

Temporal trend and spatial distribution of syphilis in pregnancy and congenital syphilis in Goiás, Brazil, 2007-2017: an ecological study

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Abstract

Objective: To analyze temporal trend and spatial distribution of syphilis in pregnancy and congenital syphilis in Goiás State, Brazil, between 2007 and 2017. **Methods:** This was an ecological time series and spatial distribution study with data obtained from the Notifiable Health Conditions Information System. Prais-Winsten Regression was used to analyze indicator trends by health macro-region. Descriptive spatial analysis was performed to verify case distribution in three different years in the period. **Results:** Between 2007 and 2017, 7,679 cases of syphilis in pregnancy and 1,554 congenital syphilis cases were reported. A rising trend was found in the rates of syphilis in pregnancy (annual percent change [APC] = 18.0 – 95% confidence interval [95%CI] 15.3;20.8) as well as in congenital syphilis rates (APC=16.8 – 95%CI 20.1;33.8); and a 326% increase in the number of municipalities with a congenital syphilis incidence rate >0.5/1,000 live births. **Conclusion:** Growth in syphilis in pregnancy and congenital syphilis detection rates was identified, as was growth in the number of municipalities reporting cases.

Keywords: Syphilis; Syphilis, Congenital; Pregnant Women; Time Series Studies; Geographic Mapping.

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Introduction

Syphilis has been a serious health problem since it was discovered in 16th century Europe until the present day when prevalence is now estimated as being 6.3 million new cases (2016 data), including 0.69% pregnant women, resulting in 200,000 cases of perinatal death.^{1,2}

Congenital syphilis can have serious repercussions for the health of the fetus, hence the global efforts to address it, expressed in the definition of the goal of reducing vertical transmission of syphilis to rates below 0.5 cases per 1,000 live births.

In Brazil, surveillance of congenital syphilis and syphilis in pregnancy has been compulsory since 1986 and 2005, respectively, by means of official notification on the Notifiable Health Conditions Information System (SINAN).^{3,4} Congenital syphilis can have serious repercussions for the health of the fetus, hence the global efforts to address it, expressed in the definition of the goal of reducing vertical transmission of syphilis to rates below 0.5 cases per 1,000 live births.^{1,5}

Guidance documents on management of syphilis care and public policies to combat syphilis have been prepared in recent years. A review which analyzed guidelines for management of syphilis in pregnancy in World Health Organization (WHO) member countries found 64 guidelines with recommendations on management of syphilis in pregnant women published over a 15-year period.⁶

Following the same global perspective of the fight against syphilis and other maternal and infant health conditions, the Stork Network (*Rede Cegonha*) was set up in Brazil in 2011 to provide actions and services with the aim of offering humanized health care during pregnancy, childbirth and the postpartum period and ensuring the right to safe childbirth and healthy child growth and development. Implementation of *Rede Cegonha* led to expansion of prenatal screening for syphilis, by means of decentralizing rapid tests to Primary Health Care services so as to increase detection capacity.⁷

With the aim of strengthening the policy on preventing mother and child morbidity and mortality

in Brazil, the federal and state governments have organized a variety of actions included in the Agenda for a Rapid Response to Syphilis in Health Care Networks, which was launched in 2017.⁸ Also in 2017, the state of Goiás set up its Mother-to-Child Syphilis Transmission Investigation Committee by means of Ordinance GAB/SES-GO No. 512, dated June 12th 2017, with the aim of investigating, planning and monitoring congenital syphilis prevention and control actions in the state.^{9,10}

Diverse studies have been published showing the evolution of congenital syphilis and syphilis in pregnancy on the national scenario, in the states and in the Federal District. It should be noted that studies on the regions of individual states will be important references for comparison when evaluating recent strategies proposed, identifying progress achieved and persistent challenges, with the aim of eliminating syphilis at the local level.

The objective of this study was to assess the temporal trend and spatial distribution of syphilis in pregnancy and congenital syphilis in Goiás State, Brazil, between 2007 and 2017.

Methods

This was an ecological time series and spatial distribution analysis study, intended to assess the temporal trend and geographical distribution of the detection rate of syphilis in pregnancy and the incidence rate of congenital syphilis in Goiás state in the Midwest region of Brazil between 2007 and 2017.

According to the 2015 demographic census, Goiás' population was estimated as being 6,778,772 inhabitants, distributed over 246 municipalities which are divided into five health macro-regions: Northeast, Center-West, Center-North, Center-Southeast and Southwest. Goiás' demographic density is 17.6 inhab. per km², and its human development index is 0.73, coming in 8th place among the Brazilian states.¹¹

The criteria for notifying syphilis in pregnancy and congenital syphilis underwent changes during the period studied. The previous definition was used up until 2014;¹² while new criteria were used in the period from 2015 until 2017. Among the changes, absence of information on treatment of the mother's sex partner ceased to be one of the criteria for notifying congenital syphilis, so that only cases of sex partners known not to have been treated for syphilis continued to be notified;

apart from that, the definition of syphilis in pregnancy now includes women detected in the postpartum period.¹³

The population of this study was comprised of all cases of syphilis in pregnancy and congenital syphilis notified in the municipalities of Goiás state between 2007 and 2017.

The indicators analyzed were the detection rate of syphilis in pregnancy and the incidence rate of congenital syphilis for Goiás as a whole and for each of the state's macro-regions.

The calculations were performed as follows:

- a) Detection rate of syphilis in pregnancy (per 1,000 live births)

Numerator – number of notified cases of syphilis in pregnancy, in a given year of diagnosis and place of residence.

Denominator – total number of live births born to mothers resident in the same place in the same year. Multiplication factor: 1000

This indicator measures annual frequency of syphilis in pregnancy and guides planning of epidemiological surveillance actions for syphilis control.¹³

- b) Incidence rate of congenital syphilis (per 1,000 live births)

Numerator – number of notified cases of congenital syphilis in infants under one year old, in a given year of diagnosis and place of residence.

Denominator – total number of live births born to mothers resident in the same place in the same year.

Multiplication factor: 1,000

This indicator measures risk of occurrence of new cases of congenital syphilis due to vertical transmission of *Treponema pallidum*.¹³

Cases of syphilis in pregnancy and congenital syphilis in Goiás were retrieved from the SINAN system, while the number of live births was retrieved from the Live Birth Information System (SINASC). Both information systems are available on the website of the National Health System Information Technology Department (DATASUS).

The data were analyzed using the Stata statistical software, version 14.0, and the TerraView program to produce maps. With regard to the temporal trend element of the study, the analysis units were individual years in the period 2007-2017, thus comprising 11

points on the time series; trend was examined for Goiás as a whole and for each of the state's macro-regions. Prais-Winsten linear regression with robust variance was used. In the regression analysis, the dependent variable 'Y' was considered to be the indicators analyzed (syphilis in pregnancy detection rate and congenital syphilis incidence rate), while the independent variable 'X' was taken to be the year of the study, based on the following linear regression equation:¹⁴

$$\text{Log}(Y_t) = \beta_0 + \beta_1 X$$

Where:

Log(Y_t) corresponds to the value

β₀ is the constant or intercept

β₁ is the coefficient of linear trend

X is the residual

The trends were classified as rising, falling or stationary. Trends were considered to be stationary in cases in which the p-value was not significant in the trend analysis. In cases in which p was significant, the trend was considered to be rising if β₁ was positive, while the trend was considered to be falling if β₁ was negative.

Statistical significance was established by the regression *t* test. P-values <0.05 were considered to be statistically significant.

Once the trend analysis had been performed, spatial analysis of the syphilis in pregnancy detection rates and congenital syphilis incidence rates was then undertaken. The unit of analysis for spatial distribution was comprised of Goiás' 246 municipalities. Spatial analysis was conducted using data from three of the years comprising the study period: 2007 (first year), 2012 (midway) and 2017 (last year), with the aim of verifying spatial evolution in the period. When analyzing congenital syphilis, the municipalities were classified as having rates <0.5 or ≥0.5 cases of congenital syphilis per 1,000 live births. This was done to check whether or not the Millennium Development Goal was being met, i.e. reduction of congenital syphilis incidence to below 0.5/1,000 live births.⁵ When analyzing the syphilis in pregnancy detection rate, the municipalities were classified taking the mean rate in Goiás in the period (<5.0 or ≥5.0/1,000 live births). Presence of global spatial dependence in each year analyzed was verified using Moran's global index.¹⁵ This method measures the correlation of a variable with itself in space, varying between -1 and +1: values close to zero indicate spatial randomness, while positive values indicate positive

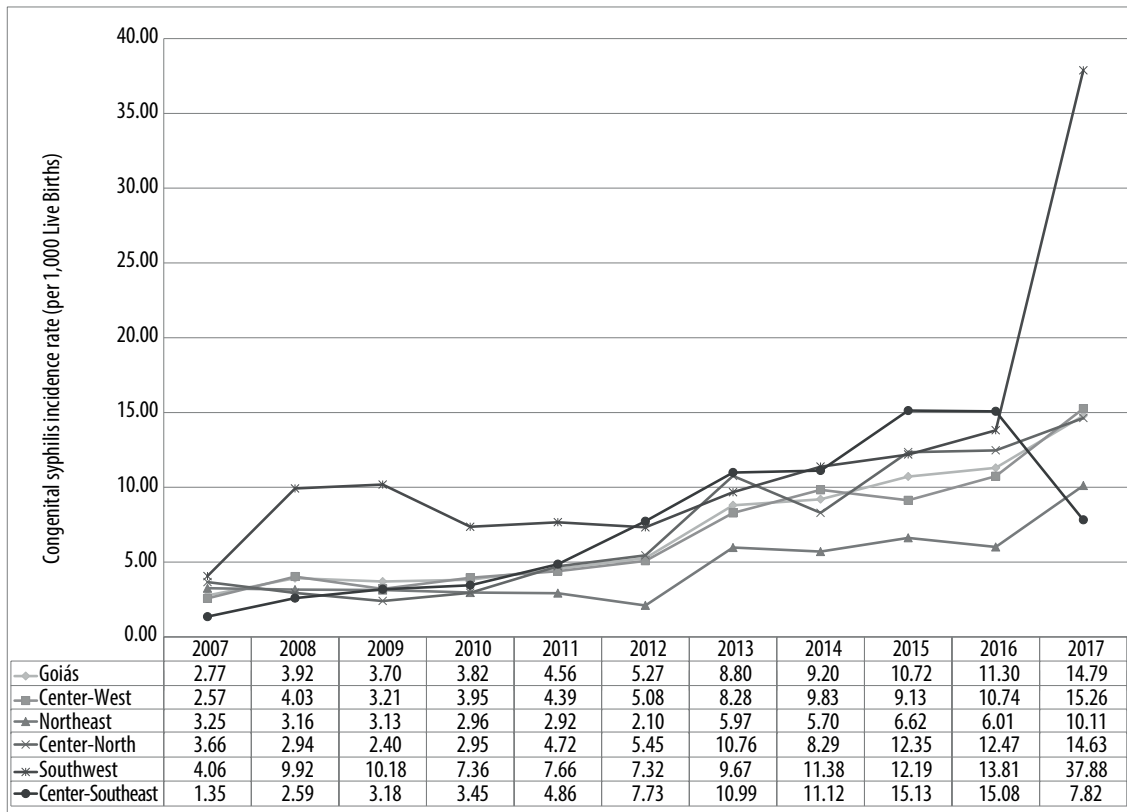


Figure 1 – Syphilis in pregnancy detection rate by health macro-region, Goiás state, 2007-2017

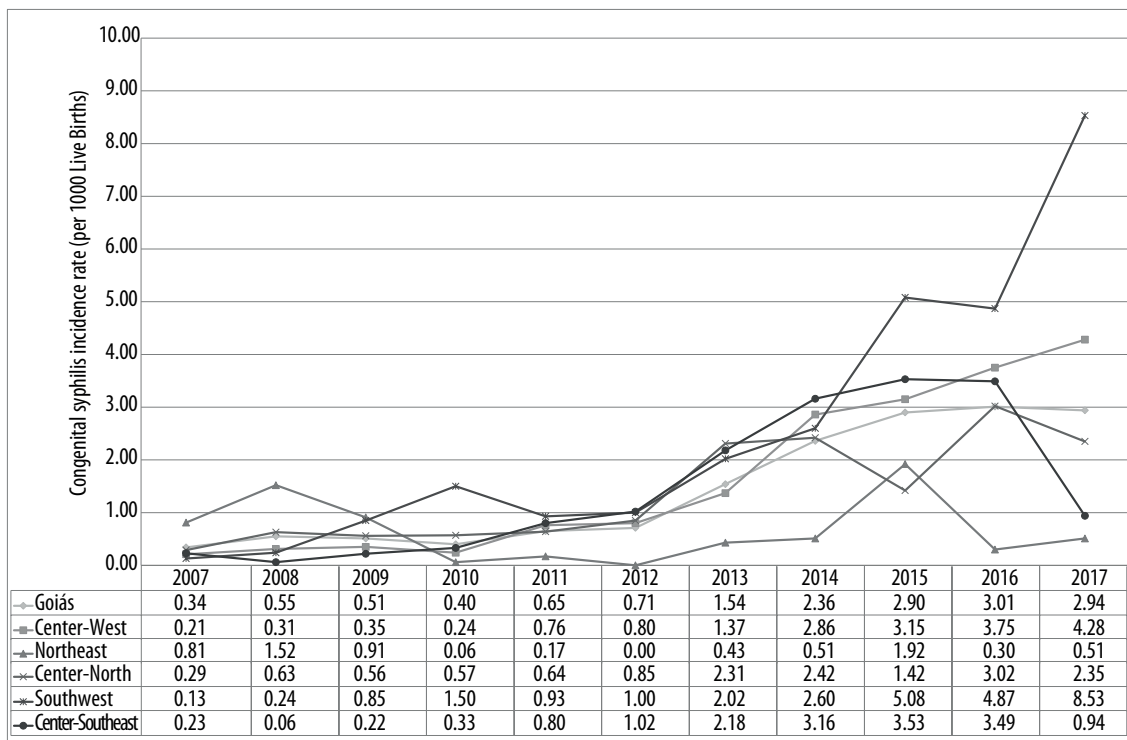


Figure 2 – Congenital syphilis incidence rate by health macro-region, Goiás state, 2007-2017

spatial autocorrelation and negative values indicate negative spatial autocorrelation. The spatial analyses were conducted using ArcGIS, version 10.5.

Results

Between 2007 and 2017, 7,679 cases of syphilis in pregnancy and 1,554 cases of congenital syphilis were notified in Goiás. Taking the state as a whole, an increase was found in the syphilis in pregnancy detection rate, from 2.8 in 2007 to 14.8/1,000 live births in 2017 (Figure 1). The congenital syphilis incidence rate rose 0.3 in 2007 to 2.9/1,000 live births in 2017, as shown in Figure 2.

Table 1 shows the analysis of the trends of the syphilis in pregnancy detection rate and the congenital syphilis incidence rate between 2007 and 2017. A statistically significant rising trend was found in the syphilis in pregnancy detection rate in the state of Goiás (APC 18.0% – 95%CI 15.3;20.8), as well as in each of the state’s health macro-regions: Center-West (APC 18.2% – 95%CI 14.7;21.8), Northeast (APC 12.1% – 95%CI 5.8;18.6), Center-North (APC 20.0% – 95%CI 12.4;28.0), Southwest (APC 15.4% – 95%CI 3.2;29.2) and Center-Southeast (APC 22.2% – 95%CI 5.3;41.8).

A statistically significant rising trend was also found for the congenital syphilis detection rate for Goiás state as a whole between 2007 and 2017: APC 16.8% – 95%CI 20.1;33.8. A rising trend was also found for the majority of the state’s health macro-regions (APC 40.2% – 95%CI 33.1;47.6), Center-North (APC 24.1% – 95%CI 17.6;31.0), Southwest (APC 45.5% – 95%CI 31.4;61.0) and Center-Southeast (APC 33.4% – 95%CI 4.3;70.7). In the Northeast macro-region, the congenital syphilis detection rate was stationary: APC -1.4% – 95%CI -17.7;18.3 (Table 1).

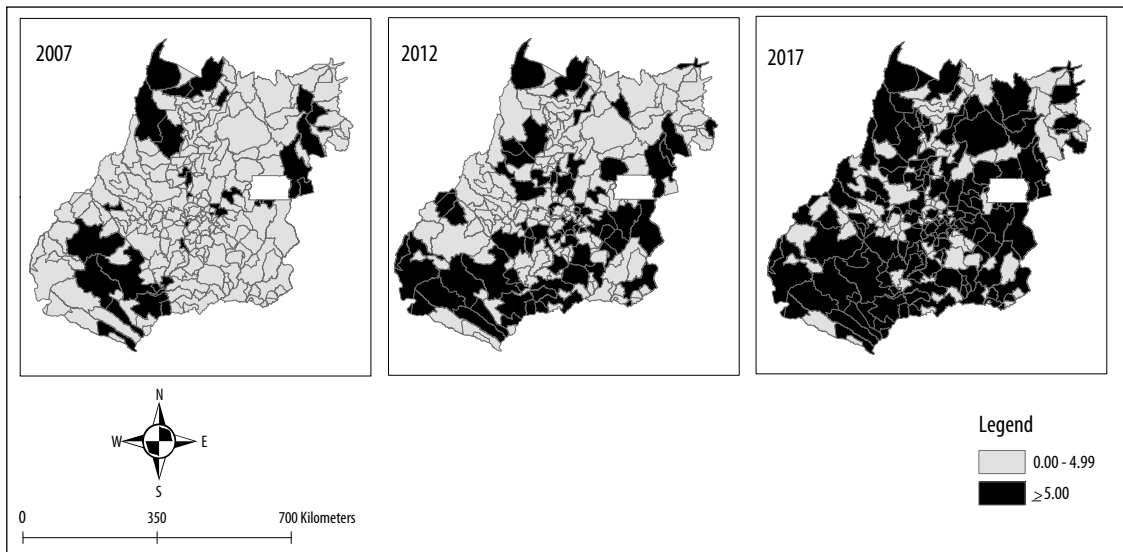
Figure 3 shows the analysis of the spatial distribution of the syphilis in pregnancy detection rates in 2007, 2012 and 2017. The municipalities were classified according to the mean syphilis in pregnancy detection rate in the period analyzed (≥ 5.0). An increase was found in the syphilis in pregnancy detection rate between the three years selected from the time series. In 2007, 26 (10.6%) municipalities had detection rates ≥ 5.0 cases per 1,000 live births in Goiás. In 2012, this had risen to 67 (27.2%) municipalities and to 147 (59.8%) municipalities in 2017. According to Moran’s global index, calculated for the years 2007 ($I = 0.006$; $p = 0.390$), 2012 ($I = 0.075$; $p = 0.060$) and 2017 ($I = 0.010$; $p = 0.280$), the municipalities were

Table 1 – Syphilis in pregnancy and congenital syphilis detection rate trends by health macro-region, Goiás state, 2007-2017

Goiás health macro-region	APC ^a (95%CI ^b)	p-value ^c	R2 ^d	Trend
Syphilis in pregnancy detection rate				
Center-West	18.2 (14.7;21.8)	<0.001	0.938	↑
Northeast	12.1 (5.8;18.6)	0.002	0.569	↑
Center-North	20.0 (12.4;28.0)	<0.001	0.812	↑
Southwest	15.4 (3.2;29.2)	0.021	0.415	↑
Center-Southeast	22.2 (5.3;41.8)	0.016	0.336	↑
Goiás	18.0 (15.3;20.8)	<0.001	0.925	↑
Congenital syphilis incidence rate				
Center-West	40.2 (33.1;47.6)	<0.001	0.933	↑
Northeast	-1.4 (-17.7;18.3)	0.872	0.001	–
Center-North	24.1 (17.6; 31.0)	<0.001	0.855	↑
Southwest	45.5 (31.4; 61.0)	<0.001	0.867	↑
Center-Southeast	33.4 (4.3;70.7)	0.030	0.498	↑
Goiás	16.8 (20.1;33.8)	<0.001	0.812	↑

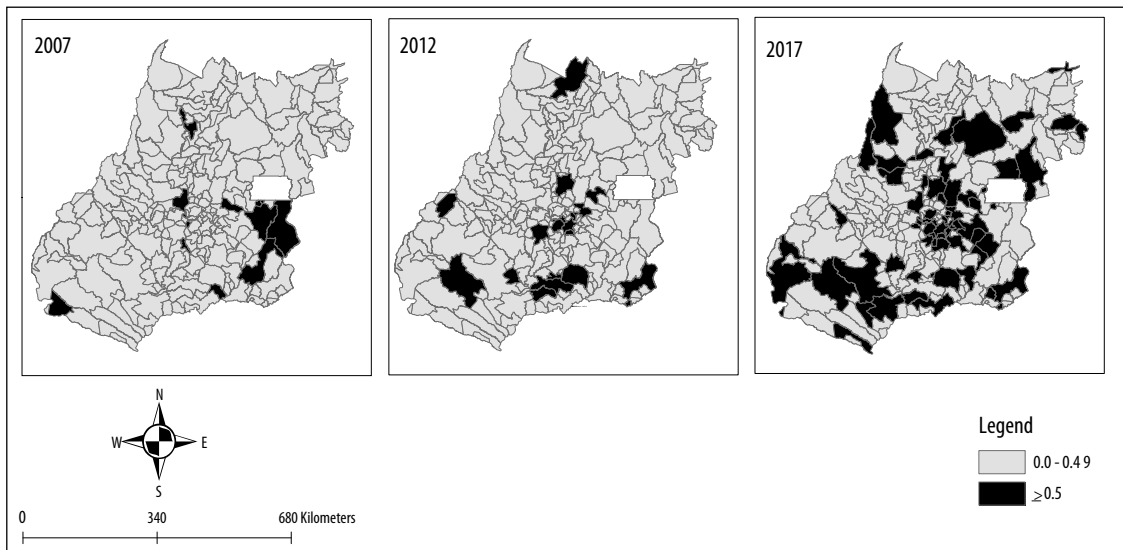
a) APC: annual percent change (%).
 b) 95%CI: 95% confidence interval.
 c) Statistical significance established by the Prais-Winsten t regression test.
 d) R2: coefficient of determination.

Notes:
 ↑ Rising
 ↓ Falling
 – Stable



Epidemiological data source: Notifiable Health Conditions Information System (SINAN) and Live Birth Information System (SINASC).
Cartographic data source: Brazilian Institute of Geography and Statistics (IBGE).

Figure 3 – Spatial distribution of the syphilis in pregnancy detection rate (per 1000 live births), by municipalities of Goiás state, 2007 (A), 2012 (B) and 2017 (C)



Epidemiological data source: Notifiable Health Conditions Information System (SINAN) and Live Birth Information System (SINASC).
Cartographic data source: Brazilian Institute of Geography and Statistics (IBGE).

Figure 4 – Spatial distribution of the congenital syphilis incidence rate (per 1000 live births), by municipalities of Goiás state, 2007 (A), 2012 (B) and 2017 (C)

spatially independent which regard to the change in the incidence rate, indicating absence of spatial clusters of syphilis in pregnancy in Goiás.

Figure 4 shows the analysis of the spatial distribution of the congenital syphilis incidence rates also in 2007,

2012 and 2017. The analyses highlight the increase in the number of municipalities with a congenital syphilis incidence rate ≥ 0.5 cases per 1,000 live births, over the period between the three years selected. In 2007, 15 (6.0%) municipalities had rates higher than the

millennium goal for congenital syphilis elimination, increasing to 18 (7.3%) in 2012 and 64 (26.0%) in 2017. The evolution of Moran's global index in 2007 ($I = -0.015$; $p = 0.450$), 2012 ($I = -0.019$; $p = 0.230$) and 2017 ($I = 0.079$; $p = 0.070$) shows that the municipalities were spatially independent with regard to the change in the incidence rate, indicating absence of spatial clusters of congenital syphilis in Goiás.

Discussion

The number of municipalities notifying cases and the occurrence of syphilis in pregnancy and congenital syphilis in the state of Goiás increased between 2007 and 2017. This increasing trend in these conditions over the years is in line with the growth in syphilis in pregnancy in Brazil as a whole, which increased from 2.3 cases in 2007 to 17.2 cases/1,000 live births in 2017, as did the congenital syphilis incidence rate, which increased from 1.9 to 8.6 cases/1,000 live births in the same period.¹³

A limitation of this study is the use of secondary data derived from passive notification of cases of syphilis in pregnancy and congenital syphilis, which may represent only part of existing cases. Another issue to be highlighted relates to changes in the notification criteria over the time series and its possible influence on case notification. Moreover, the possibility exists of the number of congenital syphilis cases being overestimated, given that confirmation of vertical transmission of syphilis only occurs when the child has been followed up for 18 months from birth, with nontreponemal testing at 1,3 and 6 months old, and treponemal testing at the end of this period once maternal antibodies have disappeared.⁹

The growth in the rates seen over the years shows that Goiás state and its health macro-regions have been getting further away from the goal for reducing congenital syphilis to levels below 0.5 cases per 1,000 live births.⁵ This reality of increased cases of syphilis in pregnancy and congenital syphilis also occurs in other Brazilian states and it is important to emphasize the alert as to the epidemiological scenario of syphilis in Brazil.^{16,17}

The increasing trend in congenital syphilis cases, however, cannot be interpreted as a condition peculiar to some Brazilian states or to Brazil as a whole. An international study revealed a picture of high rates in countries in South America, Africa and Asia,

highlighting the need to scale up access to syphilis screening to above 90% of pregnant women, with the same percentage of treatment for those diagnosed as being infected.^{2,18,19}

Goiás' Northeast health macro-region showed a stationary trend for congenital syphilis in the period studied. This result should be analyzed with caution, as it is a region containing part of the municipalities surrounding the Federal District, characterized by an intense flow of people commuting daily from their homes to the Brazilian capital every day to work or even to use health services there. A study showed that 31.6% of congenital syphilis cases notified in the Federal District referred to children who lived in the state of Goiás, so that the stationary trend of congenital syphilis cases in Northeast Goiás could reflect underreporting in state records rather than an improvement in congenital syphilis indicators in that health macro-region.²⁰

In particular the Southwest health macro-region showed a substantial increase in syphilis in pregnancy and congenital syphilis rates at the end of the time series. This result can be explained, at least in part, by the late implementation of the *Rede Cegonba* in the region, which only happened in 2015. As such, it is possible to assume that this increase reflects improvements in identifying pregnant women with syphilis and improvements in the performance of mother and child health condition surveillance systems.²¹

Although there are well-established protocols and the possibility of low-cost treatment, there has been a progressive increase in the rates of syphilis in pregnancy and consequently in congenital syphilis rates as well.¹³ One of the main causes of failing to prevent vertical transmission of syphilis in pregnancy is late or inadequate treatment of syphilis during prenatal care, apart from sociodemographic and behavioral aspects involving women's exposure to infection.²²

A study conducted in the Suzhou region of China identified immigration as a new component of risk of mother and fetus exposure to syphilis. The finding of this Chinese study serves as an alert to several countries, including Brazil, where immigration has increased in recent years.¹⁸

According to Brazilian Health Ministry recommendations, and similarly to those of other countries, ideal treatment for syphilis in pregnancy is based on prescribing benzathine penicillin G, with doses phased according to the stage of the disease.^{8,12}

Treatment should be started as soon as diagnosis is obtained, since the earlier and more complete the treatment, the lower the chance of vertical transmission: prevention rates of between 90% and 98.2% have been achieved when these interventions took place up to the 28th week of pregnancy. Early diagnosis and adequate treatment are powerful tools for effective prevention of vertical transmission of syphilis and, therefore, all efforts should be made in this direction.^{2,23}

In Brazil, irregularity in the supply of penicillin for congenital syphilis prevention is a factor that may have contributed to the increase in cases of infection between 2014 and 2016, when there was a lack of raw materials for it to be manufactured, culminating in penicillin stockouts in health centers throughout the country.²⁴ A study that analyzed scarcity of benzathine penicillin worldwide, identified lack of this drug in at least 39 countries, drawing attention to the difficulty in achieving global targets for eliminating congenital syphilis unless pitfalls in benzathine penicillin supply are resolved, which implies taking into consideration variables such as supply, production, demand and distribution of this unique and universally adopted antibiotic for treating and preventing mother-to-child syphilis transmission.²⁵

In Brazil, despite improvement in prenatal care coverage over the years, only 20% of pregnant women receive adequate care and, in many municipalities, fewer than 50% of them are tested for syphilis during pregnancy, despite Health Ministry recommendations, thus resulting in later diagnosis and making timely treatment infeasible.²⁶

Another factor possibly associated with the increase in syphilis cases is low Primary Health Care coverage. A study conducted in Goiás found increased coverage of the Family Health Strategy (FHS) between 2007 and 2014, although when analyzing by (coverage) strata, municipalities with FHS coverage below 75% had a greater increase in the number of congenital syphilis cases in that period. Moreover, the correlation between the increase in FHS coverage and occurrence of syphilis in pregnancy and congenital syphilis was found to be positive for nearly all years.¹⁹

Notwithstanding improvements seen in the surveillance network with regard to disease notification, they are still insufficient to have an impact on syphilis case reduction. It is important to invest in tools that improve information sharing within the health care

network, seeking agility in identification of infected pregnant women and their immediate treatment. Congenital syphilis prevention programs tested in countries that used rapid testing for syphilis detection and ensured immediate treatment, drastically reduced their vertical transmission rates.²³

In addition to concern about the increase in the number of municipalities with cases of syphilis in pregnancy and congenital syphilis, other important issues need to be rethought in the context of Health for addressing this disease, including (i) failure to treat sex partners, (ii) inadequate use of protection and prophylaxis methods and (iii) incipient sexual and reproductive health actions.²⁷ They are factors that contribute to occurrence of reinfection and maintaining the chain that spreads infection, and may exert even more pressure on the health system, given the need for support structure and specialized care for congenital and late alterations arising from exposure to *T. pallidum*.^{23,28}

One of the pillars of congenital syphilis prevention consists precisely of ample and diverse public health service structure, to improve surveillance, monitor trends, identify outbreaks of the disease and diagnose shortcomings in care, so as to enable targeted interventions. Specific programs, focused on more susceptible populations – female immigrants, women deprived of liberty, with multiple partners, illegal drug users, for instance –, can also be considered as being strategic for controlling congenital syphilis, through implementation of improved access and reaching these populations.²³

In conclusion, this study found a rising trend in syphilis in pregnancy and congenital syphilis in the decade analyzed, as well as spatial expansion of infections in Goiás, revealing a departure from the goal of eliminating vertical transmission of syphilis in the state.

Authors' contributions

Nunes PS, Guimarães RA, Rosado LEP took part in the study concept and design, data analysis and interpretation and drafting the manuscript. Turchi MD, Aquino EC and Marinho TA contributed to relevant critical reviewing of the intellectual content of the manuscript. All the authors have approved the final version of the manuscript and declare themselves to be responsible for all aspects thereof, including the guarantee of its accuracy and integrity.

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