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Impact of El Niño on the dynamics of American cutaneous leishmaniasis in a municipality in the western Amazon

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A R T I C L E I N F O

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A B S T R A C T

Vector-borne diseases are some of the leading public health problems in the tropics, and their association with climatic anomalies is well known. The current study aimed to evaluate the trend of American cutaneous leishmaniasis cases in the municipality of Manaus, Amazonas-Brazil, and its relationship with climatic extremes (ENSO). The study was carried out using a series of secondary data from notifications on the occurrence of several American cutaneous leishmaniasis cases in the municipality of Manaus between 1990 and 2017 obtained through the Sistema de Informação de Agravos de Notificação. Data regarding temperature, relative humidity, and precipitation for this municipality were derived from the Instituto Nacional de Meteorologia (INMET) and the National Oceanic and Atmospheric Administration (NOAA) websites. Coherence and wavelet phase analysis was conducted to measure the degree of relationship of the occurrence of the cases of cutaneous leishmaniasis and the El Niño–Southern Oscillation (ENSO). The results show that during La Niña events, an increase in American cutaneous leishmaniasis (ACL) cases is anticipated after the increase in rainfall from November, resulting in a more significant number of cases in January, February, and March. It was observed that in the municipality of Manaus, the dynamics of ACL cases are directly influenced by ENSO events that affect environmental variables such as precipitation, temperature, and humidity. Therefore, climatic variations consequently change the ACL incidence dynamics, leading to subsequent increases or decreases in the incidence of ACL cases in the area.

1. Introduction

Interference in the planet's ecological balance causes climatic anomalies that are directly related to the environment. Localized events may have an impact on the global climate (Dias et al., 2007). Thus, the most crucial phenomenon that causes climatic variations in South America is the El Niño-Southern Oscillation (ENSO), resulting from atmospheric-oceanic variations occurring in the tropical Pacific Ocean. These variations are characterized by irregular fluctuations, at intervals from 2 to 5 years, between hot (El Niño –EN), associated with the increase in the Sea Surface Temperature (SST) and cold phases (La Niña -LN), associated with the cooling of the SST (Berlato and Fontana, 2003; Grimm et al., 1998).

Various indices are used to monitor the tropical Pacific, all based on

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SST anomalies in a given region. The Niño 3.4 index is one of the most commonly used indices in the definition of the El Niño and La Niña events. It can represent the average equatorial SST values in the Pacific region from the data line to South America's coast (Trenberth, 2019).

Evidence of the impact of changing interannual climate variability has been observed in relation to malaria, arboviruses (such as dengue, chikungunya and zika), Rift Valley fever, Japanese encephalitis, human African trypanosomiasis, leishmaniasis and many other diseases with important epidemiological aspect (Altamiranda-Saavedra et al., 2020; Anyamba et al., 2019). The effect of changing temperature and precipitation, as well as extreme events, have been considered the main cause of outbreaks and are alarming the global community. Among the main determining factors, the climate strongly influences the geographical distribution of insect vectors, which is changing rapidly due to climate change (Anyamba et al., 2019; Fouque and Reeder, 2019). Climate change, has an impact on local vegetation, host populations and reservoir animals and on the development, survival and seasonal activity of the vector. Together, these factors culminate in changes in the dynamics of local and sometimes regional transmission of these diseases (Anyamba et al., 2019; Mannelli et al., 2012). In the Amazon, ENSO's climatic variability interferes with flora and fauna through scarcity or excessive rainfall during El Niño and La Niña events (Marengo, 1992). The spatio-temporal variability in precipitation and temperature modulates vegetation phenology. Changes in climatic elements within the soil-plant-atmosphere interfaces directly affect the regional dynamics of ecosystems. This makes ENSO a climatic anomaly of great interest in understanding disease occurrence as directly influenced by the environment (Hay et al., 2016).

Extreme weather events can also directly cause epidemics or the spread of infectious diseases. One example is American cutaneous leishmaniasis (ACL), a parasitosis caused by *Leishmania* species transmitted by insects of the genus *Lutzomyia*. This disease presents seasonality and a strong connection to climatic conditions since the life cycle of the vectors, reservoir, and hosts are strongly affiliated with the dynamics of its ecosystem and climate variability (Cabaniel S et al., 2005b; Cardenas et al., 2006; Delgado et al., 2004; Gagnon et al., 2002). This neglected disease poses a serious global public health problem, predominantly affecting rural and low-income communities, where most of the population have difficulty accessing basic health services (Alvar et al., 2012; Ministério da Saúde, 2017; WHO, 2010)

The current epidemiological scenario presents northern Brazil as the most endemic for ACL as data from 2007 to 2017 show that the North contributed 40%, the most significant contribution, of the total cases registered in the country (SINAN, 2020). The state of Amazonas, which is experiencing rapid urban expansion, presents a vital characteristic to be considered in the epidemiology of ACL; urban encroachment into the world's largest tropical forest, which contains a biological mega-diversity, including vectors (Aguiar and Medeiros, 2003; Castellón et al., 2000; Chagas et al., 2006; Rangel and Lianson, 2003).

In the state of Amazonas, four species of *Leishmania* are of epidemiological importance; *Leishmania (V.) guyanensis, L. (V.) braziliensis, L. (V.) naiffi,* and *L. (L.) amazonensis*, all of which are only associated with cutaneous and mucous forms of leishmaniasis. *L. (V.) guyanensis* is dominant in the region (Coelho et al., 2011), responsible for about 95% of infections reported in the city of Manaus (Benício et al., 2015; Mendes et al., 2021) and is transmitted mainly by *Lutzomyia umbratilis* and *Lutzomyia anduzei* (Barbosa et al., 2008; Guerra et al., 2006). These vector species feed on the blood of wild animals, mostly *Didelphis marsupialis*, domestic animals and humans (accidental hosts), connecting the zoonotic, periurban and urban cycles in Manaus (Arias et al., 1981; Arias and Naiff, 1981; Guerra et al., 2007; Chagas et al., 2018).

The influence of climate on other vector-borne diseases like malaria and dengue has received much attention in Brazil. However, there is a paucity of published studies describing associations between changes in climatic variables and ACL occurrences in north Brazil, especially in the commercially important and highly populated municipality of Manaus, Amazonas state. Such information is of great relevance owing to the epidemiological importance of ACL, endemic to the region. There are still significant challenges and issues that need to be better understood. Studies focused on this subject could provide evidence to support public policies, such as leishmaniasis prevention programs. Herein, the present study aimed to evaluate the influence of the occurrence of extreme climatic events (ENSO) on the trend of ACL cases in the municipality of Manaus.

2. Materials and methods

2.1. Study area

Manaus is the capital of Amazonas (Fig. 1), located at the Negro and Solimões rivers' confluence. The city covers 11.401.092 km^2 with an estimated population of 2.219.580 inhabitants in 2020 (IBGE, 2020).

Based on epidemiological criteria, the municipality of Manaus was selected as the study location. For eligibility, the number of ACL cases used was extracted from the Sistema de Informação Agravos de Notificação (SINAN), through municipality notification. Manaus was the municipality with the highest number of cases in the state, contributing 40% of the notifications between 2012 and 2017 (SINAN, 2020)

2.2. Data collection

Data collection was carried out in the Entomology department of the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (FMT-HVD). The climatology and anomaly analyses of the series studied were carried out at the Meteorology and Water Resources Laboratory at the Escola Superior de Tecnologia of Universidade do Estado do Amazonas, in Manaus.

2.3. ACL cases

The monthly and annual time series of the reported ACL cases from 1990 to 2017 was organized for the municipality of Manaus. The notification data were obtained from the SINAN online database.

2.4. Climatic data

Climatic variables such as air temperature, relative humidity, total precipitation, and the El Niño 3.4 index were obtained from information available on INMET and NOAA websites.

2.5. Precipitation and temperature

Monthly data on precipitation and air temperature were obtained from the Physical Sciences Division (ESRL) V5.01. These data have a spatial resolution of 0.5° latitude x 0.5° longitude (720 × 360, 89.75N - 89.75S, 0.25E - 359.75E) for the period from 1900 to 2017 (Willmott, 2001).

2.6. Humidity

The monthly averages of Relative Air Humidity were obtained from the INMET website and corresponded to the station data located at -3.13° latitude and -59.95° longitude (INMET, 2020)

2.7. El Niño

The global monthly SST data used were derived from the equatorial area of the Pacific, limited by the spatial resolution of 5° x 5° latitude/longitude and 170° W to 120° W. This Central Pacific region is known as El Niño 3.4. The monthly SST index of this area was used to verify the occurrence of ENSO variations for the period evaluated in this study (information available at https://climatedataguide.ucar.edu/climat

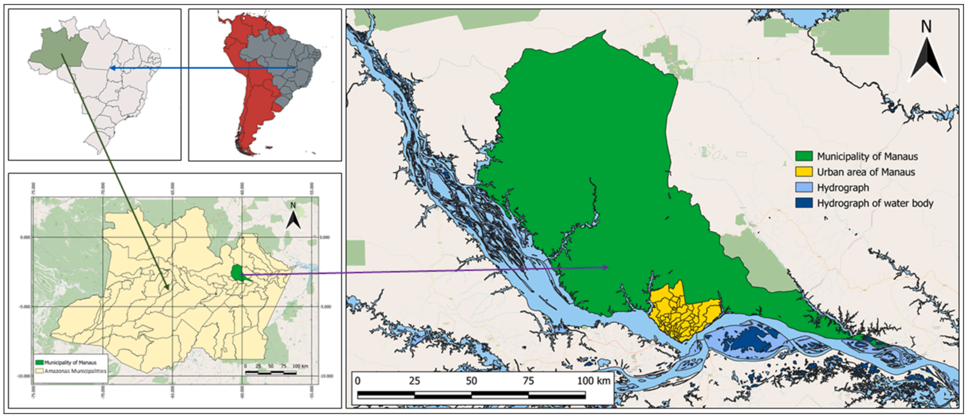

Fig. 1. Map of Manaus Municipality; the study area.

e-data/nino-sst-indices-nino-12-334-4-oni-and-tni). From the Niño 3.4 index, the periods of occurrence of El Niño and La Niña events were identified.

2.8. Statistical analysis

2.8.1. Descriptive analysis

Calculations of monthly averages of the ACL cases, precipitation, temperature, and humidity series, for the period from 1990 to 2017, and box plot diagrams for exploratory data analysis were performed. These analyses made it possible to assess the seasonal behaviour of ACL and climatic variables. In addition, a box plot was built based on the median and quartiles associated with the data set, which made it resistant to outliers within the limits of extreme values and, consequently, attractive in data analysis (Wilks, 2006). Subsequently, monthly anomalies were calculated. The anomalies were defined as the difference between the value observed in a given month and its corresponding climatological value for the entire period evaluated, including the El Niño 3.4 index. As the difference between the value observed in each month and its corresponding climatological value for the entire period evaluated and for the stations data and monthly gridded precipitation and temperature time series. Anomalies made it possible to assess the degree of variability in the variables analyzed and their relationship with extreme events. The monthly gridded precipitation and temperature anomalies were submitted to composition analysis to observe average seasonal anomalous patterns of these variables during El Niño and La Niña events.

2.8.2. Waveform coherence and phase difference analysis

The complete time series of precipitation, temperature, humidity, and El Niño 3.4 index were related to ACL cases from the analysis of wavelet coherence and phase difference (Grinsted et al., 2004; Torrence and Webster, 1999).

The analysis of the phase difference of the wavelet's cross-spectrum can determine the separation time (lag) between the two series analyzed. The angle of inclination of the arrows characterizes and illustrates the phase difference or lag between the series. The slope of the arrows represents the time lag between the variables. Arrows pointing horizontally to the right (0°) indicate series occurring in the same phase (mutual relation); arrows positioned to the left (180°) suggest that the series occur in opposite phases (inverse relation). Arrows pointing vertically downwards (-45°, -90°, or -135°) suggest that the first series studied is ahead of the second series; vertical arrows upwards (45°, 90°, or 135°) suggest that the first series analyzed is outdated, occurring after the second series.

This study considered precipitation, temperature, humidity, and the El Niño 3.4 index as independent variables. The number of ACL cases was considered as the dependent variable. The calculation of the lag definition was based on the slope of the vector angle. All these variables were used to analyze the lag times (when one variable precedes the other). The abscissa axis in the phase difference spectrum analysis of the wavelet's cross-spectrum corresponds to the annual period, subdivided into years: levels 1, 2, 4, and 8 that appear standardized in the axes correspond to the period from 1 to 8 years, respectively. The results for this type of analysis often vary at the intervals of these levels.

2.8.3. Stratification of the series for years of the occurrence of ENSO

Table 1 shows the years selected as years of ENSO occurrence, that is, the years of El Niño and La Niña and the years considered neutral, according to the classification available on the NOAA website. Since the life cycle of El Niño and La Niña events begins around June and persists for 12 to 18 months, the ACL time series and climatic variables were organized from July of the year when the event began until June of the following year for all years. Subsequently, the average monthly values for the years of El Niño, La Niña, and Neutral were calculated.

3. Results

3.1. Composition of precipitation and temperature series to identify cyclical patterns, trends, and seasonal variations

The composition of the series of precipitation and temperature anomalies in the years of El Niño and La Niña occurrence in the municipality of Manaus showed significant precipitation anomalies occurring in the range of -140 mm to -60 mm for the years of El Niño and +80 mm to +120 mm for La Niña years. The temperature was higher in El Niño years; the temperature anomalies for Manaus varied between 0.6°C and 0.64°C, and between -0.46°C and -0.38°C in the years when La Niña occurred. These values demonstrate that the occurrence of ENSO interfered with the climatological pattern of rain and temperature for the entire municipality (Fig. 2). Since this ENSO signal covers the entire study region, precipitation and temperature series representing the study area's total average were used.

3.2. Frequency of American cutaneous leishmaniasis for the municipality of Manaus between 1990 and 2017

3.2.1. Historic series

According to SINAN data, 23,107 cutaneous leishmaniasis cases were confirmed in the period 1990-2017 for the municipality of Manaus, with an average of 825.25 cases/year (Fig. 3 a). The highest record of notification of cases was observed for 2003 with 2,051 (8.87%) cases. In that year, April presented the highest number of cases, with 376 (18.3%), and the least representative months were January and February, with 90 (4.4%) cases each. The year 1994 had the lowest values for the disease's occurrence, with 205 (0.88%) cases. In that year, January was the most abundant month with 47 (22.9%) cases, and

Table 1
Classification of years of the occurrence of El Niño-Southern Oscillation.

Years										
El Niño	1991-1992	1994-1995	1997-1998	2002-2003	2004-2005	2006-2007	2009-2010	2014-2015	2015-2016	
La Niña	1995-1996	1998-1999	1999-2000	2000-2001	2005-2006	2007-2008	2008-2009	2010-2011	2011-2012	2016-2017
Normal	1990-1991	1992-1993	1993-1994	1996-1997	2001-2002	2003-2004	2012-2013	2013-2014		

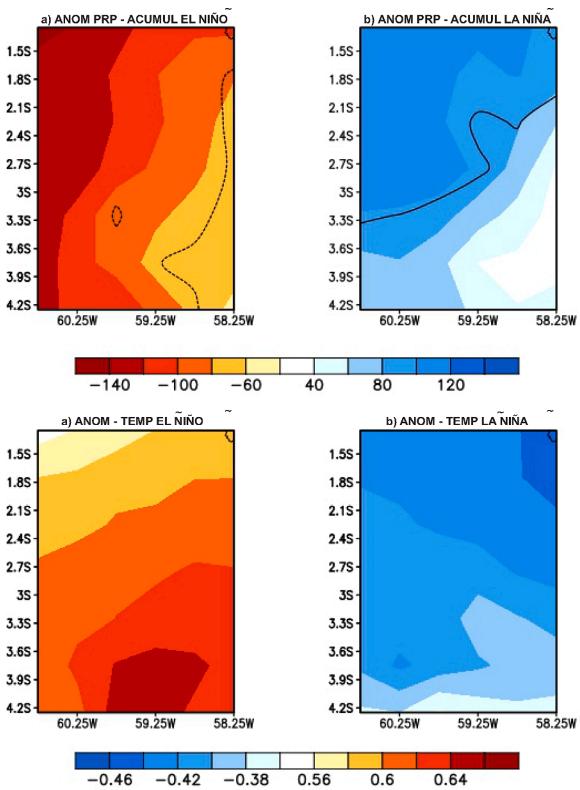

Fig. 2. Composition of the series of Precipitation and Temperature anomalies in the years of the occurrence of the El Niño (left column) and La Niña (right column) events in the municipality of Manaus from 1990 to 2017.

June/July the months with the lowest registration with only 2 (0.9%) reported cases (Fig. 3 a).

Concerning the climatic variables, the total precipitation for the period studied was 61,414 mm. The year with the highest rainfall recorded was 2006 with 2,448 mm; January having the highest rainfall, 299.52 mm; and August the lowest, 104.59 mm. The lowest recorded precipitation was in 1992 with 1,959.26 mm, March had the highest rainfall at 250.83 mm, while the lowest recorded was in June with 111.11 mm (Fig. 3b).

The annual average air temperature was 32°C for the years studied, with the highest temperature in September 2015 (37°C) and lowest in November 2001 (28.5°C) (Fig. 3 c).

The relative humidity data showed an average of 81.5% per year for the series studied, with the highest recorded in May 1999 (92.7%) and lowest in October 2015 (62.8%) (Fig. 3 d).

3.2.2. *Climatology*

A boxplot presentation showed that the highest number of ACL cases was between November and April, with the highest median in January. The lowest number of cases was from June to September, with the lowest median in August (Fig. 4 a). The seven-month time interval between the highest and lowest median indicates an asymmetric seasonal cycle. The most extensive ACL dispersion occurred in March and April, as indicated by the interquartile range values, accompanied by maximum values. The lowest value was in July, as indicated by the lowest interquartile range and the lowest value this month. Outliers above the upper quartile from January to December suggest epidemic outbreaks (Fig. 4 a).

In the municipality, the highest precipitations happened between December and May, where the highest media was recorded in March. The lowest rainfall was recorded from June to September, with the lowest median being in August. High temperatures were noted between July and October, with the highest median in September. Outliers above the upper quartile in February and March indicate they may represent extreme weather events (Fig. 4 c).

The highest values for relative air humidity were recorded between November and May, with the highest median in April and the lowest in September (Fig. 4 d). The outliers below the lower quartile between November and January indicate that the humidity was below average for the series studied for these months.

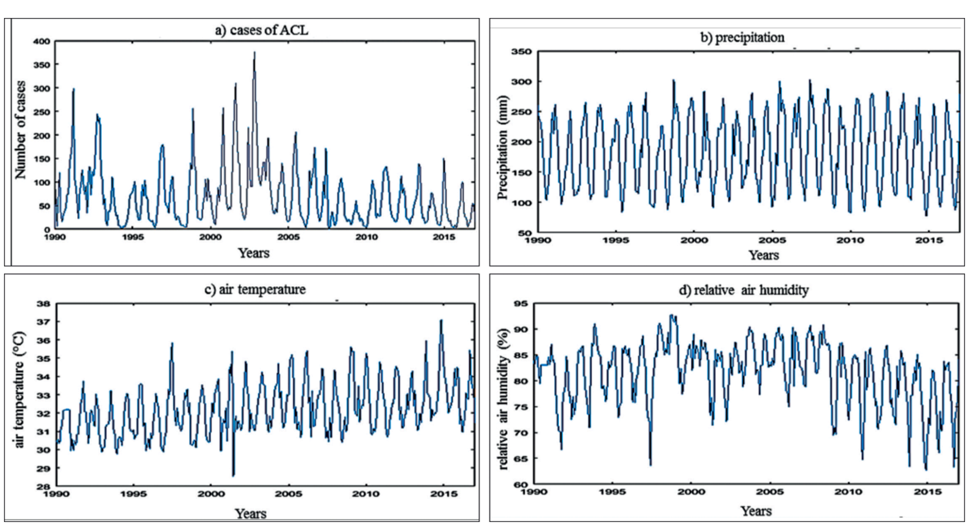

Fig. 3. Monthly distribution of historical series data for a) cases of ACL; b) precipitation; c) air temperature; d) relative air humidity for the municipality of Manaus between the years 1990-2017.

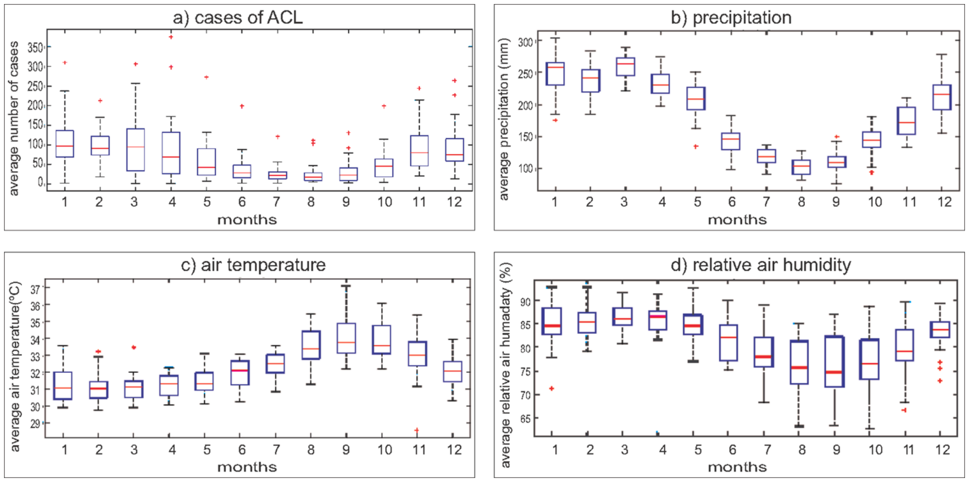

Fig. 4. Box plot of the monthly historical series of a) ACL cases; b) precipitation c) air temperature; d) relative air humidity for the municipality of Manaus from 1990 to 2017.

3.3. Assessment of the degree of relationship of the climatic elements with ACL dynamics the municipality

3.3.1. Total series waveform analysis

The following images present the wavelet analysis results (Fig. 5 a-d) for the entire series of analysed variables, showing the wavelet transform's local power spectrum. For all data series, the annual cycle contained most of the variants (Fig. 5 a-d), except for the humidity series in the years between 2000 and 2005 (Fig. 5 d). For the ACL case series, the significant sign on the annual time scale occurred from 1999 to 2009. Weaker signs without statistical significance occurred on the scales of two to three years and from four to six years for the case series, temperature, and humidity (Fig. 5 a,c,d).

The precipitation data and the total cases that occur on the one-year scale indicate a strong relationship between the two variables with a phase difference of around 45 degrees; that is, the maximum peak of the precipitation series is lagged by at least three months to the peak of total cases. Another representative sign can be observed at the beginning of the series for a scale of four to six years. In this case, the lag between the series indicates that a maximum peak of precipitation precedes the maximum peak of ACL cases by a period of 12 months (arrows at 180°) when considering the 4-year time scale (Fig. 6 a).

The temperature and total case series showed a lag of around -135° on the annual scale, indicating that maximum temperature precedes a maximum peak of ACL cases by approximately five months. A significant discrete signal occurred at the beginning of the series for the two-year scale, and the lag time between the series was also five months (Fig. 6 b).

The humidity and ACL data analysis results suggest that on an annual scale, the humidity series is out of date, and its maximum value occurs three months in advance of the peak of the total of cases (inclination of the arrows at 45°). Significant events could be observed in the two-year and four to six-year scales between 1990 and 2008. Arrows at 135° occurring on the four to six-year scale infer that the humidity series lagged and that its peak occurs approximately 5 months before the peak of cases (Fig. 6 c).

3.3.2. Wavelet transform analysis for anomaly series

The local wavelet power spectrum for the series of anomaly cases presents significant values in the annual scale occurring between 2003 and 2005. Non-significant values occurred in the scales of 2 and 4 to 6 years. More significant variances occurred on the scale of two to three years in the case of precipitation, with the most significant period occurring between 1995 and 2000. The temperature and humidity series did not show significant results; however, greater variances occur on an interannual scale. The El Niño 3.4 index showed significant signs on the two to four scales throughout the analyzed period (Fig. 7 a-e).

Coherence and phase difference of the wavelet transform analysis for the series of case anomalies, precipitation, temperature, humidity, and

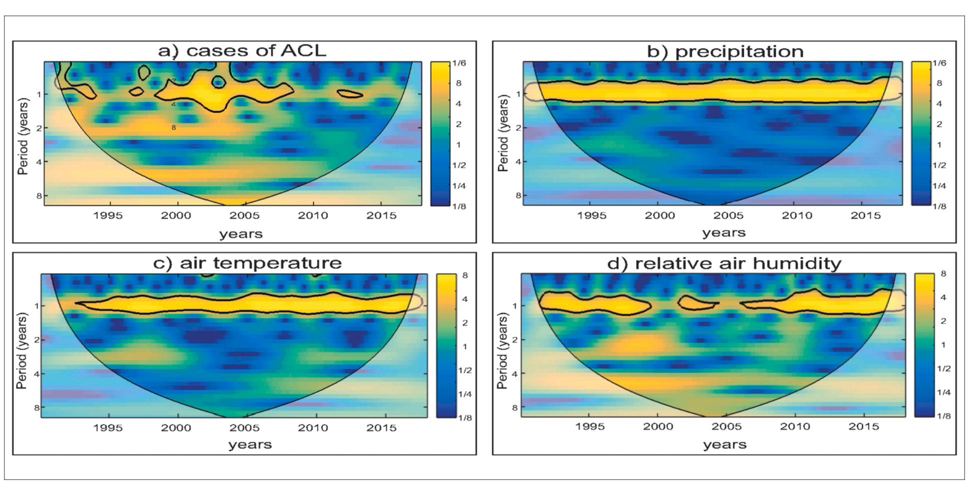

Fig. 5. Spectrum of the local power of the wavelet for the series: a) the number of ACL cases, b) precipitation, c) temperature and d) humidity. The U-shaped curve represents the Cone of Influence. The closed contour indicates areas where the wavelet power spectrum is significant at the 95% confidence level.

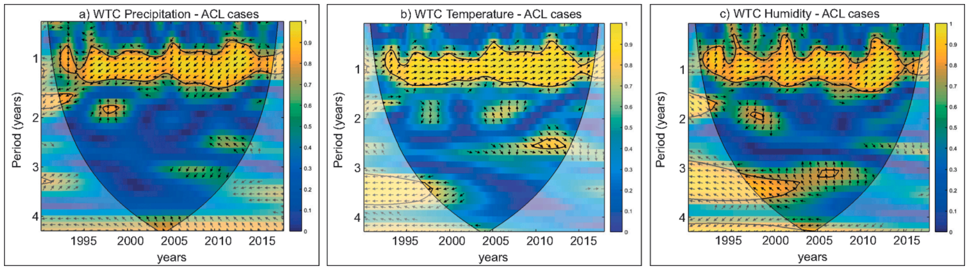

Fig. 6. Analysis of Coherence and phase difference of the Wavelet Transform for the total series: a) WTC Precipitation - ACL Cases, b) Temperature WTC - ACL Cases, c) Humidity WTC - ACL Cases. The shaded area represents coherence values and ranges from 0 to 1.0. Continuous contours encompass areas with significant values at 95% confidence level. The region where edge effects are important is under the U-shaped curve.

El Niño 3.4 is shown in Fig. 8 a-d. Results of wavelet analysis for the analyzed variability scales appear to be dependent on the period. The relationship between precipitation anomalies and case anomalies had the strongest indication of occurring between the initial years of the series 1990 to 1997 for the 4-8 year scale, with a phase difference of 180°. For the scale of 1-2 years, this occurred practically in phase. For the 3-year scale, maximum values of coherence occurred from 2009 to 2015, with a phase difference of approximately 45°, indicating a lag of approximately 6 months (Fig. 8 a).

The wavelet graph of the temperature anomaly and case anomaly (Fig. 8 b) showed less intense signs in the interannual scales (2-3 years and 4-8 years) compared to the precipitation analysis. Regarding humidity, the analysis showed significant signs occurring on a scale of four to six years between 1990 and 2003, with a phase difference of 135°, which corresponds to an interval of around 12-18 months of lag (Fig. 8 d). It is known that for timescales of over 2 years, ENSO has an important role in the climatic variability of the Amazon. Thus, analysis of coherence and phase difference was carried out to evaluate the relationships between the climatic variability linked to ENSO and ACL variation.

In the coherence analysis considering the El Niño 3.4 index and ACL cases for the four to eight-year scale, it was observed that the series of anomalies of these two variables were in phase (arrows at 0°). The maximum peak coincided in the period between 1990 and 2005 (Fig. 8

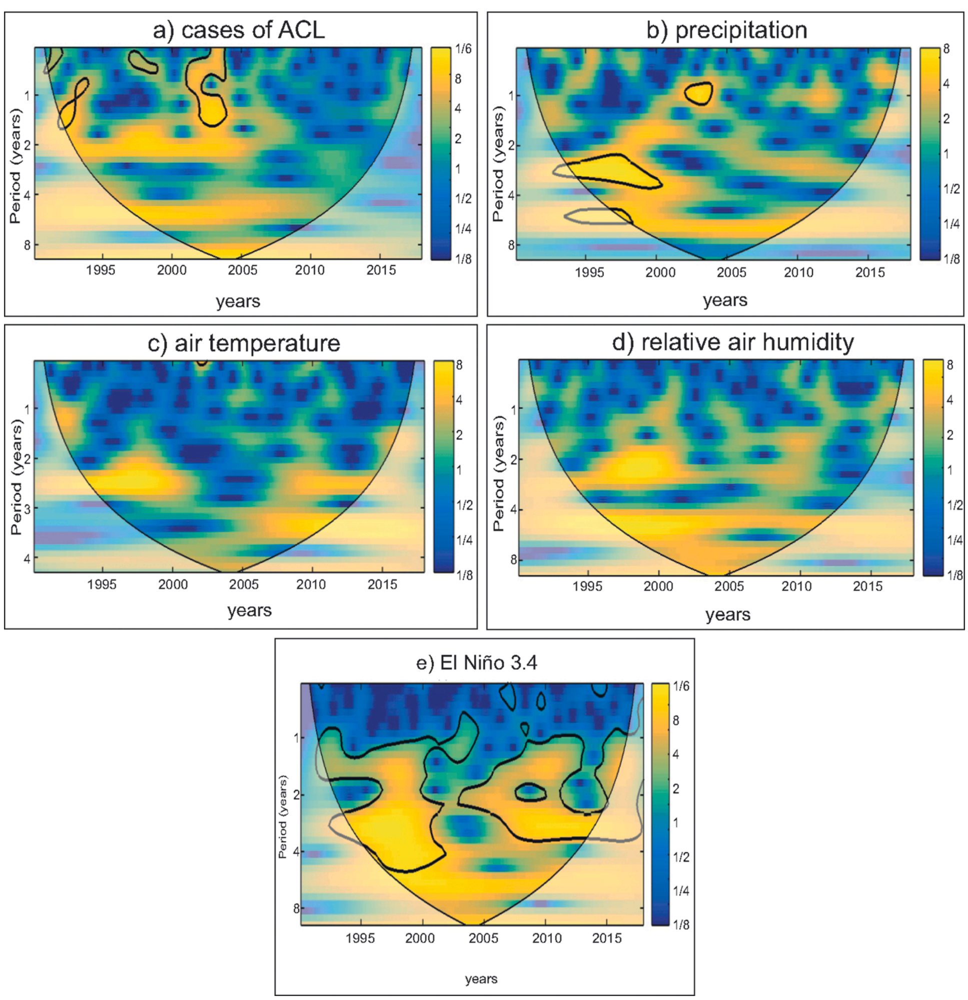

Fig. 7. Spectrum of the local Power of the wave for the series: a) the number of cases of ACL, b) precipitation, c) temperature, d) humidity and e) El Niño 3.4. The U-shaped curve represents the Cone of Influence. The closed contour indicates areas where the wavelet power spectrum is significant at the 95% confidence level.

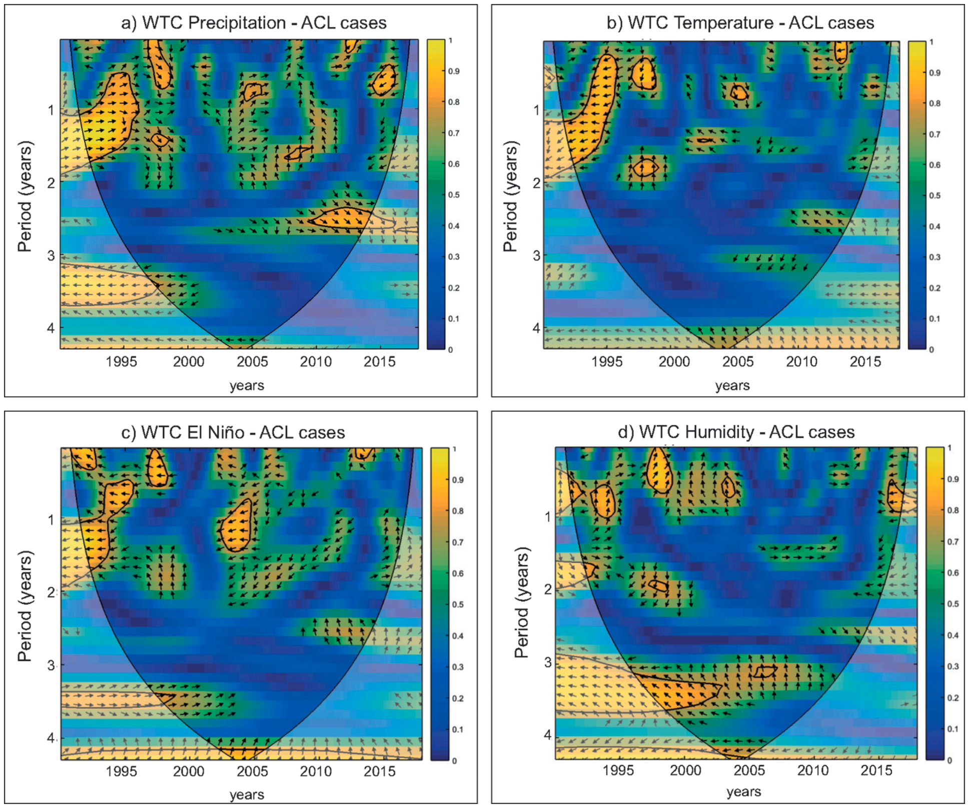

Fig. 8. Analysis of Coherence and phase difference of the Wavelet Transform for the total series: a) Precipitation – ACL Cases, b) Temperature - ACL Cases, c) Humidity - ACL Cases, d) El Niño 3.4 - ACL Cases and e) humidity - ACL Cases. Shaded areas represent coherence values and range from 0 to 1.0. Continuous contours encompass areas with significant values at the 95% confidence level. The region where edge effects are important is under the U-shaped curve.

c).

Since the analysis of coherence and phase difference results indicates a relationship between the ENOS variations and ACL cases, the average annual cycles of ACL cases during El Niño, La Niña, and Neutral were analyzed (Fig 9 a). In La Niña years, there was an anticipation of maximum values of ACL recording in January, February, and March (average of 100 to 120 cases), while for El Niño years, the maximums occurred later: March, April, and May (the average varied between 95 and 110 cases).

The increase in precipitation was above average for the La Niña years, with the wettest month (January) presenting an average value of 350 mm. The month of January for normal and El Niño years presented averages of ± 285 mm and 245 mm, respectively. The temperature and humidity variables also altered due to the occurrence of the climatic phenomena El Niño and La Niña (Fig. 9 c and d). The effects of ENSO on rainfall patterns and its the impact on the dynamics of ACL cases are shown in Fig. 9 a and b.

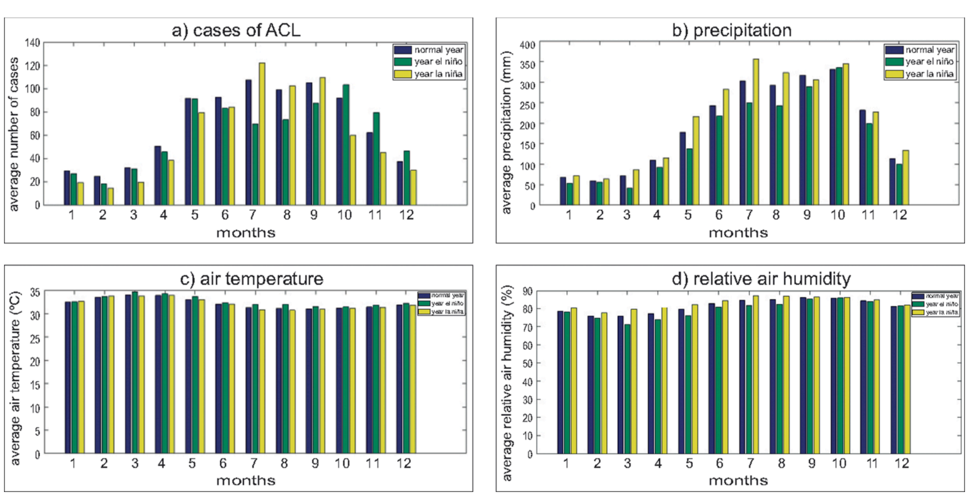

Fig. 9. Annual cycle adapted for El Niño year (annual cycle starting in July and ending in June). A) monthly average of ACL cases; B) monthly average of precipitation; C) monthly average temperature; D) monthly average humidity. Blue bars represent years without weather changes, green ones represent years of the occurrence of El Niño and yellow ones represent years of La Niña.

4. Discussion

American cutaneous leishmaniasis (ACL) is a neglected parasitosis. Its occurrence is favoured mainly by factors linked to economic, social, environmental, and climatic conditions (Guerra et al., 2019; Guerra et al., 2015; Ministério da Saúde, 2017). In Brazil, the North Region accounts for the highest number of cases, and according to the data in this study, in the state of Amazonas, in the last 30 years, the municipality of Manaus accounted for 54.2% of the reported cases. The vast majority of reported cases come from municipalities that make up the Metropolitan Region of Manaus, located along two highways - AM 010 and BR 174, which provide easy access to Manaus. In general, in the state of Amazonas, and the whole Amazon, the wild *Leishmania* cycle, mainly for *L. guyanensis*, is favoured by various human activities that make the population vulnerable, consequently contributing to their exposure and infection (Guerra et al., 2015).

Among the socioeconomic conditions, work activities such as military training in the jungle, ecotourism, mining, and agricultural activities close to the forests are factors of vulnerability to the disease's occurrence (Guerra et al., 2019; Torrence and Webster, 1999). Together with associated environmental changes (caused by man) and climatic phenomena, these changes result in changes in the seasonal patterns of disease occurrence. As observed in the current study, leishmaniasis has a marked seasonality for all the climatic variables analyzed, with the highest number of cases occurring mainly in the wettest months, which coincides with the highest humidity lowest temperature.

The first quarter: January to March (Fig. 9 a-d) are rainy months; La Niña events modify the precipitation cycle, causing increased rainfall levels or early rains in years experiencing the La Niña phenomenon. As a result, ACL cases begin to emerge a few months earlier than expected (from November). An inverse effect is observed in years when El Niño events are recorded, where the majority of the ACL cases occur later: March to May.

Thus, the El Niño and La Niña events, which occur on a global scale, significantly change rainfall amounts and temperature. Their impact is felt and observed at a local level (Fig. 2), as characterized by changes in the seasonal ACL patterns and the population density of its vectors, as previously described in several studies carried out on this theme (Cabaniel et al., 2005a; Cardenas et al., 2006; Delgado et al., 2004; Gagnon et al., 2002). The importance of these climate events on ACL transmission dynamics cannot be overemphasized. This is because most vector development and activity take place under the direct influence of temperature and humidity at the microclimatic level. Furthermore, vegetation cover and animal host populations are affected by climate, as well as by interactions among all of the components of the cycle (Mannelli et al., 2012). These changes in vector and animal-reservoir behaviours induced by climate change and ENSO events subsequently contribute to either an observed expansion or reduction of the geographical range or frequency of ACL cases.

In the Americas, the ENSO phenomenon has been studied as an event responsible for the occurrence of climatic anomalies and responsible for directly affecting the annual ACL cycle. This demonstrates that the disease occurrence varies because of anomalies occurring in the climatic elements (Cardenas et al., 2006; Azimi et al., 2017; Souza et al., 2015).

Cabaniel et al. (2005a), analyzed the potential effect of El Niño-Southern Oscillation (ENSO) on the occurrence of new cases of leishmaniasis in the state of Sucre, Venezuela, 1994-2003, and showed a large number of cases of the disease during La Niña and one low occurrence during El Niño in that region, corroborating with our data. However, in the northeast of Colombia, it was during the El Niño period that leishmaniasis cases increased, and during the La Niña events held between 1985-2002, a much smaller number was observed (Cardenas et al., 2006). It is noteworthy that the species of *Leishmania* and vectors circulating in these areas are different. In Colombia, 98% of cases of cutaneous leishmaniasis are mainly produced by *L. braziliensis, L. guyanensis* and *L. panamensis*, transmitted by *Lutzomyia gomezi, Lutzomyia ovallesi* and *Lutzomyia panamensis* (Altamiranda-Saavedra et al., 2020; Valderrama-Ardila et al., 2010). While in Brazil, as previously mentioned, *L. guyanensis* is the main species causing disease in man, with *L. umbratilis* being its primary vector and *L. anduzei* the secondary (Barbosa et al., 2008; Benício et al., 2015; Coelho et al., 2011; Guerra et al., 2006). Despite this, studies regarding potential wild reservoirs show that opossums (*Didelphis marsupialis*) are the most common species in the entire American territory, being, therefore, the most successful ACL reservoir, according to the several studies carried out in both countries (Alemán et al., 2006; Alvar et al., 2012; Arias et al., 1981; Arias and Naiff, 1981; Calderón et al., 1999; Chagas et al., 2018; Guerra et al., 2007).

Franke et al. (2002) showed that in Bahia, the annual incidence of visceral leishmaniasis also changed during the ENSO occurrence in the area, especially during intense El Niño episodes. This reinforces the need for studies that demonstrate how climatic changes influence the occurrence of leishmaniasis along with the inter-annual time scales.

Additionally, climatic conditions may favour or prohibit ACL vectors' reproduction, consequently contributing to the disease transmission cycle's maintenance (Chagas et al., 2006, 2018; Guerra et al., 2015; Souza et al., 2015). Adequate precipitation stimulates the population growth of several species of sandflies (Rangel and Lianson, 2003). However, excess rain can cause a decrease in the supply of substrate and food, hindering development and causing the death of the immature forms of these insects (Castellón et al., 2000). The increase in rainfall observed during the period studied may have influenced the increase or decrease in the number of cases of ACL in the municipality of Manaus for the evaluated series.

The finding that most ACL cases occur in the rainy season corroborates with the results by Souza et al. (2015) and Guerra et al. (2015), who suggested that hot and dry conditions favoured vector reproduction followed by a maximum number of cases occurring in the ensuing rainy season. Despite the absence of publications that portray the ACL incubation period in the city of Manaus, what has been observed in the routine care in the leishmaniasis outpatient clinic of the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (which serves about 500 to 800 cases annually), is an estimated average incubation of 2 to 8 weeks. However, this incubation period was not a limiting factor in this study since patients in the studied region have continued exposure to vectors, due to the fact that the municipality is surrounded by areas of forests and forest fragments and the vast majority of these patients reside in rural locations, places of sustained transmission (Barrett and Senra, 1989; Guerra et al., 2015; Peixoto, 2020). Therefore, it is not possible to establish a precise incubation period. The average incubation period is estimated based on the care of patients who eventually attend these areas, where there is a greater risk of transmission, but who then return to their homes in the urban area of the municipality.

The observed temperature readings did not demonstrate significant changes and remained at a threshold that varied between 28.5°C and 37°C. According to Harvell et al. (2002), studying temperature is important because an increase can accelerate the development of sandflies while, on the other hand, also being responsible for decreasing their life span.

Relative humidity also did not show any significant tendency in the evaluated series, remaining at a threshold that varied from 62.8% (for the hottest month) to 92.7% (in the rainiest month). According to Queiroz et al. (2012), relative humidity is another factor that contributes to the occurrence of ACL vectors since its increase supports the availability of necessary substrate for the development of immature forms of sand-flies. However, excessive relative humidity can present a physical risk for these insects (Lindgren et al., 2006; Peterson and Shaw, 2003). It is worth noting that all these factors combined may or may not be responsible for the increase in the number of ACL cases in the municipality of Manaus.

Noteworthy consistencies occurring on two to four-year scales for total precipitation and ACL series (Fig. 8a) are important because they coincide with the ENSO variability period. The results from the analysis agree with and complement the findings by Souza et al. (2015), emphasizing how ENSO events influence the occurrence of leishmaniasis in South America.

Another important fact worth highlighting from this study is the discrepancy found in the total series between the different climatic variables and the number of cases of ACL on the annual scale, for instance, in the precipitation series, where a discrepancy of three months in advance was observed relative to the peak of ACL. This can be explained by the prolonged incubation period of the disease (on average 30 to 60 days after the vector bite) and the appearance of the lesions, associated with the notification period (generally done during diagnosis, which occurs on average 30 days after the lesions appear).

The humidity series' lag with the peak occurring approximately three months before the peak of disease cases coincides with the precipitation series. The increase in rainfall contributes to higher humidity, which, when not in excess, possibly also favours vector reproduction and development, increasing the sand-fly population density, as previously described (Chagas et al., 2018; Queiroz et al., 2012). This explanation is also applicable to the temperature series.

The series of anomalies showed a greater coherence in the scales of the frequency of ENSO occurrence, for example, the total number of cases and precipitation (Fig. 7 a-b). The effects of these events influence a change in the patterns climatic variables studied and the trends of occurrences of ACL cases in the municipality of Manaus. Wolfarth-Couto et al. (2019) also applied this form of analysis when studying the anomalies present in the malaria time series with precipitation and river level in different municipalities in the state of Amazonas.

It is important to note that the coherence found between the anomaly in the precipitation series and the number of cases of ACL on the scale of four to six years (period of occurrence of ENSO) showed a lag of 6 months. A possible explanation for this increase in the gap between the series when the annual cycle is removed (calculation of anomalies) is that the changes in precipitation during ENSO, particularly in El Niño years, greatly influence periods of greater and lesser vector density. The changes in vector density consequently delay episodes of ACL in the municipality and extend the notification period.

The incidence of ACL, the occurrence of ACL outbreaks, as well as the abundance, diversity, and distribution of the insect vectors and relationship with the climate, have been previously studied by several authors who all agree that this relationship is strongly significant (Azimi et al., 2017; Guerra et al., 2015; Dias et al., 2007; Peterson and Shaw, 2003; Queiroz et al., 2012).

Our work highlights the importance of climatic anomalies, such as the ENSO events, in the local trends of ACL, emphasizing that the wild and synanthropic reservoirs of *Leishmania sp*., play an important role in maintaining transmission of ACL in the Brazilian Amazon. According to the study by Roque and Jansen (2014), wild hosts would probably support the maintenance of the *Leishmania* species cycle, especially those animals considered synanthropic, such as *Didelphis* spp. In Manaus, several species of mammals such as *Choloepus didactylus, Tamandua tetradactyla, Proechimys sp.*, which are also important natural reservoirs of *Leishmania* spp, contributing to the maintenance of wild and peri-domestic transmission cycles of ACL, and man becomes susceptible due to his proximity to these animals mainly when conducting their work activities. In areas with *L. guyanensis* circulation, where the vectors are also present (Barbosa et al., 2008; Chagas et al., 2018), and due to its ability to adapt to environmental and climatic changes, presence of *D. marsupialis* in the peridomestic space, places man closer to the ACL transmission cycle (Arias and Naiff, 1981; Guerra et al., 2007)

The main vector of cutaneous leishmaniasis in this region is *L. umbratilis*, an insect with a habit restricted to the wild environment, and of great importance in the ACL zoonotic cycle (Arias et al., 1981; Arias and Naiff, 1981; Barbosa et al., 2008; Guerra et al., 2015; Guerra et al., 2007). In a recent study on the dynamics of transmission of the ACL in a rural area of transmission of the disease in the city of Manaus, Chagas et al. (2018) demonstrated a low frequency of sandflies in and around the house, and a higher proportion in the forest, including those infected with *Leishmania* sp. However, the vast majority of residents of that area, where entomological surveillance and vector control actions have not been feasible (Ministério da Saúde, 2017)), have already been affected by CL, mainly due to exposure when conducting work activities. In this sense, minimizing human-vector contact through personal protective clothing or repellents during work activities in the forests (hunting, deforestation, foraging, burning charcoal and extracting fruit) is the main method of preventing the disease.

Historically, the occurrence of ACL in the region is related to the urbanization and industrialization processes in the Amazon, which greatly contributed to the outbreak and emergence of outbreaks and epidemics. As a result of the urban and demographic growth of Manaus, as well as the implementation of development projects of great socio-environmental impact, in 1988, more than 50% of the cases of ACL reported in Amazona were treated at a tertiary referral hospital in Manaus (Guerra et al., 2015), and most patients were from the periphery, mainly from irregular settlements called “invasions” and land subdivisions that spread to other areas of the city. In these places, deforestation coupled with poor sanitary conditions, favorable biological conditions and contact with insect vectors and vertebrate hosts infected by *Leishmania*, were the factors responsible for the severe ACL outbreaks between the 1970s and 1990s (Barrett and Senra, 1989). In the early 2000s, urbanization stabilized, and the relationship between the eco-epidemiology of leishmaniasis, the dynamics of vegetation, climatic factors, and the density of sand flies in endogenous areas, showed that the seasonal distribution of the ACL during the year is more linked to the variations that occur during the rainy season from November to June, and that these risk areas are greater during this period, while from July to October, the low rainfall season, the risk of transmission decreases considerably (Peixoto, 2020).

Vector-borne diseases, such as leishmaniasis, are susceptible to climatic variations. Predicting how these variations in climate can influence disease prevalence in specific regions is a health challenge. Studies on this subject should be intensified to predict outbreaks, plan for and execute control interventions and implement measures to adapt to climate change. This is particularly important when these climatic variations directly cause changes in the period of occurrence of these diseases, consequently affecting the disease transmission cycle and increasing or decreasing its incidence in certain locations. Preparations for these changes may result in better diagnoses and patient management, considering that the supply of medicines depends on planning based on the demand from the annual cases registered by location.

5. Conclusion

During La Niña events, an increase in the number of ACL cases is expected because of the increase in rainfall from November, resulting in many cases reported in January, February, and March. Thus, it can be concluded that El Niño and La Niña events, which occur on a global scale, significantly affect local weather patterns, such as the amount of rain and temperature and their effects. Subsequently, these changes in local weather patterns promote changes in the seasonal patterns of Leishmaniasis cases and the population density of its vectors. This was shown for the municipality of Manaus, where dynamics of ACL cases are directly influenced by ENSO, which modifies the behaviour of environmental variables that, in turn, rapidly influence changes in the leishmaniasis transmission cycle and incidence.

Ethical issues

The data referenced in the city of Manaus were collected from secondary data banks and did not require information that identified the individual considered as a "registered case".

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Author contributions

Silva AS: Formal analysis; Investigation; Writing – original draft & review, **Andreoli RV:** Conceptualization; Methodology; Supervision; Writing – review & editing, **Souza RAF:** Conceptualization; Methodology; Supervision; Writing – review & editing, **Chagas ECS:** Writing – review & editing, **Moraes DS:** Formal analysis and Investigation, **Figueiredo RC:** Formal analysis and Investigation, **Smith-Doria S:** Data collect, **Mwangi VI:** Writing – original draft & review, **Moura ES:** Formal analysis and Investigation, **Souza ES:** Writing – review & editing, **Morais RF:** Writing – original draft, **Monteiro MM:** Data collect, **João FM:** Writing – original draft, **Guerra MGVB:** Conceptualization; Methodology; Supervision; Writing – review & editing**, Guerra JAO:** Project administration; Conceptualization; Methodology; Supervision: Writing – review & editing.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

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