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ORIGINAL ARTICLE

Congenital syphilis in the Brazilian Amazon region: temporal and spatial analysis

Sífilis congênita em região da amazônia brasileira: análise temporal e espacial

Bianca Alessandra Gomes do Carmo[1], Deborah Favacho dos Santos[1], Késsia Ailly Santos Hayase[1], Marcus Matheus Quadros Santos[1], Glenda Roberta Oliveira Naiff[1], Eliã Pinheiro Botelho[1]

ABSTRACT

Objective: To analyze the temporal trend and spatial distribution of congenital syphilis in a region of the Brazilian Amazon. **Methodology:** Ecological study conducted with cases of congenital syphilis in children under one year of age in Pará using data from the Information System of Notifiable Diseases and the Live Birth Information System, 2007 to 2017. Moran's spatial autocorrelation analysis and temporal analysis using the joinpoint model were applied. **Results:** The crude and mean incidence rates of congenital syphilis for the study period were 3.8 and 0.345 (x1,000 live births), respectively. The incidence of congenital syphilis showed an increasing trend with an annual percentage change of 12.0% (CI 9.8–14.8; p=0.000). Congenital syphilis presented territorial expansion, with highest rates in the municipalities of northeast, southeast and southwest of Pará. **Conclusion**: Congenital syphilis showed a continuously growing trend in Pará and territorial expansion. The results suggest ineffective prenatal follow-up.

Descriptors: Syphilis, Congenital; Spatial Analysis; Sexually Transmitted Diseases.

RESUMO

Objetivo: Analisar a tendência temporal e distribuição espacial da sífilis congênita em uma região da Amazônia brasileira. **Metodologia:** Estudo ecológico realizado com casos de sífilis congênita em crianças menores de um ano de idade no Pará empregando dados do Sistema de Informação de Agravo de Notificação e do Sistema de Informações sobre Nascidos Vivos, 2007 a 2017. Aplicou-se análise de autocorrelação espacial de Moran e análise temporal pelo método joinpoint. **Resultados:** A taxa de incidência bruta e média de sífilis congênita para o período do estudo foi de 3,8 e 0,345 (x1.000 nascidos vivos), respectivamente. A incidência de sífilis congênita apresentou tendência crescente com variação percentual anual de 12,0% (IC 9,8–14,8; p=0,000). A sífilis congênita apresentou expansão territorial, com as maiores taxas nos municípios do nordeste, sudeste e sudoeste paraense. **Conclusão:** A sífilis congênita apresentou tendência crescente contínua no Pará e expansão territorial. Nossos resultados sugerem ineficácia do acompanhamento de pré-natal.

Descritores: Sífilis Congênita; Análise Espacial; Infecções Sexualmente Transmissíveis; Enfermagem.

[1]Federal University of Pará – Belém (PA), Brazil. E-mails: biancagomesdocarmo@gmail.com, favachodeborah@gmail.com, quadros.santosmm@gmail.com, grnaiff@gmail.com, elipinbt@gmail.com

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INTRODUCTION

Congenital syphilis (CS) is caused by the transmission of the etiological agent of syphilis, *Treponema pallidum*, from mother to child during gestation and can have serious consequences for the fetus, such as malformations, stillbirth, and fetal and neonatal death. Although easy to diagnose and treat, syphilis is considered a global health problem and is estimated to account for more than 300,000 neonatal and fetal deaths worldwide[1,2]. In 2016 alone, 473 cases of CS were reported for every 100 thousand live births around the world[3]. In Latin America, gestational syphilis is estimated to account for 2.6% of all syphilis cases[4].

In 2016, the World Health Organization (WHO) launched a program to eliminate syphilis, implementing rapid diagnostic laboratory tests and adequate treatment for pregnant women, with the goal of reaching 50 cases per 1,000 live births, or less, of CS in 80% of countries by the year 2030. Currently, four countries have already achieved these goals, namely Maldives, Cuba, Malaysia and Armenia[5]. In Brazil, however, 24,666 cases of CS were reported in 2017 alone. Between 2010 and 2017, the incidence rate of CS increased 3.6-fold (2010: 2,4; 2017: 8,6; /1,000 live births)[6].

Temporal trend studies have shown that CS exhibits a growing trend in different regions of Brazil. In the state of Santa Catarina, for example, an exponential increase of 0.9% per year in the incidence of CS was reported from 2007 to 2017, while, in the state of Rio de Janeiro, an increasing annual percentage change of 16% was observed between 2017 and 2016[7,8].

In this scenario, geoprocessing and temporal trend analysis techniques are extremely useful because they allow a better situational diagnosis aimed at developing more effective health strategies to combat CS. Moreover, geoprocessing techniques can identify a geographical space with higher incidences of the disease and the associated territorial factors. Temporal trend analysis allows visualization of how a disease will behave in time based upon the characterization of its trend[9,10].

In the literature review, the authors of this study found four studies on CS in Brazil in which geoprocessing was used[11-14]. These studies were conducted in the states of Rio Grande do Sul and Espírito Santo, in the Paraíba Valley region (SP), and in the city of Caxias (MA).

The analysis carried out in the states of Rio Grande do Sul and Espírito Santo revealed microregions with significant local spatial dependence by the Local Moran's Index. Both studies associated the increase in CS cases with a deficit in the quality of prenatal care[11,12].

In the city of Caxias (MA), point density analysis revealed the predominant occurrence of gestational and congenital syphilis, from 2013 to 2017, in the western and eastern zones, respectively. The highest number of cases were reported in regions with greater social vulnerability and areas without primary health care coverage[13]. In turn, in the Paraíba Valley study, thematic maps of the variables resembled a mosaic, that is, random distribution with a non-significant Global Moran's Index. According to the authors, municipalities with the lowest CS rates had a greater coverage of Family Health Strategy, which guarantees greater access to health services for pregnant women[14].

None of the studies found were conducted using temporal trend analysis and geoprocessing for CS in Pará. In 2017 alone, the state of Pará accounted for 3.2% of total CS cases in Brazil, with an increase of 8.21% in the last 10 years, and the seventh highest infant mortality rate for CS among all the Brazilian federal units[6]. In such a geographically large country with characteristically different regions, geoprocessing techniques are fundamental to achieve the WHO goals for CS.

In view of these facts, this paper aims to analyze the temporal trend and spatial distribution of CS in Pará using geoprocessing and temporal trend analysis techniques. The results of the present study may support the development of health strategies with a more effective and specific focus on the fight against CS in the state.

METHODOLOGY

Study design

This is an ecological study carried out with cases of CS in children under one year of age in the state of Pará and notified to the Information System of Notifiable Diseases ("SINAN"). Pará is located in the northern region of Brazil and it is the second largest state in Brazil, with 1,247,689.52 km^2. The state is divided into 144 municipalities, including the capital city Belém, and the estimated population was 8,513,497 in 2018. Despite its abundant natural resources, Pará has the third lowest HDI among the federal units of Brazil and low territorial coverage of the Family Health Strategy (FHS) (54.5%). In addition, most of the FHSs are located in urban areas and are difficult for the rural population to access due to regional geographical factors and the poverty of its inhabitants[15].

Ethical aspects

This study is part of the macro-project "Diagnóstico Situacional das Infecções Sexualmente Transmissíveis no Contexto Amazônico: Análise Geoespacial, Rastreio e Desenvolvimento de Tecnologias Cuidativas Educacionais" approved by the Research Ethics Committee of the Institute of Health Sciences under CAAE No. 10821819.0.0000.0018.

Study design

The population included in the study consisted of new cases of CS in Pará in children under one year of age and

reported to SINAN between 2007 and 2017. Notifications of children born in Pará whose mothers resided in other states were excluded.

Notified cases of children aged from zero to 364 days were considered cases of CS in children under one year of age. Notifications of children aged 0–6 days were classified as early CS cases and notifications of children aged 7–27 days were classified as late CS cases. Children diagnosed with CS between 28 and 364 days were classified as postnatal CS[16].

As a criterion for diagnosing CS, cases that fell into one or more of the following situations were considered: titrations in ascending nontreponemal tests; reagent nontreponemal tests after six months of age; titration in nontreponemal tests higher than that of the mother[17]. Moreover, stillbirth, or fetal death, in mothers with syphilis were considered cases of CS. A total of 5,949 CS notifications were obtained.

Data collection

All information was collected from April to May 2019. Information regarding CS cases was obtained from SINAN and data on the numbers of live births in Pará were obtained from the Live Birth Information System ("SINASC"). Both systems were accessed through the website of the Department of Informatics of the SUS (Datasus). The data were exported to a Microsoft Office Excel® spreadsheet and double-checked. Inconsistencies and redundancies were corrected.

Variables

The following variables were used: mother's municipality of residence, year of notification, and age group of the child (in days) at the time of CS diagnosis. For the mothers of the notified children, the following variables were used: age group (in years), education, prenatal care, appropriate pharmacological treatment, whether their partner was treated, and the incidence of CS.

The crude annual incidence rate of CS was calculated using the direct method, whereby the number of new cases of CS in children up to 364 days of age was divided by the number of live births of mothers residing in the state of Pará in the same year of the notifications. The results were then standardized by 1,000. To calculate the indicator of the age classification of CS at the time of clinical diagnosis, specific age groups were used as numerator and the number of live births as denominator, multiplied by 1,000.

Data analysis

A descriptive analysis of the data was performed using absolute frequency and relative frequency of the variables obtained for the entire study period.

The Joinpoint® program (version 4.2.02) was used to verify the trend of annual incidence rate of CS, according to the CS classification at the time of clinical diagnosis, and the crude rate (children from 0 to 364 days of age) in the study period according to a previous study[16]. The clinical classifications of CS at the time of diagnosis were considered as dependent variables, while the year of notification was considered as the independent variable. In the trend analyses, annual percentage changes (APC) with 95% confidence intervals (95%CI) were taken as an adjustment to the linear model. The following regression model was used to estimate APC:

$\log(Ry)=b_0+b_1y$, where $\log(Ry)$ is the natural log of the rate in year y;

The APC from year y to year y + 1 = $(R_{y+1}-R_y/R_y) \times 100$

$=\{e^{b0+b1(y+1)}-e^{b0+b1(y)}\} \times 100$

$=(e^{b1}-1) \times 100$

Where:

R = rate

b = regression coefficient - constant

b1 = angular coefficient

e = Napier's constant

y = year

In the spatial analysis, the crude CS incidence rate was considered. These data were grouped into three time periods (2007–2009, 2010–2013, 2014–2017) to reduce annual fluctuations. Then, incidence was calculated for all municipalities, considering the number of live births for 2008 as a population base for the period 2007–2009 and mean live births for the four years of each period for the periods 2010–2013 and 2014–2017.

After calculating municipal incidences, the data were georeferenced and analyzed using ArcGis® Geographic Information System (GIS) software (version 10.6.1). The georeferenced grids in shapefile format (.shp) of municipal boundaries of Pará were obtained from the Brazilian Institute of Geography and Statistics. The maps were created in ArcMap on a scale of 1: 25,000,000, Datum Horizontal SIRGAS-2000, longlat projection system EPSG 4674, in the geographic coordinate system.

The next step was to evaluate whether there was spatial autocorrelation of the incidence of CS among the municipalities of Pará. For this step, Global Moran's univariate analysis was applied in each study period, followed by the statistical method of Local Indicators of Spatial Association (LISA) by Local Moran's. For the construction of the LISA maps, the queen contiguity W matrix was used and neighboring municipalities were considered as those that shared borders and nodes.

Global Moran's index (i) indicates whether or not there is a spatial correlation of the studied variable, but does not indicate the locations of the clusters. Values from –1 to 0 indicate inverse correlation, 0 no correlation, and values from 0 to + 1 direct correlation. Local Moran's method provides

the location of the clusters, with their classifications: high-high, low-low (direct correlation), low-high and high-low (inverse correlation)[18].

In all statistical analyses, those with p values ≤.05 were considered statistically significant.

RESULTS

From 2007 to 2017, 5,949 cases of CS were reported in Pará, with an increase of 110.08% in the incidence throughout the state (2007: 2.48; 2017: 5.22; x1,000 live births). For the entire period, the crude incidence rate of CS was 3.80 and the mean incidence rate was 0.345, both standardized per 1,000 live births. Table 1 describes the epidemiological profile of the mothers of the notified children. As shown in the table, syphilis was prevalent among mixed-race mothers aged 20 to 29 years, with few years of schooling.

Table 1. Epidemiological characterization of mothers of congenital syphilis cases in Pará notified to Information System of Notifiable Diseases, 2007–2017. Pará, Brazil.

Variables	Absolute frequency (n=5,949)	Relative frequency (100%)
Age group (years)		
10–14	86	1.45
15–19	1,498	25.18
20–29	3,041	51.12
30–39	736	12.37
≥40	65	1.09
Unknown	523	8.79
Schooling		
Illiterate	70	1.17
Finished/Did not finish primary school	3,013	50.65
Finished/Did not finish high school	1,138	19.13
Finished/Did not finish university	64	1.08
Unknown	1,664	27.97
Race/color		
White	393	6.61
Black	207	3.48
Yellow/Asian/Oriental	16	0.27
Brown/Mixed-race	4,697	78.95
Indigenous	18	0.30
Unknown	618	10.39

Although most mothers attended prenatal consultations, Table 2 reveals a lower frequency of diagnosed gestational syphilis in the prenatal period when compared to the sum of diagnoses in childbirth/curettage and postpartum periods. Additionally, there was a higher frequency of inadequate treatment of pregnant women for syphilis and non-treatment of their partners.

Graph 1 shows the annual distribution of the crude incidence rate of CS during the study period. This rate reveals only a period of increasing trend with annual percentage change (APC) of 12% (95%CI 9.6–14.6; p=0.000) (Graph 1).

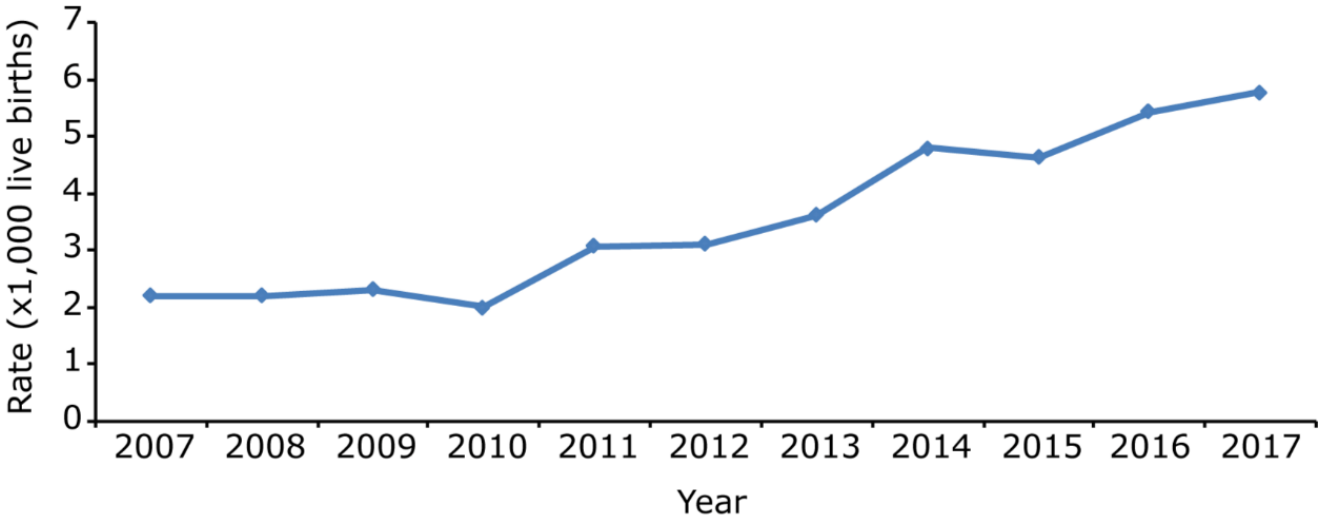
In relation to the age group of the child at the time of diagnosis, early CS predominated (early CS: 5,129 cases, 86.22%; late CS: 149 cases, 2.50%; postnatal CS: 106 cases, 1.78%; unknown: 565 cases, 9.28%). Graph 2 shows the distribution of the incidence rate of CS, according to age classification, in the study period. All classifications revealed a single period of increasing trend, with the highest APC observed for early CS (12.3%; 95%CI 9.8–14.8; p=0.000) (Table 3).

When the incidence rate is spatially analyzed, it can be observed that CS expanded in Pará and the municipalities with the highest incidence are located in the south southwest,

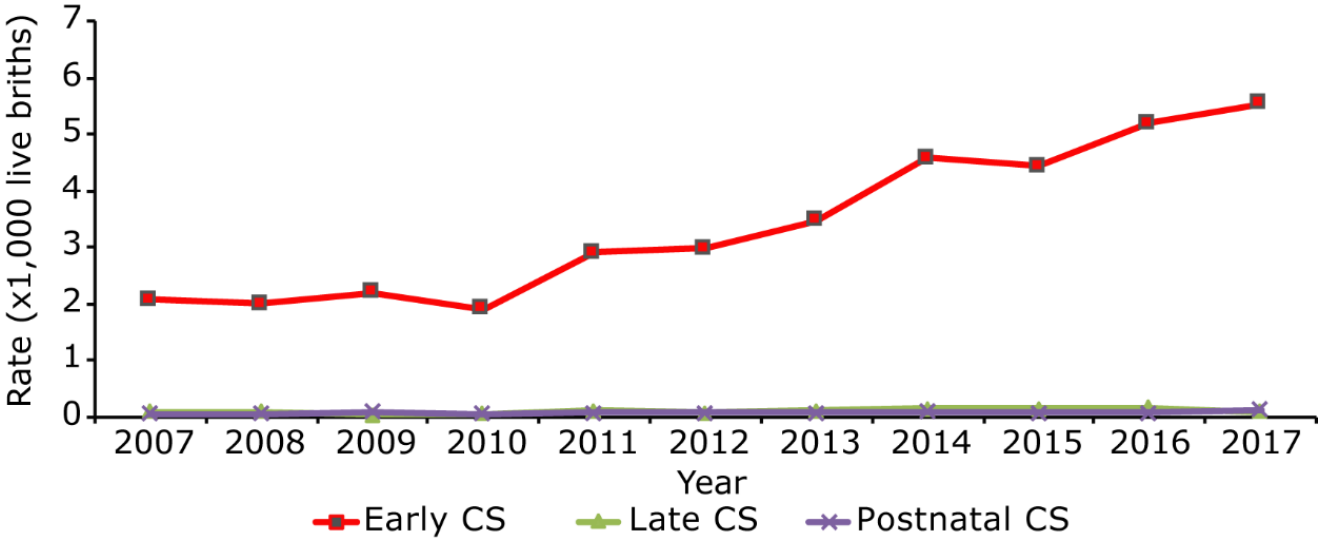
Table 2. Epidemiological characterization regarding prenatal follow-up of mothers diagnosed with syphilis in cases of congenital syphilis notified in Pará, 2007–2017. Pará, Brazil.

Variable	Absolute frequency (n=5,949)	Relative frequency (100%)
Performed prenatal care		
Yes	5,005	84.13
No	802	13.48
Unknown	142	2.39
Diagnostic moment		
Prenatal	2,237	37.60
Childbirth/Curettage	1,706	28.68
Postpartum	1,197	20.12
Unknown	809	13.60
Treatment of mother		
Adequate	495	8.32
Inadequate	3,052	51.30
Not completed	1,467	24.66
Unknown	935	15.72
Treatment of partner		
Completed	1,018	17.11
Not completed	3,450	57.99
Unknown	1,481	24.90

southeast and northeast. Global Moran's analysis indicated a direct and statistically significant spatial autocorrelation in the periods 2010–2013 (I=0.14; p=0.000) and 2014–2017 (I=0.27; p=0.001). The LISA maps revealed a high-high incidence cluster between 2010-2013 formed by municipalities of southwestern Pará (Altamira, Novo Progresso, Jacareacanga, Itaituba, Trairão and Aveiro), while, in 2014–2017, two high-high and low-low incidence clusters were identified. The high-high clusters were composed of municipalities in southeastern Pará (São Geraldo do Araguaia, Marabá, Itupiranga, Nova Ipixuna, Bom Jesus do Tocantins, São João do Araguaia, São Domingos do Araguaia, Eldorado



Graph 1. Annual distribution of the crude incidence rate of congenital syphilis 2007–2017. Pará, Brazil.



CS: congenital syphilis.

Graph 2. Annual distribution of the incidence rate of congenital syphilis, according to clinical classification, 2007–2017. Pará, Brazil.

Table 3. Temporal trend of the incidence of early, late and postnatal congenital syphilis, 2007–2017. Pará, Brazil.

Clinical classification of congenital syphilis	Incidence (/1,000 live births)		APC (%) (95%CI)	p-value
	2007	2017		
Early	2.07	5.5	12.3 (9.8–14.8)	0.000
Late	0.08	0.09	8.5 (1.7–15.8)	0.010
Postnatal	0.05	0.13	6.4 (1.1–12.1)	0.020

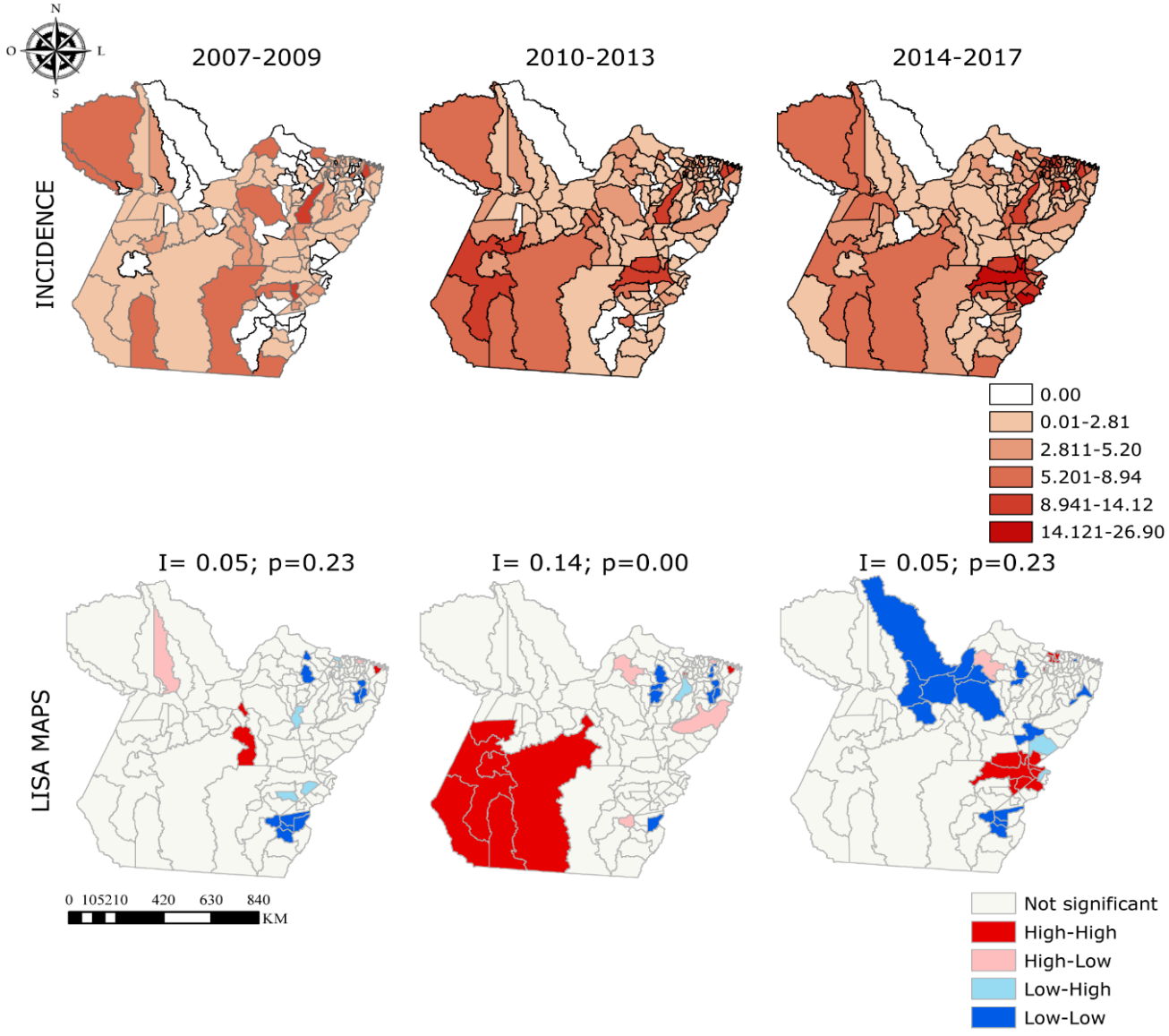
APC: annual percentage changes

do Carajás and Curionópolis) and northeastern Pará (Curuçá, São Caetano De Olivelas, Vigia, Colares, São João da Ponta and Terra Alta). In contrast, the low-low clusters were in the southeast (Rio Maria, Banach, Redenção and Pau D'Arco) and another was formed by municipalities of Marajó with municipalities of Baixo-Amazonas (Marajó: Curupá, Melgaço and Portel; Baixo-Amazonas: Almeirim, Porto de Moz, Prainha and Medicilândia) (Map 1).

DISCUSSION

The results of the temporal analysis of CS in Pará revealed an increasing trend in the study period, with most cases possibly diagnosed as early CS. Although the majority of mothers of notified children under one year of age with CS had follow-up prenatal care, the diagnoses of gestational syphilis were late, the mothers receiving inadequate pharmacological treatment and their partners were not treated. Moreover, although in a lower proportion of diagnosis, the rate of late CS and postnatal CS showed a growth trend during the study period. Spatial analysis revealed an expansion of CS in Pará. From 2010 to 2013, a high-high incidence cluster was observed in the southwest of the state, while between 2014 and 2017, two high-high clusters were identified, one in the southeast and the other in the northeast.

As in Pará, CS has shown a tendency to grow in other Brazilian states, such as Minas Gerais (30.6%) and Sergipe (14.78%)[19,20]. This trend, however, also applies to other countries. In developed countries, CS is already considered a re-emerging disease. In England, 21 cases were reported



LISA: Local Indicators of Spatial Association; I: Global Moran's index.

Map 1. Spatial distribution of the incidence of congenital syphilis and LISA method, 2007–2017. Pará, Brazil.

between 2011 and 2017, and these cases were correlated with mothers who did not undergo prenatal follow-up due to difficulty in accessing health services[21]. In the United States, between 2013 and 2017, there was a 153% increase in cases of CS, which is associated with low testing for syphilis during prenatal care and the lack of knowledge of pregnant women about syphilis and the importance of diagnosis[22].

Other studies suggest that the expansion of CS in Brazil can be explained by the improvement of the notification system and the extended provision of screening tests for syphilis and prenatal coverage[11,23]. A previous study, however, showed that in the region of the Americas and the Mediterranean, most cases of CS came from mothers who had prenatal care, but who were diagnosed at the time of delivery or in the postpartum period[3].

The quality of prenatal care in Brazil presents important regional inequalities and the northern region has the worst evaluation rate of prenatal care, according to a study conducted with secondary data from 2013–2014 throughout Brazil. Among the northern states, Pará had the worst assessment, with low quality of services provided in prenatal care, inadequate infrastructure of the primary care network, inadequate clinical actions and low capacity of management teams to ensure access to the population and quality of care[24]. This fact corroborates the growing trend of CS in Pará, as well as the relationship with most diagnoses of syphilis in pregnant women at the time of delivery or after, inadequate treatment for syphilis, and failure to treat partners.

The spatial analysis showed that the municipalities of Pará with the highest incidence rates of CS were those of the south northeast, southeast and southwest. The southeast and southwest regions are undergoing a process of urbanization due to the vigorous development of their economy based mainly on the extraction of ores, which attracts a large number of immigrants in search of jobs. In contrast, the municipalities that made up the high-high incidence cluster attract large numbers of tourists due to their beaches, carnival and other folk festivals.

The incidence rate of STI is known to be directly related to increase in population and the flow of people in municipalities with low investment in public health policies. In mining regions, STIs are identified as a frequent problem due to factors such as high migration flow, social inequality caused by disorderly growth, low educational level of individuals, consumption of alcoholic beverages, and prostitution[25].

The low-low incidence clusters of CS observed in this study can be interpreted as municipalities with effective public policies aimed at combating CS. However, such results may also be associated with underreporting cases.

The high incidence of CS in Pará is concerning. In 2017 alone, the crude CS rate in the state was 104.4 times above the WHO target (0.05/1,000 live births)[6]. Investments in public policies are needed to eliminate CS in Pará. However, funding from the Brazilian Ministry of Health to the northern region is lower than the national average, which makes it difficult to implement and establish primary care networks in the region. In addition to the low coverage of primary care in Pará, it is mostly concentrated in urban areas. The vast territorial extent of the Legal Amazon and the poverty of the population are factors that prevent its inhabitants from accessing health centers[16].

The limitations of the present study include the use of secondary data and the presentation of results that may not represent the real epidemiological situation of Pará due to the possibility of underreporting. To obtain a better diagnosis of the situation, further studies should focus on municipalities of epidemiological interest, such as those of the high-high incidence groups.

CONCLUSION

Our study showed an increasing trend in the incidence of CS in Pará between 2007 and 2017, suggesting the inefficiency of prenatal follow-up for pregnant women. This hypothesis is corroborated by the growth of CS, high percentage of inadequate treatment of pregnant women, and non-treatment of their partners. Additionally, the growing trend of late CS and postpartum CS reinforces the need to improve the quality of postpartum childcare. The longer the time until CS diagnosis, the greater the chances of sequelae in the child.

Spatial analysis showed the expansion of CS in the state, especially in the municipalities of southwest, southeast and northeast Pará. This fact may be associated with disorderly population growth promoted by the immigration flow of people seeking employment in the municipalities of the southeast-southwest, tourism in the municipalities of the northeast and low coverage of primary care in these municipalities. In order to deal with CS in Pará, it is necessary to have focal public policies that suit the local specificities of each municipality. Our results showed the municipalities with the greatest epidemiological pressures and with interventional needs in terms of the local, state and federal health authorities.

Improvements in the quality of prenatal care are essential to combat CS, as well as strategies that facilitate the adherence of pregnant women to prenatal care. In a state with immense territorial vastness, where its inhabitants have difficulties accessing health services, the expansion of FHS coverage is essential to guarantee inhabitants the universal right to health. Health education should also be provided to pregnant women and their partners on the importance of preventing and adequately treating syphilis, as well as guaranteed access to condoms and screening tests.

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