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Mapping of Congenital Zika virus syndrome, low birth weight and prematurity in Brazil: a spatial analysis

Mapeamento da Síndrome Congênita do Zika vírus, Baixo Peso ao Nascer e Prematuridade no Brasil: uma análise espacial

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Abstract

Knowledge and assessment of the consequences, mainly nutritional, that can affect children with Congenital Zika Virus Syndrome (CZS) still need to advance, mainly through spatial approaches that allow analyzing local vulnerabilities to generate better disease control and monitoring. This study aims to analyze the spatial distribution of CZS cases in Brazilian children and its association with low birth weight and prematurity. This is a retrospective ecological study with anonymized secondary data from the national public health event registration system (RESP-Microcephaly). To verify the existence of spatial association, the Local Indicators of Spatial Association (LISA), univariate and bivariate, were calculated. Therefore, we found that CZS is locally associated with low birth weight and prematurity. Of the 1,834 confirmed cases of CZS from 2015 to 2021 in Brazil that were part of the research universe, 31.2% of babies were born with low weight and 14.7% were premature. Furthermore, the results of LISA's bivariate analysis show clusters of municipalities with a high incidence of CZS and a high incidence of low birth weight and prematurity in the Northeast region of the country. Finally, our findings demonstrated that there is a spatial association of CZS in Brazil and between CZS and childhood nutritional risks. Given the spatial analysis carried out, this study can contribute to the detection of vulnerable areas with a high incidence of CZS and thus assist in monitoring and evaluating their impacts.

Keywords:
Zika Virus Infection, Public Health Surveillance, Health Information Systems, Geographic Information Systems, Secondary Data Analysis.

Resumo

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O conhecimento e avaliação das consequências, principalmente nutricionais, que podem acometer crianças com Síndrome Congênita do Zika Vírus (SCZ) ainda precisam avançar, principalmente por meio de abordagens espaciais, que permitam analisar vulnerabilidades locais para gerar melhor controle e monitoramento de doenças. Este estudo tem como objetivo analisar a distribuição espacial dos casos de SCZ em crianças brasileiras e sua associação com baixo peso ao nascer e prematuridade. Trata-se de um estudo ecológico retrospectivo com dados secundários anonimizados do sistema nacional de registro de eventos de saúde pública (RESP-Microcefalia). Para verificar a existência de associação espacial foram calculados os Indicadores Locais de Associação Espacial (LISA), univariados e bivariados. Como resultados, encontramos que a SCZ está localmente associada ao baixo peso ao nascer e à prematuridade. Dos 1.834 casos confirmados de SCZ no período de 2015 a 2021 no Brasil que fizeram parte do universo da pesquisa, 31,2% nasceram com baixo peso e 14,7% foram prematuros. Além disso, os resultados da análise bivariada do LISA mostram aglomerados de municípios com alta incidência de SCZ e alta incidência de baixo peso ao nascer e prematuridade na região Nordeste do país. Em conclusão, nossos achados demonstraram que existe uma associação espacial da SCZ no Brasil e entre a SCZ e os riscos nutricionais infantis. Diante da análise espacial realizada, este estudo pode contribuir para a detecção de áreas vulneráveis, com alta incidência de SCZ, e assim auxiliar no monitoramento e avaliação de seus impactos.

Palavras-chave:
Infecção por Zika vírus, Vigilância em Saúde Pública, Sistemas de Informação em Saúde, Sistemas de Informação Geográfica, Análise de Dados Secundários.

I. INTRODUCTION

The spread of the Zika virus (ZIKV) generates a worrying epidemiological situation, given the association of the infection with childhood complications such as microcephaly, neurological syndromes, and congenital malformations (STEFANIK et al., 2018). In Brazil, between 2015 and 2023, 21,779 suspected cases of Congenital Zika Syndrome (CZS) were reported. CZS is characterized by a set of congenital, structural, and functional disorders with repercussions on growth and development caused by intrauterine exposure to the ZIKV (BRASIL, 2023).

The impact on the fetus can be caused by direct or indirect transmission as a result of maternal infection, leading to Intrauterine Growth Restriction (IUGR) or triggering premature birth. Congenital ZIKV infections can be asymptomatic at birth or have clinical manifestations, whether early or late, with multisystem involvement and impaired Neuropsychomotor Development (NPMD). Some malformations may only become evident years later, compromising cognitive capacity at school age or with other later impairments (CUNHA et al., 2016; DEHLENDORF et al., 2017).

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Low Birth Weight (LBW) determines infant morbidity and mortality. In addition to being associated with cognitive and growth deficits, it leads to an increased risk of Non-communicable Diseases (NCDs) in adulthood (WHO, 2004). It can also be a consequence of prematurity and/or IUGR. These two conditions can occur in isolation or simultaneously, as they can also be due to maternal malnutrition and, therefore, compromise fetal growth and increase the risk of short stature and micronutrient deficiency (TOURINHO; REIS, 2013; WELLS et al., 2020). Thus, birth weight is an indicator that reflects the nutritional conditions of the newborn and the pregnant woman (BRASIL, 2012; ZAGO et al., 2017).

Situations of nutritional deficits promote and aggravate infections, which, in turn, act as a triggering factor for deficiency processes such as malnutrition, creating a cycle with clinical and severe forms capable of producing malformations of the Central Nervous System (CNS), including microcephaly, and become a serious public health problem (CRUZ et al., 2016). In this challenging epidemiological scenario and concomitant with the consequences of nutritional disorders in childhood, it is essential that actions to control new outbreaks and epidemics occur effectively. To overcome this perverse situation that makes up the Brazilian scenario, efficient and urgent measures are necessary.

Knowledge and assessment of the implications, mainly nutritional, that can be caused by arboviruses is an approach that must be adopted to plan, manage, and analyze the health situation for assertive decision-making (PEREIRA; TOMASI, 2016). Therefore, monitoring CZS cases, incorporating spatial statistical models and geoprocessing techniques, constitutes an important tool that allows the direction of health actions to be expressed in more resolute, comprehensive, and, above all, humanized services.

Recognizing the conditions of greater biological and social vulnerability of the population affected by arboviruses, which can be aggravated by infections during pregnancy, such as ZIKV, and that nutritional status has a decisive influence on growth, child development, morbidity risks, and mortality with repercussions for adult life, the present study aims to analyze the spatial distribution of CZS cases in Brazilian children and its association with important indicators of maternal and child health, LBW, and prematurity.

II. Materials and Methods

Design and data source

This is a retrospective ecological study with anonymized secondary data from the national Public Health Event Registry system (RESP-Microcephaly), made periodically available by the Ministry of Health on the DATASUS open data platform and accessible for tabulation at the electronic address:

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https://datasus.saude.gov.br/transferencia-de-arquivos/. Information was extracted from the years 2015 to 2021, between epidemiological weeks 45/2015 and 52/2021 (8/11/2015 to 31/12/2021), the period referring to the beginning of mandatory notification in RESP-Microcephaly until now with availability in the consolidated data system.

This period was characterized by the beginning of the ZIKV epidemic and the declaration of a Public Health Emergency of National Importance (ESPIN), with notification of cases of microcephaly and/or malformations in the CNS, possibly associated with congenital ZIKV infection, characterizing CZS.

Participants and scope

The 1,834 confirmed cases of newborns and children with CZS throughout Brazil reported in RESP – Microcephaly in the period from 2015 to 2021 were included in the study (Table 1). The national scope of the cases reported in RESP - Microcephaly and the relevance of Brazil in the context of CZS stand out, as it represents the country most affected by the microcephaly epidemic, adopting an attitude of vigilance compared to ESPIN. Cases classified as probable, under investigation, inconclusive, or discarded were not included. Incomplete data was also not included.

Table 1 - Characteristics of the studied population

Characteristics	n (%)
Race/skin color declared in the notification	
1 – White	172 (9.38)
2 – Black	86 (4.69)
3 – Yellow	15 (0.82)
4 – Brown	776 (42.31)
5 – Indigenous	5 (0.27)
9 - Ignored	780 (42.53)
Biological sex declared in the notification	
1 – Male	790 (43.07)
2 – Female	950 (51.80)
9 – Ignored	94 (5.13)
Birth weight in grams (g)	
< 2,500g	572 (31.19)
2,500 – 3,999g	963 (52.51)
≥ 4,000g	14 (0.76)
9 – N/A	285 (15.54)

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Types of congenital disorders detected	
1 – Microcephaly only	755 (41.17)
2 – Microcephaly with CNS malformations	493 (26.88)
3 – Microcephaly with other congenital malformations	192 (10.47)
4 – Congenital malformations without microcephaly	53 (2.89)
9 – N/A	341 (18.59)
Classification according to gestational period	
1 – Preterm birth (less than 37 weeks of gestation)	270 (14.72)
2 – Term (gestational age between 37 and 41 weeks and 6 days)	1292 (70.45)
3 – Post-term (gestational age equal to or greater than 42 weeks)	29 (1.58)
9 – N/A	243 (13.25)

Source: The authors, RESP-Microcephaly – Brazil (2015 – 2021). Legend: N/A = missing data or skipped completion.

Variables

The variables investigated were the incidence of CZS in Brazil, as well as the incidence of Low Birth Weight (LBW) and prematurity in this population. The number of confirmed cases of CZS, LBW, and prematurity were used to calculate incidence rates, which were expressed continuously per 1,000 inhabitants at the municipal level.

The LBW classification was defined as less than 2,500g (BRASIL, 2011). Moreover, prematurity was defined as less than 37 completed weeks (less than 259 days) of gestation (BRASIL, 2002).

Spatial analysis

To understand the spatial dynamics of CZS in Brazil, case concentration maps were created for the years studied using geoprocessing techniques. To map the affected areas, it was necessary to use the geographic location of all Brazilian municipalities (IBGE, 2022). The municipality was considered the basic unit, as it is the smallest spatial unit in which spatial data is available in the RESP-Microcephaly system. All municipalities were included in this spatial analysis, regardless of the existence of reported cases. The Geocentric Reference System for the Americas (SIRGAS 2000) was the utilized reference system.

The Scatterplot of Local Indicators of Spatial Association (LISA) was used to compare the value of each municipality with its neighbors, considering them, and to verify spatial dependence. Furthermore, LISA allows for identifying a specific value for each territorial unit, clustered regions, and significant patterns of spatial association in both univariate and bivariate analyses. The concept of Bivariate Local Indicators of Spatial Association (Bivariate LISA) is complex and often misinterpreted. Generally, it is considered the correlation between a variable and the spatial displacement of another variable; however, the bivariate LISA does not take

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into account the inherent correlation between the two variables (ANSELIN, 1995; BANERJEE; SINGH; CHAURASIA, 2020).

While univariate LISA measures calculate the correlation of neighbor values around a specific spatial location, they also determine the extent of spatial grouping present in the data. Bivariate LISA measures calculate the local correlation between a variable and the weighted average of another variable among its neighbors. Therefore, the definition of neighborhood criteria is crucial for an adequate interpretation of the data (ANSELIN, 1995; BANERJEE; SINGH; CHAURASIA, 2020). In this study, two border municipalities were considered neighbors.

Graphically, regions with spatial association are separated into quadrants: high-high, low-low, high-low, and low-high (VISSSOCI et al., 2018; COSTA et al., 2018). Quadrant 1 with high-high values are municipalities with high incidence and also their neighbors; quadrant 2 with low-low are municipalities with low incidence and also their neighbors; the third quadrant, low-high, are municipalities with low incidence, but their neighbors have high incidence; and the last high-low quadrant are municipalities that have high incidence but are surrounded by municipalities with low incidence. These last two quadrants contain the units of analysis that are considered exceptions in their respective regions (VISSOCI et al., 2018; COSTA et al., 2018).

The mapping was carried out in QGIS version 3.28. LISA analysis was performed using GEODA software version 1.14.0. The significance level adopted for spatial association was 5%.

Ethical approval

As it is secondary data in the public domain and anonymized, that is, without personal information that allows the identification of the cases studied and confidentiality is guaranteed, evaluation by the Human Research Ethics Committees is not required, under the Resolution of the National Health Council (CNS) no. 466 of December 12, 2012.

III. RESULTS AND DISCUSSION

From 2015 to 2021, the RESP-Microcephaly system confirmed 1,834 cases of CZS in Brazil. Of the confirmed cases, 572 (31.2%) were born with a low birth weight, and 270 (14.7%) were premature (Table 1).

In the univariate LISA analysis, municipalities with a high incidence of CZS were identified, located in the high-high quadrant, in the North, Northeast, South, and Southeast regions. However, most of the municipalities in the high-high quadrant were concentrated in the Northeast region of Brazil, mainly in the state of

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Pernambuco. This cluster in Pernambuco was also reported in the study by Vissoci et al. (2018), who pointed out that the greatest burden of the Zika virus microcephaly epidemic occurred in the Northeast.

Furthermore, there are insights that the state of Pernambuco is the likely point of introduction and spread of ZIKV in Brazil (COSTA et al., 2020). A published study on income inequality and segregation in Brazilian cities found that nine out of ten cities with the highest income inequality and poverty in Brazil are in the Northeast region (SOUZA FILHO et al., 2022). These and other factors, such as urban infrastructure, access to water, and basic sanitation, directly impact the dispersion capacity of arboviruses and highlight priority areas for government action, as found by Cruz et al. (2020).

However, it is observed that the incidence of CZS is spatially distributed throughout the national territory (Figure 1). This finding corroborates the fact that the vector that transmits ZIKV, the *Aedes aegypti* mosquito, is present in practically all Brazilian municipalities (ZARA et al., 2016).

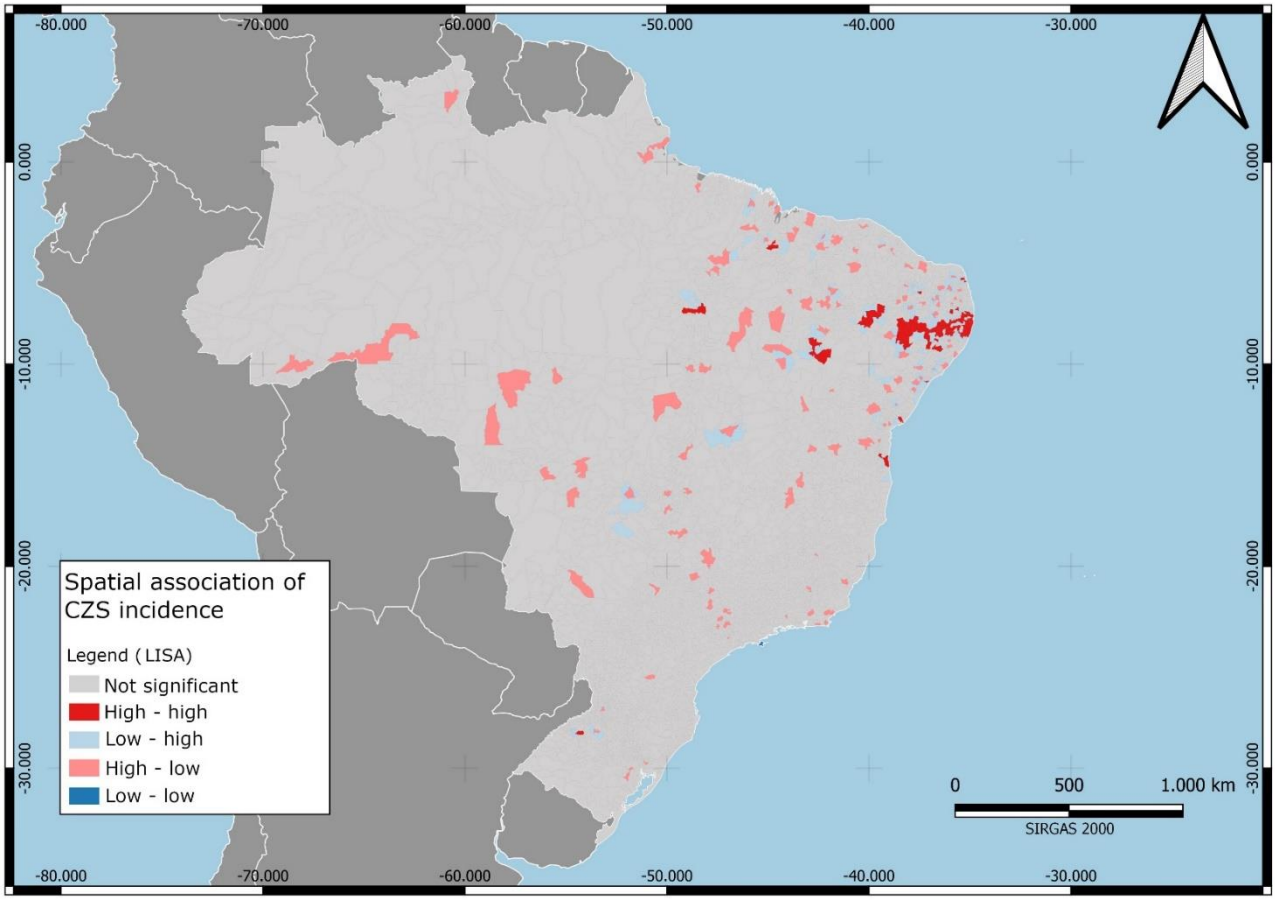

Figure 1 - Spatial association of CZS incidence, univariate LISA. (Source: Prepared by the authors, IBGE (2022) and SIRGAS 2000).

In the bivariate LISA analysis, we focused on evidence of a possible spatial relationship between the pattern of ZIKV dissemination and LBW and prematurity. This analysis classifies the municipality based on its

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neighbors, using continuity (border) as a criterion. In bivariate analyses, we found that low birth weight and prematurity are spatially associated with CZS, highlighting the high incidence of these outcomes in the studied population: 31.2% for low birth weight and 14.7% for premature babies. In the Brazilian population, the incidence of low birth weight was 8.5% in 2017, according to data from the Live Birth Information System (SINASC) (BRASIL, 2019), while prematurity ranged from 10.87% to 9.95% between 2012 and 2019 (MARTINELLI et al., 2021).

These results show clusters of municipalities with a high incidence of CZS and a high incidence of low birth weight in the South, Central-West, Southeast, and Northeast regions. Similar to the incidence of ZIKV in the univariate analysis, municipalities in the high-high quadrant of low birth weight tended to be concentrated in the Northeast.

The spatial distribution patterns of LBW become more diffuse in the low-high (light blue) and high-low (light red) quadrants. These are municipalities with a low incidence of CZS surrounded by areas with a high incidence of low birth weight, while the high-low areas (light red) are the opposite (Figure 2).

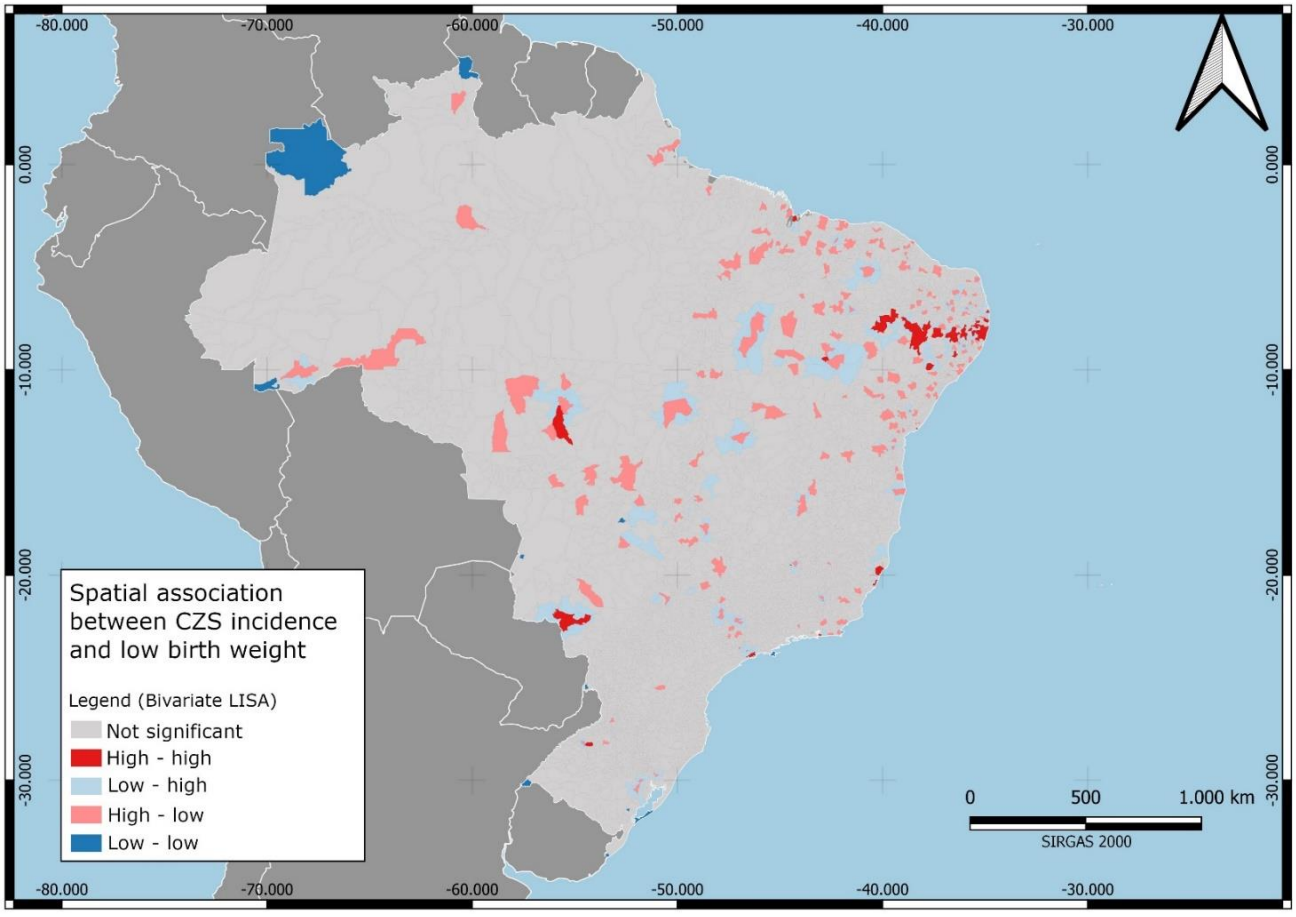

Figure 2 - Spatial association between CZS incidence and low birth weight, bivariate LISA. (Source: Prepared by the authors, IBGE (2022) and SIRGAS 2000).

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In the LISA bivariate analysis of the incidence of CZS spatially associated with prematurity, there are municipalities in the high-high quadrant in the South, Central-West, Southeast, and Northeast regions. Despite this dispersion, high-high clusters are observed mainly in the Northeast region. It is also observed that in the high-low quadrants (light red), municipalities with a high incidence of CZS surrounded by municipalities with a low incidence of premature babies, and the opposite in municipalities in the low-high quadrant (light blue) are dispersed throughout the Brazilian territory (Figure 3). This same spatial distribution pattern was found with LBW.

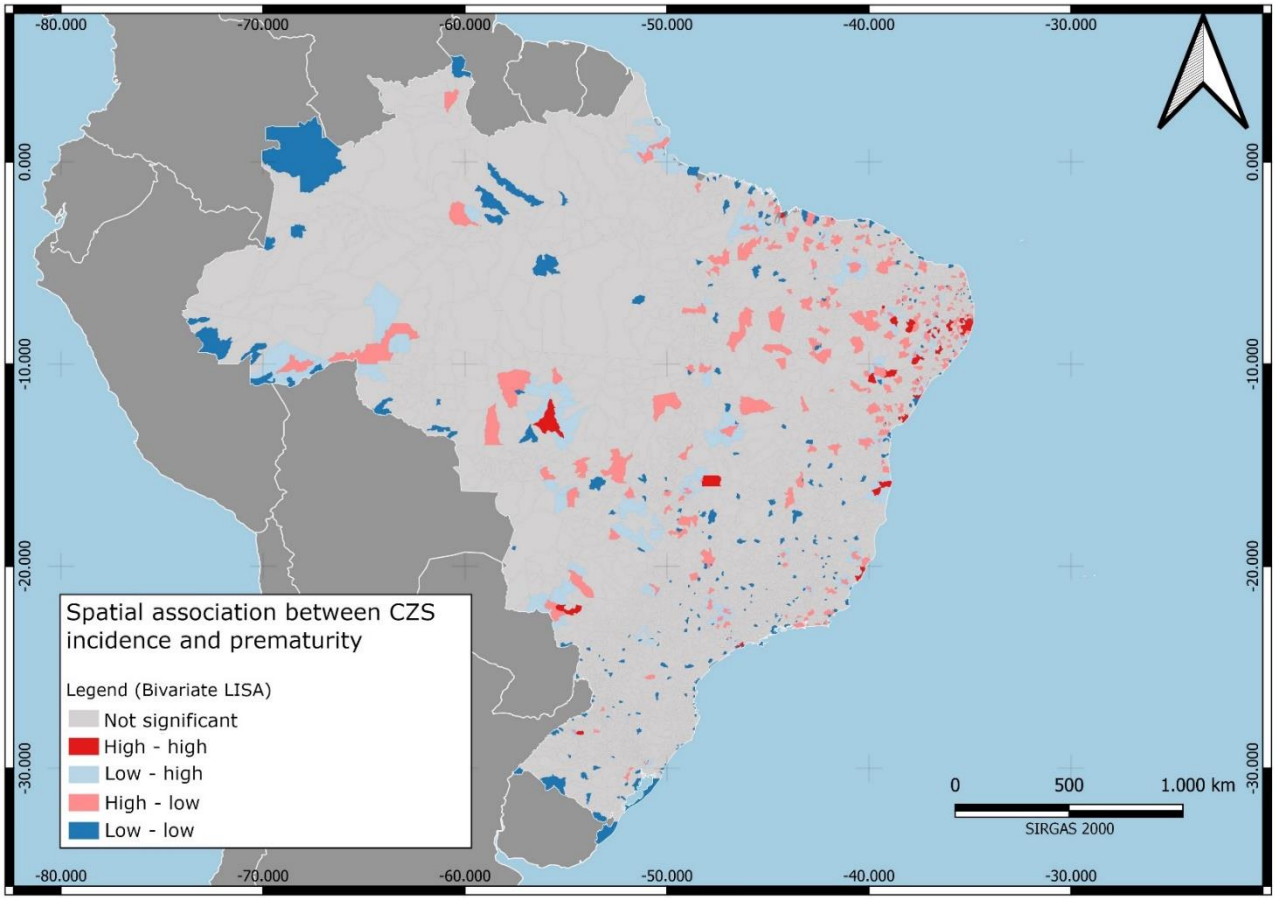

Figure 3 - Spatial association between the incidence of CZS and prematurity, bivariate LISA. (Source: Prepared by the authors, IBGE (2022) and SIRGAS 2000).

The study data reaffirm the high incidence of low birth weight and prematurity in children with CZS, and reinforce the complex public health problem of these outcomes, with greater impact in regions with worse socioeconomic conditions. In the LISA bivariate analysis maps, a dispersed spatial distribution of high-low and low-high classifications is observed. In other words, municipalities such as Porto Velho/RO, Rio Branco/AC,

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Manaus/AM, and Belém/PA have a high incidence of CZS but a low incidence of low birth weight and prematurity (light red), as well as municipalities like a large part from the Metropolitan Region of São Paulo/SP with a low incidence of CZS but a high incidence of low birth weight and prematurity (light blue) (Figure 4). This finding reinforces the relationship between neonatal and child nutritional and health conditions, with social, environmental, and economic issues, which need to be explored territorially since these variables also influence the occurrence of ZIKV and unfavorable outcomes at birth (CARVALHO, 2013; COSTA et al., 2018).

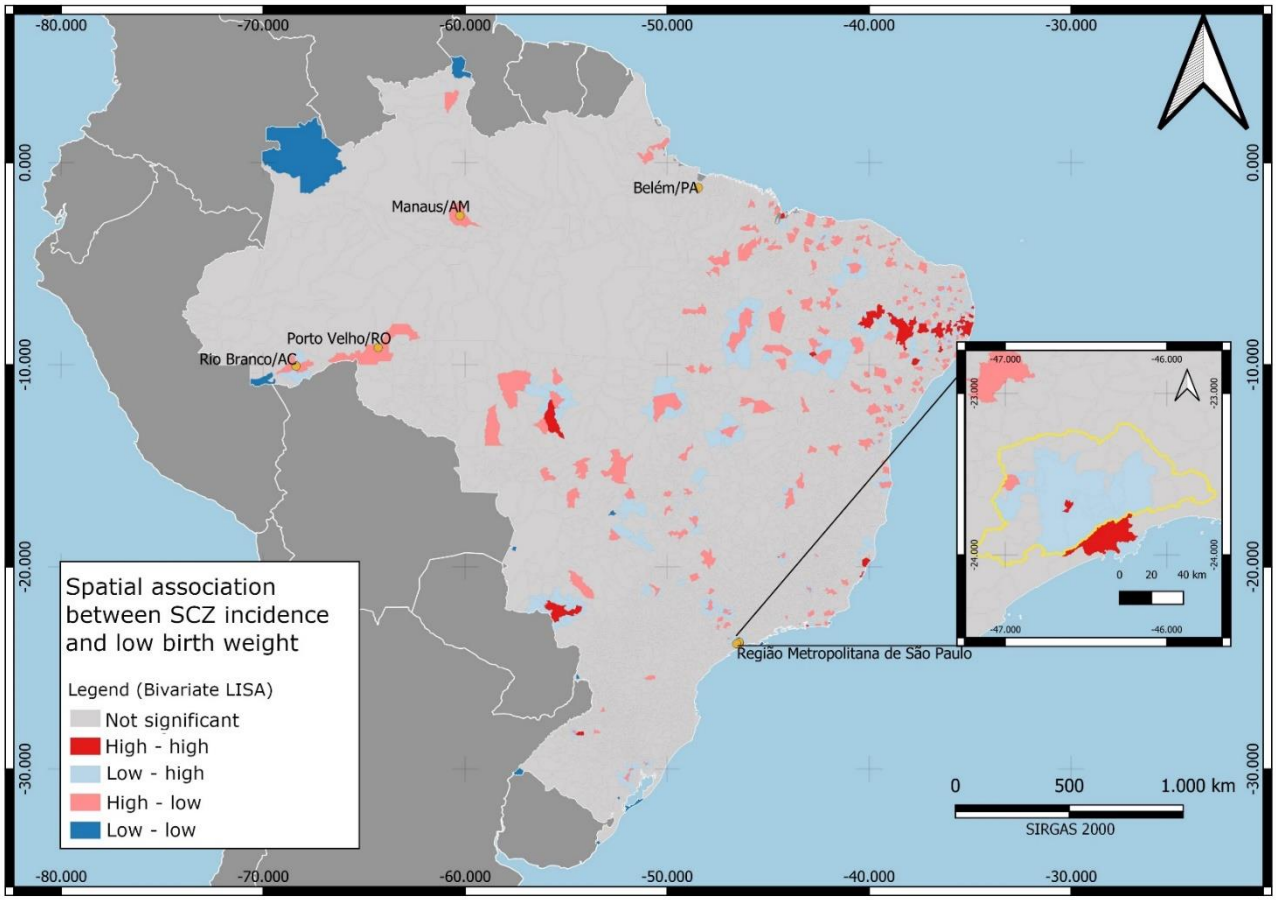

Figure 4 - Spatial association with emphasis on High-Low and Low-High, bivariate LISA. (Source: Prepared by the authors, IBGE (2022) and SIRGAS 2000).

From this perspective, the spread of ZIKV in Brazil raises many concerns: the social and ecological context, with precarious sanitary conditions, favors the proliferation of the transmitting mosquito (SALVI, 2021); the current strategy to combat mosquitoes in most areas has been ineffective; the tropical climate and environmental conditions are favorable to the activity and reproduction of vectors; and crowded cities with an intense flow of travelers make Brazil not only vulnerable to large outbreaks but also a point of dispersion of cases to the rest of the world (VERAS et al., 2016; DONATELI et al., 2019).

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Thus, despite the end of the epidemic and arboviruses having receded from the public debate, ZIKV continues to be a real threat (MOURÃO, 2020) and current with an increase in the notification of cases in Brazil this year and returning to the public debate, establishing itself as well as a constant alert for public health (AVELINO-SILVA; RAMOS, 2017; MOURÃO, 2020).

A limitation of this study was the use of data from only one system, RESP - Microcephaly, as there are limitations in the presence of socioeconomic and demographic variables, in addition to the absence of variables on neonatal health, such as results of neonatal screening exams and nutrition in the first hours of life, whether through breastfeeding, with or without formula supplementation. Another limitation was considering the analysis period in its entirety, disregarding year-to-year variations; thus, it is suggested that future studies evaluate the influence of seasonality. As a strong point, we highlight the use of spatial methods to analyze CZS in the five regions of Brazil and the use of maternal and child health indicators, such as low birth weight and prematurity, aspects little explored in the scientific literature. Therefore, more studies are needed to advance knowledge about the nutritional, growth, and development consequences caused by CZS.

IV. CONCLUSIONS

The present study made it possible to recognize the distribution of CZS throughout the Brazilian territory, with some more striking and more concentrated clusters in the Northeast region of the country, mainly in the state of Pernambuco. Therefore, the detection of vulnerable areas (high-high and high-low) helps in monitoring and evaluating the impacts of the high incidence of CZS in the territory. This mapping is essential given the recent ZIKV epidemic and the possibility of a new global outbreak of the disease. Through this analysis, it is possible to determine patterns regarding the situation of CZS in an area, highlighting spatial disparities that lead to the delimitation of areas at risk for low birth weight and prematurity.

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