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Modeling of Dengue by Cluster Analysis and Probability Distribution Functions in the State of Alagoas in Brazilian

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HIGHLIGHTS

- A model to jointly assess the spatial distribution of reported dengue and severity.
- The utility of cluster analysis is demonstrated for PDF characterization;
- Cluster analysis identifies regions with similar PDF structure;
- Cluster analysis will be a straightforward model evaluation and analysis tool;
- Climate change affects human infectious disease.

Abstract: Dengue is a viral disease whose number of cases has increased in Brazil. This study aimed to characterize the spatio-temporal distribution patterns of the reported dengue infection cases in the state of Alagoas (AL), Northeastern Brazil (NEB). The data of the officially reported dengue cases from 2000 to 2015 was retrieved from the State Health Secretariat of Alagoas (SESAL), which captures national demographic and health data from the System for the Reporting of Notifiable Conditions (SINAN). After applying the Kernel Density Estimation (KDE) function, maps were generated based on the Inverse Distance Weighting (IDW) interpolation method. By using the clusters analysis (CA) technique, three homogeneous groups of dengue in AL were determined. Next, the LN (Lognormal), GUM (Gumbel) and GEV (Generalized Extreme Value) probability distributions were applied to monthly model dengue case data in AL, with the LN continuous probability distribution standing out. Maceió and Arapiraca have a higher number of dengue cases than other cities, being the main reason for their interpretation as separate groups. The coefficients of determination (R^2) of dengue cases analysis as a function of month of each year for the studied years were low (between 0.03 and 0.63) and many regression slopes were not significant. Pearson's correlation coefficient (r) between dengue and the Human Development Index (HDI) of LA was considered moderate (0.53) and the correlation between dengue and demographic density was high (0.76). The importance of constant monitoring and assistance for these areas is reinforced.

Keywords: Dengue cases; Health Geography; Urban space.

INTRODUCTION

Dengue is an infectious disease transmitted to humans by arthropods [1], with approximately 50 million infected people worldwide each year [2]. To date, there is no vaccine or specific therapy to treat the disease; therefore, these mosquitoes transmitted disease control strategies mostly focus on vector control measures. Unfortunately, vector control has a limited effectiveness in preventing dengue transmission [3,4,5]. Thus, it is necessary to analyze registered dengue cases, identify risk patterns to potentially develop more targeted and thus more effective strategies for efficient epidemics control and even possibly its prevention is specific areas [6,7].

The environment of urban centers favors the dispersion and density of the populations of *Aedes aegypti* [8], and there are flaws in the strategies for combating it, thus, the circulation of dengue viruses has been established and expanded, becoming a serious public health problem in the world [9,10].Infestation by *Aedes aegypti* has grown in recent years, due to the disordered demographic expansion and the lack of planning of cities, with precarious conditions of basic sanitation, creating favorable environments for mosquito breeding sites and its spread throughout Brazil, mainly in the Northeast region [11,12,13].

The use of clusters analysis (CA) is a relevant tool to understand the dynamics of any infectious disease dispersion, particularly spatial distribution [11,12,14]. Additionally, CA allows the identification of hotspots which in turn can improve disease control. Few studies have been carried out for the state of Alagoas, based on an analysis of the temporal/spatial trends and the identification of dengue high risk areas in the state. For example, both [13] and [15] recent studies have not utilized an integrated methodological approach, based on Geographic Information Systems (GIS) tools, but statistics on socioeconomic and environmental data. Thus, this study aimed to characterize the spatiotemporal distribution patterns of notified dengue cases in the state of Alagoas using an integrated methodological approach.

MATERIAL AND METHODS

Study Area

This is a descriptive epidemiological study with a quantitative approach. The study was carried out for Alagoas, located in the Northeast region of Brazil (NEB). Alagoas is geographically divided into three climatic mesoregions, namely: Agreste, Leste and Sertão Alagoano, comprising of 102 municipalities and a population of 3,358,963 inhabitants, with a demographic density of 112.3 and HDI of 0.683, the lowest in the country [16]. The territorial area corresponds to 27,848.14 km^2, representing 0.33% of the national territory, and borders the states of Pernambuco, Sergipe and Bahia (north and west, south and southwest, respectively) and the Atlantic Ocean (east) – [17] - (Figure 1).

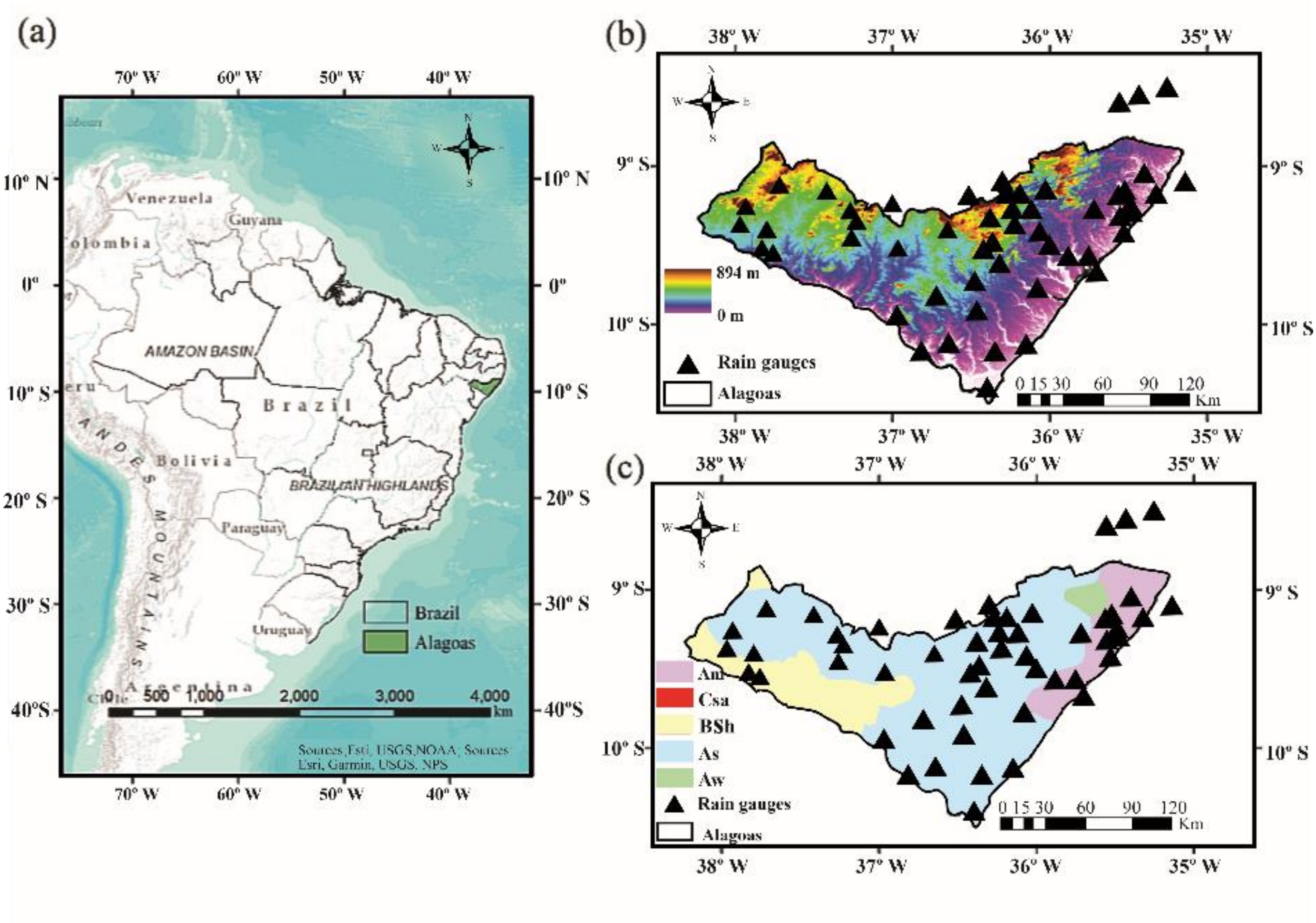

Figure 1. The location of the state of Alagoas, Brazil (**panel a**), climatic classification (**panel b**), digital elevation model - DEM (**panel c**) and the location of the meteorological stations within the state.

According to the Köppen climatic classification, most of the state is characterized by the “As” climate type (savanna climate), and is observed in the humid zone, the floodplain of the São Francisco River, the hinterland and part of the coastal zone. The “Am” climate type (monsoon climate) is observed in the northern part of the coastal zone, while the “BSh” climate type (arid and semi-arid climate) is observed in arid zone of the São Francisco River [18].

Data collection

The monthly reported dengue cases data from 2000 to 2015 was collected from the State Health Secretariat of Alagoas (SESAL), which is derived by the Diseases Information and Notification System (SINAN).

Data analysis

In this study, the Kernel Density was applied and maps were generated based on the Inverse Distance Weighting (IDW) interpolation method. The LN (Lognormal), GUM (Gumbel) and GEV (Generalized Extreme Value) probability distributions were considered to model the monthly dengue speared in the state of Alagoas. The probability density functions (pdfs) and their corresponding cumulative distribution functions (CDF) are shown in Table 1.

Table 1. List of the probability density function (pdfs), cumulative distribution function (cdfs) and supports of LN, GUM and GEV distributions.

pdf	pdf	cdf	Support
LN	$f(x) = \frac{1}{x\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{\ln x-\mu}{\sigma}\right)^2}$	$F(x) = \Phi\left(\frac{\ln x - \mu}{\sigma}\right)$	$x > 0$
GUM	$f(x) = \frac{1}{\sigma} e^{-\left(\frac{x-\mu}{\sigma}\right) - e^{\frac{x-\mu}{\sigma}}}$	$F(x) = e^{-e^{-\left(\frac{x-\mu}{\sigma}-\mu\right)/\sigma}}$	$x \in \mathbb{R}$
GEV	$f(x) = \frac{1}{\sigma}\left(1 + \xi\left(\frac{x-\mu}{\sigma}\right)\right)^{-\frac{1+\xi}{\xi}} e^{-\left(1+\xi\left(\frac{x-\mu}{\sigma}\right)\right)^{-\frac{1}{\xi}}}$	$F(x) = e^{-\left(1+\xi\left(\frac{x-\mu}{\sigma}\right)\right)^{-\frac{1}{\xi}}}$	$x < \mu - \frac{\sigma}{\xi}$ for $\xi < 0$ $\mu - \frac{\sigma}{\xi} < x$ for $\xi > 0$

Where Φ is the standard normal distribution cdf.

The parameter μ Ɛ R is a position parameter, σ > 0 is a scale and ξ > 0 is a shape parameter. The parameter ξ is related to the tail weight of the GEV distribution, and for this reason, it is also called the tail index. The GUM distribution appears as a particular case of the GEV distribution when the shape parameter tends to zero (ξ — 0).

The estimates of the parameters for each distribution were obtained using the maximum likelihood method (ML). The log-likelihood functions of the LN, GUM and GEV distributions are given, respectively, by the following Equations (1), (2) and (3):

$$lnL\ (\mu,\sigma,X) = -\sum_{i=1}^{n} lnx_i - nln\sigma - \frac{n}{2}ln2\pi - \sum_{i=1}^{n}\frac{(lnx_i-\mu)^2}{2\sigma^2} \quad \textbf{(1)}$$

$$lnL\ (\mu,\sigma,X) = -nln\sigma - \sum_{i=1}^{n}\frac{x_i-\mu}{\sigma} - \sum_{i=1}^{n} e^{-\frac{x_j-\mu}{\sigma}} \quad \textbf{(2)}$$

$$lnL\ (x,\sigma,X) = \sum_{i=1}^{n}\left\{-ln\sigma - \left(\frac{1+\xi}{\xi}\right) ln\left[1+\xi\left(\frac{x_i-\mu}{\sigma}\right)\right] - \left[1+\xi\left(\frac{x_j-\mu}{\sigma}\right)\right]^{\frac{-1}{\xi}}\right\} \quad \textbf{(3)}$$

Estimates of the distribution parameters were obtained by maximizing the log-likelihood function in relation to the parameters. The likelihood equations were obtained by taking the partial derivatives of the *LnL* function with respect to each of the parameters and making these derivatives equal to zero. The solutions to these equations are called maximum likelihood estimates of the parameters.

The nonparametric Kolmogorov-Smirnov (KS) test was used in this study to assess whether the maximum extreme temperatures come from a hypothetical continuous distribution. This test is based on the CDF. Assuming that a random variable $x_1, x_2, \ldots\ldots, x_k$ was collected with cdf denoted by *F(X)*. The empirical CDF is given by Equation (4):

$$F_n(x) = \frac{1}{n}\sum_{1}^{n} l_{x_i \le x} \quad (\textbf{4})$$

Where $l_{x_{i\le x}}$ is the number of observations smaller or equal to *x*.

The Kolmogorov-Smirnov D statistic is based on the largest vertical difference between the theoretical and empirical CDF given by Equation (5):

$$D = max_{1\ll i\ll n}\left[\left|\hat{F}(x_i) - \frac{i-1}{n}\right|, \left|\frac{i}{n} - \hat{F}(x_i)\right|\right] \quad (\textbf{5})$$

Where the F(x) cdf is estimated and $x_1, x_2, \ldots\ldots, x_k$ the observations are in ascending order.

The null hypothesis that empirical distribution is equal to one of the estimated distributions is rejected (the data does not follow the specified distribution), at the chosen level of significance (α), if the test statistic D > D(α), where D(α) it is critical value of the KS test. Values of α=0.01 or α=0.05 are commonly used for the verification of the null hypothesis H_0. The value 0.05 is the most popular and was therefore adopted in this study.

The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were calculated for all models being under the estimation procedures. The model that presented the lowest value of these two criteria was selected for further analysis [19]. The AIC and BIC criteria were calculated using the following Equations (6) and (7):

$$AIC = -2lnL + 2k, \quad (6)$$

$$BIC = -2lnL + klnn \quad (7)$$

Where the ln L presents the natural logarithm of the model evaluating the likelihood function and k is the number of parameters in the model.

When the ratio between the sample size (*n*) and the number of the model parameters (*k*) are less than 40, the use of corrected AIC (AICc) is recommended, as suggested by [19] and [20]. As the number of observations in the study is *n* = 12, the AIC was adopted, given by Equation (8):

$$AIC_c = -2lnL + 2k + \frac{2k(k+1)}{n-k-1}, \quad (8)$$

The coefficient of determination (R^2) and the root of the mean square error (*RMSE*) were also used to measure the goodness-of-fit of the examined pdfs used to model the temperature data. The R^2 and *RMSE* statistics are calculated as follows Equation (9):

$$R^2 = \frac{\sum_{i=1}^{n}\left(\hat{F}(x_i) - \bar{F}\right)^2}{\sum_{i=1}^{n}\left(\hat{F}(x_i) - \bar{F}\right)^2 + \sum_{i=1}^{n}\left(F_n(x_i) - \hat{F}(x_i)\right)^2} \quad (9)$$

Where $\widehat{F}(x)$ is the estimated cdf and $\bar{F} = \frac{1}{n}\sum_{i=n}^{n}\widehat{F}(x_i)$. The empirical cdf is given by $F_n(x) = \frac{1}{n}\sum_{i=1}^{n} I(x_{(i)} \leq x)$, where $I\left(x_{(i)} \leq x\right) = 1$ if $x_{(i)} \leq x$ or 0 otherwise. *RMSE* statistics is described by Equation (10):

$$RMSE = \left[\frac{1}{n}\sum_{i=1}^{n}\left(F_n(x_i) - \hat{F}(x_i)\right)^2\right]^{\frac{1}{2}} \quad (10)$$

The distribution with the lowest AIC, BIC and RMSE and the highest R^2 has the best fit to the dengue data. The return time (return levels) represents the inverse of the probability that a given event has occurred. Given the occurrence of an event, the turnaround time is the average time required (in years) for that event to recur, in any given year. In practical terms, its meaning is: if an event occurs, what is the estimated average interval time (*T*) expected for the event to reoccur in a similar size or intensity? By definition, the turnaround time associated with the event is given by:

$$T = \frac{1}{P(E)} = \frac{1}{p} \quad (11)$$

In this study, the event is the maximum number of dengue cases, which exceeds a certain value of dengue infections, and therefore the probability of exceeding that value is obtained by:

$$T = \frac{1}{p} = \frac{1}{1 - F(x_p)} \quad (12)$$

whereas *F(x)=1-p* is the temperature return (X_p) level which the maximum monthly dengue is expected to exceed, in average, every *T* years, and is obtained by the Eq.(13):

$$F\left(x_p\right) = 1 - p \rightarrow x_p = F^{-1}(1-p) \quad (13)$$

From this equation, the $p = \frac{1}{T}$ relation and the cdfs of the LN, GUM and GEV distributions, the quantile functions of these distributions are as follows:

$$x_p(T) = e^{\mu + \sigma \phi^{-1}\left(1 - \frac{1}{T}\right)} \quad \textbf{(14)}$$

$$x_p(T) = \mu - \sigma ln\left[-ln\left(1 - \frac{1}{T}\right)\right] \quad \textbf{(15)}$$

$$x_p(T) = \mu - \frac{\sigma}{\xi}\left[1 - ln\left(1 - \frac{1}{T}\right)^{\xi}\right] \quad \textbf{(16)}$$

The estimated return levels $\hat{x}_p$ were obtained by replacing the maximum likelihood estimates of the parameters in Equations (14), (15) and (16).

All statistical analysis were performed using the software [21].

Clusters Analysis (CA)

For CA, the averages and annual totals of dengue cases in each municipality in the state of AL were used. The Euclidean distance (Ed) was used to measure dissimilarity (Equation 17) and the agglomeration was performed using Ward's hierarchical method [22, 23]. Ward's method is a grouping method in which the similarity measure is calculated as the sum of squares between two clusters with the lowest value in the global sum of squares within the clusters and that tend to connect to other clusters of similar sizes due minimizing its internal variation [11].

$$Ed = \left[\sum_{j=1}^{n}\left(v_{p,j} - v_{k,j}\right)\right]^{0.5} \quad \textbf{(17)}$$

The Euclidean distance (Ed, dimensionless), $v_{p,j}$ and $v_{k,j}$ are the quantitative characteristics of the various municipalities of the total (*p*) and average (*k*) number of cases in a specific year.

Group validation was performed using the Dunn index, the ratio between the minimal distance between data points in different clusters, ranging from zero to infinity, with higher values indicating better clustering results, with larger separation between clusters and smaller separation between data points within the same cluster [14].

Time Distribution Analysis

The temporal analysis of dengue notifications was made through graphical analysis in which the dependent variable was time (in months) and the independent variable was the number of case notifications. The temporal analysis was performed for each group following cluster analysis. The regression analysis was used as a statistical procedure to verify whether the number of the monthly dengue notifications has a temporal trend. For this purpose, the dependent time variable was in years, and the simple linear model was used ($Y = \beta_0 + \beta_1 X$). Student's t-test was applied to the slope of the regression (β_1) to verify whether β_1=0. The rejection of the null hypothesis (H_0; β_1=0) confirms a time series trend. The regression was established for each group, and the statistical significance adopted level was 5%. The temporal analysis of the data was performed for homogeneous groups in terms of dengue cases in the state of LA, established by the CA.

Spatial Distribution Analysis

For the 1st Stage, the sum of the values for each month from Jan/Dec between 1960 to 2016 was carried out for all municipalities in the state of AL with recorded dengue cases data. Elaboration and standardization of the table for entry purposes as a parameter in the python script for geographic plots (maps). Next, the data was standardized and plotted geographically using the urlib, json, folium and pandas python libraries. Lastly, maps were generated using the folium python library.

RESULTS AND DISCUSSION

Map of the distribution of dengue cases

From the confirmed notifications of dengue in the period from 2000 to 2015, there were 246,228 cases of dengue in the state of AL, with an average of 12.6 cases per municipality. The highest number (87,278) was reported in Maceió, with an annual average of 454.6 notifications, and lowest number of notifications [19] was reported in Red Sea, with an average of 0.10 cases per year. The month with the highest number of notifications was May (rainy season). The greater concentration number of notifications observed within Maceió is most likely due to its urban lifestyle and population density.

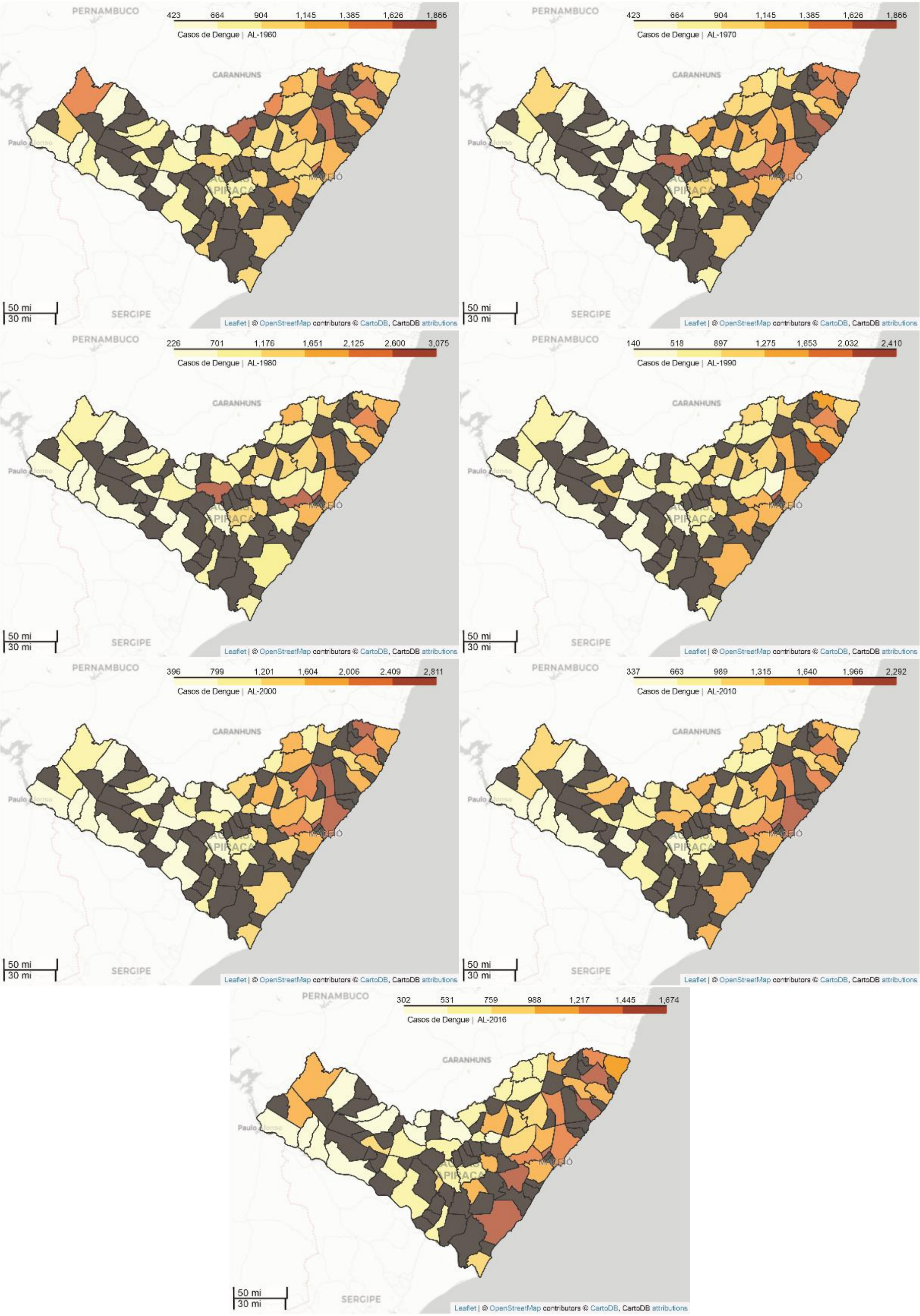

Figure 2. Map of the distribution of dengue cases in the state of Alagoas in the years: A-1960; B-1970; C-1980; D-1990; E-2000; F-2010; G- 2016.

In Figure 2, of the 102 municipalities in the state of Alagoas illustrates the numbers of dengue cases 42, 40, 27, 20, 15, 23 and 20 municipalities (during 1960, 1970, 1980, 1990, 2000, 2010 and 2016, respectively) that presented critical levels above 700 cases. During 2000-2009, the peak of diseases occurred in several endemic areas, a period which deserves an attention for dengue in several states.

In Alagoas, the reported dengue cases are gradually increasing each year. Thus, the understanding of dengue epidemiology by the analysis of epidemiological data, outbreak prediction and hot spot analysis is of critical importance. In this study, we examined the epidemiological scenario and the spatial distribution of dengue using the CA technique applied to the state of Alagoas, in Brazil, in the period from 2000 to 2015.

The results obtained revealed that the reported number of dengue cases was higher among men than women, corresponding to other studies carried out by the World Health Organization [10]. This may be due to the following reasons: i) men may be exposed to mosquito bites more frequently than women; ii) men may not be wearing protective clothing or using precautionary measures against mosquitos, such as the application of repellents, and are thus more exposed for mosquito bites. In addition, there may be an influence for diverse patterns resulting from behavioral and lifestyle habits differences between men and women associated with health. [24, 25] reported that 90% of dengue morbidity was observed in individuals between the ages of 15 and 25. In agreement with this, our study revealed that the largest number of cases was found in adults aged 20-29 years old, the most affected with 24.4%, concentrating approximately a quarter of all confirmed dengue cases. It is possible that this high number of cases is recorded since the level of awareness and notification by this group age is higher when compared with the general population. The greatest number of cases in this age group may also be due to the serotype and strain of the circulating dengue virus, changes in the susceptibility of the population to primary or secondary infection in accordance to one's immune system status. Dengue can also create lifelong immunity for the individual, so that elderly people who have been exposed more often can potentially more resistance, therefore decreasing the rate of morbidity [26].

These regions have emerged as hot spots since they are frequently a destinations of immigrants and are rapidly urbanizes. A decade ago, Gubler predicted that if the global trends in unprecedented population growth, continuous globalization and urbanization will last as projected, there will be a constant increase in the severity, frequency, geographical distribution and magnitude of dengue epidemics in the future [27]. All of the above factors can contribute to the increased risk of dengue in the state of Alagoas, since it is the seventeenth largest state in population in Brazil according to the 2010 census [17]. Therefore, the prevention or reduction of dengue virus transmission highly depends on the control of vector mosquitoes and the interruption of human-vector contacts [28].

There are certain limitations to this study. First, the local data on mosquito density is not available; therefore the effect of vector control interventions on disease management analysis was not included. Secondly, we have not included several factors, such as climate change, population growth and socioeconomic conditions, for the incidence of dengue in this study. However, this study includes data collected over fifteen years, but future attempts for integrated dengue control need to consider the above mentioned points.

In our study, we found spatial and temporal clusters of dengue, hot spot and cold spot regions in the state of Alagoas, using GIS techniques. The identification of spatial dengue clusters is essential for policy planning and for estimating the necessary local resources and the deadlines by which targets can be achieved. These spatial and temporal clusters can also be useful to inform and adjust the local interventions for dengue for higher effectiveness. Likewise, our study also suggests that spatial and temporal analyzes of population-based disease surveillance data would be useful in managing vector-borne diseases, such as dengue, in highlighting where and when the limited public health resources should be concentrated. The temporal distribution curve revealed the absence of a pattern in the case of annual occurrence of cases, as some years presented high dengue incidences followed by years with similar incidences, while other were followed by years with lower dengue case incidence.

Cluster analysis dengue cases

The formation of groups, validated by the Dunn index resulted with three homogeneous groups (G1, G2 and G3) in the state of AL. The Dunn index values for the formation of 2, 3, 4, 5 and 6 groups were, respectively, 1.4739, 1.4923, 0.7062, 0.2511 and 0.2682. From the seventh group onwards, there was a downward trend in the Dunn index. The Ward criterion showed discrimination between the municipalities of Maceió (Eastern Alagoas) - (Group 1 - G1), Arapiraca (Agreste from Alagoas) - (Group 2 - G2) for the formation of G1 and G2, while the remaining 92 cities (Sertão, Leste and Agreste) in the mesoregion of the state of Alagoas formed Group 3 (G3). Figure 3 shows the dendrogram using Ward's hierarchical grouping, illustrating the greatest distance from the most populous municipalities in Alagoas (Maceió and Arapiraca) in relation to the rest of the municipalities in the state.

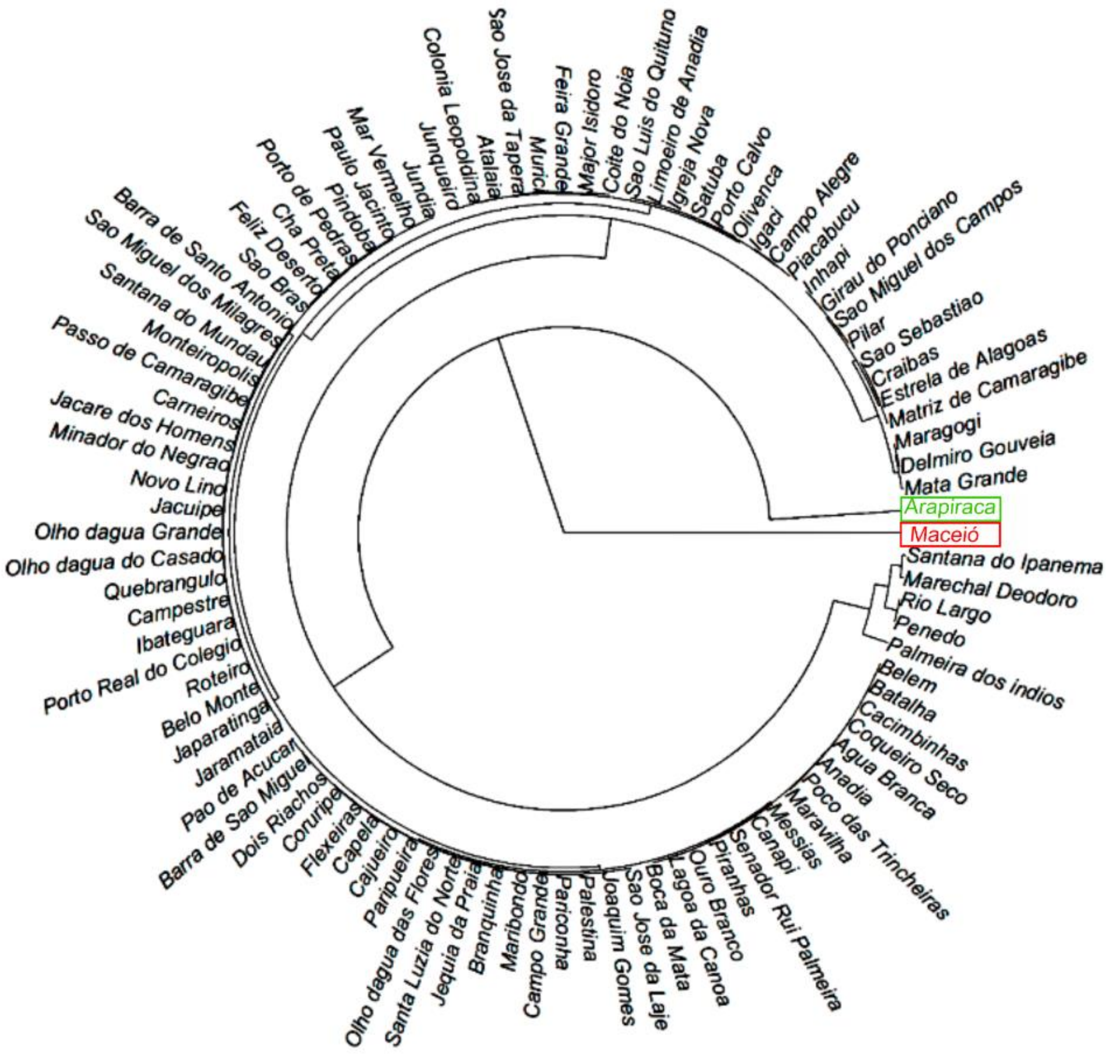

Figure 3. Dendogram of the cluster analysis of the state of Alagoas, during 2000 to 2015 using the Ward method for hierarchical agglomeration.

Figure 4 shows the number of dengue cases in G1, G2 and G3. In G1 (Maceió), a total of 35,291 cases were reported in the studied period, and an average of 183 monthly cases. G2 (Arapiraca) presents a total of 87,278 cases with an average of 455 monthly cases. Lastly, in G3 (formed by 92 municipalities), a total of 126,073 cases with an average of 7 monthly cases were reported. The average and total values in Maceió, Arapiraca and the other municipalities were extremely different on an annual or monthly scale, which provides this disposition of the groups. The difference between Maceió and Arapiraca is due to population size [16], followed by the transformation of land use and occupation [29] and the rainfall regime in both cities [7,30].

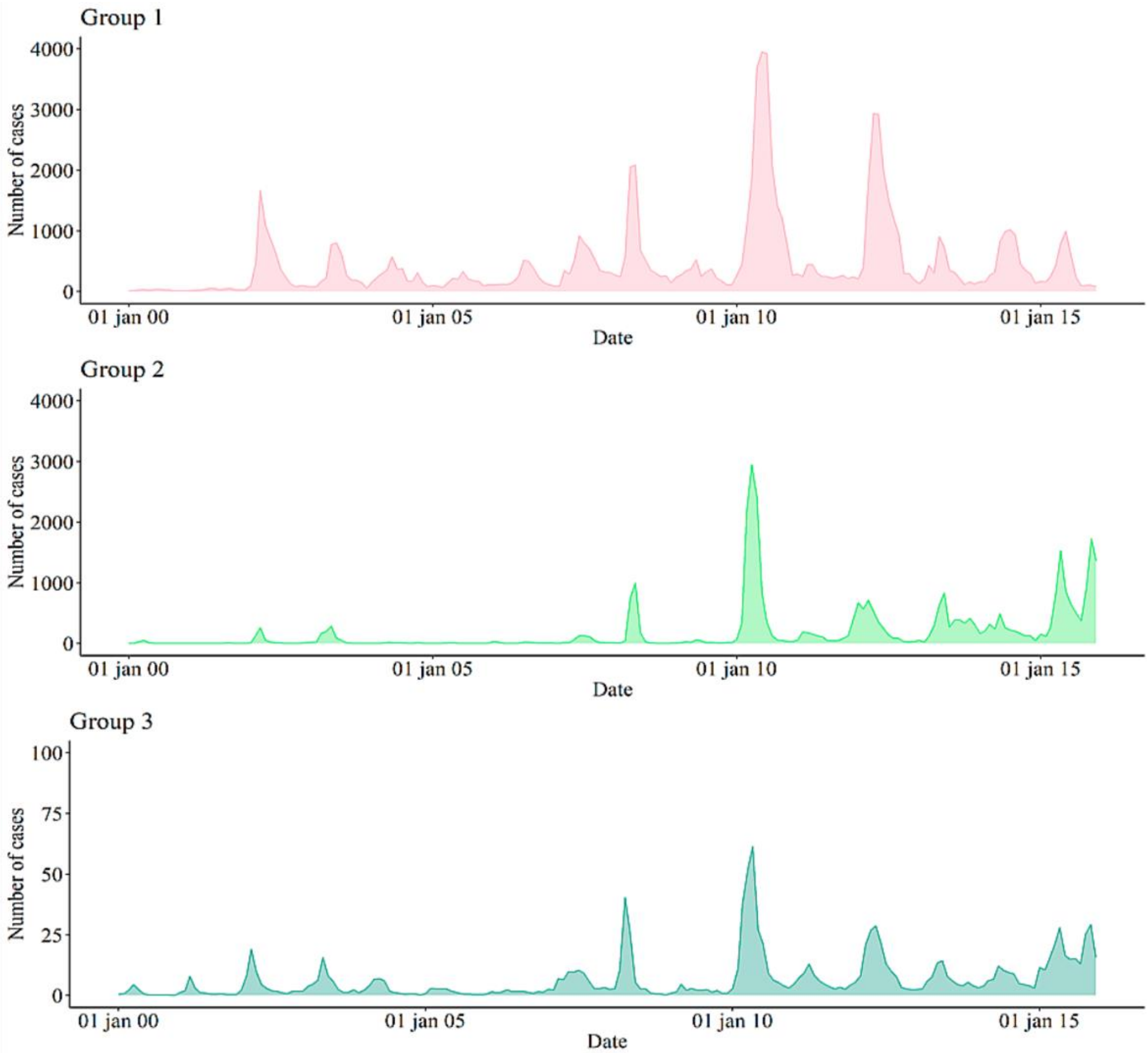

Figure 4. Number of dengue cases per month in homogeneous groups (G1, G2 and G3) for the state of Alagoas in the period from 2000 to 2015.

The results indicates that there is significant variation in the spatial distribution of dengue in the state of Alagoas, and that the geographical distribution of the cases expanded throughout the studied period, owing to the changes in land use and occupation, mainly in the last decade, as recently pointed out by [7, 29]. Many of the dengue endemic areas in Alagoas are on interstate borders. Neighboring villages and districts frequently share similar ecology, human behavior, social patterns and lifestyle, characters which can give rise to a positive or negative association with the occurrence of dengue also in neighboring areas.

The spatial distribution pattern of dengue cases in Alagoas was significantly grouped into three homogeneous groups (G1, G2 and G3). Consistent hot spots of dengue during the studied period were identified in Arapiraca, Palmeira dos Índios, Penedo and Maceió (Figure 2), located mainly in the central and northeastern regions of the state. The size of the entire region is related to the geographical characteristics of the territory, as the highlights are the regions: Arapiraca is the second largest municipality in the state, located in the west state and a part of the Agreste zone and has an HDI = 0.649 and a demographic density of 650.6, knowns an industrialized city where several cases of dengue were previously identified [31]. Palmeira dos Índios is the fourth largest municipality in the state, also an industrialized city and a part of the Agreste zone, with an IDH of 0.638 and a demographic density of 161.6. Penedo municipality is located in the south of the state, on the banks of the São Francisco River and on the border with the state of Sergipe, its economy consists of primary products and tourism, with HDI = 0.63 and a demographic density of 92. Maceió economy is diverse, and is the largest producer of salge, chemical, sugar and alcohol, cement and food industries [16, 32]. Its demographic density, as of 2025, is considered high and has an urbanization rate of 99.75 and HDI value of 0.735.

Table 2 shows the parameter values of the linear regression analysis of dengue cases as a function of years, for each month. Based on the analysis of the angular coefficient, trends were found to increase the number of notifications in all groups. In G1 (Maceió), a trend was only observed in January (12.3 cases per year). In G2 (Arapiraca), trends were observed from May to December, with the strongest trend observed in May (74 cases per year) and the lowest in September (23.3 cases per year). In G3, with the majority of municipalities in Alagoas and where the lowest averages and totals were observed, trends were observed from June to December, with rates of increase in the number of notifications between 0.56 and 1.11 cases per year. The coefficients of determination (R^2) of the regressions were considered low, ranging from 0.03 to 0.63, with the highest regressions values observed were statistically significant by the Student's t test ($\beta_1 \neq 0$). Thus, the increasing trends in cases should be considered when planning and combating the vector of dengue transmission, the *Aedes aegypti* mosquito. Figure 5 presents the number of dengue cases as a function of time and confirms the trends of increase in the number of cases, over time.

Table 2. Parameters and adjustment statistics for linear regressions for groups (G1, G2 and G3) in Alagoas from 2000 to 2015.

Months	**Group 1**			**Group 2**			**Group 3**		
	β_0	β_1	r^2	β_0	β_1	r^2	β_0	β_1	r^2
January	-24547,90	12.30	0.45	-33513,09^{ns}	16.73^{ns}	0.23	-749,77	0.37	0.44
February	-18676,17^{ns}	9.40^{ns}	0.10	-33007,32^{ns}	16.49^{ns}	0.24	-637,72^{ns}	0.32^{ns}	0.21
March	-41639,10^{ns}	20.99^{ns}	0.03	-68610,63^{ns}	34.31^{ns}	0.09	-1117,03^{ns}	0.56^{ns}	0.08
April	-108367,62^{ns}	54.32^{ns}	0.09	-106921,89^{ns}	53.45^{ns}	0.12	-2307,20^{ns}	1.16^{ns}	0.14
May	-174637,16^{ns}	87.47^{ns}	0.16	-148116,64	74.00	0.27	-3148,15^{ns}	1.58^{ns}	0.23
June	-163822,26^{ns}	82.01^{ns}	0.16	-93773,00	46.82	0.49	-2227,23	1.11	0.44
July	-133029,14^{ns}	66.63^{ns}	0.12	-53553,88	26.74	0.51	-1713,31	0.86	0.44
August	-96471,37^{ns}	48.30^{ns}	0.19	-46677,50	23.30	0.54	-1490,60	0.74	0.63
September	-58343,48^{ns}	29.24^{ns}	0.15	-38762,35	19.35	0.52	-1121,51	0.56	0.58
October	-33957,19^{ns}	17.04^{ns}	0.36	-58631,56	29.26	0.36	-1558,10	0.78	0.37
November	-30431,09^{ns}	15.26^{ns}	0.29	-98023,20	48.91	0.29	-1634,08	0.82	0.31
December	-16997,07^{ns}	8.53^{ns}	0.31	-81383,98	40.61	0.31	-1007,54	0.50	0.41

Legend: ns = not significant in Student's t test at 5% probability of error, for the null hypothesis that the parameter is equal to zero.

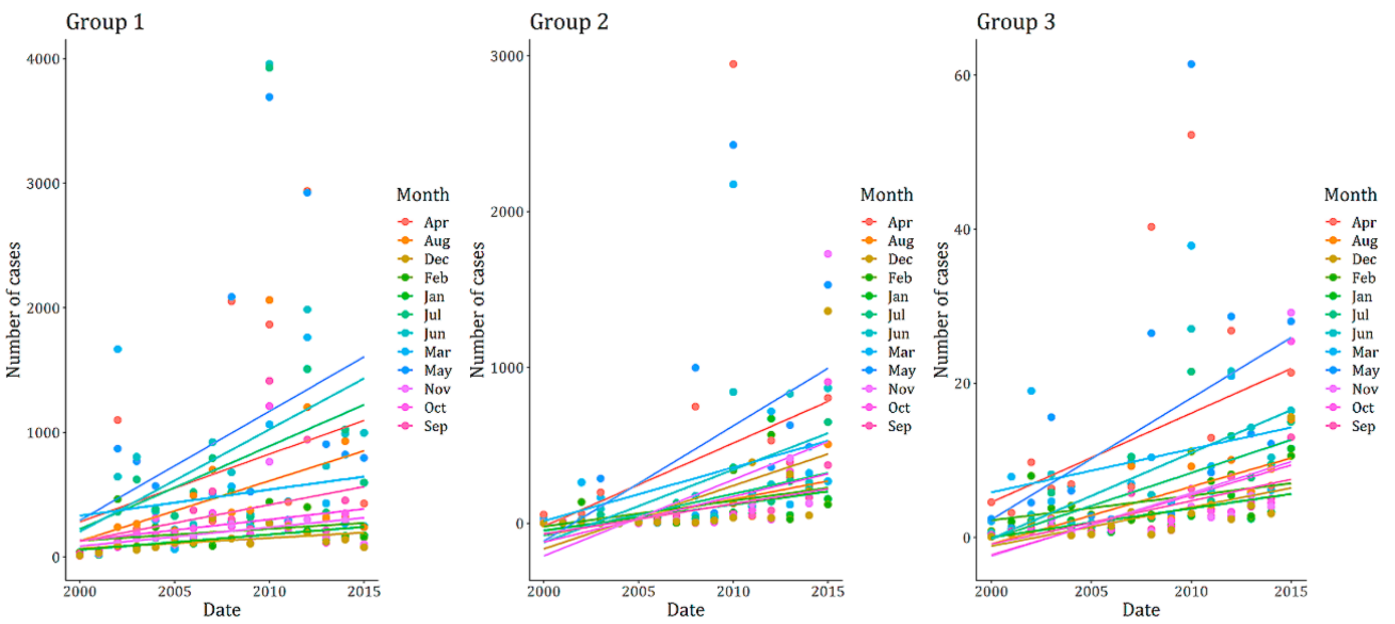

Figure 5. Linear regressions for temporal characterization of the number of dengue cases in groups G1, G2 and G3 in Alagoas from 2000 to 2015.

The parameters of the probability density functions are shown in Tables 3.

Table 3. Estimates of the parameters of pdfs for the monthly dengue data.

Months	GEV			Gumbel		Log-Normal	
	$\hat{\mu}$	$\hat{\beta}$	$\hat{\xi}$	$\hat{\mu}$	$\hat{\beta}$	$\hat{\mu}$	$\hat{\sigma}$
January	28.042	40.799	1.186	62.985	79.839	3.860	1.629
February	68.230	83.778	0.540	95.469	110.733	4.299	1.634
March	174.967	321.702	1.684	198.157	284.708	5.015	1.629
April	241.829	539.342	2.169	245.410	392.827	5.115	1.838
May	291.344	674.877	2.246	347.404	501.797	5.366	1.999
June	235.167	346.069	1.127	258.766	378.492	5.063	2.008
July	167.560	395.537	2.296	96.661	562.560	4.774	2.021
August	86.350	156.637	1.672	142.262	214.645	4.494	1.906
September	87.701	185.488	2.033	109.179	156.498	4.293	1.829
October	56.387	118.522	2.048	95.292	137.609	4.141	1.823
November	25.542	46.176	1.733	35.669	246.782	3.912	1.867
December	29.415	44.007	1.224	31.327	186.968	3.810	1.766

Table 4. Number of dengue cases expected in city, for return times of 10, 20, 30, 40, 50 and 100 years.

Months	Distributions	Return times (in years)					
		10	20	30	40	50	100
January	GEV	490.05	1159.59	1899.17	2687.81	3514.89	8054.94
	GUM	242.65	300.12	333.18	356.49	374.51	430.26
	LN	382.73	691.62	941.01	1155.46	1346.14	2098.50
February	GEV	436.24	684.92	878.45	1043.39	1189.98	1775.14
	GUM	344.66	424.37	470.22	502.55	527.54	604.86
	LN	597.97	1082.68	1474.58	1811.85	2111.92	3297.08
March	GEV	NC	NC	NC	NC	NC	NC
	GUM	838.85	1043.80	1161.69	1244.81	1309.07	1507.86
	LN	1216.01	2197.78	2990.55	3672.27	4278.49	6670.55
April	GEV	NC	NC	NC	NC	NC	NC
	GUM	1129.41	1412.18	1574.85	1689.54	1778.20	2052.47
	LN	1755.94	3423.60	4846.01	6109.31	7258.50	11979.11
May	GEV	NC	NC	NC	NC	NC	NC
	GUM	1476.63	1837.84	2045.63	2192.13	2305.39	2655.75
	LN	2774.50	5736.25	8371.10	10770.28	12991.43	22405.00
June	GEV	3806.07	8655.57	13845.17	19266.87	24867.25	54703.28
	GUM	1110.51	1382.96	1539.69	1650.20	1735.62	1999.88
	LN	2074.40	4303.07	6290.50	8102.71	9782.13	16912.39
July	GEV	NC	NC	NC	NC	NC	NC
	GUM	NC	NC	NC	NC	NC	NC
	LN	1578.24	3288.55	4818.62	6216.46	7513.60	13034.03

Cont. Table 4

August	GEV	4030.38	13451.24	26895.06	43831.45	63936.03	205562.57
	GUM	625.29	779.80	868.68	931.35	979.79	1129.66
	LN	1029.47	2057.58	2950.28	3751.52	4485.84	7542.29
September	GEV	NC	NC	NC	NC	NC	NC
	GUM	461.36	574.01	638.81	684.50	719.82	829.09
	LN	763.13	1483.14	2095.85	2639.28	3133.16	5158.43
October	GEV	NC	NC	NC	NC	NC	NC
	GUM	404.96	504.02	561.00	601.18	632.23	728.31
	LN	650.30	1261.19	1780.26	2240.22	2657.97	4369.16
November	GEV	1315.27	4582.12	9392.91	15579.90	23038.05	77265.04
	GUM	NC	NC	NC	NC	NC	NC
	LN	547.37	1078.62	1535.23	1942.60	2314.36	3850.12
December	GEV	558.73	1358.11	2259.26	3232.89	4263.98	10034.01
	GUM	NC	NC	NC	NC	NC	NC
	LN	433.76	823.82	1150.28	1437.00	1695.79	2744.10

NC – Not calculated.

Dengue is already recognized as a multifactorial disease and its occurrence and patterns of behavior in a region involve viral, socioeconomic, ecological and environmental aspects [33]. Therefore, an investigation is necessary to define whether the factors that influence the spread of dengue in Alagoas are similar in each year or differentiated. It is recognized that in Brazil, with each introduction or reintroduction of a different serotype, there is an increase in the number of cases, which sometimes leads to epidemics [5, 23, 34]. In Alagoas, in the time scale of this study, 2002, 2007, 2008, 2010, 2011, 2012, 2014 and 2015 were identified as epidemic years. Years characterized as years of occurrences of the phases of El Niño-South Oscillation (ENSO) - (El Niño and La Niña) - [35,36].

The most epidemic years in the state were 2010 and 2015. The high number of cases may have been due to the natural occurrence of the disease in the area accounting for a greater dispersion of viruses to other municipalities, since in 2010 more than 90% of the municipalities in the state registered high presence of *Aedes aegypti*. However, one can also consider an improvement in the surveillance system, in the notification of cases, or even an improvement in diagnostic procedures compared to previous years. Another point of consideration regarding the 2010 epidemic is the vector type, and that at the time the state applied the larvicide temephos, an organophosphate insecticide as a control strategy.

The municipalities of Maceió and Arapiraca comprised an individual group each, of high relative risk, as in both areas, the risk of dengue transmission is about five times higher. This suggests that the chemical control was ineffective, thus the *Aedes aegypti* infestation. *Aedes aegypti* could be elevated, rapidly increasing the number of dengue cases.

Nonetheless, the western region municipalities comprising G3 are mainly rural with low demographic density. It is agreed that areas with high demographic densities are prone to suffer from explosive dengue epidemics, due to disordered urbanization [9]. However, it is extremely important to understand how an area with low demographic profile could influence the occurrence of dengue. Low-income families are most affected by reduced access to basic sanitation services, especially sewage services [37]. A study in rural areas across Brazil found that the lower the GDP per capita and the rate of sanitation, the greater the risk of dengue infection in the population [6]. The low-risk municipalities in the northwest region of G3, on the other hand, hold altered characteristics. Regarding climate for example, G3 aggregates municipalities of all the climatic types that characterize the state (semi-arid tropical, mild semi-arid, sub-humid, humid and sub-sub-hot) [18]. Moreover, some municipalities are coastal, while other is in the highlands. It is possible that in distant regions, that less influenced from the general flow in Alagoas, the transmissibility of dengue was lower, compared to other and more geographically connected regions. The northwest region (NW) of Alagoas, stands out as an area with low relative risk during the 15 years studied in this work, with the exception of cluster one (Maceió) - (Figure 2).

Considering the spatial statistics used, one of the reasons for these areas to be identified as having a low relative risk, is possibly the fact that more cases were recorded in other areas of the state. Thus, another relevant issue is the level of under reporting and under diagnosis in this area. It is understood that in endemic areas the real incidence of the disease is not presented due to underreporting and under diagnosis [38].

Underreporting is a major problem identified in epidemiological surveillance. This may be due to the lack of consultation for asymptomatic or mild cases, the difficulty of doctors in recognizing the disease and differentiating it from others, and the low adherence to notification by health professionals [39]. The barrier to accessing health services can also be a contributing factor to underreporting.

Access to health services in Brazil is strongly influenced by the social condition of people and their residence [40]. Among the barriers to access health services in the Northeast is the cost of commuting to health centers [12]. Thus, people who live far from health units tend to seek medical help only in serious situations [39]. All the above mentioned points lead to an absence of notification of cases when the symptoms of patients are “treatable” at home, or even not recognized as dengue.

Between 2010 and 2015, two areas were of high relative risk were identified, one located in the south, center and east of the state with a medium-sized municipality and the others small. It is important to note that in addition to the smaller population, the cluster was formed by municipalities that had only part of their population living in an urban area. From 2000 to 2010, the percentage of urbanization in the municipalities varied. While the others are still mostly rural (UNDP). This demonstrates that dengue is not limited to large urban areas in Alagoas. However, this profile is still little explored and investigated, due to the attention turned to large urban centers.

From the years 2000 to 2010, more than 80% of the resident population of each municipality in the northwest region in this cluster lived in conditions of vulnerability and poverty and less than 50% had piped water. In some places, the deficit in drinking water and deficiencies in the distribution system contribute to the emergence of new cases and the spread of the disease. In the case of rural areas, the risk of dengue may be greater than in urban areas, explained in large part by the lack of piped water supply [41], especially in highly densely populated regions with high degree of urbanization process [5]. Even though the state of Alagoas has presented sequential epidemics, areas classified as low relative risk have been identified in the west and in the east. The highlight is this cluster in the western region, which brought together small municipalities, with low MHDI and poor conditions of water supply and poverty (PNUD).

In a previous study, we analyzed the association between the incidence of dengue and climatic factors in the state of Mato Grosso do Sul using a time series Poisson regression model; minimum monthly temperature, wind speed and minimum humidity and artificial neural network (ANN) were found to be significantly related to the incidence of dengue, [7] and [42]. It appears that the dengue reports in LA were higher in the months of greater rainfall and high levels of relative humidity, indicating that these variables are important for greater proliferation of the vector. Likewise, it was noticed that in the periods following the months with high number of confirmed dengue cases the average temperature was higher.

Correia Filho [31] evaluated precipitation in Alagoas, which is highly influenced by several multiscale meteorological systems, such as trade winds, the Intertropical Convergence Zone (ITCZ), Trade Wave Disturbances (TWD), Bolivia High (BH) and South Anticyclone Subtropical Atlantic (SASA). In hierarchical clustering using Ward's algorithm, five homogeneous groups in Alagoas were identified. The stations were grouped according to the distance from the coast and orography. Rain not uniformly distributed in time and space in all regions, as in two groups within the arid zone, more than 60% of the annual precipitation occurred in a period of 5 months (March to July), even during dengue. The showers were greater in the coastal regions and in the high-altitude areas of the state, due to the orographic rains. In general, the precipitation associated with dengue over the state of Alagoas is characterized by strong gradients from the coast to the continent and from north to south due to the region's physiography and the influence of multi-scale meteorological systems.

It is believed that the mesoregion of the Sertão Alagoano presents weakness in the notification of cases. Because it supports the notion that dry places lead the population to store water, due to the deficit in the supply and collection of waste. In addition, areas with high temperature, rainfall rates and variable air humidity [18,31,36] maintain favorable conditions to the proliferation of the vector and the increase in the number of cases. The complex interactions between the vector, the host and the influence of climatic and environmental factors a make the transmission dynamics difficult to understand.

In the present study, as well as in the analysis by [13], the predominance of the dengue (67.2%) was observed. However, it should be considered that the Eastern Alagoas region registered 0.9% of severe disease cases, above the total average (0.61%). Since it is the most populated and crowded region of the State and where the capital of the State, Maceió, is located, the probability of serious cases of the disease increases. This also explains why this mesoregion was recorded the highest percentage of cure in the state. The Sertão Alagoano mesoregion had a percentage of inconclusive dengue cases, higher than the total average (29.8%), and severe dengue cases can be underestimated.

It is worth mentioning the 5.5% increase in cases of the disease in children in the Sertão Alagoano mesoregion. Dengue in this age group has clinical manifestations similar to other childhood diseases, making diagnosis more difficult [43] and in the presence of comorbidities such as asthma, diabetes and sickle cell anemia, the risk of worsening dengue becomes greater [44].

Climate change has a high impact on health, morbidity and mortality in infectious diseases and remains poorly investigated in the modeling of probability distribution. Souza and coauthors [45,46], analyzed the adjustments of the distributions of Burr (Bu), Inv Gaussian 3P (IG3P), Lognormal (LN), Pert (Pe), Rayleigh 2P (Ra 2P) and Weibull 3P (W3P) of the series history of hospitalizations for respiratory diseases (total hospital admissions) in the period from 2004 to 2018, in Campo Grande, MS. For the data series, the shape and scale parameters of the distributions were determined to verify the quality of the fit of the observed data, the Adequacy Tests (GOF): Kolmogorov-Smirnov test, Anderson-Darling test, test Chi-square tests were used to verify an ideal estimate for hospital hospitalization data. All PDFs were capable of describing the characteristics of hospitalizations well. The results presented (total admissions), (summer) show that the Weibull 3P (W3P) and Inv Gaussian 3P (IG3P) functions; (fall) show that the functions Burr and Weibull 3P (W3P); (winter) shows that the Burr and Inv Gaussian 3P (IG3P) and (spring) functions for lognormal and Rayleigh (2P) functions provided the best adjustment observed for hospital admissions (Table 3).

Using the theory of extreme values, in the table 4, the distributions of GEV, GUM and LN for dengue in the state of Alagoas were estimated. Based on this, the probability and the average time that must elapse before the index reaches a new high record have been estimated. GEV, GUM and LN distributions were adjusted satisfactorily each month and can be used to inform of extreme levels of dengue. The estimated distributions were used to calculate the monthly probabilities of dengue occurrence during the year. No trend associated with or time on month with dengue spread was found. Dengue estimates from January to December were calculated for 2, 5, 10, 30, 50 and 100 years return periods and show that dengue is increasing over time (Table 4)

The AIC, BIC, RMSE and the R^2 coefficient were used to identify the distribution that gave the best results for each month. The GEV/LN distribution presented the highest return values. It is recommended to use GUM distributions in the hottest months of the year in the state of AL (January and February), and the LN distribution for the rest of the year, including the coldest months, which exhibited the best performance. The results obtained are highly effective, since the theory of extreme values and GEV distributions is focusing on the analysis of extreme observations of random variables.

The information obtained can serve as a basis for interpreting the influence of demographic density and the IDH formation of hot dengue areas and cold areas. It can be useful to determine limits of tourist tolerance and to evaluate the risk of exceeding the maximum values decisive for the existence of dengue. Understanding the characteristics of climatic extremes at regional and local levels is fundamental not only for the development of preparedness and early warning systems, but it is also fundamental in the development of a strategy to adapt to climate change, mainly with mitigation actions in relation to the effects of climate change extremes of precipitation (intense rainfall and prolonged drought), population density and social isolation in the population [5, 24].

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REFERENCES

1. Kuno G. Review of the factors modulating dengue transmission. Epidemiol. Rev. 1995 Jul; 17(2): 321–35.
2. Troyo A, Calderón O, Fuller D, Solano M, Avendaño K, Dave CH. Seasonal profiles of *Aedes aegypti* (Diptera: Culicidae) larval habitats in an urban area of Costa Rica with a history of mosquito control. J. Vector Ecol. 2008 Jun, 33(1): 76–88.
3. Derouich M, Boutayeb A, Twizell E. A model of dengue fever. Biomed. Eng. Online. 2003 Feb, 2(4): 1–10.
4. Clark G, Rubio-Palis Y. Mosquito vector control and biology in Latin America. J. Am. Mosq. Control Assoc. 2008 Dec,24(1): 571–82.
5. Oliveira Júnior JF, Gois G, Silva EB, Teodoro PE, Silva Junior CA. Non-Parametric Tests Applied to Reported Dengue Cases in South east Region, Brazil. Biosci. J. 2018 Jul, 34(4): 1010-6.
6. Rodrigues NCP, Lino VTS, Daumas RP, Andrade MKDN, O'Dwyer G, Monteiro DLM. Temporal and spatial evolution of dengue incidence in Brazil, 2001-2012. PLoS One. 2016 Nov, 11(1): 1-12.
7. Souza A, Abreu MC, Oliveira-Júnior JF. Impact of Climate Change on Human Infectious Diseases: Dengue. Braz. Arch. Biol. Technol. 2021 Jan, 64(1): e21190502.
8. Teixeira MG, Barreto ML, Guerra Z. Epidemiologia e medidas de prevenção do Dengue. Informe Epidemiológico do SUS. 1999 Dec, 8(4):5-33.
9. Mendonça FA, Souza AVE, Dutra DA. Saúde pública, urbanização e dengue no Brasil. Soc. Nat. 2009 Dec, 21(3): 257-69.
10. World Health Organization (WHO). Dengue guidelines for diagnosis, treatment, prevention and control. WHO. 2009, pp.1-147.
11. Silva JCB, Machado CJS. [Associations between Dengue and Socio-environmental Variables in Capitals of Northeast Brazil by Cluster Analysis]. Ambiente Soc. 2018 Jan, 21(1): e01332.
12. Oliveira Júnior JF, Gois G, Silva EB, Teodoro PE, Johann J, Silva Junior CA. Non-Parametric Tests, Multivariate Analysis and Descriptive and Exploratory Statistics Applied to Reported Dengue Cases in Brazil. Environ. Monit. Assess. 2019 Jun, 191(1): 473-91.
13. Santos LCGB, Silva NL, Vasconcelos BM, Ferreira KBAN, Ferreira LC, Santos RFEP, et al. [Epidemiological profile of the state of Alagoas related to dengue arboviruses]. Braz. J. Health Rev. 2019 Mar, 2(3): 1604-8.
14. Sangkaew S, Tan LK, Ng LC, Ferguson NM, Dorigatti I. Using cluster analysis to reconstruct dengue exposure patterns from cross-sectional serological studies in Singapore. Parasit. Vectors. 2020 Jan, 32(13): 1-10.
15. Dantas DM, Patrício LGL Gomes DL, Santos EMC, Santos AM, Araújo KD. [Temporal analysis of rainfall related to dengue cases: a case study in Jacintinho, Maceió, Alagoas]. Rev. Craibeiras de Agroecol. 2019 Fev, 4(1): e8881.
16. IBGE - Instituto Brasileiro de Geografia e Estatística. Área da unidade territorial: Área territorial brasileira. Rio de Janeiro, 2020. Available from: cidades.ibge.gov.br/brasil/al/panorama
17. IBGE - Instituto Brasileiro de Geografia e Estatística. 2010. Available from: ww.ibge.gov.br
18. Gois G, Souza JL, Silva PRT, Oliveira Júnior JF. [Characterization of desertification in the state of Alagoas using climate variables]. Rev. Bras. Meteorol. 2005 Aug, 20(3): 301–14.
19. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. Sociol. Meth. Res. 2004 Jan, 33(2): 261-304.
20. Fabozzi FJ, Focardi SM, Rachev ST, Arshanapalli BG. The basics of financial econometrics: Tools, concepts, and asset management applications. New Jersy: Wiley. 2014. 206 pp.
21. R Core Team. R: A language and environment for statistical computing [Internet]. R Foundation for Statistical Computing, Vienna, Austria. 2020. Available from:<https://www.R-project.org/>.
22. Ward JH. Hierarquical grouping to optimize an objective function. J. Am. Stat Assoc. 1963 Apr, 58(301): 236–44.
23. Oliveira RADD, Duarte CMR, Pavão ALB, Viacava F. Barriers in access to services in five Health Regions of Brazil: perceptions of policymakers and professionals in the Brazilian Unified National Health System. Cad. Saúd. Pub. 2019, 35(11): e00120718.
24. Kumar A, Sharma SK, Padbidri VS, Thakare JP, Jain DC, Datta KK. An outbreak of dengue fever in rural areas of northern India. J. Commun. Disord. 2001 Dec, 33(4): 274-81.
25. Dung NT, Cam NN. Dengue fever/dengue hemorrhagic fever in Hanoi–2003. J. Vietnam Prev. Med. 2005 Dec, 1(1): 73-7.
26. Toan DT, Hoat LN Hu W, Wright PP, Martens P. Risk factors associated with an outbreak of dengue fever/dengue hemorrhagic fever in Hanoi, Vietnam. Epidemiol. Infect. 2015 Jun, 143(8): 1594-8.
27. Gubler DJ. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. Trends Microbiol. 2002 Feb, 10(2): 100-3.
28. Fan J, Lin H, Wang C, Bai L, Yang S, Chu C, Yang W, Liu Q. Identifying the high-risk areas and associated meteorological factors of dengue transmission in Guangdong Province, China from 2005 to 2011. Epidemiol. Infect. 2014 Mar, 142(3): 634-43.
29. Santos FS, Gomes HB, Barros GVP, Alves LER, Silva DF, Costa RL, et al. [Seasonal Analysis of Biophysical Parameters Using the MODIS Sensor for the State of Alagoas]. Rev. Bras. Meteorol. 2021 Jan, 35(1): 955-68.
30. Lyra GB, Oliveira-Júnior JF, Zeri M. Cluster analysis applied to the spatial and temporal variability of monthly rainfall in Alagoas state, Northeast of Brazil. Int. J. Climatol. 2014 Nov, 34(13): 3536-58.

31. Correia Filho WLF. Influence of Meteorological Variables on Dengue Incidence in the Municipality of Arapiraca, Alagoas, Brazil. Rev. Soc. Bras. Med. Trop. 2017 May, 50(3): 309-14.
32. Correia Filho WLF, Santiago DB, Oliveira Júnior JF, Silva Junior CA. Impact of Urban Decadal Advance on Land Use and Land Cover and Surface Temperature in the City of Maceió, Brazil. Land Use Policy 2019 Sep, 87(1): 104026.
33. Moraes BC, Souza, EB, Sodré GRC, Ferreira DBS, Ribeiro JBM. Seasonality of dengue reporting in state capitals in the Brazilian Amazon and impacts of El Niño/La Niña. Cad. Saúde Pública 2019 Sep; 35(9): e00123417.
34. Barreto ML, Teixeira MG. Dengue fever: a call for local, national, and international action. The Lancet 2008 Jul, 372(9634): 205.
35. Lyra GB, Oliveira-Júnior JF, Gois G, Cunha-Zeri G, Zeri M. Rainfall Variability Over Alagoas Under the Influences of SST Anomalies. Meteorol. Atmos. Phys. 2017 Sep, 129(1): 157-71.
36. Costa MS, Oliveira Júnior JF, Santos PJ, Correia Filho WLF, Gois G, Blanco CJC, et al. Rainfall Extremes and Drought in Northeast Brazil and its Relationship with El Niño-Southern Oscillation. Int. J. Climatol. 2021 Jan, 41(S1): E2111-E2135.
37. Veson AH, Jacintp PA, Sbicca A. (2019). [Access To Sanitary Sewage Of Poor Families In Brazil]. Rev. Desenvol. Eco. 2019 Dez, 3(44):199–229.
38. Böhm AW Costa CDS Neves RG, Flores TR, Nunes BP. [Trend in dengue incidence in Brazil, 2002-2012]. Epidemiol. Serv Saúde. 2016 Oct, 25(4):725-33.
39. Diaz-Quijano FA. Dengue severity: A key determinant of underreporting. Trop. Med. Int. Health. 2015 Oct,20(10):1403.
40. Travassos C, Oliveira EXG, Viacava F. [Geographical and social inequalities in access to health services in Brazil: 1998 and 2003]. Ciênc. Saúde Colet. 2006 Dez,11(4):975-86.
41. Schmidt WP, Suzuki M, Thiem VD, White RG, Tsuzuki A, Yoshida LM, et al. Population density, water supply, and the risk of dengue fever in Vietnam: Cohort study and spatial analysis. PLoS Medicine. 2011 Aug, 1(8): 1-10.
42. Soares DG, Souza A, Heck C, Faris H, Oliveira APG. Statistical Modeling of the Effect of Meteorological Variables on Dengue Transmission. Sumerianz J. Med. Health. 2020 Feb, 2(1): 185-95.
43. Jain A, Chatuverdi UC. Dengue in infants: an overiew. FEMS Immunol. Med. Microbiol. 2010 Jul, 59(2):119-30.
44. Guzman MG, Vasquez S, Kouri G. Dengue: where are we today? Malays. J. Med. Health Sci. 2009 Jul,16(3):5-12.
45. Souza A, Santos DAS, Oliveira-Júnior JF, Oliveira APG, Silva EB. Modeling of Hospital Admissions for Respiratory Diseases as a Function of Probability Distribution Functions. Res. Soc. Dev. 2020 Sep, 9(8):E869986501.
46. Souza A, Flavio A, Widinei A, Fernandes ZO, Abreu MC, Oliveira Júnior, et al. Statistical Behavior of Hospital Admissions for Respiratory Diseases by Probability Distribution Functions. J. Infect. Dis. Epid. 2019 nov,5(6):2-12.