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ORIGINAL ARTICLE

ANALYSIS OF THE FACTORS THAT INFLUENCE THE OCCURRENCE OF HUMAN VISCERAL LEISHMANIASIS

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ABSTRACT
Objective: to analyze the factors that influence the occurrence of Human Visceral Leishmaniasis in the state of Paraíba, Brazil. Methods: ecological study, developed with data from 2012 to 2017, collected in a reference laboratory in the state and in the Atlas of Human Development in Brazil. Data analysis was by binomial regression model, Pearson correlation and Kolmogorov-Smirnov Test. Results: 327 cases of human visceral leishmaniasis and 6,353 cases of canine visceral leishmaniasis were confirmed. The main municipal indicators have a significant relationship with the number of cases of the disease in the state, and a strong relationship with the number of positive cases for Human Visceral Leishmaniasis. Conclusion: the model can be used as a reference to analyze the distribution of cases of human visceral leishmaniasis and the possible factors that influence its occurrence, providing municipal managers with another alternative for carrying out control/prevention measures for the disease, involving several sectors.

DESCRIPTORS: Leishmaniasis, Visceral; Ecological Studies; Regression Analysis; Risk Factors; Parasitic Diseases.

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INTRODUCTION

Visceral leishmaniasis (VL) is an infectious and parasitic disease considered an anthropozoonosis that is part of the group of the six priority tropical diseases in the world[1-2]. In Brazil, VL is caused by the protozoan *Leishmania chagasi*, transmitted by the bite of the sand fly *Lutzomyia longipalpis*[3-4].

VL, also known as Kala azar, is considered a neglected disease and a serious public health problem worldwide(5-8). In Brazil, about 96% of cases are concentrated in South America[8]; distributed throughout the country, VL is present in 21 of the 27 Federative Units[9].

The Ministry of Health, through the Notifiable Diseases Information System (SINAN), reported that 3,556 cases were reported throughout Brazil in 2015, with 2,148 (60.41%) registered in the Northeast Region. In Paraiba, an increase in registered cases has been observed in recent years. From 2007 to 2015, the notifications almost doubled, from 25 to 46 cases of VL, with its peak occurrence in 2014, with 59 cases. According to SINAN, in 2015 VL presented in Paraiba a lethality rate of 15.21%, being above the regional and national values of 7.73% and 7.85%, respectively[10].

Thus, because it is a disease of great importance to public health, it is necessary to understand more about the distribution of VL in Paraiba and identify possible factors related to its occurrence, since the number of studies in the state is scarce.

To this end, regression models, which are mathematical models, help to understand and explain how the behavior of certain variables can alter others. In the literature, there is many statistical methods used in data modeling[11]. An example of this is the logistic regression model used by other scholars[5,12] to identify the possible factors that interfere in the occurrence of VL; however, this model applies when the variable of interest is of dichotomous type.

VL has been showing important changes in recent years, also occurring in large urban centers and in the peri-urban region. It is believed that some factors, such as the urbanization process, deforestation, migration, expansion of slums, environmental changes, malnutrition, absent or inadequate basic sanitation, deficiencies in vector and dog population control, among others, have contributed to this expansion and incidence of VL[4].

The present study aims to analyze the factors that influence the occurrence of Human Visceral Leishmaniasis (HVL) in the state of Paraiba, Brazil.

METHOD

This is an ecological study with a quantitative approach, developed during the period from September 2017 to August 2018, based on data recorded between 2012 and 2017 in the Laboratório Central de Saúde Pública Dra. Telma Lobo (LACEN PB) and in the Brazil Atlas - Atlas of Human Development in Brazil. This laboratory performs medium and high complexity exams throughout the state, aiming to generate information necessary for decision making in health surveillance, as well as monitors and supervises the activities developed at all levels of the State Laboratory Network[12].

Among the 223 municipalities in Paraiba, 64 presented positive cases of VL, which constituted the initial sample of the present study. However, through Cook's distance analysis, we found evidence that three of these observations - Campina Grande, Catolé do

Rocha and João Pessoa - were influential in the analysis. For this reason, it was preferred to adjust a model without their presence, thus characterizing a more homogeneous behavior of the other municipalities. Thus, the present study had a sample of 61 municipalities in Paraiba.

It is noteworthy that the state of Paraiba is in the Northeast Region, with a population of 3,766,528 people, according to the 2010 Census[13]. Currently, the state is divided into four Intermediate Geographic Regions and 15 Immediate Geographic Regions[14].

At LACEN, the Immunochromatography and Indirect Immunofluorescence Reaction (IFR) tests were performed for suspected cases of LVH. For suspected cases of Canine Visceral Leishmaniasis (CVL), the laboratory performed the following tests: Enzyme-linked immunosorbent assay (ELISA), Immunochromatography and the Indirect Immunofluorescence Reaction (IFR). The latter test for the diagnosis of suspected cases of CVL has been disused by the laboratory since 2014, due to the technical note published by the Ministry of Health in 2011[15].

In Brazil Atlas[16], information on the socioeconomic and demographic conditions of municipalities that had a positive case for VL was collected, based on the last Demographic Census of 2010.

The variable of interest is the number of positive cases for VL, obtained from the clinical results of the tests performed by LACEN PB, in which the number of human individuals who tested positive were counted.

For auxiliary variables, the study relied on 28 indicators: number of dogs with positive serology for CVL; municipalities that belong to the Intermediate Geographic Region of João Pessoa (IGRJP); municipalities that belong to the Intermediate Geographic Region of Campina Grande (IGRCG); municipalities that belong to the Intermediate Geographic Region of Patos (IGRP); Proportion of urban population; Proportion of rural population; Municipal Human Development Index (MHDI) and other municipal indicators of education, housing, income and vulnerability, listed below. It is noteworthy that the definition of municipal indicators is described in the Brazil Atlas[16].

Educational Indicators: Illiteracy rate; Expected years of study; Percentage of children between zero and five years old out of school; Percentage of children between six and 14 years old out of school.

Housing Indicators: Proportion of the population in homes with piped water (PPDAE); Proportion of the population in homes with garbage collection (PPDCL); Proportion of the population in homes with a density greater than two; Percentage of people in homes without electricity (PPDSEE); Percentage of people in homes with inadequate walls (PPDPI); Percentage of people in homes with inadequate water supply and sanitation (PPDAAEI).

Income Indicators: Gini Index; Per Capita Income; Proportion of Poor; Proportion of Vulnerable to Poverty; Unemployment Rate - 18 years or more.

Vulnerability indicators: Aging rate; Percentage of children in households where no one has completed basic education (PCDNEFC); Percentage of people in households vulnerable to poverty where no one has completed basic education; Percentage of vulnerable people who spend more than one hour to work in the employed population; Percentage of mothers who are heads of household without basic education and with a minor child, in the total number of mothers who are heads of household.

Data analysis was performed using the R software. Through the negative binomial regression model, it was verified whether the auxiliary variables provide evidence that can help explain the occurrence of VL in the identified municipalities. The negative binomial regression model was chosen as the model to be tested because, according to chi-square test of adherence, the data of the variable of interest did not follow Poisson distribution.

The negative binomial regression model is more appropriate than the Poisson model in cases where data overdispersion is observed[17].

For model selection, the stepwise method[17] was used. In addition, Pearson's correlation test was performed to verify the possible collinearity among all independent variables. Those variables that presented correlation coefficients greater than or equal to 0.8 were considered collinear, and only one of them was selected based on other parameters, such as ease of understanding in decision making. It is noteworthy that this selection method is of great relevance, since it involves the search for a set of variables that can provide with a high degree of accuracy good estimates regarding the outcome from the observed data[18].

The analysis of residuals is considered one of the most important steps in statistical modeling[19]. To evaluate the adequacy of the model presented, graphs were shown to verify the normality of the data by means of the Kolmogorov-Smirnov Test, adequacy of the link function of the variance function, and Cook's distance graph to identify the discrepant points.

The research project was approved by the Ethics and Research Committee of the Center for Sciences and Health of the Federal University of Paraiba, under opinion number 3.062.466.

RESULTS

The results revealed that in Paraiba, between 2012 and 2017, 1,524 cases of HVL and 13,827 cases of CVL were investigated, of which 327 and 6,353 cases were confirmed, respectively. The number of LVH cases had a statewide average of 54 (±19) cases, while the number of CVL cases had a statewide average of 1,059 (±295) cases.

After several combinations, the final adjustment of the model selected 14 of the 28 variables, presented in Table 1, where it is possible to observe that the increase in the variables number of cases of CVL, number of inhabitants, MHDI, percentage of poor people, unemployment rate, years of study expectation, percentage of children in households where no one has elementary school education, percentage of children aged six to 14 years out of school and belonging to the Intermediate Geographic Region of Campina Grande, contribute proportionally to the growth of HLV cases. Regarding the other variables, they contribute inversely proportionally to the growth of human cases of kala-azar.

Table 1 - Variables resulting from the final negative binomial regression model for all investigated municipalities. João Pessoa, PB, Brazil, 2018 (continues)

Variable	β	Standard Error	P-value	expβ
Intercept	-20	5,657	<0,001	-
Number of CVL cases	0,001	0,000	0,002	1,001
Number of inhabitants	0,000	0,000	0,016	1,000
MHDI	3,246	7,651	<0,001	25,69
Income per capita	-0,005	0,002	0,005	0,99
Percentage of poor people	0,053	0,021	0,014	1,05

Unemployment rate	0,061	0,029	0,038	1,06
Years of study expected	0,615	0,186	<0,001	1,85
Percentage of children in households with no one in elementary school	0,098	0,023	<0,001	1,1
Percentage of children zero to five years old out of school	-0,051	0,017	0,002	0,95
Percentage of children between the ages of 6 and 14 who are not in school	0,180	0,087	0,039	1,2
Percentage of population in households with piped water	-0,050	0,010	<0,001	0,95
Percentage of people in households with garbage collection	-0,036	0,012	0,004	0,96
Percentage of people in homes with inadequate water supply and sanitation	-0,071	0,018	<0,001	0,93
Belonging to the Intermediate Geographic Region of Campina Grande	0,525	0,237	0,027	1,69

Legend: β: beta coefficient; exp=exponential; MHDI=Municipal Human Development Index. Source: Research Data, 2018.

In Figures 1 and 2, it is possible to observe the adequacy of the model by checking the normality of the data, adequacy of the link function, the variance function, and Cook's distance plot to identify the discrepant points.

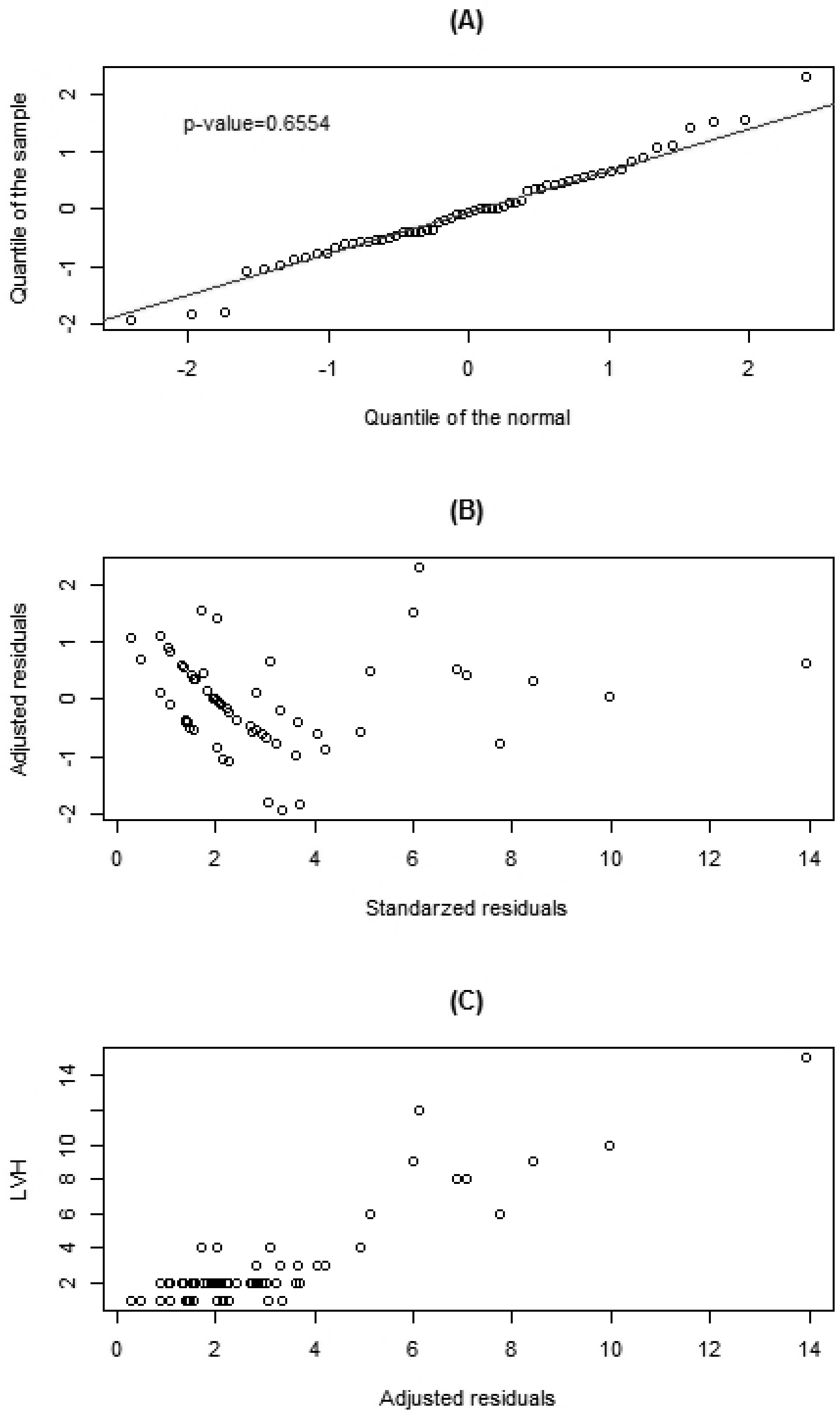

Figure 1 - Graphs of the adjusted residuals referring to the Negative Binomial Regression model to the data on the number of cases of HVL in Paraiba. João Pessoa, PB, Brazil, 2018
Source: Authors (2018)

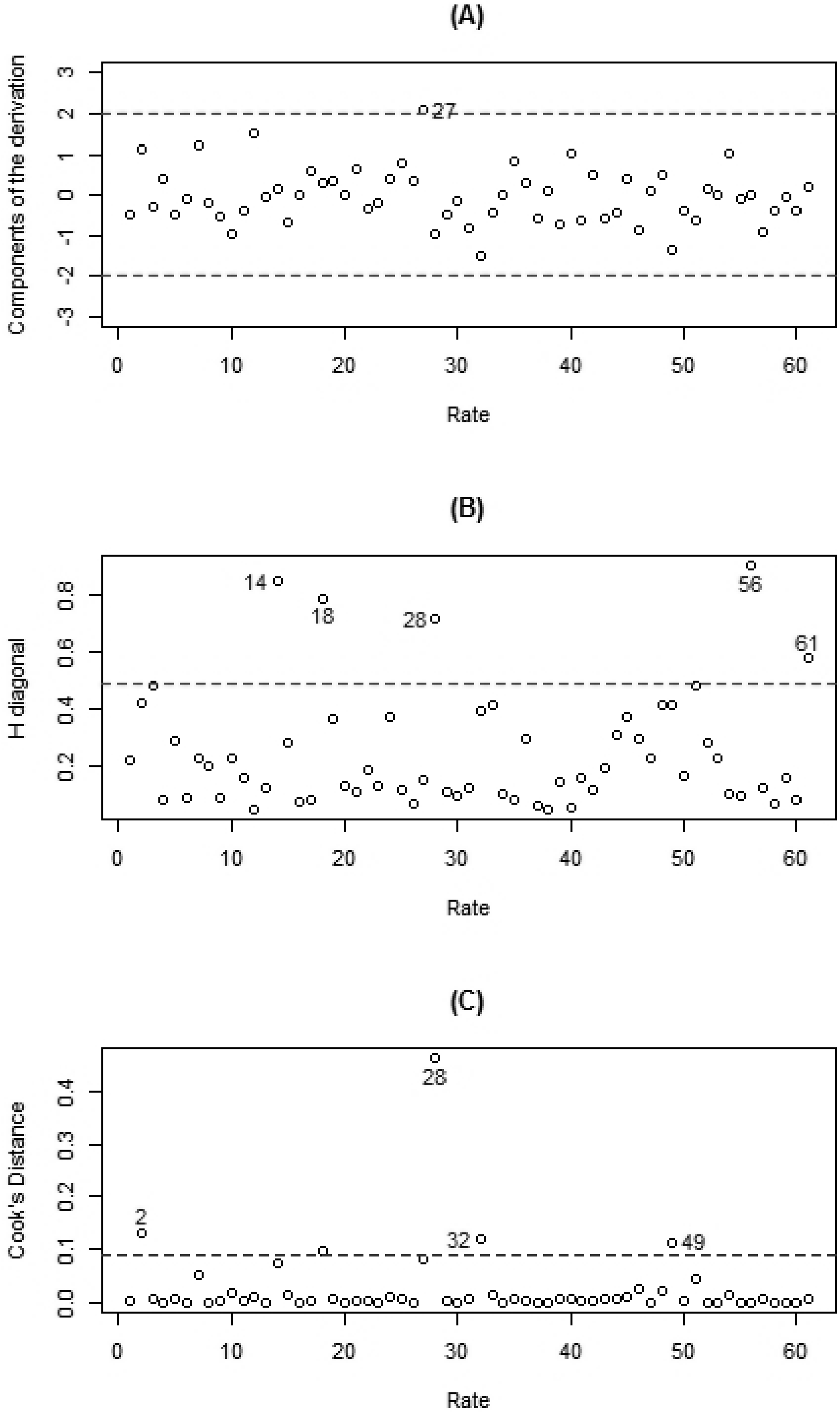

Figure 2 - Graphs of diagnostic measures regarding the Negative Binomial Regression model adjusted to the data on the number of cases of LVH in Paraiba. João Pessoa, PB, Brazil, 2018
Source: Authors (2018)

In Figure 1-A, the hypothesis of normality is observed (p-value>0.05). In Figure 1-B the points are randomly arranged around zero, so the values do not present any trend, indicating that the variance function is adequate for the final model. In Figure 1-C, the values are approximately linearly distributed, therefore, the link function is adequate.

Based on Figure 2-A, the residuals are randomly distributed and that observation #27, represented by the municipality of Itaporanga with 12 cases of HVL, was outside the interval (-2,2), thus considered an outlier. In Figure 2-B, it is observed that five leverage points were identified, observations #14, #18, #28, #56, #61, represented by the municipalities of, in the following order: Cabedelo, Conde, Lastro, Sousa and Umbuzeiro, which recorded two, 15, two, 10 and nine cases of LVH, respectively. The municipalities of Alagoa Nova (nine cases), Lastro (two cases), Natuba (one case) and Santana de Mangueira (one case) were identified as influential points by Cook's statistics (Figure 2-C).

DISCUSSION

Evaluating the estimate found for the number of cases of CVL in the adjusted model, an increase of one case of CVL implies an expected increase of 0.1% of cases of HVL in the municipalities. This same behavior was found by other authors[20] who detected a positive trend between CVL and the coefficient of HVL incidence per 100,000 inhabitants in the city of Fortaleza-CE between the years 2006 and 2012, in which, by means of the linear regression model, it was noticed that with an increase of one case of the disease in dogs, there is an increase of 0.2 in the value of the incidence in humans in the capital of Ceará.

According to scholars[21], with the increase in population, areas are deforested and the availability of food sources for vectors is reduced, making dogs and humans the most accessible sources. Moreover, CVL precedes and is one of the main risk factors for the occurrence of the disease in humans[6,21-23]. According to the study[23] conducted in five cities of Paraíba (João Pessoa, Campina Grande, Patos, Sousa and Cajazeiras), street dogs are four times more likely to develop CVL than domestic animals. Thus, it is necessary to intensify the monitoring of possible hosts.

In the present study, the estimate found for the number of inhabitants assumed that an increase of 1,000 inhabitants in the municipalities studied could generate a 1% increase in cases of HVL. Another study[24] assumes that large urban centers, where there is a larger number of inhabitants, have a better quality of notification of cases of kala azar, while in smaller and more distant municipalities, the chances of underreporting are greater.

Through the model, it was also observed that a 0.1 increase in the MHDI will lead to an increase of about 2.6 times in the number of LVH cases in the municipality. This means that, on the MHDI measurement scale (between zero and one), the value 25.69 becomes 2.569, thus justifying the interpretation of the number of LVH cases. It is believed that this is because one of the dimensions of MHDI is education[16] and municipalities with better development indices have better educational conditions, so the population has more access to information. Thus, health education is considered one of the essential tools for health promotion since it allows the population to be trained on the importance of disease prevention[25].

VL presented an expansion in almost the entire Brazilian territory, gaining prominence in those municipalities with increasing urbanization and high poverty rates[21]. This statement confirms what was verified in the present study, because according to the model presented, the 1% increase in the Percentage of the Poor results in a 5% increase in the chances of cases of the disease.

Another important factor is per capita income, since according to the estimate found in the present model, an increase of one real in the per capita income of the municipality generates an expected 1% reduction in HVL cases. Thus, it is possible to state that Paraiba municipalities that present a low economic development possibly have a higher number of VL cases. This result corroborates the study[26] conducted in the state of Minas Gerais between 2002 and 2013, which states that the persistence of VL in the northern mesoregions of the state is attributed to the low socioeconomic level of this region.

In this study, the estimate found for the number of years of schooling assumed that an increase of one year in this value increases by 85% the chances of occurring cases of HVL in the city, so kala-azar is also affecting people with a higher level of education. Despite being pointed out in another study[27] that health problems are related to the low education of the population and, consequently, to the low living conditions.

The estimate found in the present model for the PCDNEFC assumes that by increasing this percentage by 1% - due to the growth in the number of children living in households where none of the residents has completed elementary school, a 10% increase in HVL cases occurs.

Scholars[24,26,28] have pointed out that VL is related to low education. The low education of family members, added to the susceptibilities of children, may be influencing the occurrence of the disease in the municipalities of Paraiba.

When evaluating the estimate found for the Unemployed Rate in the model, it is observed that a 1% increase in the number of unoccupied people increases by 6% the chance of the municipality presenting an increase in HVL cases. And, with respect to the estimate found for the PPDAE, it was shown that the increase of 1% in this percentage can generate a 5% reduction in cases of HVL.

According to a systematic review and meta-analysis study[22], there is a close relationship between VL and poor living conditions and lack of infrastructure services. This relationship may be explained because generally people who have low socioeconomic conditions tend to reside in peripheral areas of the city, where there is a plant density favorable to the presence of vectors and wild reservoirs. In addition, there is a possible lack of responsible practices by owners with domestic animals, putting them at risk of contracting the disease[22].

In agreement with the scholars, there is also an estimate for the proportion of the population in households with garbage collection, showing that an increase of 1% of this percentage can generate a decrease of 4% of HVL, i.e., the higher the percentage of people who have garbage collection in their homes, the lower the chances of contracting kala-azar.

We observed that the municipalities of the RGICG have a 69% greater chance of presenting a higher number of HVL cases than the municipalities of the other regions of the state. It is believed that this occurs because the municipalities of the RGICG have low socio-demographic conditions when compared to municipalities in other regions of Paraiba; for example, about half of the municipalities of the RGICG have a percentage of poor people higher than 38.47%[16], and as seen previously, the cases of VL are expanding in places that have high poverty rates[21].

In statistical modeling, the analysis of model fit is important because it allows one to verify whether the assumptions for the model are correct, especially for the random component and the systematic part. It is also noteworthy that it is at this stage that the possible existence of discrepant observations - defined as outliers, with some disproportionate interference in the adjustment results - is verified[13].

This study presented as a limitation the heterogeneous behavior presented by the municipalities with positive cases of VL, making it necessary to exclude some of them for the final model. Furthermore, it is important to note that the associations observed here among aggregates do not necessarily mean that this same association occurs at the individual level.

FINAL CONSIDERATIONS

Given the above, and because these are extraordinarily complex activities that involve three elements - the insect vectors, dogs, and humans - and the interaction among them and with their environment, the VL control/prevention activities should not be limited only to the municipality's health sector, but also to others, such as the social and economic sectors.

This is justified because, as observed in this study, the worse the social and economic conditions of the population of a municipality in Paraiba, the greater the chances of growth in the number of cases of the disease. Thus, it is also necessary to develop social programs to improve the financial and social conditions of the population throughout the state.

It is noteworthy that the present study realized that the Negative Binomial regression model emerges as one of the possible methods of choice for understanding the problem studied, identified among the municipal indicators, such as the number of dogs with VL, the percentage of poor people, the rate of unoccupancy and the MHDI, are important variables that act as risk factors for the growth in the number of cases of HVL in Paraiba. It is relevant to emphasize that the model used serves as a protocol for decision making by managers for municipalities where there are registered cases of HVL.

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Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work - Silva AB, Coêlho HFC, Lima CMBL; Drafting the work or revising it critically for important intellectual content - Silva AB, Freitas FI de S, Mota C de AX, Freire MEM, Coêlho HFC, Lima CMBL; Final approval of the version to be published - Silva AB, Freitas FI de S, Mota C de AX, Freire MEM, Coêlho HFC, Lima CMBL. All authors approved the final version of the text.

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