

Incidence of human visceral leishmaniasis: the importance of municipal socio-economic indicators in the state of Pernambuco, Brazil

Incidência de leishmaniose humana visceral: a importância dos indicadores socioeconômicos municipais no estado de Pernambuco, Brasil

Incidencia de la leishmaniasis visceral humana: la importancia de los indicadores socioeconómicos municipales en el estado de Pernambuco, Brasil

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Abstract

Objective: To analyze the main municipal socioeconomic factors associated with the incidence of HVL in the state of Pernambuco, northeastern Brazil. Methods: It is a analytical cross-sectional study. Data on the incidence of HVL and socioeconomic factors were collected from 954 cases notified by the SINAN (National System of Notifiable Diseases) and SIM (Mortality Information System). The cases considered were reported by municipalities in the state of Pernambuco, Brazil, from 2005 to 2014. Statistical differences were analyzed by

Pearson's correlation test, followed by multiple regression analysis. Significant differences were considered when $p < 0.05$. Results: The FIRJAN Municipal Development Index was the variable that showed the most remarkable statistical robustness and strong negative association with the incidence of HVL. The municipal spending on health and residing in the metropolitan region also influenced its mean incidence rates. Conclusion: The indicators that had an influence on the performance of the incidence of LVH were the FIRJAN Municipal Development Index, health expenditure and residing in the metropolitan region.

Keywords: Visceral leishmaniasis; Epidemiology; Health care outcome assessment.

Resumo

Objetivo: Analisar os principais fatores socioeconômicos municipais associados à incidência de LVH no estado de Pernambuco, nordeste do Brasil. **Métodos:** Trata-se de um estudo transversal analítico. Os dados de incidência de LVH e fatores socioeconômicos foram coletados em 954 casos notificados pelo SINAN (Sistema de Informação de Agravos de Notificação) e SIM (Sistema de Informação sobre Mortalidade). Os casos considerados foram notificados por municípios do estado de Pernambuco, Brasil, no período de 2005 a 2014. As diferenças estatísticas foram analisadas pelo teste de correlação de Pearson, seguido de análise de regressão múltipla. Diferenças significativas foram consideradas quando $p < 0,05$. **Resultados:** O Índice FIRJAN de Desenvolvimento Municipal foi a variável que apresentou maior robustez estatística e forte associação negativa com a incidência de LVH. Os gastos municipais com saúde e residir na região metropolitana também influenciaram suas taxas médias de incidência. **Conclusão:** Os indicadores que apresentaram influência no desempenho da incidência da LVH foram o Índice FIRJAN de Desenvolvimento Municipal, gastos com saúde e residir na região metropolitana.

Palavras-chave: Leishmaniose visceral; Epidemiologia; Avaliação de resultados em cuidados de saúde.

Resumen

Objetivo: Analizar los principales factores socioeconómicos municipales asociados con la incidencia de HVL en el estado de Pernambuco, noreste de Brasil. **Métodos:** Es un estudio analítico transversal. Los datos sobre la incidencia de HVL y factores socioeconómicos se recolectaron de 954 casos notificados por el SINAN (Sistema Nacional de Enfermedades Notificables) y SIM (Sistema de información sobre mortalidad). Los casos considerados fueron reportados por municipios del estado de Pernambuco, Brasil, de 2005 a 2014. Las

diferencias estadísticas se analizaron mediante la prueba de correlación de Pearson, seguida de un análisis de regresión múltiple. Se consideraron diferencias significativas cuando $p < 0,05$. Resultados: El Índice de Desarrollo Municipal FIRJAN fue la variable que mostró mayor robustez estadística y fuerte asociación negativa con la incidencia de HVL. El gasto municipal en salud y residencia en la región metropolitana también influyó en sus tasas medias de incidencia. Conclusión: Los indicadores que influyeron en el desempeño de la incidencia de HVI fueron el Índice de Desarrollo Municipal FIRJAN, gasto en salud y residente en la región metropolitana.

Palabras clave: Leishmaniasis visceral; Epidemiología; Evaluación de resultado en la atención de salud.

1. Introduction

Leishmaniasis is part of the group of neglected infectious diseases; it frequently occurs in poorer countries and affects the most vulnerable populations that face difficulties in accessing health services (OPAS, 2019). This zoonosis is associated with numerous factors, such as malnutrition, poor housing, changes in the immune system, financial resources, and environmental changes (WHO, 2020). Furthermore, they occur mainly in remote rural areas with precarious housing with little or no access to modern health installations (Okwor & Uzonna).

Human Visceral Leishmaniasis (HVL) is also known as kala-azar; it is the most severe form of the disease, with the potential for outbreak and mortality. It can be fatal in more than 95% of cases when left untreated (WHO, 2020). It is a zoonosis caused mostly by the intracellular parasite called *Leishmania infantum* (Dantas-Torres, 2006) e *Leishmania donovani* (Ready, 2014). It is transmitted through the bite of infected female sandflies; the clinical picture is characterized by irregular fevers, weight loss, enlarged spleen and liver, and anemia (WHO, 2020).

Early diagnosis and treatment are essential to minimize the impacts of the disease. However, there is a time gap between symptom onset and the diagnosis of Leishmaniasis. On average, the individual visits seven healthcare services until the diagnosis is confirmed. However, the reference hospitals are primarily responsible for making the diagnosis based on clinical and laboratory criteria (Luz et al., 2019).

According to the World Health Organization (2020), around 50,000 to 90,000 new cases of HVL occur annually worldwide. In 2018, more than 95% of the reported cases came from Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan, and Sudan.

In the Americas region, considering the period from 2001 to 2017, 59,769 new cases were registered. Among these, 96% (57,582) were cases notified by Brazil (OPAS, 2019).

Although Brazil has the Visceral Leishmaniasis Surveillance and Control Program, which has guidelines focused on reducing disease morbidity and lethality, with reservoir and vector control and health education, the disease has expanded in the country (Zuben & Donalísio, 2016). More than 51 thousand HVL cases were reported in Brazil from 2003 to 2018, with an average lethality of 7.2%. It is emphasized that most cases of the disease in the country are concentrated in the northeast region (Albuquerque e Silva et al., 2019).

The epidemiological aspects of Leishmaniasis in northeastern Brazil have changed in recent years. Although the incidence of the disease has decreased in children, there has been an increase in adults (Lima et al., 2018). The high numbers of cases in the Northeast region indicate that studies are still needed to provide results and create guidelines of future intervention strategies developed from the knowledge of factors associated with HVL in priority areas.

In this way, the objectives of the Pan American Health Organization and the World Health Organization, regarding the consolidation of actions to reduce the morbidity and mortality of Visceral Leishmaniasis in the Americas, will be achieved soon (PAHO, 2020). Therefore, this study's objective was to analyze the main socioeconomic factors associated with the incidence of Human Visceral Leishmaniasis in Pernambuco's municipalities in the northeast region of Brazil.

2. Method

An analytical cross-sectional study was conducted in a historical series containing information on HVL from 184 municipalities in the state of Pernambuco, Brazil.

Visceral Leishmaniasis notifications (ICD-10 code: B550) from 2005 to 2014 were included, reported by the SINAN (Notifiable Diseases Information System) and as a primary cause of death reported by the SIM (Mortality Information System) of the National Health System (SUS - Sistema Único de Saúde). The municipality of residence for each case was used as a filter. Duplicate cases were excluded.

The sample consisted of 954 reported cases (924 records at SINAN and 30 records notified by SIM).

First, the data were described on means (\pm Standard Deviation). Subsequently, the incidence of HVL per 100 thousand inhabitants was transformed to a logarithmic scale. The Neperian logarithm was used to reduce the dependent variable's spreading degree and minimize the asymmetry problem generated by the high proportion of zeros in the analysis (Fletcher, MacKenzie & Villouta, 2005).

Through the Pearson Test, we performed the correlation of the average effects of the independent variables on the Neperian logarithm of the incidence of HVL per 100 thousand inhabitants.

Afterward, the significance and magnitude of the impact of each independent variable (estimated by the parameters β_1 , β_2 , β_3 , β_4 , β_5 , and β_6) on the incidence of HVL in the municipalities were verified through Multiple Regression Analysis by Ordinary Least Squares (OLS), according to the equation described in Figure 1.

Figure 1: Equation for estimating data.

$$HVL_{mt} = \alpha + \beta_1 GDPpercapita_{mt} + \beta_2 Expenditure_{mt} + \beta_3 Coverage_{mt} \\ + \beta_4 Pbolsa_{mt} + \beta_5 Ieduc_{mt} + \beta_6 Ihealth_{mt} + e_{mt}$$

Source: Authors.

The explanatory variables were introduced one by one to check the sensitivity of their effects in the inclusion of other determining factors. Besides, all models had time fixed effects: dummy variables representing each year of investigation. Also, the dummy variable Metropolitan Region was included.

The incidence of HVL per 100 thousand inhabitants was the dependent variable; the independent variables were those that refer to the municipality's socioeconomic characteristics (m) in year t , as described in Figure 2.

Figure 2: Study variables.

Variables	Definition
<i>ln HVL_{mt}</i>	The HVL_{mt} is the dependent variable and refers to the Neperian logarithm (ln) of the incidence of HVL per 100 thousand inhabitants of municipality m in the year t ;
<i>GDPpercapita_{mt}</i>	Gross Domestic Product (GDP) per capita (reais) is GDP divided by the number of inhabitants of each municipality;
<i>Expense_{mt}</i>	Health expenditure (reais) is the expenditure on public health actions and services by inhabitants;
<i>Coverage_{mt}</i>	Population coverage estimated by Primary Care teams is the estimated percentage of the population that is covered by Primary Health Care health teams;
<i>Pbolsa_{mt}</i>	Percentage of Bolsa Família coverage is the percentage of low-income families served by the Bolsa Família Program;
<i>Ieduc_{mt}</i>	Firjan Education Index is the annual monitoring of municipal socioeconomic development in education; the result ranges from 0 to 1.
<i>Ihealth_{mt} -</i>	Firjan Health Index is the annual monitoring of municipal socioeconomic development in the health area; the result ranges from 0 to 1.
<i>e_{mt}</i>	Error term.
<i>Metropolitan region</i>	Metropolitan region. The Dummy variable was considered equal to 1 if the municipality is part of the Greater Recife region and 0, otherwise.

m = municipality; t = year (2005 a 2014). Source: Authors.

The validation of the significance of the coefficients obtained from the primary analysis was carried out as described by Angrist & Pischke (2008). We adopted the model with a linear trend (through a variable that, in increasing order from 1 to 10, represents the years studied in this work) followed by a model with a quadratic trend (through the variable constructed in the linear squared analysis). The analyzes were performed using the Stata/SE 13 for Windows program (StataCorp LP, College Station, TX, USA). Significant differences were considered when $p < 0.05$.

The Research Ethics Committee of the Universidade Federal de Pernambuco approved the study, under a certificate n° 50724815.7.0000.5208.

3. Results

Table I presents the descriptive analysis of the average incidence per 100 thousand inhabitants and socioeconomic variables associated with HVL in Pernambuco's state in the initial (2005) and final year (2014) study period.

The average incidence of HVL was 1.78 cases per 100 thousand inhabitants in 2005. After ten years, an average of 3.63 cases per 100 thousand inhabitants was observed. The highest municipal socioeconomic indicators were observed in 2014.

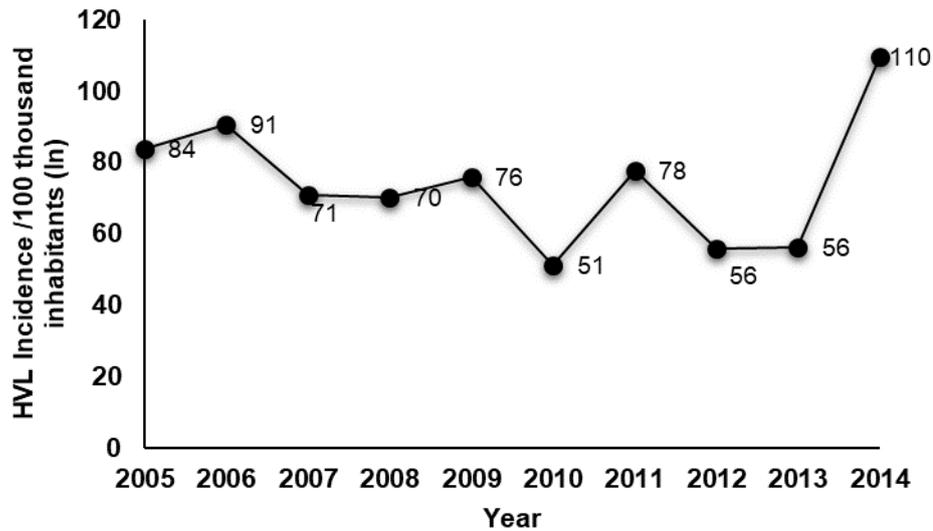
Table 1: Average incidence per 100 thousand inhabitants and socioeconomic factors associated with Human Visceral Leishmaniasis in the state of Pernambuco, in the period 2005 - 2014.

Socio-economic variables	2005	2014
	Average (\pm SD)	Average (\pm SD)
Incidence of HVL (per 100 thousand inhabitants)	1.78 (\pm 4.91)	3.63 (\pm 13.46)
Gross Domestic Product per capita (reais)	3615.96 (\pm 4543.24)	8394.93 (\pm 10851.59)
Health Expenditure (reais)	138.63 (\pm 46.95)	462.68 (\pm 130.09)
Primary Care Coverage (%)	79.86 (\pm 25.61)	92.55 (\pm 26.36)
Beneficiaries with Bolsa Família (%)	10.46 (\pm 3.15)	19.88 (\pm 4.54)
Firjan Education Index	0.57 (\pm 0.07)	0.77 (\pm 0.11)
Firjan Health Index	0.63 (\pm 0.08)	0.88 (\pm 0.11)

The results were expressed as mean \pm standard deviation. Source: Research data.

The temporal evolution of the incidence in Neperian logarithm (ln) of HVL per 100 thousand inhabitants for the state of Pernambuco was described in Figure 3. The lowest incidence of the disease was described in 2010 (ln = 51/100 thousand inhabitants), and, in 2014, there was an express increase in the incidence of HVL in the region (ln = 110/100 thousand inhabitants).

Figure 3: Evolution (in Neperian logarithm) of HVL incidence per 100 thousand inhabitants, in the state of Pernambuco, from 2005 to 2014.



The data were expressed in Neperian logarithm (ln) of the incidence of Human Visceral Leishmaniasis per 100 thousand inhabitants.

Source: Research data

The average incidence of HVL per 100 thousand inhabitants from 2005 to 2014 was correlated with the municipal socioeconomic variables. It was highlighted that the Firjan Health Index and the Primary Care Coverage showed a negative correlation with the HVL incidence index and $p < 0.05$ (Table 2).

Table 2: Correlation between the average incidence of Human Visceral Leishmaniasis and associated socioeconomic variables, in the state of Pernambuco, from 2005 to 2014.

Socioeconomic variables	HVL Incidence
	Correlation coefficient
Gross Domestic Product per capita (R\$)	0.0269
Health Expenditure (R\$)	-0.015
Primary Care Coverage (%)	-0.0642*
Beneficiaries with Bolsa Família (%)	0.01
Firjan Education Index	0.019
Firjan Health Index	-0.0653*

Through Pearson's Correlation Test, we evaluated the results. * Statistical difference ($p < 0.05$).

Source: Research data

In the multiple regression analysis, it was observed that the municipality's Firjan Health Index has a strong negative influence on the number of HVL cases ($p < 0.05$). The

municipality's Health Expenditure variable was also associated with the disease's incidence ($p < 0.05$). GDP *per capita* had a negligible effect on the number of cases of the disease; the other coefficients were not statistically significant ($p > 0.05$) (Table 3).

Table 3: Matrix of the regression analysis for Ordinary Least Squares estimates.

Socioeconomic variables	Incidence of Human Visceral Leishmaniasis (per 100 thousand inhabitants)						
	Models						
	1	2	3	4	5	6	7
Gross Domestic Product per capita (R\$)	0.000*	0.000	0.000	0.000*	0.000*	0.000*	0.000**
Health Expenditure (R\$)		-0.001*	-0.001	-0.001	-0.001*	-0.001*	-0.001*
Primary Care Coverage (%)			-0.002*	-0.003**	-0.003**	-0.002*	-0.001
Beneficiaries with Bolsa Família (%)				0.012	0.013	0.008	-0.004
Firjan Education Index					0.506	0.658	0.419
Firjan Health Index						-0.935**	-0.542*
Metropolitan region							-0.259*
Constant	0.570	0.797	0.940	0.772	0.411	1.154**	1.264**
R-square (R2)	0.013	0.013	0.015	0.018	0.022	0.029	0.048

The results were evaluated by Multiple Regression Analysis. *Statistical difference ($p < 0.05$) and ** $p < 0.01$. One thousand eight hundred forty observations were obtained (184 municipalities in the state of Pernambuco x 10-year period).

Source: research data

Table 4 presents robustness tests to verify the consistency of the association of the analyzed socioeconomic variables. There was a robustness in the significance of the coefficients related to the variables: Firjan Health Index ($p < 0.05$) and Metropolitan Region ($p < 0.001$).

Table 4: Ordinary Least Squares Estimates - Robustness Tests.

Socioeconomic variables	Incidence of Human Visceral Leishmaniasis
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	(per 100 thousand inhabitants)	
	Models	
	Linear Trend	Non-Linear Trend
Gross Domestic Product per capita (R\$)	-0.033	-0.033
Health Expenditure (R\$)	0.018	0.018
Primary Care Coverage (%)	-0.001	-0.001
Beneficiaries with Bolsa Família (%)	-0.006	-0.006
Firjan Education Index	0.264	0.264
Firjan Health Index	-0.604*	-0.604*
Metropolitan region	-0.248**	-0.248**
Trend	0.035*	0.003*
Constant	0.760	0.792
R-square (R2)	0.043	0.041

Through Multiple Regression Analysis, we evaluated the results. * Statistical difference ($p < 0.05$) and ** $p < 0.01$. 1840 observations were obtained (184 municipalities in the state of Pernambuco x 10-year period).

Source: research data

4. Discussion

HVL is a significant public health problem that is difficult to reduce its incidence rates in endemic regions. In the state of Pernambuco, in a 10-year temporal analysis (2005 to 2014), there were variations in the disease incidence rates, with a higher value (3.63 cases per 100 thousand inhabitants) at the end of the studied period.

The incidence verified in 2014 was higher than the national average incidence (1.7 cases per 100 thousand inhabitants) observed from 2003 to 2018. Possibly, the fact that the northeast region, in 2014, had a higher rate of disease incidence in Brazil corroborated the observed fact. Furthermore, this region presented a more significant number of cases of the disease annually, considering the period from 2003 to 2018 (Albuquerque e Silva et al., 2019).

An epidemiology study of HVL analyzed data from 2001 to 2014, it described the northeast Brazil region an incidence rate per 100 thousand inhabitants of 3.9 from 2001 to 2006 and 3.5 from 2007 to 2014. In Brazil's northeast region, the Maranhão State presented the disease's highest incidence in both periods: 2001 to 2006 - 9.7 / 100 thousand inhabitants and 2007 to 2014 - 7.3/100 thousand inhabitants. Meanwhile, Paraíba and Pernambuco's states had the lowest incidence of HVL in the region (Reis et al., 2017).

As of 2004, Visceral Leishmaniasis's surveillance and control were implemented in Brazil to reach all the axes involved in the disease transmission chain: parasite (reservoirs), man (hosts), and vector. In 2011, the rapid human test was made available to all states (Albuquerque e Silva, 2019).

The Sanar Program-Neglected Diseases implemented in Pernambuco state in 2011 has contributed to HVL by making + 4000 tests on dogs and the acquisition of over 2000 collars impregnated with insecticides, besides the decentralization of rapid human tests (Pernambuco, 2020).

The rapid test's greater availability contributed to improving the disease cases detection (WHO, 2020), reflecting on the increased incidence observed in 2014s. The spread of HVL is a multifactorial issue that involves the environmental context, such as deforestation and climate change. It also includes other factors such as immunosuppression, drug resistance, human mobility, and animals. However, low socioeconomic levels stand out as contributing to the spread of the disease (Oryan & Akbari, 2016).

In the state of Pernambuco, the municipal socioeconomic indicators were higher in the year 2014. However, The Pearson test indicated a negative correlation between primary care coverage and the Firjan Health index. The multiple regression analysis showed that the average health level of the municipalities (Firjan Health Index) was the variable that had the most significant association with the incidence of HVL. Even with the Metropolitan Region variable's inclusion in the model, it showed a negative and significant association at the 5% level, revealing its robustness.

Although the percentage of people attended by basic health units was not associated with significant direct effects on the incidence of HVL in the state of Pernambuco, it is highlighted that these services are essential for the population. Advancing coverage of primary health care services contributes to improving the monitoring of chronic diseases, improving diagnosis, and greater access to medicines (Pinto & Giovanella, 2018). Furthermore, the expansion of primary care coverage does not necessarily guarantee efficiency in the service provided. In this sense, the Firjan index of municipal development in health and essential sanitation services is positively associated with efficiency in the services provided by Primary Care in a municipality (Silva et al., 2018). This fact can contribute to more significant detection of new cases of the disease.

Investment in urban infrastructure is also of fundamental contribution to the fight against Visceral Leishmaniasis, given that this disease is found frequently in areas lacking urban infrastructure, with no garbage and sewage collection; except cases of HIV co-infection

that are associated with higher levels of education and evidence of higher socioeconomic status (Lima et al., 2018).

The investment in development improvements in the municipality's health and infrastructure, such as adequate basic sanitation, are essential points for applying resources. Thus, it is possible to promote primary health care services' efficiency and reduce unnecessary public spending (Silva et al., 2018).

In this study, through multiple regression analysis, it was observed that Municipal Health Expenditure was also associated with the incidence of HVL ($p < 0.05$). With the inclusion of the other variables, it can be said that, on average, R \$ 1000 reais more spent on health reduces the incidence by 1%. Meanwhile, GDP per capita had a negligible effect on the incidence of the disease.

However, the amounts spent on health in Pernambuco's state are still below the national and macro-regional average. From 2000 to 2007, there was an average increase of 190.76% in municipal health expenditures, but with reduced per capita values (R \$ 183.79). Furthermore, the values were distributed quite unevenly among the regions, which demonstrates the inequality between the municipalities in distributing public resources for health (Espírito Santo, Fernando & Bezerra, 2012).

In Brazil, Leishmaniasis is among the diseases characterized as a priority health problem, and treatment is offered free of charge by the SUS (Albuquerque e Silva et al., 2019). Even with free treatment access, the costs arising from HVL for patients and their families are elevated (Uranw et al., 2013). These low-income families' costs can contribute to further impoverishment and reinforce the vicious cycle of disease and poverty. For this reason, public investment in treatment and control contributes to alleviating poverty and the impacts of the disease (Alvar, Yactayo & Bern, 2006).

In Brazil, the resources allocated to states and municipalities to promote their services are limited, so it is essential to invest and manage resources in a planned way (Silva et al., 2018). Despite the limitations associated with the use of secondary data and underreporting of cases, it can be inferred that investing in health development in the municipalities of Pernambuco State is a central point to reduce the incidence of HVL in that region. To contribute to the understanding of the factors associated with HVL in this state, future studies that consider individual factors, both biotic and abiotic, are necessary.

5. Conclusion

The mean incidence of HVL in the municipalities of the state of Pernambuco, in a

temporal analysis from 2005 to 2014, presented a negative correlation with the percentage of Primary Care Coverage and the FIRJAN Municipal Development Index. However, in a multifactorial regression analysis, the FIRJAN Municipal Development Index was the variable with the most remarkable statistical robustness, indicating a strong negative association with this disease's incidence.

Strategic investments in health in the municipalities of the state of Pernambuco are indispensable to obtain reductions in the incidence of HVL, mainly those that contribute to an increase in the FIRJAN Municipal Development Index.

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Percentage of contribution of each author in the manuscript

Cicero Emanuel Alves Leite – 55%

Ocilma Barros de Quental – 15%

Patrícia Lopes Olveira – 15%

Ramiro Moreira Tavares – 15%