Spatio-Temporal Patterns of Dengue Fever in Cali, Colombia

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ABSTRACT

Dengue fever is an arboviral disease typical of the tropics that can be life-threatening and if not controlled properly may result in an epidemic. The absence of an effective vaccine makes strategies to prevent the virus transmission the most effective means of control. The planning of such strategies, however, is difficult due to the constant movement of individuals and mosquito host (Aedes aegypti). In this paper, the spatial and temporal relations that might exist between infected individuals during a dengue-epidemic year are explored. This research is motivated in that a deep understanding of potential transmission patterns between individuals might lead to a better design and planning of control strategies. A GIS-based Health Exploratory AnaLysis Tool (HELP) is used to compute space-time relationships by means of spatial K-function, kernel density, space-time K-function and linking pairs of cases within significant time and space intervals. Significant clustering was observed at a scale of 50 meters and 750 meters, respectively while temporal significance was determined at two days and five to eight days. While an increase of cases occurs in the months following severe droughts due to an El Niño phenomenon, the location of clusters remains relatively stable. These are observed near areas where potential habitats for the mosquito exist such as storm drains, hard surfaces where water accumulates (e.g., vases, containers), but also in poorer neighborhoods. The results from the spatial analysis provide valuable information for health care managers to take preventive actions at the municipality level.

Keywords: Cali-Colombia, Clustering, Dengue Fever, Health Exploratory AnaLysis Tool (HELP), Spatio-Temporal Analysis

INTRODUCTION

Dengue fever is an arboviral disease of considerable importance due to its endemic nature. In recent decades it has grown dramatically, reaching a global presence in more than one hundred countries (Kittayapong et al., 2008), while it remains a threat to more than 2.5 billion people, particularly in tropical and subtropical areas, in rural as well as urban settings. Between fifty to one hundred million people are infected every year, creating a burden to communities and health entities that need to control and prevent the virus from becoming an epidemic (Méndez et al., 2006; WHO, 2009).

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The disease is transmitted to humans by mosquitoes of the genus *Aedes* (Monath, 1988). The mosquito, *Aedes aegypti*, inhabits and reproduces in warm temperature areas generally between 18° and 25° C (Wu et al., 2009). There is a temperature threshold below which the mosquito cannot survive and as temperature increases it is required to feed, which may eventually lead to an increasing rate of biting events. Higher temperatures, therefore, shorten the probability of mosquito survival (Kolivras, 2006). The *Aedes aegypti mosquito* tends to be more active during daytime, especially in the close proximity of houses (Halstead, 1997). The mosquito's habitat is, most often, artificial water holding containers where they develop and lays eggs. This fact ties them to households, given that it is here where these containers are kept to store water for drinking and other household shores (a practice often observed in the developing world countries both in rural and urban areas). This means that transmission is generally focal, clustering in households and nearby neighbors over short periods of time (Kuno, 1995; Getis et al., 2003; Morrison et al., 1998). Only adult females transmit the virus to humans. The incubation period of the virus is around ten days, after which the virus replicates in the salivary glands of the *Aedes aegypti* mosquito. Symptoms of the disease include fever, joint and back pain (which has given the disease the name "break bone fever" (Suarez et al., 2005), severe headache, and nausea (Kolivras, 2006).

Dengue fever studies have focused in understanding patterns between mosquito infected areas and infected individuals (Chang et al., 2009); identifying causal relationships, in particular weather and vegetation (Tipayamongkholgul et al., 2009; Kolivras, 2006; Arboleda, Jaramillo-O and Peterson, 2009; Braga et al., 2010; Johansson, Dominici & Glass, 2009; Maciel-de-Freitas et al., 2010; Maria & Valencia, 2011; Wu et al. 2009); and spatio-temporal patterns of infected individuals (Eisen & Lozano-Fuentes, 2009; Getis et al., 2003; Mammen et al., 2008; Morrison et al., 1998; Rosa-Freitas et al., 2003; Tran et al., 2004; Kan et al., 2008). The disease is known to vary through time and space, due to a number of factors including the human host, the virus, the mosquito vector and the environment (Mammen et al., 2008). Determinant factors in the transmission include: mosquito density, circulating virus serotypes, and susceptibility of human populations (Kuno, 1997).

In the Americas, in spite of efforts to eradicate dengue fever during the 1950s and 1960s (OPS, 1960), a reinvasion occurred following a reduction in surveillance and control strategies (WHO, 1997). Between 2001 and 2007 more than thirty countries reported a total of 4,332,731 dengue cases (Cali, 2010) including the four different dengue serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). In Colombia, in particular, the population living in areas at-risk of contracting the disease amounts to 26,000,000 people. These are areas with an elevation below 1,800 meters above sea level; a total of 900,000 square kilometers out of a total extension of 1,138,000 of the national territory (Colombianos, 2011). Dengue fever in Colombia was eradicated between 1952 and 1966, with a re-infestation occurring in the early 1970s (Romero-Vivas, Leake and Falconar, 1998). Since then the disease has become endemic in many areas presenting periodic outbreaks in 1991, 1994, 1998, 2001, 2006, and the most recent in 2010. This shows an epidemiological cycle every 2 to 3 years through the 1990s. Most of the outbreaks reported have been of serotype 1 (DENV-1) and 2 (DENV-2) (Mendez et al., 2010) but in the last decade 3 (DENV-3) and 4 (DENV-4) have also been present (Cali, 2010).

Cali, the focus of this study, is located 1,000 meters above sea level and is considered as an endemic dengue zone. During 2009 and the first quarter of 2010 more than 7,000 cases of dengue fever were reported with 2,500 being severe (Cali, 2010). By January of 2010 a total of 990 cases had been registered, with 106 cases being of hemorrhagic dengue fever. By week 10 of 2010 the cases had increased to 3,540 from which 296 were severe and 5 fatal (Cali, 2010). At this point the signs of an epidemic were evident and apparently intensified by the presence of El Niño Oscillation (IDEAM Instituto de Hidrología, 2010). This led the health municipality officials to take action and try to understand the environmental factors as well as case reporting and diagnosing, in order to create and design control plans and interventions against the transmission of the disease in the area.

In the absence of a licensed vaccine, emphasis has been given to control strategies, of which the most successful are based on entomological, viral, serologic, and clinical surveillance. Serological and viral surveillance are typically resource intensive and difficult to implement in developing countries. Therefore, with the ultimate goal of an early detection of potential epidemic events, countries with limited resources have focused their control efforts on reducing the mosquito habitat and conduct an active surveillance of the disease (Getis et al., 2003; Mendez et al., 2006). Health officials of the City of Cali adhered to these guidelines and outlined a plan consisting of the following strategies: vector control at at-risk sites in the city, community participation, education, and epidemiological surveillance.

To design and plan such strategies it is necessary to understand the spatio-temporal patterns of the transmission of the disease. Discovering those patterns can also help in understanding underlying social and environmental factors responsible for disease transmission. In particular, focusing on finer scales in space and time is needed to refine dengue surveillance and control strategies (Mammen et al., 2008; Kan et al., 2008). When data on mosquito occurrence is not available using the location of dengue cases can provide a basis for estimating where mosquitoes can be found leading to the identification of transmission patterns (Arboleda et al., 2009; Mammen et al., 2008). Dengue case data can also be of significant value when compared to the prohibitive cost of collecting adult female mosquitoes and the difficulty in identifying the mosquito breeding sites (large artificial water containers located in households (Eisen & Lozano-Fuentes, 2009).

The spatio-temporal methods used in this paper are developed to facilitate the understanding of the mechanisms behind dengue fever, that is they are retrospective. These methods can assist in identifying potential space-time patterns. The aim of the paper is therefore not geosurveillance (Rogerson & Sun, 2011; Yamada et al., 2009), yet from a public policy perspective the results for the space-time analysis can inform health decision makers on planning and design of control strategies to diminish disease incidences, for instance through locally focused prevention at critical times (Delmelle et al., 2011).

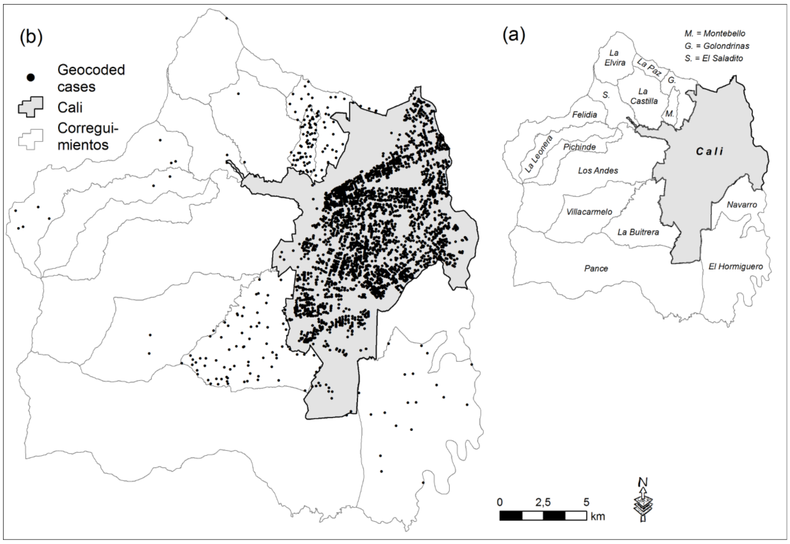
The rest of the paper is organized as follows. The second section describes the study area. The data set and data preparation are explained in a later section. The following section outlines the methodology, while the last two sections present a discussion of the results and a set of conclusions.

STUDY AREA

The city of Cali (Figure 1a) is located in the valley of the *Cauca* river, with its urban area located to the west of the river and contained by the Farallones mountains. Cali has a tropical climate with two rainy seasons. The first, usually from April to July, the second from September to December. The average temperature is 26°C (79°F), with an average low of 19°C (66°F), and an average high of 34°C (93°F) (Cali, 2008). Annual Precipitation reaches 900 mm in the driest zones and 1,800mm in the rainiest, with a city average of 1000 mm which covers most of the Metropolitan area (Cali, 2008). Peripheral areas to the east and west of the city suffer from unplanned urbanization (Restrepo, 2006). To the east multiple neighborhoods are the result of squatter settlements along the river banks (see Figure 2, right). To the west the settlements are in the hillsides of the Farallones mountains.

The city is divided into 22 administrative regions called Comunas (Communes). Comunas are created by grouping neighborhoods with homogeneous demographic and socio-economic characteristics (see Figure 2, left).

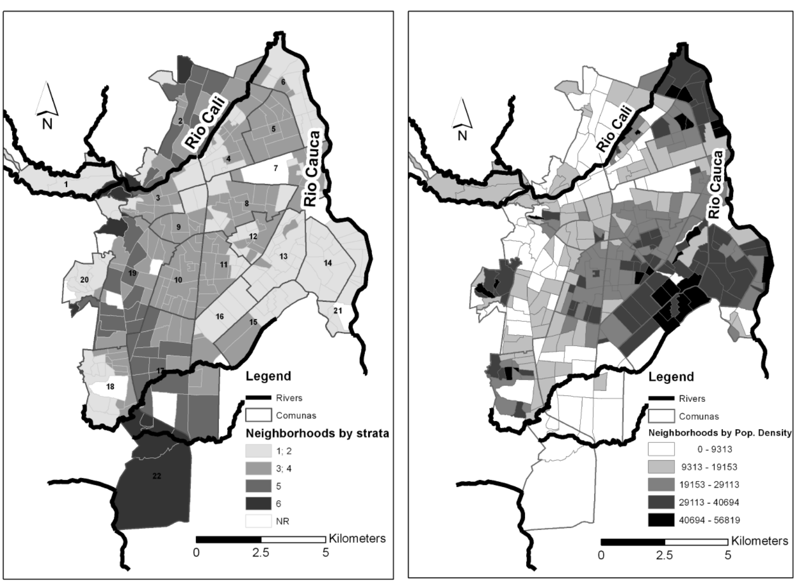
Figure 1. Geocoded cases of dengue fever from January 1 2010 to August 22 2010



Neighborhoods are classified based on their socioeconomic strata into six different classes; strata six representing the highest income group, and one the lowest (see Casas et al., 2010 for a thorough investigation).

Based on data from the health municipality, between 1989 and 2007 the worse dengue fever

Figure 2. Neighborhood stratification by comuna and population information



outbreak occurred in 1995 with 6,433 reported cases (Cali, 2010). After 1998 endemic years occurred less often, and in the last decade there have been only two endemic years that account for 44% of the total cases reported in the last ten years. In 2002 there were 4,358 cases reported (Méndez et al., 2006). This epidemic year was possibly the result of an eight-month period interruption in the vector control program and a climatic anomaly with the El Niño Oscillation. The next epidemic year occurred in 2005 with 2,338 cases and the appearance of DENV-3 (Cali, 2010). In the decade between 1989 and 1998 there were 32,646 dengue fever cases reported in the City of Cali while in the decade between 1998 and 2007 there were 14,946. This is a reduction of 54.2%, which is contrary to what was happening in Colombia and the Americas (Cali, 2010).

Until August 22 of 2010, a total of 9,310 dengue cases had been reported in the epidemiological surveillance system of the health municipality of the City of Cali (Cali, 2010). The health municipality reported these to be the highest in the last 25 years and identified comunas 17, 18, 19, and 22 to be the ones at highest risk of contracting dengue fever, and comunas 13, 14, and 15 to be at the lowest, setting them to face an epidemic year.

DATA SET

The data set used for this project corresponds to the dengue fever cases reported in the "Sistema de Vigilancia en Salud Pública" (SIVIGILA, English: Public health surveillance system) for the City of Cali (provided by the health municipality of the City of Cali). SIVIGILA is, according to the Colombian Ministry of Social Protection: "a set of users, norms, procedures, resources (financial and technical) and human talent, organized for the compilation, analysis, interpretation, updating, dissemination and systematic and on time evaluation of information regarding health events to take proper action" (translation from Spanish by authors) (Social, 2006). SIVIGILA has a set of actors at the national, departmental (a territorial subdivision equivalent to states in the United States), and municipal levels that report on the different aspects of public health surveillance in the country. The areas in which public health surveillance is conducted are: contagious diseases, dietary security, chronic ailments, microbial resistance and drugs, mortality, interventions of interest to public health, chemical substances, and sanitary conditions and other environmental risk factors (Social, 2006).

Cases on dengue fever are reported as part of the contagious diseases surveillance section of the system. Information on dengue fever includes: patient information (name, sex, age, race, address, phone number, neighborhood, patient's occupation), date of diagnosis, epidemiological week, day symptoms started, if patient was hospitalized (if so, includes the date this happened), final condition (dead or alive), movement of the patient in the last 15 days if any, and symptoms. It also includes the reporting institution and patient's insurance information. In this paper only the first set of information will be used as well as the date of diagnosis. The information provided by this system allows health officials to monitor the disease. In particular, the City of Cali health officials prepared a set of protocols to use this information to their advantage with the purpose on identifying areas at high risk of contracting the disease and areas where high mortality was occurring as a result of contracting the disease. Their analysis is based at the comuna and neighborhood level. Their protocol consists of (Cali, 2010):

- A regularly scheduled weekly analysis comparing the current week to the same week in previous years,
- A daily morning and early afternoon revision conducted by an epidemiologist of the reported cases verifying the classification procedures and the measures taken based on the type of dengue case
- A follow up of reported cases conducted via a phone interview in order to identify any potential complications.

SIVIGILA mostly manages information regarding patients through traditional databases, while aggregated information is mapped using current GIS software, often aggregated at the neighborhood level. The system in place does not carry out space-time modeling analysis. In the case of this research the analysis of surveillance data is taken a step further to account for spatio-temporal patterns. It is also conducted at a finer more disaggregate scale, which can aid in identifying patterns and potential causes that might be clouded at a larger scale.

The data corresponds to the first eight months of 2010. The database structure of the SIVIGILA system was modified during the early months of 2010, therefore two different datasets were provided which had to be merged and common fields identified. With the complete data set, the next step consists of geocoding individual cases based on their addresses. The nomenclature for the address system in Cali is very different than in the United States, therefore geocoding to the home address proves to be a challenge. In addition, a large percentage of the addresses were entered in a variety of formats that had to be corrected one at a time. Due to inconsistencies in the quality of the data, a decision was made to geocode to the intersection level using a Geographic Information System (ArcGIS). Geocoding at that level guarantees privacy (Kwan, Casas & Schmitz, 2004), however caution should be adopted when interpreting results from spatial distribution methods, as clustering will de facto occur at very small scales. As such, we expect two spatial levels of clustering: one at very small, focal scale and one at a largest scale. The latter is mapped.

A total of 9310 dengue cases were reported in the City of Cali from January 1 to August 22 2010, as stated previously. Ninety-five percent of the cases were successfully geocoded at three levels of accuracy. The first group contained sixty-six percent of the cases (n=6164), which were geocoded at the closest street intersection level, the second group consisted of twenty-six percent of the cases (n=2448), geocoded at the neighborhood level due to incomplete and incorrect home addresses, while the last group had 207 cases (2%) which were at the rural area level (Spanish: corregimiento) surrounding the city (Figure 1a). For the remaining five percent, the data was missing information making it impossible to geocode. Figure 1b illustrates the spatial distribution of the 8612 cases (level 1 and 2 geocode) with a clear linear pattern for those cases within the city of Cali, along the *Cali* river. Those patients geocoded at the neighborhood levels usually did not provide an accurate home address and were randomly located within their neighborhood, while the patients from the outskirts of Cali were randomly allocated within their respective corregimiento. The latter was not included in the spatial analysis however, due to the low number of cases allocated randomly in such large areas.

Temporal Variation in Dengue Fever

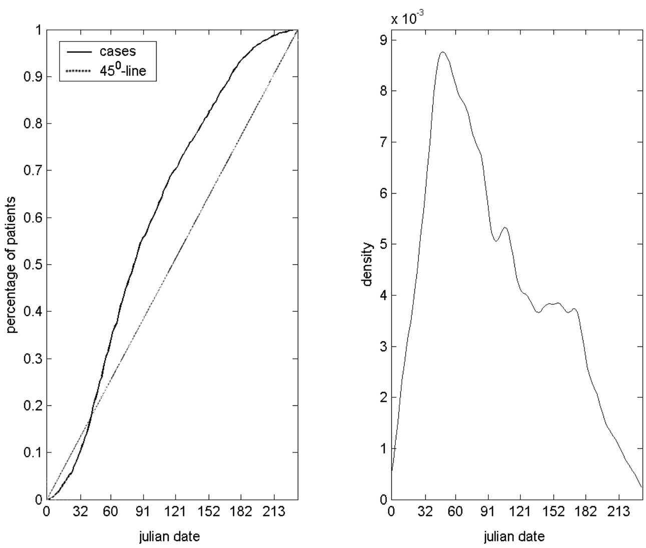
Patients went to the closest hospital for a consultation the same day they exhibited dengue symptoms (fever, joint and back pain). Figure 3 to the left illustrates the cumulative distribution function (CDF) of the dengue cases against the Julian dates corresponding to each individual visit to the hospital when dengue fever was diagnosed (January: 0-31, February: 32-59, March: 60-90, April:91-120, May: 121-151, June: 152-181, July: 182-212, August: 213-234). For a particular Julian date, the CDF represents the probability that an event will occur at a value less than or equal to that date. Figure 3 to the right reflects the probability density function (PDF), or the likelihood that an event occurs at a particular time. Few individuals were diagnosed with dengue in the early weeks of January, but a rapid increase was noticed in the month of February and a decline of cases in the summer months starting in May. The prevalence of the disease in February can be associated to the lack of rain, temperatures of 23 Celsius or higher, and most importantly the El Niño phenomenon that made the incubation period of the virus shorter resulting in a propagation of the virus[1]. As is well known, the

Aedes aegyti requires hard surfaces with water deposits (such as tires storing water, vases, storm drains, other water containers) to lay its eggs, therefore a day with minimal rainfall followed by hot dry days creates an environment for the mosquito to thrive (Cali, 2010).

The outbreak in mid-February can be explained in part by the favorable weather conditions for the reproduction and transmission of the virus. Towards the end of January, rain allowed eggs that had been laid by the mosquitoes earlier in the month to progress through their life cycle (larvae and pupae). After this rain period a dry period occurred, which gave enough time for the pupae to fully develop, become mosquitoes and start feeding[2]. Hot temperatures are known to increase the feeding and incubation period of the mosquito (Kolivras, 2006; Chang et al., 2009). This weather pattern that covered a two week span (last week of January and first week of February, repeated itself in the second week of February, making this month the most vulnerable (IDEAM Instituto de Hidrología, 2010). The number of cases begins to decline when the rainy season approaches in mid March, a month characterized by the lack of rain. Another reason for the decline in the number of cases after the February outbreak, is the quick response by the health municipality. After identifying the increase in number of cases in the month of February, the health officials set in motion a plan to control the mosquito habitat and follow every case that was reported.

Figure 4 summarizes the cumulative distribution function for all dengue fever cases by age. Although several factors increase the risk of contracting dengue fever, such as age and previous exposure to the disease (Ospina, Diaz, & Osorio, 2010), natural breaks occurred in the distribution of cases as a function of age (see also Morrisson et al., 1998 and Mammen et al., 2008). The children age group (18 years old or less) represents half of all reported cases. This population group is more susceptible to contracting the virus given their lack of exposure and immunological defenses to the serotype DENV – 2, which had not circulated in the area in more than a decade (Cali, 2010, See also Mendez et al. for a discussion about the presence of the different serotypes in Colombia). There are far

Figure 3. Cumulative distribution function (left) for dengue cases and associated probability density function (right)



fewer cases reported for the elderly population (only ten percent of the cases are for individuals of 55 years or more).

SPATIAL AND SPACE-TIME MODELING

To estimate whether dengue cases exhibit dispersion, randomness or clustering, the K-function is utilized, which explicitly considers inter-separation distance between dengue events, while the amount of clustering is computed at various scales (also called radii) (Bailey & Gatrell, 1995). The K-function determines the scale at which the magnitude of clustering is maximum. To compute the statistic, a circle of a specified radius *(h)* is placed over each point in the set *(i)*. Events within this radius *(j)* are counted and the circle is moved to the next event, repeating the process sequentially. For all (*n*) existing cases, the radius is increased and the process continues in a similar fashion until a specified maximum radius is reached (Delmelle, 2009). Specifically, the K-function is defined as:

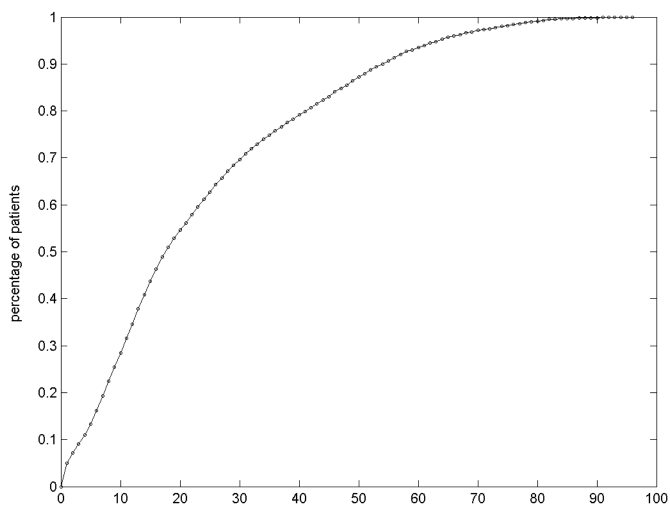
$$\hat{K}(h) = \frac{A}{n^2} \sum_{i \neq j} \sum I_h(d_{ij}), \quad (1)$$

where d_{ij} is the distance between two dengue cases i and j within the study region, A is the size of the study area, and $I_h(d_{ij})$ an indicator function defined in Equation 2 as:

$$I_h(d_{ij}) = \begin{cases} 1 & if \quad d_{ij} \leq h, \\ 0 & o.w. \end{cases} \quad (2)$$

The value of $\hat{K}(h)$ can be graphed against different radii values (h) to estimate at what distances the point pattern exhibits randomness, clustering, or dispersion. To confirm whether the observed pattern is statistically significant, a high number of Monte Carlo simulations (randomly distributed points throughout the study area) must be performed to which the same statistic is computed. For each random simulation, the K statistic is calculated at each distance interval, and the upper and lower en-

Figure 4. Cumulative Distribution Function for dengue cases by age



velopes of the Monte-Carlo simulations are reported. Assuming a random process, the expected number of cases within a distance (h) of a randomly chosen patient would be $\lambda\pi h^2$, where λ is the Poisson parameter, reflecting the intensity of the point process. Given that the value of $K(h)$ may be greater than πh^2 when events are clustered, the estimated value of $K(h)$ is compared from its theoretical value $K(h) = \pi h^2$, by estimating an L-function, informing on the scale at which the magnitude of clustering is maximum (Delmelle, 2009):

$$\hat{L}(h) = \sqrt{\frac{\hat{K}(h)}{\pi}} - (h) \tag{3}$$

Clustering results give valuable information on the scale at which clustering is predominant, but do not provide explicit geographic information as to where clustering is occurring. A kernel density function can be thought of a "heat map", and visualizes the location of clusters, by overlaying a grid on a map and reporting the density of events in the neighborhood (also called bandwidth τ controlling the amount of smoothing). The size of τ is determined by using the value of (h) corresponding to the greatest value of the L-function (Delmelle et al., 2011). Mathematically, the kernel density at a grid point is denoted $\hat{\lambda}_\tau(g)$ and estimated in Equation (4), where d_i is the distance from an event *i* to the gridpoint *g* (Bailey and Gatrell, 1995):

$$\hat{\lambda}_\tau(g) = \sum_{h_i \le \tau} \frac{3}{\pi\tau^2}\left(1 - \frac{d_i^2}{\tau^2}\right) \tag{4}$$

Spatio-Temporal Analysis

The K-function and associated Kernel heat map density function inform on the scale and magnitude of the concentration of dengue cases, yet they do not provide insight on process dynamics. Since the day of hospital visit is reported in the database, dengue cases have a time stamp associated with them, making it possible to further investigate whether a space-time link exists between two events. For dengue for instance, there is a strong correlation between the time of disease infection and the distance separating events because the mosquito can travel limited distances (Chang et al., 2009; Koenraadt et al., 2008). It is important to quickly detect and identify origins of patients exhibiting a similar disease to provide health care assistance and more importantly eradicate the source of the infection, in this case the *Aedes Agypti* mosquito. A logical approach to test for space-time clustering is by using a bivariate "space-time" K-function, which now integrates the temporal dimension into the K-function. As discussed in Delmelle et al. (2011), the Knox and Mantel tests are usually used to confirm space-time clustering at a given distance and time. The space-time K-function however evaluates the strength of this clustering for a range of space and time intervals, which is computationally more intensive. Space-time interaction is computed at different time windows (*t*) and distance intervals (*h*) (Bailey & Gatrell, 1995; Boots & Getis, 1988). A count statistic tests the hypothesis that space and time are independent from one another, once the scale at which clustering is the highest has been identified. In other words, the space-time K-function evaluates whether there is an interaction among the location of individuals presenting dengue symptoms, and the day they visited the hospital for diagnosis. Due to the nature of the disease, it would be expected that individuals diagnosed with dengue fever who live close to one another are likely to visit the hospital in a similar period of time, while patients living far away from each another would probably be less likely to visit the hospital simultaneously (Bailey & Gatrell, 1995; Casas et al., 2010). The space-time K-function is computed as:

$$\hat{K}(h,t) = \frac{L \cdot R}{n^2} \sum \sum_{i \neq j} I_{h,t}(t_{ij}, d_{ij}) \tag{5}$$

with the indicator function $I_{h,t}(t_{ij}, d_{ij})$ defined as:

$$I_{h,t}(t_{ij}, d_{ij}) = \begin{cases} 1 & if \quad (t_{ij} \leq t\ AND\ d_{ij} \leq h), \\ 0 & o.w. \end{cases} \tag{6}$$

The value in Equation 5 will increase with increasing intervals of time (t) and distance (h). When there is no space-time interaction, Equation (5) reduces to the product of the spatial K-function and its temporal counterpart, namely $\hat{K}(h) * \hat{K}(t)$, while a test for space-time dependence can be conducted by subtracting the product of separate spatial and temporal K-function $\hat{K}(h) * \hat{K}(t)$ from the combined space-time K-function (Gatrell et al., 1996):

$$\hat{D}(h,t) = \hat{K}(h,t) - \hat{K}(h) * \hat{K}(t) \tag{7}$$

ANALYSIS AND DISCUSSION OF RESULTS

Spatial and space-time analysis was computed using the Health Exploratory and anaLysis tool for Practitioners (H.E.L.P.) module, specifically developed by Delmelle et al. (2011) for the purpose of analyzing point events. H.E.L.P. is an ArcObjects-based application (ArcGIS, ESRI), built to tightly interact with Matlab, a powerful matrix software. While ArcGIS performs the GIS functionality (that is kernel density and mapping interdependent space-time cases), Matlab is used to determine the scales at which space and spatio-temporal clustering are the greatest. The communication between the two occurs via COM objects.

Spatial Analysis

Figure 3 clearly indicates a monthly trend in dengue occurrences, and hence cases were partitioned into one-month interval. To estimate the spatial clustering at each month, a K-function and associated L-function were derived in H.E.L.P. (Delmelle et al. 2011), first for a range of 50 meters to 10,000 meters with intervals every 100 meters with strongest clustering systematically observed at 750 meters except in August. Given the small-scale nature of the disease however (Morrison et al., 1998), the analysis was repeated at scales from 0 meters to 500 meters, with a smaller separation of 25 meters. Estimating clustering at small separation distances is motivated by the fact that adult female mosquitoes (the ones transmitting the disease) generally travel a short distance from where they first feed and lay their eggs (Chang et al., 2009; Koenraadt et al., 2008). Hence, individuals that live closer together are more likely to interact than individuals that live far apart becoming more susceptive to infection. A total of 100 simulations were run; at any given scale, if the estimated L-function is above these two envelopes, clustering occurs at that scale, but if between the envelopes the pattern is considered random. The L-function reinforces that strong clustering occurs at two distinct scales: one at a relatively medium distance of 750meters (not shown here, yet roughly coinciding with the neighborhood scale), and one at a short separating distance of 25 meters, which can partly be explained by (1) the geocoding process which forces addresses to match at the closest block intersection level, (2) the infectious nature of the disease and (3) the limited range of the vector. This is also confirmed by the high probability function of small separation distances (at a separation distance of zero, the L-function equals zero).

HELP produces kernel density maps using the optimal kernel bandwidth τ. HELP assists the user in identifying the distance at which the L-function departs the most from simulation envelopes; at that distance the magnitude of clustering is usually the strongest. Kernel maps for each month were combined together in Figure 4 AND Figure 5 and a similar pattern is observed throughout the months, yet the magnitude decreases after the month of April. For each month, a few clusters are observed and assigned a number. The five clusters are located in areas with two characteristics in common: (1) there is a concentration of vulnerable populations (non-African descent, See Figure 6) and (2) the areas present favorable conditions for the mosquito to breed. Breeding sites can emerge where there is any kind of standing water combined with hard surfaces where the female mosquito can attach to lay her eggs. Standing water can result from water storage containers where people do not have the proper sewer system or from waste water channels where trash and soil banks result in stagnant waters (storm sewers are part of the later). The first cluster occurs in the northern part of Cali directly to the South of the *Cali River,* a river flowing through the city, draining into the *Cauca River*. Cluster number 2 is also directly located to the south of *Cali River*, but also in close proximity of *Parque de la Cana*, an attraction park with several swimming pools and small ponds. These first two clusters have in common that people in these areas tend to live in crowded rooms with poor water supply making them a more vulnerable population (Cali, 2008). Cluster number 3 is in a strategic location west of *Planta de Purificación*, a water treatment plant, which is next to an air force base where there is a concentration of population. Clusters number 4 and 5 occur around a military area (*Ejercito Tercera División*) that has a small water channel running through and are close to the foothills where a high percentage of the population resides in poor quality and overcrowded housing.

Although the intensity of the pattern fluctuates over time (stronger in February and March, and much weaker in July and August), the spatial pattern is stable. There is no evidence of a relationship between dengue cases and the income levels of the neighborhoods, which supports findings by Rosa-Freitas et al. (2003) of dengue being found even in high-income neighborhoods. This can be the result of prevention and control strategies set in place by the health municipality when the February outbreak occurred. The municipality put in place a plan to fumigate storm drains in neighborhoods of low strata every fifteen days. Therefore, clustering is better explained, in the case of the City of Cali, by high population concentrations (see Figure 2), in particular in areas where the population is not characterized for being of African descent (i.e., mestizo, rom, indigenous, see Figure 6). People from African

Figure 5. Kernel density maps for each month, using a bandwidth of 750meters, keeping the legend similar for each time period

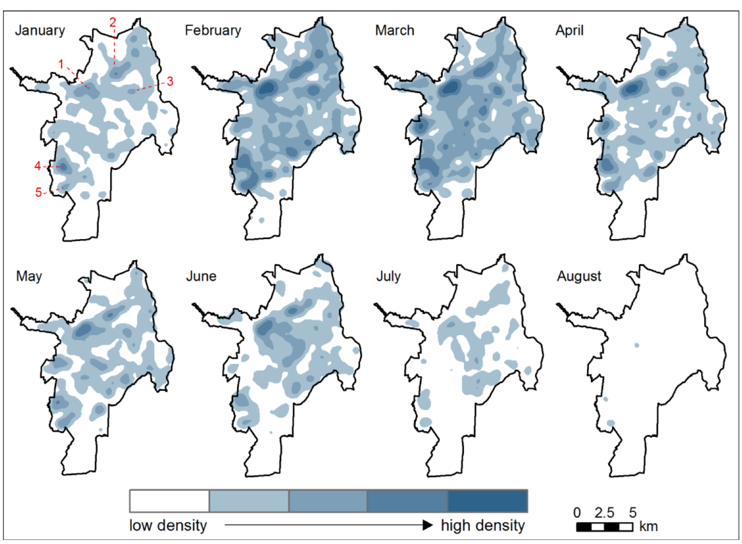
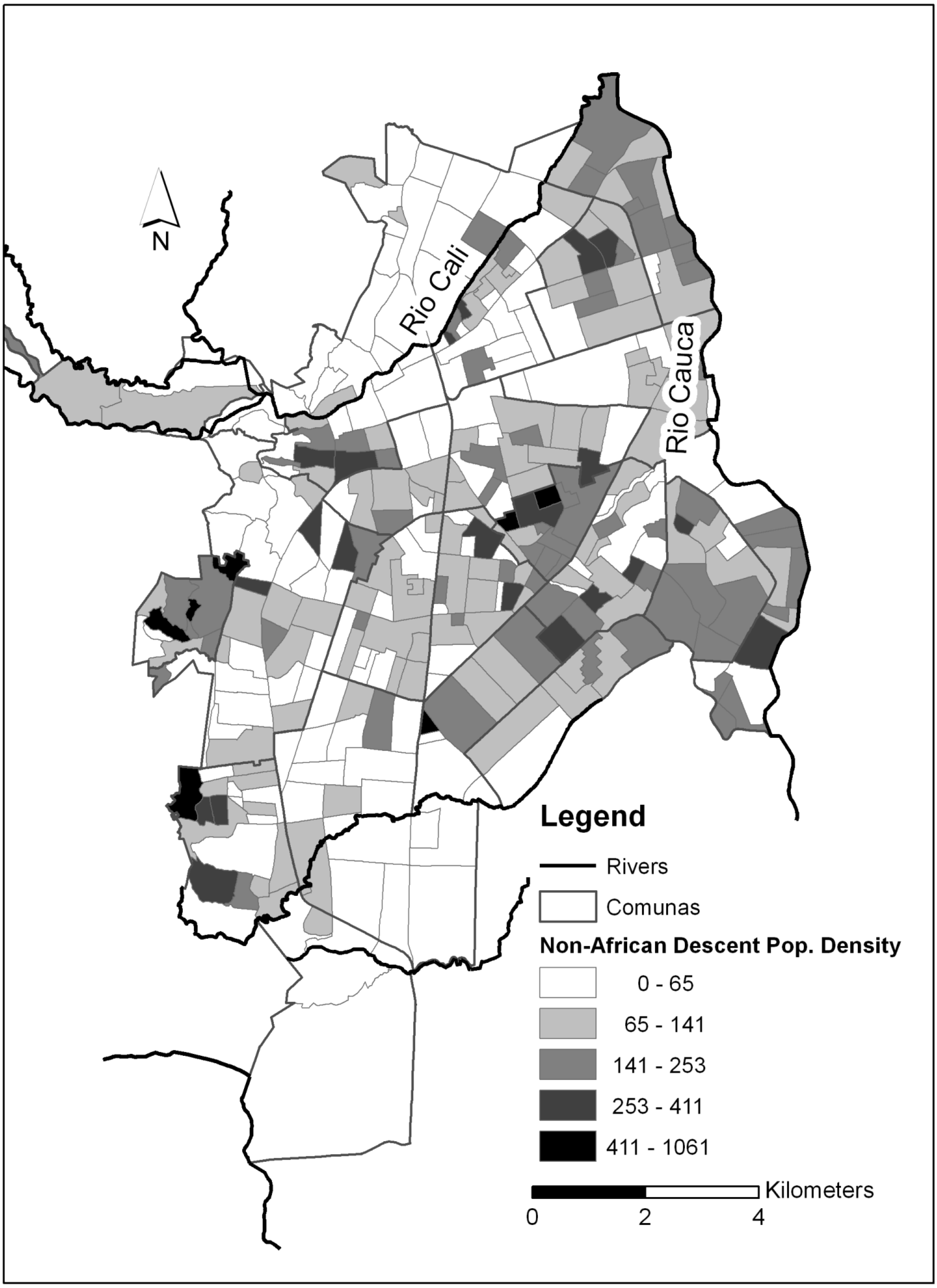


Figure 6. Non-African descent population totals (as reported to the Census including missing data)



descent have shown to be less likely to contract the virus than people from other races (Cali, 2010). The results presented here support the original observation made by the municipality in Cali (2010), where they identified comuna 18 as being on the list of comunas at highest risk of contracting the virus.

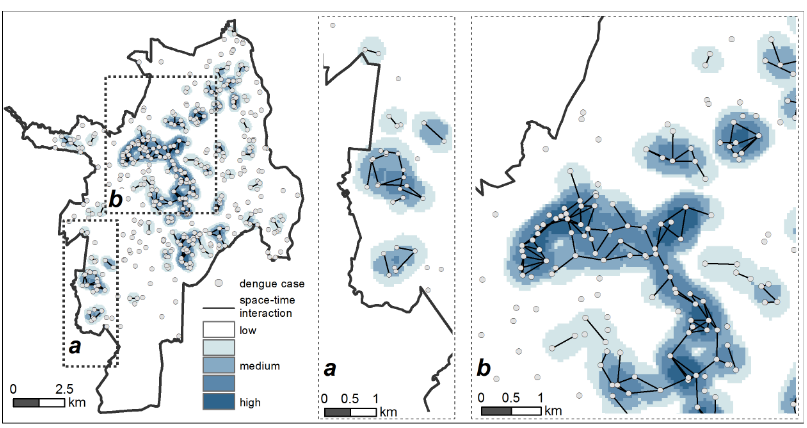
Spatio-Temporal Analysis

Dengue appears to spread rather quickly around specific sources, which correspond to infected female mosquitoes. Female mosquitoes that have had their first blood meal are to start oviposition approximately after three days, when they typically leave the house (or living quarters) to go outdoors to lay their eggs (Morrisson et al., 1998). Therefore, a temporal pattern is expected to emerge at a three day interval. A probability density function for all dengue cases confirms these results, exhibiting highest values at a separation of two days, sustained for six to seven days. Beyond this time separation, the relationship decreases rapidly.

A space-time K-function was computed on monthly partitioned datasets; we illustrate its interaction in Figure 7. Dengue counts are lower during the month of July, but clustering analysis is significant. The results provide valuable knowledge on the strength of space-time interaction, which is crucial to facilitate the understanding and modeling of contagious diseases. A temporal wave-like pattern is observed, but quasi-linear distancewise, which confirms literature findings indicating that the incubation time and oviposition phenomena is stronger at six days of interseparation time (Aldstadt, 2007; Kolivras, 2006). When population lives close to stagnant water, it is not surprising to see this pattern. In other words, a greater interdependence exists between patients who are diagnosed at two to three days intervals, and again at six days.

H.E.L.P. is used to map space-time clusters for those cases in July separated by two days and 550 meters, using a mapping pair function (Delmelle et al., 2011). A linear kernel density visually reinforces the strength of this space-time interdependency. Figure 7 to the right reveals that the majority of the pairs are located in the vicinity of the City Center, but the middle figure denotes strong interdependency among patients at the military base. These two locations are characterized by high concentrations of population of non-African descent. Mapping space-time pairs provide valuable tool for decision makers; especially in understanding the dynamics of a disease and identifying potential sources. In this case, for example, both areas

Figure 7. Space-time interaction for patients exhibiting symptoms of dengue in July 2010. Cases separated by 2 days and 550meters are linked. The zoom-in areas are for clusters 1 and 5, respectively (see Figure 5)



(East and West) share similar environmental conditions, with water deposits in homes that allow the incubation of the virus.

CONCLUSION

In this paper the dynamics of dengue fever in Cali, Colombia have been investigated for the first eight months of 2010. A database with addresses and data of visits was made available by the Public health surveillance system for the City of Cali. There was a clear pattern indicating an increase of cases in the weeks following an intense period of rain and drought, but also a clear age group difference. Dengue cases were geocoded at the street intersection level or neighborhood level, mapped in Geographical Information System. A module tightly coupling ArcGIS and Matlab was used to estimate and map clustering in space and time, while linking those cases showing strong interdependency.

Five clusters were identified. The first around the *Cali river*, the second near the water park, the third next to the airforce base, and the last two in and around the military base. Regardless of the month under analysis, these clusters remain stable indicating the prevalence of a population highly susceptible to the virus. It also indicates that these areas form a more favorable habitat for the mosquito to breed, especially if the storm drains are in closer proximity to the homes and this is particularly the case in Cali. The space-time clustering analysis confirms the cyclic pattern of the disease that was the strongest at two and six days intervals.

Even though this research did not have as an objective to identify the potential factors that produce the observed clusters, a set of hypotheses can be considered. As mentioned earlier, the five clusters have concentration of vulnerable populations that live in areas favorable for the mosquito to breed. This suggests areas with a high population density, where sewer infrastructure and utilities are minimal are at a higher risk of contracting the virus. These groups tend to live under poor sanitary conditions and to make up for the lack of basic services are forced to surround themselves with stagnant water, a perfect habitat for the mosquito. In these areas in particular, and in others around the city (like the military base) there are waste water channels. These are concrete structures, not too far away from the houses, where water deposits form. Especially when a rainy day is followed by a dry period, these channels can become breeding grounds for the Aedes Agypti. A different hypothesis to examine is to consider that the infected individual came from a different area, allowing the infection to spread. This could potentially have happened in areas where the population is more mobile, like the military and army base cluster areas.

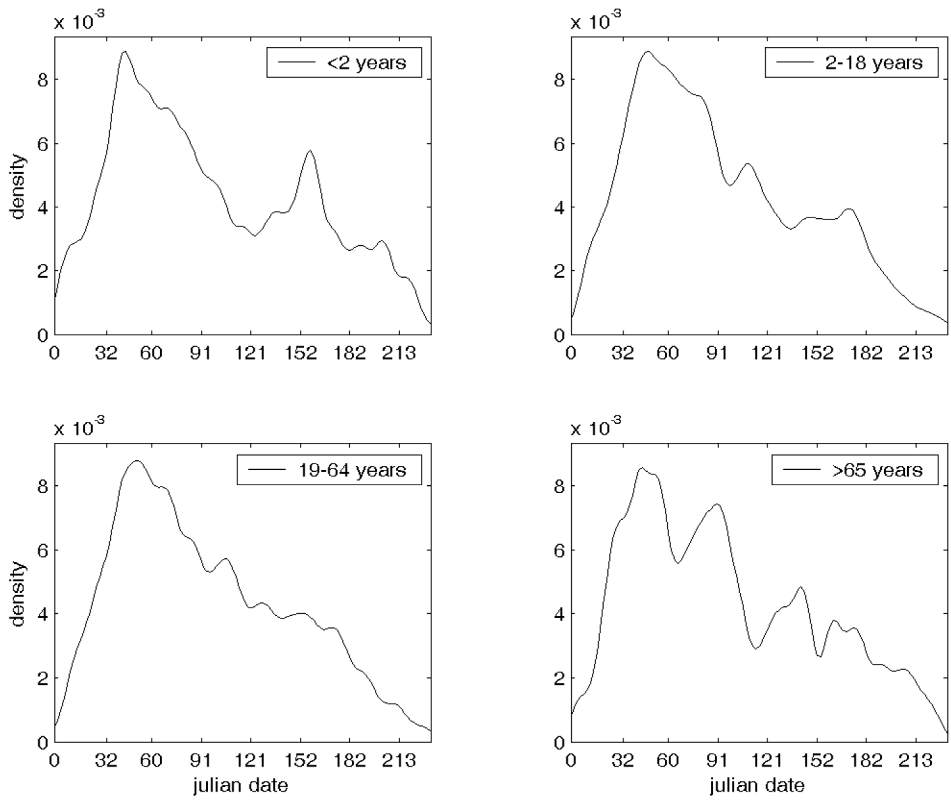
Active dengue surveillance through an application of a set of protocols for monitoring and analysis of information, allows for the detection of signs that can alert health officials to what areas can be at high risk of contracting the disease as well as where high mortality rates are taking place. With this information they can plan and act accordingly. Given a limited budget, this research indicates that the strength of coupling a Geographic Information System with space-time methodology can help identify the emergence of a potential epidemic.

The methodology presented in this paper can also be used as a base for planning control and prevention strategies targeted to particular areas of the city that have exhibited certain patterns. For example, the health municipality of the City of Cali could design strategies that focused in particular ethnic groups (i.e., people from non-African descent) that appear to be at a higher risk. They could work with the utility company to identify areas with poor infrastructure, where the virus is concentrating and try to propose a solution that can help the community. They could also target education plans on how to keep living spaces clean to avoid mosquito breeding sites. In terms of controlling the mosquito habitat, this methodology and analysis can help in deciding the distribution of resources. There are three types of spraying sites: outside public spaces (to kill larvae), inside of houses, and places where there are human concentrations like schools (the last two to kill the adult mosquito). By being able to identify where clusters are more resources can be allocated to those areas to increase control. And most importantly, having a methodology in place which provides results and information for the planning of control strategies will push the local government to maintain continuity in funding such initiatives. In the past, lack of funds became an impediment for the implementation of effective control strategies which resulted in an increase in the transmission of the virus (Cali, 2010).

Dengue incidences on different age groups was also investigated, specifically those children less than two years old, children from 2 to 18 years of age, adults from 19 to 64 years and the elderly population group (Figure 8), indicating a sharp increase in mid-January with a peak of cases during the middle of February, with a constant decline starting around mid-March. A notable exception, however, is for the first age group (children <2 years old) where the peak is much narrower and a second increase is observed at the end of May. Finally, the elderly group exhibits various fluctuations. From Figure 8, it is evident that it will be critical in future research to incorporate population densities, age and race to identify. A better understanding of the relationship between incidence and population characteristics can redefine prevention measures. Current research focuses on applying the methodology suggested in this paper to these different cohorts.

From a methodological perspective, directions for future research need to incorporate habitat information, for instance point source diffusion modeling with a certain rate of occurrence (Elliott et al., 2001), similar to

Figure 8. Probability Density Function of dengue fever cases by age groups



geostatistical models recently proposed in Goovaerts (2005). Finally, given the scale at which we geocoded dengue cases, caution must be adopted in interpreting results from the spatial distribution analysis. It is recommended to improve clustering and kernel density estimates when the underlying population densities are varying spatially as suggested in Bailey and Gatrell (1995).

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ENDNOTES

1 Weather data obtained from: http://clima.meteored.com/clima-en-cali+alfonso+bonill-802590-2010-Noviembre.html

2 http://clima.meteored.com/

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