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Dengue Epidemiology In An Urban Slum Community In Salvador, Brazil

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DENGUE EPIDEMIOLOGY IN AN URBAN SLUM COMMUNITY IN SALVADOR, BRAZIL

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ABSTRACT

Brazil has experienced a major increase in the incidence of dengue fever and severe dengue since the mid-1990s. Due to incomplete vector-control and transmission prevention efforts, all four serotypes of the dengue virus now circulate in Brazil [1]. Communities such as Pau da Lima, an urban slum in the city of Salvador, Brazil, face a high burden of disease. Beginning in 2009 enhanced surveillance for dengue fever and other acute febrile illnesses has been conducted at the São Marcos Emergency Center (CESM), the only public urgent care health center in Pau da Lima. This sentinel surveillance site serves as a model for acute febrile illness surveillance site for Brazil and other dengue-endemic countries. However, dengue epidemiology and patterns of disease transmission within the community are poorly understood. The objective of this study is to assess dengue risk factors by comparing the demographics of laboratory-confirmed dengue patients with the population of patients who presented to CESM with fever within a two-year period, from January 2009 to December 2010. A total of 282 laboratory-confirmed cases were identified. Univariate logistic regression revealed that young age, brown/mixed race, lower income, and fewer self-reported days of illness at the time of presentation were statistically significant predictors of dengue infection. Dengue cases were significantly clustered in space and time, indicating local transmission of dengue within and between households. The presence of these factors serves as an impetus for targeting vector control and other preventive measures in this community and throughout the rest of the city.

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OBJECTIVES

The objective of this study is to identify risk factors and describe the spatio-temporal patterns of dengue fever in an urban slum community. This objective was evaluated through the following specific aims:

1) To perform descriptive analysis of a population of patients who presented with acute febrile illness due to dengue from January 2009 to December 2010.
2) To assess risk factors for confirmed dengue.
3) To map and assess spatio-temporal patterns of disease.

INTRODUCTION

Dengue virus (DENV) is a re-emerging infectious agent that causes dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). This vector-borne disease is caused by a single-stranded RNA virus belonging to the genus *Flavivirus*, of the family *Flaviviridae*, which contains about 70 viruses including Yellow Fever, Japanese Encephalitis, and St. Louis Encephalitis [2]. Two and a half billion people, over 40% of the global population, are at risk for dengue infection and this number continues to rise [3-5]. Dengue is endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia and the Western Pacific [3, 4]. The disease affects people across all socioeconomic levels, but the disease burden may be highest among poor communities with inadequate sanitation, lack of a reliable water supply, and conditions that favor breeding of the mosquito vector [4, 6, 7].

The virus is transmitted to humans, the main amplifying host, through the bite of an infected female *Aedes aegypti* mosquito. These mosquitoes are highly domesticated vectors that feed, rest, and breed largely inside or around human habitation. *A. aegypti* prefer clean, manmade sources of water for breeding, such as plastic containers that store water, discarded disposable containers, bottles, and used tires [8]. Rapid urbanization has led to an increase in the number and size of urban slum communities, leading to ideal conditions for vector populations and enhanced disease transmission [9]. Substandard housing construction, high population density, inconsistent waste management and unreliable fresh water supplies pose challenges to *A. aegypti* vector control in tropical urban slums. Dengue virus is endemic within the geographic range of *A. aegypti* between latitudes of 35° N and 35° S. Up until the mid-1990s, Southeast Asia was the area most heavily affected by dengue in the world. Since then, the incidence of disease has heavily increased in both Central and South America, with a significant burden of disease localized in Brazil [1].

Infection with a dengue virus can produce a spectrum of clinical illness, ranging from a nonspecific viral syndrome to fatal hemorrhagic disease [10]. With the wide range of clinical

presentations and the high percentage of non-apparent cases, it is difficult to quantify the burden of disease [11, 12]. Most patients infected with dengue experience asymptomatic or self-limited flu-like symptoms, which only rarely progress to severe disease or death. Sudden onset "breakbone fever" and a variety of nonspecific signs and symptoms such as frontal headache, retro-orbital pain, myalgias, nausea, vomiting, arthralgias, weakness and rash are common symptoms [9, 13]. Symptoms last on average 2-7 days following the 4-7 day incubation period of the virus after a bite from an infected female mosquito. Approximately 2% of clinical apparent dengue cases progress to severe dengue. Hemorrhagic manifestations may range from mild, such as skin petechiae or purpura, to severe mucosal bleeding, hematuria, and gastrointestinal hemorrhage [9, 14]. Shock symptoms, which are potentially fatal are due to leakage of blood plasma, fluid accumulation, respiratory distress, severe hemorrhage, or organ impairment [3].

There is no specific treatment for dengue fever. Treatment interventions are mainly supportive, with a focus on rehydration therapy [4]. Oral rehydration, or in some cases cautious intravenous fluid resuscitation, is the therapy of choice. Patients should also be monitored for severe symptoms that may require additional treatments such as blood transfusion or other resuscitative measures [4]. Antipyretic therapy is another mainstay of treatment and is administered for patient comfort. While most patients are managed conservatively, DHF and DSS patients are at risk for serious complication and require close monitoring [4].

There are four distinct but closely related serotypes of the virus, DENV-1, DENV-2, DENV-3, and DENV-4 [4, 15, 16]. Infection with one serotype confers lifelong protection against that particular serotype, but does not confer long-term or complete cross-serotype immunity. Subsequent infection with a heterologous serotype of dengue virus is associated with the more severe clinical disease manifestations seen in DHF and DSS [13, 17]. Although the pathogenesis of severe disease is controversial, antibody dependent enhancement has been proposed as the mechanism for this phenomenon [17, 18]. This hypothesis states that individuals exposed to a second serotype of the dengue virus have a significantly higher risk for developing DHF and DSS because preexisting dengue antibodies recognize the infecting

virus, forming antigen-antibody complexes. The complex is internalized by immunoglobulin Fc receptors on the surface of leukocytes, especially macrophages, where the virus is free to replicate once inside. The affected cells produce and secrete vasoactive mediators in response to infection that are responsible for the more severe manifestations of disease [17, 19]. These severe forms of illness are the consequence of a very complex mechanism where virus and the host's immune response interact, and are seen in 2–4% of individuals with secondary infection [20].

Dengue surveillance

The fundamental goal of dengue surveillance is to monitor incidence of dengue transmission to guide treatment and prevention efforts in the community [21]. Additionally, surveillance provides information on disease severity, can be used to assess the cost-effectiveness of public health interventions, and to estimate the burden of disease in a community [21]. A key endpoint of dengue surveillance is to act upon the information obtained from surveillance by triggering mosquito control efforts and mobilizing a health care response [21, 22]. Compared to passive surveillance systems, active surveillance has better sensitivity to identify cases during inter-epidemic periods, when clinical suspicion of disease is low [23]. A "lag phase" is seen in the period between the initial increase in incidence and the beginning of epidemic transmission. This is a critical time to deploy disease prevention efforts. If effectively applied at this time, vector control efforts can reduce transmission of the disease by impacting the number of dengue-carrying mosquitoes.

After cessation of aggressive *A. aegypti* eradication in the 1950s and 1960s, *A. aegypti* and the dengue virus were reintroduced to Brazil in the late 1970s [1, 10]. The intensification of dengue control by the Brazilian Ministry of Health since re-emergence has not curbed the spread of the disease, and now all four serotypes of the dengue virus have been circulating in Brazil since 2010 [1]. The number of cases remains alarming, with 61% of the world's cases reported in Brazil from 2000 to 2005 [1, 3]. Gaps in knowledge in the epidemiology of dengue in both human and mosquito populations remain. Further study

of the transmission dynamics of dengue in Brazil are needed to understand how to generate effective vector control programs and educational campaigns. Active surveillance sites such as CESM site in Pau da Lima provide enhanced detection of dengue incidence and disease patterns that can be used to direct efforts to prevent dengue transmission in a critical period before widespread outbreaks.

Dengue transmission

The goal of spatio-temporal analysis in the study of dengue fever is to identify patterns of local transmission that can provide insights into the biological and ecologic mechanisms that drive transmission [24]. Cases that are clustered in space and time within biologically realistic parameters can be identified as transmission events. Sequential transmission of dengue among individuals who live near one another is likely attributable to multiple factors, including mosquito-driven spread and short-distance mobility of viremic humans [25, 26]. The identification of high-risk spatial areas can help guide local health departments to formulate public health interventions, initiate early preventive measures and conduct enhanced surveillance in an effort to reduce transmission and the event of a more widespread outbreak [27-29].

Relevant parameters for spatio-temporal analysis include the time course of dengue virus' incubation and the flight range of its mosquito vector. The intrinsic and extrinsic incubation periods are two temporal parameters that can influence clustering of cases. The intrinsic incubation period, or the time in which the dengue virus completes its development in the host, ranges from 4.5 to 7 days [18, 30]. The extrinsic incubation period is the period between a mosquito's bloodmeal from a viremic person to the time it can infect a susceptible host; for dengue this has been determined to be approximately 11 to 14 days [18, 30]. By combining the intrinsic and extrinsic incubation intervals the time period that is relevant to secondary transmission can be determined and has been cited as 20 days [25].

Dispersal distance of *A. aegypti,* the main mosquito vector of dengue in Pau da Lima, is another important parameter in the spatio-temporal analysis of dengue. The dispersal distance of *Aedes* has been

measured in a number of studies using a number of different methodologies in a variety of settings. Based on several mark-release-recapture studies the maximum flight distance of *A. aegypti* ranges from 154 to 1,207 meters [31, 32]. In a study in an urban environment in Rio de Janiero, Brazil, Honório et al. concluded that *A. aegypti* have a flight range of at least 800 meters [33]. The wide variety and inconsistent results of maximum flight distance does not establish a clear consensus for the dispersal patterns of *A. aegypti* [32, 34, 35].

While some studies identify the maximum flight distance of *A. aegypti* or the average daily flight distance, the most informative data are those that look at the mean flight patterns. Many studies indicate that the flight range of *Aedes* is generally < 80 meters [36-38]. To this end, strategies for vector control for *A. aegypti* have mainly focused on dispersal distances of 50 to 100 meters, and have been found to be effective [35, 39, 40]. To achieve maximum benefit from vector control efforts, an accurate dispersal distance must be considered for the community of interest. Therefore it is imperative to determine the patterns of disease dynamics specific to the community of Pau da Lima, and consider a range of possible *Aedes* dispersal distances.

Clustering of dengue cases and mosquitoes in space and time has been observed in a variety of settings. Early epidemiological studies described the clustering of cases within households and an apparent diffusion through communities from first observed cases [26]. More recent studies have quantified the spatio-temporal dimension of dengue transmission within complex urban environments and have identified both origins of outbreaks and optimal locations for control operations [25, 41]. The interaction of clustering of dengue cases and areas of mosquito reproduction is also an important consideration in the space-time dynamics of dengue transmission [42, 43].

Dengue control

Due to the rapidly increasing public health importance of dengue widespread research has been dedicated to its control [44]. Several studies have identified that vector control in many communities is insufficient and in need of further development to become successful [45-47]. Traditional control measures, including elimination and treatment of breeding habitats and insecticide spraying must be implemented at the appropriate space-time scale to effectively interrupt transmission in a given community [9, 48-51]. The dynamics of dengue transmission in Pau da Lima need to be further characterized in order to deploy the most effective vector control and disease prevention efforts.

METHODOLOGY

Study area

Pau da Lima is an urban slum community in the coastal city of Salvador, Brazil (city population 2,675, 656; 2010 Brazilian Institute of Geography and Statistics (IBGE National Census). Salvador was founded in 1549 as the first national capital of the Portuguese colony of Brazil. The city remained the last Portuguese stronghold during the war for Brazilian independence until 1823 [52]. Today it is the largest city in the state of Bahia and the third most populous in the country. It has a tropical climate throughout the year and is generally warmest January through March (average low temperature ~75 ^{o}F, average high temperature ~86 ^{o}F), while April to July tend to be the cooler months and also correspond with the rainy season (average low temperature ~70-73 ^{o}F, average high temperature ~79-82 ^{o}F) [53, 54].

The community of Pau da Lima is situated among a series of hills and valleys in the periphery of the city. It consists of about 76,000 inhabitants (2010 IBGE estimate) and is a *favela* community, where squatters occupy vacant land located at the outskirts of the developed areas. The area is densely populated and lacks public services such as safe and legal connections to piped water, adequate sanitation such as a closed sewage system and garbage collection services [55, 56]. The qualities of housing structures vary from shanties made of discarded materials to fairly well constructed homes with modern amenities. Population-based surveillance for acute febrile illness in the Pau da Lima community has been in place since 2009 at the São Marcos Emergency Center (CESM). It is the only public urgent care clinic in the Pau da Lima area. Due to a high incidence of dengue, the community residents' association and the medical administration of the CESM have voiced strong support for dengue studies in the community. The CESM is centrally located in Pau da Lima and 85% of residents report that in the event of a febrile illness they would seek medical attention at CESM.

Active surveillance

Dengue case data were collected by performing enhanced population-based surveillance for clinical dengue infection at CESM. Enrollment of study participants was conducted by CPqGM/Fiocruz and ISC/UFBA researchers with funding from FAPESB and CNPq and support from CESM. Data for the study were collected from January 14, 2009 to December 17, 2010. The study team identified and interviewed patients with acute febrile illness and measured their axillary temperature. A patient was deemed eligible for the study if he/she fulfilled the following inclusion criteria:

1) Resides in the community of Pau da Lima for ≥3 nights per week
2) Is ≥ 5 years old
3) Reports symptomatic fever or has an axillary temperature >38.0ºC for ≤21 days duration

Enrollment of study participants occurred from Monday to Friday from 8:00am to 4:00pm. The study participants represented approximately 64% of patients who fulfilled the study criteria and presented to CESM during enrollment days and times. Patients who sought care due to an acute febrile illness multiple times in a 30 days period were only enrolled once at their first presentation and were excluded from the study at subsequent presentations. Subjects who lacked decision-making capacity or lacked the capacity to provide consent were also excluded from the study. Subjects were enrolled in the study if they provided written informed consent, and in the case of minors, assent to participate in the study with informed consent from the parent/legal guardian.

During the recruitment phase trained technicians interviewed study participants and collected demographic data and relevant medical history in standardized forms during a 20-minute interview. At the time of subject enrollment, participating subjects were recorded in a study register and assigned an individual non-identifiable numerical indicator for use on questionnaires and blood samples and environmental samples. Information was entered into a handheld-based questionnaire (QDS v2.5) according to the subject's non-identifiable number. Data was maintained with REDCap (Vanderbilt University, Nashville, TN, USA) software by trained data management technicians.

The study team invited study participants to return to the same health center two weeks after discharge for convalescent blood collection. Patients who did not return to CESM were visited at home by a trained field team. During these visits, the field study team performed a 10-minute interview to obtain information on recent symptoms, hospitalizations, or outpatient evaluations that occurred after discharge from CESM, and collected convalescent-phase blood samples. Regardless of follow-up visit location, the geographic location of each study participant's home was confirmed with a field visit by the study team. Study participants reported their address of residence and identified a local landmark (i.e. intersection, nearby business, etc.) at the time of enrollment in the acute febrile illness study. These addresses were visited and the subject's name and age were confirmed by one of the following persons: the subject, the subject's family member at the address, and/or a neighbor who resides near the address. To aid in locating the subject's residence, a phone call to the phone number on file was used to verify the address. Geographic locations were marked on hard copy aerial photograph maps, and then transcribed as point locations in ArcMap (ArcGIS 10.1 Environmental Systems Resource Institute, Redlands, California, USA).

Data obtained through the enrollment and convalescent questionnaires were provided by self-report or by parental report for minors. For evaluation of household income, as reported in the enrollment questionnaire, reported figures were converted to USD using the Oanda Currency Converter (http://www.oanda.com/currency/historical-rates/) using the mean monthly exchange rate from the Brazilian Real to the United States Dollar (0.54) for the study period (January 2009 to December 2010).

Ten-milliliter blood samples were collected by peripheral venipuncture at the time of enrollment and at the follow-up visit approximately two weeks later. The samples were labeled with the subject's non-identifiable number and then transported at 4ºC to Fiocruz by the study motorist within 12 hours of collection. Whole blood samples were centrifuged and serum was frozen -70ºC until laboratory testing was performed.

Cases of acute febrile illness were evaluated for dengue using the NS1 antigen assay (Panbio), ELISA IgM (Panbio Dengue Early ELISA) in paired samples, and RT-PCR (Lanciotti method) [57]. A

case of acute dengue infection was defined as a subject who fulfills laboratory criteria as having *one* of the following: positive NS1 antigen assay for samples collected within 7 days of onset of illness, IgM seroconversion between acute and convalescent samples, or positive RT-PCR for dengue virus RNA for samples collected within 7 days of onset of illness who tested positive for NS1 or IgM. Clinical sample data was maintained with REDCap (Vanderbilt University, Nashville, TN, USA) software by trained data management technicians.

Research protocols were approved by the Yale University Human Investigation Committee (HIC Protocol # 1202009697), by the Fiocruz Ethical Committee on Human Subject (protocol # 154) and in the Brazilian National Ethical Committee on Human Subject (CONEP) (protocol # 11451).

City-wide case data

Reported dengue case data for 2009 and 2010 for the entire city of Salvador was obtained separately through the Tabnet Database (CITE; http://www.tabnet.saude.salvador.ba.gov.br/) that is maintained by the Municipal Secretary of Health of the City of Salvador.

GIS data and census tract level data

High-resolution GIS shapefiles and census tract level epidemiological data were obtained from the Brazilian Institute of Geography and Statistics (IBGE; http://ibge.gov.br). IBGE is an organization maintained by the Brazilian Federal Government and provides statistical and geographical data on the entire nation. Data for this study were obtained from the 2010 national census data for the study area.

Statistical analyses: Software

Epidemiological and clinical sample data were extracted from REDCap as Microsoft Access (Microsoft Corporation, Redmond, WA, USA) databases and analyzed using Microsoft Excel (Microsoft

Corporation, Redmond, WA, USA) and SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Spatio-temporal analyses were performing using Crimestat III version 3.3 (Ned Levine & Associates, Houston, TX, USA).

Statistical analyses: Knox Index

The Knox Index was used to measure the spatio-temporal interaction of cases in Pau da Lima from 2009-2010. It tests for possible interaction between the distance and time separating pairs of cases, by examining the number of pairs of cases found in a particular space-time window (e.g. the number of pairs of cases separated by less than *M* meters and *T* days) [25, 58, 59]. The Knox Index is useful to determine whether cases are more clustered than what would be expected based on the underlying geographical distribution of the population or any temporal trend alone [58]. In this setting, a significant Knox Index indicates that dengue cases are clustered in both time and space, demonstrating that transmission of these cases may be linked.

The distance and time between points are divided into two groups: "close" and "not close" in distance and in time [58, 59]. The Knox Index produces a 2 x 2 table that compares closeness in distance and closeness in time (**Table 1**).

	Close in Time	Not Close in Time	
Close in Distance	O_1	O_2	S_1
Not Close in Distance	O_3	O_4	S_2
	S_3	S_4	N

Table 1. *Structure of the Knox Index.* $N=O_1+O_2+O_3+O_4$ *while* $S_1=O_1+O_2$; $S_2=O_3+O_4$; $S_3=O_1+O_3$; $S_4=O_2+O_4$

The observed numbers of pairs from the four cells are then compared to the expected numbers [58, 59]. As demonstrated by **Table 2**, the expected numbers are obtained from the cross-products of the columns and rows [58, 59]. A Chi-square statistic (with one degree of freedom) is then generated from the

difference between the observed numbers of pairs and the expected numbers, $\chi 2 = \sum \frac{(Oi-Ei)2}{Ei}$. When a space-time interaction is present, the distances between pairs of cases will be small, and the test statistic will be large.

	Close in Time	Not Close in Time
Close in Distance	E_1	E_2
Not Close in Distance	E_3	E_4

Table 2. *Expected frequencies for the Knox Index. $E_1 = S_1 \times S_3/N$; $E_2 = S_1 \times S_4/N$; $E_3 = S_2 \times S_3/N$; $E_4 = S_2 \times S_4/N$*

CrimeStat III was utilized to calculate the Knox Index for dengue cases in Pau da Lima from 2009 to 2010. It is a spatial statistics program that was designed for the National Institute of Justice to analyze crime location data and other point locations, and is also used by epidemiologists to analyze spatial-temporal trends in infectious disease [59].

This software allows the user to enter the mosquito dispersal distance (*M*) and the viral incubation period (*T*) to define the criteria for "close" and "not close" in space and time. Previous studies have evaluated a Knox Index with a space-time window of *M* and *T* as 100 meters and 20 days, respectively [25, 60, 61]. The *T* value of 20 days accounts for the sum of the virus' extrinsic and intrinsic incubation periods [25]. To account for the variability of *A. aegypti* dispersal distances, analysis of spatio-temporal clusters was examined by a series of models. Eight different Knox Index permutations were calculated, with a constant viral incubation period of 20 days but varying dispersal distances between 100 and 800 meters. CrimeStat III also allows the analyst to select the number of Monte Carlo simulations applied to each model. For this study, each model was run for a total of 999 Monte Carlo simulations, which allows for exploration of the variability in this complex system by varying parameters within statistical constraints.

Statistical analyses: Logistic regression

Univariate logistic regression analyses were conducted to identify risk factors for the presence/absence of dengue infection. The logistic regression model is the most frequently used model for modeling a binary or dichotomous outcome, as in this study where patients either are diagnosed with dengue or are not [62]. A series of univariate logistic regression models were used to examine the association between the individual level variables (listed in **Table 3a**) and the binary outcome of laboratory-confirmed dengue stipulating a screening significance level of $P < 0.05$ [62]. The association between census tract level variables (listed in **Table 3b**) and the binary outcome of laboratory-confirmed dengue were also assessed at the $P < 0.05$ level of significance. Logistic regression compares the odds of having laboratory-confirmed dengue versus not having dengue for these various risk factors.

Altitude of home
Age
Sex
Race
Household income
Number of days since onset of symptoms

Table 3a. *Individual level variables.*

Average household income
% of homes with adequate trash collection
Number of houses
Number of residents
Distribution of race

Table 3b. *Census tract level variables.*

RESULTS

Descriptive epidemiology

A total of 2,962 patients were enrolled in the Acute Febrile Illness Study from January 14, 2009 to December 17, 2010. Georeferencing of the patient's home was completed for 85.58%, or 2,535 of these individuals. This group of study participants represents the dataset used for statistical analysis. **Table 4** presents general characteristics of the acute febrile illness study population. The age range was 5 to 101 years with the mean age of all patients was 21.58 ± 14.67 (19.91 ± 13.27 for cases, 21.79 ± 14.82 for non-cases, *P* value = 0.0426). Approximately 46.5% of the study participants were male, and 53.5% were female. Of the 2,317 patients self-reporting their race, 49.6% were black, 39.6% were mixed, 8.9% were white, and 1.9% answered other.

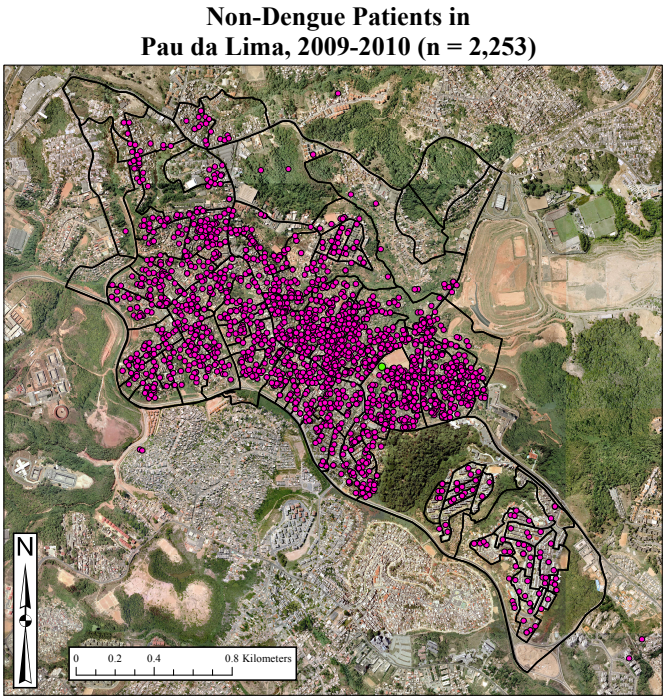
Characteristic	N (%) or Mean ± S.D.
Age (years)	21.58 ± 14.67
Sex	
Male	1175 (46.5%)
Female	1353 (53.5%)
Race/ethnicity	
White	206 (8.9%)
Black	1150 (49.6%)
Brown/mixed	918 (39.6%)
Other	43 (1.9%)
Monthly household income (USD)	4.34 ± 5.53
Number of days w/ symptoms	3.25 ± 3.10

Table 4. *General characteristics of the study population.*

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables.

[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.

Two hundred and eighty two (11.12%) of these patients were confirmed to have an acute dengue infection by one of the three diagnostic criteria (NS1 ELISA, IgM seroconversion, or RT-PCR for dengue virus) while 2,253 did not. The household locations of non-dengue study participants and laboratory-confirmed dengue patients are presented in **Figure 1a** and **Figure 1b**, respectively.



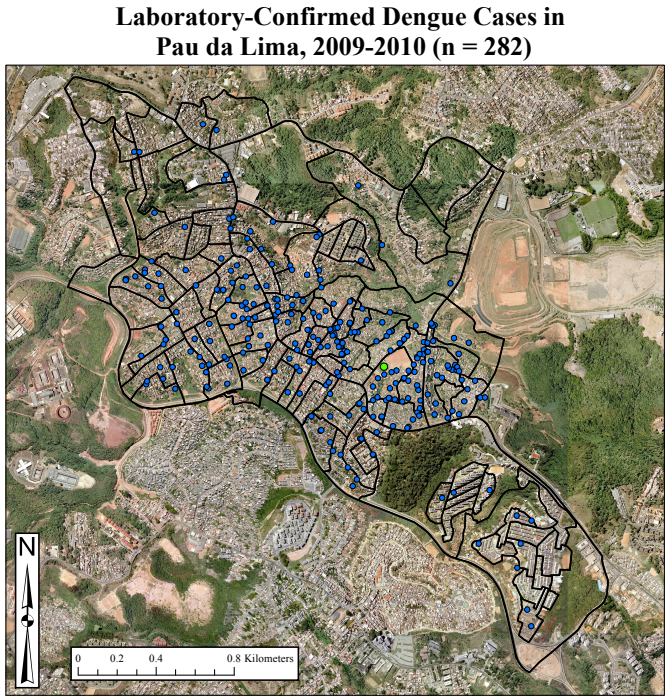


Figure 1a. *Household locations of acute febrile illness patients without laboratory-confirmed dengue in Pau da Lima from 2009-2010. CESM, the reference health center and site of study enrollment is indicated with a green dot.*

Figure 1b. *Household locations of laboratory-confirmed dengue cases in Pau da Lima from 2009-2010. CESM, the reference health center and site of study enrollment is indicated with a green dot.*

The incidence of dengue was seasonally variable and varied in Pau da Lima and throughout the city of Salvador from 2009 to 2010 (**Figure 2**). Periods of relatively high transmission and periods of relatively low transmission are seen throughout each year for both datasets. Of note, surveillance was not conducted at CESM in Pau da Lima from March 2, 2009 to March 27, 2009.

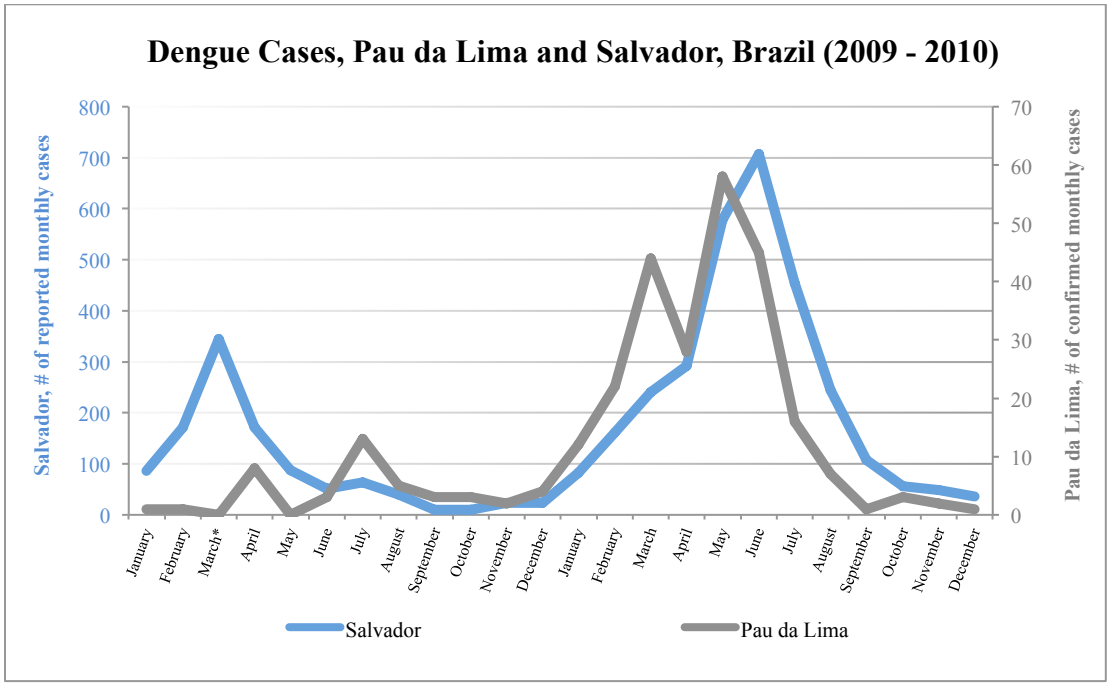


Figure 2. *Temporal distribution of dengue cases in Pau da Lima and Salvador, Brazil from January 2009 to December 2010.*
***** Surveillance did not occur between March 2, 2009 and March 27, 2009.

Knox Index

The Knox Index identified space-time associations from January 2009 to December 2010. **Table 5** summarizes the findings of the Knox Index at varying *A. aegypti* dispersal ranges (*M*) with a constant dengue virus incubation period (*T*). The number of pairs of cases that were "close in space and close in time" varied from 106 to 1513 as the dispersal range, *M,* was increased. All space-time interaction pairs were significant at the $\alpha = 0.05$ level, with a greater number of observed pairs of cases being both "close in space and time" as compared to the number of expected pairs of cases. The maximum χ^2 value among

the 8 models was 21.71, at *M* of 300 meters, and *T* of 20 days. Each permutation of the model was examined with 999 Monte Carlo simulations.

(*M* meters, *T* days)	Number Close in Space and Time	Expected Number Close in Space and Time	χ^2	*P* value	Monte Carlo Simulation Runs
100 meters, 20 days	106	87.19	4.62	0.0001	999
200 meters, 20 days	379	316.28	15.04	0.0001	999
300 meters, 20 days	732	630.19	21.71	0.0001	999
400 meters, 20 days	1105	1004.67	14.86	0.0001	999
500 meters, 20 days	1513	1410.1	12.85	0.0001	999
600 meters, 20 days	1886	1791.15	10.05	0.0001	999
700 meters, 20 days	2259	2153.3	12.37	0.0001	999
800 meters, 20 days	2576	2480.36	10.63	0.0001	999

Table 5. *CrimeStat III Knox Index simulation results.*

Logistic Regression

Univariate logistic regression of all variables was performed to investigate risk factors for acute dengue infection. This analysis revealed statistically significant associations with younger age (continuous variable; OR 0.885, 95% CI 0.800-0.979), brown/mixed race (with respect to the reference group, white; OR 1.745, 95% CI 1.005-2.994), lower per capita daily income (with respect to the reference group, <$1 (USD) per capita income per day; for 1-2 USD OR 0.482, 95% CI 0.306-0.760 and for >2 USD OR 0.555, 95% CI 0.417-0.739), and fewer number of days of illness at presentation (continuous variable; OR 0.939, 95% CI 0.897-0.983). **Table 6** presents the results from the statistical analyses of individual level risk factors (odds ratio [OR], 95% confidence intervals [CIs]). Similarly, **Table 7** presents the results from the statistical analyses of census tract level risk factors (odds ratio [OR], 95% confidence intervals [CIs]). None of the census tract level variables were statistically significantly associated with dengue.

Variables	OR	95% CI	*P*-value
Altitude	0.994	0.983-1.004	0.233
Age	0.885	0.800-0.979	0.017
Male sex	1.201	0.937-1.539	0.149
Race[a]			
Black	1.168	0.675-2.023	0.579
Brown/mixed	1.735	1.005-2.994	0.048
Other	2.309	0.887-6.012	0.086
Highest grade completed in school	0.993	0.961-1.026	0.678
Receives Bolsa Familia	0.986	0.759-1.279	0.913
Household population density	1.026	0.952-1.107	0.500
Per capita daily income[b]			
1-2 USD	0.482	0.306-0.760	0.0017
>2 USD	0.555	0.417-0.739	<.0001
# of days ill at presentation	0.939	0.897-0.983	0.0066

Table 6. *Estimated odds ratios (OR) for the univariate analysis of the association between individual level risk factors and the presence of dengue.*

[a] ORs are calculated with respect to the reference group, white.

[b] ORs are calculated with respect to the reference group, <$1 (USD) per capita income per day.

Variables	OR	95% CI	*P*-value
# of houses in census tract	1.001	1.000-1.003	0.167
# of residents	1.000	1.000-1.001	0.127
Race			
White (%)	0.971	0.940-1.002	0.065
Black (%)	1.000	0.986-1.015	0.987
Asian (%)	1.036	0.944-1.137	0.458
Mixed (%)	1.006	0.991-1.022	0.434
Indigenous (%)	1.077	0.873-1.329	0.491
Average household income	1.000	0.999-1.000	0.208
% of houses with piped water	1.022	0.963-1.085	0.468
% of houses with sewer	0.999	0.994-1.003	0.650
% of houses with trash collection services	0.993	0.983-1.004	0.217

Table 7. *Estimated odds ratios (OR) for the univariate analysis of the association between census track level risk factors and the presence of dengue.*

[a] Each race category, measured as the percentage of the census tract reporting the corresponding race, was evaluated as an independent risk factor for dengue infection.

DISCUSSION

This study contributes to a better understanding of the epidemiology and spatio-temporal dynamics of dengue in an urban slum community. Implementation of the dengue surveillance program by CPqGM/Fiocruz and ISC/UFBA researchers at CESM serves as a model sentinel surveillance site in the city of Salvador, and indicates that enhanced surveillance in the setting of an urban slum plagued by endemic dengue transmission is possible and feasible. Analysis yielded several risk factors for dengue, including young age, brown/mixed race, lower per capita daily income, and fewer self-reported days of illness at the time of presentation. The finding of space-time interactions suggests that there is local dengue transmission at the level of the individual household in this community.

The acute febrile illness study at CESM is based on laboratory-confirmed diagnoses of dengue, which can more accurately predict the disease trends than diagnosis based on clinical-suspected diagnoses alone. Passive surveillance systems that rely on clinical diagnosis lack sensitivity, especially during inter-epidemic periods where the index of suspicion may be lower [51, 63]. Furthermore, passive surveillance systems often lack specificity because other diseases may present with similar symptoms in the acute phase of illness. A large proportion of patients with acute dengue often present with undifferentiated acute febrile illness. For these reasons, active surveillance at sites such as CESM are capable of providing better data to drive dengue response measures and to detect future outbreaks of dengue.

While the importance of a dengue surveillance system is widely known, the feasibility of supporting such a system is expensive and time-consuming. Furthermore, although dengue fever is a reportable disease in Brazil, many barriers exist that prevent widespread, accurate surveillance efforts. Sentinel surveillance is an attractive alternative to universal population-based surveillance that monitors disease incidence in a select population. This enhanced, laboratory-based surveillance for dengue fever is more sensitive and specific than passive surveillance that prevails in much of Brazil. Data can be used to monitor the stability or change in the incidence of dengue in this population, which may be representative

of transmission in similar communities. Information from the sentinel surveillance site can then be used to make informed population-level decisions about the proper utilization of control efforts in these areas.

Univariate logistic regression identified four individual risk factors for dengue in the community of Pau da Lima: young age, brown/mixed race, lower income, and fewer self-reported days of illness. None of the census tract level risk factors were associated with disease, indicating that census data is not informative for defining at-risk populations in this setting. Intensive vector control interventions, active surveillance efforts, and educational programs should be prioritized in communities with high-risk populations to protect these individuals from infection. Young children, who are less likely to have been exposed to all serotypes of the virus, are at highest risk for illness, and the burden among children is increasing [18, 64]. Parents of young children should be educated to protect their families by reducing vector-breeding habitat near and inside their homes.

Several studies have described similar risk of dengue among low-income individuals in Brazilian, American, and Puerto Rican communities with persistent dengue transmission [[8, 65-68]. In contrast, Heukelbach et al. found that socioeconomic variables were not associated with dengue in a favela in Fortaleza, Brazil [69] and another study in Fortaleza cited an inverse relationship between wealth and risk of dengue [70]. It is notable that the differences of socioeconomic status among individuals in that community were small, while population density is so high that transmission was likely independent of social factors. While studies examining the risk of dengue across income levels have drawn variable conclusions, several studies demonstrate the burden of disease among the poor. Identification of a socioeconomic risk suggests that in slum communities with overall high levels of poverty, social differences contribute to unequal risks of dengue. In addition to social programs targeting socioeconomic inequality, mosquito breeding habitat removal and educational campaigns aimed at reducing dengue transmission should be implemented in these communities in particular.

Results from the Knox Index indicate secondary transmission occurred in Pau da Lima from 2009 to 2010. Throughout a series of analyses with varying dispersal distance and a set dengue virus incubation period, all models concluded statistically significant results. The maximum χ^2 was seen at an *A. aegypti*

dispersal range of 300 meters, indicating that secondary transmission may occur at a greater distance than the generally cited <80-meter flight range of female *Aedes*. This suggests that vector control efforts focused on a dispersal distance of 50 to 100 meters are insufficient in this community. Considering that studies regarding mosquito dispersal distances have not established a uniform distances across various habitats, the dispersal patterns of A. aegypti in Pau da Lima should be further characterized to more accurately inform vector control efforts.

This study's spatio-temporal findings are consistent with those from Aldstadt et al. that used the incremental Knox test (IKT) in a series of overlapping time intervals to evaluate cases occurring within given spatial and temporal windows. They examined the clustering of cases at spatial distances between 100 to 500 meters across varying temporal windows, from on the same day/next day up to cases occurring 39-41 days apart. Their results from two studies concluded that the strongest spatial clustering occurred at the 18-19 day interval and the 15-17 day interval and was consistent across all distances [71, 72]. The findings confirm that the temporal window of successive infections is approximately the sum of the virus' intrinsic and extrinsic incubation period [30, 71, 72].

Results from several other studies provide evidence of clustering of cases in time and space using various methodologies [73-76]. Fine-scale spatio-temporal clustering was studied Yoon et al. in rural Thailand, where the scale of transmission was found to be at the level of the household, where certain houses contributed a disproportionate level of transmission [75]. Molecular phylogeny studies conducted by Mondini et al. in São Paulo State, Brazil provided data on spread patterns of the virus that are consistent with mosquito dispersal range, but are also influenced by human transport [74]. Salje et al. identified that immunity of dengue serotypes occurs at the neighborhood level in an urban setting in Bangkok, which further justifies the potential benefit of targeted prevention efforts [76]. This study's findings, taken in consideration with other dengue literature, show that dengue prevention efforts should be targeted to high-risk transmission areas while considering the flight range of the local vector(s) as a guide.

One limitation of this study is its incomplete enrollment because surveillance was not available 24 hours per day, 7 days per week, and because it only captures patients who present for medical care. While not wholly inclusive, this study examined the clinically apparent cases of dengue, which from a clinical standpoint are arguably the more severe cases. Due to the often mild or asymptomatic nature of dengue, however, additional study, such as a cohort study of seroincidence, is needed to more thoroughly capture the characteristics of the disease and its transmission. Although two years of transmission were analyzed in this study, further investigation encompassing a longer time frame would enhance the analysis. It is also important to note that univariate logistic regression does not allow for simultaneous analysis of multiple risk factors in a single model. This method of analysis does not assess for confounding, such as patient access to CESM or interaction of variables. Furthermore, the study does not account for movement of humans within the community, thus does not capture imported and exported cases of dengue. Future studies include those that test for other causes of acute febrile illness that are known to be prevalent in this community, such as influenza, typhoid fever, and acute hepatitis. This surveillance program has also identified that leptospirosis accounts for approximately 2% of acute febrile illness in this population, which should be further investigated (unpublished results from the CPqGM/Fiocruz and ISC/UFBA study team).

In conclusion, ongoing dengue transmission in Brazil continues to be a public health threat. The enhanced case detection at CESM has identified several risk factors for dengue as well as spatio-temporal clustering and also serves as an important model enhanced sentinel surveillance site for the city of Salvador, and beyond. Future studies that continue to explore the spatio-temporal patterns of dengue are important to further characterize transmission, and should focus on multivariate modeling, and the study of the clustering of cases and vectors in space and time.

REFERENCES

1. Teixeira, M.G., et al., *Dengue: twenty-five years since reemergence in Brazil.* Cadernos de Saúde Pública, 2009. **25**: p. S7-S18.

2. Kuno, G., et al., *Phylogeny of the genus Flavivirus.* Journal of Virology, 1998. **72**(1): p. 73-83.

3. Dengue and severe dengue fact sheet 2013 [cited October, 16, 2013].

4. Research, S.P.f., et al., *Dengue: guidelines for diagnosis, treatment, prevention and control*, 2009: World Health Organization.

5. Gubler, D.J., *Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century.* Trends in Microbiology, 2002. **10**(2): p. 100-103.

6. Barrera, R., J. Avila, and S. Gonzalez-Tellez, *Unreliable supply of potable water and elevated Aedes aegypti larval indices: a causal relationship?* Journal of American Mosquito Control Association, 1993. **9**(2): p. 189-95.

7. Ilkal, M.A., et al., *Entomological investigations during outbreaks of dengue fever in certain villages in Maharashtra state.* Indian Journal of Medical Research, 1991. **93**: p. 174-8.

8. Rigau-Pérez, J.G., et al., *Dengue and dengue haemorrhagic fever.* The Lancet, 1998. **352**(9132): p. 971-977.

9. Gubler, D.J., *Dengue and dengue hemorrhagic fever.* Clinical Microbiology Reviews, 1998. **11**(3): p. 480-496.

10. Gubler, D.J. and G.G. Clark, *Dengue/dengue hemorrhagic fever: the emergence of a global health problem.* Emerging Infectious Diseases, 1995. **1**(2): p. 55.

11. Barreto, F.R., et al., *Spread pattern of the first dengue epidemic in the city of Salvador, Brazil.* BMC Public Health, 2008. **8**: p. 51.

12. Teixeira, M.d.G., et al., *Dynamics of dengue virus circulation: a silent epidemic in a complex urban area.* Tropical Medicine & International Health, 2002. **7**(9): p. 757-762.

13. Simmons, C.P., et al., *Dengue.* New England Journal of Medicine, 2012. **366**(15): p. 1423-1432.

14. Halstead, S.B., *Dengue.* The Lancet, 2007. **370**(9599): p. 1644-1652.

15. Allicock, O.M., et al., *Phylogeography and population dynamics of dengue viruses in the Americas.* Molecular Biology & Evolution, 2012. **29**(6): p. 1533-43.

16. De Melo, P.R.S., et al., *The dynamics of dengue virus serotype 3 introduction and dispersion in the state of Bahia, Brazil.* Memorias do Instituto Oswaldo Cruz, 2007. **102**(8): p. 905-912.

17. Halstead, S., *Observations related to pathogensis of dengue hemorrhagic fever. VI. Hypotheses and discussion.* The Yale Journal of Biology and Medicine, 1970. **42**(5): p. 350.

18. Kuno, G., *Review of the factors modulating dengue transmission.* Epidemiologic Reviews, 1995. **17**(2): p. 321-35.

19. Halstead, S. and E. O'rourke, *Dengue viruses and mononuclear phagocytes. I. Infection enhancement by non-neutralizing antibody.* The Journal of Experimental Medicine, 1977. **146**(1): p. 201-217.

20. Guzmán, M.G. and G. Kouri, *Dengue: an update.* The Lancet Infectious Diseases, 2002. **2**(1): p. 33-42.

21. Ooi, E.-E. and D.J. Gubler, *Dengue in Southeast Asia: epidemiological characteristics and strategic challenges in disease prevention.* Cadernos de Saúde Pública, 2009. **25**: p. S115-S124.

22. Badurdeen, S., et al., *Sharing experiences: towards an evidence based model of dengue surveillance and outbreak response in Latin America and Asia.* BMC Public Health, 2013. **13**(1): p. 607.

23. Gubler, D.J., *Surveillance for dengue and dengue hemorrhagic fever.* Bulletin of the Pan American Health Organization, 1989. **23**(4): p. 397-404.

24. Cuong, H.Q., et al., *Spatiotemporal dynamics of dengue epidemics, southern Vietnam.* Emerging Infectious Diseases, 2013. **19**(6): p. 945-53.

25. Vazquez-Prokopec, G.M., et al., *Quantifying the spatial dimension of dengue virus epidemic spread within a tropical urban environment.* PLoS Neglected Tropical Diseases, 2010. **4**(12): p. e920.

26. Neff, J.M., et al., *Dengue fever in a Puerto Rican community.* American Journal of Epidemiology, 1967. **86**(1): p. 162-184.

27. Jeefoo, P., N.K. Tripathi, and M. Souris, *Spatio-temporal diffusion pattern and hotspot detection of dengue in Chachoengsao province, Thailand.* International Journal of Environmental Research & Public Health, 2011. **8**(1): p. 51-74.

28. Mondini, A. and F. Chiaravalloti-Neto, *Spatial correlation of incidence of dengue with socioeconomic, demographic and environmental variables in a Brazilian city.* Science of the Total Environment, 2008. **393**(2): p. 241-248.

29. Galli, B. and F. Chiaravalloti Neto, *Temporal-spatial risk model to identify areas at high-risk for occurrence of dengue fever.* Revista de Saude Publica, 2008. **42**(4): p. 656-63.

30. Siler, J.F., M.W. Hall, and A. Kitchens, *Dengue: Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity and Prevention.* Philippine Bureau of Science, 1926(Monogr. 20).

31. Harrington, L.C., et al., *Dispersal of the dengue vector Aedes aegypti within and between rural communities.* The American Journal of Tropical Medicine and Hygiene, 2005. **72**(2): p. 209-220.

32. Reiter, P., *Oviposition, dispersal, and survival in Aedes aegypti: implications for the efficacy of control strategies.* Vector-Borne and Zoonotic Diseases, 2007. **7**(2): p. 261-273.

33. Honório, N.A., et al., *Dispersal of Aedes aegypti and Aedes albopictus (Diptera: Culicidae) in an urban endemic dengue area in the State of Rio de Janeiro, Brazil.* Memórias do Instituto Oswaldo Cruz, 2003. **98**(2): p. 191-198.

34. Sheppard, P., et al., *The dynamics of an adult population of Aedes aegypti in relation to dengue haemorrhagic fever in Bangkok.* The Journal of Animal Ecology, 1969: p. 661-702.

35. Reiter, P. et al., *Short Report: Dispersal of Aedes aegypti in an Urban Area After Blood Feeding as Demonsrated by Rubidium-Marked Eggs.* The American Journal of Tropical Medicine and Hygiene, 1995. 52(2): p. 177-179.

36. Trpis, M. and W. Hausermann, *Dispersal and other population parameters of Aedes aegypti in an African village and their possible significance in epidemiology of vector-borne diseases.* The American Journal of Tropical Medicine and Hygiene, 1986. **35**(6): p. 1263.

37. Morlan, H.B., R.O. Hayes, and H. Schoof. *Urban Dispersal and Activity of Aedes aegypti.* The American Hournal of Tropical Medicine and Hygiene, 1958.

38. Muir, L.E. and B.H. Kay, *Aedes aegypti survival and dispersal estimated by mark-release-recapture in northern Australia.* The American Journal of Tropical Medicine and Hygiene, 1998. **58**(3): p. 277-282.

39. Chang, A.Y., et al., *Combining Google Earth and GIS mapping technologies in a dengue surveillance system for developing countries.* International Journal of Health Geographics, 2009. **8**(1): p. 49.

40. Kittayapong, P., et al., *Suppression of dengue transmission by application of integrated vector control strategies at sero-positive GIS-based foci.* The American Journal of Tropical Medicine and Hygiene, 2008. **78**(1): p. 70.

41. Er, A., et al., *Spatial mapping of dengue incidence: A case study in Hulu Langat District, Selangor, Malaysia.* International Journal of Human and Social Sciences, 2010. **5**: p. 410-414.

42. Padmanabha, H., et al., *The interactive roles of Aedes aegypti super-production and human density in dengue transmission.* PLoS Neglected Tropical Diseases, 2012. **6**(8): p. e1799.

43. Sanchez, L., et al., *Aedes aegypti larval indices and risk for dengue epidemics.* Emerging Infectious Diseases, 2006. **12**(5): p. 800.

44. Farrar, J., et al., *Editorial: Towards a global dengue research agenda.* Tropical Medicine & International Health, 2007. **12**(6): p. 695-699.

45. Horstick, O., et al., *Dengue vector-control services: how do they work? A systematic literature review and country case studies.* Transactions of the Royal Society of Tropical Medicine and Hygiene, 2010. **104**(6): p. 379-386.

46. Barrera, R., et al., *Stratification of a hyperendemic city in hemorrhagic dengue.* Pan American Journal of Public Health, 2000. **8**(4): p. 225-233.

47. Pinho, S.T., et al., *Modelling the dynamics of dengue real epidemics.* Philosophical Transactions of the Royal Society A (Mathematical, Physical & Engineering Sciences), 2010. **368**(1933): p. 5679-93.

48. Gubler, D. and D. Trent, *Emergence of epidemic dengue/dengue hemorrhagic fever as a public health problem in the Americas.* Infectious Agents and Disease, 1993. **2**(6): p. 383-393.

49. Getis, A., et al., *Characteristics of the spatial pattern of the dengue vector, Aedes aegypti, in Iquitos, Peru*, in *Perspectives on Spatial Data Analysis*. 2010, Springer. p. 203-225.

50. Teixeira, M.d.G., et al., *Dengue and dengue hemorrhagic fever epidemics in Brazil: what research is needed based on trends, surveillance, and control experiences?* Cadernos de Saúde Pública, 2005. **21**(5): p. 1307-1315.

51. Gubler, D.J. *Dengue and dengue hemorrhagic fever*. in *Seminars in Pediatric Infectious Diseases*. 1997. WB Saunders.

52. *Salvador*, in *Encyclopaedia Britannica*, 2013. [cited October, 16, 2013].

53. *Brazil Travel Information. Brazil Travel Guide, 2013.* [cited October, 16, 2013].

54. *Salvador, Bahia*. Wikipedia, 2013. [cited October, 16, 2013].

55. Reis, R.B., et al., *Impact of environment and social gradient on Leptospira infection in urban slums.* PLoS Neglected Tropical Diseases, 2008. **2**(4): p. e228.

56. de Araújo, W.N., et al., *Knowledge, Attitudes, and Practices Related to Leptospirosis among Urban Slum Residents in Brazil.* The American Journal of Tropical Medicine and Hygiene, 2013. **88**(2): p. 359-363.

57. Lanciotti, R.S., et al., *Rapid detection and typing of dengue viruses from clinical samples by using reverse transcriptase-polymerase chain reaction.* Journal of Clinical Microbiology, 1992. **30**(3): p. 545-551.

58. Kulldorff, M. and U. Hjalmars, *The Knox Method and Other Tests for Space-Time Interaction.* Biometrics, 1999. **55**(2): p. 544-552.

59. Levine, N., *Crime mapping and the Crimestat program.* Geographical Analysis, 2006. **38**(1): p. 41-56.

60. Knox, E. and M. Bartlett, *The detection of space-time interactions.* Journal of the Royal Statistical Society. Series C (Applied Statistics), 1964. **13**(1): p. 25-30.

61. Russell, R.C., et al., *Mark–release–recapture study to measure dispersal of the mosquito Aedes aegypti in Cairns, Queensland, Australia.* Medical and Veterinary Entomology, 2005. **19**(4): p. 451-457.

62. Hosmer Jr, D.W., S. Lemeshow, and R.X. Sturdivant, *Applied logistic regression*. 2013: Wiley. com.

63. Gubler, D.J., *Aedes aegypti and Aedes aegypti-borne disease control in the 1990s: top down or bottom up. Charles Franklin Craig Lecture.* The American Journal of Tropical Medicine and Hygiene, 1989. **40**(6): p. 571-578.

64. Teixeira, M.G., et al., *Recent shift in age pattern of dengue hemorrhagic fever, Brazil.* Emerging Infectious Diseases, 2008. **14**(10): p. 1663.

65. Siqueira, J.B., et al., *Household survey of dengue infection in central Brazil: spatial point pattern analysis and risk factors assessment.* The American Journal of Tropical Medicine and Hygiene, 2004. **71**(5): p. 646-651.

66. Waterman, S., et al., *Dengue transmission in two Puerto Rican communities in 1982.* The American Journal of Tropical Medicine and Hygiene, 1985. **34**(3): p. 625-632.

67. Costa, A.I.P.d. and D. Natal, *Geographical distribution of dengue and socioeconomic factors in an urban locality in Southeastern Brazil.* Revista de Saúde Pública, 1998. **32**(3): p. 232-236.

68. Reiter, P., et al., *Texas lifestyle limits transmission of dengue virus.* Emerging Infectious Diseases, 2003. **9**(1): p. 86.

69. Heukelbach, J., et al., *Risk factors associated with an outbreak of dengue fever in a favela in Fortaleza, north-east Brazil.* Tropical Medicine & International Health, 2001. **6**(8): p. 635-642.

70. Vasconcelos, P., et al., *Dengue epidemic in Fortaleza, Ceara: randomized seroepidemiologic survey.* Revista de saude publica, 1998. **32**(5): p. 447-454.

71. Aldstadt, J., *An incremental Knox test for the determination of the serial interval between successive cases of an infectious disease.* Stochastic Environmental Research and Risk Assessment, 2007. **21**(5): p. 487-500.

72. Aldstadt, J., et al., *Space-time analysis of hospitalised dengue patients in rural Thailand reveals important temporal intervals in the pattern of dengue virus transmission.* Tropical Medicine & International Health, 2012. **17**(9): p. 1076-85.

73. Banu, S., et al., *Space-time clusters of dengue fever in Bangladesh.* Tropical Medicine & International Health, 2012. **17**(9): p. 1086-91.

74. Mondini, A., et al., *Spatio-temporal tracking and phylodynamics of an urban dengue 3 outbreak in Sao Paulo, Brazil.* PLoS Neglected Tropical Diseases, 2009. **3**(5): p. e448.

75. Yoon, I.K., et al., *Fine scale spatiotemporal clustering of dengue virus transmission in children and Aedes aegypti in rural Thai villages.* PLoS Neglected Tropical Diseases, 2012. **6**(7): p. e1730.

76. Salje, H., et al., *Revealing the microscale spatial signature of dengue transmission and immunity in an urban population.* Proceedings of the National Academy of Sciences of the United States of America, 2012. **109**(24): p. 9535-8.