Cogitare Enfermagem

ORIGINAL ARTICLE

SPATIO-TEMPORAL PATTERN AND FACTORS ASSOCIATED WITH TUBERCULOSIS MORTALITY IN A NORTHEASTERN STATE - BRAZIL

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ABSTRACT

Objective: to identify the spatio-temporal pattern of tuberculosis mortality and its related factors. Method: ecological study, using as unit of analysis the municipalities of the state of Ceará, Brazil, during the period from 2001 to 2017. Tuberculosis mortality was analyzed by temporal and spatial analysis techniques. Results: in the period, 1,513 deaths from tuberculosis were reported. An average annual increase of 15% in mortality was detected (95% Confidence Interval: 6.2 - 24.6). The indicators that most influenced mortality were life expectancy at birth (β=3.38), households with inadequate water supply and sanitation (β=-0.01) and probability of survival to 60 years (β=-2.26). Conclusion: this study evidenced the increase in the temporal pattern of tuberculosis mortality over the years. Care strategies aimed at treatment adherence and public health strategies aimed at improving the environment of the population should therefore be emphasized.

DESCRIPTORS: Tuberculosis; Mortality; Time Series Studies; Spatial Analysis; Epidemiology.

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INTRODUCTION

Tuberculosis (TB) is an important public health disease both in Brazil and worldwide[1,2,3], considered the second leading cause of death from infectious disease (surpassed by COVID-19 in 2021). It is estimated that, worldwide, in 2020 alone, about 9.9 million people became ill and 1.3 million deaths occurred due to the disease[4].

In 2014, the WHO designed the Global Strategy and Goals for TB Prevention, Care and Control, which aim to achieve three key points by 2035, namely: reducing mortality by 95.0%, reducing incidence by 90.0%, and eliminating exorbitant costs for the families of patients[5]. In Brazil, in line with the WHO goals, the National Plan for the End of Tuberculosis as a Public Health Problem was launched, which considers a reduction in TB mortality of about 10 cases/100,000 inhabitants by 2035, that is, a reduction of 4.0% to 5.0% per year[6].

Currently, mortality rates in Brazil remain high, which reinforces the severity of TB in the country. According to the Ministry of Health, 4,543 deaths from the disease were recorded in 2020, corresponding to a rate of 2.1 deaths/100,000 inhabitants. In the state of Ceará, 2,844 new cases of TB were reported in 2020, of which 171 died, corresponding to a mortality rate of 1.9 deaths/100,000 inhabitants[4].

TB mortality recurs wherever social disparities are more pronounced. Factors such as poor access to health care and food security, unemployment, poor housing, and low education levels, among others, contribute to the death of the sick individual.[6] This is particularly important when considering the socioeconomic characteristics of Ceará, since it is a state with heterogeneous population distributions, including poor sanitation, low *per capita* income, and high illiteracy rates in people aged 15 years or older. Therefore, it is vital to understand how such factors influence TB mortality to propose and develop effective actions to control mortality from the disease[3,7,8].

To understand how TB mortality occurs in time and space, it is necessary to know that geoprocessing techniques are highly effective. The authors identified few studies that use spatial analysis and evaluate TB mortality in the Northeast, thus, it is expected that the results of this investigation will be the starting point for decision-making aimed at controlling the disease and its mortality, since the areas that have clusters of deaths as well as those in which there is greater social vulnerability will be pointed out. In view of the above, this study aims to identify the spatial-temporal pattern of tuberculosis mortality and its related factors.

METHOD

This is an epidemiological study of the ecological type, which used as units of analysis the municipalities of the state of Ceará - BR. The state has the eighth largest population in the country (estimated at about 9.13 million inhabitants), distributed in 184 municipalities with a demographic density of 56.76 inhabitants per Km² (11th place in the national ranking) and a nominal monthly *per capita* income of about 850 Brazilian reals[9].

The data source used were the TB deaths recorded in the Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação SINAN), which occurred among residents of Ceará during the period from January 2001 to December 2017. The SINAN is formed by a set of variables obtained through the notification form and monitoring of the disease, including death. Thus, the variables used to characterize the individuals who died because of TB were age, race/color, education, area of residence, and type of entry (new case, relapse, reentry after abandonment, transfer, unknown)[10].

The database used for this study was made available by the State Health Secretariat of Ceará, which included all cases notified as "new TB cases" whose closing situation was "death due to TB". Thus, the study had a population of 1,513 TB deaths during the analyzed period. The crude average TB mortality rate was calculated for each municipality in Ceará during the indicated period using the average number of deaths in the numerator and the reference population of the year 2009 (middle of the period) as the denominator, multiplied by 100,000 inhabitants.

The time trend analysis was performed by means of regression by inflection points. Its results are possible to estimate the Annual Percentage Change (APC) of the trend studied, as well as its 95% confidence interval (95%CI) and statistical significance[11]. For the spatial analysis, we initially prepared the thematic map of crude TB mortality in the municipalities of Ceará and the map of mortality rates after smoothing by the local empirical Bayesian method, aiming at reducing the instabilities caused by crude rates.

For the identification of spatial clusters of TB mortality, two methods were used. The first concerns the spatial autocorrelation function of crude rates by means of the Global and Local Moran Index. The Global Moran Index was used to test the spatial dependence hypothesis and provide a general measure of association for the entire study area. Once the presence of global spatial autocorrelation was verified, the Local Index Spatial Analysis (LISA) was applied to verify the presence of spatial clusters.

Thus, from the identification of spatial autocorrelation, the clusters can be presented by means of the Moran Map and the Lisa Map. The Moran Map allows one to graphically visualize the degree of similarity between neighbors, being represented by four quadrants. In the first are the municipalities and neighbors with high rates and (High/High pattern); in the second are the municipalities and neighbors that have low rates (Low/Low pattern). The municipalities in the third (High/Low pattern) and fourth quadrant (Low/High pattern) represent areas of epidemiological transition and have municipalities and neighbors with high and low rates[12].

The second method used was purely spatial scan analysis using the Scan statistical technique. The discrete Poisson model was used, and the following requirements were applied: no geographic overlap of clusters; maximum cluster size equal to 50.0% of the exposed population; circularly shaped clusters; and 999 replications. The relative risk (RR) was calculated for each municipality in Ceará, and those with values >1 had a higher relative risk of dying from TB than the risk for Ceará as a whole.

Finally, after a vast literature review and using the epidemiological criteria, socioeconomic indicators of the Ceará municipalities were collected to support the construction of the Ordinary Least Squares (OLS) multivariate non-spatial linear regression model, to identify factors related to the average mortality rate from the disease.

The socioeconomic indicators inserted into the model were: Unemployment rate; percentage of occupied people with complete primary education; percentage of occupied people with complete secondary education; percentage of occupied people with complete higher education; average income of occupied people and all for the population aged 18 years or more. In addition, we also used the Theil Index, Gini Index, population in households with piped water (%), population in households with density > 2 (%), life expectancy at birth, people in households with inadequate water supply and sanitation (%), Municipal Human Development Index (MHDI), probability of survival to 60 years, aging rate, and vulnerable to poverty (%). All these indicators were taken from the Atlas of Human Development in Brazil (2010 census)[13].

Those that remained in the final OLS regression model were also entered into a Geographically Weighted Regression (GWR) model, since this model can 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. The result of the GWR regression was presented in the format of two thematic maps.

The calculation of the local empirical Bayesian rate and the spatial autocorrelation function were performed by the software Terra View 4.2.2. In turn, the purely spatial scan analysis was performed with the aid of the software SaTScan 9.6. Non-spatial OLS regression was performed in Stata 12 software and GWR spatial regression was performed in GWR 4.0.9 software. All maps were produced in QGIS 2.4.17 software.

The project was submitted for ethical review by the State University of Ceará and approved under protocol number 2,687,046. It is reiterated that at the time of data collection any attributes identifying the population were removed.

RESULTS

From 2001 to 2017, 1,513 deaths from TB were reported in Ceará. We observed a predominance of males (n=1,081; 71.5%) and individuals who self-declared as brown (n=1,123; 76.8%). Most deaths occurred among illiterate people (n=197; 21.6%) or with incomplete primary education (n=298; 32.6%) and were reported in urban areas (n=1,266; 86.8%). It is noteworthy that 8.7% (n=131) of the entries were as relapses and 8.5% (n=128) were by post-dropout re-entry (Table 1).

Table 1 - Sociodemographic characteristics of individuals who died from tuberculosis in Ceará in the period from 2001 to 2017 (n=1,513). Fortaleza, CE, Brazil, 2021

Caracteristics	**n**	**%**
Age (median)	50	38 – 67
Gender		
Male	1,081	71.5
Female	432	28.5
Race/color*		
White	164	11.2
Black	97	6.6
Yellow	12	0.8
Brown	1,123	76.8
Indigenous	68	4.6
Education**		
Illiterate	197	21.6
Elementary School I Incomplete	298	32.6
Elementary school I Complete	115	12.6
Elementary School II Incomplete	158	17.3
Elementary School II Complete	47	5.1
Incomplete High School	38	4.1
Complete High School	41	4.5
Incomplete Higher Education	5	0.5

Complete Higher Education	15	1.6
Housing Zone***		
Urban	1,266	86.8
Rural	186	12.7
Peri-urban	6	0.4
Type of Entry		
New Case	1,120	74
Relapse	131	8.7
Post-dropout re-entry	128	8.5
Don't know	14	0.9
Transfer	86	5.7
Post-obit	34	2.2

*We excluded 49 deaths with the race/color variable as "unknown" or "not informed".
**599 deaths for which the education variable was "unknown" or "not informed" were excluded.
***55 deaths for which the residence zone variable was "unknown" or "not informed" were excluded.
Source: Authors (2021).

During the period 2001-2008 there was significant growth of 43.5% in the APC of TB mortality (95% CI: 19.3 - 72.7; p<0.001). In the year 2008, there was the presence of an inflection point and, from then on, during the period 2008-2017 there was a decrease in mortality by 3.2% per year, however, without statistical significance (95%CI: -9.4-3.4; p>0.05). If the entire period analyzed was considered, an increase of 15.0% per year in TB mortality was detected (95% CI: 6.2 - 24.6; p<0.001) (Figure 1).

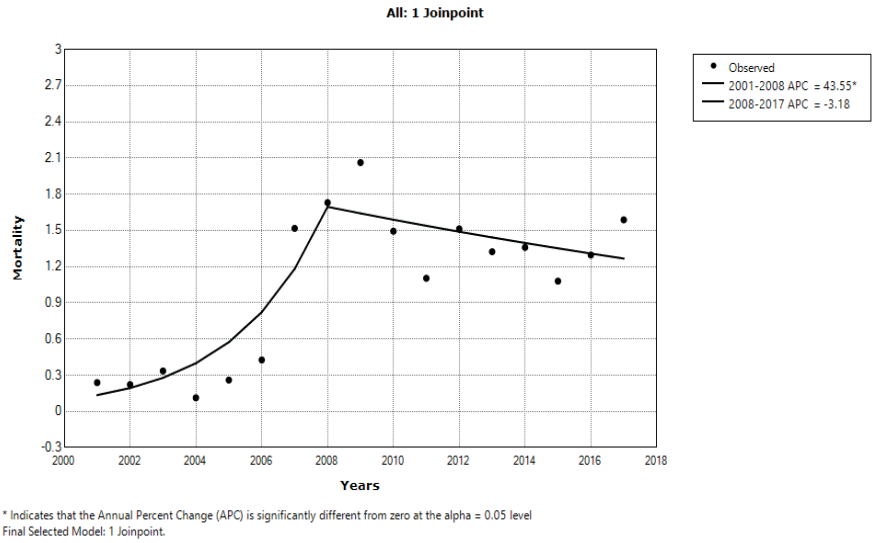

Figure 1 - Analysis of the temporal trend of TB mortality in Ceará, Brazil, 2001-2017. Fortaleza, CE, Brazil, 2021

Source: Authors (2021).

Figure 2A shows that deaths from TB were registered in 63.0% (n=116) of the Ceará municipalities, and the highest mean crude mortality rate in the state was registered in the municipality of Sobral (3.4 deaths/100,000 inhabitants). The application of the local empirical Bayesian method (Figure 2B) allowed smoothing of the rates in which the highest average Bayesian mortality rate was seen in the municipality of Forquilha (2.88/100,000 inhabitants). In addition, the municipalities with the highest mortality rates aggregated, showing more apparent spatial patterns in cities of the metropolitan region of Fortaleza and around Sobral. We also noticed that, even with the application of this method, several municipalities continued to have TB mortality rates equal to zero.

For the detection of clusters, the spatial autocorrelation test was performed using the Global and Local Moran indexes. The Global Moran Index was equal to 0.14 (p=0.02), indicating positive spatial autocorrelation. Once the Global Moran Index proved significant, we proceeded to calculate the Local Moran Index to identify spatial clusters of TB mortality (Figure 2C). According to the map, the high pattern of distribution of deaths is found in the capital city Fortaleza and in some municipalities of its metropolitan region as well as in Juazeiro do Norte, located in the south of the state, and in cities near Sobral, an important city in the interior of the state. In the LISA map (Figure 2D) it is possible to verify the intensity of statistical significance of each of the clusters identified.

The purely spatial scanning technique confirms the result obtained by the spatial autocorrelation test. It was possible to identify that a significant portion of the municipalities in Ceará have a risk of death from TB lower than the average risk for the state (in blue) (Figure 2E). In contrast, the capital city Fortaleza, Maracanaú (metropolitan region of Fortaleza) and Sobral have 3.00 to 3.69 times the risk of dying from TB when compared with the state. Through this technique, it was also possible to identify three clusters in the state (Figure 2F), the first two being significant ($p<0.05$). The primary cluster (in red), that is, the one with the lowest probability of having occurred by chance was composed of the capital city Fortaleza and municipalities in its metropolitan region, including Eusébio, Aquiraz, Pindoretama, Horizonte, Itaitinga, Pacatuba and Maracanaú with RR equal to 4.0 and coverage radius of 30.05Km².

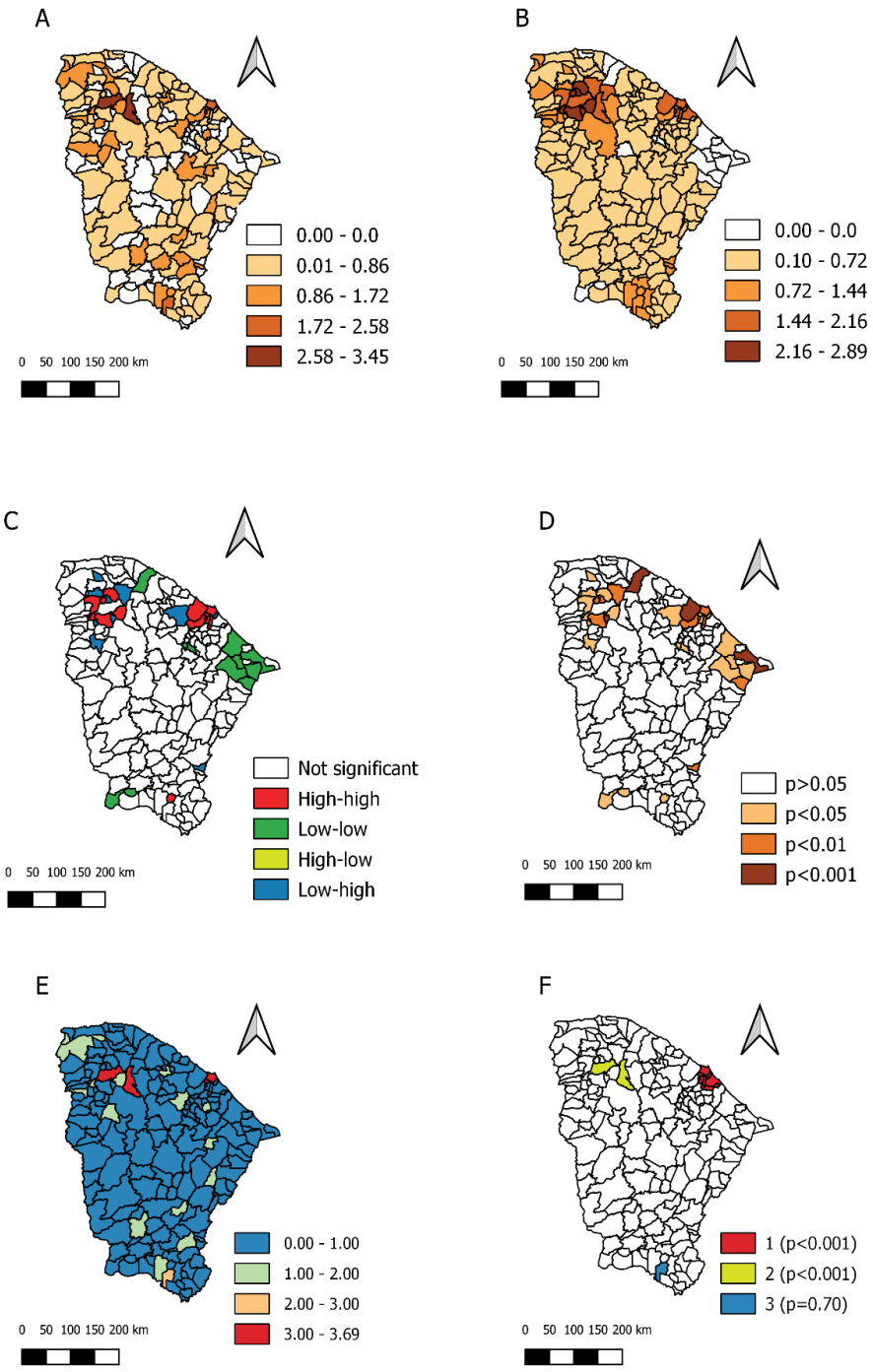

Figure 2 - Spatial distribution of crude (A) and Bayesian (B) TB mortality rates. Spatial clusters of TB described by Moran Map (C) and Lisa Map (D). Maps of the relative risk (E) and of spatial clusters (F) defined by the purely spatial Scan statistic. Ceará, Brazil, 2001-2017. Fortaleza, CE, Brazil, 2021

Source: Authors (2021).

Table 2 shows the social indicators that proved significant in the final OLS and GWR regression models. The OLS model was able to explain 24.0% of the variation in mortality. By assuming the hypothesis that space influences the outcome, the GWR spatial model was applied. Thus, once geographic space was considered in the regression calculation, it

was observed that GWR performed better than OLS, explaining 34.0% of the variation in TB mortality.

According to the GWR model, it was observed that the social indicators influencing TB mortality were higher life expectancy at birth (β=3.38); Proportion of people with inadequate sanitary supply (β=-0.01); and Probability of survival to age 60 (β=-2.26). It should be noted that, although significant, the relationship between the proportion of people with inadequate sanitation and TB mortality was very close to zero, so this result should be interpreted with caution (Table 2).

Table 2 - Final OLS and GWR regression models of socioeconomic indicators influencing tuberculosis mortality in the state of Ceará. Fortaleza, CE, Brazil, 2021

	OLS Model			GWR Model	
	Coefficients	**Standard deviation**	**p**	**Coefficients**	**Standard deviation**
Life expectancy at birth	4.58	0.79	<0.001	3.38	1.53
Households with inadequate water supply and sanitation (%)	-0.01	0.003	0.01	-0.01	0.002
Probability of survival until age 60	-2.68	0.47	<0.001	-2.26	0.89

Source: Authors (2021).

Figure 3 shows the thematic maps derived from the GWR spatial regression results. It was found that throughout the state, except in eastern Ceará, there was a significant positive relationship ($p<0.05$) between the variable life expectancy at birth and TB mortality (Maps A and B). In turn, in municipalities in the north and south of Ceará, the greater the proportion of households with inadequate supply and sewage, the lower the TB mortality rate ($p<0.05$) (Maps C and D). In a significant portion of the state, the lower the probability of survival to 60 years of age, the higher was the TB mortality rate (Maps E and F).

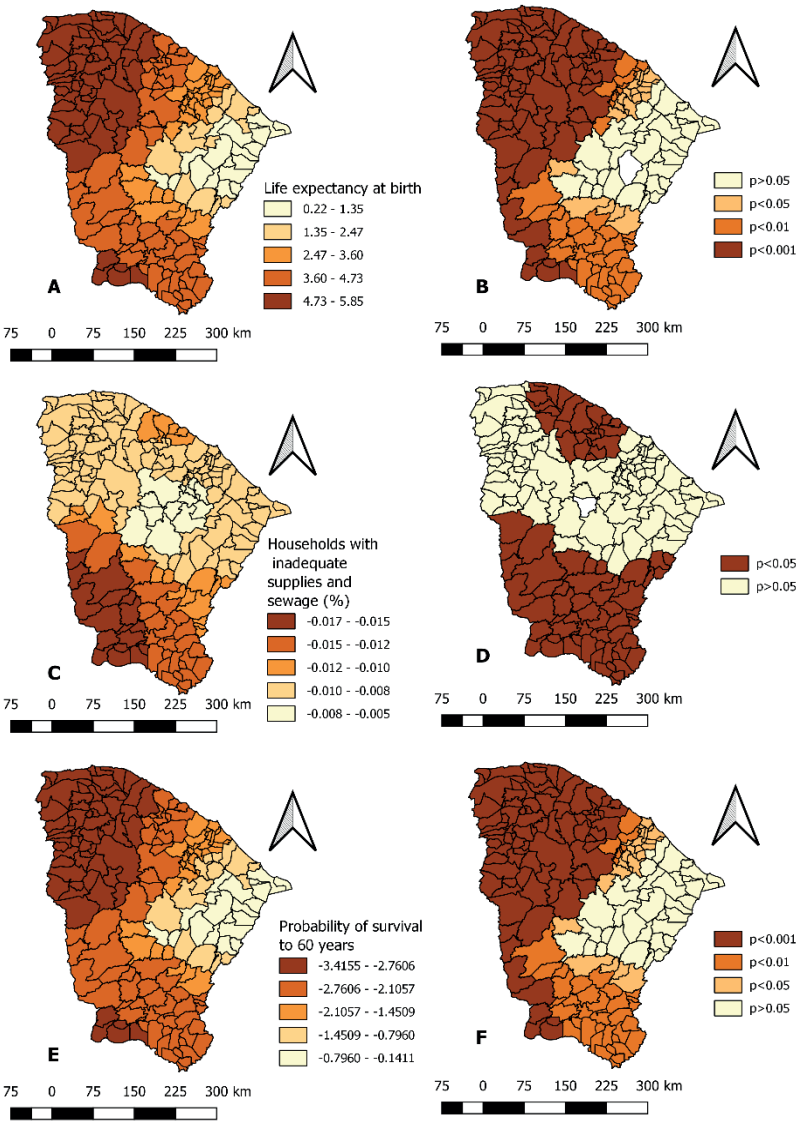

Figure 3 - GWR regression results for socioeconomic indicators influencing tuberculosis mortality in the state of Ceará, Brazil. Fortaleza, CE, Brazil, 2021

Source: Authors (2021).

DISCUSSION

Studies have shown that mortality from TB is associated with some factors exposed during the discussion that permeate populations of municipalities in the state of Ceará, Brazil, from 2001 to 2017[15]. Besides the stigmatization that the disease provides, it is known that the male population tends to distance itself from seeking treatment due to the influence of work activities in their daily lives. Moreover, the predominance of the race/color brown among those who died of TB may be directly related to most of the state's population being self-declared brown, but it may also be associated with the lower availability of health services to the black/brown population[8].

Low education, on the other hand, disfavors the understanding of the disease and the comprehension of the importance of treatment and its consequences in case of non-adherence or abandonment. Moreover, factors involving the place of residence, especially in urban areas, are directly related to mortality, since urbanization favors social stratification and the formation of slums in peripheral areas with high domiciliary densification[7,8,16,17].

Still, regarding the area of residence, this study showed that populous cities of the

state of Ceará (Fortaleza, Sobral, Juazeiro do Norte) concentrated the highest mortality rates of the disease. The higher proportion of deaths in these areas, besides the factors previously exposed, may also be related to the offer of health services. Even though they offer more opportunities for care, the high concentration of cases in these cities predisposes to an accumulation of deaths. These places are also reference points in terms of care, which promotes the displacement of patients to these cities. In addition, the patient can provide the service with an address in the large urban center and, for this reason, be included in their notification records.

Through the analysis of the temporal pattern, it was possible to observe the significant growth of TB mortality in Ceará. This data is alarming since it highlights the weaknesses of the state in the management of the disease. In this panorama, the WHO, in 2014, proposed a global strategy to combat the disease (*End TB Strategy*) that aims for a world free of tuberculosis by the year 2035. The strategy aims to address the disease as a multicausal phenomenon, which involves more than a biomedical context, since it innovates by using a person-centered approach in research and social protection of infected patients and the communities where they live[6].

By incorporating this strategy, Brazil is prioritizing the most vulnerable populations, supporting civil society, and formulating public policies that aim to eliminate TB nationally, since the country still has a high incidence rate and mortality from the disease6. Thus, if there is no reduction in the abandonment of TB treatment, it is estimated that the mortality rate in Brazil in 2035 will be reduced to 1.2/100,000 inhabitants. It is worth noting that deaths will still be observed, however, with an improvement of 5% of this indicator, as proposed by the WHO, about 7,092 deaths will be avoided in the country[18].

Among the findings of the spatial regression, it was observed that life expectancy at birth showed a positive association with the increase in TB mortality. This indicator, which is used as a synthetic measure of the quality of health and life of countries and regions, has been increasing not only in Ceará, but throughout Brazil. Programs such as the Family Health Strategy (FHS), the Program of Community Health Agents (PACS), and the Stork Network were essential for the growth of such indicator [19].

It is noteworthy that the improvement of this indicator was more evident in rural areas, where social inequality is more present[19]. However, even with the growth of an indicator that shows an improvement in the quality of life of the population, it is interesting to stress the importance of considering other indicators that more reliably explain the phenomenon of TB mortality in the state[20].

An inverse relationship was found between the proportion of households with inadequate water supply and sanitation and mortality from TB. Even though the map indicates significant areas, the results very close to zero should be interpreted with caution, since this paradoxical finding contradicts what is evidenced in the literature. It has been well established that social inequality favors the expansion of the disease as well as influences mortality, and that countries with less per capita spending on health and less access to sanitation have higher death rates from tuberculosis[17,21,22].

In this context, it is important to note that TB can be related to the social organization of countries, especially in low- and middle-income underdeveloped countries. In these countries, infectious diseases are one of the main causes of death, which demonstrates the relationship between TB and poverty. In addition to the parameter of socioeconomic deprivation, there are inadequate working conditions and difficulties in accessing health services, which reinforces the importance of the individual's environmental conditions (such as pollution and housing) for the progression of the disease[23]. Therefore, it is observed that tuberculosis can operate as a marker of social inequities in health linked to poor living conditions[24].

Finally, spatial regression also showed that the probability of living to age 60 was inversely related to deaths from TB. It is known that age over 60 years favors the

development of active TB with a high mortality rate[25,26,27] However, the findings showed that in the Northwest and the Sertões mesoregions, the lower the probability of survival expectancy until age 60, the higher the mortality from TB. It is important to note that the literature demonstrates an epidemiological transition of diseases that can change the scenario of care for infectious diseases such as TB[28,29].

This study has some limitations, such as the use of a secondary database with incomplete data on several socio-demographic variables and, especially, on the outcome of patient treatment. Even so, the results of this study are important for the epidemiological characterization of death from TB and the identification of important social predictors.

CONCLUSION

This study shows a significant increase in the temporal trend of TB mortality. As regards the spatial pattern, we observed the formation of clusters involving Sobral, the capital city of Fortaleza, and its metropolitan region. The factors associated with death from TB were life expectancy at birth; households with inadequate water supply and sanitation; and probability of survival to 60 years of age.

Thus, public health strategies targeting people with tuberculosis in areas where clusters of deaths have been identified need to be more effective. In addition, promoting adequate sanitation can lead to a decrease in the alarming mortality rates from the disease. Therefore, the importance of the environment in the TB chain can be seen.

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Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work - Sousa GJB, Maranhão TA, Pereira MLD; Drafting the work or revising it critically for important intellectual content - Sousa GJB, Cabral BVB, Silva MAS, Alves MR, Pereira MLD; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved - Sousa GJB, Pereira MLD. All authors approved the final version of the text.

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