Spatiotemporal clustering, social vulnerability and risk of congenital syphilis in Northeast Brazil: an ecological study

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Abstract

Background: To investigate the spatial distribution of congenital syphilis (CS) and its association to social vulnerability indexes in Northeast Brazil.

Methods: This was an ecological study referring to all cases of CS and CS-deaths recorded in the Northeast region of Brazil from 2008 to 2015. Data were obtained from three Brazilian information systems. We examined statistical correlations between CS indicators by state and municipality and their socio-economic and social vulnerability characteristics. We used Bayesian empirical local models to identify fluctuations of the indicators. Scan spatial statistic tests were used to identify spatial clusters and the municipalities at high risk of CS.

Results: The incidence of CS ranged from 2.1 cases/1,000 live births (LB) in 2008 to 6.9/1,000 in 2015, with an annual increase of 19.9% ($p<0.001$). The mortality coefficient of CS ranged from 2.9/1,000 LB in 2008 to 6.5/1,000 in 2015, resulting in an annual increase of 15.1% ($p<0.001$). Nine spatial clusters were identified. Cases of congenital syphilis occurred in well-defined spatiotemporal clusters and in areas with high levels of social vulnerability.

Conclusions: The CS incidence is associated with social vulnerability. CS control programs should target to spatial clusters and populations with high levels of social vulnerability.

Keywords: Congenital Syphilis; Spatiotemporal distribution; Social Vulnerability Index; Risk factors; Brazil.

Introduction

Syphilis is a re-emerging sexually transmitted infection (STI) caused by *Treponema pallidum*, which is spread through sexual contact (horizontal transmission) or from the mother to the child during pregnancy or delivery (vertical transmission).[1] Syphilis is the fourth most common STI worldwide, with 5.6 million annual incident cases,[2] affecting over one million pregnant women, causing 600,000 cases of congenital syphilis (CS) and over 300,000 foetal and neonatal deaths.[2]

From 2012 to 2016, there was a global decrease in the incidence of CS despite a stable prevalence of maternal syphilis, reflecting continued progress towards CS elimination. The incidence however was still at some distance from the World Health Organization (WHO) target of 50 CS cases per 100,000 live births (LB) and at least 95% antenatal care coverage, that incudes syphilis screening and treatment.[3] The reduction in CS however were not uniform, with steep declines in high-income countries,[3] but increasing rates in several low- and middle-income countries (LMICs).[2,3] Rates have also changed unevenly within countries and in Brazil, CS incidence rates are higher in the Southeast and Northeast regions, with 9.7 and 9.6/1,000 LB, respectively, compared to 6.0, 7.1 and 8.9 in the West Central, North and South regions, respectively.[4]

CS is a marker of STIs transmission among adults and an important indicator of failure in the health care system,[5] and therefore identifying populations at high risk and their geographical distribution would allow tailoring interventions to prevent transmission.

This study examines the spatiotemporal distribution of CS and its association with indicators of social vulnerability in Northeast Brazil.

Materials and Methods

Study Design

We performed a mixed ecological study involving all cases of CS and CS-deaths recorded in the Northeast region of Brazil from 2008 to 2015, and described its geographical distribution by state and municipality, which are the main administrative subdivisions of the country.

Study area

The Northeast region comprises nine states (Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraiba, Pernambuco, Alagoas, Sergipe and Bahia) and 1,793 municipalities (see Supplementary Figure 1) and is the second most populous region with 56.9 million population. The Region also has the lowest Human Development Index (HDI) among the five regions in the country (HDI 0.663).[6]

Data source and measures

Data on CS and live births were obtained from the National Information System for Notifiable Diseases (SINAN, http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinannet/cnv/sifilis br.def) and the National Live Birth System (http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinasc/cnv/nvbr.def) and were used to estimate the infant CS incidence and mortality coefficients. We examined statistical correlations between CS indicators obtained from http://indicadoressifilis.aids.gov.br/ by state and municipality and their socio-economic and social vulnerability characteristics and by maternal age and ethnicity/skin colour, education, time of diagnosis of maternal syphilis and maternal treatment regimen, partner treatment, prenatal care and age of the child at the time of CS diagnosis and final diagnosis.

The municipal incidence coefficient was calculated as the average number of cases of CS in the period divided by the number of livebirths in the middle period per 1,000. The Social Vulnerability Index (SVI) was obtained from the Institute of Applied Economic Research (IPEA; http://www.ipea.gov.br). This index estimates the degree of vulnerability and social

exclusion of the population and is composed of 16 social indicators comprising domains of urban infrastructure, human capital, income and work.[7] The urban infrastructure domain includes the percentage of the population living in households with inadequate water supply, sewage or rubbish collection services; and the proportion of households with a per capita income below half the Brazilian minimum salary of households with workers who spend more than one hour commuting to work. The human capital domain includes the infant mortality rate; the percentages of 0- to 5- and 6- to 14-year-old children not attending preschool or school; the illiteracy rate among minors >15 years-old; the percentage of mothers heading households or without primary education who have at least one child <15 years of age; the proportion of 10- to 17-year-old females with children; and the percentage of children living in households where none of the residents has completed primary education. The income and work domain includes the proportion of families with a per capita household income below half the minimum wage with workers who spend more than 1 h commuting to work; the unemployment rate and the proportions of adults without primary education and in informal employment; and the proportion of people in households with income per capita below half the 2010 minimum wage dependent on the elderly and the economic activity of 10- to 14-year-old children. The SVI is the overall arithmetic mean of the three domains. These variables made up five blocks of distinct variables to avoid multicollinearity. The SVI score ranges from 0 to 1, and we classified the municipalities into very low (0–0.2), low (>0.2–0.3), moderate (>0.3–0.4), high (>0.4–0.5) and very high SVI (>0.5).[7,8]

Data analysis

Data analysis included describing the characteristics of the study population using descriptive statistics and a temporal modelling analysis of the CS indicators using the

joinpoint regression model. This model tests whether a multithreaded line is suited to describe the temporal evolution of a set compared to a straight line or fewer segments.[9] We classified trends as increasing, decreasing or stable according to the slope of the regression line using the Joinpoint regression software (version 4.5.0.1, National Cancer Institute, Bethesda, MD, USA) and estimated the annual percentage changes (APC) with 95% confidence intervals (CI) for all indicators. We then conducted a spatial modelling using Moran Global and Local statistic to identify areas of high risk for CS.[10] Syphilis rates by municipality were smoothed using Bayesian empirical local modelling to reduce random variations caused by rare events, small populations and/or underreporting.

The Moran Global statistic was used to identify spatial autocorrelations, and when these were identified, we used the Local Index of Spatial Association (LISA).[10] Scattering diagrams were generated to position the municipalities in quadrants and calculated the neighbouring municipalities average into: Q1 (high/high, positive values and positive averages), Q2 (low/low, negative values and negative averages), Q3 (high/low, positive values and negative averages) and Q4 (low/high, negative values and positive averages). The municipalities in quadrant Q1 were considered a priority. Subsequently, thematic maps were constructed with the Moran diagram using the software Terra View 4.2.2 (Brazilian Space Research Institute (INPE), São José dos Campos, SP, Brazil) and QGis 2.14.11 (Open Source Geospatial Foundation (OSGeo), Beaverton, OR, USA).

Finally, we examined the spatial association considering the smoothed rate of CS as the dependent and the social indicators as the independent variables. For this, we used a decision model as proposed by Luc Anselin,[11] which uses Lagrange multiplier tests to define whether it is more appropriate to apply the Spatial Error or the Spatial Lag Models. In the Spatial Error Model, spatial effects are noises that should be removed, while the Spatial Lag

Model assigns to the response variable Y the ignored spatial autocorrelation using the GeoDa 1.10 (Center for Spatial Data Science, Computation Institute, The University of Chicago, Chicago, IL, USA).

Results

A total of 28,624 cases of CS were notified in the Region during the study period, and 28,534 (96.0%) infants were diagnosed when they were <1 year-old. Abortions and stillborn together accounted for 2,628 (9.2%) CS cases and 314 (1.1%) infants died of CS in the first year after birth.

The full characteristics of infants with CS and their mothers are described in Supplementary Table 1. Half of the mothers were 20-39 years old (14,698/51.3%), 21,606 (75.5%) had mixed ethnicity and 16,664 (51.7%) low education. In total, 12,523 (43.8%) CS cases were diagnosed at the time of delivery or curettage and more than half (15,537, 54.2%) mothers received inadequate treatment, with 5,158 partners not receiving treatment. Only 21,078 (73.6%) mothers attended antenatal care (ANC) and in 27,468 (96.0%) CS cases the diagnosis was confirmed postnatally, in the first seven days after birth.

There was increasing trend of the proportion of CS among mothers aged 15-19 years old (APC: 2.2%; 95% CI: 0.7% to 3.8%), those with mixed ethnicity (APC 1.5%; 95% CI: 0.8% to 2.2%), higher education (APC: 22.6%; 95% CI: 4.8% to 43.3%), a prenatal diagnosis (APC: 3.1%; 95% CI: 1.0% to 5.2%), inadequate maternal treatment (APC 3.6%; 95% CI: 0.8% to 6.6%), early diagnosis in the child (<7 days) (APC: 0.2%; 95% CI: 0.1% to 0.4%) and recent congenital syphilis (APC 1.2%; 95% CI: 0.2% to 2.1%). Conversely, there was a decreasing trend of the proportion of women with untreated partners (APC -1.4%; 95% CI -1.8% to -1.0%) (Table 1).

156 The incidence of CS in the region ranged from 2.1 cases per 1,000 live births in 2008 to 6.9
157 cases per 1,000 live births in 2015, with an annual increase of 19.9% (p<0.001) and an
158 average of 3,567 cases per year (see Supplementary Figure 2A). The states of Ceará (n =
159 6,837), Pernambuco (n = 6,426) and Bahia (n = 4,722) reported 63.0% of all cases, but the
160 mean incidence per 1,000 LB was highest in Sergipe (7.6), Ceará (6.6) and Alagoas (5.8). All
161 states had increasing trends, with largest increases observed in Piauí (APC: 61.6%; 95% CI:
162 19.4% to 74.8%), Bahia (APC: 31.1%; 95% CI: 27.4% to 34.7%) and Paraíba (APC: 25.5%; 95%
163 CI: 16.0% to 35.8%) (Table 2).
164 The CS mortality coefficient by 1,000 live births ranged from 2.9 in 2008 to 6.5 in 2015, with
165 an 15.1% annual increases (p<0.001) (see Supplementary Figure 2B). The highest average
166 mortality rate per 1000 live births was observed in Pernambuco (8.4), followed by Alagoas
167 (7.0) and Maranhão (5.1). However, only Maranhão (APC: 46.2%) and Bahia (APC: 32.6%)
168 increases in incidence were statistically significant (Table 2).
169 Figure 1 describes the spatial distribution of the CS indicators. There was spatial
170 dependence on crude (I Moran 0.571; p=0.01) and smoothed indicators (I Moran 0.797;
171 p=0.01). However, the Bayesian model showed a reduction in the random fluctuation of the
172 CS indicators, with i) a decrease in the number of silent (not reporting) municipalities (from
173 531 to 20), ii) an increase in the number of municipalities with rates between 0.1 and 2.0
174 per 1,000 live births (from 631 to 1087), between 2.1 and 5.0 per 1,000 live births (from 390
175 to 450) and between 5.1 and 10.0 per 1,000 live births (from 193 to 203). Two hundred and
176 sixty-five (14.8%) municipalities had high CS rates and were considered at high risk of CS
177 transmission (Q1 Moran Map) (Figure 2 and Supplementary Table 2).
178 Nine spatial clusters were identified, with the highest incidence rates occurring in *Cluster 7*
179 (incidence per 1000 live births = 7.71; comprising 62 municipalities), *Cluster 6* (incidence =

7.07; 39 municipalities) and *Cluster 1* (incidence = 6.8; seven municipalities). Bahia state had the largest number of clusters (*Clusters 7, 8* and *9*) and Sergipe had the highest proportion of municipalities with high incidence rates (81.3%) (Figure 2 and wee appendix Table 2).

The Spatial Lag Model was the best fitting model by Lagrange multiplier tests for the association between CS incidence and the social indicators of social vulnerability. Overall the SVI and its three domains were not statistically associated with the incidence of CS. However, when the indicators for each SVI domain were analysed separately, there was a significant association between 14 of the 16 indicators, three of these for the SVI urban infrastructure domain, six for the SVI human capital and four for the SVI income and work (Supplementary Table 3). There was however no association between the CS rate and the states' primary health care coverage (Supplementary Table 3). The municipalities with the highest SVI had higher trends for CS (Table 3).

Discussion

The Northeast region of Brazil has a high incidence of CS, with increasing trends between 2008 and 2015, which is opposite to the global reduction in incidence between 2012 and 2016 [3]. This study highlights that CS has a heterogeneous geographic distribution in the region, with spatiotemporal clusters located in areas with a high degree of social vulnerability, but no association with the availability of primary health care coverage. Similar to other studies,[12–14] there was an increasing trend of births with CS, with a higher risk in young mothers less than 20 years-old, with low education and mixed ethnicity, reflecting a context of vulnerability in these populations, especially when they are located in areas of deprivation.

The prevention of CS depends on an early diagnosis before or during pregnancy and the timely treatment of pregnant women and their partners. Brazil adopted in the 1990s a

policy to expand antenatal coverage in primary health care facilities; and since the 2000s offers laboratory tests free of charge for STIS to all pregnant women, including rapid tests for HIV, hepatitis B and syphilis, which should facilitate linkage to treatment.[15] The Brazilian Health System (Sistema Único de Saúde, SUS) also provides further testing for STIs at the time of delivery to identify cases missed during antenatal visits. However, given the high proportion of cases identified at birth, it is clear that many women are not screened during pregnancy and STI detection occurs too late in nearly half of the children.

Surprisingly, there was no relationship between the municipalities' primary health care coverage and the incidence of CS. Although the SUS offers free, large-scale screening for syphilis through all its primary health care services, the uptake of screening is clearly incomplete and other barriers are likely to play a significant role. Moreover, there is a strong correlation between an increasing syphilis incidence among adults and infants with CS at birth.[3,16,17]

A low frequency of antenatal visits is a risk for CS,[13,18,19] with a 5- to 12-fold increased risk among women attending less than 6 prenatal consultations.[12,13] In our analysis however, although the mothers of 73% of infants with CS that attended at least 6 consultations, but only 4% had received adequate treatment before delivery , with a high proportion of infections (44%) being diagnosed at the time of delivery. Given the high proportion of partners who also failed to receive adequate treatment, these characteristics altogether indicate systemic failures in the quality of antenatal care delivery.

Quality of care can be compromised by late attendance to antenatal care, especially among younger women with high social vulnerability; shortages and stockouts of diagnostic tests, the poor timeliness of laboratory results,[20] and the difficulty of engaging the partners into treatment.[21] There is evidence that the introduction of rapid diagnostics tests with better

timeliness of laboratory confirmation can improve actioning on results and linkage to treatment.[22] Furthermore, Brazilian health services also have attributed the increases in syphilis to shortages of medicines for treatment, especially of Benzathine Penicillin, due to shortages of resources for its manufacture, and that these shortages have led to an increase in CS since 2014.[21]

Missed opportunities for the early treatment of syphilis in pregnant women include a lack of documented treatment for syphilis infection when diagnosed before or during pregnancy; the absence of serologic tests during pregnancy; late maternal treatment or receiving treatment with a nonpenicillin regimen.[23–25] A study in Brazil reported that non-white women, low education, being single, poverty, a history of syphilis before pregnancy, a low number of antenatal care visits (<6) and the last antenatal visit occurring before the third trimester were associated with increased risk of syphilis.[23]

The inclusion of partners in antenatal care is an important strategy to promote adherence to antenatal care and improving maternal and child health outcomes.[26,27] Although Brazilian services encourage this practice,[28] the men's reluctancy to participate in health services including for screening and treatment of STIs, results in a low uptake of services.[21,29,30]

Besides the quality of services, socio-economic factors are likely to play a role in the Northeast Region. Areas with social and income inequalities often have less access to water supply, inadequate sanitation and refuse collection services and a disproportionally high population with low education.[8,31] These populations have less access to information, give a low priority to preventive interventions and have a higher frequency of unwanted pregnancies and infections. We thus found clusters of CS in municipalities with high SVI indicating that the more heterogeneous the distribution of resources, the higher the odds of the municipality reporting CS as an important health problem.

The data presented here needs to be interpreted considering the study limitations. The data were obtained from surveillance information systems and therefore only represent women who have accessed the health system. Women who did not attend antenatal care or delivered at home are missing and their underreporting may have influenced the detection rates. We are aware studies have suggested the increase in the proportion of men who have sex with men in some countries has resulted in increased syphilis rates as CS.[32] Given our study is based on secondary aggregated data we could not include this variable in our analysis. Aggregate data do not allow to examine confounding factors on individuals and our analysis needs to be supplemented by prospectively collected data from individuals. Moreover, missing data is irretrievable, and it is unlikely to have occurred at random, with health services being less accessible to remote populations, people with social and societal barriers and data gaps may have underrepresented at risk populations.

In conclusion, CS has a heterogeneous geographic distribution in the Northeast region, with well-defined spatiotemporal clusters in areas with a high degree of social vulnerability. The spatial distribution patterns of CS could support focusing interventions for the timely identification of pregnant women at high risk of infection and to prevent transmission.

Contributors

CDFdeS and VSS conceptualised and designed the study. CDF, MFM, DSC and RFdoC were involved in data collection. CDFdeS and VSS performed the statistical analysis. CDFdeS, MFM and RFdoC wrote the initial draft with support from LEC and VSS. All authors contributed equally to data interpretation, critically reviewed the manuscript and approved the final version. CDFS and VSS are guarantors of the paper.

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Table 3. Trend of congenital syphilis incidence rate per 1,000 live birth by the Social Vulnerability Index.

388 **Table 1. Annual Percentage Change (APC) of congenital syphilis, by sociodemographic and**
389 **clinical characteristics. Northeast, Brazil, 2008-2015.**

Variable	APC (CI95%)	P-value	Trend
Maternal age (years)			
10-14	2.0 (-2.8 to 6.7)	0.3	Stable
15-19	2.2 (0.7 to 3.8)	<0.001	Increasing
20-29	-0.8 (-1.7 to 0.2)	0.1	Stable
30-39	-0.4 (-2.1 to 1.3)	0.1	Stable
≥ 40	-3.2 (-9.2 to 3.3)	0.3	Stable
Unknown	0.8 (-8.3 to 10.6)	0.7	Stable
Ethnic group			
White	-5.8 (-7.6 to -4.0)	<0.001	Decreasing
Black	-0.1(-2.8 to 2.8)	0.1	Stable
Asian	4.1 (-3.2 to 14.3)	0.3	Stable
Mixed	1.5 (0.8 to 2.2)	<0.001	Increasing
Indigenous	-1.3 (-9.2 to 7.4)	0.4	Stable
Unknown	-2.1 (-7.5 to 3.6)	0.4	Stable
Maternal education			
Illiterate	-15.8 (-18.8 to -12.7)	<0.001	Decreasing
Incomplete primary education	-7.2 (-10.2 to -4.1)	<0.001	Decreasing
Complete primary education	-9.3 (-13.0 to -5.5)	<0.001	Decreasing
Incomplete secondary education	2.5 (1.2 to 3.7)	<0.001	Increasing
Complete secondary education	1.4 (-2.4 to 5.4)	0.3	Stable
Incomplete high school	2.5 (-0.0 to 5.0)	0.1	Stable
Complete high school	6.8 (3.7 to 10.0)	<0.001	Increasing
Incomplete graduate	11.2 (2.4 to 20.9)	<0.001	Increasing
Complete graduate	22.6 (4.8 to 43.3)	<0.001	Increasing
Not applied	6.5 (-4.3 to 18.5)	0.1	Stable
Unknown	1.2 (-0.5 to 2.9)	0.1	Stable
Time of diagnosis of maternal syphilis			
Pre-natal care	3.1 (1.0 to 5.2)	<0.001	Increasing
Delivery/curettage	-2.9 (-3.9 to -1.9)	<0.001	Decreasing
Postpartum	-1.3 (-6.0 to 3.7)	0.4	Stable
Not tested	-0.9 (-9.4 to 8.4)	0.8	Stable
Unknown	9.0 (4.8 to 13.5)	<0.001	Increasing
Maternal treatment scheme			
Adequate	-10.6 (-19.4 to -0.8)	<0.001	Decreasing
Inadequate	3.6 (0.8 to 6.6)	<0.001	Increasing
Not performed	-3.6 (-9.4 to 2.5)	0.4	Stable
Unknown	-10.6 (-19.4 to -0.8)	<0.001	Decreasing
Treatment of the mother's partner			
Yes	0.6 (-3.6 to 5.0)	0.3	Stable
No	-1.4 (-1.8 to -1.0)	<0.001	Decreasing
Unknown	4.1 (1.3 to 7.0)	<0.001	Increasing
Antenatal care			
Yes	2.2 (1.1 to 3.4)	<0.001	Increasing
No	-4.7 (-7.7 to -1.7)	<0.001	Decreasing
Unknown	2.8 (-3.5 to 9.4)	0.6	Stable
Age of the child at the time of diagnosis			

<7 days	0.2 (0.1 to 0.4)	<0.001	Increasing
7 to 27 days	-3.3 (-11.2 to 5.2)	0.5	Stable
28 to 364 days	-5.4 (-11.3 to 1.0)	0.1	Stable
1 year	-5.6 (-20.5 to 12.2)	0.4	Stable
2 to 4 years	5.9 (-2.4 to 15)	0.3	Stable
5 to 12 years	-4 (-12.4 to 5.1)	0.1	Stable
Final diagnosis classification			
Recent congenital syphilis	1.2 (0.2 to 2.1)	<0.001	Increasing
Late congenital syphilis	-26.7 (-45.7 to -0.9)	<0.001	Decreasing
Abortion due to syphilis	-0.3 (-8.1 to 8.3)	0.6	Stable
Stillborn due to syphilis	-10.1 (-20.1 to 1.2)	0.2	Stable

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Table 2. Infant congenital syphilis incidence and mortality coefficient by State. Northeast, Brazil, 2008-2015.

Geographic unit	Incidence rate			Joinpoint Regression Model				
	2008	2015	2008-2015	Period	APC	CI95%	P-value	Trend
Congenital syphilis incidence rate per 1,000 live births								
Northeast	2.1	6.9	4.24	2008-2015	19.9	16.8 to 22.9	<0.001	Increasing
Maranhão	1.6	3.7	2.0	2008-2010	-15.3	-46.6 to 34.3	0.3	Stable
				2010-2015	27.0	14.5 to 40.8	<0.001	Increasing
				2008-2015	13.1	3.1 to 24.1	<0.001	Increasing
Piauí	0.3	8.0	2.2	2008-2015	61.6	19.4 to 74.8	<0.001	Increasing
Ceará	4.0	8.6	6.6	2008-2012	17.0	17.1 to 27.6	<0.001	Increasing
				2012-2015	5.1	-8.2 to 20.3	0.3	Stable
				2008-2015	11.8	6.7 to 17.1	<0.001	Increasing
Rio Grande do Norte	3.6	8.9	5.5	2008-2015	12.6	7.9 to 17.4	<0.001	Increasing
Paraíba	1.1	5.4	3.0	2008-2011	38.4	10.1 to 73.9	<0.001	Increasing
				2011-2015	16.6	0.9 to 34.8	<0.001	Increasing
				2008-2015	25.5	16.0 to 35.8	<0.001	Increasing
Pernambuco	2.7	9.4	5.7	2008-2015	21.6	16.6 to 24.6	<0.001	Increasing
Alagoas	3.2	7.4	5.8	2008-2013	23.1	9.3 to 27.4	<0.001	Increasing
				2013-2015	-4.5	-43.9 to 62.5	<0.001	Increasing
				2008-2015	14.5	2.8 to 27.4	<0.001	Increasing
Sergipe	3.0	10.5	7.6	2008-2013	32.8	22.7 to 43.6	<0.001	Increasing
				2013-2015	-5.5	-33.5 to 34.3	0.6	Stable
				2008-2015	20.5	12.3 to 29.3	<0.001	Increasing
Bahia	0.9	5.6	2.8	2008-2015	31.0	27.4 to 34.7	<0.001	Increasing
Congenital syphilis mortality rate per 1,000 live births								
Northeast	2.9	6.5	4.66	2008-2015	15.1	9.5 to 20.9	<0.001	Increasing
Maranhão	1.4	9.4	5.1	2008-2015	46.2	22.3 to 74.7	<0.001	Increasing
Piauí	3.8	4.1	2.3	2008-2015	34.1	-33.2 to 170.4	0.3	Stable
Ceará	3.0	3.8	2.5	2008-2013	-10.3	-20.4 to 1.1	0.1	Stable
				2013-2015	58.6	-7.1 to 170.1	0.1	Stable
				2008-2015	5.6	-5.2 to 17.6	0.3	Stable
Rio Grande do Norte	0.0	4.1	4.4	2008-2015	57.5	-9.3 to 173.5	0.1	Stable

Paraíba	1.6	1.7	3.7	2008-2013	43.3	-0.0 to 102.6	0.1	Stable
				2013-2015	-59.7	-91.7 to 95.5	0.2	Stable
				2008-2015	-0.8	-27.8 to 36.4	1.0	Stable
Pernambuco	6.9	9.7	8.4	2008-2015	7.1	-2.2 to 17.3	0.1	Stable
Alagoas	5.2	7.7	7.0	2008-2015	-0.4	-21.7 to 26.8	1.0	Stable
Sergipe	2.7	5.7	4.3	2008-2015	-7.5	-48.0 to 64.5	0.8	Stable
Bahia	1.4	6.3	3.6	2008-2015	32.6	5.2 to 67.0	<0.001	Increasing

Table 3. Trend of congenital syphilis incidence rate per 1,000 live birth by the Social Vulnerability Index.

Social Vulnerability Index	Number of municipalities	Period	Annual Percentage Change	(95%CI*)	Trend
Very low	1	-	-	-	-
Low	32	2008-2012	34.8	15.6 to 57.1	Increasing
		2012-2015	6.2	-16.7 to 35.3	Stationary
		2008-2015	21.7	11.9 to 32.3	Increasing
Moderate	314	2008-2015	22.1	11.9 to 33.2	Increasing
High	859	2008-2015	23.6	16.6 to 31.0	Increasing
Very high	587	2008-2015	25.0	19.3 to 30.9	Increasing
Infrastructure domain					
Very low	436	2008-2015	22.2	12.4 to 32.9	Increasing
Low	503	2008-2015	22.9	15.1 to 31.2	Increasing
Moderate	425	2008-2015	23.7	17.5 to 30.2	Increasing
High	221	2008-2015	26.0	21.5 to 30.7	Increasing
Very High	208	2008-2015	25.2	17.2 to 33.8	Increasing
Income and work domain					
Very low	1	-	-	-	-
Low	8	2008-2015	13.7	8.7 to 18.9	Increasing
Moderate	71	2008-2015	21.6	13.4 to 30.4	Increasing
High	393	2008-2015	24.2	15.7 to 33.4	Increasing
Very high	1320	2008-2015	24.2	17.7 to 30.6	Increasing
Human capital domain					
Very low	1	-	-	-	-
Low	4	2008-2015	19.0	10.1 to 28.6	Increasing
Moderate	68	2008-2015	22.8	16.5 to 29.6	Increasing
High	443	2008-2015	28.3	17.6 to 40.1	Increasing
Very high	1277	2008-2015	22.3	16.6 to 28.3	Increasing

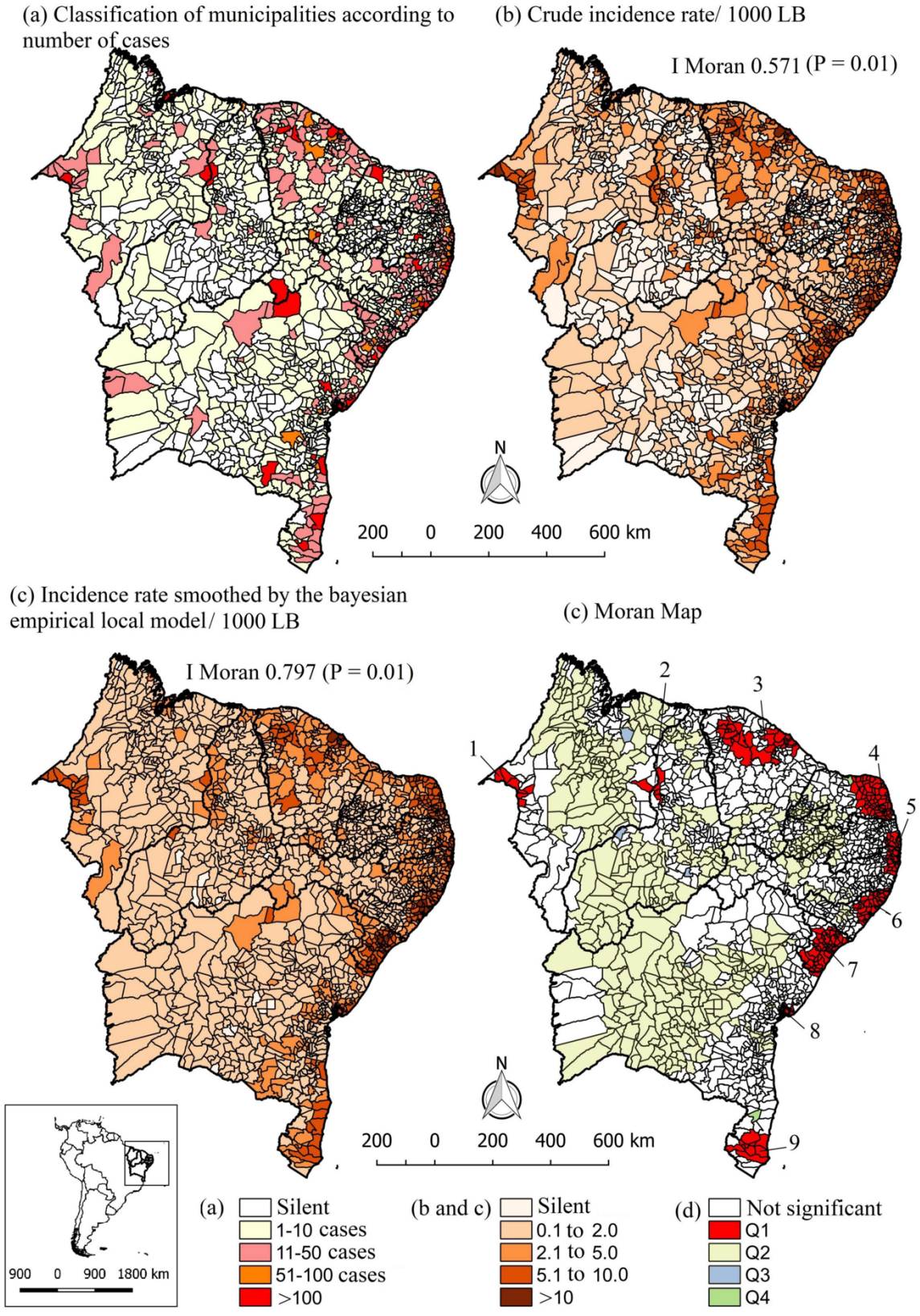
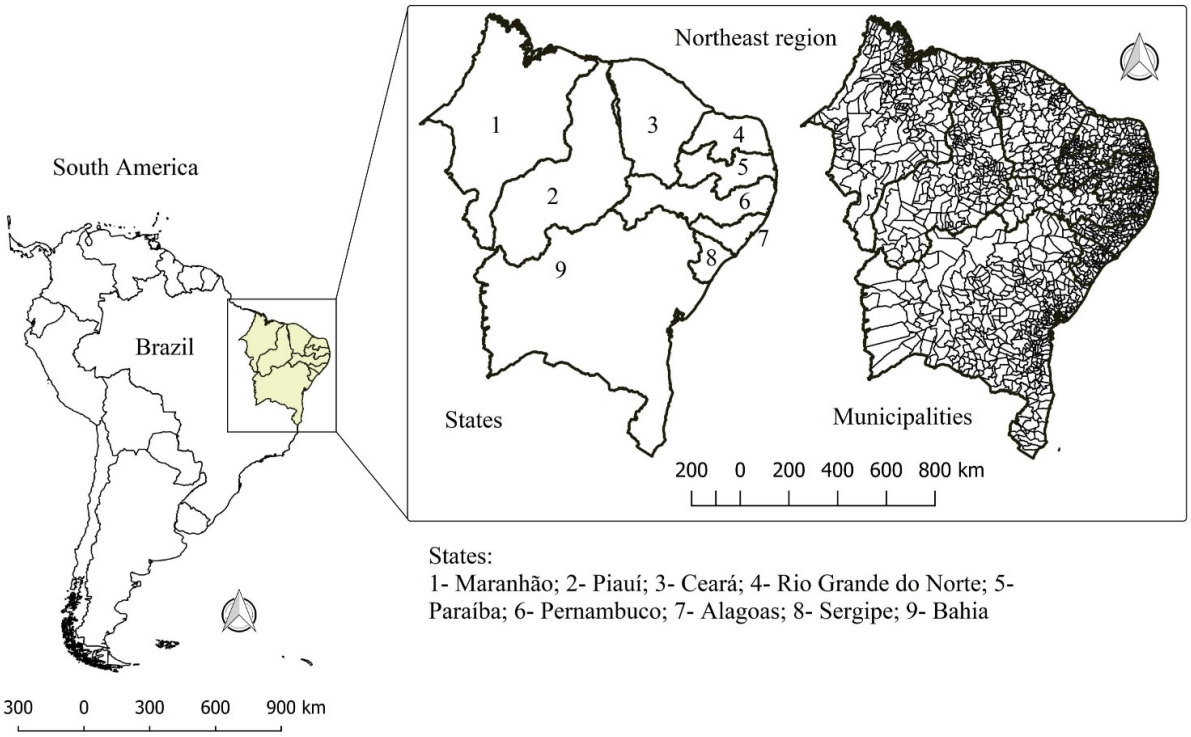


Figure 1. Spatial distribution of congenital syphilis by municipality of residence. Northeast, Brazil, 2008-2015.

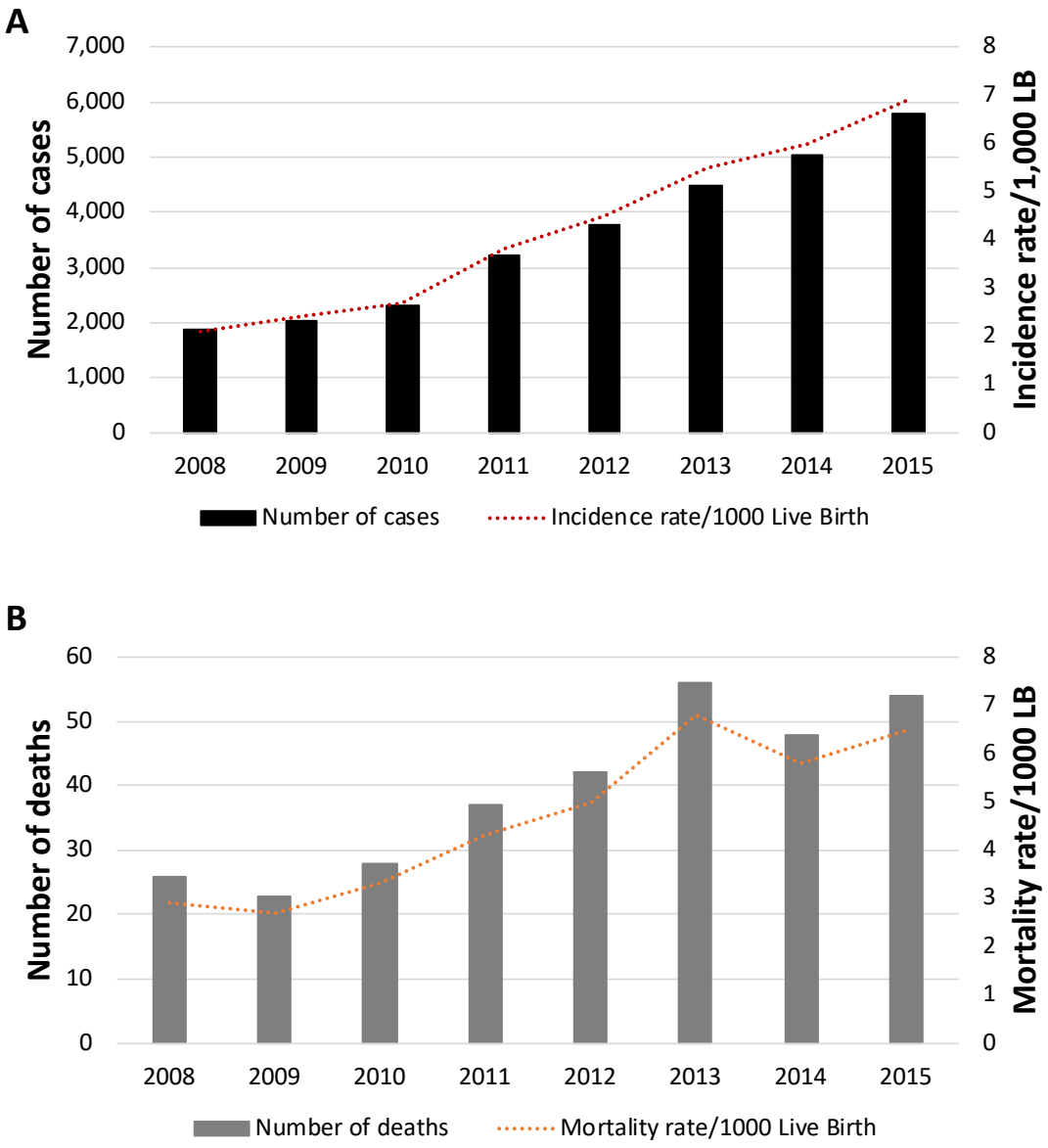
Suplementar Material

Supplementary Figure 1. Geographic localization of the study area. Northeast, Brazil.



States:
1- Maranhão; 2- Piauí; 3- Ceará; 4- Rio Grande do Norte; 5- Paraíba; 6- Pernambuco; 7- Alagoas; 8- Sergipe; 9- Bahia

Supplementary Figure 2. Temporal evolution of incidence and mortality rates due to congenital syphilis. Northeast, Brazil, 2008-2015.



Supplementary Table 1. Demographic characteristics of cases of congenital syphilis. Northeast, Brazil, 2008-2015.

Variable	N (%)
Maternal age (in years)	
10-14	335 (1.2)
15-19	6445 (22.5)
20-29	14,698 (51.3)
30-39	5699 (19.9)
≥ 40	589 (2.1)
Unknown	858 (3.0)
Ethnicity	
White	2456 (8.6)
Black	1996 (7.0)
Asian	84 (0.3)
Mixed	21606 (75.5)
Indigenous	68 (0.2)
Unknown	2414 (8.4)
Maternal education	
Illiterate	677 (2.4)
Incomplete primary education	3453 (12.1)
Complete primary education	1793 (6.3)
Incomplete secondary education	8831 (30.8)
Complete secondary education	1910 (6.7)
Incomplete high school	2395 (8.4)
Complete high school	2786 (9.7)
Incomplete graduate	147 (0.5)
Complete graduate	102 (0.4)
Not applied	137 (0.5)
Unknown	6393 (22.2)
Time of diagnosis of maternal syphilis	

Pre-natal care	10745 (37.5)
Delivery/curettage	12523 (43.8)
Postpartum	3671 (12.8)
Not tested	181 (0.6)
Unknown	1504 (5.3)
Maternal syphilis treatment	
Adequate	991 (3.5)
Inadequate	15537 (54.2)
Not performed	8704 (30.4)
Unknown	3392 (11.9)
Treatment of the mother's partner	
Yes	3301 (11.5)
No	18.555 (68.9)
Unknown	6768 (23.6)
Antenatal care	
Yes	21078 (73.6)
No	5158 (18.1)
Unknown	2388 (8.3)

Supplementary Table 1 Continued

Age of the child at the time of diagnosis	
<7 days	27468 (96.0)
7 to 27 days	552 (1.9)
28 to 364 days	514 (1.8)
1 year	39 (0.1)
2 to 4 years	29 (0.1)
5 to 12 years	22 (0.1)
Final classification	
Recent congenital syphilis	25899 (90.5)

Late congenital syphilis	97 (0.3)
Abortion due to syphilis	1047 (3.7)
Stillborn due to syphilis	1581 (5.5)

Supplementary Table 2. Spatial clusters of the incidence of congenital syphilis. Northeast, Brazil, 2008-2015.

Cluster	Geographic location	No. of municipalities	No. of cases	Incidence rate per 1,000 live births
1	West of Maranhão	7	299	6.80
2	West of Piauí and east of Maranhão	5 (4 in Piauí e 1 in Maranhão)	509	4.01
3	Ceará	33	5627	5.32
4	Rio Grande do Norte	66	2014	5.90
5	Metropolitan region of Recife and *mata paraibana*	40 (25 in Pernambuco and 15 in Paraíba)	5795	5.62
6	East of Alagoas and south of Pernambuco	39 (2 in Pernambuco and 37 in Alagoas)	2223	7.07
7	Northeast of Bahia and Sergipe	62 (1 in Bahia and 61 in Sergipe)	2048	7.71
8	Metropolitan area of Salvador/Bahia	6	2158	4.81
9	South of Bahia	7	288	5.98

Supplementary Table 3. Spatial Lag Model between Congenital Syphilis incidence and social indicators, Northeast, Brazil, 2008-2015.

Social Determinants	Coefficient	z-Statistic	P-value
Block 1. Social Vulnerability Index - Global			
Social Vulnerability Index	-0.003	-0.034	0.972
Block 2. Social Vulnerability Index (SVI) - domains			
SVI Urban infrastructure	4181.25	0.2385	0.811
SVI Human capital	-0.0001	-0.0099	0.992
SVI Income and work	-0.0001	-0.0189	0.811
Block 3. SVI Urban infrastructure			
% of the population living in households with inadequate water supply and poor sanitation	21,7789	13,3218	<0.001
% of the population living in households without rubbish collection services	6,4261	3,1734	0.001
% of households with a per capita income below half the Brazilian minimum salary of households with workers who spend more than 1 h commuting to work	16,6334	10,8889	<0.001
Block 4. SVI Human capital			
Infant mortality rate	14,4527	7,01013	<0.001
% of 0- to 5-year-old children not attending preschool	-1,2569	-0,5697	0.568
% of 6- to 14-year-old children not attending school	31,3298	16,4623	<0.001
% of 10- to 17-year-old children/adolescent not attending school	-20,2562	-8,7738	<0.001
% of mothers heading households or without primary education who have at least one child <15 years of age	-28,4842	-11,7116	<0.001
Illiteracy rate among minors >15 years-old	15,2612	6,2108	<0.001
% of children living in households where none of the residents have completed elementary school	16,0865	8,287	<0.001
% of 10- to 17-year-old females with children; and the percentage of children living in households where none of the residents has completed primary education	3,7490	1,7449	0.081
Block 5. SVI Income and work			

of families with a per capita household income below half the minimum wage	30,2753	22,8746	<0.001
Population unemployment rate of 18 years and over	22,6787	19,733	<0.001
% of people aged ≥18 years without complete elementary school and in informal occupation	-3,2828	-2,2818	0.0225
% of people in households with per capita income below half the minimum wage and dependent on the elderly	-11,4933	-9,0978	<0.001
Activity rate of people from 10 to 14 years of age.	-10,266	-6,3210	<0.001