BMJ Open

Social determinants of deaths from pneumonia and tuberculosis in children in Brazil: an ecological study

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ABSTRACT

Objective To identify the risk areas of deaths due to unspecified pneumonia and tuberculosis (TB) in children, and to identify if there is a relationship between these events with higher TB incidence and social determinants.

Methods Ecological study carried out in Brazil. All cases of TB or unspecified pneumonia deaths in children under 5 years of age reported between 2006 and 2016 were included and collected through Department of Informatics of the Unified Health System (Brazil's electronic database). The Spatial Scan Statistics was used to identify areas at higher risk of dying from this event. The spatial association was verified through the Getis-Ord techniques. The Bivariate Moran Global Index was used to verify the spatial autocorrelation between the two events. To identify the association of TB and pneumonia deaths with endemic areas of pulmonary TB and social determinants, four explanatory statistical models were identified.

Results A total of 21 391 cases of pneumonia and 238 cases of TB were identified. Spatial scanning analysis enabled the detection of four clusters of risk for TB (relative risk, RR, between 3.30 and 18.18) and 22 clusters for pneumonia (RR between 1.38 and 5.24). The spatial association of the events was confirmed (z-score 3.74 and 64.34) and spatial autocorrelation between events (Moran Index:0.031 (p=0.001)). The zero-inflated negative binomial distribution was chosen, and an association for both events was identified with the TB incidence rate (OR 5.3, 95% CI 2.85 to 9.84; OR 6.63, 95% CI 5.62 to 7.81), with the Gini Index (OR 1.78, 95% CI 1.12 to 2.82; OR 4.22, 95% CI 3.63 to4.92). Primary care coverage showed an inverse association for both events (OR 0.10, 95% CI 0.67 to 0.17; OR 0.18, 95% CI 0.15 to 0.21) for pneumonia). Finally, a family that benefited from the Bolsa Família Programme had an inverse association for deaths from pneumonia (OR 0.81, 95% CI 0.52 to 1.25).

Conclusions The results do not just contribute to reduce mortality in children, but mainly contribute to prevent premature deaths through identification of critical areas in Brazil, which is crucial to qualify health surveillance services.

Strengths and limitations of this study

► Considering that Brazil is a signatory of the 'end tuberculosis (TB)' strategy, it is relevant to highlight the mortality of unspecified pneumonia and also conduct a diagnosis of TB deaths in children in the country.

► Through a literature review considering the descriptors 'pneumonia deaths in children' and/or 'TB deaths in children' there are few studies with this approach.

► Among the limitations of the study is the use of secondary data sources that may lead to incomplete or inaccurate data.

► With the methodologies used (spatial analysis and logistic regression), it is possible to find patterns and connections between the analysed data and also to identify the social determinants of the studied events, which is crucial for solving problems and making a correct decision.

► This study may become a reference for the definition of strategies at the national level to prioritise states or municipalities for investments aimed at reducing deaths from TB and pneumonia.

INTRODUCTION

Pneumonia is the leading cause of death in children under 5 years of age, accounting for about 15% of all deaths in this age group worldwide.[1] There is evidence from clinical studies and autopsies that in regions with a high incidence of tuberculosis (TB), many cases of childhood TB are misdiagnosed as bacterial or viral pneumonia,[2] which worries health authorities around the world. This is because the diagnosis of TB in children is difficult, given the absence of tests that are considered as gold standard for the confirmation of these cases.[3]

In 2015, TB killed 210 000 children worldwide, with 80% of the deaths occurring in

children under 5 years of age in Africa and Southeast Asia. The current mortality rate for TB cases in children aged 0–5 years is 21%.[4] The American continent has a mortality rate of 8%, 2% in Europe and up to 34% in Africa, with the TB-induced mortality among untreated children being estimated at 21.9% in total and 41.6% in children under 5 years of age.[5]

Previous studies[6] have shown that TB may be a direct cause of severe pneumonia or underlying comorbidity that increases the risk of secondary bacterial pneumonia, but studies with this approach are lacking.[2] Most pneumonia tests when performed are not sensitive to TB, which may lead to under-reporting or a false impression of isolated pneumonia. Another aggravating factor is the lack of diagnostic elucidation of the pneumonia situation, which is due to the weaknesses in case of management by the health services.[2]

International initiatives to control the problem have been based on protocols such as The International Union Against Tuberculosis and Lung Disease (The Union), which was developed by WHO's Child Lung Health Programme for early diagnosis and quality of life of children, which offered a broad spectrum of diagnostic technologies and more chances of success in deciphering the type of pneumonia and its causes, whether primary or triggered by a TB infection. Also, through this initiative, better data qualification and better diagnostic elucidation have been guaranteed; however, their experience is still very isolated.[7]

According to WHO, 'social determinants of health' are defined as the conditions of the physical, social, and economic environment in which individuals are born, live and develop, and deaths from pneumonia and TB are strongly associated with these determinants.[8] The global Commission on Social Determinants of Health (2005–2008) emphasises the importance of addressing the social determinants of health, in particular for health inequities, including in children. The 2030 Agenda for Sustainable Development also underlines the importance of understanding social determinants in terms of equity in health. According to the literature, deaths from pneumonia as well as TB are strongly associated with these determinants.[8]

In addition, unspecified pneumonia (PNE) may be misdiagnosed and closely related to TB, especially to its signs and symptoms. A study[9] conducted in Brazil showed that the most common secondary cause of deaths from TB was unspecified micro-organism pneumonia. Another study[10] sought to explore the relationship between TB and other infectious diseases in the paediatric age group, and, among its findings, pneumonia is among the main related diseases.

A Global Burden Disease[11] study found an inverse relationship between sociodemographic factors and TB deaths, where countries with the highest TB mortality rate have lower socioeconomic indexes. Thus, according to authors[12] who studied the effects of the Bolsa Familia Programme (BFP) on the outcome of TB treatment, they showed that the impact of income transfer programmes on the health status of the population is positive.

Several measures have been launched in Brazil in the sense of social protection and safety of children, but there is a lack of national studies that can show the impact on the deaths due to pneumonia or even TB in children. It is also important to identify areas of risk for the occurrence of deaths from TB and non-specific pneumonia (PNE) and to verify their relationship with endemic areas of TB, the only transmissible form of the disease.

Thus, the study aimed to perform a spatial analysis of PNE and TB deaths in children under 5 years of age in order to investigate whether there is an association between these events in the areas with a higher incidence of TB and the social determinants of health.

METHODS
Study design and research scenario
We conducted an ecological study[13] that used as a unit of analysis all Brazilian municipalities. Brazil is located in South America and has a territorial extension of 8.55.767 km² and an estimated population of 208.4 million inhabitants, distributed in 5570 municipalities.[14] It has a fertility rate of 1.77 children/woman, infant mortality rate of 12.35 deaths/1000 live births, annual Gross domestic product (GDP) per capita of RS31 833.50, illiteracy rate of 6.7%, Human Development Index, (HDI) of 0.761 and Gini Index of 0.515.[14]

It is noteworthy that the TB mortality rate in children under 5 years old is 1.72 deaths/100 000 children, and the death rate due to PNE in the same age group is 155.05 deaths/100 000 children.

Study population and information sources
All the cases of deaths of children under 5 years of age reported in the period between 2006 and 2016, residing in the Brazilian territory, whose basic cause of death was due to TB (A15.0–A19.9) and PNE (J18) were included. The death data were collected through the Department of Informatics of the Unified Health System (DATASUS), and the population data were extracted from the Brazilian Institute of Geography and Statistics.

Patient and public involvement
No patient involved.

Statistical analysis
To identify areas of spatial risk for TB and PNE deaths, the Spatial Scanning Statistics[15] technique was used through the SatScan V.9.5 software. Thus, we call a risk area a group of events that are geographically limited (in concentration and size), of differing risk and unlikely to occur, whose risk measure is considered relative risk (RR) (the higher the RR value, the greater the risk of that area).

We used the discrete Poisson model, with no geographical overlap of the clusters, a circular format and 999

replications. The size of the exposed population was stipulated by the Gini coefficient, and we chose to identify only high clusters, considering high risk when the RR was greater than one. For the statistically significant clusters, p<0.05 was adopted, and a 95% CI was estimated.

The spatial association was verified using the Getis-Ord General G and Getis-Ord Gi* techniques, using the crude mortality rates for TB and PNE.[16] The Incremental Spatial Autocorrelation tool of the ArcGis V.10.5 software was used to obtain the best distance in which spatial clusters were most pronounced.[17]

The Getis-Ord General G measures the concentration of high or low values for a given study area and is an inferential statistic, which means that the results of the analysis are interpreted within the context of the null hypothesis that there is no spatial clustering of feature values. When the p value is statistically significant, the null hypothesis can be rejected, and then the sign of the z-score becomes important, indicating whether there is grouping of low or high values.[18]

While the Getis-Ord G analysis gives a general analysis of the area, indicating whether there is a tendency for cluster formation, the Getis-Ord Gi* technique shows us where these areas are in the studied region through the values of p (considered significant when less than 0.05) and the z score sign (indicates if the cluster formed is a hotspot (case accumulation) or a coldspot (absence of cases).[18]

The Global Bivariate Moran Index was used to identify the existence of spatial autocorrelation between TB and PNE deaths through the GeoDa V.1.0.1 software. This method was used to obtain an overall spatial autocorrelation coefficient in a bivariate context in order to analyse if the value of an attribute observed was spatially related to the values of another variable.[19]

In this technique, the average and the variation of the attribute under study are calculated, and for each attribute value, the average value is subtracted by creating a deviation from the average. This value is multiplied by all neighbours to create a cross product, where the values for neighbouring resources are higher or lower than average, and the cross product will be positive. When one value is less than average and the other greater than average, the cross product will be negative. It is worth noting that the Moran Index numerator is normalised by variation, so that the index value will always be between −1.0 and +1.0.[20]

In order to identify the association of deaths due to TB and PNE and the endemic areas of pulmonary TB and other social determinants, eight explanatory variables were defined related to the characteristics of the Brazilian municipalities. The variables selected for understanding the social determinants of health were obtained based on the scientific literature and were related to early childhood.[21–24]

Thus, independent variables were established as general incidence rates of TB (all age groups), the Municipal (HDI—index comprising indicators of three dimensions

of human development: health, education and income), Basic attention coverage (BAC—set of actions located in the first level of attention of health systems, focused on health promotion, disease prevention, treatment and rehabilitation), percentage of children in extreme poverty, percentage of poor children, Gini Index (used to measure social inequality), percentage of infants with low birth weight and percentage of families with children benefiting from the BFP. The data were collected through DATASUS and the Human Development Atlas of Brazil.

Prior to the insertion of the variables in the multiple model, a dichotomisation of these variables was performed by their own medians, with 0 being assigned to values that are less than or equal to the median, and 1 to values greater than the median.

The use of the dichotomisation of a quantitative variable can result in a loss of statistical power in the analyses. However, when considering this condition, the authors decided to use the median as the choice of cut point in order to balance the study municipalities between the two analysis groups, resulting in a gain in statistical power. Making many divisions in the quantitative data would result in greater losses of statistical power. Undoubtedly, the dichotomisation simplifies the data for which they were analysed; however, this simplification has purposes of facilitating the understanding of the Brazilian scenario, mainly by managers of professionals who develop intersectoriality to modify social determinants of health.[25] Then, the multicollinearity was verified by the inflation factor of variance (VIF), where values greater than 3 were removed from the statistical modelling.[26]

Considering the dependent variables (deaths by TB and PNE) as counts, four explanatory statistical models were selected with the following probability distributions: poisson, negative binomial (NB), poisson inflated zero and zero-inflated NB (ZINB). The objective of using four different models was to verify the most suitable model given the nature of the data used.[27]

The best model was weighted from the largest log-likelihood values of the model and the lowest values from the Akaike information criterion (AIC).[28] It should be noted that for the model with the best parameters of comparison, the OR and its 95% CI were calculated. Statistical models, adjusted OR and 95% CI were estimated using the R software. A fixed type I error at 5% was considered as statistically significant (p<0.05).

RESULTS

A total of 21 629 cases were identified, of which 21 391 were PNE cases and 238 deaths were due to TB between 2006 and 2016 in Brazil.

The spatial analysis of the deaths from TB allowed the detection of four statistically significant spatial risk areas in Brazil (figure 1). Cluster 1 (p<0.001) was formed from 11 municipalities in the state of Rio de Janeiro, in the southeast region of Brazil, with a population of 641 419
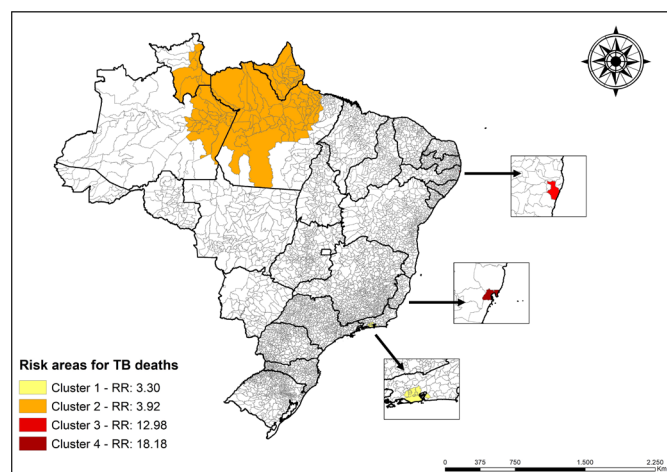
Figure 1 Risk areas for deaths due to tuberculosis in children under 5 years old, Brazil (2006–2016). RR, risk ratio; TB, tuberculosis.

inhabitants, 33 deaths from TB, and RR 3.30, 95% CI 2.28 to 4.77.

Cluster 2 (p<0.001) was formed from 107 municipalities, of which 22 were from Amazonas, 16 from Amapá, 60 from Pará and 9 from Roraima, all located in the north of the country, with a population of 794 462 inhabitants, 46 deaths from TB and RR 3.92, 95% CI 2.84 to 5.41. The spatial cluster 3 (p<0.001) was composed of the municipality of Recife in Pernambuco, in the northeast region of Brazil, with a population of 96 846 inhabitants, 20 deaths from TB and RR 12.98, 95% CI 8.20 to 20.51.

Finally, cluster 4 (p=0.020) was constituted by the municipality of Vitória in Espírito Santo, in the southeast region of Brazil, with a population of 19 598 inhabitants, 6 deaths from TB and RR 18.18, 95% CI 8.08 to 40.88.

Regarding the PNE deaths, it was possible to identify 22 spatial risk clusters that were classified into four groups according to their RR (figure 2). Thus, group 1 was formed of 10 clusters (p<0.001 to 0.036), with a population of 3 677 657 inhabitants, 9280 deaths from
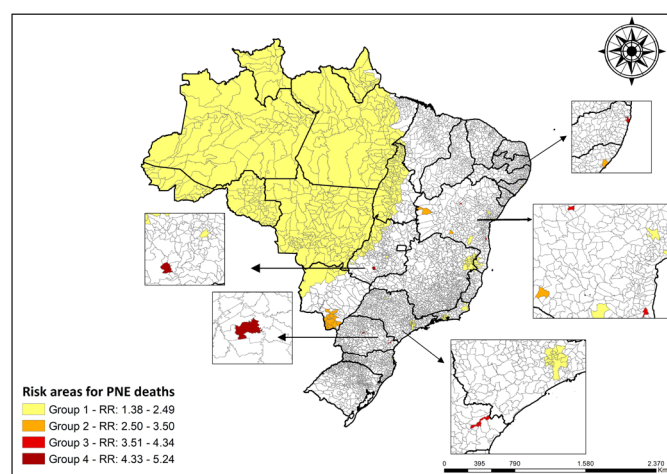

Figure 2 Risk areas for deaths due to unspecified pneumonia in children under 5 years of age, Brazil (2006–2016). PNE, non-specific pneumonia. RR, risk ratio.

PNE and RR from 1.38 to 2.49, 95% CI 1.31 to 2.90. It was composed of 612 municipalities, of which 22 were from Acre, 62 from Amazonas, 92 from Pará, 52 from Rondônia, 15 from Roraima, 105 from Tocantins, 15 from Amapá (north region), 9 from Bahia, 4 from Maranhão, 28 from municipalities of Goiás, 7 from Mato Grosso do Sul, 141 from Mato Grosso (central–west region), Vitória in Espírito Santo, 22 from municipalities of Minas Gerais, 15 from Rio de Janeiro and 21 from São Paulo (southeast region), besides Itajaí in Santa Catarina, in the southern region of the country.

Group 2 consisted of four clusters (p<0.001), with a population of 199 515 inhabitants, 849 deaths from PNE, and RR of 2.50–3.50, 95% CI 2.24 to 5.00. It was composed of 16 municipalities, including 4 in the northeast region, Goiânia in Goiás, and another 13 municipalities in Mato Grosso do Sul, in the centre west region of Brazil.

Group 3 consisted of three clusters (p<0.001 to 0.003), with a population of 102 562, 641 PNE and RR deaths from 3.51 to 4.23, 95% CI 2.61 to 6.48. It was composed of three municipalities, including Recife, Pernambuco and Irecê, Bahia in the northeast region, and Campina Grande do Sul, Paraná, in the southern region of the country.

Finally, group 4 (p=0.000–0.011) had a population of 59 022 inhabitants, 455 deaths from PNE and RR of 4.34–5.24, 95% CI 3.53 to 8.52. It was composed of four municipalities, including Aracaju, Sergipe and Itabuna, Bahia in the northeast; Santa Helena de Goiás, Goiás, in the midwest; and Ivaiporã, Paraná, in the southern region of the country.

Figure 3A shows the local spatial association (Gi*) of the TB death rate, allowing the identification of hotspots in the north, northeast and centre west regions of Brazil and coldspots in the northeast, centre west, southeast and the entire region south of the country. With a z-score of 3.74 and pseudosignificance test, it was possible to confirm the non-randomness of the clusters (p<0.01) (figure 3B).

Figure 3C shows the local spatial association (Gi*) of the PNE death rate, allowing the identification of hotspots in the north, northeast and centre west regions of Brazil. It also shows coldspots in two municipalities in the northeast region, in the central–west, in the southeast, and throughout the southern region of the country. With a z-score of 64.34 and pseudosignificance test, it was also possible to confirm the non-randomness of the clusters (p<0.01) (figure 3D).

The Global Bivariate Moran Index was calculated between the crude TB and PNE mortality rates, obtaining a value of 0.031 (p=0.001), confirming the existence of a positive spatial autocorrelation between the two events of interest.

Tables 1 and 2 present the four explanatory models for TB and PNE mortality. Only five variables were included in the multiple models, according to VIF selection criteria. From the models tested, the probabilistic ZINB distribution was the one that best fit the nature of both dependent variables. This was observed due to
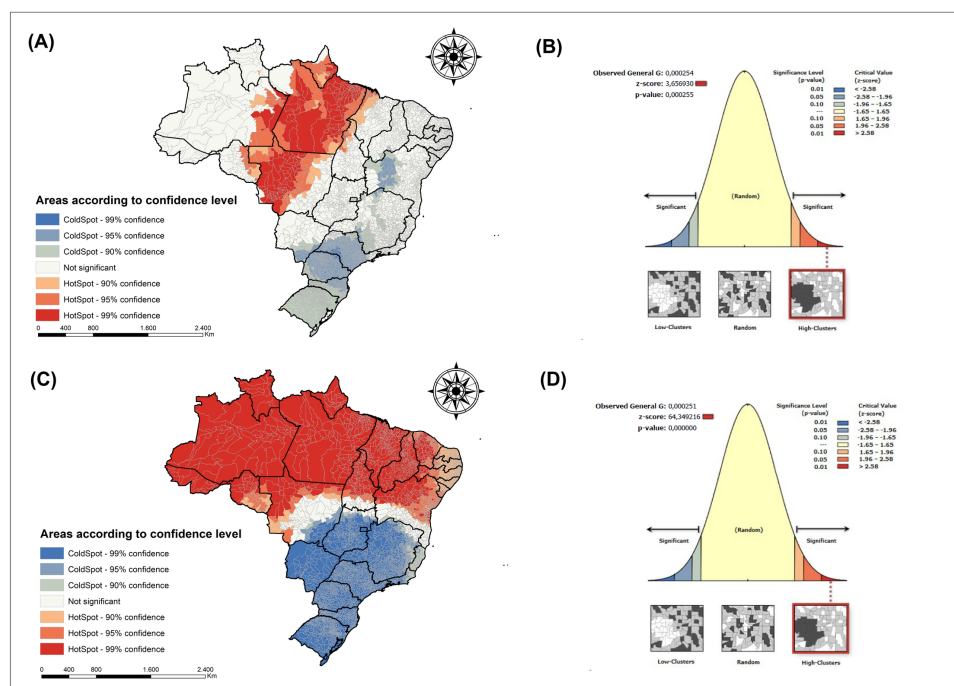
Figure 3 Hotspots and coldspots for tuberculosis death and unspecified pneumonia, Brazil, 2006–2016. (A) Spatial clusters of tuberculosis deaths in children under 5 years of age according to the level of confidence. (B) Level of statistical significance of Getis-Ord G for deaths due to tuberculosis in children under 5 years of age. (C) Areas of spatial clusters of deaths due to pneumonia not specified in children under 5 years of age according to the level of confidence. (D) Level of statistical significance of Getis-Ord G for deaths from pneumonia not specified in children under 5 years of age.

their higher Log-likelihood values (−696 and −7643) and the lower AIC values (1417 and 15 312) for TB and PNE, respectively.

For TB deaths, the municipalities presented an OR 5.3, 95% CI 2.85 to 9.84, and for PNE, the OR 6.63, 95% CI 5.62 to 7.81, indicating an association of these events with municipalities that had rates of general incidence of TB above 15.33 cases per 100 000 inhabitants. Regarding the Gini variable, the Brazilian municipalities with indices above 0.49 had a positive association with deaths due to TB (OR 1.78, 95% CI 1.12 to 2.82) and PNE (OR 4.22; 95% CI 3.63 to .92).

The municipalities with BAC of 96.4% had an inverse association with TB deaths (OR 0.10, 95% CI 0.67 to 0.17) and PNE (OR 0.18, 95% CI 0.15 to 0.21). Municipalities that had more than 83.21% of those receiving BFP had an inverse association with PNE (OR 0.81, 95% CI 0.52 to 1.25). Finally, the zero-inflated model for the ZINB distribution did not identify variables associated with PNE and TB.

DISCUSSION

The aim of the present study was to map the deaths from PNE and TB in children under 5 years old under the hypothesis that cases of deaths are being reported as PNE while in reality it could be undeserved/diagnosed TB. To test the hypothesis, first we performed spatial analysis of PNE and TB separately, and then we analysed whether there was an association between these areas with those

with higher incidence of TB and their social determinants of health.

It is worth noting that the diagnosis of childhood TB is one of the most significant challenges for the elimination of the disease, mainly due to the low positivity in the bacteriological examinations when performed in this age group, due to the paucibacillary nature of TB in childhood.[3] Since TB is one of the main causes of morbidity and mortality in all age groups in the world (especially in low/middle-incomeg countries, such as Brazil), in children, its symptoms are often related to the presence of acute pneumonia, favouring late or misdiagnosis and the consequent evolution of the disease.[2 29]

It was verified that PNE in children under 5 years old is a common event in Brazil, affecting mainly the north, centre west, and northeast of Brazil and showing unequal distribution in the country when compared with the south and southeast. The study evidenced that the areas with highest incidence of TB were associated with PNE deaths, possibly because the determinants of both diseases are very similar, a context of social privation and inequity.

A hypothesis of this association also is that a small proportion of PNE would be misclassified as TB. Since there are hyperendemic areas for TB and there is a failure by the services to diagnose TB early, mainly in children, some cases could be classified as pneumonia when it could not be true. Authors have used exactly the unspecific pneumonia cases because they are sensitive

Table 1 Explanatory models for deaths from tuberculosis in children under 5 years of age, Brazil (2006–2016)

Variables	Poisson coefficient (p value)	Binomial negative coefficient (p value)	Poisson inflated from zero counting model coefficients (p value)	Poisson inflated from zero coefficients of the inflation model (p value)	Binomial negative inflated from zero counting model coefficients (p value) and OR (95% CI)	Binomial negative inflated from zero coefficients of the inflation model (p value) and ORs (95% CI)
Tuberculosis incidence rate (>15.33)	1.90 (<0.01)	1.82 (<0.01)	1.53 (0.16)	−0.38 (0.74)	1.66 (<0.01) 5.30 (2.85 to 9.84)	−2.01 (0.21) 0.13 (<0.01 to 3.31)
Basic care coverage (>96.40%)	−1.94 (<0.01)	−1.88 (<0.01)	−1.66 (<0.01)	0.29 (0.43)	−2.22 (<0,01) 0.10 (0.67 to 0.17)	−15.17 (0.91) <0.01 (<0.01 to >100,00)
Gini Index (<0.49)	0.7 (<0.01)	0.74 (<0,01)	0.67 (0.02)	−0.02 (0.94)	0.57 (0.01) 1.78 (1.12 to 2.82)	−1.90 (0.24) 0.14 (<0.01 to 3.70)
Percentage of infants with low birth weight (>3.41%)	0.39 (<0.01)	0.44 (<0.01)	−0.33 (0.11)	−0.80 (<0.01)	0.31 (0.15) 1.36 (0.88 to 2.12)	−1.87 (0.25) 0.15 (<0.01 to 3.91)
Percentage of family with child beneficiary of Bolsa Família Programme (>83.21%)	−0.38 (<0.01)	−0.41 (<0.01)	0.20 (0.36)	0.59 (0.02)	−0.20 (0.35) 0.81 (0.52 to 1.25)	3.00 (0.07) 20.11 (0.73 to 55.35)
Akaike information criterion	1742	1419	1506	1506	1417	1417
Log-likelihood	−865	−701	−741	−741	−696	−696

indexes of a misdiagnosis and weakness of monitoring and surveillance of the deaths in children under 5 years.[30]

In terms of the determinants, such as BFP and BAC, it was possible to identify the weakness of these policies on children's access to health services. The issue of income inequality was strongly associated with both PNE and TB deaths in the same age group.

In this study, it was possible to identify the risk factors for TB deaths in the states of Rio de Janeiro, Espírito Santo, Amazonas, Amapá, Pará, Roraima and Pernambuco. A study[31] carried out in the state of Espírito Santo showed that 49.9% of TB deaths were prevalent in the age range of 1–5 years, and the region was considered a priority for disease control. No studies were found to address TB deaths in the states of Amapá and Roraima.

The areas with a risk of death due to PNE involving all regions of the country were also identified, but there were a few studies that proposed to study deaths due to pneumonia in children and did not have a national coverage approach. A study[32] in Minas Gerais described high death rates from pneumonia, showing that this was an old health problem and needed further investigation. A study published in Santa Catarina[33] pointed out that pneumonia was among the main causes of hospitalisation in children under 5 years of age.

More studies on pneumonia deaths in children are needed to highlight the critical nodes of the system as one of the most lethal diseases in childhood, killing more than 2 million children per year in this age group, accounting for 19% of all deaths.[34]

When comparing the maps of risk areas for TB and PNE, it could be observed that the states of Rio de Janeiro and Espírito Santo in the southeast region; Amazonas, Pará, Roraima and Amapá in the north; and the Pernambuco regions in the northeast were risk areas for both diseases, in addition to being endemic places for TB, with incidence rates above 26 cases/100 000 inhabitants. Thus, public policies and incentives, the active search for new cases and public awareness about the symptoms of TB and pneumonia should be stimulated in these regions and, in view of the current results, investigated thoroughly for cases of PNE that were not diagnosed as TB.

With the use of the G and Gi* techniques, it was possible to identify that TB and PNE follow patterns and are influenced by certain spatial variables, confirmed by the use of the Global Bivariate Moran Index, proving the global and local spatial association and the non-randomness in the formation of the agglomerates.

Hotspots were identified in the north, northeast and centre west regions of the country for TB and PNE, and

Table 2 Explanatory models for deaths from unspecified pneumonia in children under 5 years of age, Brazil (2006–2016)

Variables	Poisson coefficient (p value)	Binomial negative coefficient (p value)	Poisson inflated from zero counting model coefficients (p value)	Poisson inflated from zero coefficients of the inflation model (p value)	Binomial negative inflated from zero counting model coefficients (p value) and ORs (95% CI)	Binomial negative inflated from zero coefficients of the inflation model (p value) and ORs (95% CI)
Tuberculosis incidence rate (>15.33)	2.08 (<0.01)	1.92 (<0.01)	1.72 (<0.01)	−0.58 (<0.01)	1.89 (<0.01) 6.63 (5.62 to 7.81)	−0.29 (0.59) 0.74 (0.25 to 2.20)
Basic care coverage (>96.40%)	−1.81 (<0.01)	−1.81 (<0.01)	−1.27 (<0.01)	1.47 (<0.01)	−1.70 (<0.01) 0.18 (0.15 to 0.21)	12,51 (0.91) 0.18 (0.15 to 0.21)
Gini Index (<0.49)	1.43 (<0.01)	1.50 (<0.01)	1.17 (<0.01)	−0.61 (<0.01)	1,44 (<0.01) 4.22 (3.63 to 4.92)	−0.76 (0.11) 0.46 (0.18 to 1.19)
Percentage of infants with low birth weight (>3.41%)	0.09 (<0.01)	0.19 (<0.01)	0.04 (<0.01)	−0.44 (<0.01)	0.04 (0.59) 1.04 (0.88 to 1.22)	−2.99 (0.38) 0.04 (0.01 to 4.41)
Percentage of family with child beneficiary of Bolsa Família Programme (>83.21%)	−0.70 (<0.01)	−0.57 (<0.01)	−0.63 (<0.01)	0.02 (0.69)	−0.64 (<0.01) 0.52 (0.44 to 0.61)	−0.87 (0.19) 0.41 (0.11 to 1.56)
Akaike information criterion	81 990	15 324	69 816	69 816	15 312	15 312
Log-likelihood	−40989	−7655	−34900	−34900	−7643	−7643

coldspots in the northeast, southeast, south and centre west regions for TB and PNE, indicating once again that both diseases have associated factors in common, such as space.

Four explanatory models were tested, and the ZINB model was the one with the lowest AIC value; however, caution is needed when considering these models, as the AIC values have been reduced slightly compared with other models. As a result, it was identified that municipalities that presented a general incidence rate of TB above 15.3 cases/100 000 inhabitants were associated with TB and PNE deaths in children. This is an important indicator that in municipalities with high TB rates, children die more due to PNE, again raising questions about the possibility of the erroneous diagnosis of PNE.

The results also pointed out that municipalities with a Gini Index greater than 0.49 had an association with mortality due to TB and PNE. According to Brazil's Institute for Applied Economic Research,[35] among the main infectious diseases considered neglected, such as TB, because they have as a characteristic the involvement, mainly, of the most vulnerable and socially disadvantaged population, the development of new drugs is not a priority for the pharmaceutical industries when compared with others that can be more profitable. In this way, the character of infectious diseases as a disease of the poor strongly associated with social stigma still prevails.

In an inverse relation, the final model indicated that municipalities with BAC above 96.4% are associated with deaths from TB and PNE. Being close to the primary care unit, waiting time for consultation, bonding with the health team, provision of supplies and human resources, and the presence of a Family Health Strategy team are factors that are positively associated with the detection of TB cases.[36] In addition, a study[36] conducted in Brazil found an inverse association between BAC and the TB detection rate, corroborating the results of the present study, which may indicate the effect that primary care has on TB control through the identification and early-onset treatment.

Finally, the results indicated that municipalities with more than 83.2% of families with children receiving BFP had an inverse association with PNE deaths. Public social protection policies have placed Brazil on the world stage in relation to disease control, and studies have already verified that the BFP has alleviated socioeconomic inequalities in the country.[37]

Contact tracing and TB prevention in children are absolutely necessary to avoid new episodes and fatalities. They must be linked to appropriate care, ensuring the success of treatment and survival. In the long term, it is also required in terms of TB prevention strategies not only to identify TB disease earlier, or even rule out this diagnosis, but to prevent it, tackling its determinants such as higher illiteracy rates, violence against children, infant work, poor sanitation, housing conditions and greater difficulty in accessing health services at all levels of care.[4]

The main limitation of an ecological study is the ecological fallacy, in which the relationship between the exposure factor and the event may not occur at the individual level. This bias can happen when drawing an erroneous conclusion about an association found between variables at the aggregate level that does not necessarily represent an association at the individual level. It is also worth mentioning the use of secondary data sources that can lead to incomplete data or typos.

The use of tools and methods of spatial analysis in public data has been emphasised in public health since, in addition to considering the information of the object under study, it also takes into account the place of occurrence of facts becoming strategies increasingly useful for epidemiological surveillance evaluation of health services, urbanisation and the environment.[38] Future studies may consider the methods used as a reference, but the authors point to the need to test other types of methodologies to identify other determinants and also to validate the relationships found in the present result.

CONCLUSIONS

This study may become a reference for the definition of strategies at the national level to prioritise states or municipalities for investments aimed at reducing deaths from TB and pneumonia. This study is also the first with national coverage and aligns with two equally important goals: the 2030 agenda of the Pan American Health Organization, specifically vested in reducing child mortality and poverty, and the 'end TB' strategy, whose main task is to reduce inequalities in the population's access to health services and reduce preventable deaths, mainly in children.

Map disclaimer The depiction of boundaries on this map does not imply the expression of any opinion whatsoever on the part of BMJ (or any member of its group) concerning the legal status of any country, territory, jurisdiction or area or of its authorities. This map is provided without any warranty of any kind, either express or implied.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Since this study uses public domain data, it was not necessary to submit any application to the Research Ethics Committee, according to resolution no. 466/12.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The death data were collected through the Department of Informatics of the Unified Health System (DATASUS). DATASUS manages health information (health indicators, medical care, epidemiological and morbidity information, health care network information, vital statistics, demographic and socioeconomic information)

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REFERENCES

1. Mouro F, Mosha N, Hildenwall H, *et al*. Variability of respiratory rate measurements in children suspected with non-severe pneumonia in north-east Tanzania. *Tropl Med Int Health* 2017;22.
2. Oliwa JN, Karumbi JM, Marais BJ, *et al*. Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review. *Lancet Respir Med* 2015;3:235–43.
3. Cano APG, Romaneli MTN, Pereira RM, *et al*. Tuberculose em pacientes pediátricos: como tem sido feito o diagnóstico? *Rev Paul Pediatr* 2017;35:165–70.
4. Word Health Organization. *National guidelines on management of tuberculosis in children [online]*. Geneva: World Health Organization, 2016. http://apps.who.int/medicinedocs/documents/s21974en/s21974en.pdf
5. Jenkins HE, Yuen CM, Rodriguez CA, *et al*. Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2017;17:285–95.
6. França EB, Lansky S, Rego MAS, *et al*. Principais causas da mortalidade na infância no Brasil, em 1990 e 2015: estimativas do estudo de carga global de doença. *Rev Bras Epidemiol* 2017;20:46–60.
7. Enarson PM, Gie RP, Mwansambo CC, *et al*. Reducing deaths from severe pneumonia in children in Malawi by improving delivery of pneumonia case management. *PLoS One* 2014;9:e102955.
8. Organização Pan-Americana da Saúde. *Saúde nas Américas, Edição de 2017. Resumo do panorama regional e perfil do Brasil*. Washington, DC: Organização Pan-Americana da Saúde, 2017.
9. Rossetto EV, Albuquerque LEJ. Relacionamento entre bases de dados para vigilância da pandemia de influenza A (H1N1) pdm09, Brasil, 2009-2010. *Cad Saúde Pública* 2016;32.
10. Whittaker E, López-Varela E, Broderick C, *et al*. Examining the complex relationship between tuberculosis and other infectious diseases in children. *Front Pediatr* 2019;7:233.
11. Kyu HH, Maddison ER, Henry NJ, *et al*. The global burden of tuberculosis: results from the global burden of disease study 2015. *Lancet Infect Dis* 2018;18:261–84.
12. Oliosi JGN, Reis-Santos B, Locatelli RL, *et al*. Effect of the Bolsa família programme on the outcome of tuberculosis treatment: a prospective cohort study. *Lancet Glob Health* 2019;7:e219–26.
13. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.
14. Instituto Brasileiro de Geografia e Estatística. Brasil em síntese [online], 2018. Available: https://brasilemsintese.ibge.gov.br/ [Accessed 1 Mar 2019].
15. Kulldorff M, Nagarwalla N. Spatial disease clusters: detection and inference. *Stat Med* 1995;14:799–810.
16. Getis A, Ord JK. The analysis of spatial association by use of distance statistics. *Geogr Anal* 1992;24:189–206.
17. Environmental Systems Research Institute. How incremental spatial autocorrelation works [online]. Available: https://pro.arcgis.com/en/pro-app/tool-reference/spatial-statistics/how-incremental-spatial-autocorrelation-works.htm
18. Environmental Systems Research Institute. How high/low clustering (Getis-Ord General G) works [online]. Available: https://pro.arcgis.com/en/pro-app/tool-reference/spatial-statistics/h-how-high-low-clustering-getis-ord-general-g-spat.htm
19. Anselin L, Syabri I, Kho Y. GeoDa: an introduction to spatial data analysis. *Geogr Anal* 2006;38:5–22.
20. Environmental Systems Research Institute. How spatial autocorrelation (Global Moran's I) works [online]. Available: https://pro.arcgis.com/en/pro-app/tool-reference/spatial-statistics/h-how-spatial-autocorrelation-moran-s-i-spatial-st.htm
21. Van Minh H, Giang KB, Hoat LN, *et al*. Analysis of selected social determinants of health and their relationships with maternal health service coverage and child mortality in Vietnam. *Glob Health Action* 2016;9:1–9.
22. Sucupira A, Andrade LOM, Barreto I, *et al*. Determinantes sociais da saúde de crianças de 5 a 9 anos da zona urbana de Sobral, Ceará, Brasil. REV BRAS EPIDEMIOL 2014; 160-177. BRASIL. Comissão Nacional Sobre Determinantes Sociais da Saúde. As causas sociais das iniquidades em saúde no Brasil [online], 2008. Available: http://bvsms.saude.gov.br/bvs/publicacoes/causas_sociais_iniquidades.pdf [Accessed 24 Jan 2020].
23. Comissão Nacional Sobre Determinantes Sociais da Saúde. As causas sociais das iniquidades em saúde no Brasil [online], 2008. Available: http://bvsms.saude.gov.br/bvs/publicacoes/causas_sociais_iniquidades.pdf [Accessed 24 Jan 2020].
24. Carvalho AI. Determinantes sociais, econômicos e ambientais da saúde. In Fundação Oswaldo Cruz. A saúde no Brasil em 2030 - prospecção estratégica do sistema de saúde brasileiro: população e perfil sanitário [online]. *Rio de Janeiro: Fiocruz/Ipea/Ministério da Saúde/Secretaria de Assuntos Estratégicos da Presidência da República* 2013;2:19–38.
25. Ravichandran C, Fitzmaurice GM. To dichotomize or not to dichotomize? *Nutrition* 2008;24:610–1.
26. Zuur AF, Ieno EN, Elphick CS. A protocol for data exploration to avoid common statistical problems. *Methods Ecol Evol* 2010;1:3–14.
27. Lambert D. Zero-inflated poisson regression, with an application to defects in manufacturing. *Technometrics* 1992;34:1–41.
28. Wagh YS, Kamalja KK. Zero-inflated models and estimation in zero-inflated Poisson distribution. *Commun Stat Simul Comput* 2018;47:2248–65.
29. World Health Organization. Global tuberculosis report 2018, 2018. Available: http://www.who.int/iris/handle/10665/274453
30. Burstein R, Henry NJ, Collison ML, *et al*. Mapping 123 million neonatal, infant and child deaths between 2000 and 2017. *Nature* 2019;574:353–8.
31. Sales CMM, Figueiredo TAMde, Zandonade E, *et al*. Análise espacial dA tuberculose infantil no estado do Espírito Santo, 2000 a 2007. *Rev Soc Bras Med Trop* 2010;43:435–9.
32. Camargos PAM, Guimarães MDC, Drumond EdeF. Mortalidade POR pneumonia em crianças menores de cinco anos de idade em localidade do Estado de Minas Gerais (Brasil), 1979-1985. *Revista de Saúde Pública* 1989;23:388–94.
33. Mariano TSO, Nedel FB. Hospitalização POR Condições Sensíveis Atenção Primária em menores de cinco anos de idade em SANTA Catarina, 2012: estudo descritivo. *Epidemiol e Serviços Saúde* 2018;27:1–10.
34. Imperador DV, Araújo A, Prigenzi ML. Manejo dA pneumonia em crianças de 1 a 4 anos de idade Na comunidade. *Rev Fac Ciênc Méd Sorocaba* 2014;16:46–9.
35. Instituto de Pesquisa Econômica Aplicada. Doenças transmissíveis e situação socioeconômica no Brasil: análise especial [online]. Brasília, Rio de Janeiro: Ipea, 2016. Available: http://repositorio.ipea.gov.br/bitstream/11058/7364/1/td_2263.pdf [Accessed 20 Feb 2019].
36. Pelissari DM, Bartholomay P, Jacobs MG, *et al*. Oferta de serviços pela atenção básica E detecção dA incidência de tuberculose no Brasil. *Rev Saúde Pública* 2018;52:53.
37. Campello T, Neri MC. Programa Bolsa Família: uma década de inclusão e cidadania [Internet]. Brasília: Ipea, 2013. Available: http://www.ipea.gov.br/portal/images/stories/PDFs/livros/livros/livro_bolsafamilia_10anos.pdf [Accessed 20 Feb 2019].
38. Lucena KDTde, Silva ATMCda, Moraes RMde, *et al*. [Spatial analysis of domestic violence against women from 2002 to 2005 in João Pessoa, Paraíba State, Brazil]. *Cad Saude Publica* 2012;28:1111.