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Exploratory spatial analysis of HBV cases in Brazil between 2005 and 2017

Análise exploratória espacial de casos de HBV no Brasil entre 2005 e 2017

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ABSTRACT: ***Objective***: To analyze the pattern of spatial distribution of hepatitis B virus (HBV) cases and the mortality attributed to this disease throughout the Brazilian territory, in 2005, 2016 and 2017. ***Methods***: This is an ecological study of spatial analysis, using data from the Information System for Notifiable Diseases and the Brazilian Mortality Information System. HBV detection and mortality rates were analyzed. The spatial analysis from 2005 to 2017 was held through the Global Moran's Index (I) for global data and the Local Indicators of Spatial Association (LISA) for the 5,564 municipalities of the country. ***Results***: The North region stands out with the highest HBV detection and mortality rates in the country. The Global Moran's I showed a spatial correlation of HBV cases in Brazil, and the LISA Map evidenced the presence of hotspots or spatial clusters (high-high type), mainly in the North region and also in some municipalities of Santa Catarina, Paraná, Rio Grande do Sul, Espírito Santo, São Paulo and Rio de Janeiro. ***Conclusion:*** The spatial analysis of the HBV distribution pattern in Brazil shows areas with a large concentration of cases, particularly in the North of the country and in other points distributed throughout the national territory. These data reinforce the urgency of intervention actions related to prevention, diagnosis and treatment of hepatitis B.

Keywords: Hepatitis B. Detection. Spatial analysis. Ecological studies. Epidemiology.

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RESUMO: ***Objetivo:*** Analisar o padrão de distribuição espacial dos casos de hepatite causada pelo vírus B (HBV) e a mortalidade atribuída a esse agravo em todo o território nacional, nos anos de 2005, 2016 e 2017. ***Métodos:*** Trata-se de um estudo ecológico de análise espacial, utilizando dados do Sistema de Informação de Agravos de Notificação e do Sistema Nacional de Mortalidade. Analisaram-se as taxas de detecção e mortalidade de HBV. A análise espacial no período de 2005 a 2017 foi realizada por meio do Índice Global de Moran para os dados globais e dos Indicadores Locais de Associação Espacial (Lisa) para os 5.564 municípios do país. ***Resultados***: A região Norte destaca-se pelas maiores taxas de detecção e mortalidade de HBV do país. O Índice Global de Moran revelou uma correlação espacial dos casos de HBV no Brasil, e o Lisa Map evidenciou a presença de bolsões (tipo *high-high*), principalmente na região Norte e também em alguns municípios de Santa Catarina, Paraná, Rio Grande do Sul, Espírito Santo, São Paulo e Rio de Janeiro. ***Conclusão:*** A análise espacial do padrão de distribuição do HBV no Brasil revela áreas com grande concentração de casos, particularmente no Norte do país e em outros pontos distribuídos pelo território nacional. Esses dados reforçam a urgência de ações de intervenção relativas à prevenção, diagnóstico e tratamento da hepatite B.

Palavras-chave: Hepatite B. Detecção. Análise espacial. Estudos ecológicos. Epidemiologia.

INTRODUCTION

Viral hepatitis is a major public health challenge. Data from the World Health Organization (WHO) show that, in 2013, about 1.46 million deaths were attributed to viral hepatitis, surpassing all other infectious diseases in terms of world mortality. In the context of viral hepatitis, hepatitis B and hepatitis C stand out[1]. The WHO estimates that about 257 million people are infected by hepatitis B virus (HBV) globally and that HBV was responsible for approximately 887 thousand deaths in 2015[2].

The areas with the highest prevalence rate of HBV in the world are found in the Western Pacific region and in the African continent, with about 6% prevalence rate. In the Eastern Mediterranean, the prevalence rate is 3.3%; in Southeast Asia, 2%; and in Europe, 1.6%. In the Americas, the estimate is that 0.7% of the population is infected[2], with important local variations. For example, in the Amazon region, the prevalence rate of HBV in 2012 presented values higher than 8%. In the United States of America and in part of South America, the estimate for the prevalence rate of HBsAg (surface antigen of HBV) is less than 2%[3]. According to the Brazilian Ministry of Health, from 1999 to 2017 218,257 confirmed cases of HBV were reported nationwide[4].

The endemicity of HBV infection is represented by the percentage of HBsAg in the population studied, being classified as low (<2%), intermediate-low (2–4.9%), intermediate-high (5–7.9%) or high (>8%)[5,6]. In the past, Brazil was classified by the WHO as a region of moderate endemicity for HBV, and a detailed analysis showed a highly heterogeneous distribution of this infection, whereas the North region stood out with the highest endemicity[3].

A large population-based study conducted in Brazil between 2004 and 2009 observed 0.37% of HBsAg presence in all capitals. On the other hand, the overall prevalence rate result (presence of anti-HBc exposure marker) in the capitals was 7.4% (confidence interval – CI 95%). This result may be higher according to age, being male and having lower socioeconomic status. However, the study included only the capitals, whereas Brazil's inlands historically presents rather heterogeneous rates[7]. The North region has a significant number of cases of hepatitis Delta (hepatitis D), whose association with high HBV rates constitutes an additional complication in terms of public health[4].

Data available up to 1999 classified the Southeast, Northeast and Center-West regions as having low to moderate prevalence rate, with the exceptions of the north of Mato Grosso, Espírito Santo and Western parts of the Paraná and Santa Catarina states[8].

Vaccination is the best way to prevent HBV[9]. The vaccine was incorporated in Brazil gradually, firstly in Western Amazon (1989), and subsequently throughout the Legal Amazon, Santa Catarina, Espírito Santo, Paraná and Distrito Federal (1992) for children under 5 years, having been scaled up to the entire country in 1998[10]. Since then, vaccination has been expanded by age groups and groups of higher exposure, but only in 2016 the vaccine started being offered to the entire population, regardless of age[11]. Still, the adult population has low vaccination coverage[12]. Hepatitis B is a notifiable disease in Brazil since 1998[13], and is currently reported through the Information System for Notifiable Diseases (Sinan), implemented by the Ministry of Health in 1993. The Brazilian Mortality Information System (SIM) was developed and implemented in Brazil by the Ministry of Health in 1975, but has been improved and automated since the end of the 1990s in the Brazilian Unified Health System (SUS) database (DataSUS).

Analyzing the distribution of indicators according to geographic areas is a powerful tool in health research and it can contribute to the understanding of the processes involved in a particular phenomenon to be studied, allowing the analysis of characteristics and differences of each territorial space to go beyond the simple geographic view, encompassing the socially constructed space[13]. Georeferencing is the analysis of spatial distribution, and the use of thematic maps in health constitutes a technique of great importance for analyzing risks to public health, offering wide possibilities to evaluate the health situation in the territory[14,15].

METHODOLOGY

This is an ecological study of spatial analysis that aimed to estimate the detection and mortality rates from hepatitis B in the 27 federative units (FU) of Brazil, comparing the years of 2005 and 2016-2017, besides evaluating the correlation of prevalence rates of the infection by hepatitis B among neighboring municipalities. For such analyses, the reported cases of HBV in Brazil in 2005 and 2017 were considered. For mortality, death cases having HBV as basic cause, according to available data referring to 2005 and 2016, were considered.

Because this is an investigation based on databases and aggregated information, this study needs no submission to research ethics committees[16].

Detection and mortality rates due to hepatitis B were calculated to evaluate a possible tendency of increase or decrease of the rates in the 27 FU during the years surveyed. In this study, a significance level at 95% and 99 permutations were used, meaning that the areas with statistically significant spatial autocorrelation will be those whose p-value is less than or equal to 0.05. In the end, thematic maps were elaborated to better visualize and understand data through the QGIS 2.8.3 software program.

To verify whether the distribution of hepatitis B cases by municipality in 2005 and 2017 occurred randomly in space, or if the occurrence of cases in the municipalities influences the occurrence of cases in neighboring municipalities, the GeoDa software, version 1.4.1, was used. For this spatial analysis, Global Moran's Index (I) and Local Indicators of Spatial Association (LISA) were used to observe the local data of 5,564 municipalities in Brazil.

The Global Moran's I and Lisa indexes performed a spatial autocorrelation that measures the relationship between observations with spatial proximity, considering that spatially close observations have similar values[17]. The global indicators of spatial autocorrelation (Moran's I) provide a single measure for all municipalities, characterizing the entire region of study. For this calculation, a spatial autocorrelation is performed as a covariance, based on the product of the deviations in relation to the mean. This index tests whether the neighboring areas have a greater similarity as to the indicator studied than what is expected at random. The result of I varies from -1 to +1, in which positive values (between 0 and +1) indicate autocorrelation, that is, the object tends to be similar to the values of its neighbors, whereas negative values (between 0 and -1) correspond to an inverse correlation, i.e. the value of the attribute in a region does not depend on the values of this same variable in different areas[16]. According to Druck et al., the global Moran's I represents stands for the autocorrelation considering only the first neighbor[18].

The distribution patterns of the indicators were examined on a smaller scale by Lisa, producing a specific value for each municipality and allowing the visualization of groupings of municipalities with similar values for the selected indicators. High-high correlations show municipalities with high proportions of the indicator, surrounded by other municipalities also with high proportions of the same indicator; low-low correlations indicate municipalities with a low proportion, surrounded by municipalities with a low proportion of the same indicator; high-low correlations denote municipalities with high proportions, surrounded by municipalities with low proportion of this indicator; and low-high correlations describe municipalities with a low proportion, surrounded by municipalities with a high proportion of the same indicator.

Data were presented according to the diagram known as Moran's scatter plot. This diagram is a scatter graph between the standardized values of the attributes (variables) z and the mean of the neighbors (also standardized) wz, which is divided into quadrants. According to Druck et al., these quadrants can be interpreted as: Q1 (values and positive means) and Q2 (values and negative means) indicate areas of positive spatial association, considering that in a region there are similar neighbors, whereas Q3 (positive values, negative means) and Q4 (negative values, positive means) indicate areas of negative spatial association, indicating locations with neighbors of distinct values[18].

In this study, Q1 indicates the presence of municipalities or regions with normalized number of detected HBV cases, with the normalized mean of values of the equally positive neighboring sectors.

RESULTS

HBV detection rates for 2005 and 2017 can be observed in Figure 1 and Table 1. Both years present an increase in detection rates in some FU of the North region, such as Rondônia, where there is an increase of 25.5 to 26.6 cases/100,000 inhabitants; Amazonas, where there is also an increase of 4.5 to 16.6 cases/100,000 inhabitants; Roraima, with an increment of 12.5 to 14.4 cases/100,000 inhabitants; and Acre, with the highest detection rates of this disease in Brazil, presenting 38.7 cases/100,000 inhabitants.

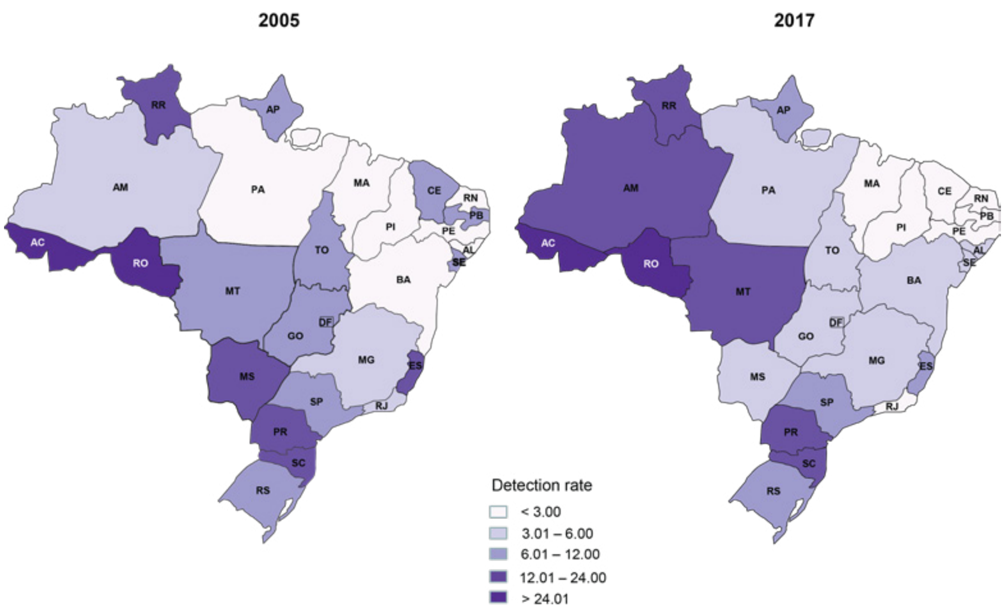

Figure 1. Hepatitis B detection rate per 100,000 inhabitants, according to federated unit per notification year, Brazil, 2005 and 2017.

Source: Information System for Notifiable Diseases (Sinan), 2018.

The South region remains stable, showing a detection rate of 15.5 cases/100,000 inhabitants in 2005 and 14.3/100,000 inhabitants in 2017. In the Central-West region, the Mato Grosso state stands out with an increase of 8.7 to 14.9 cases/100,000 inhabitants.

Table 1. Confirmed and notified cases of hepatitis B[1] according to federated unit and region of residence in 2005 and 2017 and deaths due to hepatitis B[2] as basic cause according to federated unit and region of residence in 2005 and 2016, in Brazil (rates and mortality coefficient per 100,000 inhabitants).

COUNTRY	CASES[1]				DEATHS[2]			
REGION/FU	2005		2017		2005		2016	
	No.	Rate	No.	Rate	No.	Coef.	No.	Coef.
Brazil	12,000	6.5	13,482	6.5	479	0.3	477	0.2
North	1,066	7.3	2,000	11.3	64	0.4	88	0.5
Rondônia	391	25.5	475	26.6	10	0.7	13	0.7
Acre	223	33.3	316	38.7	12	1.8	10	1.2
Amazonas	144	4.5	664	16.6	23	0.7	41	1
Roraima	49	12.5	74	14.4	4	1	4	0.8
Pará	136	2	323	3.9	8	0.1	14	0.2
Amapá	44	7.4	51	6.5	1	0.2	3	0.4
Tocantins	79	6.1	97	6.3	6	0.5	3	0.2
Northeast	1,255	2.5	1,594	2.8	61	0.1	79	0.1
Maranhão	124	2	197	2.8	8	0.1	12	0.2
Piauí	30	1	59	1.8	–	0	6	0.2
Ceará	250	3.1	170	1.9	8	0.1	8	0.1
Rio Grande do Norte	29	1	57	1.6	5	0.2	4	0.1
Paraíba	135	3.8	77	1.9	4	0.1	2	0.1
Pernambuco	238	2.8	192	2	17	0.2	19	0.2
Alagoas	82	2.7	162	4.8	4	0.1	6	0.2
Sergipe	93	4.7	118	5.2	1	0.1	6	0.3
Bahia	274	2	562	3.7	14	0.1	16	0.1
Southeast	4,259	5.4	4,637	5.4	218	0.3	177	0.2
Minas Gerais	615	3.2	823	3.9	49	0.3	37	0.2
Espírito Santo	551	16.2	422	10.6	14	0.4	11	0.3
Rio de Janeiro	504	3.3	473	2.8	33	0.2	31	0.2
São Paulo	2,589	6.4	2,919	6.5	122	0.3	98	0.2
South	4,101	15.2	4,196	14.3	98	0.4	93	0.3
Paraná	1,592	15.5	1,721	15.3	49	0.5	42	0.4
Santa Catarina	1,339	22.8	1,170	16.9	16	0.3	15	0.2
Rio Grande do Sul	1,170	10.8	1,305	11.6	33	0.3	36	0.3
Central-West	1,301	10	1,052	6.7	38	0.3	40	0.3
Mato Grosso do Sul	319	14.1	124	4.6	6	0.3	7	0.3
Mato Grosso	243	8.7	491	14.9	8	0.3	13	0.4
Goiás	583	10.4	368	5.5	18	0.3	14	0.2
Federal District	156	6.7	69	2.3	6	0.3	6	0.2

[1]Confirmed cases were considered those who presented at least one of the following reagent tests: HBsAg, or Anti-HBC IgM, or detectable HBV-DNA; [2]Death from hepatitis B: basic cause B 16.2 (acute hepatitis B without delta agent, with hepatic coma), or B 16.9 (acute hepatitis B without delta agent, without hepatic coma), or B 18.1 (chronic viral hepatitis B without delta agent).

Sources: Information System for Notifiable Diseases (Sinan), 2018[(1)]; Mortality Information System (SIM), 2018[(2)].

[(1)]Population: MS/SE/DataSUS. Available from: www.datasus.saude.gov.br, in the menu "Acesso à Informação > TABNET > Demográficas e Socioeconômicas".

[(2)]Population: MS/SE/DataSUS. Available from: www.datasus.saude.gov.br, in the menu "Acesso à Informação > TABNET > Demográficas e Socioeconômicas".

In the states of the Northeast region, although the rates are the lowest in the country, about 70% of the region showed an increase in the detection rate when comparing 2005 and 2017, with the highest rates found in the states of Alagoas, Sergipe, Bahia and Maranhão.

In the Southeast region, the state of Espírito Santo stands out, which, despite presenting a drop in the number of cases detected – from 16.2, in 2005, to 10.6 cases/100,000 inhabitants in 2017 –, it still presents twice the mean rate of the Southeast, which is 5.4 cases/100,000 inhabitants.

In relation to the mortality data attributed to HBV between 1999 and 2016, 7,828 deaths that had HBV as basic cause were reported in the SIM. Mortality rates had no significant variation when comparing 2005 and 2016 – only 0.1 case/100,000 inhabitants (Figure 2 and Table 1).

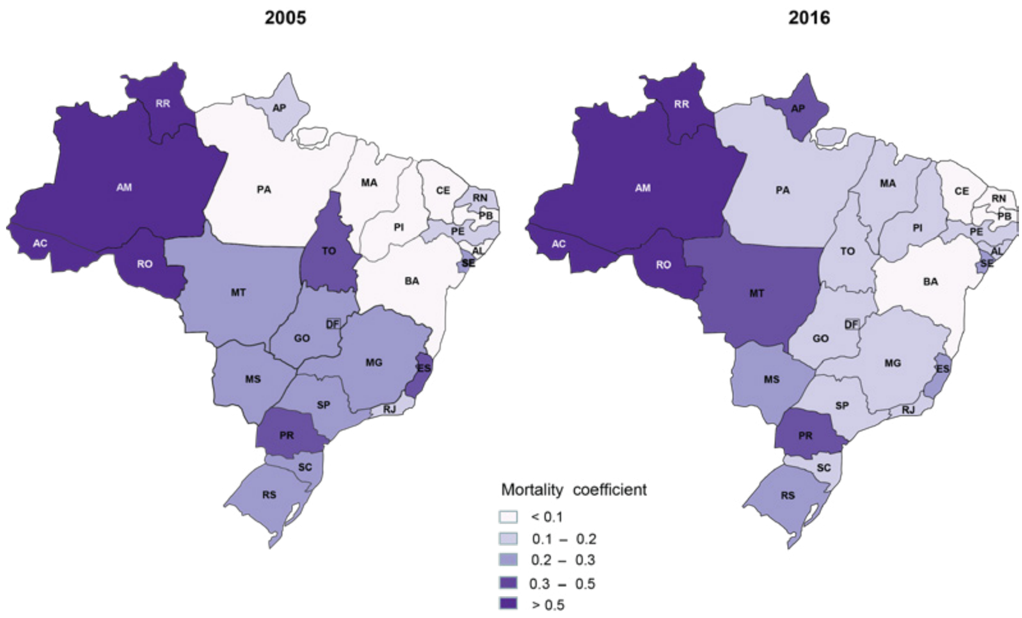

Figure 2. Mortality map for 2005 and 2016 per federated unit, Brazil.
Source: Mortality Information System (SIM), 2018.

The North region has the highest mortality coefficient for hepatitis B, which is 0.5/100,000 inhabitants in 2016, whereas the mean rate of the country was 0.2/100,000 inhabitants in the same year.

Acre, Amazonas, Rondônia and Roraima are the four states with the highest mortality rates in the North and in Brazil, with over 0.5 deaths/100 thousand inhabitants, with emphasis for the states of Roraima and Rondônia, with 0.8 and 0.7 deaths/100,000 inhabitants, respectively.

GLOBAL MORAN'S INDEX (I)

The Global Moran's Index obtained for the period between 2005 and 2017 (I=0.0918973) presented a positive spatial association. In the Moran scatter plot, one can observe a scattering in quadrant Q1, indicating the presence of a positive spatial correlation.

LOCAL INDICATORS OF SPATIAL ASSOCIATION (LISA)

Figure 3 shows the Lisa Cluster Map for the variable referring to HBV cases in the period from 2005 to 2017. The red color represents the high-high quadrant, whose index of HBV cases has the highest rates found in the country. This group, or cluster, has a value higher than the average of its neighboring municipalities (positive deviation). All areas in red indicate the municipalities and adjacent regions that have a strong spatial correlation among themselves, comprising an area of 270 municipalities. We can note that the largest proportion of these municipalities (with strong correlation among themselves) by region is concentrated in the North, reaching 11.1% (50 municipalities); however, small niches or hotspots can be observed in other regions of the country, mainly in the South and Southeast.

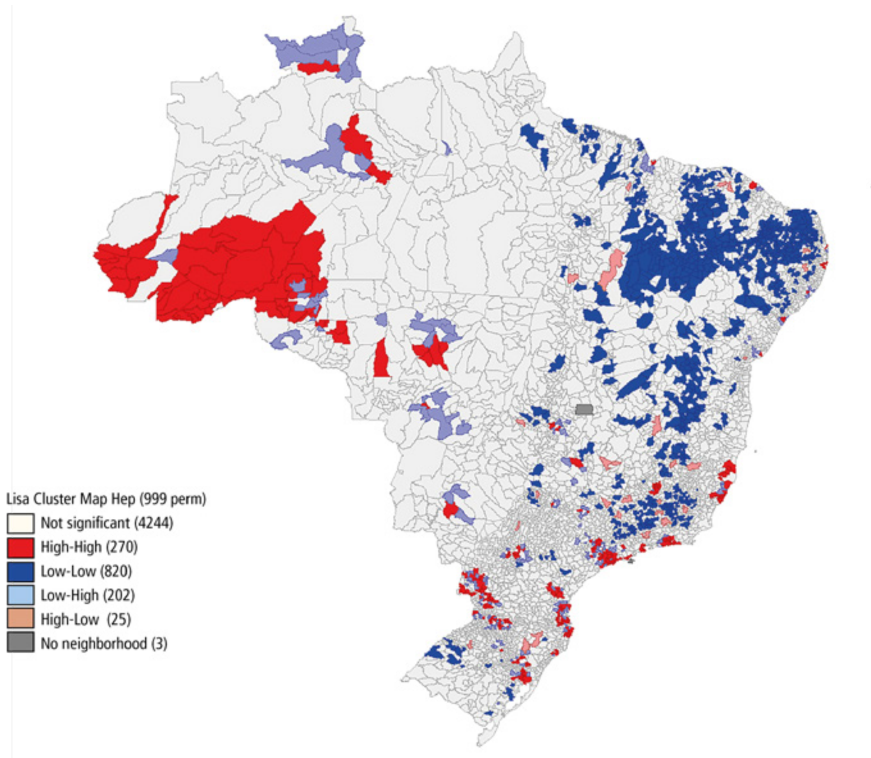

Figure 3. Local Indicators of Spatial Association (Lisa) for hepatitis B.

Source: Information System for Notifiable Diseases (Sinan), 2018.

The color blue (low-low quadrant) stands for the areas that have an attribute and mean of the neighbors below the global mean. These areas are mainly located in the Northeast – reaching 32.8% (588) of its municipalities – and in sparse points (less concentrated) in all regions. All areas add up to 820 municipalities (Figure 3).

Low-high and high-low quadrants are those representing the municipalities with high HBV density and the mean of neighboring municipalities with opposite behavior, i.e.: the low-high quadrant shows the municipalities with HBV index below the mean and whose neighbors have a mean above the global mean (total of 202 municipalities); whereas the high-low quadrant consists of areas with HBV index above the mean and whose neighbors have a mean below the global mean. We observe that few municipalities belong to this high-low quadrant – only 25 municipalities, distributed similarly in all regions (Figure 3).

All municipalities in the 4 areas (high-high, low-low, low-high and high-low) included in the Lisa Cluster Map showed significant values, with p-value<0.05, whereas 4,244 municipalities presented results without significance.

DISCUSSION

Data from our study confirm the North region as the one with the highest detection and mortality rates from HBV in Brazil, and also suggest an increase in detection rates in some federated units of this region, particularly in the states of Acre, Amazonas, Rondônia and Roraima. This finding corroborates other studies that identified a high number of cases and mortality due to HBV in the North region[17-19]. Still in relation to HBV detection rates in our country, the global spatial correlation of this infection was clearly demonstrated through the analysis of the Global Moran's Index, which presented a positive spatial association. In Lisa analyses, hotspots were also evident, especially in the North region (high-high), but also in the states of Santa Catarina, Paraná, Rio Grande do Sul, Espírito Santo, São Paulo and Rio de Janeiro, and in some municipalities of the Northeast region. The presence of the hotspots identified in our study corroborates the hypothesis of higher prevalence of this infection and its circulation in these regions. Regions of high endemicity for HBV in our country, particularly in the North region, have already been identified by different authors[20-23]. Similarly, the description of other regions of high endemicity, as specific regions of the states of the South and Southeast, also appears in several studies[17-19].

Regarding mortality rates, the analyzed data showed no significant changes when comparing the years of 2005 and 2016, despite the increase in the number of cases detected in the same period, as previously described. This finding could somehow reflect that the detection rates of HBV infection in fact remained similar over the years analyzed, indicating an increase in the number of cases reported in the Sinan, and not a real increment in the number of cases in these regions. Another possibility would be an increase in mortality rates associated with this disease to be observed in a near future, since hepatitis B is a chronic infection whose complications occur after a long time of evolution[9,19,20]. Therefore, further studies will need to observe the behavior of these indicators over time, in order to better analyze this situation.

Diverse and specific cultural or socioeconomic characteristics of different regions and population groups are probably involved in the genesis of these differences observed throughout Brazil. For example, the Amazon region is characterized by the presence of indigenous and riverside populations that face greater difficulty to access vaccination and treatment, representing population groups that are more vulnerable to this infection[24]. In the South and Southeast, migratory flows from endemic regions to HBV, which took place at the end of the 20th century, are possibly associated with higher rates of detection of this disease in these regions still in nowadays[8,18,25.] On the other hand, in urban areas with higher population concentration, we can assume that the sexual transmission of this infection is responsible for a significant number of cases, particularly among men who have sex with men and people living with the human immunodeficiency virus (HIV)[26.]

However, we must emphasize some limitations of this study. Firstly, our investigation used secondary data obtained from Sinan and SIM. Studies using secondary data are subject to underreporting and/or duplicity of records, which could interfere with the evaluation of real rates of disease detection. Moreover, as long as aggregated data are used, the identification of more vulnerable population groups may be compromised, making it difficult to analyze some important epidemiological characteristics for the real understanding of the dynamics of these infections in the different populations[19,27].

Secondly, the mortality rate in our study was calculated using hepatitis B as the basic death cause, based on SIM data referring to 2005 and 2016. The use of the HBV diagnosis as a basic death cause could lead to an underestimation of the actual mortality rate attributed to HBV, because most death causes associated with this infection occur as a consequence of its complications, such as hepatic cirrhosis and hepatocellular carcinoma. Therefore, this type of analysis certainly may have contributed to a decrease in the actual mortality rate attributed to this infection over the period studied[4].

We must also mention that Sinan, source of the number of notified cases, is a system that was created in 1993 and gradually implanted in the different regions of the country. It is plausible to assume that, in some states, the differences observed in our study, regarding detection rates in the observed period, actually reflect the quality of the surveillance system in the different localities analyzed, and not the actual number of notified cases. In addition, the expansion of rapid HBV test distribution starting from 2011 by the Ministry of Health[11] and the improvement of care to patients diagnosed throughout the national territory may somehow have contributed to the increase in the number of reported cases[4].

Despite the limitations presented, the study's data and the use of exploratory spatial analysis may help to understand the global and local distribution of HBV infection, providing evidence on the distribution pattern of this aggravation in a national scope and identification of regions with higher endemicity and focus with high presence of this infection.

CONCLUSION

Despite the investments in the areas of prevention, diagnosis and treatment of hepatitis B in Brazil, the data from our study confirm that HBV infection still reaches extensive regions of the country, being the North region the one with the highest detection and mortality rates due to HBV. Our data also suggest an increase in the detection rates of this disease in some federated units of this region, particularly in the states of Acre, Amazonas, Rondônia and Roraima. In addition, spatial distribution analysis evidenced hotspots of this infection, mainly in the North region (high-high), but also in parts of the states of Santa Catarina, Paraná, Rio Grande do Sul, Espírito Santo, São Paulo and Rio de Janeiro, and in some municipalities in the Northeast region.

Our data show that, despite the high availability of diagnostic tests and the universal and free-of-charge offer of specific treatment to the entire population, the HBV infection is still an important public health problem throughout the national territory.

Interventions to improve immunization in the regions with higher circulation of HBV are necessary, especially in specific regions of the western Amazon, which has areas of forest, riverside and indigenous populations with largely restricted access due to hours of navigation along large rivers. Differentiated vaccination schemes are needed to improve the coverage of these regions.

It is also essential to intensify information actions for the entire population about the severity of the infection, inform about the need for the complete vaccination scheme and vaccinate all susceptible adults, especially those older than 20, a range in which the vaccination coverage of the entire country is still very below the necessary[12]. It is also essential to scale up new diagnoses and treat all eligible people[11].

Regarding mortality rates attributed to HBV infection, the analyzed data showed no significant changes when comparing the years of 2005 and 2016, despite the increase in the number of cases detected in the same period.

The data observed in this study reinforce the urgent need for intervention actions related to prevention, diagnosis and treatment of hepatitis B in almost the entire national territory.

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