 and 95% confidence intervals (C.I.) that do not include the null value. Statistical analysis was performed with the software package STATA 13.1.

3. Study #3 (Aim 3)

This is a spatio-temporal analysis applied to two cities at two specific timepoints: Hermosillo (2010) and Navojoa (2008). The purpose was to assess the spatio-temporal dynamics of dengue and their association with changing socioeconomic patterns of cases during the course of the outbreaks to determine if case transmission spread similarly during both outbreaks. Using geocoded individual dengue cases, the study assessed two aspects of dengue dynamics: 1) the spatio-temporal patterns of clustering, and 2) the association between dengue occurrence by week and neighborhood characteristics of the cases. A total 2,730 and 493 dengue cases, from Hermosillo and Navojoa respectively, were geocoded by residence in ArcGIS 10.1 and assigned socioeconomic neighborhood characteristics delimited at census unit level.

Statistical analysis

- Space-time analysis: Cases grouped in five sequential 4-week periods of the epidemic year were analyzed with Kernel density estimation in ArcGIS 10.1 to define high density areas of dengue in both cities. Maps of high density zones were created for each of the sequential 4-week periods. Space-time retrospective cluster analysis was performed in SaTScan v9.3 in order to detect high-risk clusters of dengue. Significant clusters were tested using a p-value<0.05 after running 999 Monte Carlo simulations (103). Progressions of the two outbreaks across the city-scapes were mapped.

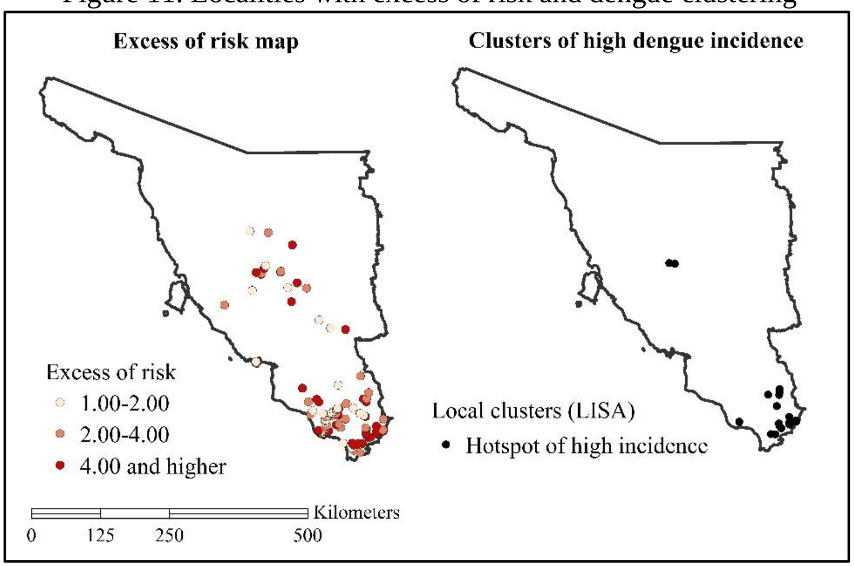
- Socioeconomic pattern analysis: Ordinary Least Square (OLS) regressions were used to assess trends for each the socioeconomic characteristic (dependent variable) of cases across weeks (independent variable). First, cases from both cities were merged into a unique database. Effect modification by city was assessed by creating interaction terms between week and city in order to determine those association modified by the city. It was determined that there was significant interaction (p-value<0.1) for several of the socioeconomic variables. Therefore, 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 tested using a p-value <0.05. Statistical analysis was performed with the software package STATA 13.1. Maps were created in ArcGIS 10.1.

C. Main results

1. Study #1: *Social and Climatic Factors of Dengue Fever in the Sonoran desert of Mexico, 2006-2011. (Paper 1-APPENDIX A)*

A total of 4,992 dengue cases were confirmed in the State of Sonora for the period 2006-2011 (18.5 cases per 10,000 inhabitants). Descriptive statistics by locality (n=1,158 localities) showed a highly skewed dengue incidence with an excessive number of localities with zero-incidence (mean=88.2/median=21.9, SD=210.7/range=0.12 - 2000) which confirmed the pertinence of ZINB modelling (Table 1 of APPENDIX A). The ESDA analysis showed higher transmission in the southern and central parts of Sonora with clusters in the southern parts of the state (Figure 11).

Figure 11. Localities with excess of risk and dengue clustering



ZINB According to the modeling, incidence rates were associated with all the climatic variables. However, there was evidence of multi-collinearity, so best performing models were selected using subsets of climate variables. The best model indicated that dengue incidence increases 31.4% (IRR=1.314, 95% CI: 1.204, 1.435) per 1 inch increment in cumulative rainfall and 56.8% (IRR=1.568, 95% CI: 1.255, 1.959) per 1.0 C° increment in average maximum temperature. In relation to social factors, incidence is positively associated with percent of population with no basic education (IRR=1.038, 95% CI: 1.012, 1.064) and log-transformed population (IRR=1.255, 95% CI: 1.049, 1.503). There were no associations with dengue incidence and lack of piped water or lack of access to healthcare. The zero-inflated component of the model detected potential problems of underreporting associated with higher distance to the highway (OR=1.033, 95% CI: 1.016, 1.051) and lower log-transformed population density (OR=0.368, 95% CI: 0.212, 0.639) (Table 4 of APPENDIX A).

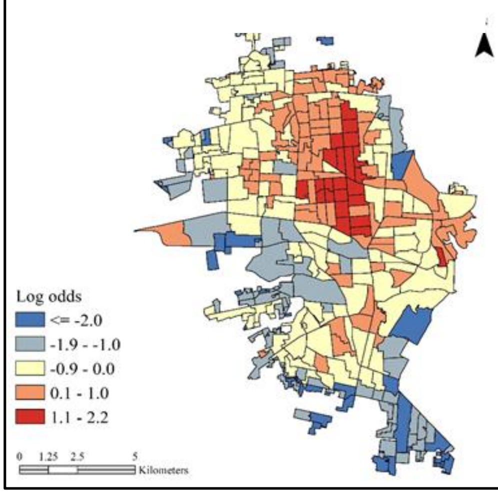
2. Study #2: *Socioeconomic and water supply neighborhood factors related to an outbreak of dengue in an arid city of Mexico, 2010 (Paper 2 – APPENDIX B)*

A total of 2,843 of dengue cases (40.0 cases per 10,000 inhabitants) occurred during the outbreak in 2010 in Hermosillo. Around 58% of cases were female and almost half of the cases (46%) were age 10-29 years. There was a 6:1 ratio between DF and DHF, but sensitivity analysis found no significant difference between associations of neighborhood characteristics between the DHF and DF cases.

The results of the logistic regression modeling indicated higher probabilities of dengue for individuals living in neighborhoods with higher median age (OR=1.053, 95% CI: 1.029, 1.078) and lower access to healthcare (OR=1.066, 95% CI: 1.042, 1.089). Higher population density and higher proportion of occupied houses were also significant in crude analyses, but the associations decreased after controlling for water supply characteristics. The relationship of dengue with the Index of Goods was not linear with lower probabilities of dengue in those areas classified as having a very low or very high

Index of Goods. Unexpectedly, the probability of dengue transmission was lower for people living in neighborhoods with a lower proportion of the population connected to piped water (OR=0.989, 95% CI: 0.979, 0.998). Lower transmission was also noted in neighborhoods with higher migration (OR=0.908, 95% CI: 0.863, 0.956). There was a strong relationship between water supply characteristics and dengue. According to water restrictions in place in 2010, the water catchment zone La Victoria was supplied was associated with a much higher probability of transmission (OR=7.056, 95% CI: 4.904, 10.151) (see Table 2 of APPENDIX 2). Based on the obtained coefficients from the overall model a prediction map of relative dengue risk was created. Figure 12 shows higher log-odds of dengue in the northern and central neighborhoods of the city.

Figure 12. Probability model of dengue (Log odds)



3. Study #3: *Spatio-temporal and socioeconomic characteristics of a dengue outbreak in two arid cities of Mexico (Paper 3 – APPENDIX C)*

The outbreaks of Hermosillo and Navojoa were comprised of 2,843 (39.8 per 10,000 inhabitants) and 511 cases (44.8 per 10,000 inhabitants) confirmed cases, respectively. Temporal patterns during the two outbreaks were similar. In both cities, the onset of the outbreaks started on week 35 (early September) with their peaks during week 42 (mid-October) and a decline with few cases occurring until late December.

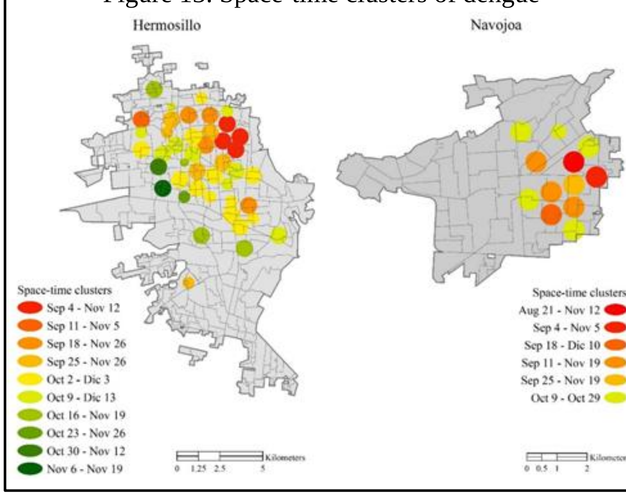
The kernel density analysis showed no significant difference in the total geographic area covered with high densities of dengue cases between cities from the onset of the outbreaks until the period of weeks 37-40. However, there were significant differences for the third and fourth period with continued geographic expansion in Hermosillo and a more rapid geographic regression and cessation of the Navajoa outbreak (Table 3) (see also Figure 2 of APPENDIX B).

Table 3. Progression of high density areas of dengue

Period	Hermosillo 13,541 ha (100%)	Navojoa 3,403 ha (100%)	x2 *p*-value
36 and lower	191 (1.4)	34 (1.0)	0.063
37-40	1,402 (10.4)	319 (9.4)	0.111
41-44	3,977 (29.4)	754 (22.2)	<0.001
45-48	2,293 (16.9)	293 (8.6)	<0.001
49-52	14 (0.1)	0 (0.0)	0.060

The space-time cluster analysis in SatScan showed mainly a contiguous transmission pattern. Significant space-time dengue clusters were detected at the beginning of the outbreaks (onset was early September in Hermosillo and late August in Navojoa). These clusters arose and were generally sustained for 2-3 months with progressive dissemination to contiguous neighborhoods (Figure 13).

Figure 13. Space-time clusters of dengue



Finally, the analysis of neighborhood characteristics of cases across time showed that, as weeks passed, the socio-demographics of cases changed in both cities. Changes included a progression from neighborhoods with less to more access to healthcare neighborhoods with high to low levels of no access to healthcare (Hermosillo: β=-0.212, *p*-value<0.001 Vs Navojoa: β=-0.212, *p*-value<0.001), higher to lower percents of occupied houses (Hermosillo: β=-0.039, p-value<0.01 Vs Navojoa: β=-0.056, *p*-value<0.01), and higher to lower population density (Hermosillo: β= -1.9, *p*-value<0.001 Vs Navojoa: β= -0.687, *p*-value<0.05). In relation to population density, effect modification analysis showed a steeper slope in Hermosillo compared to Navojoa (*p*-value<0.01) (see Table 4, Table 5, and Figure 4 of APPENDIX C).

CHAPTER 3. CONCLUSIONS

A. Summary of findings

Study #1 aimed to assess the association between dengue incidence and social and climatic factors in localities of Sonora. The broad overview of this study showed that climate exerts a significant influence on the spatial distribution dengue even on a regional level in an arid area. Hypothesis #1 was supported that dengue incidence is higher in localities closer to the coast where there are climatic conditions of higher temperature, precipitation and humidity. There were also strong positive associations between dengue incidence rates and cumulative rainfall, vapor pressure, and average minimum and maximum temperatures, however the best fit was found using average maximum temperature and cumulative rainfall. ESDA analysis showed higher incidence rates in the south and, to a lesser extent, the center of the state where higher temperature and humidity are present (9).

Social factors showed a more modest influence at this coarser, regional or locality scale. The clearest result was the association of dengue incidence with Log-population size. This result supports hypothesis #1 of expecting higher dengue incidence in urban areas. This finding was also consistent with the arguments that there is a minimum population size needed to establish and maintain dengue transmission (62) and that *Ae. aegypti's* capacity to readily adapt to urban conditions and exploit man-made container as oviposition sites is associated with higher dengue potential (1,26). On the other hand, the ZINB modelling also revealed potential problems of underreporting especially in rural areas with larger distance to the land transportation infrastructure which may reflect differential reporting related to geographical barriers. Therefore, these results reinforce the importance of improving surveillance capacity in rural localities of Sonora considering the observed expansion of dengue from urban to rural settings reported in the last decade (1). These results also suggest the importance of studies using surveillance data to adjust for variability in reporting when determining associations across broad geographic regions.

Social factors were analyzed on a smaller geographic scale in Studies #2 and #3 allowing an exploration of associations between urban conditions and dengue incidence. Study #2 aimed to assess the effects of water supply and socio-economic factors associated with the distribution of a dengue outbreak in Hermosillo. The findings showed higher probabilities of dengue occurring in neighborhoods supplied by wells of the water catchment zone of La Victoria during the afternoon schedule. Further investigation into this area should be explored. The water supply information used in this study was limited to categorized zones, therefore, it is recommended to use better water supply indicators to include quality of water services as well as water storage practices of the community that promote the creation of breeding sites. Despite these limitations, this is one of the first studies to demonstrate a likely relationship between water restrictions and dengue transmission. This issue requires more exploration as dengue incidence expands further into arid areas where water restrictions and government sanctioned intermittent water supply may become more common.

The findings also indicate higher probabilities of dengue transmission for people living in neighborhoods with higher median age, lower access to health care, and higher population density. These results support the relationship of the urbanization process on the transmission of the disease (1,52,65,104). These results contribute to the overall assessment of the associations among social factors and dengue transmission. Currently the literature is inconclusive and these results support the complexity of the relationships. Hypothesis 2 states that the probabilities of dengue during the 2010 outbreak in Hermosillo would be higher in the poorer neighborhoods. Therefore, wealthy neighborhoods would have lower probabilities of having dengue cases. The hypothesis was partly substantiated. According to findings based on the Index of Goods, people living in wealthy neighborhoods had lower probabilities of being a dengue case; however, the association was not linear. Unexpectedly, people living in the most deprived neighborhoods had lower dengue probabilities compared to intermediate levels of wealth. This non-linear relationship could explain the lack of associations between SES indexes with dengue incidence and mosquito distribution reported by several studies (69,73–76). Therefore, it is recommended to explore non-linear associations in further modelling analyses. Other contradictions were the lower probabilities of being a case for people living in neighborhoods with higher connection to piped water and lower migration.

These unexpected findings are intriguing and different explanations can be made. Medium wealth neighborhoods tend to be located in the city center where population density and probability of dengue is higher while the very low wealth areas are in the margins of the city. A similar situation was observed with the positive association between dengue and percent of households with piped water. The low percent of households with no water infrastructure usually are in the most deprived areas or informal settlements at the margins of the city. Another possibility is residual confounding.

Finally, results from Study #2 revealed a 6:1 ratio between reporting of DF and DHF. Before the 2010 outbreak, the Health Ministry reported the circulation of only DEN-1 serotype within the state (13). The high proportion of DHF cases possibly reflects reinfection of previously infected individuals and may provide support to the hypothesis that the outbreak was in part related to the introduction of DEN-2 serotype. This serotype was not recognized as being transmitted in Sonora at that time (13,33). With the circulation of multiple serotypes, the dynamics and severity of transmission in Sonora will be greatly influenced over the next years. This study's results underscore the importance for regular, even if limited, monitoring of the circulating strains of DENV in a region.

The strategy of generating random points (geographic locations) weighted by population density to serve as controls in this study provided a comparison population that can be used for analysis of surveillance data. However, the lack of temporal information that could be attached to the randomly identified points, as well as the static nature of the water supply and census information, limited the analysis. Further studies could assign temporal information by generating time points randomly assigned from the distribution of time-frames during the transmission period.

Dengue transmission is also impacted by temporal changes in weather patterns and other factors (47). Study #3 initiated an assessment of the temporal patterns of dengue cases and compared two localities with the same level of information allowing an assessment of the space-time patterns and the neighborhood characteristics that occurred in the two dengue outbreaks of Hermosillo and Navojoa. Assessments of the commonalities in the dynamics of transmission were facilitated by the homogenous nature of the datasets.

The findings demonstrated a similar time-frame for onset of the outbreaks for each city. Epidemic curves demonstrated significant increases of numbers of cases between September and December, with both outbreaks peaking in mid-October. These results support the traditionally held assumption that in the arid region of Sonora, outbreaks arise during and after the summer monsoon season and disappear with the introduction of the winter season (9).

Hypothesis #3 stated that spatial-temporal clustering would be detected during the 2008 outbreak in Navojoa and the 2010 outbreak in Hermosillo. The findings of the space-time clustering analysis supported this hypothesis. In both cities, the transmission initiated focally and transmission was maintained for two to three months (105). These foci were sustained while there was also a geographical progression of case transmission to contiguous neighborhoods. This pattern of progression is defined in this study as a contiguous dissemination pattern (106).

The sustained transmission in specific areas suggest the importance of early detection and localized interventions (27). These findings were based on laboratory confirmed cases. Similar results from future studies based on notified cases could help to determine the pertinence of using a combination of passive-active surveillance, as well as the inclusion of syndromic surveillance to improve early detection and initiate peri-focal vector control measures in these neighborhoods (107).

Hypothesis #4 stated that socio-demographic conditions of neighborhoods affected during the outbreak will initiate in lower socio-economic neighborhoods and expand to neighborhoods with higher socio-economic characteristics. This hypothesis was supported by the detection of changes in the case composition from areas with lower to higher access to care, higher to lower population density, and higher to lower percent of occupied houses. These three factors were also significant in Study #2 before controlling for water supply characteristics.

Finally, Hypothesis 5 stated that spatio-temporal and socioeconomic patterns will be similar between the two cities/outbreaks. The summary of the results support this hypothesis. Both cities presented a seasonal distribution according to the expected for the arid region of the Sonoran desert. The focus of initial transmission started in specific populated neighborhoods with low access to healthcare and was maintained by a period of 2-3 months and progressed into contiguous areas.

B. Strengths and limitations

The present series of studies contribute to the understanding of the dynamics of dengue transmission and its determinants in arid regions. The use of different geographical scales of analysis provides different perspectives about the relative significance of social and climatic factors related to dengue transmission. The analysis by locality in Study #1 provides a level of analysis beyond current national level studies and generates a better understanding of the influence of climatic and urbanization factors on the differential distribution of dengue. Also, the use of novel statistical strategies, such as the ZINB modeling, was useful not just to control for potential reporting bias, but also to inform public health services about potential transmission in those places associated with underreporting. These places include rural localities with suitable climatic conditions and provide substance for recommendations to have enhanced surveillance in these areas.

Because these analyses used a relatively short six-year period of dengue data and multi-year averages of climatic information, the analysis was focused on the spatial dimension of the problem. The future inclusion of longer-term dengue and weather data will allow a better understanding of the impact of fluctuations in weather on the dynamics of dengue transmission in the Sonoran desert.

In relation to the analyses at the urban scale, the quality of the surveillance information allowed for geocoding of individual cases by residence and to have specific dates of onset of the disease. This level of detail gave opportunities for interesting methodological strategies. The creation of random locations to serve as controls is a strategy more commonly used in the fields of ecology and archaeology (108–112). The addition of population weighing to this control-selection strategy provided an efficient and cost-effective method to create a representative population sample to support the implementation of a case-control design. This is an uncommon strategy in the analysis of surveillance data and may serve as a way forward to overcome issues with identifying an appropriate control population. This study design allowed the probabilities of dengue to be estimated for the neighborhood characteristics of the cases and to create a disease probability map.

The detailed information for the space-time analysis in Study #3 allowed the detection of specific times and zones of high dengue transmission. Also, the inclusion of neighborhood characteristics of cases provided insights about the socioeconomic trends on the evolution of an outbreak within this region across time. Moreover, the inclusion of two localities allowed the identification of common socioeconomic and space-time clustering patterns that could inform prevention and control measures.

However, there were also some limitations related to the information used in the Studies #2 and #3. The analyses assumed that the transmission occurred at the place of residence of cases, which was the only location variable available in the surveillance data. Despite this fact, its assumption is reasonable based on the time that people spend at home and the known peaks for biting periods of the *Ae. aegypti* being early morning and before dusk (113).

Other limitations present in all the studies are the unknown effects of non-measured factors, like the immunological status of the population, vector density, and vector control activities over the locations and time periods. Also, only laboratory confirmed cases were analyzed. Inclusion of clinical and sub-clinical cases not detected by the surveillance system could produce different results to our findings. Finally, water supply is a critical issue for arid lands and water storage practices may lead to increased number and availability of vector oviposition sites (71). However, the variable of access of the locality to piped water that was available from census data may not be a good indicator of water disruption and resultant water storage behavior. It is possible that individuals without piped water already have stable practices while in areas unaccustomed to water restrictions, more *ad hoc* storage methods that are vulnerable to increasing vector habitat, are common.

C. Future directions

The present study analyzed the available state-level dengue surveillance information for the period 2006-2011. From the last year to the date of publication of this dissertation, dengue transmission has been present within the state of Sonora, Mexico with significant outbreaks occurring in several localities, including a more recent outbreak in Hermosillo in 2014. The inclusion of these new surveillance data and their corresponding temporal, climatic data would allow a new opportunity to analyze the effect of climatic patterns of desert over dengue incidence across time. Continued collaboration of the current research team members and the State Ministry of Health is anticipated.

The use of randomly created control sites in the case-control design in the present study was an alternative to the identification of a population reference for comparison; but this choice limited analyses to the spatial dimension. Study #3 tried to solve this situation by including the temporal dimension and by comparing different cities, but differences between study areas in population size, level of development, population densities, represent another limitation. The integration of new surveillance data from the recent outbreaks in 2014 can provide new groups of comparison within each locality. Future analyses of the new and merged data will allow an opportunity to determine whether individual characteristics, the spatio-temporal and the socioeconomic patterns associated to dengue transmission are consistent within these localities and will provide validation to the findings of this study.

Future analyses in these localities will also benefit with the inclusion of environmental information related to temperature, vegetation, relative humidity and precipitation using high resolution remote sensing data, as well as, weekly information. This information will allow a better understanding about the effects of weather on the spatial and seasonal variability of transmission within these localities.

The collection of primary data is another potential alternative against the limitations of having only socioeconomic information estimated from census data for the locality. Direct observation, community surveys, and qualitative approaches can provide information about the knowledge, attitudes, and practices of the population as they relate to dengue transmission. These approaches will allow better information about household conditions, waste management, water disruptions and resultant water storage behavior. A 400 household survey focused on knowledge, attitudes, and water practices in Hermosillo was administered in 2014 which could allow the incorporation of more direct indicators of dengue risk. .

Finally, the high levels of underreporting and the presence of a new serotype in Sonora suggest the pertinence of implementing serological surveys either across the state or in specific regions of the state. This will help to determine the sero-prevalence, susceptible populations, and potential scenarios of the severity of transmission. The economical and logistical challenges of this type of study will require an efficient sampling design at the state and/or urban level.

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APPENDIX A: Study #1

Social and Climate Factors of Dengue Fever in the Sonoran desert of Mexico, 2006-2011

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

[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

Abstract

Background: Dengue fever is currently endemic in the Mexican Sonoran Desert. This study assessed the association between 2006-2011 dengue incidence and social and climatic factors in localities of the state of Sonora, Mexico. *Methodology*: Locality-level data on laboratory confirmed dengue cases (N=1,158 localities), census data, and remotely sensed climate data were used in zero-inflated negative binomial modeling. Association between dengue incidence with social (education, population density, access to health care services, lack of piped water) and climate (vapor pressure, cumulative rainfall average maximum and minimum temperature) were examined in the primary binomial model. The zero-inflated component was used to assess whether localities reporting no cases might be associated with factors related to under-reporting (population size and distance to main highway). Exploratory Spatial Data Analysis (ESDA) was used to examine the data for case clustering. *Results:* Dengue incidence increased 31.4% (IRR=1.314, 95% CI: 1.204, 1.435) per 1 inch increment cumulative rainfall and 56.8% (IRR=1.568, 95% CI: 1.255, 1.959) per 1.0 C° increment in average maximum temperature. Incidence was positively associated with percent of population with no basic education (IRR=1.038, 95% CI: 1.012, 1.064) and log-transformed population size (IRR=1.255, 95% CI: 1.049, 1.503). There were also positive associations between locations that reported no cases and distance to the highway (OR=1.033, 95% CI: 1.016, 1.051) and a negative association with log-transformed population size (OR=0.368, 95% CI: 0.212, 0.639). There is higher transmission in the southern and central parts of Sonora with clusters identified in the southern part of the state. *Conclusions*: Dengue incidence within Sonora was associated with climate variables such as increased rainfall and temperature, and social factors related to urbanization and lack of education. Potential problems of underreporting could in rural localities also need to be considered.

Introduction

Dengue is a vector-borne disease transmitted by mosquitoes in the *Aedes* genus; primarily *Ae. aegypti*. There are 4 viral serotypes (Den-1, Den-2, Den-3 and Den-4) and humans are the primary host (1). Over 390 million cases are estimated to occur worldwide annually including 96 million symptomatic cases and 24,000 deaths (2,3).

Social and climatic factors have been shown to play specific roles in the process of virus transmission. *Ae. aegypti* is well-adapted to human environments. It is highly anthropophilic and exploits man-made containers as habitat for immature stages (1). Therefore, human social factors such as migration, population growth, uncontrolled urbanization and deficiencies in water supply and garbage collection promotes the creation of breeding sites (4–7). Lack of resources in affected areas limits implementation of control and prevention measures, leading to expansion of transmission (8,9).

Climate influences multiple aspects of the dengue transmission system. Higher temperatures lead to decreased generation time of the *Ae. aegypti* vector, as well as a decrease in the extrinsic incubation period (EIP), the time between when a mosquito becomes infected and when they are infectious, increasing the percentage of infected mosquitoes (10). In immature stages, eggs and larvae are affected and destroyed by freezing temperatures present at higher altitudes and in the winter (11). Precipitation provides habitat for the immature stages of *Ae. aegypti* and higher humidity is associated with greater feeding activity, egg development and survival (12).

Climate strongly influences dengue transmission and hyperendemic areas are characterized by wet tropical climates. Given these areas are at the highest risk of transmission, most research on dengue has focused on tropical or sub-tropical regions. In regions outside of the hyperendemic zones of the wet tropics, the mosquito population becomes virtually extinct when conditions are too cool or too dry for egg-laying and hatch activity (13). However, human interactions with the environment can modify the role that climate directly plays on vector dynamics. Water storage and rain harvesting become common practices in places where water supply is irregular and has been associated with higher dengue transmission (14) and micro-climates can provide resting sites even when general conditions are unfavorable to maintenance of the vector population (15). This interaction between social and climatic factors can lead to transmission of dengue even in arid regions, such as those found in Sonora, Mexico. Analyzing the role of social variables in the context of current climatic conditions can facilitate an understanding of transmission dynamics in these regions.

Sonora, Mexico (MX) is an arid and semi-arid state located on the fringe of the winter 10°C isotherm limit where the distribution of *Ae. aegypti* is geographically constricted (1,16–18). The first reports of dengue outbreaks were registered in 1982 in southern Sonora (although no detailed information are available than the occurrence of the disease) (19). While the state now has areas of endemic dengue and has experienced outbreaks of dengue, little research has been conducted to determine how risk factors for dengue in arid regions may differ from those in tropical regions. The aim of this study is to assess the association between the 2006-2011 dengue incidence and social and climatic factors in localities of the arid region of Sonora, Mexico.

Methods

An ecological analysis was performed to assess the association between dengue incidence from 2006-2011 in inhabited localities of Sonora, MX (N=1,158 localities) with social and climatic factors. According to the National Institute of Statistics and Geography (INEGI) a locality is defined as every place confined to a municipality or delegation, occupied by one or more houses, which may be inhabited or not (20).

Data sources and definitions

Dengue Incidence. Surveillance data for laboratory confirmed dengue cases was obtained from the Health Ministry of the state of Sonora. Cases were confirmed in the state laboratory using immunosorbent assay (ELISA) for detection of viral antigen NS1, IgM or IgG, depending on the period of evolution of the infection (21). Confirmed cases were defined as those with a positive result in at least one of the three tests. Incidence rates for 2006-2011 were calculated by locality using 2010 population estimates as the population at risk. Cumulative dengue incidence was reported as number of cases per 10,000 inhabitants.

Social determinants. Social and population level information about localities was obtained from the 2010 Mexican census (22). Locality population estimates were identified for population without health insurance (%), population with no basic school (% with <nine years of school), and houses with no piped water (%). Population size was the criteria used by the Mexican Census to create an urban-rural classification (20). Log-transformed 2010 population size was included as a continuous proxy of urban-rural condition. Additionally, Euclidean distance of localities to the main highway (km) was calculated and used as a factor to indicate presence of efficient transportation systems.

Climate determinants. Gridded, multi-year monthly averages of climate variables over Sonora were obtained from version 1 of the Daymet dataset (23,24). Daymet is a 1 km x 1 km spatial resolution dataset. The multi-year averages were calculated from the 5 most recent years for which reliable climatic data were present in over the dataset of Sonora: 2004, 2005, 2006, 2007 and 2009. Four climate variables were included: maximum temperature (C°), minimum temperature (C°), water vapor pressure (pa) as a measure of humidity, and yearly cumulative rainfall (inches). Values of climate variables were assigned to the centroids of the localities.

Statistical analysis

All surveillance, social and climate data were joined in localities shapefile in ArcGIS 10.1. Statistical and Exploratory Spatial Data Analysis (ESDA) were performed with the software packages STATA 13.1 and GeoDa 1.4.6.

Preliminary statistics: Univariate descriptive statistics including mean, median, standard deviations (SD), minimum and maximum values were calculated for the cumulative dengue incidence and the independent social and climatic variables. Bivariate Spearman's Correlation was used to assess associations between variables.

Spatial Clustering: ESDA based on a contiguity Rook weight matrix was used to assess the presence of spatial dependency between neighbor locations. The global Moran's I was calculated for associations between dengue incidence and each of the independent variables to assess the presence of spatial autocorrelation. The global Moran's Index was used to assess if patterns were identified as: clustered, disperse or random. The Moran's Index can take values from +1.0 (clustering) to -1.0 (dispersion). Local Indicators of Spatial Association (LISA) is a local Moran's I statistic which decomposes the global Moran's for each observation in order to detect significant spatial clustering of similar values around the each observation (25). The global Moran's I statistic is the mean of the LISA statistics. A map of hotspots of high transmission was created using results from the LISA and a map of excess of risk was generated based on the actual incidence rate of the locality divided by the average overall risk of the study region.

Multivariable modeling: Underreporting is an important concern when using public surveillance data. Less rigorous surveillance strategies and lower access to health services have been associated with lower reporting of dengue in rural areas (1,4). Deficiencies in surveillance in rural places with less access to transportation infrastructure may lead to locations that do not have reported cases because of insufficient surveillance and not actual zero incidence. Therefore, zero-inflated models were used to adjust for zero-inflation related to underreporting (26–28). ZINB modelling is commonly used to model count data with excessive number of zeros (29,30). In this study, ZINB modelling was used to assess the association between dengue incidence and the explanatory variables. The ZINB model is divided into the negative binomial component for count data and a logistic component for examining factors related to localities with zero reported cases (31). The *negative binomial component* of the model included the dependent variable (number of cases) and the social and climate covariates (no education, no health care, no piped water, log population size, cumulative rainfall, max temp, min temp, vapor pressure). Population size of the locality was used as an offset to account for differences in population size. Additionally, a spatial lag of the dependent variable was created in GeoDa1.4.6 based on a Rook contiguity weight matrix and included in the equation to control for potential spatial dependency (32,33). This weight matrix helped to define the spatial connection of localities based on the contiguity between them to avoid biased estimators in the regression model. In relation to the *logistic component*, the ZINB model assumes the presence of two different origins of zero observations: “sampling zeros” which are part of the negative binomial distribution and have a probability of $1\text{-}p_i$, and the “structural zeros” (excessive zeros or excess zero incidence locations) due to the structure of the data and a probability of p_i (31,34). We hypothesized that the probability of structural (excessive) zeros was influenced by a small population size (log-transformed) and a longer distance to the main highway, both factors which could reduce the probability a case would seek attention in health centers and be registered in the surveillance system.

Variance Inflation Factor (VIF) was employed to assess potential problems of multicollinearity, especially between climate variables. A cut point of VIF = 2.5 was used such as variables <2.5 were included in the same model. Three highly correlated variables were detected (VIF>2.5) (vapor pressure, maximum and minimum temperature); therefore, three separate multivariate models were created that included the three climate variables separately. Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were used to compare the fit of the three models. Models were considered equivalent if they had a difference less than two (35). Incidence Rate Ratios (IRR) and odds ratios (OR) were estimated for the negative binomial and the logistic component, respectively for each model. Significant associations were considered for association with *p*-values<0.05 and 95% confidence intervals (C.I.). The Vuong test was performed to determine the preference of ZINB over the standard negative binomial model (35).

Results

Dengue incidence: The total number of laboratory confirmed dengue cases reported to the Department of Health in Sonora, MX during the period 2006-2011 was 4,992, which represents a cumulative incidence of 18.5 cases per 10,000 inhabitants for the time period and all localities. Table 1 shows the descriptive statistics of the cumulative incidence and the determinants. Dengue incidence by locality ranged between 0 and 2000 with a median incidence of 0 cases per 10,000. Because the data were highly skewed, we also report the incidence in just those localities experiencing dengue (mean=88.2/median=21.9, SD=210.7/range=0.12 - 2000).

Descriptive social and climatic factors: The proportion of individuals with access to health services averaged 28.8% across all localities with the average distance to the main highway of 38.8 km. Localities averaged 6.7% of the population having no basic schooling and 15.8% did not have piped water. Population size was skewed averaging 2,268 persons, with range of 28 to 715,061 and a median of 174. This variable was log transformed in further analysis (36). The mean yearly values for the localities for the climatic factors were 1,102 pa for vapor pressure (SD=180.7), cumulative rainfall 12.5 in (SD=5.7), and an average minimum and maximum temperature of 14 C° (SD=2.3) and 32.2 C° (SD=1.8), respectively. Figure 2 shows maps of the climatic factors for Sonora.

Correlation between explanatory factors and dengue incidence: Table 2 shows the correlations among variables. Associations between dengue incidence rates and explanatory factors were low to moderate, log-population size (ρ=0.364, p-value<0.001) and vapor pressure (ρ=0.199, p-value<0.001) showed the highest positive correlations with dengue incidence. Moderate and high correlations (ρ>0.6) were identified among the climatic factors of vapor pressure, minimum and maximum temperature.

Multicollinearity was confirmed with VIF values above 5 (mean=4.6) when all the climatic factors were included in the model and separate models were created for vapor pressure and temperature.

Spatial Autocorrelation: The global Moran's I (Table 3) showed a weak spatial autocorrelation of the dengue incidence (I=0.093, p-value<.01) and distance to highway and the climatic factors showed high spatial autocorrelation (I>0.880). Figure 3 shows excess risk of dengue in the south and center of Sonora and clusters of high incidence in the south of the state.

Multivariable models: Three separate models were constructed to examine the relative performance of the three correlated climatic variables to predict dengue incidence rates at the localities (Table 4). Each model showed strong positive associations between dengue incidence rates and the climate variables. The social variable % no basic education, log-transformed population size, and the spatial lagged variable were also associated with dengue incidence. The Vuong test was significant (p-value<0.05) in all the models; confirming the ZINB models were a better fit than negative binomial regression and the treatment of excessive zeros was adequate. The lower values of the AIC and BIC indicate Model 1 had superior performance to the other two models. Based on this model, locality-level dengue incidence rates increased 56.8% (IRR=1.568, 95% CI: 1.255, 1.959) per 1.0° C in average maximum temperature, and 31.4% (IRR=1.314, 95% CI: 1.204, 1.435) per 1 inch in cumulative rainfall. There also was an increase of 3.8% (IRR=1.038, 95% CI: 1.012, 1.064) in the incidence for each percentage unit of population with no basic school education and a positive association with urbanization measured using log-transformed population size (IRR=1.255, 95% CI: 1.049, 1.503).

There was no significant association with percent population with access to health services and no piped water.

The logistic component of the model showed a positive association between the probability of having localities reporting no cases and the distance to the highway (OR=1.033, 95% CI: 1.016, 1.051). An increment of 33.4% in the probability of reporting no cases was observed for each 10 km distance of the locality from the major highway. Also, the probability of reporting no cases increased for those localities with lower population size (OR=0.368, 95% CI: 0.212, 0.639). These results suggested there was a higher probability of lower reporting from localities with smaller population sizes and greater distance to the land transportation infrastructure.

Discussion

This broad-scale assessment of dengue transmission in Sonora confirmed that climate still exerts a significant influence on the spatial disease patterns in an arid environment, and at the scale of localities, have more influence than those social variables available for analysis. Strong positive associations between dengue incidence rates and the climatic factors of cumulative rainfall, vapor pressure, and average minimum and maximum temperature were identified. More modest associations were identified between education and urbanization variables.

Maps of dengue incidence show disease concentration principally in the south and center of the state suggesting the constriction of the disease in those places with conditions of high temperature and humidity which are more predominant in the southern areas of Sonora (19). Although the average annual maximum temperature for the overall region or state was 32° C, temperatures in this region can reach levels above 40° C during the summer season in several localities and which are levels where potential transmission drops drastically according to prior climatic models (37). The current analysis did not include number of days exceeding the threshold of 40° C as a variable and there are may be additional impacts of these extreme temperatures on dengue transmission. However, there is no conclusive field-based evidence to suggest that field extreme high temperatures affect the survival of mosquito in arid regions. Previous studies have shown increases in environmental water vapor as a result of increases in temperature can partially reduce the impact of desiccation on mosquito survival (37). Moreover, human environments can provide microclimates or thermal buffers indoors for adult mosquitoes and stable oviposition sites through human interventions, such as water tanks, household materials, and use of coolers (15,17,37).

At the level of locality, there was no significant association between dengue incidence and the percent of houses without piped water. This variable may not be the most adequate indicator of water disruptions and resultant water storage behavior which is the actual variable of interest from the standpoint of vector ecology. Vectors, especially *Aedes aegypti*, have been shown to breed in water storage containers (1). In Sonora, more than 96% of the population has piped water in their homes (31), even though there remain substantial water supply and distribution problems. These problems are particularly evident in the capital and most populous city of the state which also has a high incidence of dengue (37.8 per 10000) (38,39). It is recommended that future studies consider not only water infrastructure information, but also the frequency of water supply disruptions and water storage behaviors. For example, a study in the dry regions of Australia found that the historical expansion of dengue in the country seemed to be related to the distribution of domestic water tanks as a population response to regional drying and water restrictions (17,40).

The association between dengue incidence and the percent of the population with no basic school education may be directly related to lack of taking preventive measures or may be a proxy for residing in areas with poorer infrastructure. A study in southern Mexico showed higher number of larval breeding containers in households with lower-educated mothers (41). Education about dengue may also be directly taught during educational programs in school (42). Educational interventions administered in Brazilian primary schools resulted in increased knowledge related to the vector, prevention and control measures (43). Lower education is also commonly associated with low socioeconomic status and may be acting as a proxy for this factor. Unfortunately, there was no available information related to income by locality and it was not possible to control for this potential confounder.

Population size was also positively associated to dengue incidence. This was expected given the vector's highly anthropophilic nature and its ability to exploit man-made containers as oviposition sites (1). The implementation of the ZINB modelling approach also allowed us to explore the potential effect of rural residence on underreporting as a result of two factors. Rural residence was approximated using two variables, population size and distance to highway, both positively associated with excessive zeros. This indicates potential problems of underreporting, especially in rural localities with larger distance to the land transportation infrastructure. Therefore, dengue incident cases could be reported differently in those localities as a result of deficiencies in the surveillance system related to geographical coverage. These results could also explain the presence of dengue clusters in in southern rural localities close to the highway and urban localities. Active surveillance strategies and serological surveys would improve the surveillance system in those locations and validate these results. Urban and peri-urban populations with high population densities report most of the dengue cases worldwide; however, the expansion of the incident cases from urban to rural in the last decade coupled with our results that found under-reporting is likely occurring in more rural areas, highlight the importance of improving surveillance capacity in rural settings (1,40).

Several limitations are present in this study. The analysis is based on laboratory confirmed cases included in the database of the surveillance system which increases the specificity of the study. However, asymptomatic cases are not included and potential selection bias is present. Case locality is also based on the place of residence of the cases and does not consider the potential mobility of persons within and outside of the state. Therefore, we assume that the transmission occurred in the locality of residence of the cases. This can introduce a distortion in the geographical distribution of the disease and its association with the social and climatic conditions of the localities. While the unit of analysis of locality allows higher accuracy of the specific environmental conditions, several relevant socioeconomic variables are discarded due to the high level of missing values. Finally, this study focuses on the spatial dimension of the problem using aggregated data across multiple years. Inclusion of the temporal dimension in future studies will allow a better understanding of the spatio-temporal dynamics of dengue and the potential association with temporal fluctuations of the climatic determinants in this arid region.

In summary, dengue incidence in Sonora was associated to climatic variables of higher levels of temperature, humidity and rainfall. In addition, social factors related to higher population size and lack of education were also associated with dengue transmission. These results may inform preventive measures in localities that share these characteristics. However, there were also potential problems of underreporting in rural areas with higher distance to the highway. Further investigation using strategies like serological surveys and active surveillance into these localities will help to confirm these findings.

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Table 1. Descriptive statistics of potential factors associated with dengue in Sonora, Mexico, 2006-2011

Variable	Mean	Median	Std. Dev.	Min	Max
Dengue incidence (per 10000)	12.0	0.0	83.3	0.0	2000.0
Access to health services (%)	28.8	25.7	17.3	0.0	100.0
No basic school (%)	6.7	6.6	1.4	2.3	14.9
No piped water (%)	15.8	0.0	27.1	0.0	100.0
Distance to main Highway (Km)	38.8	25.8	42.4	0.0	226.4
Population	2,268	174	24,816	28	715,061
Vapor pressure (pa)	1,102.1	1,157.9	180.7	649.0	1,459.0
Average minimum temperature (C°)	14.0	15.1	2.3	2.4	16.8
Average maximum temperature (C°)	32.2	32.9	1.8	22.0	34.6
Cumulative rainfall (in)	12.5	12.1	5.7	0.9	41.7
Spatial Lag	13.8	0.0	47.6	0.0	517.0

Figure 1. Localities with dengue incidence in Sonora, Mexico, 2006-2011

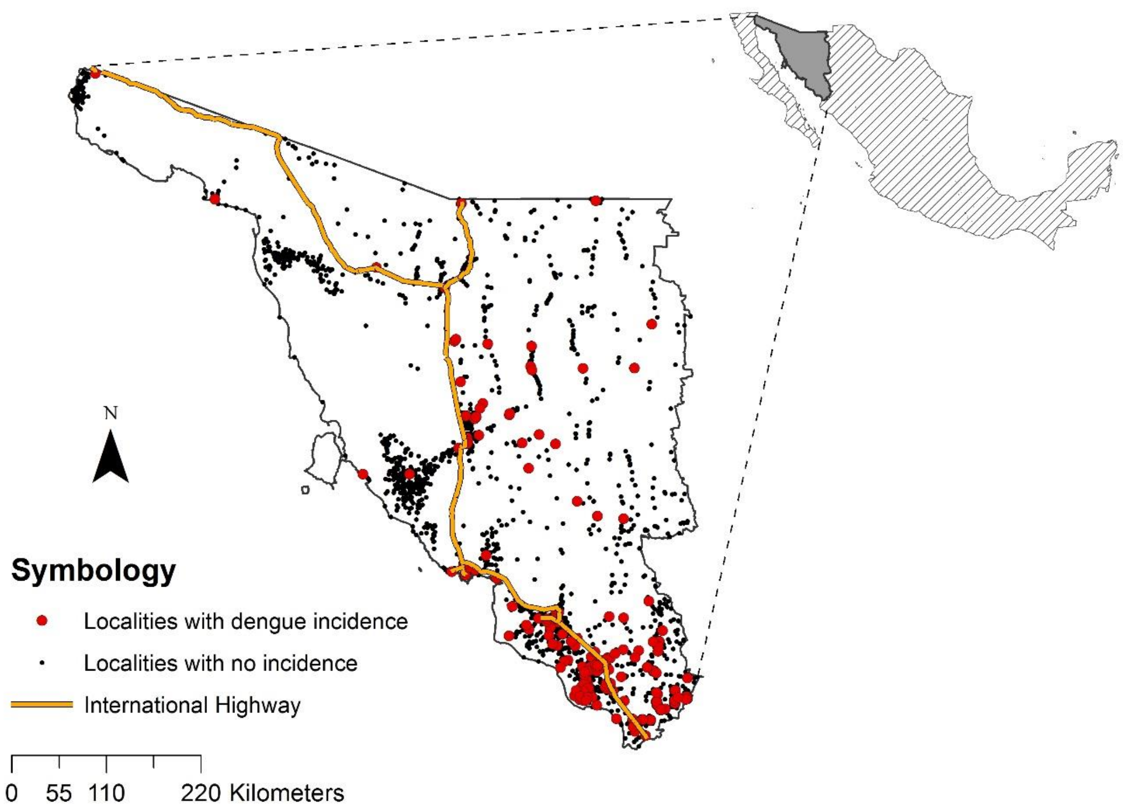

Figure 2. Map of climatic factors across Sonora, Mexico

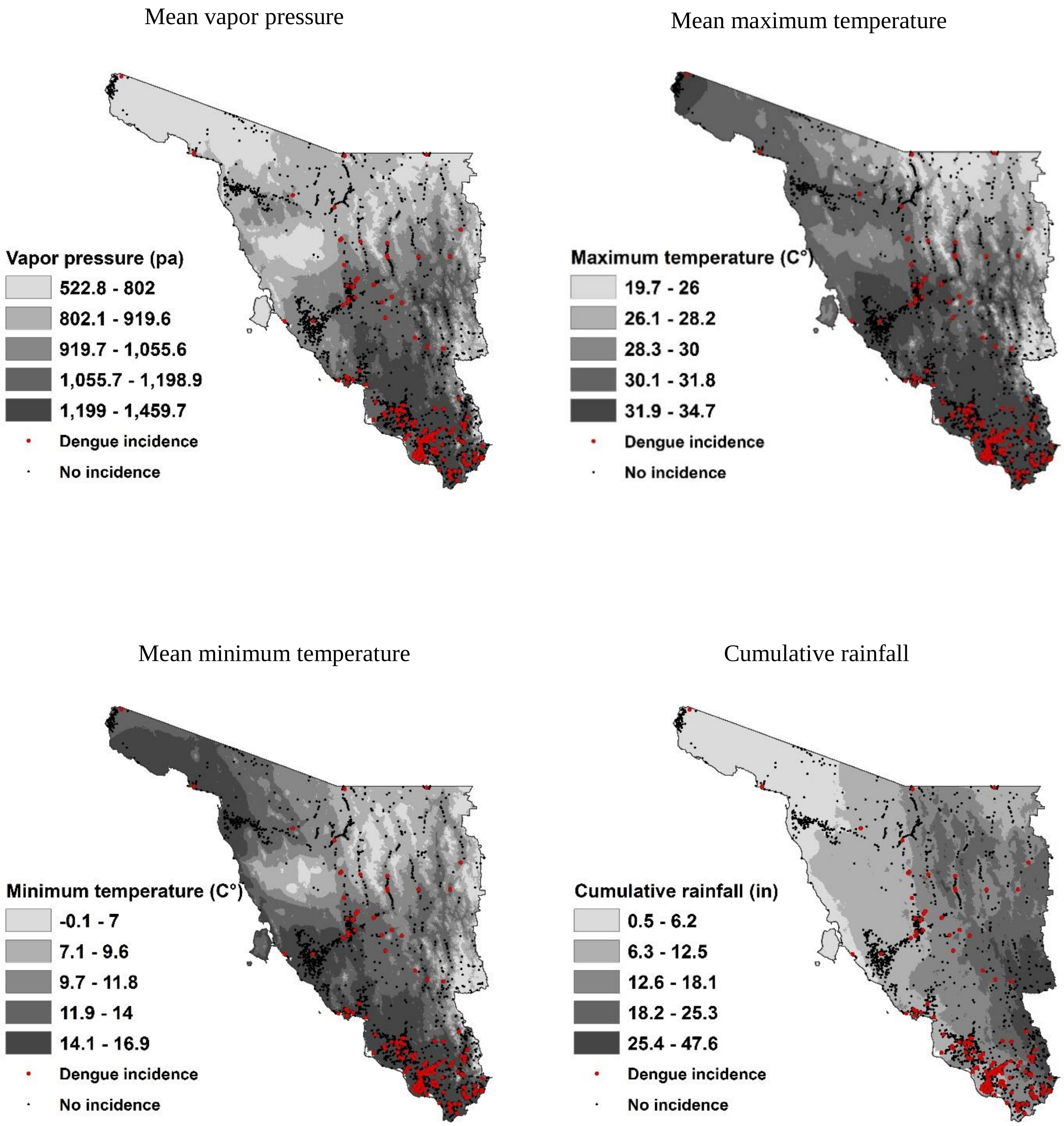

Table 2. Spearman correlation matrix between dengue related factors in Sonora, Mexico

	Variable	1	2	3	4	5	6	7	8	9	10
1	Dengue incidence (per 10000)	1									
2	Access to health services (%)	-0.124***	1								
3	No basic school (%)	-0.228***	0.324***	1							
4	No piped water (%)	-0.084**	0.093**	0.040	1						
5	Distance to highway (Km)	-0.076**	-0.003	0.284***	-0.037	1					
6	Log population size	0.365***	-0.123***	-0.399***	-0.179***	-0.129***	1				
7	Vapor pressure (pa)	0.199***	-0.236***	-0.261***	0.040	-0.242***	0.108***	1			
8	Avg. min temp (C°)	0.153***	-0.132***	-0.326***	0.072*	-0.406***	0.066*	0.641***	1		
9	Avg. max temp (C°)	0.173***	-0.161***	-0.232***	0.059*	-0.303***	0.033	0.868***	0.699***	1	
10	Cumulative rainfall (in)	0.105***	-0.175***	-0.075*	0.013	0.269***	0.103***	0.540***	-0.085*	0.237***	1

p*-value<.05, ***p*-value<0.01, * *p*-value<0.001

Table 3. Global Moran's I of the study variables

Variable	Moran's I
Dengue incidence	0.093**
No basic school (%)	0.333***
Access to health services (%)	0.277***
Houses with no piped water (%)	0.184***
Distance to main highway (Km)	0.958***
Log population size	0.065***
Cumulative rainfall (in)	0.952***
Mean maximum temperature (C°)	0.884***
Mean minimum temperature (C°)	0.888***
Vapor pressure (pa)	0.935***

p*-value<.05, ***p*-value<0.01, * *p*-value<0.001

Figure 3. Spatial distribution of dengue incidence in Sonora, Mexico, 2006-2011

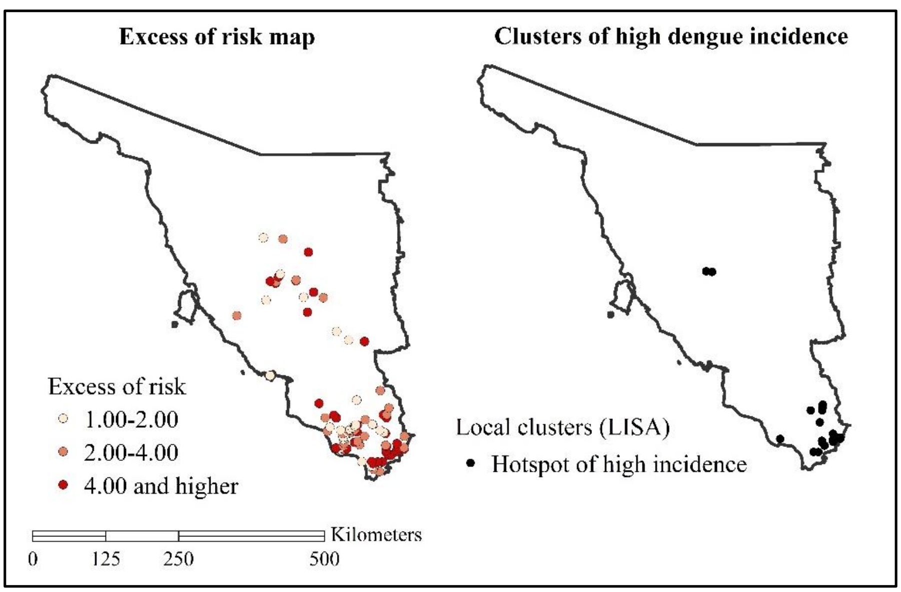

Table 4. Zero-inflated negative binomial models of dengue incidence in Sonora, Mexico, 2006-2011

Factors	Model 1		Model 2		Model 3	
	IRR	C.I.	IRR	C.I.	IRR	C.I.
Negative binomial component						
No basic school (%)	1.038**	(1.012, 1.064)	1.039**	(1.012, 1.067)	1.043**	(1.016, 1.071)
Access to health services (%)	0.983	(0.962, 1.005)	0.985	(0.963, 1.007)	0.983	(0.962, 1.003)
Houses with no piped water (%)	0.995	(0.979, 1.011)	0.993	(0.977, 1.010)	0.993	(0.977, 1.009)
Log population size	1.255**	(1.049, 1.503)	1.280**	(1.070, 1.532)	1.313**	(1.087, 1.586)
Cumulative rainfall (in)	1.314***	(1.204, 1.435)	1.367***	(1.247, 1.500)	1.192***	(1.080, 1.316)
Avg. maximum temperature (C°)	1.568***	(1.255, 1.959)	---------	---------	---------	---------
Avg. minimum temperature (C°)	---------	---------	1.280**	(1.091, 1.503)	---------	---------
Avg. vapor pressure (pa)	---------	---------	---------	---------	1.005***	(1.002, 1.007)
Spatial lag	1.007*	(1.002, 1.013)	1.008**	(1.002, 1.014)	1.008**	(1.002, 1.014)
Logistic component (structural vs sampling zeros)	OR	C.I.	OR	C.I.	OR	C.I.
Distance to main road (km)	1.033***	(1.016, 1.051)	1.032***	(1.013, 1.051)	1.029**	(1.009, 1.050)
Log population size	0.368***	(0.212, 0.639)	0.362***	(0.195, 0.674)	0.374**	(0.194, 0.723)
Diagnostic tests						
AIC	1405.469		1410.820		1408.448	
BIC	1466.122		1471.474		1469.101	
p-value Vuong test	<0.05		<0.05		<0.05	
p-value LR test Alpha=0	<0.001		<0.001		<0.001	

IRR: Incidence Rate Ratio
C.I.: 95% Confidence Interval
Note: The Vuong test assesses the difference between the Zero inflated vs the Standard model. The LR test assesses whether or not there is a significant difference between the Zero inflated negative binomial vs the Zero inflated Poisson model.
p*-value<.05, ***p*-value<0.01, * *p*-value<0.001

APPENDIX B: Study #2

Socioeconomic and water supply neighborhood factors related to an outbreak of dengue in an arid city of Mexico, 2010

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

[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

Abstract

Background: In 2010, Hermosillo, a city located in the Sonoran desert region of Mexico, experienced its largest outbreak of dengue in the last decade. The aim of this study was to assess the association between dengue fever cases during the outbreak and neighborhood level socioeconomic indicators and infrastructure including water supply information.

Methodology: A total of 2,730 laboratory confirmed dengue cases reported to the Sonoran Health Department in 2010 were geocoded by residence and paired with 2,793 randomly generated “controls sites” that had been weighted by population density. Cases and controls were assigned socioeconomic and infrastructure characteristics from 2010 Mexican census units, water supply schedules and water catchment zones. Unconditional logistic regression was conducted to assess the association between probability of dengue and the neighborhood covariates.

Results: The probabilities of dengue were higher for individuals living in areas with higher median age (OR=1.053) and lower access to healthcare (OR=1.066). Higher population density and higher proportion of occupied houses were also significant, but

the ORs were attenuated after controlling for water supply characteristics. There was no linear relationship with the Index of Goods and, unexpectedly, dengue probabilities were lower for people living in neighborhoods with higher proportion connected to piped water (OR=0.989) and lower levels of migration (OR=0.908). One specific water catchment zone was associated with a much higher probability of transmission for its afternoon water supply schedule (OR=7.056).

Conclusions: Dengue transmission probability was higher for people living in neighborhoods that had older age groups, lower access to health care, and higher population densities. Fewer piped water connections and higher migration may be explained by geographic location on the fringe of the urban area or a lower proportion of the population being susceptible. Further investigation of the high risk areas in the specific water catchment zone should be explored.

Introduction

Dengue is a vector borne disease principally transmitted by the *Ae. aegypti* mosquito (1). Globally, about 390 million cases and 24,000 deaths occur annually (2,3). The incubation period ranges from 3 to 10 days and the spectrum of disease varies from completely asymptomatic to dengue fever (DF) to the most severe manifestations; dengue hemorrhagic fever (DHF) or shock syndrome (DSS) (4,5). There are four dengue serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) and the circulation of two or more serotypes in the same geographic area allows opportunity for re-infection and may increase the risk of DHF/DSS (6,7). There is no vaccine or effective treatment and the best strategy for prevention is vector control.

The dynamics of dengue virus transmission are determined by social and environmental factors. Temperature affects vector survival, replication and maturation times (8,9). The extrinsic incubation period (EIP) of the virus also decreases with higher temperatures (10). Dengue is mainly present in tropical and sub-tropical zones where temperature and relative humidity favor the presence of the vector and the maintenance of the virus (11). However, some arid and semi-arid regions have established seasonal transmission and have reports of circulation of all four serotypes (12–14).

Urban and peri-urban locations present most of the dengue cases (6,14). The *Ae. aegypti* mosquito is highly anthropophilic and well adapted to human environments. In immature states, the vector uses artificial containers as oviposition sites. Social factors associated with urbanization, population growth, housing conditions, non-reliable water supply and sanitation and mobile populations may lead to introduction of the virus and maintenance of high vector densities. Where resources are limited vector control may be deficient or absent (9).

Hermosillo is a city located in the Sonoran desert of Northern Mexico (MX). Dengue re-emerged in the state of Sonora after the termination of the Pan-American Health Organization vector eradication program implemented in the 1970s (11); subsequent reports of dengue in the state began in 1982 (15). Since then, areas in southern Sonora have become endemic and regular seasonal transmission occurs as far north as Hermosillo.

In 2010, the city of Hermosillo experienced the largest outbreak of dengue since its re-emergence in the region. Within the Mexican context, Hermosillo is a relatively well-developed urban center with very low levels of marginalization and social deprivation (16), however, internal inequalities persist. The outbreak was concurrent with water shortages and subsequent mandatory water restriction programs. Under these conditions of an irregular water supply, water storage and rain-harvesting behaviors are important concerns as potential sources of mosquito oviposition sites and increased risk of dengue transmission (17). The aim of this study was to assess the association between dengue fever and neighborhood characteristics related to socioeconomic and water supply factors during the outbreak of dengue in the urban area of Hermosillo, MX, 2010.

Methods

A retrospective case-control study was conducted in order to assess the association between dengue occurrence and neighborhood level factors related to socioeconomic and water supply characteristics.

Data sources and variables

Cases and controls: 2,843 lab confirmed cases of dengue occurred in Hermosillo in 2010 were obtained from the surveillance system of the Health Ministry of Sonora. Approximately 96% (n=2,730) of the cases were geocoded by residence in ArcGIS 10.1. ArcGIS was then used to generate 2,793 random location points weighted by population density over the study area to serve as control locations (Figure 1). This method has been demonstrated to be useful for creating control observations for cluster detection and determining epidemiological associations (18–22). When there is an appropriate selection of population controls, the case/control ratio in a subset of the study area (e.g. census unit) must to be proportional to the incidence rate (23,24). In order to verify this situation, the case-control ratio (cases/controls) by census unit was compared with the incidence rate (cases/census unit 2010 population) with Pearson correlation test to confirm the representativeness of controls (r=1.0, p-value<0.001). Neighborhood characteristics of cases and controls were assigned by overlaying the case-control map with the census and water supply polygons.

Socioeconomic factors: Socioeconomic information by census unit was obtained from the 2010 Mexican Census (25). The variables included median age, % unemployment, % population with no healthcare, % with no or less than 9th grade basic education, % migrant population in the last 5 years, % occupied houses, persons per house, % houses with no piped water, and population density (persons per hectare). Principal Component Analysis (PCA) was used to create an Index of Goods as a proxy of wealth. The goods included in the PCA included percentage of houses with refrigerator, laundry machine, car, radio, TV, PC, landline telephone, cellular phone, and internet.

Water supply factors: The municipal water supply schedule during the water restriction program in 2010 was provided by the Agua de Hermosillo. Supply schedules were divided into morning (5:00 am – 1:00 pm) and afternoon (2:00 pm – 10:00 pm) water availability. Four water catchment areas were defined by their supply from different wells. A new area classification was created based on the different combinations of supply schedules and water catchment areas (Figure 2). This final classification was used for modelling.

Statistical analysis

Cumulative incidence (cases per 10,000 inhabitants) and descriptive statistics of individual characteristics of cases are reported. Means with standard deviations (SD) and proportions (%) of neighborhood variables were estimated for cases and controls. The Index of Goods was stratified by quantiles and reported as a continuous and categorical variable. Comparison of neighborhood characteristics between cases and controls were made using *t*-test and x^2 test for continuous and categorical variables, respectively.

Unconditional logistic regression was used to assess the association between dengue fever and neighborhood factors. Univariate analysis was used to explore crude odds ratios for all factors of interest. The Index of Goods was squared to explore non-linear association by including the original and transformed variables in the models. Likelihood ratio tests were used to determine statistical difference between models with and without the quadratic term. The variable of % No Basic Education was highly correlated to the Index of Goods (r=0.810, p-value<0.001) and % Population with No Health care (r=0.773, p-value<0.001); therefore, it was excluded from the multivariate models to decrease problems of collinearity and biased estimators (26). The Index of

Goods and % Population with No Health care were moderately correlated (*r*=0.637, *p*-value<0.001) and retained in the models.

Two multivariate models were created. Model 1 included all the socioeconomic variables and the quadratic term. Model 2 added the water supply characteristics. Odds Ratios (OR) and their 95% confidence intervals (C.I.) were calculated. A dengue probability map was created by weighting each socioeconomic and water supply variable by its β coefficient.

Unconditional logistic regression was used to assess potential difference in neighborhood variables between DF and DHF. In this analysis, DF cases were used as cases and DHF as controls. The purpose was two-fold: 1) to determine if DHF cases arose in neighborhoods with specific characteristics compared to general dengue cases and 2) to determine if associations were similar for DHF cases which might be less subject to reporting bias

The threshold for statistically significant associations for all analyses was set at *p*-value < 0.05. Statistical analysis was performed with the software package STATA 13.1. Maps were created in ArcGIS 10.1.

Results

Outbreak description

A total of 2,843 of dengue cases occurred during the outbreak in 2010, which represent a cumulative incidence of 39.8 cases per 10,000 inhabitants. Most of the cases were concentrated in the northern and central part of the city (Figure 1). Table 1 shows the distribution of cases by sex and age groups. About 57.8% (n=1,646) of the cases were females and 42.2% (n=1,202) males. Both sex showed the lowest cumulative incidence in the age group 0-9 years. For the rest of age groups, females showed cumulative incidence rates above 42 cases per 10,000. On the other hand, males showed lower incidence rates compared to females except for the 10-19 age group.

About 85.8% of all cases were DF cases and the rest (14.2%) DHF, therefore, the ratio between DF and DHF was 6:1. This ratio was lower for males (5:1 for males compared to 7:1 for females). Therefore, females represented the highest proportion of the total confirmed cases, but the severity of cases was higher between males with more DHF cases. Logistic regression was used to assess potential differences in neighborhood characteristics between DF and DHF, but no differences were identified.

Descriptive statistics

Table 2 shows the descriptive statistics of the neighborhood variables of the cases and the random controls. In relation to the socioeconomic characteristics, cases were located in neighborhoods with significantly higher median age (28.9 years versus 26.9 years) higher unemployment (5.8% versus 5.5%), less access to health services (23.2% versus 21.3%), lower basic education (24.8% with no basic education versus 21.4%), higher occupied houses (98.8% versus 98.5%), and higher population density (78.0 persos per hectare versus 75.7). On the other hand, the neighborhood characteristics of controls were significantly higher in relation to percent recent migration (2.7% versus 2.0%) and percent of houses with no piped water (2.5% versus 1.4%). There were no significant differences in the average persons per house, or the Index of Goods. After stratifying the Index of Goods by quantiles, cases showed higher proportions in intermediate strata but lower number of cases in the very low (7.3%) and very high

(6.4%) strata. Controls showed a similar pattern but with a significant lesser extent. Both distributions were statistically different (*p*-value <0.05).

Water supply: There were differences in the distribution of cases and controls by water supply variables during the outbreak. Cases were more commonly located in neighborhoods supplied water only during the morning schedule (52.5%) than during the afternoon (47.6%) schedules. However, 57% of controls were located in morning supply neighborhoods and 43% in the afternoon schedule. Half of the cases (50.3%) were supplied by the set of wells comprising a specific water zone; while just 24.6% of the controls were located in the same zone.

Logistic regression modelling

Consistent with the findings above, crude estimations showed a non-linear relationship between dengue incidence and the Index of Goods (Table 3). The crude model with inclusion of the quadratic term was statistically different to a simple model (x^2=214.48, *p*-value <0.001). The crude model with the stratified Index of Goods illustrates the U-shape distribution of the dengue probabilities. There was no difference between the dengue odds of the most deprived (very high) and the wealthiest neighborhoods (very low-reference group) (OR=1.134, 95% CI: 0.891, 1.453). However, the probabilities of dengue for the intermediate quantiles were higher in relation to the very low quantile. Those persons living in high, medium and low levels were 2.7, 3.1 and 2.7 times more likely to be a case compared to the very low stratum. The quadratic term was kept for the next models because of the non-linear relationship.

Two different models were constructed to examine the association between dengue fever and the neighborhood factors (Table 3). Model 1 includes only the socioeconomic variables. All the variables in the model presented statistically significant associations except for unemployment (OR=0.969, 95% CI: 0.933, 1.006) and the Avg. Persons per House (OR=1.148, 95% CI: 0.797, 1.655).

There were consistently higher probabilities of dengue transmission (even after adjusting by water supply characteristics in Model 2) for individuals living in areas with older populations (OR=1.053, 95% CI: 1.029, 1.078) and no access to health services (OR=1.066, 95% CI: 1.042, 1.089). Unexpectedly, there were lower probabilities of transmission for people living in neighborhoods with higher levels of migration (OR= 0.908, 95% CI: 0.863, 0.956) and higher connection to piped water (OR=0.989, 95% CI: 0.979, 0.998). Also, there was a statistically significant association with the quadratic term of the Index of Goods (OR=0.982, 95% CI: 0.978, 0.987). Model 1 showed higher probabilities for people living in neighborhoods with higher percent of occupied houses (OR=1.055, 95% CI: 1.007, 1.105) and higher population density (OR=1.004, 95% CI: 1.002, 1.006). However, these associations were apparently explained after including the water supply characteristics in Model 2.

Model 2 compares the probabilities of dengue between the water supply zones. Effect modification was identified between water-catchment area and time of water supply. For better interpretation, stratified results are presented in Table 3 which shows results for the four water supply zones, sub-divided into when water was supplied, morning or afternoon. This categorization creates eight time-water catchment zones (Figure 2). The zone and time combination with the lowest probability of dengue cases is used as the reference (Willard - Morning). There was no difference in the Willard zone between schedules (OR=1.113, 95% CI: 0.650, 1.906) or to the zone of Mesa del Seri -

Afternoon (OR=1.232, 95% CI: 0.823, 1.844). However, the probabilities of dengue in La Victoria were higher for both time schedules; for the afternoon schedule they were 7 times higher (OR=7.056, 95% CI: 4.904, 10.151) and for the morning schedule they were 4 times higher (OR=3.971, 95% CI: 2.703, 5.835). In Bagotes and the morning schedule for Mesa del Seri, probabilities were higher than in the reference (Bagotes (Afternoon: OR=3.304, 95% CI: 2.268, 4.814; Morning: OR=3.181, 95% CI: 2.255, 4.489) and Mesa del Seri (OR=3.586, 95% CI: 2.371, 5.423). Therefore, both water catchment zone and time of day were associated with different dengue risks. Model 2 was used to create a predictive map after weighting the census unit characteristics by the obtained coefficients (Figure 3). The map shows higher probabilities of dengue transmission at the northern and middle parts of the city.

Discussion

The 2010 outbreak of dengue in Hermosillo was the largest one in the last decade. Before the 2010 outbreak, the Health Ministry reported the presence of just DEN-1 serotype within the state (27). During the outbreak, the ratio between DF and DHF was 6:1, this high ratio suggests the potential reinfection of cases and the presence of at least one different serotype (28). It was not until 2012, that DEN-2 was confirmed in the state. This strain was associated with more severe disease (29). It is possible that the introduction of this strain occurred during the 2010 outbreak as regular laboratory testing was not conducted to identify serotypes at that time. There are still only a small proportion of samples being tested for sero-type, and serological surveys would be needed to determine the distribution of different serotypes within the city.

The higher proportion of females from the total of cases contrasts with the study of Anker and Arima (30) where they found an excess of reported cases for ≥ 15 age males in six Asian countries. The higher proportion of cases for females as well as the lower DF/DHF ratio for males may indicate susceptibility differences for new infections within females and reinfection by a new serotype for males. It may also represent different health care seeking behaviors with girls and women seeking care more commonly for milder illness and, therefore, more likely to be included in the surveillance system. Despite these differences, the current study seems to indicate that the distribution of DF versus DHF was not related to socioeconomic or water supply characteristics which might suggest more homogenous distribution of the different serotypes.

The lower cumulative incidence in the 0-9 age group, as well as the positive association between probability of dengue and median age of the census unit, is consistent with the study by Egger and Coleman (31) where they found a relatively low risk of clinical disease after primary infection in childhood and a rapid increase in clinical disease during adolescence and early adulthood. Under this scenario, serological testing in this age group would be needed to define potential risk of reinfection and DHF later on.

The average number of persons per house and population density were used to assess the risk of transmission as a result of different proximity between individuals in outdoors and indoors environments. The average number of persons per house was not associated with dengue risk. This finding is consistent with the results of Siqueira et al. (32) from an urban setting of Central Brazil but counter to the study of Koyadun et al. (33) in urban areas of Thailand where they found that dengue risk was 2 times higher in houses with more than four members. The positive association between dengue and population density found in Model 1 is consistent with the findings of other studies and support the effect of the urbanization process on the transmission of the disease (6,8,34,35). The association between dengue and population density attenuates after controlling for water supply characteristics. However, this reduced association must to be considered with caution because the water supply variables are just a proxy of potential problems of water storage practices related to specific water supply zones and schedules, as no direct information on these practices was available.

Dengue risk was higher when a higher percentage of houses were occupied. This indicator of percentage of occupied houses was used to assess the potential contextual effect of mosquito breeding sites from backyards in empty houses. However, dengue risk in this city appears to be more driven by urbanization and population density as described above. Immigration of susceptible people or people infected with absent strains has been proposed as a potential factor that affect herd immunity and dengue risk (36,37); however, in this study the controls were more likely to reside in areas with higher migration levels than the cases and transmission during the outbreak was higher in areas with more stable population.

In this study, we did not find a linear relationship between the dengue transmission and Index of Goods. This finding is contradictory with the result of an entomologic study in a southern village of Mexico where larval breeding risk was higher in households with low socioeconomic status (38). However, an entomological study in Ciudad Juarez, an urban city also located in a US-Mexico border state, did not find an association between socioeconomic indicators and mosquito distribution (39). Moreover, similar results of no association between dengue risk and socioeconomic indicators have been found in several places in Brazil (40–44) and density of *Ae. aegypti* does not necessarily indicate the degree of vector-human contact occurring.

In Hermosillo, the probability of dengue was lower in those areas classified as having a very low or a very high Index of Goods. Lower risk in higher wealth areas makes intuitive sense, as it may result from better sanitary services in wealthy neighborhoods that minimize the oviposition sites and better housing infrastructure that minimizes vector-human contact. Lower probability in dengue in poor areas, however, seems contradictory. The location of the very low wealth neighborhoods may provide an explanation. Medium wealth neighborhoods tend to be located in the city center where population density is higher while the very low wealth areas are on the margins of the city. While population density was controlled for in the analysis, there may be residual confounding. Another possible explanation is underreporting of disease related to lack of access to health care in poorer areas; however, the positive association between dengue and access to health care indicates this may not be a significant bias (45).

The urban structure of the city could also explain the contradictory positive association between dengue and percent of households with piped water. The city of Hermosillo has a high coverage of piped water infrastructure with approximately 97% of households connected to the water infrastructure (46). The low percent of households with no water infrastructure usually are in the most deprived areas and “invasiones” or informal settlements at the margins of the city. An adequate connection to the water systems is expected to reduce the creation of breeding sites; however, a study in Brazil did not find an association (43), and a study in southern Vietnam showed no reduction in water storage practices in communities that received water supply recently (47). Therefore, it is possible that simply having water pipes to the home is not an ideal measure of water storage practices. Individuals who have no piped water may have more stable practices or experiences with storing their water, such as larger barrels regularly supplied with trucks, or may have more immediate use of available water such that the supply is replenished and not abandoned to be exploited as immature habitat by the *Ae. aegypti*.

Water source did have a highly statistically significant association depending on the water catchment zone and time of access. The highest probability of dengue occurred in the portion of La Victoria that was supplied with water in the afternoon. There is evidence that the coping strategies of residents that face water scarcity may differ by socio-economic factors. For example, a multiple case study which included six study areas with irregular water supply service found differences between privileged and under-privileged areas (48). Privileged areas tended to have well and pump systems and the irregular services did not affect them. However, under-privileged areas used more water containers which provided more opportunities to serve as breeding sites.

There are some limitations in this study. The analysis was based on the residence of subjects and does not include the potential mobility of people across the city. Therefore, the transmission is associated just to the place of residence. Only laboratory confirmed cases were analyzed and, if there were spatial differences in diagnosis, this may impact results, although an analysis of the distribution of confirmed versus suspect cases did not demonstrate a significantly different distribution. The geographical distribution and neighborhood characteristics of clinical and sub-clinical cases not detected in by the surveillance system could produce different results to our findings. Despite the fact that individual cases were used, no information about individual risk behaviors was available for this case-control analysis. Potential risk of ecological fallacy is present. However, the analysis was appropriate for assessing how the urban environment influences dengue risk. The method used to generate random points to act as controls has been successful to create a representative sample of the neighborhoods characteristics of the population in Hermosillo. It was an efficient and cost-effective method to explore neighborhood level associations with surveillance data.

In summary, the findings indicate higher probabilities of dengue in the neighborhoods supplied by the wells of the water catchment zone of La Victoria, specifically during the afternoon. Further investigation into this zone is necessary by using better water supply indicators related to the quality of water services as well as water storage practices of the community that may have promoted the creation of breeding sites. In addition, policy level changes on water, urbanization, and access to healthcare may also influence dengue risk. These results further underscore the importance of conducting more detailed assessments of how water scarcity and resulting water restrictions may influence the dynamics of dengue in arid areas.

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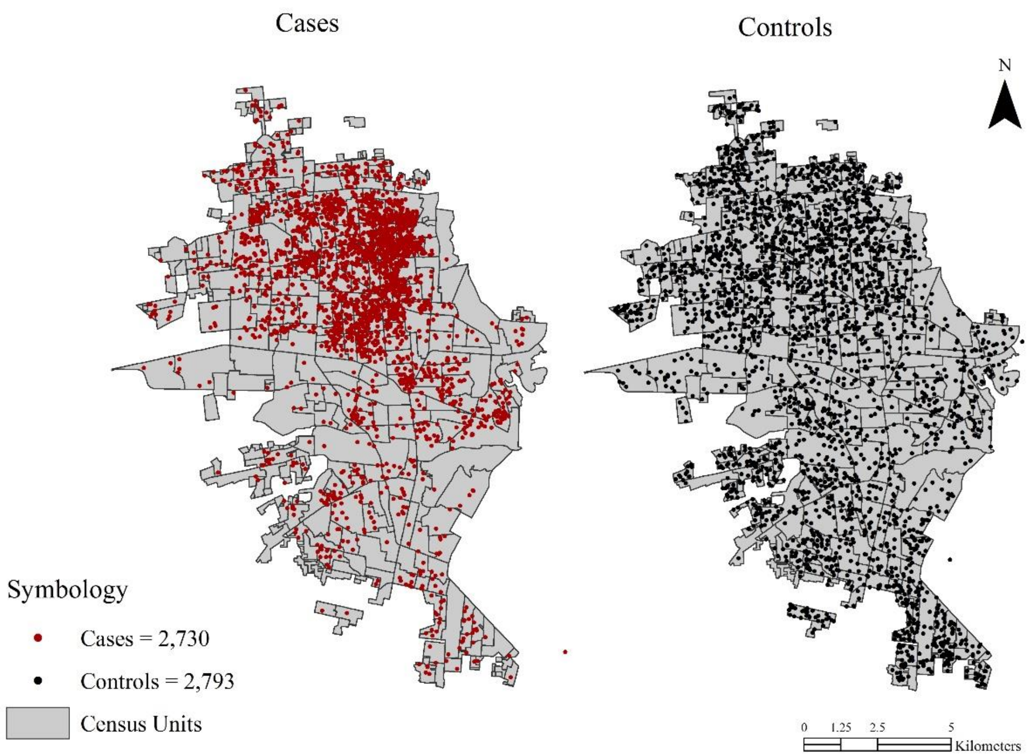
Figure 1. Distribution of Dengue Cases and Controls



Note: The cases presented in this map were geographically masked using the random perturbation donut method due to confidentiality issues related to potential reverse geocoding (49)

Figure 2. Water catchment zones and water supply schedules

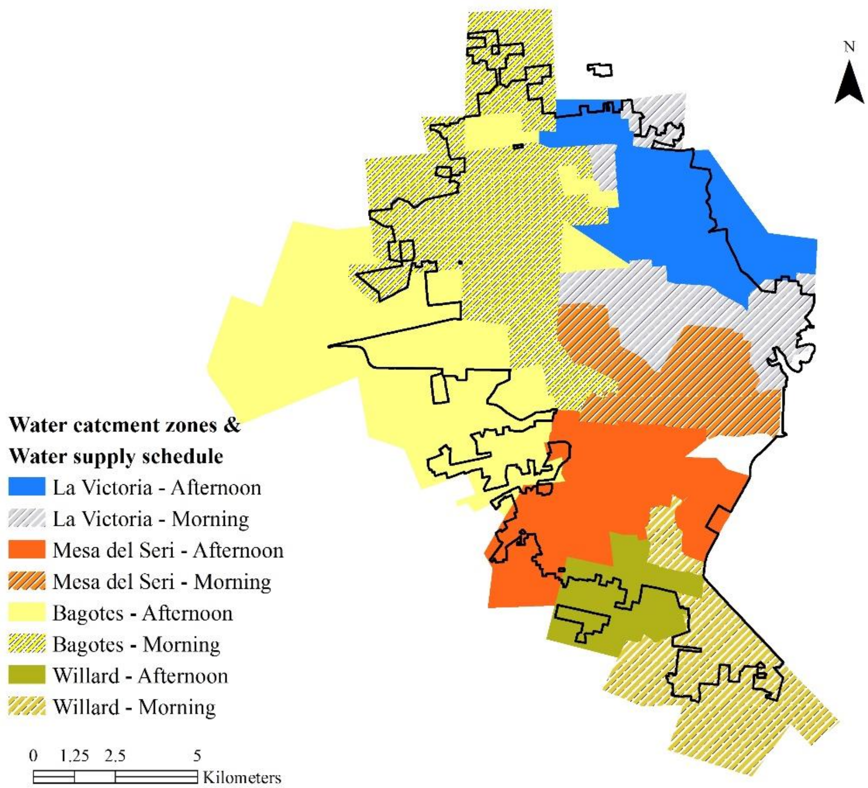


Table 1. Distribution of dengue cases by type and age groups in Hermosillo, Sonora 2010

	DF		DHF		Total		DF/FHD Ratio
	Cases N	Incidence per 10,000	Cases N	Incidence per 10,000	Cases N	Incidence per 10,000	
Total	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		

DF: dengue fever
DHF: dengue hemorrhagic fever

Table 2. Descriptive statistics of neighborhood variables for dengue cases and controls, Hermosillo, Sonora 2010

Factor	Cases n=2,730	Controls n=2,793	p-value
	Mean (SD)	Mean (SD)	t-test
Median age (years)	28.9 (6.1)	26.9 (5.4)	<0.001
Unemployment (%)	5.8 (1.9)	5.5 (2.2)	<0.001
No access to health services (%)	23.2 (4.2)	21.2 (5.4)	<0.001
No basic education (%)	24.8 (8.2)	21.4 (10.5)	<0.001
Migration (%)	2.0 (1.4)	2.7 (2.9)	<0.001
Occupied houses (%)	98.8 (1.3)	98.6 (1.6)	<0.001
Average of persons per house	3.7 (0.3)	3.7 (0.3)	0.128
No piped water into the house (%)	1.4 (6.7)	2.5 (10.5)	<0.001
Population density (persons/hectare)	78.0 (29.6)	75.7 (36.2)	<0.01
Index of goods (continuous)	0.273 (0.086)	0.268 (0.121)	0.055
Index of goods (quantiles)	%	%	x^2 test
Very high	6.4	13.1	<0.001
High	25.9	22.2	
Medium	32.9	24.3	
Low	27.4	23.6	
Very low	7.3	16.9	
Water supply schedule			
Morning	52.4	57.0	<0.05
Afternoon	47.6	43.0	
Zone of water catchment			
Victoria	50.3	24.6	<0.05
Mesa del Seri	14.8	20.7	
Bagotes	32.1	41.8	
Willard	2.8	12.9	

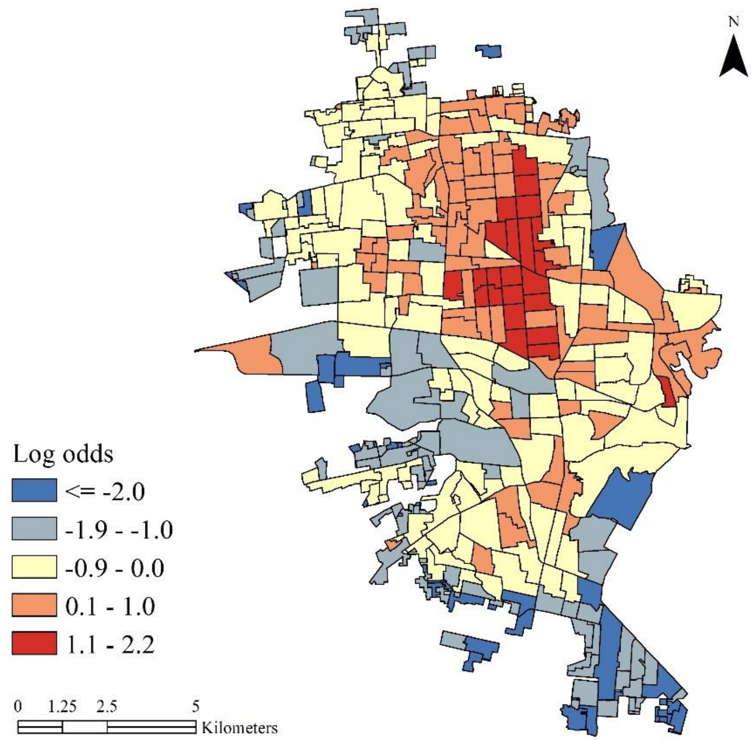
Table 3. Results of logistic regression modeling of factors associated with dengue, Hermosillo Sonora of cases and controls

Factors	**Crude**		**Model 1**		**Model 2**	
	OR	C.I.	OR	C.I.		
Median age (years)	1.062***	(1.052, 1.072)	1.073***	(1.052, 1.096)	1.053***	(1.029, 1.078)
Unemployment (%)	1.087***	(1.059, 1.115)	0.969	(0.933, 1.006)	1.023	(0.983, 1.065)
No access to health services (%)	1.089***	(1.076, 1.101)	1.125***	(1.104, 1.147)	1.066***	(1.042, 1.089)
No basic education (%)	1.038***	(1.032, 1.044)	-------		-------	
Migration (%)	0.772***	(0.744, 0.801)	0.947*	(0.902, 0.993)	0.908***	(0.863, 0.956)
Occupied houses (%)	1.101***	(1.061, 1.143)	1.055*	(1.007, 1.105)	1.042	(0.993, 1.093)
Average of persons per house	0.869	(0.725, 1.041)	1.148	(0.797, 1.655)	1.261	(0.866, 1.837)
No piped water into the house (%)	0.985***	(0.978, 0.992)	0.982***	(0.973, 0.99)	0.989*	(0.979, 0.998)
Population density (persons/hectare)	1.002**	(1.001, 1.004)	1.004***	(1.002, 1.006)	1.001	(0.998, 1.003)
Index of goods[a]	1.050	(0.999, 1.105)	1.061***	(1.041, 1.082)	1.069***	(1.048, 1.091)
Index of goods squared	0.059***	(0.039, 0.088)	0.982***	(0.978, 0.987)	0.982***	(0.978, 0.987)
Index of goods (quantiles)						
Very high	1.138	(0.891, 1.453)	-----------		-----------	
High	2.692***	(2.209, 3.279)	-----------		-----------	
Medium	3.129***	(2.580, 3.796)	-----------		-----------	
Low	2.682***	(2.206, 3.262)	-----------		-----------	
Very low	1.000	Ref	-----------		-----------	
Water catchment zone & Water supply schedule						
La Victoria - Afternoon	11.167***	(8.051, 15.490)	-----------		7.056***	(4.904, 10.151)
La Victoria - Morning	7.738***	(5.524, 10.839)	-----------		3.971***	(2.703, 5.835)
Mesa del Seri - Afternoon	1.774***	(1.232, 2.554)	-----------		1.232	(0.823, 1.844)
Mesa del Seri - Morning	5.954***	(4.186, 8.470)	-----------		3.586***	(2.371, 5.423)
Bagotes - Afternoon	3.565***	(2.523, 5.037)	-----------		3.304***	(2.268, 4.814)
Bagotes - Morning	3.666***	(2.657, 5.058)	-----------		3.181***	(2.255, 4.489)
Willard - Afternoon	1.122	(0.668, 1.883)	-----------		1.113	(0.650, 1.906)
Willard - Morning	1.000	Ref				

a. Odds ratios of the Index of goods are expressed as probabilities per 0.1 change in the Index of goods

*** *p*-value<0.001, ** p-value<0.01, * p-value<0.05

Figure 3. Probability model of dengue incidence (Log odds) in Hermosillo Sonora, 2010



Note: probability model controlled for socioeconomic and water supply factors

APPENDIX C: Study #3

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

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

[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

Abstract

Background: Identifying the most likely locations of the initiation of an outbreak is critical for effective control. This study assesses the spatio-temporal dynamics of two dengue outbreaks that occurred separately in two arid cities of northern Mexico (Hermosillo and Navojoa). It also explores the association between dengue occurrence by week and the neighborhood characteristics of the cases in order to find similar socioeconomic patterns between the cities.

Methodology: A total of 2,730 and 493 laboratory confirmed dengue cases, from Hermosillo (2010) and Navojoa (2008) respectively, were geocoded by residence and assigned socioeconomic neighborhood characteristics using units from the 2010 Mexican census. Cases were grouped by reporting date into five sequential 4-week periods of the epidemic years. Kernel density estimation was used to define high density areas in both cities. Space-time retrospective cluster analysis based on a Poisson probability model was performed to detect clusters of dengue. Additionally, Ordinary Least Square regression

was used to assess the changing socioeconomic characteristics of cases over the course of the outbreaks.

Results: In both cities, almost all cases occurred between September and December, with the peak in mid-October. Significant space-time dengue clusters were detected at the beginning of the outbreak that persisted for 2-3 months and disseminated progressively to contiguous neighborhoods. Initial foci of transmission were located in neighborhoods with higher population density, higher proportions of occupied houses, and lower access to health care and progressed to areas with lower population density, lower proportions of occupied houses, and higher access to care.

Conclusions: Both cities exhibited contiguous patterns of space-time clustering. Neighborhood characteristics related to high population density, high percent of occupied houses, and lack of healthcare were initial sources of dissemination in both places. Future research and control efforts in these regions should consider these these space-time and socioeconomic patterns.

Introduction

Dengue is a vector borne disease transmitted principally by the *Ae. aegypti* mosquito, a vector well adapted to human environments (1). Every year there are 390 million dengue infections worldwide, with 96 million symptomatic cases from mild fever to the severest manifestation of shock syndrome (2). Once a female mosquito bites an infected person by one of the 4 serotypes (DEN-1 to DEN-4), the vector remains infective for life and is able to transmit the disease to other hosts with each subsequent bite (3).

Multiple factors influence the spatio-temporal dynamic of dengue transmission. In temporal terms, warming temperature increases the frequency of blood feeding, the viral development rate, and shortens the extrinsic incubation period (4–6). These terms provide an explanation for the observed seasonal pattern with higher incidence during the warm season(7). Dengue transmission within the community also requires proximity between the vector and potential hosts. Most female *Ae. aegypti* mosquitos spend their lifetime in or close to the same place where they become adults (8). Therefore, a limited vector flight range plus human interactions within neighborhoods and human mobility across a community can determine the spatial patterns of the transmission (8,9).

Disease modeling approaches also show that dengue epidemics vary spatially on a local scale due to the nature of the human population structure (10,11). Socioeconomic characteristics of households related to uncontrolled urbanization, migration, deficient services of water supply and garbage disposal, and vector control activities can play a significant factor in the spatio-temporal distribution of dengue (12–15).

Dengue has shown to cluster in space-time (16,17). The understanding of the spatio-temporal patterns allows an identification of dengue transmission foci and the dynamics an understanding of the disease spread (17). Determining the areas and times with higher risk of spread provides guidance for more efficient disease surveillance and control (1).

A spatio-temporal study was conducted for two dengue outbreaks in two arid cities of northern Mexico in order 1) to assess the spatio-temporal clustering patterns, and 2) to determine if there are differences in the socio-demographic patterns of dengue as the outbreaks progress, and 3) to determine if these patterns are similar across the two cities/outbreaks.

Methods

Data sources and variables

Surveillance information: 2,843 and 511 laboratory confirmed cases of dengue were reported in the urban cities of Hermosillo (2010) and Navojoa, Sonora, Mexico (2008). 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 by using immunosorbent assay (ELISA) for detection of viral antigen NS1, IgM or IgG, depending on timing of specimen collection during clinical disease period of evolution of the infection (18). Confirmed cases were those with a positive result in one of the three tests. About 96% of the cases (n=2730 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.

Neighborhood characteristics: Socioeconomic characteristics of the neighborhoods of residence were assigned to cases by overlaying the case maps of both cities with the census unit maps. The socioeconomic information for the census units was obtained from the 2010 Mexican census (19). Variables included: median age, unemployment (%), population with no health care (%), migrant population in the last 5 years (%), occupied houses (%), persons per house, houses with no piped water (%), and population density (persons per hectare).

Statistical analysis

Space-time analysis: For each city outbreak, cases were grouped into five 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. 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 area of analysis was based on a search radius of 500 m which represented the 90^{th} percentile of vector flight distance in urban areas reported by Maciel-de-Freitas et al. (9).

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. Population values were obtained from census data for each census block (19). A regular grid of 250m cells was created and overlayed 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 with a circular or elliptic base and a specific height for each time period. This window moves across space and time in the study area 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 (20).

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-weeks periods. Ordinary Least Square (OLS) regressions were performed using each of the neighborhood characteristics as dependent variables and epidemiologic week of the year as the independent variable in order to determine if there were significant changes in the socioeconomic profile of neighborhoods where cases resided over the course of the outbreak. Effect modification by city was assessed by creating interaction terms between week and city. Significant interactions were set at p-value<0.1. Stratified models were created to depict specific associations in each location. Significant trends shared by the two cities were plotted in overlaying graphs with the epidemic curves. Statistical significance for the associations from OLS regression were set at *p*-value <0.05. Statistical analysis was performed with the software package STATA 13.1. Maps were created in ArcGIS 10.1.

Results

The 2010 outbreak in Hermosillo represented 2,843 laboratory confirmed cases of dengue with incidence rate of 39.8 cases per 10,000 inhabitants. Navojoa identified 511 cases in 2008 for an incidence of 44.8 cases per 10,000. Figure 1 shows the distribution of cases by epidemiologic week. Both cities showed similar distributions. 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.

In both cities, women accounted for a higher proportion of cases (Hermosillo=57.5%, Navojoa=59.5%; *p*-value=0.42). Table 1 shows the distribution of cases by age groups. The highest proportion of cases occurred among the age groups 10-19 years and 20-29 years, and accounted for almost half of the cases (in Hermosillo=46%, in Navojoa=47%). However, in Hermosillo there was a relatively equal distribution by age group, except for the 0-9 age group which presented with the lowest incidence (11.9 per 10,000). In contrast, Navojoa showed higher incidence rate for the age groups 10-19 (69.7 per 10,000) and 50-59 (71.0 per 10,000).

High density areas of dengue

Figure 2 shows the progression of high density areas of dengue by period of time. In Hermosillo, high density areas started in the northern side of the city. 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% (weeks 45-48), and during the last period (weeks 49-52) receded to a very small area (0.1%) having high density of dengue. The geographic coverage of the outbreak of Navojoa followed a similar progression. It started with two small areas of high density located in the west and south side of the city that covered 1.0% of the city (week 36 and lower). From weeks 37-40, the areas of high incidence increased to 9.4% and were focused in the southwest side of the city. During the third period of the outbreak (weeks 41-44), the high density area covered 22.2% of the city. The geographic area remained smaller in Navojoa than in Hermosillo with 8.6% of the city presenting a high density of cases in the final period (week 45-48).

Table 2 presents a statistical comparison of the high density areas between Hermosillo and Navojoa. There was no statistically significant difference in characteristics of geographic areas with high densities of cases between cities during the onset of the outbreaks; however, there were significant differences for the third and fourth periods with a greater expansion of high incidence areas in Hermosillo.

Space-time clustering

Figure 3 shows the space-time cluster analysis from SatScan. 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 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.

Case Neighborhood characteristics across time

Demographic characteristics of the neighborhoods changed over time. Results from five time periods are presented in Table 3. Population density and percent of population with no health service decreased over time in both cities. The average percent of the population with no health service in case neighborhoods in Hermosillo declined from 24.6% in the first period to 23.2% in the last period, and from 18.4% to 16.3% in Navojoa. Neighborhoods identified as part of the initial foci of reported dengue cases had higher population density than those at the end for both Hermosillo (99.2 to 69.3 persons/ha) and Navajoa (54.4 to 47.7 persons/ha).

Table 4 presents how the association between neighborhood characteristics and week is different between cities using interaction terms in the models (city x week). There were statistical differences by city for the variables of median age (*p*-value= 0.015), no basic education (*p*-value =0.017), and population density (*p*-value =0.005). To examine the differences, models for each city were created (Table 5). In both cities, as the weeks passed, cases moved from neighborhoods with higher percent of people with no health services to lower frequencies (Hermosillo: β=-0.212, p-value<0.001; Navojoa: β= -0.133, p-value<0.01). However the magnitude of the effect was greater in Hermosillo. 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. Figure 4 overlays the epidemiologic curve with the distribution of the three significant neighborhood characteristics in both cities. In conclusion, the figure shows how the changes over epidemiologic weeks were related to factors of urbanization and health care in both cities.

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-economic patterns of reported cases 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 those communities located in arid regions.

In this study, 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 (21).

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 density. Despite this difference, the infection was disseminated beyond individual households in both cities with spatio-temporal clusters maintained during several months. This is consistent with the pattern of transmission found by a space-time analysis study in a city of Puerto Rico where they report significant clusters of dengue cases within the same household over periods of three or less days; however, dengue cases were spread across the locality over longer periods of several weeks (16).

A second pattern identified in each city was the contiguity of dissemination. Kan el al. found two different spatial diffusion patterns of dengue: contiguous and relocation (22). In this current study, the transmission in both cities started in a specific neighborhood, but later showed a contiguous pattern of dispersion where the geographical progression of disease incidence moved to contiguous neighborhoods. Considering human mobility is a major factor for transmission within a community (1,8,23,24), a predominant contiguous spatial pattern of transmission across time suggests the predominance of human 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.

Our results support the disease control idea of localized interventions centered on vector control activities within case residences with a particular focus on those cases that are initially identified as part of clusters of dengue. Our study provides evidence these areas serve as a sustained source of infection to contiguous areas (8). Both confirmed and probable case clusters should be investigated. A study in a Brazilian city reported that an outbreak of dengue became apparent to public health authorities more than two months after its emergence through the passive surveillance system, although dengue-like cases were detected clinically almost immediately (25). 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 inform the implementation of opportune perifocal vector control measures (25).

In a case-control analysis of dengue in Hermosillo during the outbreak year (Reyes-Castro et al., *in prep*), we found higher probabilities of dengue in neighborhoods with lower access to health care, higher population density and higher percent of occupied houses, before controlling for water supply characteristics. In the present study, case neighborhood characterization of these factors shifted by stage of the outbreak. Higher risk neighborhood characteristics identified in the case-control study were similar to those found in the initial foci of reported dengue cases. However, over time characteristics of case neighborhoods progressed from areas with higher to lower 1) proportions of people with no health services, 2) population densities, and 3) percent of occupied houses. A study in an urban locality of Taiwan (26) found a significant influence of high population density on dengue incidence only during the peak of the epidemic. Authors concluded that population density may have significant influence on transmission only when the number of infected cases is large enough (26). The steeper slope of Hermosillo related to population density could be explained by the difference between 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) (19).

Differences in human mobility could provide an alternative explanation of the difference in the magnitude of the association of population density between both cities. 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 (27). The current study did not have information about commuting activities of the cases. 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.

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 (13). Both cities have a high coverage of piped water above 95% (19); however, there are significant problems of water supply and distribution particularly in Hermosillo (28,29).

There were some limitations in this study. The clusters obtained in the spatio-temporal analysis were based just on the residence of cases and other criteria for geocoding could lead to a different distribution. Despite this fact, an analysis based on residence was useful considering the time that people spend at home and the peak of biting periods of the *Ae. aegypti*, early morning and before dusk being times when residents are most likely to be home (30). It was not possible to determine how other potential factors like the immunological status of the population, vector density, and vector control activities during the outbreaks, influenced the spatio-temporal results. Only laboratory confirmed cases were analyzed. Neighborhood characteristics and the geographical distribution of clinical and sub-clinical cases not detected by the surveillance system could produce different results to the reported findings.

In summary, the spatio-temporal pattern of dengue transmission showed some commonalities between cities/outbreaks. Both cities presented a seasonal distribution according to the expected in the arid region of the Sonoran desert. The focus of the transmission started in specific populated neighborhoods with low access to healthcare and was maintained over a period of 2-3 months and moved or disseminated to contiguous areas in the cities. Replication of these spatio-temporal analyses using the symptomatic data for reported cases would be appropriate. Similar results would support the use of syndromic surveillance, which is less labor intensive but which could lead to earlier detection of an outbreak.

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Figure1. Epidemic curves for dengue; Navojoa 2008, Hermosillo 2010

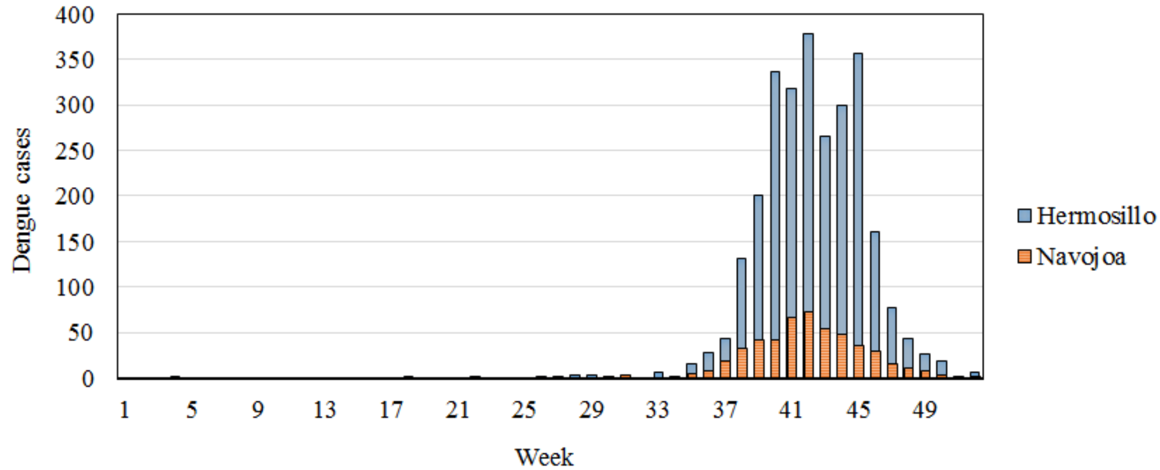

Table 1. Distribution of dengue cases by age group and city

Age	Hermosillo Cases N	Hermosillo Cumulative percent %	Hermosillo Incidence per 10,000	Navojoa Cases N	Navojoa Cumulative percent %	Navojoa Incidence per 10,000
0-9	156	5.5	11.9	61	11.9	29.2
10-19	690	24.3	51.8	139	27.2	69.7
20-29	617	21.7	49.7	101	19.8	59.9
30-39	407	14.3	35.6	56	11.0	35.6
40-49	413	14.5	46.5	43	8.4	34.5
50-59	284	10	47.2	57	11.2	71.0
60-69	158	5.6	49.1	31	6.1	64.5
70 and more	97	5.6	42.6	21	4.1	42.2
Total	2,843	5.6	39.8	511	100.0	44.8
Missing	21	5.6	-------	2	0.4	------

x^2 p-value<0.001

Figure 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

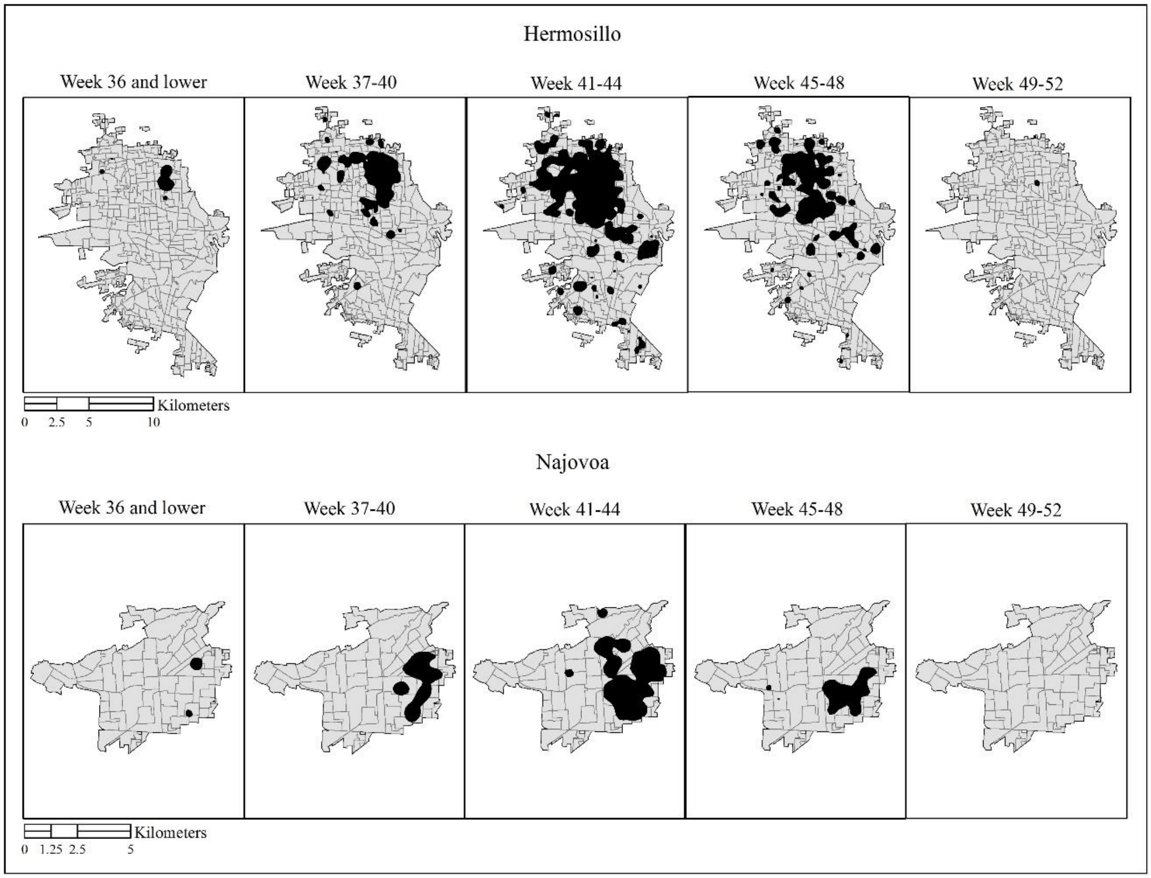

Table 2. Geographical progression of high density areas across time periods for city-outbreaks of dengue

Week period	Hermosillo 13,541 ha (100%)	Navojoa 3,403 ha (100%)	x2 *p*-value
36 and lower	191 (1.4)	34 (1.0)	0.063
37-40	1,402 (10.4)	319 (9.4)	0.111
41-44	3,977 (29.4)	754 (22.2)	<0.001
45-48	2,293 (16.9)	293 (8.6)	<0.001
49-52	14 (0.1)	0 (0.0)	0.060

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

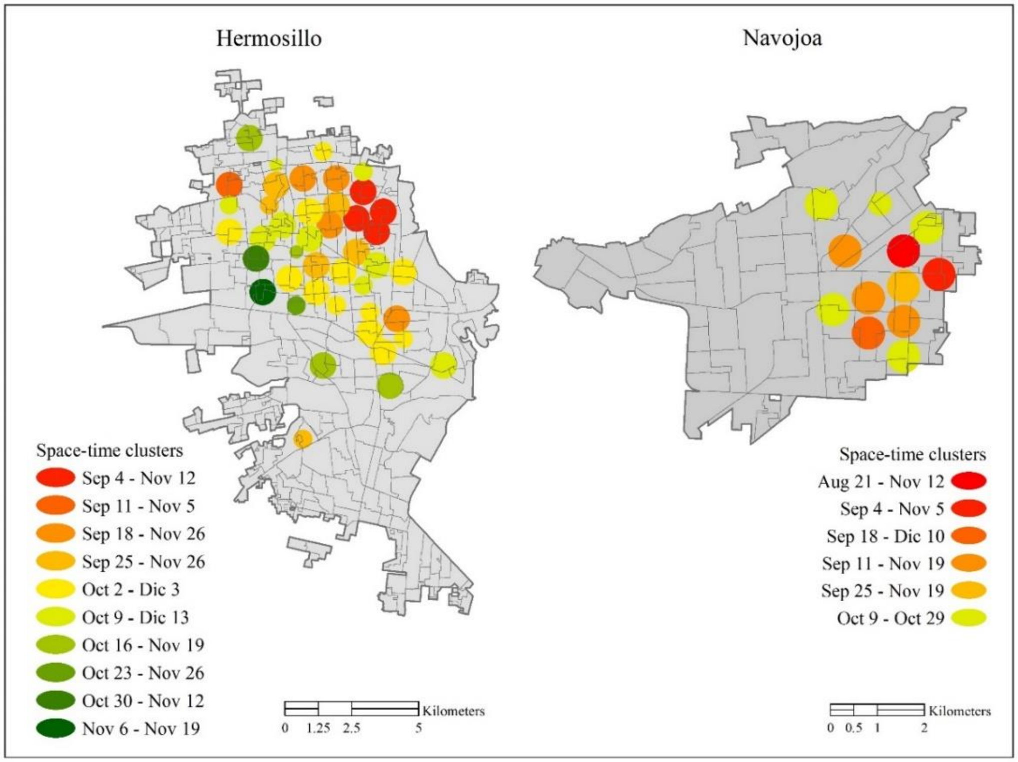

Table 3. Mean values of neighborhood characteristics of dengue cases by 4-week periods by city-outbreaks

	Weeks 36 and lower	Weeks 37-40	Weeks 41-44	Weeks 45-48	Weeks 49-52	Total
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
Unemployment (%)	5.5	5.2	5.4	5.6	5.2	5.3
No health care (%)	18.4	17.9	17.7	17.0	16.3	17.6
No basic education (%)	26.6	27.3	30.2	29.0	27.5	29.0
Migration (%)	2.3	2.2	1.9	2.1	2.0	2.0
Occupied houses (%)	99.1	99.0	98.8	98.6	98.4	98.8
Persons per house	3.8	3.9	3.9	3.9	4.0	3.9
No piped water (%)	3.5	3.0	3.8	3.5	4.4	3.5
Population density (persons/ha)	54.4	53.1	47.0	47.8	47.7	49.1
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
Unemployment (%)	4.7	5.5	5.9	6.0	5.9	5.8
No health care (%)	24.6	24.6	22.7	22.5	23.2	23.2
No basic education (%)	24.2	25.8	24.4	24.4	25.3	24.8
Migration (%)	2.2	2.0	2.0	2.0	2.0	2.0
Occupied houses (%)	98.9	98.9	98.7	98.6	98.6	98.7
Persons per house	3.8	3.7	3.6	3.6	3.7	3.7
No piped water (%)	1.2	1.3	1.3	1.9	1.8	1.4
Population density (persons/ha)	99.2	86.9	74.8	73.1	69.3	78.0

Table 4. Magnitude of effect modification (city x week) of neighborhood characteristics by city-outbreaks

Neighborhood characteristic	*p*-value
Median age	0.015
Unemployment	0.169
No health service	0.194
No basis education	0.017
Migration	0.407
Occupied houses	0.597
Persons per house	0.715
No piped water	0.902
Population density	0.005

Table 5. Bivariate association between neighborhood characteristics of cases and epidemiologic week (OLS regression) by city-outbreaks

	Hermosillo	Navojoa
	β	β
Median age	0.238***	0.022
Unemployment	0.066***	0.028
No health service	-0.212***	-0.133**
No basis education	-0.105*	0.184
Migration	-0.000	-0.016
Occupied houses	-0.039**	-0.056**
Persons per house	-0.014***	0.071
No piped water	0.079*	0.067
Population density	-1.900***	-0.687*

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

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