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Spatiotemporal pattern of the incidence of tuberculosis and associated factors

Padrão espaçotemporal e fatores associados à incidência de tuberculose: um estudo ecológico

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ABSTRACT: ***Objective:*** To analyze the spatiotemporal pattern of tuberculosis incidence and its associated factors. ***Methods:*** Ecological study, which used tuberculosis notifications during 2001-2017 and as units of analysis the municipalities of the state of Ceará of the Notifiable Diseases Information System. Time pattern analysis techniques and geographically weighted regression were used. ***Results:*** The gross incidence rate in the state reached a peak of 226.1/100 thousand inhabitants with a significant decrease of 1.9% per year (95%CI -3.0–-0.7). The main clusters were identified in Fortaleza and its metropolitan region, as well as in the Sobral region. The socioeconomic indicators that were associated with the incidence were: occupation in the agricultural sector and services, population in households with bathrooms and running water and vulnerable to poverty. ***Conclusion:*** There was a significant decrease in the incidence of the disease in the state of Ceará. The spatial clusters were mostly located in areas with high population and the indicators most related to the formation of spatial clusters were related to employment/income, housing and vulnerability.

Keywords: Tuberculosis. Incidence. Spatial analysis. Epidemiology.

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RESUMO: ***Objetivo:*** Analisar o padrão espaçotemporal da incidência da tuberculose e seus fatores associados. ***Métodos:*** Estudo ecológico, que utilizou as notificações de tuberculose ocorridas no período 2001–2017 nos municípios do estado do Ceará e registradas por meio do Sistema de Informação de Agravos de Notificação. Foram utilizadas técnicas de análise de padrão temporal e regressão geograficamente ponderada. ***Resultados:*** A taxa de incidência bruta no estado atingiu valor máximo de 226,1/100 mil habitantes, com decréscimo significativo de 1,9% ao ano (intervalo de confiança — IC95% -3,0–-0,7). Os principais *clusters* foram identificados em Fortaleza e sua região metropolitana, assim como na região de Sobral. Os indicadores socioeconômicos que se mostraram associados à incidência foram: ocupação no setor agropecuário e serviços, população em domicílios com banheiro e água encanada e vulneráveis à pobreza. ***Conclusão:*** Houve diminuição significativa da incidência da doença no estado do Ceará. Os *clusters* espaciais estiveram localizados, majoritariamente, em áreas com alto adensamento populacional, e os indicadores que mais se associaram à formação dos aglomerados espaciais estiveram relacionados a emprego/renda, moradia e vulnerabilidade.

Palavras-chave: Tuberculose. Incidência. Análise espacial. Epidemiologia.

INTRODUCTION

Tuberculosis (TB) is an infectious disease of importance to global public health. A report by the World Health Organization (WHO) points out that about 10 million new cases of TB have been reported on a global scale. Of these, more than one million people died, making the disease one of the ten leading causes of death worldwide[1]. In addition, Brazil was the only country on the American continent listed among the 30 with a high burden of TB and occupied the first position on the continent, with 32% of cases[2,3].

Although Brazil is among the countries with the most cases in the world, from 2011 to 2016 there was a decrease in this number, with a lower coefficient presented in 2016, with 34.4 cases per 100,000 inhabitants. On the other hand, in the period 2017-2019, there is an increase in incidence in the country[4]. In Ceará, the decrease occurred in the period from 2003 to 2017, with an average reduction of 1.9% per year. As a result, the state had the lowest incidence ever recorded: 34.1 cases per 100,000 inhabitants in 2017[5].

TB is associated with some population groups considered more susceptible to illnesses[6]. Furthermore, studies indicate that TB is also related to socioeconomic conditions observed in so-called developing countries, such as situations of poverty, malnutrition, poor sanitary conditions, and high population density[7].

In view of the above, the importance of using epidemiological methods of spatial analysis in health[8] for accurate knowledge of places that present clusters of high rates of TB is highlighted. Thus, this study aimed to analyze the spatiotemporal pattern of TB incidence and its associated factors.

METHODS

This is an ecological study, which used the municipalities of the state of Ceará as units of analysis. It has 184 municipalities and the eighth largest population in the country, estimated at 9.13 million inhabitants. Of the 27 states of the federation, Ceará has the 11th highest population density, with 56.76 inhabitants per km^2 and a nominal monthly per capita income of R$ 850[9].

The data in this study are of the secondary type and were obtained from the Secretary of Health of the state of Ceará (*Secretaria da Saúde do Estado do Ceará* – SESA), after prior authorization to access the information. The records contain information on TB from the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* – SINAN).

This investigation comprises all cases reported as "new TB cases" during the period from January 1st, 2001 to December 31st, 2017 in the state of Ceará. Thus, it had a population of 60,614 new TB cases during the period. The mean incidence of TB in the period studied was calculated for each municipality using the average number of cases in the numerator and the population of the central year (2009) as the denominator, multiplied by 100 thousand inhabitants. Population data from the municipalities of Ceará were obtained from the website of the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* – IBGE).

Initially, the characteristics of the cases were described, including the number of missing data in each variable. After that, the analysis of the temporal trend of the incidence of TB was conducted through regression by inflection points. This analysis indicates whether one or more line segments should be added in a linear regression to indicate any change in time trend, which refutes the null hypothesis that no points should be added. Its results are possible to estimate the annual percentage change (APC) of the studied trend, as well as its 95% confidence interval (95%CI) and its statistical significance[10].

In their results, significantly positive APC indicate a growth trend of the phenomenon studied, and negative APC indicate a decrease in the trend. Non-significant APC values indicate a stationary trend. Thus, the model was adjusted assuming that the number of inflection points could vary from zero to two, which means a straight line or a line with two or three segments. The 5% significance level was established in all trend analyses of all times[10].

For the spatial analysis, the thematic map of the average gross incidence of TB in the municipalities of Ceará was initially created, and then these rates were smoothed using the local empirical Bayesian method to reduce the instabilities caused by the gross rates. The application of this method is necessary since it generates rates closer to reality, as it considers not only the rate value of a given municipality, but weights it in relation to those that border it through a spatial proximity matrix. For the construction of the matrix, the criterion of contiguity was taken into account, assigning the value 1 to municipalities that have common borders and 0 to municipalities that do not share borders.

For the identification of spatial clusters of TB, two different methods were used, though with the same purpose. The first concerns the spatial autocorrelation function, through the global and local Moran index. The global index was used to test the spatial dependence hypothesis and provide an overall measure of association for the entire study area. Once the presence of global spatial autocorrelation was verified, the local Moran index (Local Index Spatial Analysis — LISA) was applied to verify the presence of spatial aggregates and quantify the degree of spatial association in each municipality of the sample set, considering it if $p<0.05$.

The results of the local Moran index are presented using the Moran and the Lisa maps. The first one allows you to graphically visualize the degree of similarity between neighbors and is represented by four quadrants: in red are the municipalities with high rates and that are close to municipalities with equally high rates (high/high spatial pattern); in green are the municipalities that have low rates and that are surrounded by municipalities that also have low rates (low/low spatial pattern); the municipalities in yellow (high/low spatial pattern) and blue (low/high spatial pattern) represent areas of epidemiological transition and that exhibit high and low rates, but are very close to municipalities that have low and high rates, respectively[8].

Aiming at detecting spatial clusters, as well as areas that present greater risk for TB, a purely spatial scan analysis, called Scan statistic, was carried out. For the identification of clusters, the discrete Poisson model was adopted, which considers that the number of events in each area is proportional to the size of the population[8], as well as the following requirements: no geographical overlap of clusters, maximum cluster size equal to 50.0% of the exposed population, clusters in a circular shape and 999 replications. The Scan statistic also made it possible to calculate the relative risk (RR) in each municipality in Ceará; those with values >1 have a relative risk for TB that is higher than the risk for Ceará as a whole.

To identify the influence of socioeconomic indicators on TB incidence, the ordinary least squares (OLS) regression method was used. The indicators used were: Theil L index, Gini index, unemployment rate, employed with complete high school education, employed in the agricultural sector, employed in the mining sector, employed in the manufacturing industry, employed in the construction sector, employed in the commerce sector, employed in the service sector, population in households with toilet and running water, population in households with density >2, municipal human development index (MHDI), illiteracy rate, and vulnerable to poverty. All these indicators were taken from the Atlas of Human Development in Brazil[11].

Initially, these variables were entered into a multiple linear regression (OLS) model. The variables were selected using backward selection, while the presence of multicollinearity was assessed using the variance inflation factor (VIF). Those that remained in the final OLS regression model ($p<0.05$) were also inserted into a geographically weighted regression (GWR) model, since it is able to analyze phenomena that vary according to the area in which they are studied. The GWR generated a regression coefficient for each of the 184 municipalities in the state, as a social indicator can act as a risk factor in a certain territory and a protective factor in another[12]. The result of the GWR regression was presented in

the format of two thematic maps for each socioeconomic indicator: one for the value of the regression coefficient and another that represents the statistical significance, considering $p<0.05$.

The calculation of the local empirical Bayesian rate and the spatial autocorrelation test was performed using the TerraView 4.2.2® software, while the purely spatial scan analysis was performed using the SaTScan 9.6® software. The non-spatial regression OLS was performed in the software Stata 12® and the spatial regression GWR, in the software GWR4.0.9®. All maps were produced in QGIS 2.4.17® software.

The project of which this study is a part was sent for ethical consideration by the State University of Ceará, being approved under protocol No. 2.687.046.

RESULTS

From 2001 to 2017, 60,614 new TB cases were reported in Ceará. Table 1 shows that the cases had a median age of 38 years (interquartile range — IQR 25–52) and were mainly male (62.1%; n=37,649). Most self-declared brown (74.2%; n=38,859), had less than high school education (78.4%; n=34,101), and lived in urban areas (84.1%; n=49,134).

The mean incidence of the disease in the period was 28.6/100 thousand inhabitants, with the lowest incidence occurring in 2017 (34.1 cases per 100 thousand inhabitants) and the highest in 2003 (61.2 cases per 100 thousand inhabitants). The analysis of the temporal pattern of TB incidence in the studied period showed a significant decrease of 1.9% per year (95%CI -3.0–-0.7; p=0.003). Furthermore, the regression did not insert any inflection points, which means that there was no change in trend over time, which is explained only by a line segment (data not shown in tables or graphics).

In Figure 1A, it is possible to observe that all municipalities in Ceará registered at least one case of TB during the period 2001–2017, since there are no municipalities with a rate equal to zero. The gross incidence rate in the state reached a maximum value of 226.1/100 thousand inhabitants. With the smoothing of the gross rates by the local empirical Bayesian method (Figure 1B), it is possible to perceive a more apparent spatial pattern, with the aggregation of municipalities with higher rates close to Fortaleza and Sobral. It is noteworthy that the municipality of Itaitinga, in the metropolitan region of Fortaleza, had the highest gross (226.1/100 thousand inhab.) and Bayesian (168.1/100 thousand inhab.) rates of TB.

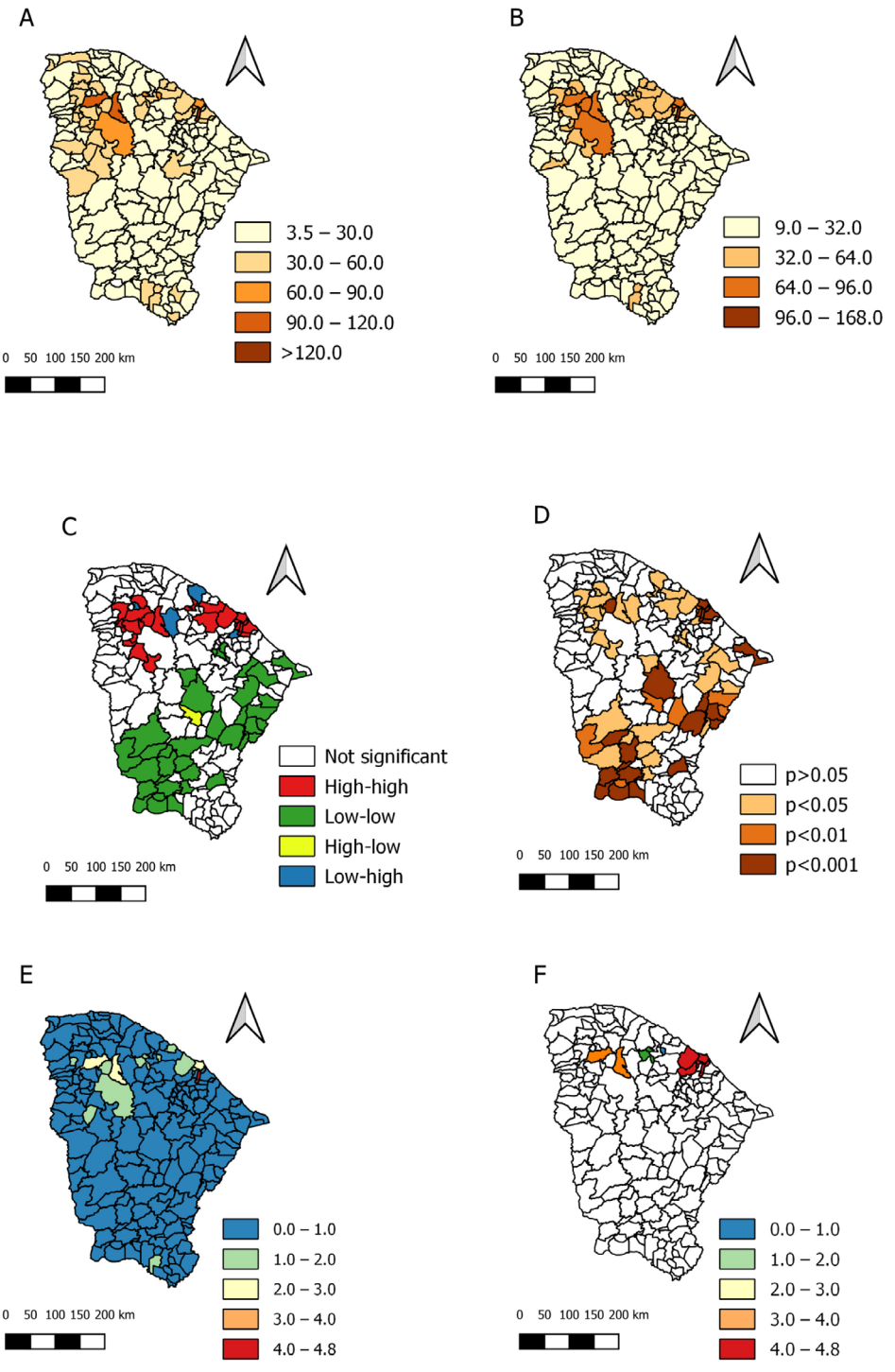
In the spatial autocorrelation analysis, the global Moran index was equal to 0.32 (p=0.01), indicating positive spatial autocorrelation. Through this index, spatial clusters can be identified (Figure 1C), in which the high-high pattern of distribution is found in Fortaleza and its metropolitan region, as well as in the region of Sobral, an important municipality in the countryside of the state. The main low-low clusters are concentrated in the Sertão Cearense and Sul Cearense mesoregions. The Lisa map (Figure 1D) shows the intensity of statistical significance of the spatial clusters pointed out by the Moran map.

Table 1. Sociodemographic characteristics of reported tuberculosis cases. Ceará, Brazil, 2001–2017 (n=60,614).

Sociodemographic characteristics	n	%
Age (median)	38	25–52
Gender*		
Male	37,649	62.1
Female	22,951	37.9
Race/color†		
Caucasian/White	8,768	16.7
Black	3,941	7.5
Yellow	617	1.2
Brown	38,859	74.2
Indigenous	212	0.4
Education‡		
Illiterate	7,785	17.9
Incomplete elementary school	9,899	22.7
Complete elementary school	2,947	6.8
Incomplete middle school/high school	10,952	25.2
Complete middle school/high school	2,518	5.8
Incomplete High school	4,440	10.2
Complete High school	3,220	7.4
Incomplete Higher education	456	1.0
Comeplte Higher education	1,285	3.0
Are of residence§		
Urban	49,134	84.1
Rural	9,113	15.5
Periurban	397	0.4

The following cases were excluded, due to missing or "ignored" data: *14 cases; †8,217 cases; ‡17,112 cases; §1,970 cases.

Using the Scan technique, it was possible to identify that the population of Itaitinga has 4.8 times more risk of contracting TB when compared to the population of other municipalities in Ceará (Figure 1E). The technique also made it possible to identify four statistically significant ($p<0.05$) clusters of TB in the state. The most likely cluster, that is, the one that has the lowest probability of having occurred by chance (in red), was composed of Fortaleza



A: raw incidence, B: Bayesian incidence, C: Moran map of raw incidence, D: Lisa map of raw incidence, E: Relative risk of TB; F: purely spatial clusters of TB.

Figure 1. Spatial distribution of tuberculosis incidence in the state of Ceará. Ceará, Brazil, 2001–2017.

and five municipalities in its metropolitan region (Caucaia, Maranguape, Maracanaú, Eusébio, and Itaitinga), whose RR was of 2.75 (Figure 1F). The characterization of the other clusters can be found in Table 2.

Table 3 shows the significant socioeconomic indicators in the OLS and GWR regression models. In the first model, the value of the Moran index (I) was 0.077 (p=0.04) and it could explain 27.0% of the outcome variation. The significant value indicates that the regression residuals have a spatial pattern and that the incidence can be explained by the neighbors of the neighbors. When applying the GWR regression, 32.0% of the model was explained and I=0.04.

Table 3 presents the final OLS non-spatial regression and GWR spatial regression models for the factors associated with TB incidence in Ceará. The socioeconomic indicators that were associated with the incidence of TB were: employed in the agricultural sector,

Table 2. Characteristics of the clusters identified by the Scan technique. Ceará, Brazil, 2001–2017.

Cluster	Cluster radius	Number of municipalities	Population	Likelihood ratio	Relative risk	p-value
1	28.30 km	6	953,316	7,659.01	2.75	<0.001
2	0 km	1	61,676	633.70	2.15	<0.001
3	10.88 km	2	23,728	29.78	1.36	<0.001
4	0 km	1	4,151	9.58	1.49	0.01

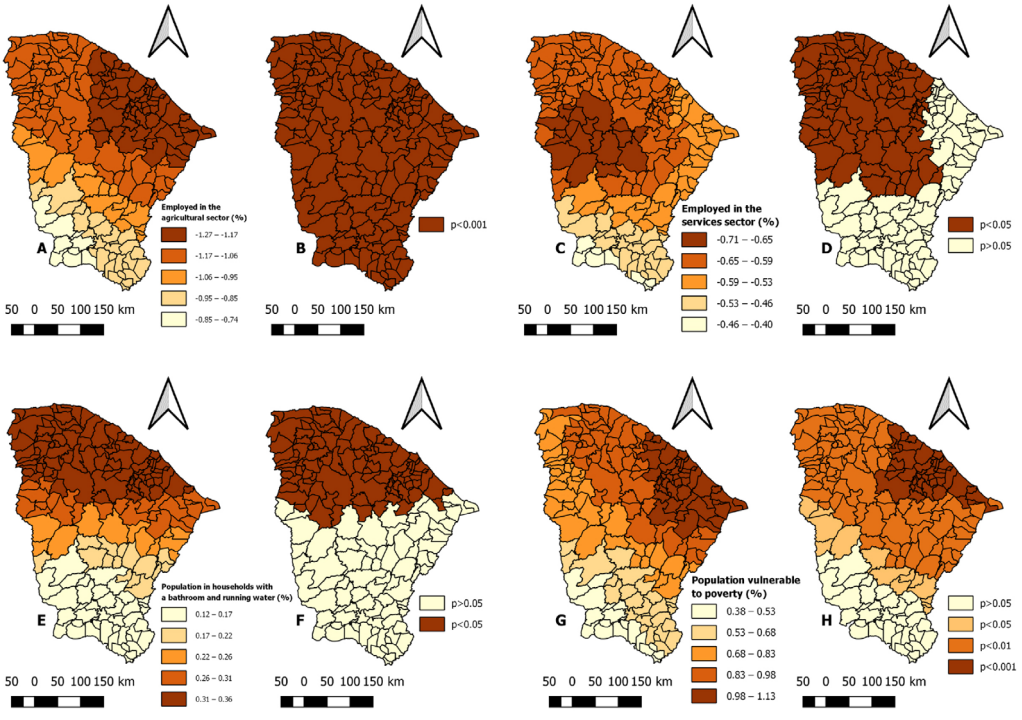
Table 3. Final ordinary least squares and geographically weighted regression models for factors associated with tuberculosis incidence in Ceará, Brazil, 2001–2017.

Socioeconomic indicators	OLS model*			GWR model†	
	Coefficient	Standard error	p	Coefficient	Standard error
Employed in the agricultural sector (%)	-1.12	0.15	<0.001	-1.08	0.13
Employed in the services sector (%)	-0.6	0.27	0.02	-0.58	0.06
Population in households with a bathroom and running water (%)	0.27	0.12	0.03	0.26	0.08
Population vulnerable to poverty (%)	0.88	0.27	0.002	0.82	0.19

*OLS: ordinary least squares; †GWR: geographically weighted regression.

employed in the service sector, population in households with bathroom and piped water, and population vulnerable to poverty. These did not show multicollinearity, as the global VIF was equal to 2.2, which indicates a low correlation between predictors.

Figure 2 shows the thematic maps derived from the GWR regression results. It was found that, throughout the state, there was a significant negative relationship ($p<0.01$) between the percentage of people employed in the agricultural sector and the incidence of TB (Figures A and B). Likewise, in the north, northwest and Sertão Cearense mesoregions, a significant negative correlation ($p<0.05$) was also found between the percentage of people employed in the service sector and the incidence of TB (Figures C and D). In addition, an increase in the incidence of TB was observed as the percentage of people living in houses with bathroom and piped water increased ($p<0.05$), mainly in northern Ceará (Figures E and F). Finally, a positive correlation ($p<0.05$) was observed between the percentage of those vulnerable to poverty and the incidence of TB, especially in municipalities far from the capital and metropolitan region (Figures G and H).



GWR: geographically weighted regression.

Figure 2. Geographically weighted regression of factors associated with tuberculosis incidence in municipalities in the state of Ceará, Brazil, 2001–2017.

DISCUSSION

The present study identified the predominance of male individuals, of mixed race, with low education, and residing in the urban area. In addition, a decrease in the incidence of TB was demonstrated in the period 2001–2017. On the other hand, the spatial analysis explained the formation of clusters in populous municipalities in the state of Ceará. Finally, the indicators that showed a relationship with the incidence of TB were: employed in the agricultural sector, employed in the service sector, population in households with bathroom and piped water, and population vulnerable to poverty.

The characterization of the population of this study shows that the disease remains in a specific segment. It is identified that, regardless of the region studied, illness from TB has social aspects in common throughout Brazil[13-17]. These findings help to perpetuate an image of TB linked to neglected and now stigmatized segments, which lack effective actions to eliminate the disease.

As for the temporal pattern, it was identified that there was a significant decrease in the incidence of TB in the period 2001-2017. This drop may be associated with the implementation of the Millennium Goals, which enabled the development of national programs to reduce the incidence of TB. However, this result is currently far from the recommended by the goals of the Sustainable Development Goals (SDG) and the End of TB strategy (End TB). These seek a 95% decline in the incidence of the disease[18,19]. Thus, it is pointed out that actions such as health education, the active search for contacts, the screening of people living with the human immunodeficiency virus (HIV/Aids) and the treatment of cases of latent TB infection are fundamental to achieve the goals set[20].

Regarding the analysis of the spatial pattern of TB incidence, spatial clusters located in Fortaleza and in municipalities in its metropolitan region were revealed, with the highest risk observed in Itaitinga, a municipality that houses a prison in its territory. It is known that this factor may have influenced the formation of clusters, since populations deprived of liberty are at 31 times greater risk of becoming ill with TB than the general population[19]. In addition, the most likely cluster is located in the state capital and in municipalities in its metropolitan region, which shows the characteristic of urban agglomerations, constant transit of people between municipalities and areas with greater poverty.

As for the indicators associated with the incidence of the disease, this study found that it decreases when the proportion of employees in the agricultural and service sectors increases. This is due to the fact that the state is one of the most economically diversified in the Brazilian Northeast[21]. Thus, it is believed that these activities showed a significant relationship as they are two of the most important in the state, employing a large portion of the population of Ceará[21]. Thus, the inverse relationship of being employed in this sector helps to highlight the importance of work/income in the incidence of TB.

In addition, this study observed that the incidence of TB was positively associated with the percentage indicator of the population living in households with a bathroom and running water. This relationship proved to be significant in regions where there are large urban agglomerations, including the capital Fortaleza and Sobral, which is an important municipality

in the interior of the state. Through this finding, it can be hypothesized that, since the disease is located in large centers, it is also possible to find households with greater access to toilets and running water. Thus, these two variables may present a correlation; however, it is important to emphasize that the greater social exclusion, the result of the strong stratification between the classes of society, is one of the main points to be verified regarding the social determinants of health, facilitating the transmission of TB in the community[22,23].

Finally, the incidence of TB also showed a relationship with the proportion of people vulnerable to poverty. Thus, this population is more prone to exposure to the bacillus, especially in the periphery or in places of agglomeration and home density in municipalities[14]. In this sense, it is understood that this variable can mediate the relationship between other variables with the incidence of TB, such as the lack of basic health services, malnutrition, inadequate nutrition, drug abuse, lack of access to information, and low education[24]. However, it is important to emphasize that these are just hypotheses to be tested in future studies, especially those that consider the individual level in order to avoid the ecological fallacy.

In this context, given that TB is a disease related to poverty, income transfer programs are effective in reducing social inequalities and the consequent incidence of diseases. In the case of Brazil, the *Bolsa Família* Program can be mentioned as a successful strategy in this regard.

Although the mechanism by which the cash transfer contributes to the reduction of the incidence of TB has not been investigated, the impact on the social determinants that influence the number of new cases is undeniable[25]. Therefore, even knowing that the program alone is not enough to contribute to the reduction of the incidence of TB, an approach that promotes the reduction of poverty and the expansion of social protection would accelerate progress toward the goals recommended by the End TB strategy[25,26].

This study has some limitations. First, the ecological design makes it impossible to establish relationships at an individual level. In this case, results must be considered only at the municipal level to avoid the ecological fallacy (inference about individual phenomena based on aggregated observations). In addition, the use of secondary databases presents incompleteness and variable information quality, which can make it difficult to interpret the results. It is known that the systems used in data collection do not have a primary character for research, but were adapted to this reality. In this sense, variables that could be considered important in this study were not included because this type of research can only use those that are maintained by the system. Even so, the results of this research are important for the epidemiological characterization of the incidence of TB and associated factors. Finally, it is suggested to carry out studies like the present one, with other designs or methods of analysis, to estimate the same effect at an individual level and strengthen the causal hypothesis.

The results of this investigation show the spatiotemporal dynamics of TB incidence in recent years. The variables related to those employed in the agricultural sector, employed in the service sector, population in households with bathroom and piped water, and population vulnerable to poverty were associated with the incidence of the disease. These findings denote the economic and social character related to the disease. Thus, focusing on these areas can help break the chain of TB transmission.

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