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Meteorological factors associated with a high prevalence of leishmaniasis in Nicaragua

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Nicaragua has an alarmingly high prevalence of cutaneous (CL) and mucocutaneous (MCL) leishmaniasis in recent years with environmental factors creating a perfect habitat for vector-mammalian reservoirs and transmission of the parasite. The aim of this study is to identify environmental risk factors that may play a role in the high prevalence of CL in Nicaragua. The epidemiological, clinical, and tissue sample diagnosis data for the study was collected from the Ministry of Health's surveillance database. The land cover and clinical geospatial data were analyzed by ArcGIS. Poisson and negative binomial regression models were created to study environmental and epidemiological risk factors for CL in Nicaragua. CL and MCL were reported predominantly in the north-central (76.54%) and Atlantic (21.63%) regions of the country. Poisson regression analysis suggested mean annual temperature at 2 m (MAT), specific humidity in meters, altitude in meters, and median average rainfall as significant risk factors. The negative binomial regression model suggested that MAT and median annual rainfall were significant risk factors for CL and MCL occurrence. It is concluded that providing anticipated warning systems using ArcGIS predictive maps based on MAT and median annual rainfall may help design vector and reservoir control for leishmaniasis in Nicaragua.

Key words: Cutaneous leishmaniasis, geographic information systems, temperature, rain, environmental risk factors.

INTRODUCTION

Leishmaniasis is a parasitic infection caused by intracellular protozoa of the family Trypanosomatidae. The parasite is transmitted by a sand-fly of the genus *Lutzomyia* in the new world and *Phlebotomus* in the old world. The disease comprises a variety of clinical syndromes that include cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis (VL) (Torres-Guerrero et al., 2017).

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According to the World Health Organization (WHO), the disease is endemic in 97 countries and territories in Africa, Asia and Latin America (World Health Organization [WHO], n.d.). It is considered a Neglected Tropical Disease (NTD) since it affects mainly vulnerable populations in low- and middle-income countries that live in poverty, without adequate sanitation, and in contact with infectious vectors and domestic animals (WHO, n.d).

The WHO has estimated an annual incidence of 700,000-1,000,000 cases and about 20,000-30,000 deaths per year. Approximately 66,941 cases of CL are reported annually in America. The incidence rate reported for the entire region was 21.71 cases per 100,000 persons in 2016. The highest incidence rates were reported in Suriname (267.9/100,000 persons), Nicaragua (197.2/00,000 persons), and Colombia (52.93/100,000 persons) (Pan American Health Organization [PAHO], 2018). In recent years, Nicaragua has presented alarmingly high numbers of cases and elevated incidence rates. The most common forms of the disease in Nicaragua are the cutaneous and mucocutaneous forms, which can lead to ulceration of skin and mucosa, leaving scars for life (Handler et al., 2015). It is distributed in the three regions of the country, with a higher burden in the Central region (85.22%), followed by the Atlantic (13.46%) and the Pacific (1.31%) (Ministerio de Salud [MINSA], 2019). Approximately 90% of the national cases correspond to CL and 5 to 10% correspond to MCL (MINSA, 2019). The Ministry of Health of Nicaragua has reported all forms of leishmaniasis, except the visceral form. CL and MCL were reported in 90 municipalities of Nicaragua in 2018. Most of the cases were reported in the municipalities of San Jose de Bocay (510), El Cua (441), and Rancho Grande (379) in the central region; Siuna (341), Waslala (314), and Bonanza (72) in the Atlantic region; Telica (13) and Managua (9) in the pacific region (MINSA, 2019).

Different studies have shown that environmental factors, such as temperature, elevation, topography, and vegetation may create a perfect habitat for the vector and intermediate hosts of the parasite and therefore enhance the transmission of the disease (WHO, 2010). Despite the efforts of the Nicaraguan Ministry of Health of reducing the number of cases, the disease still exists with a high incidence in the Central and Atlantic regions of the country (MINSA, 2019). During the last three decades, many studies have shown that computer-based geographical information systems (GIS) have provided valuable tools to map the distribution of infectious diseases and analyze environmental factors that may play a role in the spatial and temporal distribution of vector-borne diseases (Hipp, 2015; Mollalo et al., 2015). Therefore, the aim of this study is to apply the spatial analytical tools in GIS and conduct vigorous regression statistical analysis for the identification of environmental risk factors that may play a role in the prevalence of cutaneous and mucocutaneous leishmaniasis in Nicaragua.

MATERIALS AND METHODS

Study area

The study site is the Republic of Nicaragua, which is the largest country in the Central American isthmus, bordered by Honduras to the northwest, the Caribbean to the east, Costa Rica to the south, and the Pacific Ocean to the southwest. It is located between latitude 10º and 15º 45´ North and longitude 79º 30´ and 88º West. The nation occupies a landmass of 130,967 km^2 (50,567 m^2) and contains a population of 6,460, 411 inhabitants. Nicaragua has three distinct geographical regions: The Pacific lowlands, the Amerrisque Mountains (North-central highlands), and the Mosquito Coast (Atlantic lowlands/Caribbean lowlands). The climate is predominantly tropical, with variations in temperature and humidity depending on the altitude and region of the country. The country can be divided into 17 administrative departments and 139 municipalities.

Data collection

The epidemiological and clinical diagnosis was done by physicians at health posts, health centers, and primary hospitals of each SILAIS (Sistema Local de Atención Integral en Salud). The tissue sample was diagnosed at the Department of Parasitology of the National Center of Diagnosis and Reference of the Ministry of Health in Managua. 95% of the cases included in this study were diagnosed by clinical examination in endemic areas, followed by microscopic examination of the tissue sample and PCR at the CNDR. Approximately 5% of the cases were diagnosed only by clinical and microscopic examination of the tissue sample due to geographic and logistical difficulties of shipping samples to Managua for specialized diagnosis at CNDR. The Ministry of Health of Nicaragua (MINSA) provided the epidemiological data for this study (MINSA, 2014).

Geospatial data and analysis

Environmental and ecological factors such as mean annual temperature (MAT), median annual rainfall (precipitation), elevation, and humidity were retrieved from the National Aeronautics and Space Administration (NASA) database (NASA, 2020). The population density was retrieved from Instituto Nacional de Información de Desarrollo (Instituto Nacional de Información de Desarrollo [INIDE], 2017). The geospatial and climatic data were analyzed by ArcGIS version 10.8.1 (http://www.esri.com/arcgis). Shapefile point layers of municipalities, departments, regions, water bodies, elevation, and population of Nicaragua were extracted from ESRI online database for a visual representation of the study site. ESRI shapefile for Nicaraguan municipalities contains 139 divisions. Therefore, adjacent administrative municipalities were combined for better representation through ArcGIS: San José de Bocay-Alto Wangki-El Cuá, Mulukuku-Waslala, El Tortuguero-El Rama, El Ayote-Bocana de Paiwas, El Coral-Villa Sandino, Corn Island-Bluefields, and Ciudad Sandino-El Jícaro. The epidemiological distribution of cutaneous and mucocutaneous leishmaniasis was investigated at the municipal and departmental level. The relationship between the prevalence and environmental

Table 1. Prevalence of cutaneous leishmaniasis by Departments of Nicaragua, 2018.

Pacific region (1.83%)[1]	Number of cases[2]	Percentage of total cases (%)[3]
Chinandega	13	0.35
Leon	37	0.99
Managua	15	0.40
Masaya	1	0.03
Carazo	2	0.05
Granada	0	0.00
Rivas	0	0.00
Central region (76.54%)		
Jinotega	1375	36.90
Nueva Segovia	255	6.84
Madriz	11	0.30
Esteli	14	0.38
Matagalpa	961	25.79
Boaco	14	0.38
Chontales	49	1.32
Rio San Juan	173	4.64
Atlantic region (21.63%)		
Bilwi	72	1.93
Las Minas	518	13.90
RACCS	141	3.78
Zelaya Central	75	2.01
Total	3726	100

Source: Mapa de Padecimientos. MINSA. (http://mapasalud.minsa.gob.ni). [1.] Column one represents the percentage of total cases of leishmaniasis per region in Nicaragua and the different departments that are located within each region. [2.]Total number of cases of leishmaniasis in 2018. [3.]Percentage of total cases per department in 2018.

factors such as precipitation in mm day^{-1} (Precip), mean annual temperature at 2 m in °C (T2m), specific humidity at 2 m in kg kg^{-1}, altitude in meters (Altitude), and epidemiological information such population density in population/100,000 inhabitants (Popdens) were analyzed.

Statistical analysis

A multiple linear regression model was initially constructed using PROC REG to determine the risk of various environmental/epidemiological factors on the incidence of CL and MCL. The diagnostics done to determine the fit of the linear regression model resulted in a violation of the assumption of normality of residuals and homoscedasticity. Therefore, a Poisson model was constructed assuming the number of cases as independent counts. The PROC GENMOD procedure estimated the sampled parameters by municipality. The dispersion parameter was then estimated by the residual deviance and by Pearson's chi-square divided by the degrees of freedom in PROC GENMOD. To accommodate the extra-Poisson variation, detected in the variance estimates of the model, a negative binomial non-homogenous regression-based framework was created. The model used annual incidence numbers as a dependent exploratory variable and the Poisson procedure was fitted using an extra-binomial variation. These results along with the likelihood ratio test and other likelihood criteria (such as BIC for model and variable selection) were illustrated employing sampled SAS and ArcGIS datasets. The objectives in this research were to: (1) construct multiple varying regionalized land cover and meteorological ArcGIS cartographic models; and, (2) to exploit a probabilistic Poisson gamma-distributed count variable model framework in SAS (9.4) to determine statistically significant environmental covariates at a 95% confidence interval associated to CL and MCL cases time series sampled in Nicaragua.

RESULTS

Geographical distribution

Most of the cases were reported in the North Central (76.54%) and Atlantic (21.63%) regions of the country. The least number of cases were registered in the Central and South Pacific regions (1.83%) (Table 1). Seventeen out of nineteen administrative divisions of the MINSA present cases of leishmaniasis (Table 1). Only the Departments of Rivas and Granada did not presented

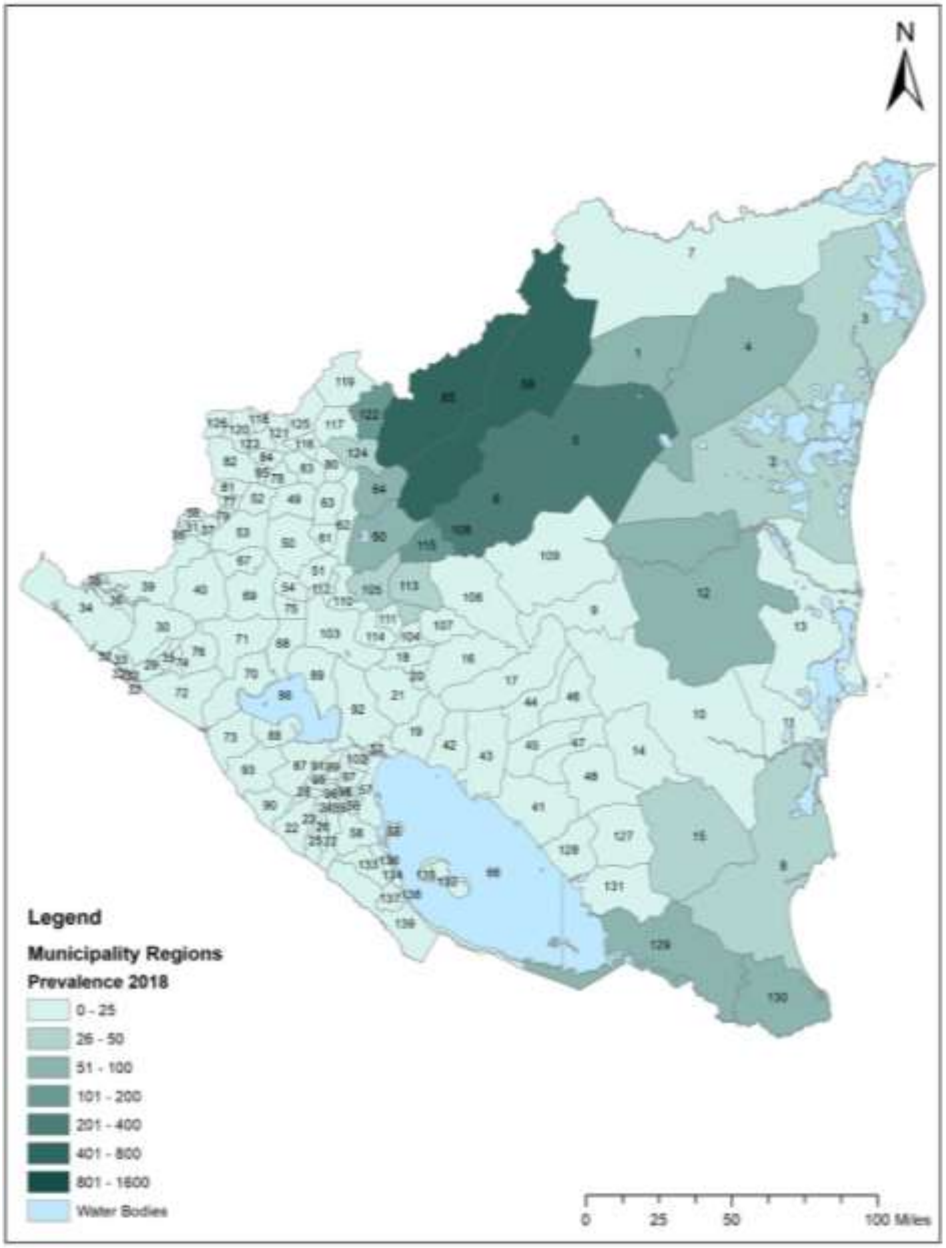

Figure 1. Prevalence of cutaneous leishmaniasis by Municipalities in Nicaragua, 2018. Source: Ministry of Health. Managua, Nicaragua.

cases of the disease (Supplementary materials). CL and MCL were reported in 90 municipalities of 139 in Nicaragua (Supplementary materials). The incidence rate for the year 2018 was 57.67 per 100,000 inhabitants. A high number of cases were reported in the municipalities of Wiwilí (770), El Cua (441), and Santa María de Pantasma (73) in the central region; Siuna (377), Waslala (314), and Bonanza (72) in the Atlantic region; Telica (13) and Managua (9) in the pacific region (Figure 1).

Environmental factors

After adjusting for the rural population and population density, the Poisson regression model reported a statistically significant association with the meteorological factors (mean annual temperature at 2 m in °C, specific humidity at meters, altitude in meters, and median average rainfall). The analysis of the parameter estimates suggests collinearity between humidity at 2 m and means

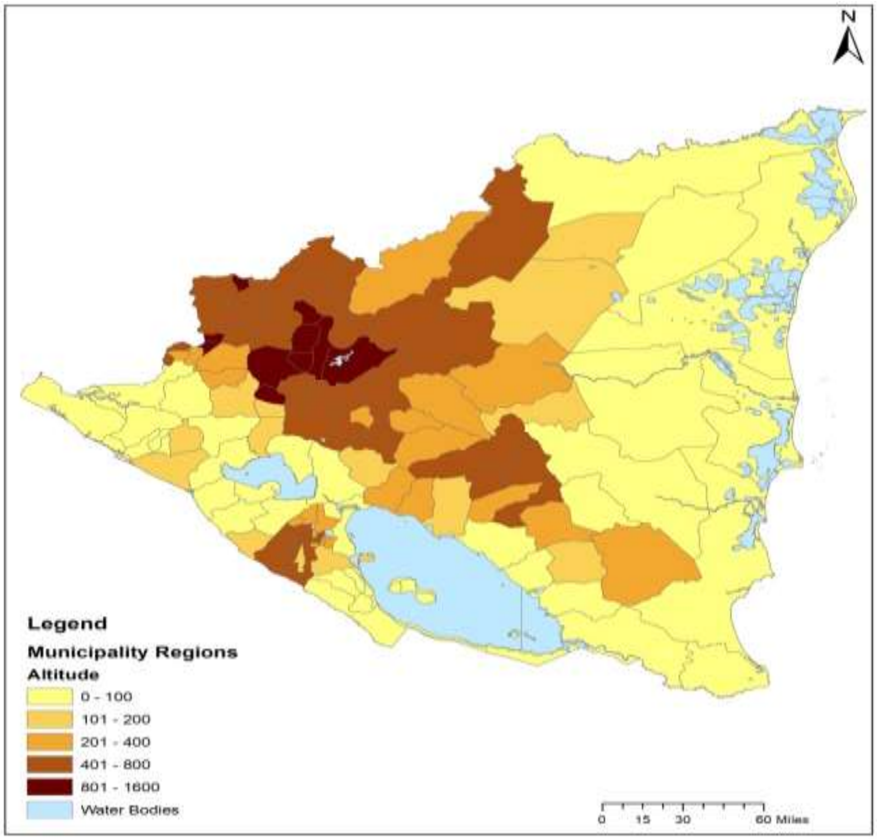

Figure 2. Altitude of territorial Nicaragua.
Source: https://www.diva-gis.org/gdata.

average rainfall. Based on the Poisson regression analysis, the mean annual temperature has a negative association with CL, and MCL incidence with a 1°C increase in average annual temperature results in risk a of 0.48 (95%CI: 0.45, 0.49) for the occurrence of CL and MCL. The model had a residual deviance proportion >1 (Value/ df = 36.9324) suggesting an over-dispersed model.

To account for this overdispersion and collinearity, a negative binomial regression model with a gamma distributed non-homogeneous mean without the variable humidity at 2 m was ran. The results of the analysis suggested the meteorological factors of mean annual temperature and median annual rainfall are significant risk factors for CL and MCL occurrence. The mean annual temperature had an inverse relationship with occurrence of CL with a risk ratio of 0.46 (95% CI: 0.33, 0.64) for a unit increase in average temperature. Similarly, while median annual rainfall had a significant association, the effect on the occurrence of CL or MCL was negligible with the risk ratio close to 1 (RR=1.003). The residual deviance for assessing the goodness of fit had a proportion close to 1 (value/df = 0.99, p=0.47), suggesting that the model is a good fit for the data.

DISCUSSION

Most of the cases of cutaneous and mucocutaneous leishmaniasis were reported in the municipalities of the Central and Atlantic region of the country, where *Lutzomyia spp.* can live in optimal conditions (Raymond et al., 2010). In Central areas and Atlantic lowland plains of Nicaragua where typical CL is common, the most common species are *Lutzomyia cruciate* and *L. barretoi \ majuscula*. These sand flies are common in agricultural areas with high altitudes and lower temperatures (Pérez et al., 2014). Many studies have reported the relationship of *Lutzomyia* species with soil rich in organic matter, high relative humidity, and high intermediate vegetation density (NDVI) values (Costa et al., 2018; Vivero et al., 2015). In this study, the highest altitudes were detected in the Central (516.89 m), Atlantic (179.13 m), and Pacific region (131.60), respectively (Figure 2 and Table 4). The spatial representation of the annual average temperature, specific humidity at 2 m above the displacement height, precipitation, and land usage for 2018 was documented in Figures 3 to 6.

As in many other parts of the world, the vector is located mainly in high altitude and rural areas of

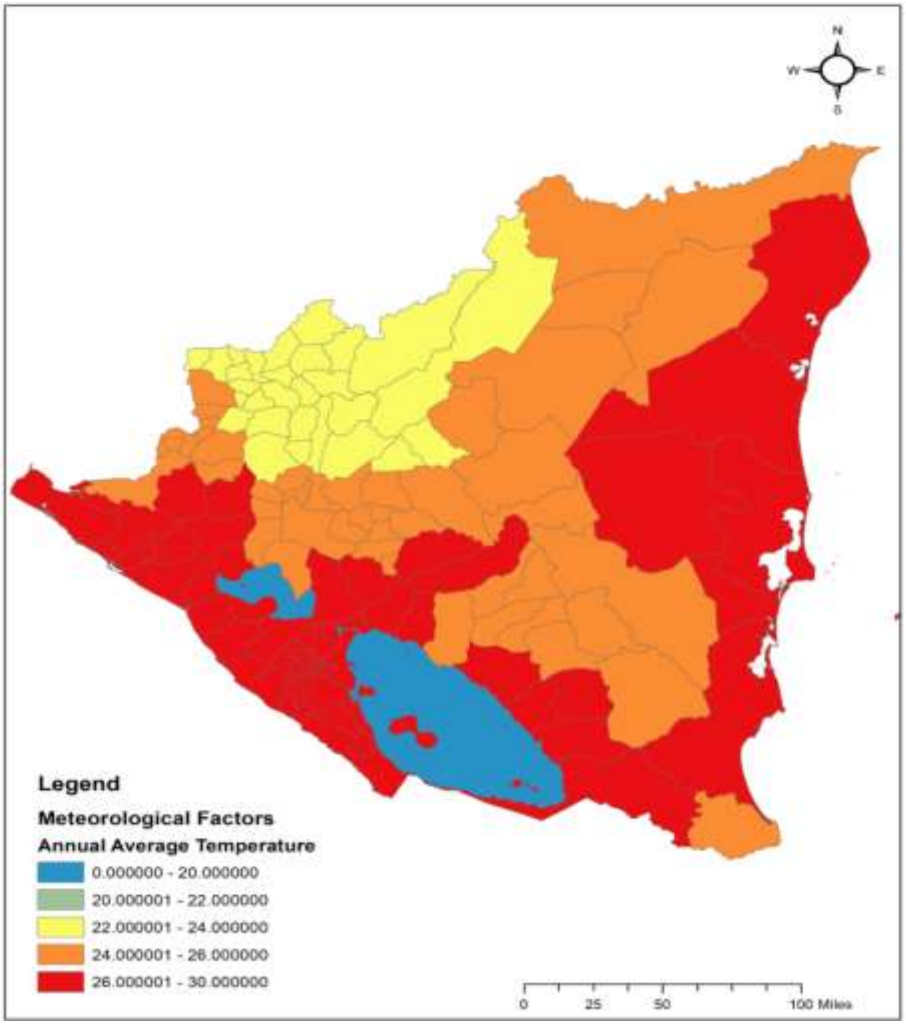

Figure 3. Annual average temperature of Nicaragua by municipality.
Source: https://power.larc.nasa.gov/data-access-viewer/

Nicaragua, especially in the Department of Jinotega and Matagalpa (Guernaoui et al., 2006; Salah et al., 2007). Furthermore, many municipalities of the Central and Atlantic regions of Nicaragua have been experiencing large scale deforestation that can be associated with the increased incidence of leishmaniasis in these locations (Gourdji et al., 2015; Zeledon and Kelly, 2009; Salah et al., 2007). In addition, most of the population living in these municipalities are vulnerable due to their social exclusion and low socioeconomic status, factors that can have a positive influence on the high incidence of leishmaniasis (Chaves et al., 2008; INIDE, 2017; Rodrigues et al., 2019). The relationship between poverty and leishmaniasis is very complex: If the poverty of a region increases, the risk of acquiring leishmaniasis and presenting severe forms of the disease also increases. Additionally, the disease by itself can exacerbate the poverty in affected families due to high expenditure in healthcare, the inability of family providers to work in the field of even high mobility/mortality for family members (Okwor and Uzonna, 2016). Concurrently, the rural municipalities of the Central and Atlantic regions of Nicaragua are the poorest of the country and also lack priority for systematic development despite the high incidence of poverty and communicable diseases prevalence (Kay, 2011).

All the variables appeared to be statistically significant when analyzed using the Poisson regression model (Table 2). However, there existed significant over dispersion in the Poissonian regression model. This phenomenon may have occurred in our leishmaniasis epidemiological model due to missing covariates, non-independent data, or excessive frequency of zeros in the parameter estimator dataset. Accounting for over

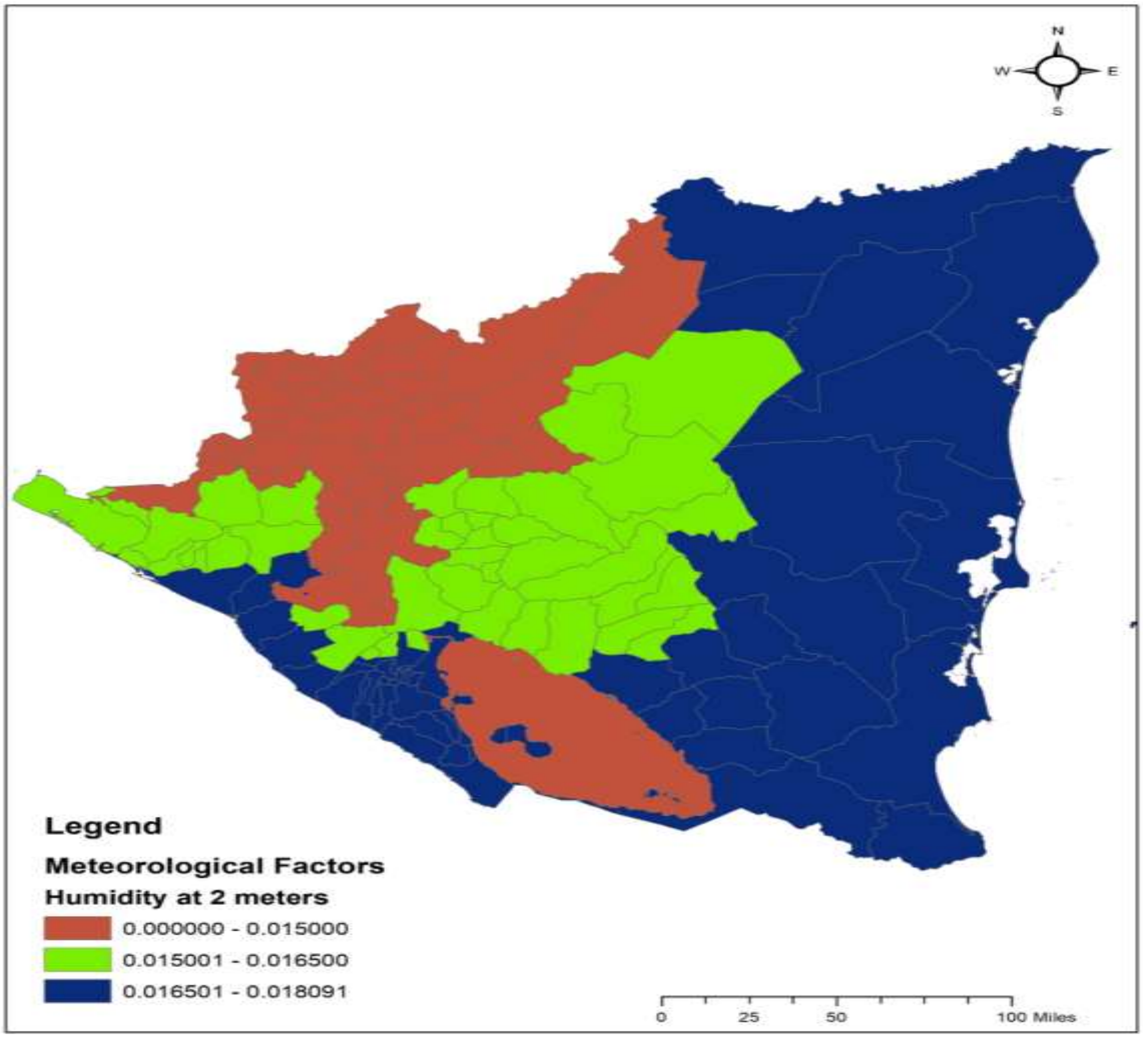

Figure 4. Specific humidity at 2 m above the displacement height data for Nicaragua by municipality.
Source: https://power.larc.nasa.gov/data-access-viewer/

dispersion in leishmaniasis epidemiology models is vital, as failing to do so can lead to biased parameter estimates and false conclusions regarding the hypothesis of interest (Harrison, 2014).

Observation-level random effects (OLRE), was employed to cope with overdispersion in our leishmaniasis model. Unfortunately, studies investigating the efficacy of observation level random data effect as a means to deal with overdispersion are scarce in the literature. Here we employ multivariate simulation to show that in cases where overdispersion is caused by random extra-Poisson noise or aggregation in leishmaniasis related count variable data, ORLE can yield more accurate parameter estimates compared to when overdispersion is ignored (Harrison, 2014). A simulation was constructed to investigate the impact of increasing the sample size on the dispersion of the variance parameters of Poisson data distribution to justify the utilization of an α-Negative binomial distribution for quantitating the over-Poissonian noise in the leishmaniasis model (Hilbe, 2011; Johnson, 2012).

The negative binomial regression model suggested the prevalence of cutaneous and mucocutaneous leishmaniasis in Nicaragua is associated with mean annual temperature, and median annual rainfall (Table 3). Many studies have reported similar results in where elevation, temperature and rainfall play a major role in the occurrence of cutaneous leishmaniasis (Mokhtari et al., 2016). A study conducted in Iran found that there was a positive relationship between mean temperature, relative humidity, and slope of the terrain with leishmaniasis incidence (Ramezankhani et al., 2018). Similarly, authors

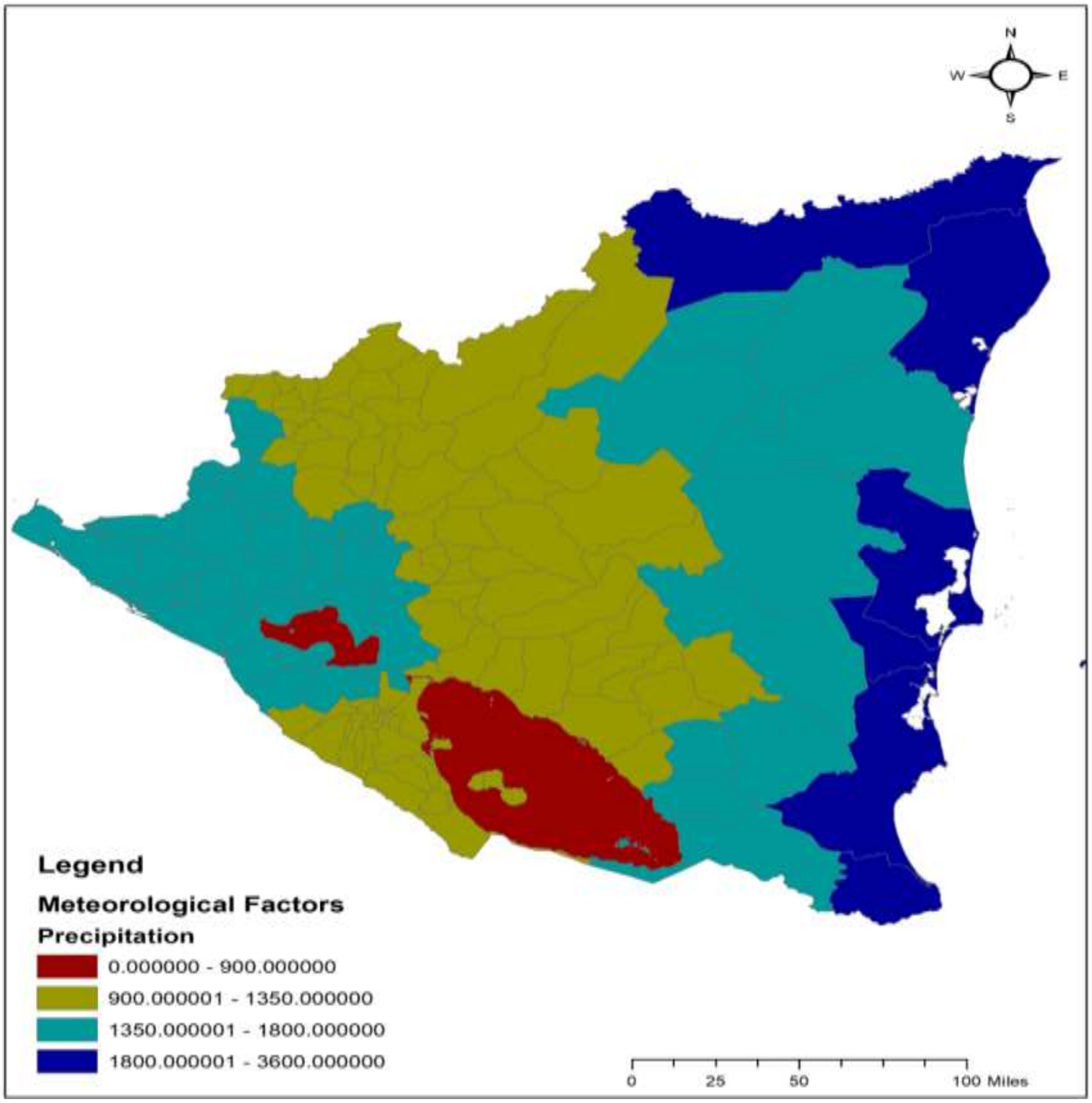

Figure 5. Precipitation data for Nicaragua by municipality.
Source: https://power.larc.nasa.gov/data-access-viewer/

Table 2. Poisson Regression Model for cutaneous and mucocutaneous leishmaniasis cases and environmental factors in Nicaragua.

Parameter	Estimate	Wald 95% confidence limits		Wald chi-square	Pr>chi-square (country)
Altitude	0.0008	0.0007	0.0010	122.71	< 0.0001
Humidity	1144.031	1025.943	1262.119	360.54	< 0.0001
Precipitation	-0.0010	-0.0013	-0.0007	53.89	< 0.0001
Mean annual temperature	-0.7324	-0.8010	-0.6639	438.65	< 0.0001

from China found a very significant association between temperature and relative humidity with visceral leishmaniasis (Li and Zheng, 2019). A systematic review of the effects of environmental and ecological conditions on the incidence of cutaneous leishmaniasis found that temperature and rainfall are the most important ecological variables to play a role in the seasonal cycle of this disease in the Old World (Mohammadbeigi et al.,

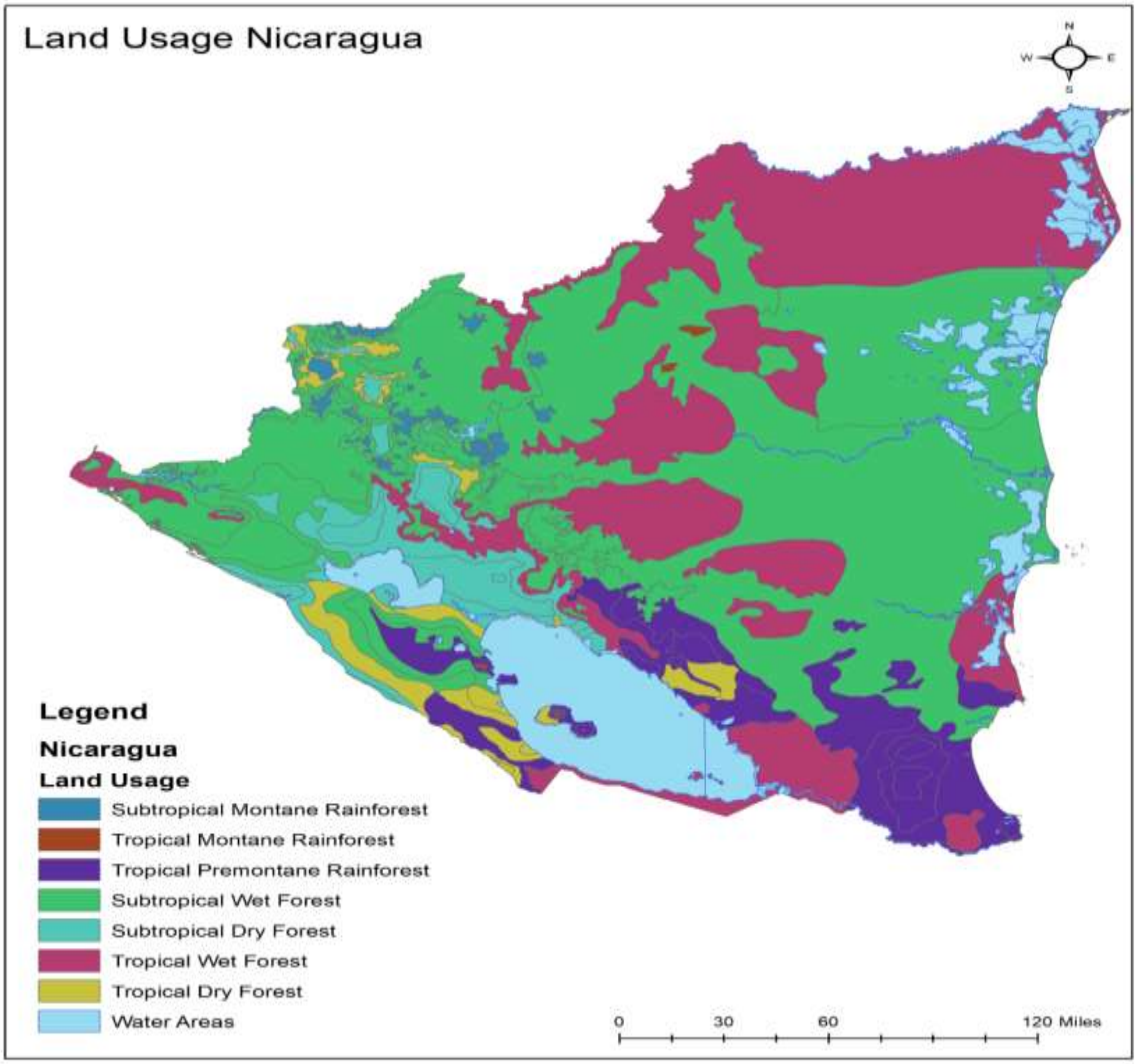

Figure 6. Land usage of Nicaragua.
Source: https://power.larc.nasa.gov/data-access-viewer/

Table 3. Negative binomial regression model for cutaneous and mucocutaneous leishmaniasis cases and environmental factors in Nicaragua.

Parameter	Relative risk	95% confidence limits		Wald chi-square	Pr>chi-square (country)
Altitude	0.998	0.996	1.0002	2.93	0.087
Precipitation	1.003	1.0009	1.005	7.90	0.0050
Mean annual temperature	0.463	0.334	0.641	21.52	< 0.0001

2020). Unfortunately, no study evaluates the relationship between ecological/environmental factors and the incidence of cutaneous leishmaniasis in the New World. Many studies have reported a higher incidence of cutaneous leishmaniasis in higher altitudes in the New World (Moo-Llanes et al., 2013; Warburg et al., 1991). On the other hand, the *Phlebotomus* spp. vectors can be found in a range of altitudes in the old world, depending

Table 4. Descriptive values for environmental and epidemiological factors associated with cutaneous leishmaniasis in Nicaragua.

Variable	Standards deviation	Minimum	Maximum	Mean (Country)	Mean (Atlantic)	Mean (Central)	Mean (Pacific)
Altitude	294.3909812	2.4400000	1280.00	355.5437226	131.5966667	516.8906154	179.1317544
Humidity	0.0011824	0.0138980	0.0180910	0.0159530	0.0171992	0.0152329	0.0164462
Precipitation	246.7770130	1194.92	3537.26	1383.97	1649.39	1331.77	1373.65
MAT	1.7319039	22.7800000	28.1900000	25.6645985	25.7186667	24.3309231	27.1712281
MaxMAT	1.2415998	27.6900000	32.4800000	30.0335036	29.3126667	29.3047692	31.0542105
Population density	387.0116641	0.8000000	3509.00	151.7182482	12.8866667	62.0615385	290.4929825
MinMAT	2.2946459	18.6300000	26.2300000	22.1843796	23.0720000	20.4780000	23.8966667

on the specie and locality (Akhoundi et al., 2016). There are several limitations to the study that needs to be considered before the interpolation of the data. The study is conducted based on mean or median environmental parameters and does not consider the daily and seasonal variations in environmental parameters. Ecological factors such as land usage and land cover, soil variety, and other topographic factors influencing CL and MCL were not considered in the analysis due to difficulty in the collection of data related to those factors. In the future, the researchers plan to run a spatial autocorrelation model to determine more specific associations between the incidence of CL and MCL and a combination of environmental and ecological factors. Spatial autocorrelation is a fundamental concept in spatial analysis (Getis, 2008). It is the correlation among values of a single variable strictly attributable to their relatively close locational positions on a two-dimensional surface, introducing a deviation from the independent observation assumption of classical statistics (Diniz et al., 2003). Spatial autocorrelation algorithms and a Markovian model can help in developing necessary predictive paradigms establishing the categories of municipalities based on the risk of CL and MCL.

Conclusions

Mean annual temperature and median annual rainfall were the environmental factors associated with a high prevalence of cutaneous and mucocutaneous leishmaniasis in Nicaragua. Jinotega, Matagalpa, and Las Minas were the most affected departments of the entire country. The combination of climatic and epidemiological factors can influence the occurrence of leishmaniasis in Nicaragua. Moreover, given the results of this study regarding the effect of mean annual temperature and median annual rainfall on the prevalence of CL and MCL in Nicaragua, it can be concluded that providing anticipated warning systems based on these meteorological conditions may help design vector and reservoir control for leishmaniasis in the most affected municipalities of the country. It is strongly recommended to carry out a spatial model to determine more specific associations between the occurrence of the disease with other environmental factors, such as slope, vegetation, landscape, and proximity to intermediate hosts.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interest.

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