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Article

Leptospirosis outbreaks in Nicaragua: identifying hotspots and exploring drivers for evidence-based planning

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Abstract: Leptospirosis is an epidemic-prone zoonotic disease that occurs worldwide. In Central America, leptospirosis outbreaks have been reported in almost all countries; Nicaragua in particular has faced several outbreaks. The objective of this study is to stratify the risk and identify "hotspots" for leptospirosis outbreaks in Nicaragua, and to perform an exploratory analysis of potential "drivers". This ecological study includes the entire country (153 municipalities). Cases from 2004 to 2010 were obtained from the country's health information system, demographic and socioeconomic variables from its Census, and environmental data from external sources. Criteria for risk stratification of leptospirosis were defined. Nicaragua reported 1980 cases of leptospirosis during this period, with the highest percentage of cases (26.36%) in León, followed by Chinandega (15.35%). 48 municipalities were considered hotspots, 85 were endemic and 20 silent. Using GIS analysis, the variable presenting the most evident pattern of association with hotspots is the percentage of municipal surface occupied by the soil combination of Cambisol (over pyroclastic and lava bedrock) and Andosol (over volcanic ashes foundation). Precipitation and percentage of rural population are also associated with hotspots. These methodology and findings could be used for Nicaragua's Leptospirosis Inter-sectoral Plan, and to identify possible risk areas in other countries with similar drivers.

Keywords: Leptospirosis; risk; outbreaks; Nicaragua; Central America

1. Introduction

Leptospirosis is an epidemic-prone zoonotic disease that occurs all over the world with highest incidence in countries with humid subtropical or tropical climates. The disease affects the most vulnerable populations and is mostly associated with poverty and ill-health. Epidemics are likely to occur more frequently in the future, as heavy rainfall and flooding increase as a result of global climate change [1].

The World Health Organization (WHO) is currently working on an estimate of the global burden of human leptospirosis, through a review of the existing evidence, the development of new epidemiological tools to evaluate the burden of the disease, and identification of technical gaps for research [1]. It is estimated that there are more than 500,000 cases of leptospirosis worldwide, the majority of reported cases presenting severe manifestations with mortality greater than 10% [2].

Two species of the bacterium are recognized: *Leptospira interrogans* and *L. biflexa*. The species of importance for public health, *L. interrogans,* has more than 200 serologic variants, called serovars, grouped into 23 serogroups [3]. The serogroups are useful for understanding the epidemiological transition of the disease. There are universal serovars, such as *icterohaemorrhagiae* and *canicola*, as well as serovars that occur only in specific regions based on its ecology. Each serovar has a preferred animal host, but each animal species may act as a reservoir for one or more serovars [3].

The epidemiological cycle includes asymptomatic rodent carriers that act as maintenance hosts and infect other asymptomatic rodents, as well as wild animals, livestock, and domestic animals. After a week of leptospiremia, these animals shed leptospires in urine into their environment. Infection in humans usually occurs through direct contact with the urine of infected animals, or with a urine-contaminated environment such as soil, water, or plants. The bacterium enters the body through cuts or abrasions on the skin, or through the mucous membranes of the mouth, nose, and eyes [4]. Although more rare, studies have also shown direct transmission through lesions between humans and animals [3]. Wild and domesticated animals are essential for the maintenance of pathogenic leptospires in nature, while human-to-human transmission is unusual.

Difficulties in establishing a clinical diagnosis and the lack of diagnostic laboratory services are causes for underreporting in many countries. Clinical signs include fever, headache and myalgia, and may cause such complications as jaundice, acute renal failure, bleeding including pulmonary haemmorhage syndrome, meningitis, myocarditis, and uveitis [1]. Cases are often misdiagnosed as meningitis, encephalitis or influenza, and outbreaks may be confused, or occur concurrently, with outbreaks of dengue or other viral hemorrhagic diseases, typhoid, rickettsial infection, malaria, or other febrile illnesses [5].

In Central America, one of the regions most vulnerable to natural disasters in the Americas, leptospirosis outbreaks have been reported in almost all countries [6-10]. Nicaragua in particular has suffered several leptospirosis outbreaks since 1995, when the first one of large impact occurred with 2,259 clinical cases, and 1998 (post-hurricane Mitch). The country has acquired significant experience in the control of the disease at the local level [7, 11-12].

Floods or heavy rain are possible drivers of leptospirosis outbreaks that have been most cited in publications of the Region [7, 12, 13-17]. Other environmental factors such as the type of soil could also be analyzed as possible drivers, since leptospira are known to survive longer in neutral to alkaline soil [3], alkaline surface water, and alkaline soil water [18]. Because it is a zoonotic disease, the presence of animals is also an important variable to explore. Another possible driver could be poverty and living conditions, as reflected in the occurrence of outbreaks in urban slum dwellers reported in various publications [19-20].

An analysis of the events recorded for WHO's International Health Regulations (IHR 2005) in the American Region shows that outbreaks of leptospirosis were among the events of potential public health emergencies of international concern in the Americas in 2007 and 2008. The fact that 70% of these events were at the animal/human health interface highlights the need for a better understanding of infectious diseases common to man and animals [21]. Carrying out proper detection, risk assessment, and verification requires collaboration among the health sciences (veterinary and human) as well as other sectors. Leptospirosis is a disease that must be tackled within a multidisciplinary approach, both to understand its causality and to determine which actions must be taken against it. It is good example for the "One Health" approach [22-23].

This study was conducted for all the above reasons, in order to support countries in developing a holistic approach to prevention and response that brings together humans, animals and the environment. Its objective is to stratify the risk and identify "hotspots" for leptospirosis outbreaks in Nicaragua, and to perform an exploratory analysis of "drivers" for those outbreaks. The analysis of Nicaragua's data will lead to the establishment of a methodology to identify possible risk areas for leptospirosis outbreaks in other Central American countries presenting similar drivers, and currently reporting few cases, as well as provide simple methodological steps to review existing surveillance and action plans related to this disease.

2. Methods

2.1 Type of study, period and data source

This is an ecological study at the second subnational level that includes the entire country (153 municipalities in 17 departments of Nicaragua) [24]. When it comes to describing outbreaks and interventions, it is retrospective and descriptive. The study's time period is from 2004, when all departments started using ELISA tests for leptospirosis, to 2010, date of the latest available information. The data were obtained only through secondary sources. The number of human cases comes from the country's information system, the human population, number of animals and socioeconomic variables from the 2005 Nicaragua Census (last information available when the study was performed), and the environmental data from other sources (list of variables in table 1).

Table 1. Selected variables and sources of information used to create a database by municipality

Variables taken from original sources	**Sources**
Name of the Department	Nicaragua
Code of First National Sublevel	UN PAHO-SALB
Name of the Municipality	Nicaragua
Code of Second National Sublevel	UN SALB & 2005 Nicaragua Census
Cases of Leptospirosis 2004-10, by month	Ministry of Health, NIC
Population of Municipality 2005	2005 Nicaragua Census
Population of Municipality 2007	Ministry of Health, NIC
Rural Population in Municipality 2005	2005 Nicaragua Census
Area of Municipality in km^2	UN SALB & 2005 Nicaragua Census
Percentage of People in Municipality Living in Poverty	2005 Nicaragua Census
Percentage of People in Municipality Living in Extreme Poverty	2005 Nicaragua Census
Population of 6-yr-olds and Over, Condition of Illiteracy in Municipality	2005 Nicaragua Census
Number of Bovine Animals in Municipality 2005	2005 Nicaragua Census
Number of Animals in Municipality, Pigs 2005	2005 Nicaragua Census
Number of Animals in Municipality, Horses 2005	2005 Nicaragua Census

Variables created from original sources	**Sources**
Percentage of Municipal Area Dedicated to Agricultural Land Use	FAO-GeoNetwork.a
Percentage of Soil with Cambisol and Andosol Soil Type	FAO-GeoNetwork.b
Percentage of municipal terrain with flat to moderate slope (25% or less)	USGS Terrain and slope sources. Topo30Derivative
Minimum Precipitation in the Municipality per Year (mm)	Global Climate Data
Maximum Precipitation in the Municipality per Year (mm)	Global Climate Data
Average Precipitation in the Municipality per Year (mm)	Global Climate Data

Variables calculated totals, rates and ratios
Total number of cases (2004-10)
Cumulative incidence rate by 10,000 population (2007)
Risk stratification
Percentage of illiteracy (2005)
Ratio number of bovines/population (2005)
Ratio number of equines/population (2005)
Ratio number of swine/population (2005)
Ratio total number of animals/population (2005)

Sources:
UN PAHO-SALB. The Second Administrative Level Boundaries data set project (SALB) http://www.unsalb.org/
Ministry of Health: http://www.minsa.gob.ni/
2005 Nicaragua Census: http://www.inide.gob.ni/censos2005/CifrasMun/tablas_cifras.htm
CRED/EM-DAT: http://www.emdat.be/
USGS Terrain and slope sources. Topo30Derivative. Analysis carried out by the authors http://eros.usgs.gov/#/Find_Data/Products_and_Data_Available/gtopo30_info
FAO-GeoNetwork.a. Land Use Systems of the World - Latin America and Caribbean http://www.fao.org/geonetwork/srv/en/metadata.show?id=31659&currTab=distribution
FAO-GeoNetwork.b. Mapa Digital del Suelo del Mundo. Base Mundial de Referencia para los recursos del Suelo (FAO/ISRIC/SICS, 1998, rev 2010. Base de datos: GeoNetwork): http://www.fao.org/nr/land/suelos/soil/es
Global Climate Data. Hijmans, R.J., S.E. Cameron, J.L. Parra, P.G. Jones and A. Jarvis, 2005.
Very high resolution interpolated climate surfaces for global land areas. International Journal of Climatology 25: 1965-1978. Records from 1950-2000 period. (http://www.worldclim.org/ Analysis carried out by the authors)

2.2 Parts of the study

The study was carried out in four stages that are described below.

2.2.1 Collection of the epidemiological history and description of actions taken

This part consisted in a description of the major outbreaks that occurred in this period. The Nicaragua Leptospirosis Intersectoral National Plan was also reviewed, including the actions for prevention, alert and response for the control of leptospirosis in the country.

2.2.2 Collection of data and analysis of the epidemiological situation, including risk stratification and identification of hotspot

The numbers of cases by municipality and department were collected and described by month and year, and a geo-coded municipal database was then created. An estimation of the cumulative incidence rate (per 10,000 population) was calculated using the population of 2007.

For the purpose of this study the following definitions were used:

- Case definitions**:** Suspected case of Leptospirosis - person with acute febrile illness with headache, nausea, vomiting, abdominal pain, arthralgia and prostration associated with conjunctival hyperemia, meningeal irritation, anuria or oliguria and/or proteinuria, jaundice and gastrointestinal and pulmonary tract bleeding. Probable case of Leptospirosis - person with clinical signs and symptoms as well as history of exposure to pets or environment contaminated with animal urine or epidemiological link with a laboratory-confirmed case.
  Confirmed case of Leptospirosis - Suspected persons with clinical symptoms of leptospirosis and laboratory confirmed diagnosis. For this database, only confirmed cases were included.
- Cumulative incidence, cumulative incidence rate (Syn: incidence proportion, average risk) The number or proportion of a group (cohort) of people who experience the onset of a health-related event during a specified time interval; this interval is generally the same for all members of the group, but, as in lifetime incidence, it may vary from person to person without reference to age [25].
- Driver: Factors that increase the probability of the event of an outbreak (increase of the incidence in a geographical area).
- Hotspot: A geographical region where the concentration of the incidence of the disease is exceptional or in excess of the endemic rate, and where it can be predicted it will last for a period of at least a year [26-28].
- Outbreak: An epidemic limited to localized increase in the incidence of a disease, e.g., in a village, town, or closed institution; upsurge is sometimes used as a euphemism for outbreak [25].
- Risk factor: An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that, on the basis of scientific evidence, is known to be associate with meaningful health-related condition (s) [25].

For the purpose of this analysis, the criteria for risk stratification of leptospirosis in Nicaragua was defined using the following categories:

- Productive area: area (in this case a municipality) where active transmission of leptospirosis cases is known to have occurred during the study period [29].
- Silent area: area (in this case a municipality) where no cases were reported during the study period.
- Endemic area: area (in this case a municipality) where active transmission of leptospirosis

cases is known to have occurred in the period analyzed and that meets no criteria of hotspot.

- Hotspot area: area (in this case a municipality) where active transmission of leptospirosis cases is known to have occurred in the analyzed period and that meets at least one of the following two criteria: the municipality is in the top quintile of the cumulative incidence rate (10,000 population) and/or the municipality is in the top quintile of the total number of cases.

Firstly, the risk stratification of the municipalities was done using an Excel spreadsheet to sort the criteria variables, and secondly, the geographic information system in epidemiology (SIGEpi) developed by PAHO was used to select the top quintiles of these two indicators using the tool "Identification of Priority Areas", in order to determine the hotspot areas on the maps and complete related tables.

2.2.3 Collection and processing of environmental, demographic and socioeconomic variables

Nicaragua's digital cartographic data were collected, updated, standardized and geo-processed using ArcGIS/Editor 10.0. The first step was to update the municipal boundaries available in the UN SALB Project [30] following the boundary depiction released by the Nicaraguan National Institute of Statistics. Area-specific statistics of precipitation patterns and slope were then calculated using ArcGIS/Editor/Zonal Statistics. The occupied municipal surface was then calculated with dominant soils, agricultural-livestock land use and flat-moderate slope using ArcGIS/Editor/Extract by Mask, converting raster to feature, calculating geometry, and using other Geo-processing techniques – intersection & dissolving- to get the municipal area statistics. All demographic and socioeconomic data were captured from Nicaragua's Census and included in the geo-coded database in DBS-Excel. The construction of rates and ratios yielded new variables (table 1).

2.2.4 Exploratory geo-referenced and statistical analysis of possible drivers using selected environmental, demographic and socioeconomic variables

The potential environmental and socioeconomic drivers selected for this study were analyzed geographically, using thematic maps overlapping with hotspot areas of leptospirosis, as well as correlation analysis.

The cumulative incidence rate (per 10,000 population) and the selected variables were explored statistically using SAS 9.2 through univariate (including boxplot) and bivariate (with Pearson correlation) analysis. The mean, standard deviation, and Pearson correlation with the cumulative incidence rate were calculated for each municipality. An analysis was performed to determine cross-correlation between annual rain patterns and case distribution by month.

3. Results and discussion

In the period of this study, between 2004 and 2010, several outbreaks were reported in Nicaragua. Outbreak reports indicate that most of them were in León and Chinandega, in 2007 (338 cases), 2008 (146 cases), and 2010 (248 cases). Several cases presented co-infection with dengue. Reports from the outbreak investigation show that in 2007 and 2010 in León, around 77% of the cases came from rural areas, and 75% were males. In the Chinandega outbreak, around 50% of the cases were among people between 15 and 49 years of age. The outbreak data disaggregated by individuals suggest that the risk factors are related to occupation (males of reproductive age living in rural areas).

The actions put in place in both departments to control the outbreak started with the creation of multidisciplinary municipal teams. Antibiotic treatment was administered to the human cases, and chemoprophylaxis was used for their contacts. On the animal side, samples from different animals were analyzed to investigate the possible sources with positive samples in different species. Activities were carried out to detect and treat leptospirosis in domestic animals. The response also included the control of vectors, community participation, training for animal and human health workers, and health communication.

Until 2000-2002, the diagnosis of leptospirosis was based on clinical management and laboratory confirmation through microagglutination (MAT), a technique only available at Nicaragua's National Center for Diagnosis and Reference (CNDR for its Spanish name), which slowed down the surveillance of the disease. As of 2003, active surveillance of cases with fever was initiated, using a standardized ELISA test available in laboratories of the national network present in all Local Systems of Integral Health Care (SILAIS for its Spanish name). In 2008 and 2009, active surveillance was put in place to detect cases using the techniques mentioned above. Since 2010, besides using ELISA as a screening method, a "quick latex agglutination test" is performed in the municipal laboratories, which enhances early detection and the management of outbreaks at the level of primary care.

Between 2004 and 2010, 1980 cases of leptospirosis were reported in Nicaragua. The number of cases by year ranged between 56 (2004 and 2006) and 685 (2007), with a high number of cases (653) in 2010 as well. León was the department with the highest percentage (26.36%), followed by Chinandega (15.35%) and the most populated department, Managua (8.84%), where the national capital city is located. Together those three departments present 50.55% of the total of cases in the period (table 2).

At the level of municipalities, the range of the total number of cases was 0 to 177, with a median of six cases and a mean of 12.94 (standard deviation of 21.98). The total number of cases by month in the period ranged from 26 in April to 1081 in October. The cumulative incidence rate (per 10,000 population) by department confirms the result mentioned above that León (with a rate of 36.03 by 10,000 population) and Chinandega (18.84) presented the highest rates in the country. The municipal rates ranged between 0 and 11.36, with a median of 0.41 and a mean of 0.83 (standard deviation of 1.45). Clearly, León presented the highest municipal rates among all (figure 1). The geographic distribution of total cases and cumulative incidence rates showed a concentration of highs in the municipalities of the pacific region (figure 2).

The analysis of the risk stratification criteria established for this study showed that out of the 153 municipalities, 133 were productive for leptospirosis:

- 48 were hotspot municipalities (31.37% of the total number of municipalities)
- 85 were endemic municipalities (55.56%)
- 20 were silent municipalities (13.07%) (figure 3).

The departments with 50% or more hotspot municipalities were León (80.00%), Chinandega (76.92%), Carazo (62.50%) and Rio San Juan (50.00%). Most of the hotspots were located on the pacific coast. On the other hand, the departments that presented 30% or more municipalities considered as silent areas were Región Atlántica Norte (37.50%), Rio San Juan (33.33%), Masaya (33.33%) and Rivas (30.00%) (table 3). The municipal mean, standard deviation, and Pearson correlation of possible drivers with the cumulative incidence rate are presented in table 4.

Table 2. Cases of leptospirosis by department, percentage of cases and rates by 10,000 population, Nicaragua, 2004-2010

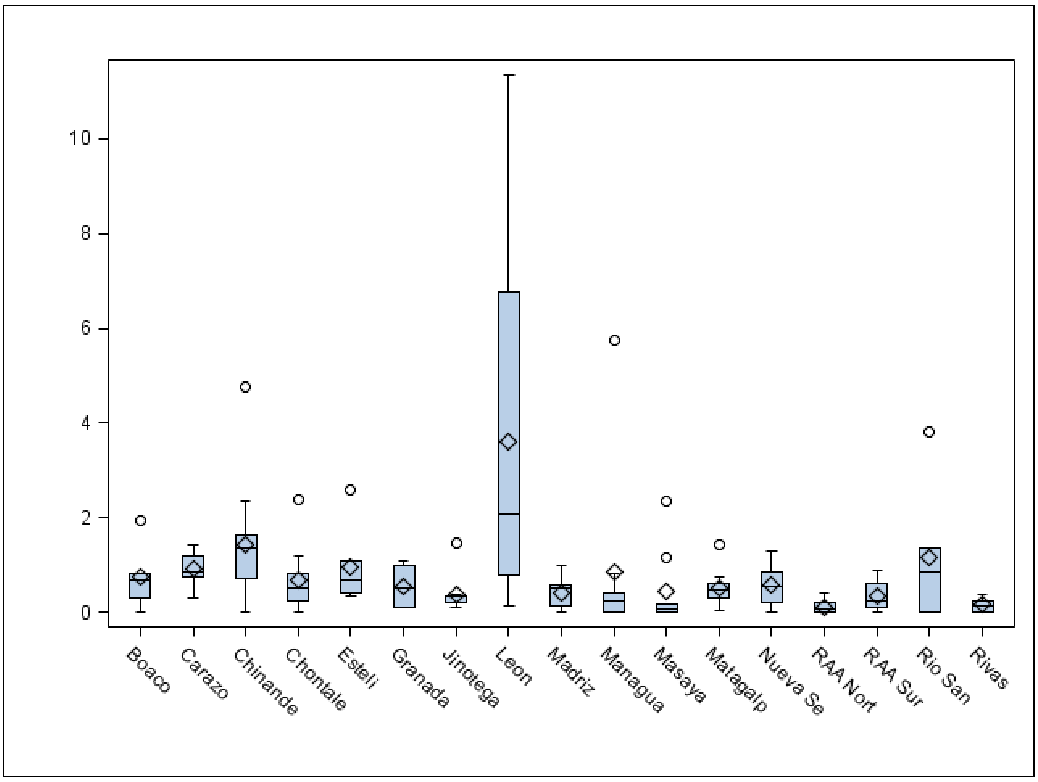
Dept.	2004	2005	2006	2007	2008	2009	2010	Total	% of total cases	Rate (10,000)
	Cases									
Boaco	4	6	0	33	13	3	31	90	4.55%	4.48
Carazo	10	2	1	2	2	1	95	113	5.71%	735
Chinandega	4	7	7	121	99	7	59	304	15.35%	18.84
Chontales	1	0	1	36	2	13	24	77	3.89%	6.73
Estelí	0	0	0	19	35	0	39	93	4.70%	5.77
Granada	1	1	1	15	6	1	12	37	1.87%	2.21
Jinotega	11	3	5	28	8	5	29	89	4.50%	13.93
León	2	44	6	229	48	7	186	522	26.36%	36.03
Madriz	0	2	2	4	14	3	8	33	1.67%	3.67
Managua	0	0	2	30	44	22	77	175	8.84%	7.60
Masaya	1	7	7	3	3	5	8	34	1.72%	3.94
Matagalpa	2	0	3	84	16	22	24	151	7.63%	6.51
Nueva Segovia	8	1	12	19	12	7	11	70	3.54%	6.93
R.A. Atlántico Norte	2	1	0	15	2	5	6	31	1.57%	0.95
R.A. Atlántico Sur	3	3	7	22	6	18	22	81	4.09%	4.13
Río San Juan	6	1	2	22	13	5	10	59	2.98%	6.90
Rivas	1	4	0	3	1	0	12	21	1.06%	1.60
Total	**56**	**82**	**56**	**685**	**324**	**124**	**653**	**1980**	**100%**	**137.57**

Source: Ministry of Health, Nicaragua, 2011

The variable identified using GIS as presenting the most visible pattern in hotspot municipalities is the percentage of municipal surface occupied by the soil combination of Cambisol and Andosol (figure 4). The Pearson correlation of this variable with the incidence rate showed a positive strength (r=0.275;p<0.01). Cambisols are young, less-structured soils with diverse parental material [31], however in this case they are settled over Ignimbrite-pyroclastic bedrock and lava strata of Andesite and Basalt. Andosols are located over a volcanic ash foundation [31-32]. This analysis was carried out ex-post-facto based on direct communication with local Nicaraguan biologists and engineers about the role of soils in leptospirosis distribution.

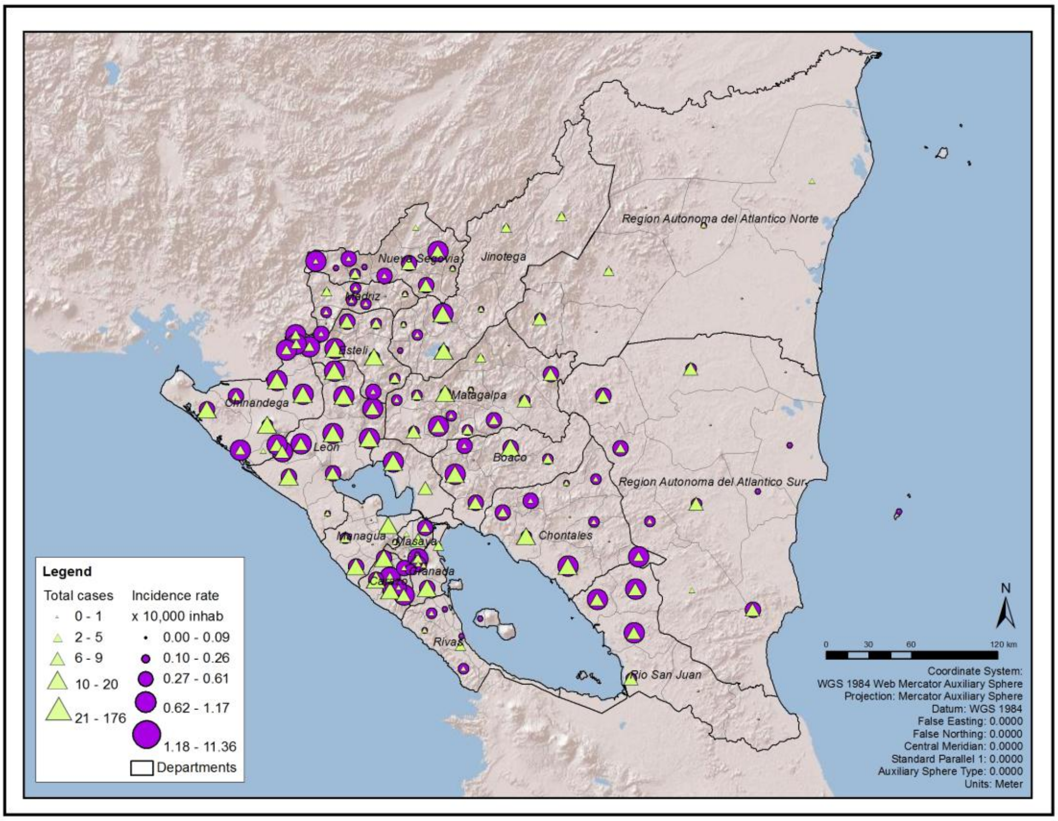
Another environmental variable explored in this study was precipitation or rainfall. The minimal precipitation per year (mm) variable was negatively correlated with the leptospirosis distribution (r=-0.239; p<0.01). The average pluvial precipitation of the two months with highest rainfall (mm) also presented a positive correlation (r=0.181; p<0.05). However, the most informative set of maps was the monthly average precipitation analyzed together with the number of cases in the same month and in the following month (figure 5). The months of March and April showed the lowest precipitation, and the average monthly numbers of cases were 37 and 26, respectively, during the time period of the study.

Figure 1. Leptospirosis rate by 10,000 population, by municipality by department, Nicaragua, 2004-2010



Source: Data from Ministry of Health of Nicaragua, analysis by authors.

Figure 2. Total number of cases of leptospirosis, cumulative incidence rate (10,000 population), by municipality, Nicaragua, 2004-2010



Source: Data from the Ministry of Health, Nicaragua, 2011. Analysis carried out by the authors

Map boundaries: UN PAHO-SALB. The Second Administrative Level Boundaries data set project (SALB)/ 2005 Nicaragua Census; Map Background: ESRI World Shaded Relieve. ArcGIS Desktop/Editor 10.0, 2011.

The months of September and October were the ones with the highest precipitation, and also the highest average number of leptospirosis cases. From 185 average total cases in September, the number jumped to 1081 cases in October in the period. Additional analysis showed a positive time lag association between amount of rain and number of leptospirosis cases. The cross-correlation analysis performed between annual rain patterns and case distribution by month showed a higher correlation with the previous month rainfall (0.558) than with the concurrent month (0.441).

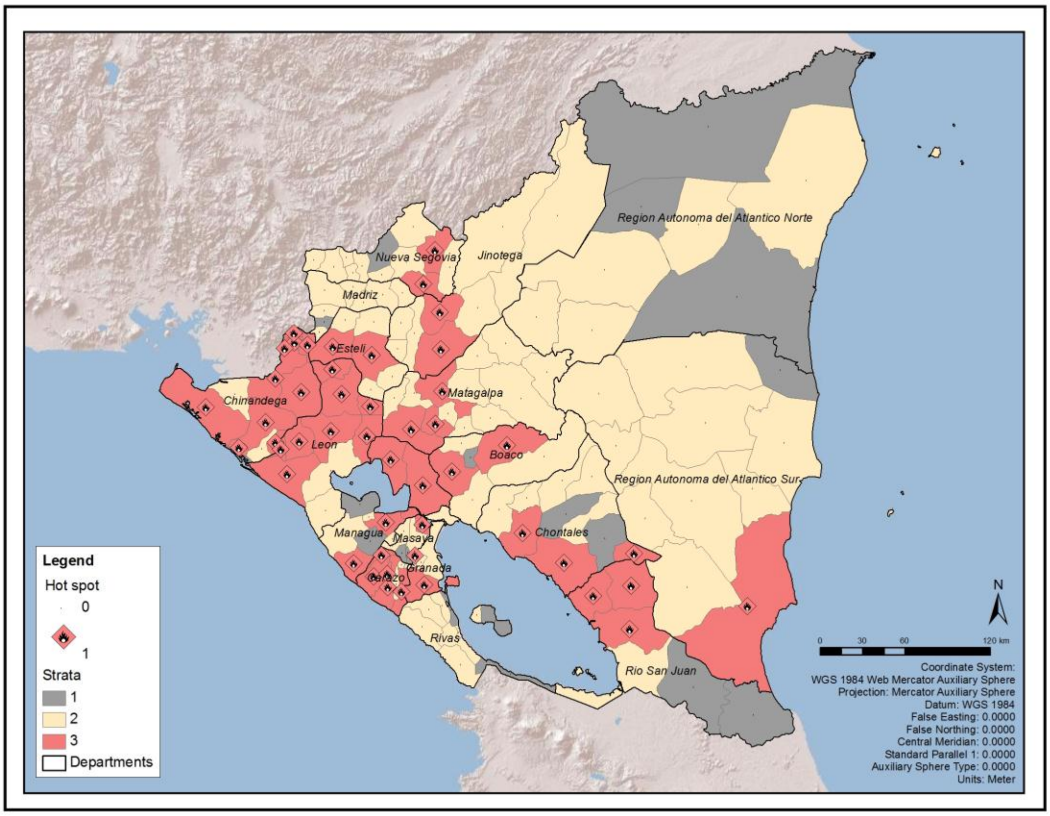
Table 3. Population, number of municipalities, risk stratification, by department, Nicaragua, 2004-2010

Department	Population	Number of municipalities	Municipalities					
			Hotspots		Endemic		Silent	
			#	%	#	%	#	%
Boaco	155,155	6	2	33%	3	50%	1	17%
Carazo	171,055	8	5	63%	3	38%	0	0%
Chinandega	390,339	13	10	77%	2	15%	1	8%
Chontales	158,550	10	3	30%	5	50%	2	20%
Estelí	207,603	6	2	33%	4	67%	0	0%
Granada	173,204	4	1	25%	3	75%	0	0%
Jinotega	306,795	8	2	25%	6	75%	0	0%
León	365,539	10	8	80%	2	20%	0	0%
Madriz	136,433	9	0	0%	8	89%	1	11%
Managua	1,300,867	9	4	44%	3	33%	2	22%
Masaya	298,688	9	2	22%	4	44%	3	33%
Matagalpa	483,247	13	3	23%	10	77%	0	0%
Nueva Segovia	214,779	12	2	17%	9	75%	1	8%
R. A. Atlántico Norte	323,554	8	0	0%	5	63%	3	38%
R. A. Atlántico Sur	315,705	12	1	8%	10	83%	1	8%
Río San Juan	98,464	6	3	50%	1	17%	2	33%
Rivas	160,971	10	0	0%	7	70%	3	30%
Total	**5,260,948**	**153**	**48**	**31%**	**85**	**56%**	**20**	**13%**

Source: Data from the government of Nicaragua, 2005 Nicaragua Census. Analysis carried out by the authors.

In the last Census available during the study (2005), Nicaragua has a population of 5,141,192, 61.32% of which is rural; the percentage of rural population presented a positive correlation with the incidence rate ($r=0.207$; $p<0,01$), confirmed in the map (figure 6). The percentage of population living in poverty (mean 30.36%, range: 11.50-43.30%) was among the socioeconomic variables analyzed as possible drivers, which in the case of Nicaragua is measured as having one type of basic unmet needs. Using GIS exploratory analysis, the concentration of hotspots with high levels of poverty (figure 7) is easily identified, even though the correlation was not significant in the statistical analysis. In the case of Nicaragua, extreme poverty (mean 43.19%, range: 4.30-87.40%) is measured as two or more basic unmet need. Along with illiteracy (mean 24.74%, range: 7.91-56.23%), it is highest in the Atlantic coast; however the environmental conditions are different in both coasts.

Figure 3. Risk stratification of leptospirosis in Nicaragua, by municipality, 2004-2010



Source: Data and analysis carried out by the authors.
Map boundaries: UN PAHO-SALB. The Second Administrative Level Boundaries data set project (SALB)/ 2005 Nicaragua Census; Map Background: ESRI World Shaded Relieve. ArcGIS Desktop/Editor 10.0, 2011.

Legend
Hotspot area (red); Endemic area (yellow); Silent area (gray)
Criteria:

- **Hotspot areas:** Area (in this case a municipality) where active transmission of leptospirosis cases is known to people in the period analyzed and meets at least one of the two criteria: The municipality is in the top quintile of the cumulative incidence rate (10,000 population) and/or the municipality is in the top quintile of the total number of cases.
- **Endemic area:** Area (in this case a municipality) where active transmission of leptospirosis cases is known to people in the period analyzed and meets no criteria of hotspot.
- **Silent area:** Area (in this case a municipality) where no cases were reported during the study period.

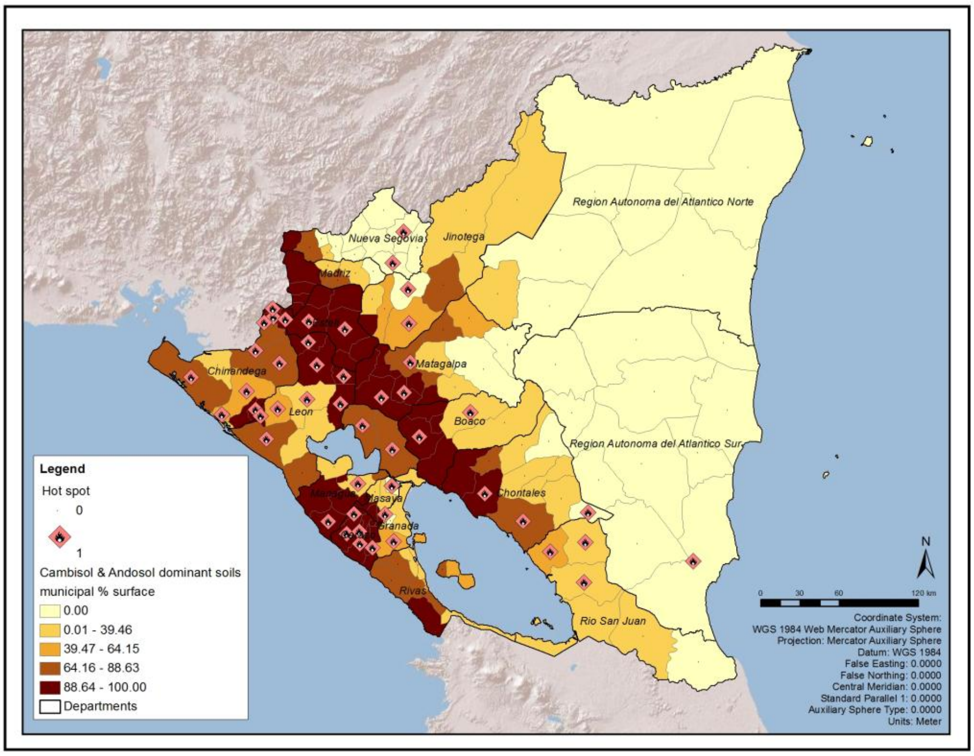
Results:
Total number of municipalities = 153
Number of hotspot municipalities = 48
Number of endemic municipalities = 85
Number of silent municipalities = 20

Table 4. Municipality mean, standard deviation, and correlation among selected possible drivers and cumulative incidence rate (10,000 population), Nicaragua

Possible drivers	Municipality mean	Standard deviation	Correlation with cumulative incidence rate
% rural population	61.317	24.246	0.20666 p= 0.0104 *
% illiterate population	24.744	9.543	-0.01502 p=0.8538
% population living in poverty	30.366	5.469	0.14971 p=0.0647
% population living in extreme poverty (n=151)	43.191	16.727	-0.00370 p=0.9641
Minimum rain precipitation per year (mm)	165.660	204.701	-0.23927 p=0.0029 *
Maximum rain precipitation per year (mm)	3250	887.127	0.02979 p=0.7147
Average rain precipitation per year (mm)	1459	536.998	-0.14710 p=0.0696
Average rain precipitation of the two months with the highest rainfall during the year (mm)	7403	1490	0.18074 p=0.0254 *
Ratio of bovines/ population (2005)	0.800	1.067	0.09954 p=0.2209
Ratio of equines/ population (2005)	0.122	0.125	0.12563 p=0.1218
Ratio of swine/ population (2005)	0.101	0.098	0.09200 p=0.2581
Ratio of total animals/ population (2005)	1.023	1.256	0.10371 p=0.2020
% land area dedicated to agricultural land use	66.016	32.928	0.09657 p=0.2351
% soil type with cambisols and andosols	51.794	42.470	0.27475 P=0.0006 *
% municipal terrain with flat to moderate slope (25% or less)	41.591	28.631	0.00024 p=0.9977

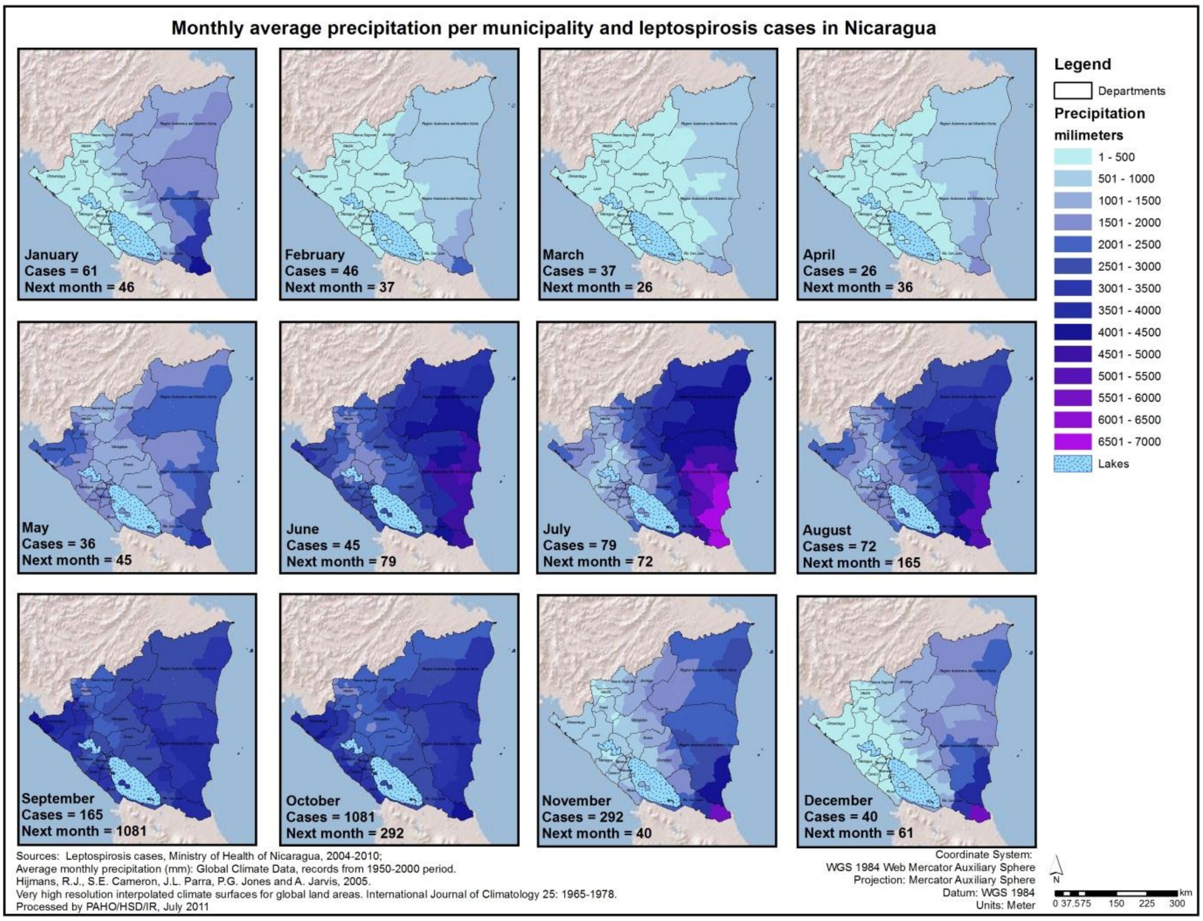
* significant p value

Figure 4. Hotspots for leptospirosis and percentage of soil with Cambisol and Andosol, by municipality Nicaragua, 2004-2010



Source: Data from FAO-GeoNetwork.b. Mapa Digital del Suelo del Mundo. Base Mundial de Referencia para los recursos del Suelo (FAO/ISRIC/SICS, 1998, rev 2010. Base de datos: GeoNetwork). Analysis carried out by the authors
Map boundaries: UN PAHO-SALB. The Second Administrative Level Boundaries data set project (SALB)/ 2005 Nicaragua Census; Map Background: ESRI World Shaded Relieve. ArcGIS Desktop/Editor 10.0, 2011.

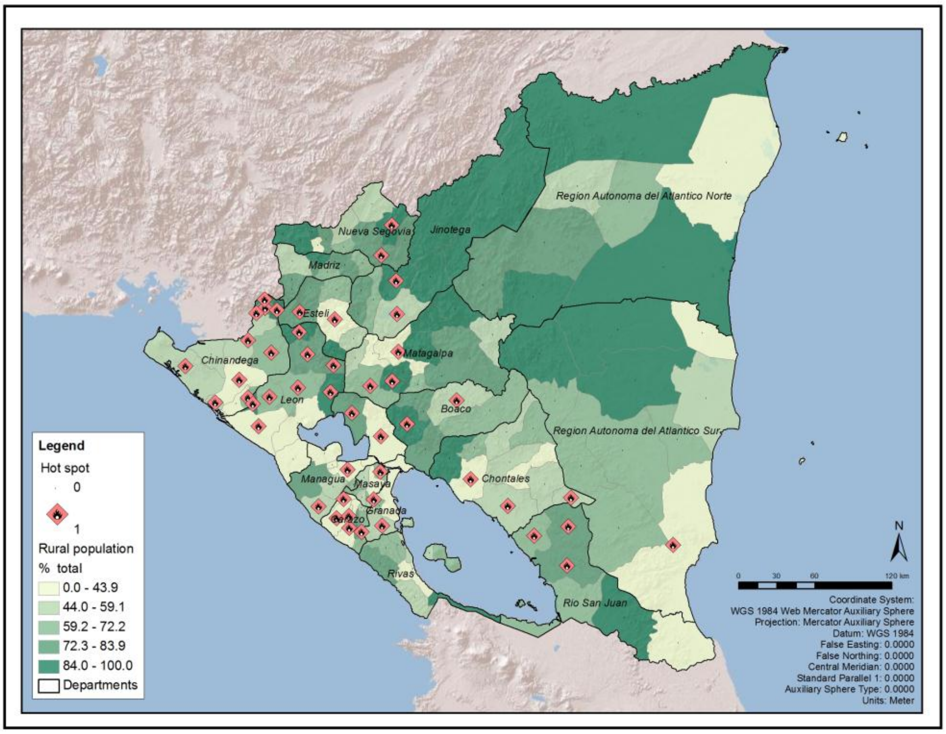
Figure 5. Average rainfall and total number of cases of leptospirosis, by municipality Nicaragua, 2004-2010



Sources: Ministry of Health of Nicaragua and Global Climate Data. Hijmans, R.J., S.E. Cameron, J.L. Parra, P.G. Jones and A. Jarvis, 2005. Very high resolution interpolated climate surfaces for global land areas. International Journal of Climatology 25: 1965-1978. Records from 1950-2000 period. (http://www.worldclim.org/ Analysis carried out by the authors)

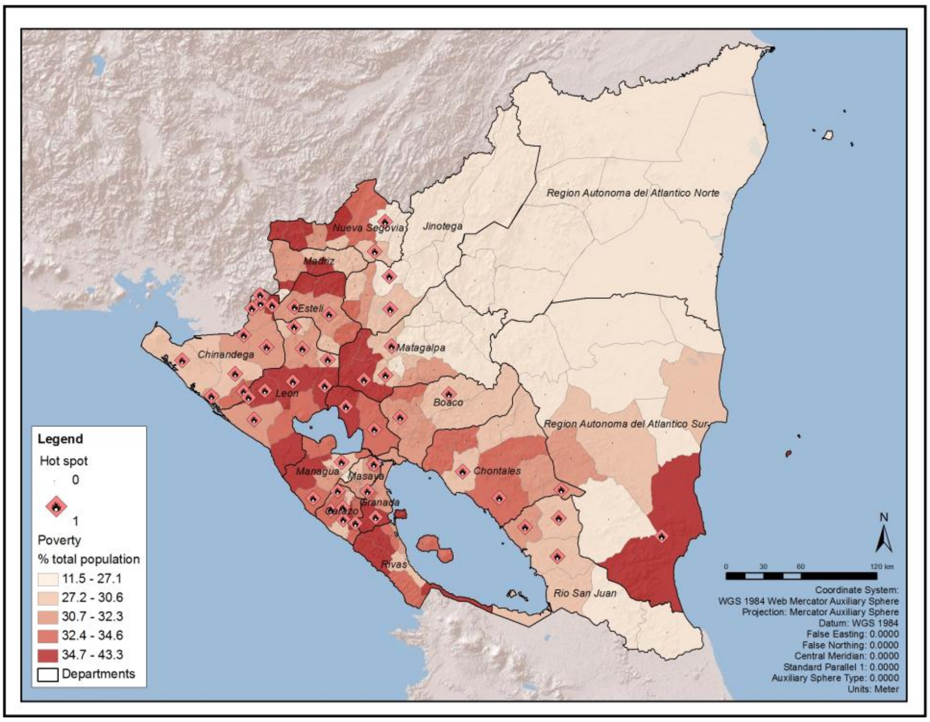
Map boundaries: UN PAHO-SALB. The Second Administrative Level Boundaries data set project (SALB)/ 2005 Nicaragua Census; Map Background: ESRI World Shaded Relieve. ArcGIS Desktop/Editor 10.0, 2011.

Figure 6. Hotspots for leptospirosis and percentage of rural population, Nicaragua, by municipality 2004-2010



Source: Data from the Ministry of Health of Nicaragua, 2005 Nicaragua Census. Analysis carried out by the authors.
Map boundaries: UN PAHO- SALB. The Second Administrative Level Boundaries data set project (SALB)/ 2005 Nicaragua Census; Map Background: ESRI World Shaded Relieve. ArcGIS Desktop/Editor 10.0, 2011.

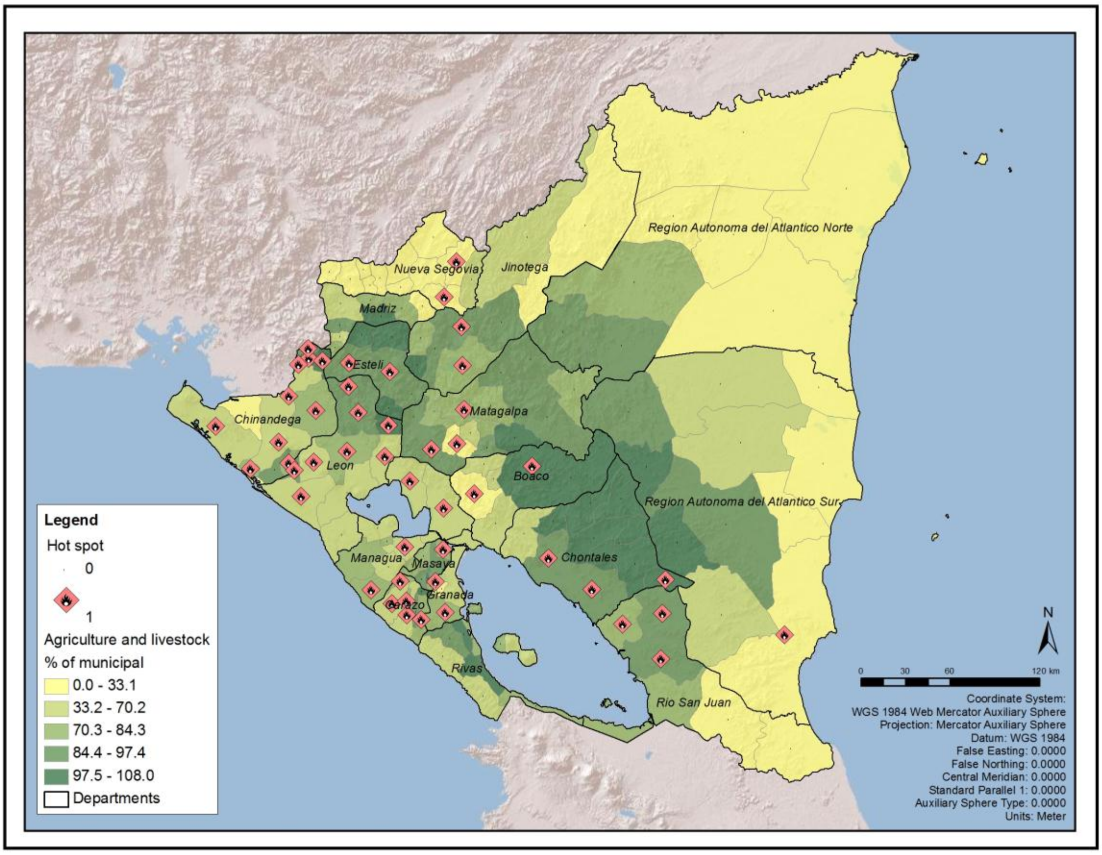
Figure 7. Hotspots for leptospirosis and percentage of population living in poverty, Nicaragua, by municipality 2004-2010



Source: Data from 2005 Nicaragua census. Analysis carried out by the authors.
Map boundaries: UN PAHO-SALB. The Second Administrative Level Boundaries data set project (SALB)/ 2005 Nicaragua Census; Map Background: ESRI World Shaded Relieve. ArcGIS Desktop/Editor 10.0, 2011.

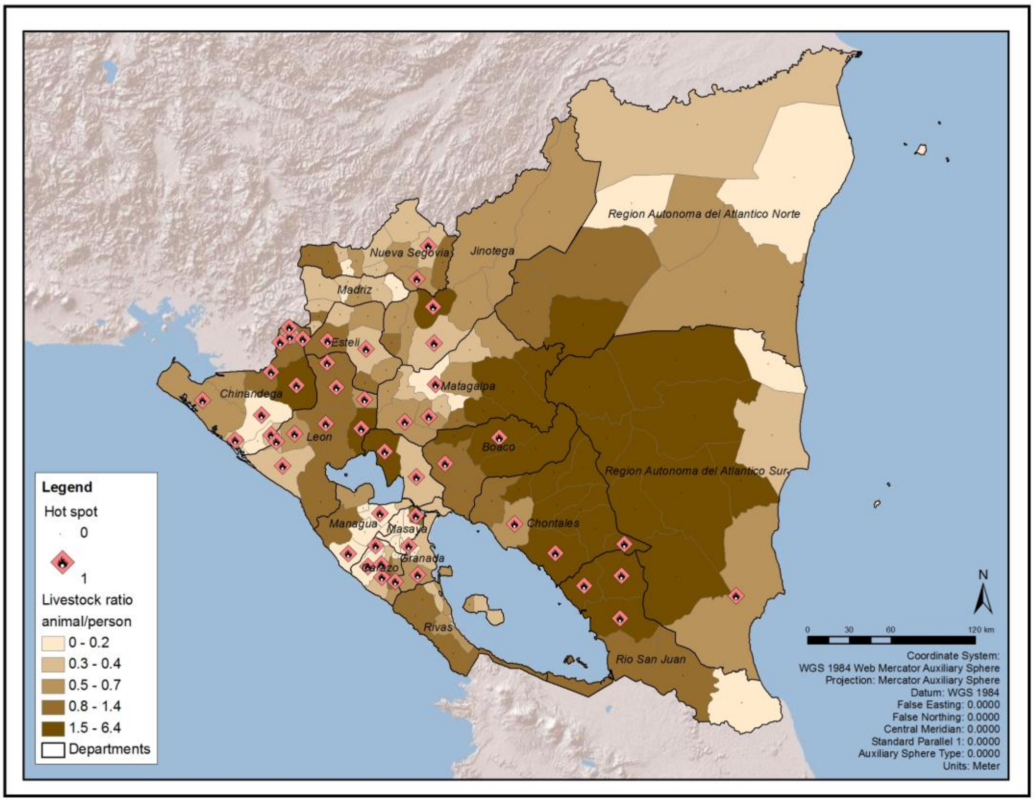
Two possible drivers that were also analyzed are the percentage of the area dedicated to agriculture land use and the ratio between the number of animals and human population (table 4). No association was found with the percentage of area dedicated to agricultural and livestock land use (figure 8). The ratio of livestock by population was analyzed by species and the sum of bovine, equine and swine livestock. The livestock with the highest number in Nicaragua was bovine, with a total number of 2,657,039 heads in 2005. The number of equine was 383,172 and swine 412,604, a total ratio of 3,452,815 animals over 5,141,192 population. The average ratio of livestock by population within the municipalities was 1.02 (range: 0.01-6.25). The map suggests a concentration of hotspots in municipalities with the highest ratios of livestock/population, even though the correlation was not statistically significant (figure 9).

Figure 8. Hotspots for leptospirosis and percentage of the land use for agriculture and livestock, Nicaragua, by municipality 2004-2010



Source: Data from FAO-GeoNetwork.a. Land Use Systems of the World - Latin America and Caribbean. Analysis carried out by the authors.
Map boundaries: UN PAHO-SALB. The Second Administrative Level Boundaries data set project (SALB)/ 2005 Nicaragua Census; Map Background: ESRI World Shaded Relieve. ArcGIS Desktop/Editor 10.0, 2011.

Figure 9. Hotspots for leptospirosis and ratio of number of livestock by population, Nicaragua, by municipality 2004-2010



Source: Data from 2005 Nicaragua census. Analysis carried out by the authors.
Map boundaries: UN PAHO- SALB. The Second Administrative Level Boundaries data set project (SALB)/ 2005 Nicaragua Census; Map Background: ESRI World Shaded Relieve. ArcGIS Desktop/Editor 10.0, 2011.

4. Conclusions

This study demonstrated that there are different risk areas for leptospirosis in Nicaragua. Most of the hotspots that were identified through the present methodology are concentrated in the Pacific region, confirming previous descriptions cited by the national authorities in the Intersectorial National Leptospirosis Plan for Nicaragua [33]. Three of the 17 departments (León, Chinandega and Managua) presented half of the human cases detected in the country during the period under study. León and Chinandega are also the departments with the highest risk as measured by the absolute number of cases (522 cases in León and 304 cases in Chinandega), the highest cumulative incidence rate (13.93 by 10,000 populations and 18.84 respectively), and also the highest percentage of municipalities considered as hotspots (around 80%). These findings also confirmed previous publications about outbreaks in 1995 and 1998 in these areas [7, 11-12]. These departments and most of their municipalities need to remain a priority for intervention in order to avoid large outbreaks.

The risk varied within the others departments. The highest percentage of municipalities (56%) was classified as endemic areas, where the disease is present but not in the highest quintiles of the country variation. Thirteen percent of the municipalities in Nicaragua had no case of leptospirosis, which could suggest difficulties in the surveillance even though the ELISA test is implemented in all Departments. These municipalities are mostly in remote areas in the Atlantic region. To analyze if leptospirosis is really absent in silent areas and to confirm the burden of the disease in the other areas, we suggest creating an indicator of reliability of epidemiological surveillance for leptospirosis. One option could be to use the proportion of rapid tests for leptospirosis related to the number of reported cases with fever. A similar type of indicator (annual proportion of dog samples for rabies test related to the dog population) has been used in Brazil for almost 20 years for rabies, and was later extended to Latin America [29, 34].

In this study, a stratification of risk is proposed based on two criteria to define hotspots both related to magnitude (number of cases and cumulative incidence rate). The frequency of events (outbreaks) is another variable that could be analyzed in the future and that may be added to this methodology when it is applied to another unit of analysis.

In the description of the outbreaks in Nicaragua in the period under study, it was noted that many leptospirosis cases occurred in combination with a dengue infection. This information is very important, as it suggests that training of health personnel in the adequate diagnostic test for the disease is crucial to avoid severe cases and mortality. This also implies that laboratory diagnosis of leptospirosis is available, most frequently serodiagnosis. WHO/ILS recommended a microscopic agglutination test (MAT) as gold standard [4]. A variety of other serological methods, including ELISA, could be relatively simple to use as a screening test [4]. Both types of diagnosis are used in the Nicaraguan health system.

The association of leptospirospis with rain is mentioned in several publications and measured in a few others [14-15, 35-36], and our study confirms this association. Figure 5 shows the monthly precipitations and the number of cases in the following month. The number of cases increased more than ten times during the rainy season. For countries such as Nicaragua with a clear rainy season (around October in the Pacific region) and where hotspots have also already been identified, this information could support the planning of monthly prevention and response activities for leptospirosis outbreaks, such as training of personnel in different aspects, alert about the disease, and others. For other areas not considered as hotspots, surveillance and readiness may be sufficient (example in figure 10). It is crucial that a leptospirosis plan take into consideration all the components of a multidisciplinary team and partnerships with others sectors, such as health care, surveillance/diagnosis, action in livestock, rodent control, communication, and others. An interprogramatic collaboration with teams working on other issues such as dengue, influenza and natural disasters is also necessary.

The analysis of possible drivers for leptospirosis outbreaks is exploratory. As explained in the methodology, several variables were created from data downloaded from webpages and transformed in our geo-referenced database. Some of them show a very clear relation with hotspots, such as the percentage of Cambisol and Andosol as dominant soils. Most of the Nicaraguan territory has a geologic igneous origin [32]. Several volcanoes, not all active, are located along the Pacific coast, where most of the hotspots are found. This physical condition may facilitate longer survival of the bacteria in the soil/water and will not change in time. According to Gordon [18], "the incidence of leptospirosis is dependent on the survival time of shed leptospires in surface water or soil water" which in turn is affected by the water acidity-alkalinity level. This, added to the humidity levels generated by substantial rainfall occurring during part of the year in that area, suggests that the country needs to be prepared for other leptospirosis outbreaks.

Figure 10. Example of possible use of this information for planning to prevent and respond to leptospirosis outbreaks in the case of Nicaragua

<table>
<tr><th>Month

Dept/Municipality</th><th>Previous Months</th><th>July</th><th>August</th><th>September</th><th>October</th></tr>
<tr><td rowspan="2">León/Achuapa (Hotspot)</td><td rowspan="2">Training of outbreak alert and response team</td><td rowspan="2">Training about rodent populations</td><td>Training of health personnel</td><td rowspan="2">Population information</td><td rowspan="2">Alert for leptospirosis</td></tr>
<tr><td>Control of rodent populations</td></tr>
<tr><td>León/Nagarote (Endemic)</td><td>Training of outbreak alert and response team</td><td>Training for surveillance</td><td>Surveillance</td><td>Surveillance</td><td>Surveillance</td></tr>
</table>

According to the Center for International Earth Science Information Network (CIESIN), Nicaragua is one of the top 15 countries exposed to three or more natural hazards (measure based on affected land area), with a total exposed territory of 3.0%, and 22.2% of its population exposed as well. Among the hydro-meteorological hazards that were analyzed, extreme flood events and tropical cyclones affect vast areas of the entire Nicaraguan territory; comparatively the geophysical hazards such as earthquakes (analyzed through their probability of occurrence, strength greater that 4.5 on the Richter scale, and volcanic activity, and measured according to their explosivity) affect less extensive areas on the west coast [37-38].

Environmental conditions such as dominant soils, rain patterns and igneous-volcanic geologic origin and ecosystem conditions are probably present in other Central American countries. There are 80 volcanoes in the sub region along the isthmus's Pacific edge, located along the Ring of Fire [39]. This combination of factors suggests that the problem may be broadly spread in the area.

These conditions demonstrate the importance of international health cooperation, including financing, to assist the country in dealing with these physical threats and their indirect consequences, such as an increase in the number of communicable diseases that could affect Nicaragua. The Nicaraguan population already has one of the lowest Gross National Income (purchasing power parity value) of the Region [40].

However, the number of reported cases of leptospirosis in these other countries is not as high as in Nicaragua. Strengthening the surveillance of leptospirosis will perhaps yield different results regarding the burden of this disease. As expressed by Aron [41], "a better understanding of the dynamic linkage between ecosystems and public health is leading to a new diverse opportunity for interventions earlier in process that could become direct threats to public health". This study could provide a reference to other countries looking for their risk areas and strengthening their surveillance of this disease, such as

Honduras that shares borders with the hotspot areas in Nicaragua. Based on the results of the study, steps could be suggested for evidence-based planning of leptospirosis prevention and response to outbreaks in areas of Central America with or without a leptospirosis surveillance system in place (figure 10).

Outbreaks with a large number of cases do not occur every year. The years with most cases during the study period were 2007 (685 cases) and 2010 (653 cases). These two years also coincided with the occurrence of natural disasters (Tropical storm Felix in 2007 and floods in 2010) [42]. Most tropical storms reached Nicaragua through the Atlantic coast where other environmental conditions are not as prominent, and which are also less populated. Higher levels of precipitations, not necessary constituting a natural disaster per se, may be enough to increase the number of cases. Further analysis including other environmental variables related to flood, ecosystems, and soil are necessary for a deeper understanding of possible environmental drivers for leptospirosis.

We also suggest studies at a more disaggregated level on livestock, not only the presence of animals in hotspots, but also what types of serovars are circulating in these areas. In Nicaragua, there is one bovine for every two people, which suggests that the cattle industry is important for the economy of the country. The type of productive process in large or small livestock and whether is raises the risk of leptospirosis could also be analyzed.

A new study with a different design, including only the highest risk areas, is recommended to better analyze the contribution of socioeconomic variables as possible drivers. A previous study suggested the importance of socioeconomic status in leptospirosis infection even after controlling the environmental factors [43]. In this present analysis, the hotspots are identified, and the association with some environmental variables present in the pacific region, such as the type of igneous-volcanic soil, is analyzed. The Atlantic region also presents lower socioeconomic indicators, and when the values for the entire country are divided into quintiles for the GIS maps, the gradient among the municipalities in the pacific region is attenuated. If the areas that share similar environmental drivers were analyzed separately, it is possible that the socioeconomic variability in the risk area could be more visible.

In the literature review, we found no study analyzing the risk of leptospirosis in the entire country and exploring possible drivers at an ecological level. The limitations of ecological studies, in this case by municipality, are well known; however the purpose of this study is to support interventions in the countries that are usually structured geopolitically in this way. Identifying hotspots and possible drivers in Nicaragua could not only support a review of their Inter-sectoral Plan, but also more importantly establish a methodology to support other countries in the identification of their risk areas even where the surveillance of leptospirosis is not strongly in place.

The use of mapping techniques, specifically GIS, is recommended for the application of research results in public health evidence-based decision making. Through the use of GIS, indicators are gathered from different sources and placed in a common database for statistical and geographical analysis [44]. In this study, geographic patterns were recognized for both leptospirosis hotspots and drivers of the disease. As a result, it was possible to assess more closely the exposure to specific environmental risks.

During the current analysis, it was suggested that a series of complementary studies in Nicaragua were needed, some of them already identified by the authors of the study and cited above, such as an analysis of the actions already carried out, and disaggregating the risk factor, in addition to the ones already cited. This study, along with the further analyses recommended above, could be part of an evidence-based approach to health planning, a stepping stone to sharing methodological experiences between the countries of Central America. They could represent the bases for a capacity development project in the subregion, or to cite the UNDP capacity development approach "a real-world application to strengthen and contribute to national capacities for development" [45].

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Conflict of Interest

The authors declare no conflict of interest.

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