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Spatial scenery of congenital syphilis in Brazil between 2007 and 2018: an ecological study

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ABSTRACT

Objective To analysis the epidemiological scenery of the congenital syphilis (CS) in Brazil employing spatial analysis techniques.

Design Ecological study.

Settings This study was conducted in Brazil

Sample A total of 151 601 CS cases notified to the Diseases and Notification Information System from 2007 to 2018 from children aged 0–23 months and born from mothers living in Brazil were included in this study.

Primary outcome measures The CS incidence rates were calculated by triad (2007–2010, 2011–2014 and 2015–2018) for all Brazilian municipalities following the Boxcox transformation to remove the discrepant values. The transformed rates were analysed through the spatial autocorrelation of Moran, Kernel density estimative and spatial scan.

Results From 2007 to 2018, the CS incidence rates increased in all Brazilian regions. The CS spread towards the interior of Brazil, and a higher expansion was noticed between 2015 and 2018. The municipalities that were greatly affected by the CS were those having a high migration of people, such as the ones bordering other countries and the touristic cities. Recife, Campo Grande, Rio de Janeiro, Porto Alegre and Manaus were the capitals with the greatest spatial and spatiotemporal risk.

Conclusion This study provides assistance to health authorities to fight CS in Brazil. More investment is necessary in prenatal care quality focusing on pregnant women and their partners to guarantee their full access to preventive resources against sexually transmitted infections.

Strengths and limitations of the study

- ⇒ This is the first study showing the real epidemiological scenery of the congenital syphilis (CS) in all Brazil employing robust spatial analysis techniques.
- ⇒ The global and local Moran analysis were employed to identify the high-pressure epidemiological zones for CS.
- ⇒ The Kernel density estimation analysis was employed to verify the direction of CS expansion in Brazil.
- ⇒ The spatial and spatiotemporal risk areas for CS were identified through the spatial scan analysis.
- ⇒ The study was limited by the CS under-reporting cases due to the use of secondary data, which can imply that the CS incidence rate may be higher than the ones shown.

INTRODUCTION

Congenital syphilis (CS) is a worldwide public health problem and is an important indicator of prenatal care quality, because it occurs from mother-to-child transmission of the *Treponema pallidum* bacterium. CS can cause spontaneous abortion, congenital malformations, stillbirth or perinatal death in approximately 40% of infected children.[1] CS can be prevented via adequate pharmacological treatment of pregnant women, and recently, the expansion of the availability of rapid tests to detect syphilis. However, the prevalence of CS remains high in developing or underdeveloped countries, and it is increasing in developed countries,[2] such as the USA, which experienced a 237.5% increase in the number of new cases between 2010 and 2018 (387 cases in 2010 vs 1306 cases in 2018).[3]

In 2007, the WHO launched the mother-to-child transmission (EMTCT) project to eliminate CS, establishing the implementation of screening and prompt treatment of pregnant women after syphilis diagnosis and maintain control.[4] The main goal is to reduce CS to 50 cases, or less, for every 100 000 inhabitants by 2030. Interestingly, in the western hemisphere, only, Cuba, Anguilla, Antigua and Barbuda, Bermuda, Cayman Islands, Monserrate and Saint Kitts and Nevis have eradicated CS.[5] Brazil, however, is far from reaching CS elimination.

Brazil is a signatory of EMTCT and has implemented its Strategic Action Agenda for CS reduction. These strategic actions strengthen the primary healthcare networks with health promotion, prevention, treatment and surveillance activity based on the health indicators recognised by WHO. Not only has Brazil not eradicated CS, but the control of this disease seems insurmountable. In the last 10 years, the CS incidence rate has increased by 182.76% (2009: 2.1×1000 live births, 2019: 8.2×1000 live births) followed by the increase in the child mortality rate caused by CS, by 208.33% (2009: 2.4 deaths×100 000 live births, 2019: 7.4×100 000 live births).[6] Policies have been implemented to fight CS in Brazil, such as the Stork Network Programme in 2011, the rapid tests for syphilis in prenatal in 2012 and the Strategic Actions Agenda for Syphilis Reduction in Brazil in 2016.[7] In 2019, in all Brazilian states' capitals, the CS detection rate was lower than the detection of syphilis in pregnant women,[6] suggestive of possible effects of the implemented policies. However, although the percentage of syphilis tests among pregnant women in Brazil increased from 2012 to 2018 (2012: 84.3%, 2018: 95.3%), the coverage of six and over prenatal care visits decreased (2012: 89.1%, 2018: 77.8%).[8] In Brazil, the quality of the prenatal and the access to HIV and syphilis tests has been directly associated with the municipalities' human development index (HDI). The high HDI, the high quality of prenatal services and the high access to syphilis tests.[9 10]

In the fight against CS, its epidemiological scenery should first be determined. In this context, spatial analysis techniques are useful tools to visualise the areas with higher epidemiological pressure and associate the studied phenomenon with the sociopolitical and economic factors that contribute to the problem.[11 12] The results generated by the spatial analysis provide information to health authorities to evaluate the already implemented strategies and to possibly implement new ones.

Despite the relevance of the problem, the literature review carried out with the descriptors 'mother-to-child transmission', 'syphilis', 'congenital syphilis' and 'spatial analysis' returned only two studies carried out nationally and both of them in Brazil; one of the studies used only spatial scan analysis,[13] while the other considered Brazilian states as the unit of analysis.[14] Thus, for a deeper understanding of the epidemiological profile of CS in Brazil, the present study employed spatial analysis considering the municipalities as the unit of analysis. Here, we analysed the distribution and spatial autocorrelation of the CS incidence rates, the expansion of CS and the spatial and spatiotemporal risk areas for CS.

METHODS

Settings and design

This ecological study employed data from the Brazilian Notifiable Diseases Information System (DNIS). Brazil is the largest country in the South American continent with a land area of 8 510 345 538 km² and an estimated population of 213 330 250 people living in 26 states, 01 federal district and 5568 municipalities. Brasília is the capital of Brazil. The Brazilian territory is divided into five regions, namely, North or Brazilian Amazon region, Northeast, Midwest, Southeast and South (figure 1). Brazil is ranked 84th in terms of the HDI (0.765) worldwide.[15] The HDI disparity can also be noticed in Brazil, in which the North region notably has the lowest HDI (0.719). The Southeast region has the lowest coverage of the Primary Healthcare network (50.99%), and the North region has the lowest prenatal assistance coverage (55.3%).[16]

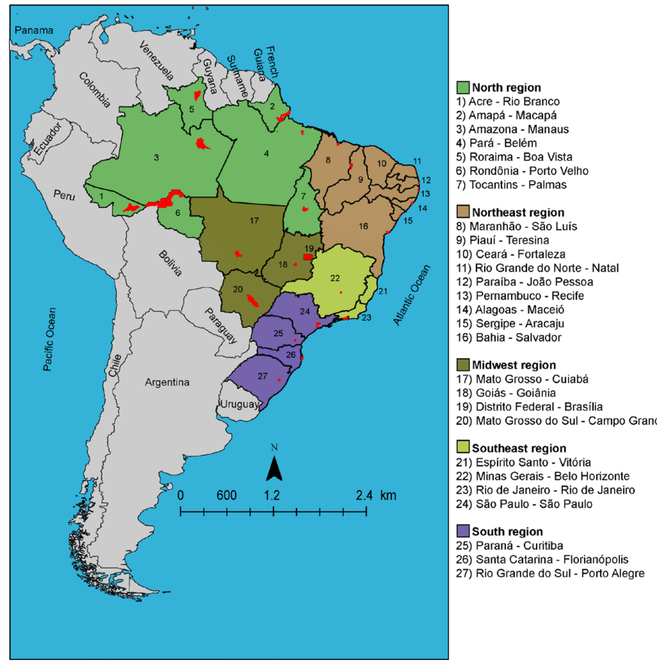

Figure 1 Map of Brazil. The Brazilian Province capitals are in red colours.

Patient and public involvement

No patients involved.

Study population and variables

The study population includes all notifications of CS to the DNIS from 2007 to 2018, in children up to 23 months of age and born from mothers residing in Brazil. The criterion for diagnosing CS include cases that fit into one or more of the following situations in the children: titrations in ascending non-treponemal tests; reactive non-treponemal tests after 6 months of age and titration in non-treponemal tests higher than that in the mother.[6] In addition, the notifications of stillborn CS and stillbirth in mothers diagnosed with syphilis were considered.

The data were collected in May 2021 and all variables were collected in the Departamento de Informática do Sistema Único de Saúde (DATASUS) website (https://datasus.saude.gov.br/). DATASUS is responsible for providing the Brazilian Unified Health System (SUS) with the information and computational systems to help Brazilian health authorities to plan and execute health interventions to improve the health of the population. The following variables were collected: child's age, the mother's residence city, year of notification and annual number of stillbirths. Data were aggregated in terms of municipalities and regions. After collection, data were double-checked in Microsoft Office Excel 365 (Microsoft Corporation, Santa Rosa, CA, USA) and all redundancies were removed. The CS incidence rate was the analysed variable.

To avoid the annual variation, we calculated the CS incidence rates for all municipalities by period (2007–2010, 2011–2014, 2015–2018) considering the mother's residence city. For this calculus, the number of CS reports for each period was divided by the number of stillbirths in the respective period. The result was then multiplied by 1000.

Before applying spatial analysis, we employed the Boxcox transformation in the CS incidence rates to remove discrepant values by using RStudio V.1.4 software (RStudio, Washington, DC, USA).[17] Then, the distribution and the autocorrelation analyses of the incidence rates were done in ArcGIS V.10.1 (ESRI, Redland, California, USA). For spatial autocorrelation analysis, the global Moran index (I) was used, followed by the Local Indicators of Spatial Association (LISA). To calculate I, we used the queen-type W contiguity matrix with 999 permutations, and neighbouring municipalities were considered as those sharing borders and nodes. Only Is with p≤0.05 were considered as having a spatial dependency.

The Global Moran index ranges from −1 to 1. Values greater than zero indicate direct autocorrelation, 0 indicates the inexistence of autocorrelation and values less than 0 indicate indirect autocorrelation. The LISA map points out the locations of spatial clusters, which are classified as high-high or low-low incidence (direct autocorrelation), and low-high or high-low (inverse autocorrelation).

To verify the direction of CS expansion in Brazil, we used the Kernel density method in TerraView V.4.2.2 (INPE, São Paulo, São Paulo, BRAZIL) employing the adaptive bandwidth and quartic Kernel smoothing function. We considered the municipalities as the unit of analysis. This method estimates how a density of a specific event occurring in one area can influence the neighbouring areas. Events occurring close to each other gain greater weight than those occurring at distant spatial points.

To identify the risk areas for CS, we employed spatial and spatiotemporal risk analysis by using SatScan V.9.7 software (Kulldorf, Cambridge, MA, USA) through the discrete Poisson model.[18] The following criteria were considered for the spatial risk analysis: non-overlapping risk areas, maximum risk area equal to 50% of the exposed population and risk area with circular format and 999 replications. We employed the same criteria for the spatiotemporal risk, with the accuracy in years and considering the maximum temporal risk area equal to 50% of the studied period. The areas with relative risks (RR)≥1 and p≤0.05 were considered risk areas for CS.

RESULTS

From 2007 to 2018, 151 601 cases of CS in children aged 0–23 months of age were reported to DNIS. Figure 2 shows the spatial distribution of the Boxcox-transformed CS incidence rates for North (figure 2A–C), Northeast (figure 2D–E), Midwest (figure 2G–I), Southeast (figure 2J–L) and South (figure 2M–O) Brazilian regions. The CS expanded in all regions in the municipalities located on the Atlantic coast, in the interior and those bordering Peru, Bolivia, Suriname and Guyana. In addition, a notable effect of CS was observed in all regions between 2015 and 2018.

Figure 3 shows the LISA maps. In the Northern region (figure 3A–C), the global Moran's I was statistically significant for the second and third periods (2008–2010: I=0.04, p=0.09; 2011–2014: I=0.10, p<0.001; 2015–2018: I=0.06, p=0.03). In the first period, the high–high CS incidence clusters were observed in the municipalities bordering Bolivia and south of Pará. In the second and third periods, the high–high clusters were observed in the south of Pará and central and northern Tocantins' portions online supplemental figure 1A—blue and red boxes).

In the Northeast region (figure 3D, E and F), a significant spatial autocorrelation was observed in all periods (2008–2010: I=0.06, p<0.001; 2011–2014: I=0.05, p<0.001; 2015–2018: I=0.03, p=0.01). High–high CS incidence clusters were observed in municipalities in the Atlantic coast region in the states of Rio Grande do Norte and Ceará in all periods (online supplemental figure 1B–D—blue and red boxes), in the municipalities of the interior of Sergipe and Piauí in the first period (online supplemental figure 1B—green and purple boxes), in Alagoas in the second period (online supplemental figure 1C—green box) and Bahia in the second (online supplemental figure 1C—purple box) and third periods (online supplemental figure 1D—green and purple boxes).

In the Midwest region (figure 3G–I), a significant spatial autocorrelation was observed in all periods (2008–2010: I=0.12, p=0; 2011–2014: I=0.15, p<0.001; 2015–2018: I=0.18, p<0.001), and the groups were concentrated in the municipalities of Mato Grosso do Sul State mainly on the border with Paraguay.

In the Southeast region (figure 3J–L), all periods showed statistically significant spatial autocorrelation (2008–2010: I=0.12, p<0.001; 2011–2014: I=0.11, p<0.001; 2015–2018, I=0.11, p<0.001), and spatial aggregation occurred in the coastal regions of the states of Rio de Janeiro and Espírito Santo (online supplemental figure 1E–G—blue box) in all periods, and São Paulo State in the second and third periods. Additionally, São Paulo presented clusters in municipalities in the interior of the state.

In the South region (figure 3M–O), a significant spatial autocorrelation was observed in all periods (2008–2010: I=0.09, p<0.001; 2011–2014, I=0.08, p<0.001; 2015–2018, I=0.05, p<0.001). High–high incidence clusters were observed in all periods in Rio Grande do Sul State, formed by its capital, Porto Alegre, and neighbouring

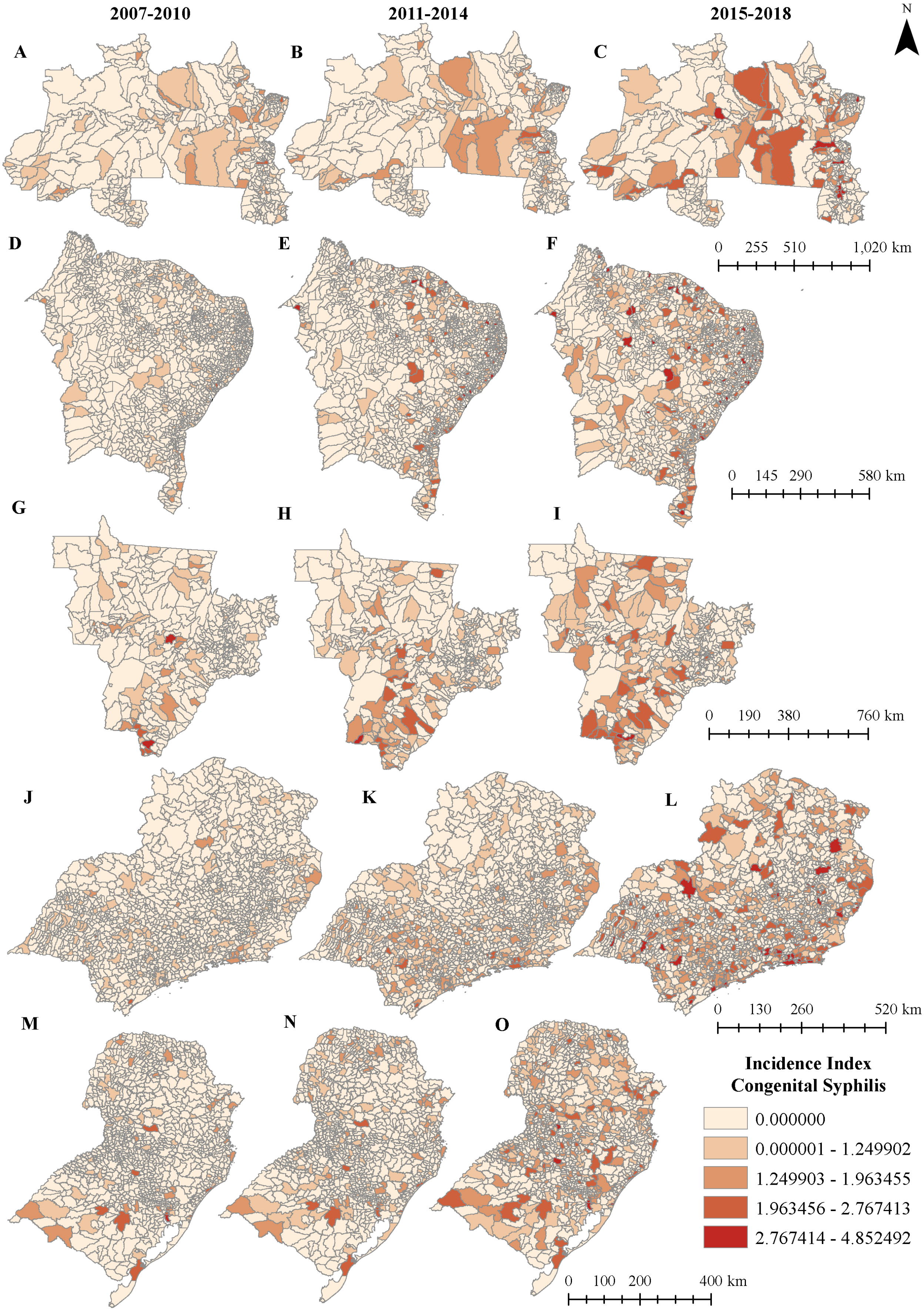

Figure 2 Spatial distribution of the congenital syphilis incidence rates per quadrennium in Brazilian regions: North (figure 1A–C), Northeast (figure 1D–F), Midwest (figure 1G–I), Southeast (figure 1J–L) and South (figure 1M–O).

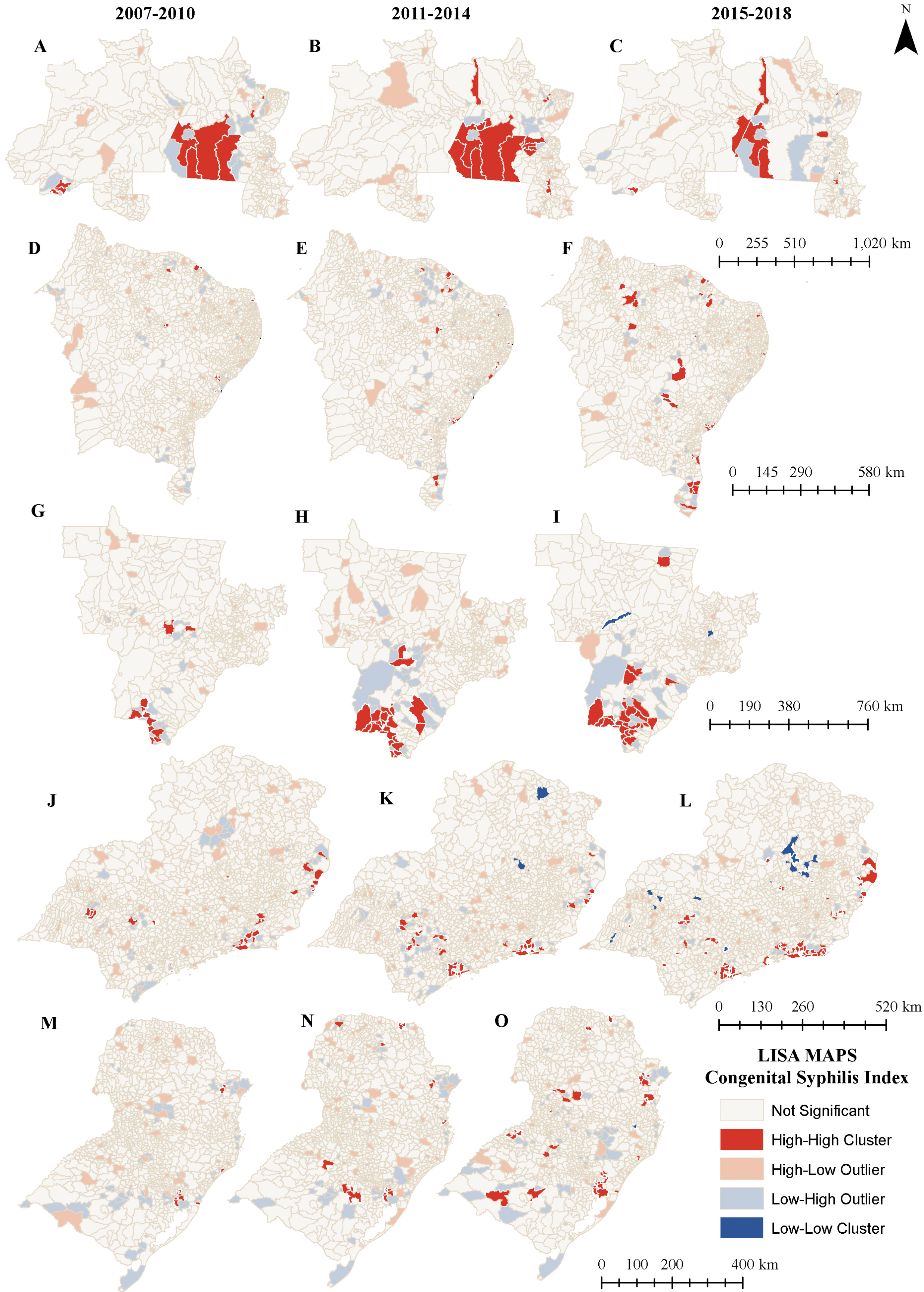

Figure 3 LISA map of the congenital syphilis incidence rates per quadrennium for each Brazilian region: North (figure 2A, B and C), Northeast (figure 2D, E and F), Midwest (figure 2G, H and I), Southeast (figure 2J, K and L) and South (figure 2M, N and O). LISA, Local Indicators of Spatial Association.

municipalities. In the last period, additional clusters were observed in the southwest of Rio Grande do Sul, Paraná and Santa Catarina (online supplemental figure 1H—blue and red boxes).

Figure 4 shows the result of the Kernel density analysis during the study period. In the North region (figure 4A–C), CS expanded in the northern and southeast of Pará and Tocantins' northern and central portions. In the Northeast region (figure 4D–F), CS expanded in the coast towards the municipalities in the states' interior. In the Midwest region (figure 4G–I), CS expanded from the municipalities bordering Bolivia and Paraguay in the State of Mato Grosso do Sul. In Southeast region (figure 4J–L), the direction of the expansion of CS occurred in the same occurred similarly the one noticed in the Northeast region. In the Southern region (figure 4M–O), CS expanded in Rio Grande do Sul in the municipalities around its capital and the municipalities bordering Argentina. In the third period, CS expansion was observed in Santa Catarina and Paraná.

Figure 5 illustrates the result of the spatial and spatiotemporal risk scan for CS in all Brazilian regions. The cities with the highest spatial risks include Augustinópolis, Tocantins (RR=9.82; p<0.001; figure 5A and online supplemental figure 2A—red box), Recife and Olinda, Pernambuco (RR=5.8; p<0.001; figure 5B and online supplemental figure 2B—yellow box), Campo Grande and surrounding areas, Mato Grosso do Sul (RR=2.76; p<0.001; figure 5C), Rio de Janeiro and surrounding areas (RR=3.73; p<0.001; figure 5D and online supplemental figure 2C—yellow labelled polygons), and Porto Alegre, Rio Grande do Sul (RR=6.49; p<0.001; figure 5E and online supplemental figure 2D—blue box). The zones with the highest spatiotemporal risk include Manaus (RR=5.14; p<0.001; figure 5F), Olinda and Recife (RR=7.82; p<0.001; figure 5G and online supplemental figure 3—blue box), municipalities in the southern meridian of Mato Grosso do Sul (RR=4.04; p<0.001; figure 5H), the city of Rio de Janeiro and surrounding cities (RR=4.77; p<0.001; figure 5I), and the Southern region involving Alvorada, Canoas and Porto Alegre, Rio Grande do Sul (RR=8.28; p<0.001; figure 5J).

DISCUSSION

This study showed the territorial expansion of CS in Brazil and the spatial heterogeneity of CS incidence rates among the Brazilian regions. Brazil is a signatory of the EMTCT policy and despite all strategies implemented to fight SC, our results suggest Brazil is far from get CS eliminated. Whereas, in China, after implementing the EMTCT, syphilis screening, infection control and pharmacological treatment of pregnant women and their partners during prenatal care were expanded. Consequently, between 2010 and 2016, the number of CS cases decreased by 59.89% (11 347 cases in 2010 vs 4552 cases in 2016).[19]

Since it is an ecological study, we cannot claim causality between CS and demographic groups or other social phenomena. In addition, we must consider that the Brazilian SC epidemiological scenery might be even worse due to the under-reporting cases. In addition, our study did not consider the COVID-19 pandemic outbreak's effect on the CS scenery and the influence of the social determinants of health on its spatial variability. Therefore, future studies employing temporal analysis and spatial regression techniques should be considered.

Although the expansion of the coverage of prenatal in Brazil and after all policies against CS, the quality of prenatal services is still low. A great number of syphilis cases in pregnant women are diagnosed late; 38.1% of 201 781 syphilis cases in pregnant women, reported to DNIS in 2019, were detected in the prepartum or postpartum period.[6] A previous study among 661 postpartum women from the State of Mato Grosso do Sul revealed that only 28.3% of pregnant women underwent a Venereal Disease Reseacher Laboratory test to detect syphilis in the third trimester, even though the Ministry of Health recommends at least three tests—one in the first care attendance, another at the beginning of the third trimester and another in the pre-delivery period.[20]

In Minas Gerais, from 2009 to 2019, the incidence rates of gestational and CS had an average percentual annual increase of 36.7% and 32.8%, respectively, suggesting failure on the syphilis treatment during the prenatal.[21] In Amazonas, Ceará, Federal District, Espírito Santo, Rio de Janeiro and Rio Grande do Sul, 43% of women who received a diagnosis of gestational syphilis progressed to CS, 59% of them received inadequate treatment, 25% were untreated and only 7.9% of partners were treated.[22] This percentage of treatment is far below the WHO recommendation for facilitating treatment in ≥95% of pregnant women diagnosed with syphilis.[4]

The spatial autocorrelation analysis showed a spatial heterogeneity of the CS incidence rates in which the municipalities with the highest epidemiological pressures are those with the greatest flow of people, such as the municipalities bordering other countries. In the North region, the municipalities in the South of Pará are experiencing economic expansion caused by the growth of the mining industry and the construction of hydroelectric plants, attracting a high number of immigrants searching for jobs. The municipalities in the Northeast and Southeast coastal regions attract a high number of tourists for their beaches and natural beauty. Likewise, in the US, the states of California, Florida, Texas, Arizona and Louisiana are responsible for 70% of CS notifications, and the first three mentioned states have the highest immigration rate in the country.[23] A study in China showed that provinces bordering other countries had high syphilis, HIV, and gonorrhoea incidence rates.[24]

The Kernel analysis showed an interiorisation of CS across the country, being more evident between 2015 and 2018. Although it can suggest the real expansion of CS, we need to consider the improvement in case detection and

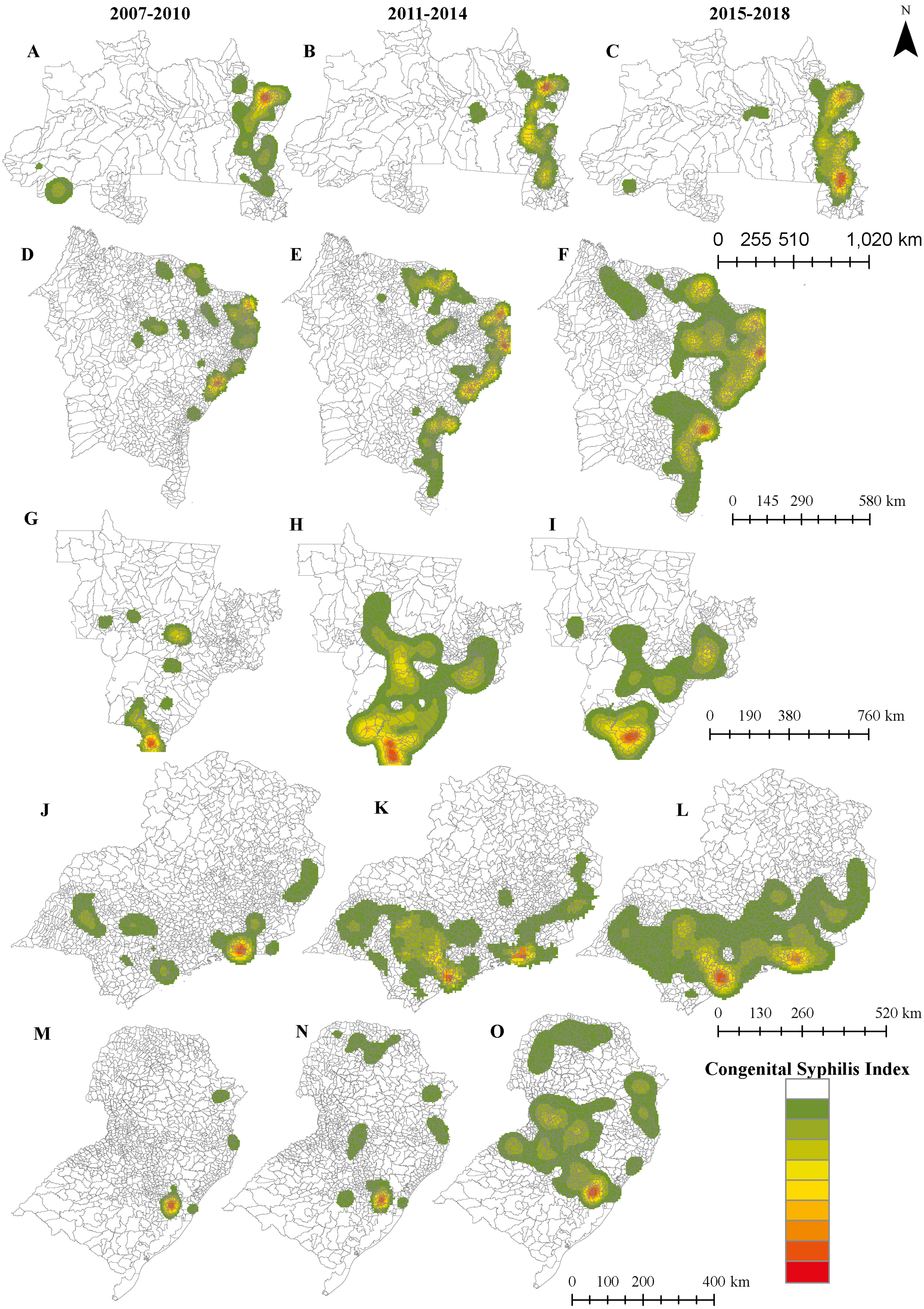

Figure 4 Kernel maps of the congenital syphilis in the Brazilian regions: North (figure 3A–C), Northeast (figure 3D–F), Midwest (figure 3G–I), Southeast (figure 3J–L) and South (figure 3M–O).

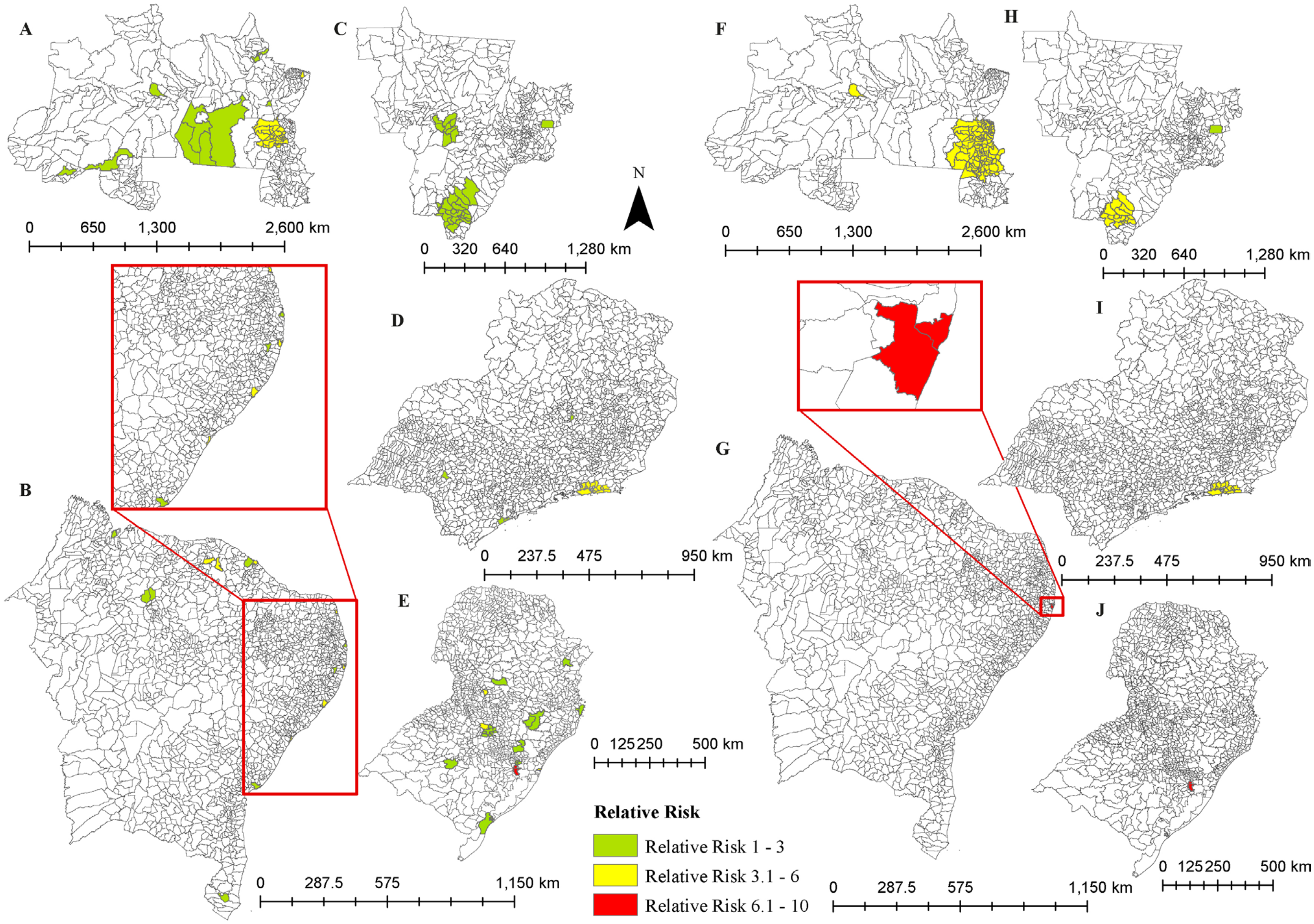

Figure 5 Spatial risk maps for the congenital syphilis spatial in the North (figure 5A), Northeast (figure 5B), Midwest (figure 5C), Southeast (figure 5D) and South (figure 5E) and spatiotemporal risk maps in (figure 5F), Northeast (figure 5G), Midwest (figure 5H), Southeast (figure 5I) and South (figure 5J) Brazilian regions.

the notification system as a result of actions implemented in Brazil as the Stork Network, in 2011,[25] and the Agenda of Strategic Actions for Congenital Syphilis Reduction in Brazil in 2016.[26] However, during this period, the worldwide shortage of penicillin between 2014 and 2017 may have promoted the increase in CS in Brazil.[27] In the city of Rio de Janeiro, between 2013 and 2017, the lack of penicillin led to a 2.3% increase in the risk for CS.[28 29]

The spatial scan indicated that the Brazilian state capitals Recife, Campo Grande, Rio de Janeiro, Porto Alegre and Manaus are the cities with the greatest spatial and spatiotemporal risk. A previous study identified these capitals with the highest percentage increases in CS, in which gestational syphilis was mostly diagnosed in the prepartum and postpartum period, and with untreated partners. Among these capitals, Manaus stood out with the lowest percentage of women who attended prenatal care.[30] The decrease in penicillin stock may be directly associated with the spatiotemporal risk for CS between 2016 and 2018 in these capitals, supporting the results of a previous study done in Rio de Janeiro.[28]

CS can be prevented by promoting a better quality of prenatal care for pregnant women, starting prenatal care in the first trimester, observing timely diagnosis, monitoring throughout the gestational period, safer sexual practices and practising adequate treatment of pregnant women and their partners. Thus, the coverage of Primary Healthcare should be increased, with a process centred on the person that goes beyond the biomedical model. Moreover, supply of clinics with rapid tests and penicillin should be ensured in addition to training nurses for, and implementation of, penicillin administration for pregnant women with reactive results. A study carried out in Bahia supports the reaction to an increase of CS with the expansion of the coverage of prenatal, highlighting the importance of improving the quality of monitoring of pregnant women.[31]

However, much more of increasing prenatal coverage and improving its quality, it is necessary to promote social equity to fight CS. CS has a higher prevalence among newborns from socially vulnerable mothers. These women have lower access to information and, consequently, low knowledge about sexually transmissible infections and their prevention forms.[22] In Uruguay, CS detection rate was higher among pregnant women followed by the public health system than those in the private one. In addition, most mothers of children diagnosed with CS had low education levels and attended less than five prenatal care visits.[32] In a province of Northern Italy, the syphilis prevalence was higher among immigrant women with most of them receiving a late diagnosis.[33] From 2008 to 2015, in the Northeast Brazilian region, the syphilis prevalence trended up among those pregnant women with low schooling levels, aged 15–19 years old and having black/brown skin colour.[34] Another national study showed a higher coverage of six or more prenatal care visits among wealthier women and those living in urban zones.[35] Therefore, health professionals should be trained to implement reproductive health education during the prenatal care visits reinforcing the importance of the use of preservatives during the sex act, of the syphilis screening, and of theirs and their partner's treatment to avoid CS. In addition, access by pregnant women and their partner to prevention, diagnosis and treatment resources must be guaranteed.

This study provides robust subsidies to Brazilian health authorities to fight CS indicating the regions with the greatest intervention needs. Considering that CS is a preventable disease, the recent change in federal funding for Primary Healthcare in Brazil may improve maternal and child health indicators. Recently, the Brazilian Ministry of Health launched the *Previne Brasil* policy that will transfer funds to municipalities based on their health indicators, such as the proportion of pregnant women with at least six prenatal care visits, and the proportion of pregnant women tested for syphilis and HIV.[36]

Correction notice The article has been corrected since it was published online. One of the co-author's name was published incorrectly, it should be "Renata Karina Reis" instead of Renata Karina Karina Reis.

Contributors Study design: IS, GRONF and EB; study conduct: IS and EB; data collection: IS and EB data analysis: IS and EB; data interpretation: IS, GRONF and EB; manuscript drafting: IS, GRONF, WS, CO, ATP, EG, RKKR and RAPF; approving final version of manuscript: all authors. EPB is the guarantor for the overall content of the study

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