DOI: 10.1590/1413-812320152012.01672015

Space-time analysis of visceral leishmaniasis in the State of Maranhão, Brazil

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Abstract *This study analyzed the spatial and temporal distribution of cases of visceral leishmaniasis in the State of Maranhão in the period from 2000 to 2009. Based on the number of reported cases, thematic maps were prepared to show the evolution of the geographical distribution of the disease in the state. The MCMC method was used for estimating the parameters of the Bayesian model for space-time identification of risk areas. From 2000 to 2009 there were 5389 reported cases of visceral leishmaniasis, distributed in all 18 Regional Health Units in the state, with the highest indices in the cities of Caxias, Imperatriz, Presidente Dutra and Chapadinha. The Regional Health Units with the highest relative risks per biennium were: Caxias and Barra do Corda (2000-2001), Imperatriz and President Dutra (2002-2003), Imperatriz and Caxias (2004-2005), Presidente Dutra and Codó (2006-2007) and Imperatriz and Caxias (2008-2009). There was considerable geographic expansion of visceral leishmaniasis in Maranhão, thus highlighting the need to adopt more effective measures for prevention and control of the disease in the state.*

Key words *Visceral leishmaniasis, Space-time analysis, Bayesian model*

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Introduction

Visceral Leishmaniasis is a serious public health problem that is widely prevalent in the world. It is currently amongst the seven endemics considered to be a priority in relation to health actions in the world. It is on the list of neglected tropical diseases that should be eradicated by 2015 according to the World Health Organization (WHO)[1,2].

Brazil accounts for 90% of the LV cases in Latin America and it is considered the country with the third highest rates of the disease in the world[3]. In Brazil, between 1999 and 2008, more than one third of districts registered autochthonous cases and in these districts the disease has not been considered a priority. Also between 1980 and 2008 70 thousand cases of LV were registered in the country which resulted in the deaths of more than 3,800 people[4,5].

Amongst all of the Federal states in Brazil, Maranhão has recorded the highest number of cases of LV. From 1999 to 2005 this state was the leader in the number of confirmed cases of the disease in Brazil. By 2009, 9,972 cases were registered with the majority being registered in the districts that make up the island of São Luís: São Luís, São José de Ribamar, Paço do Lumiar e Raposa[6,7].

Although there has been some recognition of the magnitude of the problem in Maranhão no studies have been done over the last decade covering the scale of the problem and the number of new cases. It also should be remembered that many studies[6-8] were done with a view to understanding LV's epidemiology in the districts that make up the island of São Luís (São Luís, São José de Ribamar, Paço do Lumiar e Raposa), however we do not have any data regarding the progression of the disease in the state of Maranhão. Therefore we believe that a good grasp of the nature of the problem or the risk hot spots within the regions is essential for designating adequate resources to combat the disease and for taking appropriate health care actions.

Different Bayesian saptio-temporal models have been used to get a better understanding of the dynamics involved in the transmission of LV. This type of modeling allows for the obtaining of stable estimates of the spacial variations of the relative risks or the disease incidents[9-11]. However when the number of cases and the population at risk in an area over a specified period of time are low, it becomes difficult to obtain risk estimates that are near to reality. But it may be more beneficial to use information from surrounding areas to estimate the relative risks.

The use of these models in the area of epidemiology have been present in a number of studies. Vieira et al.[12] described the spatial-temporal behavior of LVH in Birigui (SP). Other studies used the same model for other endemic diseases, such as that of Souza et al.[13]. They analyzed the spatial distribution of leprosy in the city of Recife. This was also done by Nobre et al.[14]. They analyzed the number of malaria cases in Pará between 1996 and 1998.

In this present study the aim is to analyze spatial-temporal distribution of LV cases in Maranhão between 2000 and 2009.

Methods

This is an ecological study looking back at the history of LV cases that were registered according to the residents in the state of Maranhão between 2000 to 2009.

The state of Maranhão, that has as its capital São Luís, is located in the western region in the north east of Brazil. It covers an area of 331.933,3 km², and it has a population estimated at around 6.184.538 inhabitants[15,16]. Maranhão is bordered by the following: the Atlantic ocean to the north, the state of Piauí to the east, the state of Tocantins to the south and south east and the state Pará to the west. The state has: 217 districts, 5 mesoregions, 21 microregions and 18 region health units (URS).

In this study the spatial units that were analyzed were the regional health units represented by a group of neighboring districts that had similarities in relation to their: geography, climate and socio-economic position. They all also had a political/administrative office of the state Ministry for Health in Maranhão with the task of improving health care in the state. These regional health units were: Açailândia, Bacabal, Balsas, Barra do Corda, Caxias, Chapadinha, Codó, Imperatriz, Itapecuru-Mirim, Pedreiras, Pinheiro, Presidente Dutra, Rosário, Santa Inês, São Luís, São João dos Patos, Viana and Zé Doca[15,16].

The population in the state of Maranhão between 2000 and 2009 was affected by all of the cases of Visceral Leishmaniasis. The information was collected from the Information System for the Notification of Diseases (SINAN) database. This was from the Secretary of State for Health in Maranhão. We excluded all information that could possibly be used to identify participants in the study in order to respect their privacy. We also took out information which was: inconsistent, imprecise, incomplete or duplicated (i.e. two or more registers of the same case). We included cases where the individual presented symptoms of LV such as: a fever for more than two weeks, hepatoesplenomegaly, and/or a confirmed diagnosis of the disease through a bone marrow aspiration showing positive for *Leishmania* sp. We also considered the area for URS, suggesting autochthony for the disease.

Information from the Brazilian Institute for Geography and Statistics[16] was used to estimate and calculate the density of the population in each period for URSs.

The number of incidents of LV was calculated based on the total amount of cases registered in each URS. We then divided the estimated density population in each URS and multiplied this number by 100,000. In this way we were able to ascertain the number of those stuck down by the disease per 100,000 inhabitants.

We used the bayesian spatial-temporal model in order to obtain relative risk estimates for LV. Y represented the variable which was the number of LV registered cases at the URSs (i-ésima) during *t* year. i = 1,...,18 and t = 1,..., 10 (years 2000 to 2009). For y_{it} we used the Poisson distribution with an average $\mu_{it} = e_{it}\rho_{it}$ or in a logarithmic form $log(\mu_{it}) = log\ e_{it} + log\ \rho_{it}$, being e_{it} which was the number cases expected at the URSs *i* in time *t* and ρ_{it} o the relative risk at the URSs *i* in time *t*.

The number of expected cases e_{it} were known quantities obtained from the population of each URS in the period between 2000 and 2009. This was calculated by ρ_{it}, multiplied by the number of cases at the URSs and *i* by the total population in all of the URSs. This was the equation:

$$e_{it} = p_{it} \frac{\sum_{i=1}^{r} y_{it}}{\sum_{i=1}^{n} p_{it}}$$

Using this method in this study the relative risk ρ_{it} was estimated through the use of the Bayesian spatial-temporal model that was adapted by Nobre et al.[8]. The model used assumed that $log(\rho_{it}) = \beta_t^2 + b_{it}$, and temporal effort $\beta_t = \beta_{t-1} + v_t$, for t=2, ..., 10. This model considers that the relative risk is related to the temporal effect β_t, which is dependent on the effort for the previous year with a random error of v_t, and a spatial-temporal effort b_{it}.. Apart from this, the random error v_t is normally distributed with an average of zero and an unknown variant σ_v^2, designated by v_t ~Normal(0, σ_v^2), and β_1 ~Normal(0,σ_β^2).

With the Bayesian approach is it necessary to specify the a priori distribution for the model parameters in the study. For the parameter b_{it}, an a priori autoagressive conditional distribution was primarily used (CAR) with a variant σ_t^2, as proposed by Besag and Kooperberg[17], denoted by b_{it} ~ *CAR* (σ_t^2), which determines the structure of the spacial correlation, given by:

$$b_{it} \mid b_{jt}, j \neq i \sim Normal\left(\frac{\sum_{j \epsilon \delta_i} w_{ij} b_{jt}}{\sum_{j \epsilon \delta_i} w_{ij}}, \frac{\sigma_t^2}{\sum_{j \epsilon \delta_i} w_{ij} b_{jt}}\right)$$

Where δ_i^2 is the entirety of an area considered to be neighboring the *i*-ésima area according to the criteria for neighbors; σ_β^2 represents the variability in the *t* and w_{ij} corresponds to the weight of the neighbor from the area *j* and for the area *i*, which defines the matrix for the neighborhood[18,19]. Sometime afterwards b_{it} was considered for normal distribution with an average of zero and variants σ_β^2, in other words, without considering the spatial correlation structure.

In order to define neighboring areas in specific areas *i*, and its respective weight, we used the adjacency criteria that allows for the consideration of neighbors from other areas *i* limited to that bordered. In relation to defining the weights w_{ij} we considered for w_{ij} binary values, meaning w_{ij} is going to be equal to 1, if the URS *i* and *j* are adjacent and 0 if it is to the contrary[17-19].

Finally for the hyper-parameters 1/ σ_β^2, 1/ σ_v^2 and 1/ σ_t^2, were considered a priori independent distribution gammas with an average and variance equal to one[14]. Estimates of the parameters and hyper-parameters of interest were obtained from the Monte Carlo Method via the Markov Prison (MCMC) where the WinBugs (*Win Bayesian Inference Using Gibbs Sampling*) version 1.4[9] statistical program has been implemented.

Three prisons were used simultaneously starting from different points, with each parameter monitored after a burn-in of 5,000 iterations and these simulations were discarded. Afterwards, 10,000 distribution values *a posteriori* for each parameter was generated. The criteria for convergence was based on a visual inspection of charts from Markov Prison.

Maps giving risk estimates from the Bayesian model were created in the *TerraView* Program version 3.5 and was presented biennially.

Following ethical norms involving research of human beings, in accordance with Resolutions 196/96 and 466/12 of the National Council for Health, the study was examined and approved by the Ethics Committee on Research at the University Hospital at the Federal University of Maranhão.

Results

Between 2000 and 2009 5,389 cases of LV was registered, with the highest numbers of incidents at the URSs: Caxias (36,1/100.000 Inhab.), Imperatriz (30,8/100.000 Inhab.), Presidente Dutra (10,8/100.000 Inhab.), Codó (10,4/100.000 Inhab.) and Barra do Corda (9,8/100.000 Inhab.). The cases were registered in all of the URSs, with the reemergence of former hotspots for the disease such as at the following URSs: Caxias, Imperatriz e São Luís (6,5/100.000 hab.). There was the emergence of new hotspots for cases at the following URSs: hapadinha (5,7/100.000 hab.), Itapecuru-Mirim (5,5/100.000 hab.), Balsas (5,7/100.000 hab.), São João dos Patos (5,5/100.000 hab.), and Pedreiras (5,5/100.000 hab.). See Table 1.

Upon evaluating the number LV cases per year (Table 1) we noted that from 2007 (5,5/100.000 Inhab.) and 2009 (5,6/100.000 Inhab.) there was the lowest numbers of LV incidents and in 2000 (15,6/100.000 Inhab.) we recorded the highest numbers. On the other hand a completely different situation was seen at the URS in São Luís. 790 absolute cases were registered putting it in third place and the number of incidents was 6,5/100.000 inhabitants (in sixth position). This showed an important reduction in the main focus of the disease in the state (Table 1).

Figure 1 and Figure 2 shows the temporal biennial progression of LV at the URSs in the study. The following URSs over two years showed the highest estimated relative risks: Caxias, Barra do Corda, Imperatriz and Presidente Dutra from 2000-2001 (RR = 0,8-5,2) and 2002-2003 (RR = 0,9-4,3). The following URSs over the next two years showed the highest risks: Imperatriz, Caxias, Presidente Dutra and Codó from 2004-2005 (RR = 1,2-3,7) and 2006-2007 (RR = 1,4-3,1) to greatest risks. Also the following URSs registered the highest risk for 2008-2009: Imperatriz, Caixas, Codó and Itapecuru-Mirim with relative risks that varied between 1,9 and 2,6.

Discussion

This study showed that there was an accentuated geographical distribution of LV amongst the region health units in Maranhão between 2000 and 2009. Aside from the appearance of new hotspots, previous hotspot areas continued to show occurrences of the disease. This demonstrates that the existing control measures have not been sufficient to neither control LV endemic areas nor to prevent the outbreaks in areas that were then considered safe.

LV is a recognized public health problem in the state of Maranhão since 1980[8,20]. During the period of this study we observed an expansion of the disease not only in the areas with the greatest concentration of cases such as São Luís, Imperatriz e Caxias, but also in other regions. Various factors may have contributed to the spreading of this disease in the state. Among them, we can highlight the intense inter-municipal migratory flux which has also occurred at interstate level. This is the case for cities near to the Vale de Rio Doce railway line or Teresina (PI). This is also the case for cities with a large amount of deforestation.

These types of population movements facilitate the introduction of LV etiological agents in once disease free areas. It also makes endemic areas even more susceptible to the disease. Many families that have migrated from rural areas have settled on the outskirts of the cities which vary in size. They lived in densely populated areas where there is little infrastructure or basic sanitation. This was the case in São Luis (MA) in the 80s where intense migration occurred due to the beginning of big industrial projects. This sparked an epidemic[6,7].

However we observed rises in cases in municipalities on the continent that did not previously register the disease. There was a considerable fall in the number of LV cases in the districts on the island of São Luís in the 90s[6,7,9] up to the present day. Other studies that evaluated the spatial temporal distribution of LV in various Brazilian regions, utilizing different methods, also showed a high number of cases in locations that had not registered the disease[21-23]. This geographical expansion of the disease could be associated with the low impact of the control measures that were used. It may also be due to the way how the disease is diagnosed and the registration system. This could also be the case in relation to the mobility of the people.

Table 1. Cases and Incidents (100,000 Inhab.) of Visceral Leishmaniasis per Regional Health Unit (URS) in Maranhão in the period from 2000 to 2009.

	2000		2001		2002		2003		2004		2005	
	Cases	Inc*	Cases	Inc	Cases	Inc	Cases	Inc	Cases	Inc	Cases	Inc
São Luis	155	14.7	37.	3.4	37.	3.2	78.	6.6	110	8.8	124	10.3
Rosário	0.	0.	0.	0.	0.	0.	1.	0.5	3.	1.6	1.	0.5
Itapecuru-Mirim	8.	3.0	12.	4.4	1.	0.3	8.	3.0	8.	3.5	5.	2.2
Chapadinha	21.	6.7	18.	5.7	16.	5.0	36.	11.2.	21.	6.3	15.	4.6
Codó	27.	10.7	7.	2.7.	22	8.0	32	11.6	24.	8.4	50	18.0
Pinheiro	0.	0.	3.	0.9	3.	0.9	0.	0.	3.	0.9	0.	0.
Viana	1.	0.3	0.	0.	1.	0.3	1.	0.3	2.	0.6	2.	0.6
Santa Inês	0.	0.	1.	0.3	0.	0.	1.	0.2	0.	0.	1.	0.2
Zé Doca	4.	1.6	4.	1.6	0.	0.	1.	0.3	2.	0.7	4.	1.5
Açailândia	3.	1.5	2.	1.0	5.	2.1	11	4.6	10	3.9	6.	2.4
Imperatriz	233	57.3	142	34.8	239	55.6	221	51.1	132	29.9	74	16.9.
Balsas	10	5.4	5.	2.7.	2.	1.0	21.	11.0	17	8.6	13.	6.7
S. João dos Patos	9.	4.0	14	6.1	8.	3.5	7.	3.0	6.	2.5	16.	6.9.
Presidente Dutra	38.	17.5	16.	7.3	31.	14.1	27.	12.2	12.	5.3	14	6.3
Pedreiras	16.	7.90	10	4.9	3.	1.4	7.	3.4	21.	10.0	13.	6.2
Barra do Corda	41.	18.0	11	4.8	18.	6.9.	18.	6.9.	35.	13.0	25	9.5
Bacabal	3.	1.2	9.	3.5	5.	2.0	9.	3.7.	4.	1.6	7.	2.9
Caxias	285	70.8	201	49.6	185	43.4	296	68.8	119	26.9	138	31.8
Total	854	15.6	492	8.9	573	9.9	769	13.1	508	8.4	495	8.4

	2006		2007		2008		2009		Total	
	Cases	Inc	Cases	Inc	Cases	Inc	Cases	Inc	Cases	Inc
São Luis	37.	3.4	69.	5.2	69.	5.2	27.	2.0	790	6.5
Rosário	0.	0.	1.	0.5	6.	3.2	7.	3.7.	19.	1.1
Itapecuru-Mirim	12.	4.4	16.	6.9.	30.	13.1	39.	17.0	132	5.5
Chapadinha	18.	5.7	16.	4.6	9.	2.6	16.	4.6	188	5.7
Codó	7.	2.7.	22	7.5	35.	12.0	25	8.6	289	10.4
Pinheiro	3.	0.9	1.	0.3	4.	1.2	6.	1.8	20.	0.6
Viana	0.	0.	2.	0.6	0.	0.	0.	0.	9.	0.3
Santa Inês	1.	0.3	1.	0.2	4.	1.0	1.	0.2	9.	0.3
Zé Doca	4.	1.6	0.	0.	2.	0.7	2.	0.7	20.	0.8
Açailândia	2.	1.0	11	4.1	15.	5.6	22	8.2	90	3.7.
Imperatriz	142	34.8	52	11.6	69.	15.4	67.	14.9	1338	30.8
Balsas	5.	2.7.	15.	7.4	6.	2.9	7.	3.4	110	5.7
S. João dos Patos	14	6.1	4.	1.6	35.	14.2	25	10.1	129	5.5
Presidente Dutra	16.	7.3	20.	8.8	29	12.8	30.	13.2	240	10.8
Pedreiras	10	4.9	3.	1.4	18.	8.5	16.	7.5	115	5.5
Barra do Corda	11	4.8	15.	5.5	30.	11.0	32	11.7	254	9.8
Bacabal	9.	3.5	4.	1.6	18.	7.4	4.	1.6	70	2.9
Caxias	201	49.6	92	20.4	60	13.3	39.	8.6	1567	36.1
Total	492	8.2	341	5.5	421	6.8	349.	5.6	5389	9.1

Source: SINAN.
[*] Inc=incidents.

In spite of the number of new cases that remained high through the study, we noticed a reduction in the incidents and an increase in the geographical distribution of LV in Maranhão with variations among URSs. Furlan[24] observed that the differences of the incidents among the regions maybe to do with the different contexts for each region which subsequently influenced the spread of LV.

Certainly there were other factors that must have influenced the geographical progression of LV in Maranhão. It seems that the majority of

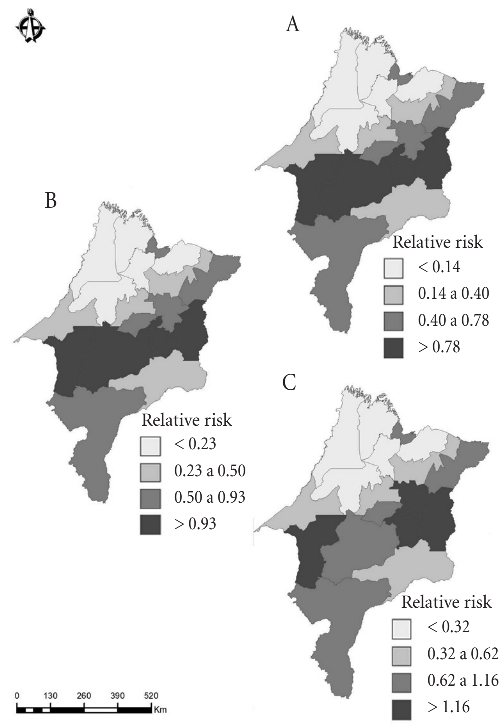

Figure 1. Spatial Temporal analysis of the areas of risk for Visceral Leishmaniasis (LV) for Regional Health Units (URS) in the state of Maranhão, bieannial: 2000-2001 (A), 2002-2003(B), 2004-2005(C).

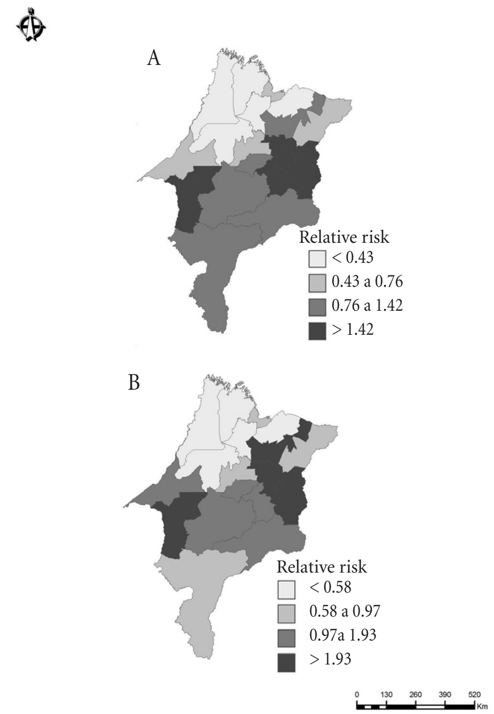

Figure 2. Spatial Temporal analysis of the areas of risk for Visceral Leishmaniasis (LV) for Regional Health Units (URS) in the state of Maranhão, bieannial: 2006-2007 (A), 2008-2009 (B).

cases are associated with anthropic pressure on the environment and the disorderly occupation of areas. Another important aspect is the capacity of the sandfly *Lutzomyia longipalpis* (*Diptera:* Which can be found in practically the entire state[25].

The elevated relative risk in the decade that the study covered in the Imperatriz e Caxias URSs, reinforce the idea detailed by Dantas-Torres and Brandão-Filho[22] that beating the disease which is typically prevalent in rural areas can and has been achieved in urban and peri-urban medium and large cities. On the other hand, the destruction of nature for the construction of social housing and to widen roads may have contributed to the increase in the vector density in the URSs, particularly in Imperatriz. This was due to the population increases because of the soya plantation and the extraction of wood in the pre-amazon region.

Mestre e Fontes[21] identified the wide geographical expansion of LV in Mato Grosso, affecting urban and peri-urban areas in various districts. This was also the case for the suburbs in the state where the spread of the disease went hand in hand with the disorderly occupation of urban areas and migratory flux. As was the case in Maranhão Werneck et al.[26] blamed the lack of an effective and permanent monitoring system with human resources and the lack of sufficient finances to aid in the control of LV in urban centers.

One of the major problems found during this study was the lack of or inconsistencies in the information which resulted in variations in numbers which could not be explained. The data that was filled in was understood as the result of routine activities in health services. In spite of the work of Epidemiological Monitoring Departments in the districts, little contentment was registered.

Despite the aforementioned limitations, the results of the study allowed for a diagnosis of the geographical expansion of LV in the state

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of Maranhão. We were able to map the areas of risks for occurrences and incidents of the cases. We hope to have contributed to the planning of health actions and in the design of a state plan for management in this area which is more closely aligned to the epidemiological and social reality of the state.

The number of cases of LV in Maranhão is still very high and can be found throughout all of the URSs. This is specially the case in areas where the population has grown during the period of the study. However what is needed are more effective prevention and control measures to control the disease in the state.

Collaborations

AS Furtado contributed substantially to the obtaining, analysis and interpretation of the data as well as drafting the document. AM Santos contributed substantially to the analysis and interpretation of the data. FBBF contributed substantially to the analysis and interpretation of the data. Contribution was also made to critically reviewing the content of this study. AJM Caldas contributed substantially to the conception, analysis and interpretation of the data as well as drafting and reviewing the document.

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Article submitted 02/03/2015
Approved 07/04/2015
Final version submitted 09/04/2015