

Spatio-temporal analysis of leptospirosis in Eastern Amazon, State of Pará, Brazil

Análise espaço-temporal da leptospirose na Amazônia Oriental, Estado do Pará, Brasil

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ABSTRACT: *Introduction:* Brazil has registered more than 62,000 confirmed cases of leptospirosis between 2001 and 2017, with more than 2,000 cases confirmed in the State of Pará. Despite a large number of cases, no study has been conducted to trace the spatio-temporal profile of the disease. *Methodology:* Confirmed cases of leptospirosis from 2001 to 2017 from the state of Pará were the basis for this space-time study. The database of the Department of Informatics of the Ministry of Health was used to access data on leptospirosis. The spatio-temporal analysis was performed in the SaTScan software for the detection of clusters, and maps were generated in the QGIS software. *Results:* The municipalities of Belém and Santarém were among the ones with the highest incidence rates of leptospirosis for the whole study period. Increased number of cases in Soure, Inhangapi, São João da Ponta and Magalhães Barata, Ponta de Pedras, Breves, Bragança, Castanhal, and São Domingos do Capim were identified in different time periods. Santarém and Belém are the main foci of leptospirosis because they are the most urbanized and densely populated municipalities in the State. The cases found in smaller municipalities may be associated with periods of more frequent rainfall and circulation of *Leptospira* sp. in marsupials and cattle, in the northeastern part of the State. *Conclusion:* Further studies are needed to help identify the risk factors that contribute to the occurrence of leptospirosis in the State of Pará, particularly in areas with lower population density.

Keywords: Leptospirosis. Spatial Analysis. Spatio-Temporal Analysis. Brazil.

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RESUMO: *Introdução:* O Brasil registrou mais de 62 mil casos de leptospirose confirmados entre 2001 e 2017, com mais de 2.000 casos confirmados no estado do Pará. Apesar da grande quantidade de casos, nenhum estudo até este momento traçou o perfil espaço-temporal da doença. *Metodologia:* Este é um estudo espaço-temporal com base nos casos confirmados de leptospirose entre 2001 a 2017 no estado do Pará. O banco de dados do Departamento de Informática do Ministério da Saúde foi utilizado para acessar os dados de leptospirose. A análise espaço-temporal foi realizada no software SaTScan para detecção de clusters e os mapas foram gerados no software QGIS. *Resultados:* O município de Belém e Santarém se mantiveram entre as maiores taxas de incidência de leptospirose durante todo o período estudado. O aumento no número de casos em Soure, Inhangapi, São João da Ponta e Magalhães Barata, Ponta de Pedras, Breves, Bragança, Castanhal e São Domingos do Capim foram identificados em diferentes períodos. Santarém e Belém são os principais focos de leptospirose por serem os municípios mais urbanizados e com maior densidade populacional do estado. Os casos observados em municípios menores podem estar associados a períodos de maior pluviosidade e circulação de *Leptospira sp.* em marsupiais e em gado no nordeste do estado. *Conclusão:* Com o exposto, torna-se necessário mais estudos visando o conhecimento dos fatores que contribuem com a ocorrência da leptospirose no estado do Pará, particularmente em áreas com menor adensamento populacional. *Palavras-chave:* Leptospirose. Análise Espacial. Análise Espaço-Temporal. Brasil.

INTRODUCTION

Leptospirosis is an infectious anthrozoosis caused by a bacteria of the genus *Leptospira* sp. It is a disease of global concern that is transmitted mainly by direct contact with the urine of infected animals. The species with the highest zoonotic interest is *Leptospira interrogans*, which includes more than 200 serovars grouped into 23 serogroups. Each serovar has a preference for a particular host, although an animal species can host more than one serovar. Humans are known to be susceptible to several serovars¹.

The main source of infection in humans is direct contact with the urine of infected domestic or wild animals such as rodents, canines, cattle, and pigs. Indirect means of infection in humans can also be contact with water bearing the spirochetes (waterborne disease). Leptospirosis has a cosmopolitan distribution, often with propensity towards regions with warm and humid climatic conditions². Although the disease is characterized by its global occurrence, its distribution is uneven, with higher incidence rates seen in underdeveloped countries due to poor sanitation service³.

Clinical manifestations of leptospirosis include high acute fever, with or without jaundice. With an incubation period ranging from 7-12 days, it is often confused with other diseases that have prodromal symptomatology in the initial phase. It may present intermittent manifestations, reappearing with the worsening of clinical conditions. Failure of adequate medical intervention can lead to progression to a more serious form, such as the Weil Syndrome, characterized by renal failure, jaundice, and multiple hemorrhage, specifically of the lungs, brain, kidneys, and liver⁴.

Between 2001 and 2017, the Department of Informatics of the Ministry of Health (DATASUS) registered more than 62,000 confirmed cases of leptospirosis in Brazil with an approximate mortality rate of 10%. It should be emphasized that the majority of cases in Brazil were documented in urban areas⁵ and only the most serious cases are usually diagnosed and eventually reported⁶.

In the State of Pará, more than 2,000 confirmed cases of leptospirosis between 2001 to 2017 were recorded in the DATASUS platform. The poor sanitary conditions and inadequate infrastructure of many municipalities within Pará favor the proliferation of rodents. It thus constitutes a public health problem, as these animals are known vectors of many infectious diseases^{1,7}.

Although it is important to impose measures for the control of leptospirosis reservoirs, other strategies that gear towards improving sanitary conditions and public knowledge must be addressed, especially in high-risk areas. In order to achieve that, areas in which the occurrence of leptospirosis is higher should be identified, which justifies the need for techniques on spatial statistical analysis. The joint evaluation of space-time variation provides a better understanding of the affected areas and the spread of leptospirosis over time, helping to identify outbreaks and their possible causes⁸.

As such, the objective of this study was to evaluate the spatio-temporal distribution of leptospirosis in the State of Pará aiming at identifying the municipalities and time periods with the highest incidence from 2001 to 2017.

METHODOLOGY

The study is a descriptive, retrospective, ecological study based on the number of confirmed cases of leptospirosis in the State of Pará. The cases reported in 2001-2017 were obtained from the database of the Department of Ministry of Health (DATASUS) through the Brazilian Information System for Notifiable Diseases (SINAN). The population data were collected from the Brazilian Institute of Geography and Statistics (IBGE). For the intercensal years, population estimates were calculated based on the 2000 and 2010 census by IBGE, which takes into account mortality, fertility, and migration and uses the methodology developed by Madeira and Simões⁹.

All the above-mentioned databases are maintained by the Brazilian government and are freely available in the public domain. The information provided by the domain does not reveal any personal data, which eliminates the need for ethical approval.

The study area was the State of Pará, in the northern region of Brazil, east of the Amazon. The state has an area of 1,247,954.666 km² and is divided by IBGE into 6 mesoregions, 22 microregions and 144 municipalities (Figure 1). According to the 2010 IBGE Census, Pará has a population of 7,581,051 people. The climate of the region is tropical and is divided into two seasons: the rainy season, between December and May, when flooding is more common; and the dry season, between June and November¹⁰.

In this study, the following variables were used: number of cases confirmed by laboratory and clinical-epidemiological criteria, age, sex, infection area, and infection environment. The number of confirmed cases and of the population in the same period were used for incidence calculation and for the spatio-temporal analysis. For the incidence calculation, no smoothing techniques were used, which is a limitation of the study. In order to reduce the rate of fluctuation, the analysis was made in periods of 4 years. In addition, another strategy for spatio-temporal analysis was performed, as detailed below.

To generate clusters of leptospirosis cases, the spatio-temporal analysis was performed in the software SaTScan™ v. 9.6¹¹. This approach allows to identify whether cases were distributed randomly or grouped in space-time. SaTScan™ makes a space-time scan through a cylindrical window with a circular base corresponding to the area, and the height corresponding to the time. That said, the window is moved in space-time with each cylinder corresponding to a possible cluster¹². The clusters were calculated using the discrete model of Poisson¹³ with the following configurations: non-occurrence of overlapping of geographical groupings, agglomerates of maximum size equal to 50% of the exposed population, circular sets, and 9,999 repetitions. The level of statistical significance considered was 5%.

The statistical technique was adjusted according to the population of cities and set to detect high and low-risk groups of leptospirosis. The significance test of the identified clusters was based on the Monte Carlo simulation¹⁴. The program showed the relative risk (RR) of each cluster in a way that different areas could be compared to each other. It is noteworthy that statistically significant clusters of high and low risk were presented in maps created in the free software QGIS 3.2¹⁵ based on Municipalities 2015, of the IBGE digital network¹⁶.

RESULTS

The characteristics of individuals infected with leptospirosis in the state of Pará from 2001 to 2017 are described in Table 1. It can be seen that there were 2,179 confirmed cases with males in larger number compared to females. With respect to age group, the highest number of cases was seen with individuals aged between 20 and 39 years old; conversely, the lowest number of cases for those aged between 0 and 9 years old. Regarding the infection area and infection environment, the urban area and domicile, respectively, had the largest number of cases (Table 1). Information regarding the spatial distribution of leptospirosis in the State of Pará is also described in Table 1 with the divisions shown according to their mesoregions (Figure 1). The highest percentage of leptospirosis cases is concentrated in the Metropolitan Region of Belém (RMB), which includes 11 municipalities, one of which is Belém, the State's capital.

Figure 2 presents leptospirosis incidence in the State of Pará divided between four periods of four years each. In the first-time frame (2002 to 2005), a small number of cases in the whole State was verified aside from the cases documented in the municipalities of Santarém and Belém. The municipality of Santarém, located in the mesoregion of Lower Amazon, had 3.9 cases per 100,000 inhabitants in the period. Santarém was the only municipality with

Table 1. Demographic profile of individuals with leptospirosis and environmental conditions associated with infection, from 2001 to 2017, in the State of Pará.

Characteristic	Confirmed cases (n = 2,179)	%
Sex		
Male	1,664	76.37
Female	515	23.63
Age group (years)		
0–9	116	5.33
10–19	380	17.44
20–39	883	40.52
40–59	596	27.35
≥ 60	204	9.36
Infection area		
Urban	1,267	58.15
Rural	207	9.50
Peri-urban	114	5.23
Ignored	591	27.12
Infection environment		
Domicile	965	44.28
Work	285	13.08
Leisure	47	2.16
Other	59	2.71
Ignored	823	37.77
Mesoregions		
Lower Amazon	198	9.09
Belém metropolitan region	1,698	77.92
Marajó Islands	40	1.84
Northeast	133	6.10
Southeast	40	1.84
Southwest	4	0.18
Ignored	66	3.03

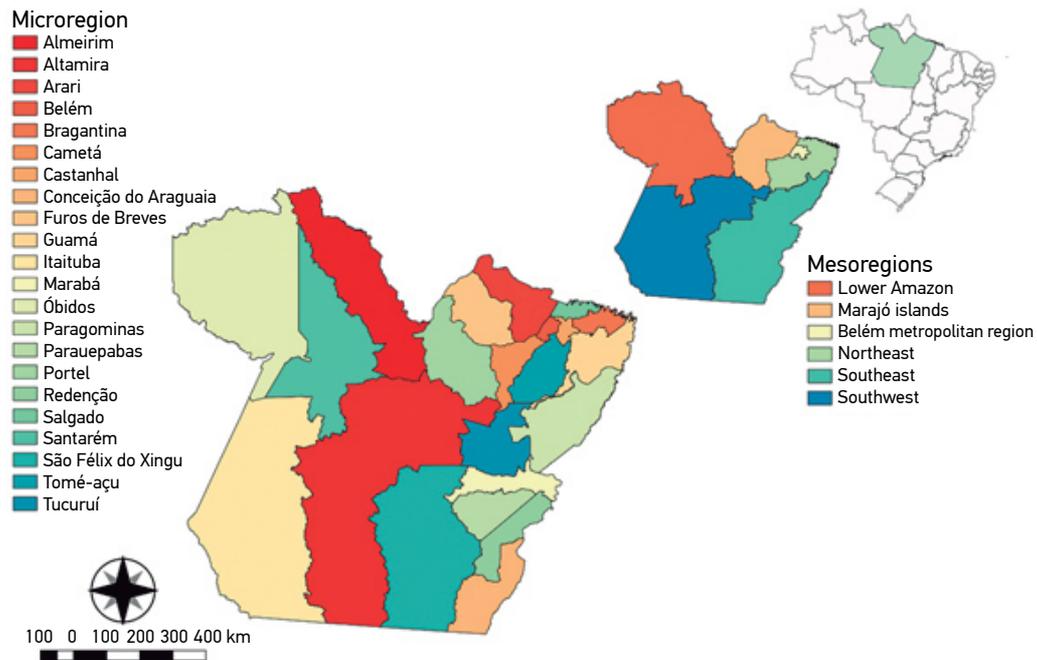


Figure 1. Geographic location of the State of Pará and its territorial divisions according to the Brazilian Institute of Geography and Statistics (IBGE), Brazil.

confirmed cases in the western portion of the State. On the other hand, the municipality of Belém, located in the mesoregion of the Metropolitan Region of Belém, had 9.3 cases per 100,000 inhabitants within the same period.

In the second time frame (2006 to 2009), Belém remained as the city with the highest incidence of leptospirosis with 6.8 cases per 100,000 inhabitants. It was followed by the municipality of Soure, in the Marajó mesoregion, with 3.4 cases per 100,000 inhabitants. In the western portion of the state of Pará, in addition to Santarém, the municipality of Oriximiná also reported cases of leptospirosis with 1.8 cases per 100,000.

In the third time frame (2010 to 2013), a large number of cases was reported in low population density municipalities compared to Belém. The highest incidence rate was seen in Inhangapi, with 41 cases per 100,000 inhabitants. The municipality of Inhangapi is located in the Metropolitan Region of Belém and has 10,037 inhabitants, according to the 2010 IBGE census. The municipality with the second highest incidence rate was São João da Ponta, with 32.4 cases per 100,000 inhabitants. São João da Ponta has 5,265 inhabitants and is located in the mesoregion of northeast Pará. The third municipality was Magalhães Barata, located in Marajó mesoregion, which has a population of 8,115 and where 24.5 cases per 100,000 inhabitants were reported. Santarém and Belém remained among the municipalities with greater incidences.

In the fourth time frame (2014 to 2017), the municipalities of São João da Ponta and Inhangapi were still showing the highest incidences, with 30 cases per 100,000 and 16 cases per 100,000 inhabitants, respectively. São Francisco do Pará, located in the northeast

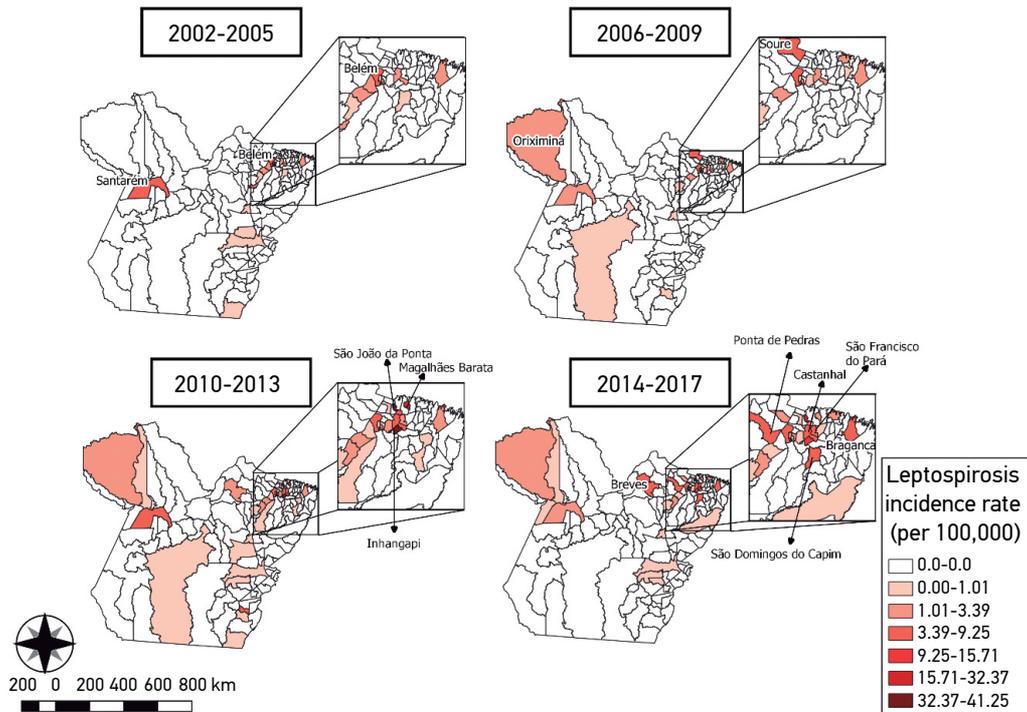


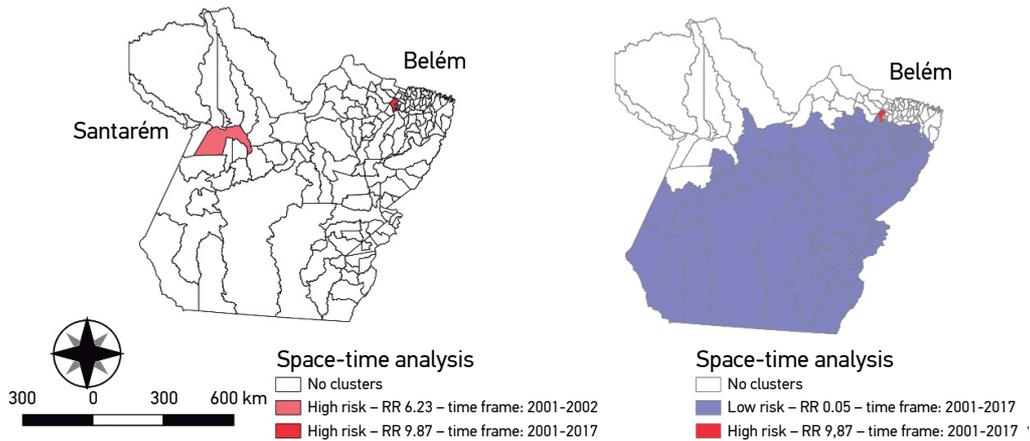
Figure 2. Maps of Pará showing average incidence rates of leptospirosis in affected municipalities. Each map represents a period of 4 years, between 2002 and 2017.

mesoregion, followed with 8 cases per 100,000 inhabitants. Ponta de Pedras and Breves, both located in the mesoregion of Marajó, had 6 and 5 cases per 100,000 inhabitants, respectively. Belém, Castanhal, Bragança, and São Domingos do Capim reported 4 cases per 100,000 inhabitants, the first two are part of the Metropolitan Region of Belém while Bragança and São Domingos do Capim are in the northeast mesoregion of the State.

The spatio-temporal analysis for the detection of high-risk clusters identified Belém during the whole study period (2001 to 2017) and Santarém (2001 to 2002) (Figure 3). When high and low-risk clusters were evaluated in the same period, two clusters were identified: high-risk in Belém during the whole period, and low-risk in all municipalities in the south of Pará, as well as some municipalities in the northeast region for the whole period evaluated (Figure 3).

DISCUSSION

The largest number of leptospirosis cases in the state of Pará was registered among men over the age of 20 years old, among individuals infected in urban areas, and in the domicile environment. These findings are in line with global standards for leptospirosis risk groups⁶.



RR: relative risk.

Figure 3. Maps of Pará with high-risk and low-risk clusters from 2001 to 2017. The map on the left shows Santarém and Belém as high-risk areas. The map on the right shows low-risk space-time clusters of leptospirosis represented in blue.

In Brazil, leptospirosis is associated with low income, poor housing, flooding, and rat infestation; all of which occur at urban peripheries in the State of Pará^{17,18}. This explains why the highest concentration of leptospirosis cases is reported in the Metropolitan Region of Belém rather than in less populated regions or rural areas of the state.

Assessment of the space-time distribution of leptospirosis incidence in Pará (Figure 2) from 2002 to 2005 shows that the municipalities with the highest incidence rate were part of the two largest metropolitan areas: Belém, and Santarém. These two cities are the largest urban poles in the state, having both a high demographic concentration and the biggest urban periphery areas. As a result, they remained throughout the evaluated years as the municipalities with the highest incidence of the disease.

Between 2006 and 2009, there were three cases of leptospirosis documented in the municipality of Soure, in the Marajó mesoregion, which drastically increased disease incidence because of the small local population. It is important to note that most municipalities in the State of Pará do not have an adequate sewerage network. As such, during periods of high rainfall in the municipality, flood water reaches the pits, and wastes may end up leaking into the river and surrounding areas. In addition, the existing solid waste collection system is made of wagons, which transport wastes to an open dump¹⁹. An interesting finding is that Soure is also characterized as an endemic area for leptospirosis in bovine and equine farms^{20,21}. Taken together, these factors may contribute to the spread of leptospirosis, and the increase in number of cases in Soure or surrounding municipalities.

Between 2010 and 2013, the municipalities that reported an increase of leptospirosis cases were Inhangapi with 17 cases (41 cases per 100.000 inhabitants), São João da Ponta with 7 cases (32.4 cases per 100.000 inhabitants), and Magalhães Barata with 8 cases (24.5 cases per 100.000 inhabitants). All of the mentioned municipalities had no cases of leptospirosis

reported from 2001 until 2010. It is important to note that all of these municipalities are located along riverbanks and that annual rainfall was higher between 2010 and 2017 compared to previous years, which favored floods in these regions and possibly led to an increase in the number of cases of leptospirosis^{22,23}.

From 2014 to 2017, São João da Ponta and Inhangapi were still leading in disease incidence; however, there was a reduction in incidence compared to the previous period in both municipalities, as well as in the State capital, Belém. This reduction could be explained by the implementation of health education programs, such as lectures and courses for professionals and local inhabitants, by the health agencies aiming at leptospirosis prevention²⁴.

Other municipalities such as São Francisco do Pará, Ponta de Pedras, Breves, Bragança, Castanhal, and São Domingos do Capim, registered increased incidence, which demonstrates the need for greater State intervention in these regions. The recent detection of anti-leptospira antibodies in wild marsupials in the municipalities of Castanhal, Peixe-boi and Viseu, in the northeast mesoregion and the same mesoregion for some of the municipalities mentioned above, demonstrate a circulation of the pathogen amongst these animals, and this can be an important source of leptospirosis infection for inhabitants in this area²⁵.

For the cluster detection, Santarém and Belém had statistically significant clusters with Belém in the whole period, and Santarém between 2001–2002 (Figure 3). The fact that Belém maintains a consistent disease burden of leptospirosis can be explained by its high population density and location in the metropolitan region of Brazil, which has the highest proportion of people living in slums or similar low-income settlements, and which is characterized by poor service of water supply, sewage disposal, waste disposal and the availability of electricity⁷. On the other hand, Santarém's space-time cluster is directly related to the intense, sprawling urban growth that creates severe problems with peripheralization. In addition, other factors such as precarious infrastructure, poor education, and absence of health assistance are also included²⁶.

The investigation of the low-risk cluster showed the southeast and southwest areas of the state with a relatively lower risk compared to other regions. This can be explained by the distribution of metropolitan regions and urban settlements concentrated mainly in the capital, with greater population density, in Belém, and in the nearby municipalities. In contrast, populations located south of the State of Pará had lower population density according to the 2010 IBGE demographic census.

CONCLUSION

The findings of this study have shown that Santarém and Belém are the main foci of leptospirosis cases in the State of Pará, and these municipalities remained among the places with the highest incidence rates of leptospirosis over the years. A subtle increase in the number of cases in some cities with low population densities was responsible for the dramatically increased incidence in certain areas such as Magalhães Barata, São José da Ponta, and Inhangapi. The circulation of *Leptospira* sp. in marsupials and cattle in the remote areas of

the northeastern part of the state, far away from Belém Metropolitan Region, in combination with floods may be associated with these increased number of cases^{19,20,24}.

The introduction of government programs such as campaigns for increased awareness and education, and instruction of health professionals about leptospirosis, such as those carried out in Inhangapi²³, is fundamental to improve the current situation. More importantly, there is a need for housing improvement, decrease in the percentage of people in slum areas, and control of main urban leptospirosis vectors. Lastly, further research related to the causes of leptospirosis in distant areas with low population density is needed.

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