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Temporal evolution and spatial distribution of leprosy in a municipality with low endemicity in São Paulo state, Brazil

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ABSTRACT

Objective: To analyze the spatial and temporal distribution of leprosy in a scenario of low endemicity in the state of São Paulo, Brazil. **Methods:** Ecological study with leprosy cases in Ribeirão Preto, between 2006 to 2016. The temporal trend of leprosy detection was verified through the decomposition of time series and identified areas of high and low occurrence of the disease using the Getis-Ord Gi* technique. **Results:** There were 890 cases, and the detection rate showed an increasing trend in the period from 2011 to 2015, with an average growth of 1% per month. Areas of high occurrence of the disease were identified in the northern region of the city (99% and 95% confidence). **Conclusion:** The temporal analysis showed that the rate of detection of leprosy presented an increasing trend, and the spatial analysis showed that the region of the municipality with the highest occurrence of the disease is characterized by presenting the greatest social inequalities.

Keywords: Leprosy; Epidemiology; Spatial Analysis; Time Series Studies; Ecological Studies.

INTRODUCTION

According to World Health Organization (WHO) data, 202,185 new leprosy cases were detected worldwide in 2019, and of these some 80% were reported in India, Brazil and Indonesia.[1] In the same period, Brazil recorded 27,863 new cases, being the country with the second highest number of cases globally.[1]

Despite the high levels of leprosy endemicity in Brazil, there have been significant improvements in the control of the disease in recent decades, especially with effect from the year 2000, following the putting in place of the international policies on leprosy elimination, which caused a reduction in the new case detection rate, from 26.2 per 100,000 inhabitants in 2001, to 11.2 cases per 100,000 inhabitants in 2019.[2,3]

Although there has been a reduction in the occurrence of the disease nationwide, it is noteworthy that its distribution is heterogeneous over the country, with differences being found between macro-regions, states and municipalities.[4] In 2019, the highest leprosy detection rates were found in the Midwest (51.8 per 100,000 inhab.), North (38.8 per 100,000 inhab.) and Northeast (26.6 per 100,000 inhab.) regions, while the lowest rates were reported by the Southeast (5.6 per 100,000 inhab.) and Southern (3.8 per 100,000 inhab.) regions of the country.[2]

Despite their having the lowest detection rates, the data for the Southern and Southeast regions should be interpreted with caution, since low case detection does not mean evidence of low transmission.[5] Studies conducted in municipalities with low or medium leprosy endemicity have described substantial increases in detection rates after intensive surveillance and active searching for cases, revealing that low endemicity sites can have 'hidden endemicity' and active *Mycobacterium leprae* transmission hotspots.[6,7]

In endemic countries, investigations focused on smaller units, such as municipalities, can provide a more realistic representation of the leprosy situation, reflecting the distribution of

Study contributions	
Main results	The leprosy detection rate showed a rising trend between 2006 and 2016 in Ribeirão Preto, SP, whereby the region of the municipality identified as having the greatest occurrence of the disease was also characterized as a region with marked social inequality.
Implications for services	The results can contribute to planning and implementing strategic health surveillance actions to control leprosy in the municipality of Ribeirão Preto, SP, especially in the region where the disease occurs most.
Perspectives	Epidemiological investigations of leprosy with the aim of identifying areas or territories with greater occurrence of and vulnerability to the disease should be encouraged, in particular scenarios in which leprosy endemicity is considered to be low.

the disease more accurately.[8] Another relevant aspect is that most scientific investigations of leprosy are carried out in regions where its endemicity is high, so that regions with lower detection rates, where endemicity is stable or falling, are little studied. Areas with low detection rates need to be investigated with the same attention as hyperendemic areas, as they can become neglected spaces that contribute to the maintenance of the transmission chain.[9]

In view of these gaps in knowledge, the objective of this study was to analyze the spatial and temporal distribution of leprosy in a scenario of low endemicity in the state of São Paulo, Brazil.

METHODS

This was an ecological study of new leprosy cases reported on the Notifiable Health Conditions Information System (SINAN) in Ribeirão Preto, SP, from 2006 to 2016, using the municipality's 988 census tracts as units of ecological analysis.[10]

Ribeirão Preto has a population of 604,682 inhabitants.[11] Its public health system is divided into five Health Districts – Central, Eastern, Northern, Western and Southern –, comprising 49 Primary Health Care establishments, of which five are primary district health centers, 18 are Family Health Strategy centers and 26 are ordinary primary health care centers.[12] Figure 1 shows the location of Ribeirão Preto.

In 2016, leprosy prevalence in Ribeirão Preto was 0.8 case per 10,000 inhab. while the detection rate was 7.7 new cases per 100,000 inhab.[13] According to parameters established by the Ministry of Health for the detection of new cases, the municipality presents low endemicity, considering the prevalence values and average strength of morbidity.[14]

The data used in the study were retrieved from the SINAN database and included clinical and sociodemographic information about reported cases, such as operational classification (paucibacillary; multibacillary), grade of physical disability (GD) at diagnosis (G0D; G1D; G2D;), date of case notification, date of birth, sex (male; female), education (no education; elementary school; high school; higher education) and home address. Regarding GD, its classification varies according to the neural impairment of
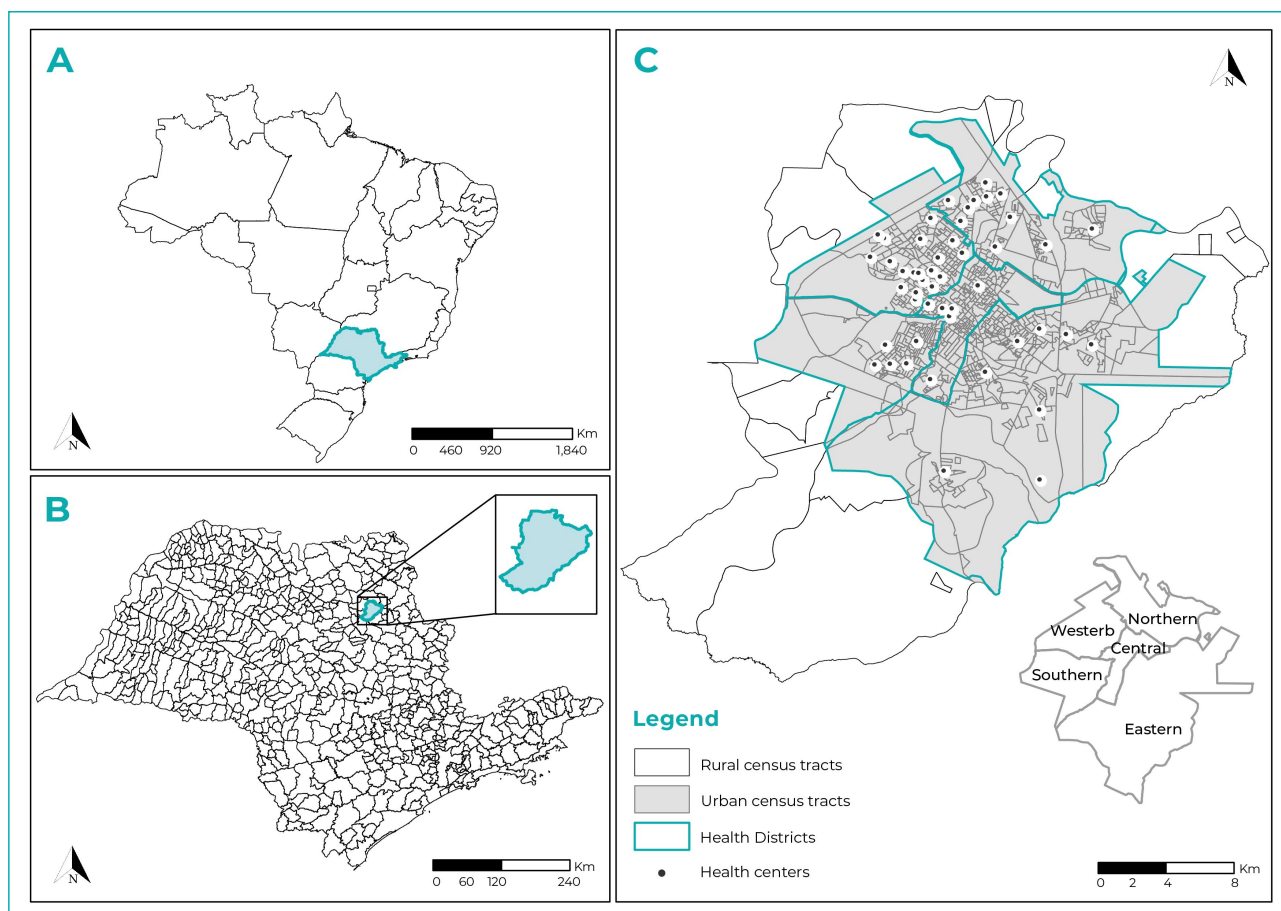
A) Brazil; B) State of São Paulo; C) Municipality of Ribeirão Preto.

Figure 1 – Map showing location of Ribeirão Preto, state of São Paulo, Brazil, 2016

the affected individual: G0D corresponds to cases without any type of functional disability; G1D corresponds to those with loss of protective sensation; and G2D corresponds to individuals who, in addition to loss of protective sensation, present complications that include trophic ulcers, claw deformity, bone resorption in hands and/or feet and various eye lesions.[15]

Access to the SINAN database was provided by the Epidemiological Survey Division of the Ribeirão Preto City Health Department.

A descriptive analysis of the clinical and sociodemographic variables of the leprosy cases was performed using RStudio software version 3.5.2.

With regard to the temporal analysis, the time series was built according to month of notification. The detection rates were calculated taking the total number of leprosy cases notified in the month as the numerator, while the denominator was the population of the municipality according to the 2010 Demographic Census and the estimated populations for each intercensal year (between the periods 2006-2009 and 2011-2016), multiplied by 100,000 inhabitants.[16]

The detection rate time series was then decomposed using the time series decomposition method originally called Seasonal-Trend Decomposition using LOESS (STL).[17] Assuming an additive form of decomposition, the leprosy detection rate in month t (Y_t) is written according to the following formula:

$$Y_t = S_t + T_t + R_t$$

where: S_t is the seasonal component; T_t is the trend component; and R_t is the residual or noise component.

Trend refers to the direction in which a time series develops over a given time interval, and may follow a rising, falling or stationary pattern. Seasonality is defined as identical patterns that a time series may follow that repeat regularly at fixed periods of time. "Noise" represents the fluctuations observed during the period covered by the series, generally irregular and random, perceptible only when the other components of the time series are removed.[18]

We chose to select only the trend component from all the components of the time series, in order to characterize the behavior of the leprosy detection rate over time. After decomposing the time series, we calculated Average Monthly Percentage Change (AMPC),[19] as the summary measure of the trend component over time, where n was the total number of months of study, expressed as follows:

$$AMPC = \frac{\sum_{i=2}^{n}\left(\dfrac{Rate_{month\,i}}{Rate_{month\,i-1}} - 1\right)}{n-1} \times 100$$

With regard to the temporal analyses, we used Rstudio version 3.5.2 to build the time series distribution graph and the detection rate trend.

In the spatial analysis, the leprosy cases were initially georeferenced based on the latitude and longitude information for their home addresses. Google Earth® was applied to identify latitude and longitude, and ArcGIS® 10.8 was used for georeferencing, building a file in shapefile format containing the location of each case. In this step, we excluded cases with no address or incomplete address information (street name or number unavailable), those who lived in the rural area of Ribeirão Preto and/or cases notified in Ribeirão Preto but who were not resident there.

After georeferencing the cases, the number of cases per unit of analysis was computed, enabling the calculation of the leprosy detection rate by census tract, by taking the number of cases per census tract as the numerator and the total population of each census tract as the denominator, and multiplying by 100,000 inhabitants.

We performed the analysis of the spatial clustering of leprosy cases using the Getis-Ord Gi* technique, based on the detection rates. This technique indicates local spatial association, taking the values for each census tract in the

municipality based on a neighborhood matrix.[20] Getis-Ord Gi* is obtained using the following formula:

$$G_i^* = \frac{\sum_{j=1}^{n} w_{ij} x_j}{\sum_{j=1}^{n} x_j}$$

where: Gi* is the spatial autocorrelation statistic of an event i over n events (total number of components); x_j characterizes the magnitude of variable x in j events over all n; and w is the spatial weight between components i and j. Inference as to the significance of Gi* is based on a standardized distribution:

$$Z\left(G_i^*\right) = \frac{\sum_{j=i}^{n} w_{i,j} x_j - \overline{X} \sum_{j=1}^{n} w_{i,j}}{S\sqrt{\dfrac{\left[n \sum_{j=1}^{n} w_{i,j}^2 - \left(\sum_{j=1}^{n} w_{i,j}\right)^2\right]}{n-1}}}$$

where: $\bar{x}$ is the mean and S is the variance:

$$\overline{X} = \frac{\sum_{j=1}^{n} x_j}{n}$$

$$S = \sqrt{\frac{\sum_{j=1}^{n} x_j^2}{n} - (\overline{X})^2}$$

Interpretation of this statistic is performed based on the *Z-score* and significance level values (α). A positive *Z* value with statistical evidence indicates a spatial cluster with greater occurrence of the event (hot spot), while a negative *Z* value with a statistical evidence indicates a spatial cluster with lesser occurrence of the event (cold spot). We used 90%, 95% and 99% confidence levels. We tested spatial association of leprosy in four different time periods (2006-2009; 2010-2013; 2014-2016; and the entire study period, 2006-2016), with the aim of verifying hot spot and cold spot distribution over time. We used ArcGIS® 10.8 to analyze spatial clustering and to prepare maps.

The study was submitted to the Research Ethics Committee of the Universidade de São Paulo Nursing School in Ribeirão Preto and was approved as per Certificate of Submission for Ethical Appraisal No. 44637215.0.0000.5393, issued on March 23rd 2018.

RESULTS

A total of 890 leprosy cases were reported from 2006 to 2016, with a predominance of multibacillary cases (732; 82.2%) and presence of G1D at the time of diagnosis (347; 39.0%). There was a higher frequency of cases in the 30-59 age group (494; 55.5%), followed by those aged 60 or older (234; 26.3%), as well as among males (542; 60.9%) and those with elementary school education (476; 53.5%). Table 1 shows the descriptive statistics of the cases.

Figure 2 shows the leprosy detection rate time series and trend. From 2006 to 2010 the trend was stationary, followed by a rising trend as of 2011, which lasted until 2015, when the rate began to show a slight falling trend until the end of the period studied. Despite the falling trend after 2015, the detection rate values were higher at the end of the time series than at the beginning. The AMPC value indicated an average increase of 1.0% per month for the series.

Of the total number of notified cases, 206 (23.1%) were excluded because their home address was outside Ribeirão Preto (they were notified in Ribeirão Preto but did not live there) and 29 (3.3%) because they lived in the rural area of the city. This left a total of 655 cases (73.6%) to be standardized for georeferencing. Of this total, 47 (7.2%) had a blank and/or incomplete address, so that the final number of cases to be georeferenced was 608 cases (92.8%) (Figure 3).

Figure 4 shows the results of the leprosy detection rate local spatial association analysis using the Getis-Ord Gi* technique, which allowed the identification of areas of high case occurrence (hot spots) and low case occurrence (cold spots) and case distribution over time.

In the period from 2006 to 2016 (Figure 4A), the clusters with higher occurrence of leprosy were found in the north of Ribeirão Preto and

Table 1 – Characteristics of leprosy cases in Ribeirão Preto, state of São Paulo, Brazil, 2006-2016

Variable	n (890)	%
Operational classification		
Paucibacillary	158	17.8
Multibacillary	732	82.2
Grade of physical disability (GD) at diagnosis		
Grade 0	287	32.2
Grade 1	347	39.0
Grade 2	146	16.4
Left blank	110	12.4
Age (years)		
<15	40	4.5
15-29	122	13.7
30-59	494	55.5
≥60	234	26.3
Sex		
Male	542	60.9
Female	348	39.1
Schooling		
No schooling	36	4.0
Elementary education	476	53.5
High school education	108	12.1
Higher education	78	8.8
Left blank	192	21.6

included census tracts located in the Northern and Central Health Districts and a small part of the Eastern Health District. The clusters with lower occurrence were identified in the southern census tracts of the city, located in part of the area of the Central, Southern and Eastern Health Districts. Although some hot spots and cold spots are found in the same Health Districts, the areas of higher and lower occurrence are well delimited and geographically opposite to each other.

In the analysis of the spatial-temporal distribution of leprosy, the periods from 2006 to 2009 (Figure 4B) and 2010 to 2013 (Figure 4C) presented similar distribution, with clusters of higher occurrences of leprosy in the north of the city; Northern and Central Health Districts and a small part of the Eastern Health District.

In the period from 2014 to 2016 (Figure 4D), similarly to the other periods, clusters with high occurrence were found in the census tracts located in the Central and Northern Health Districts. However, unlike the other years, hot spots were also identified in census tracts of the Western Health District.

DISCUSSION

Of the total leprosy cases reported in Ribeirão Preto, SP, the highest percentages corresponded
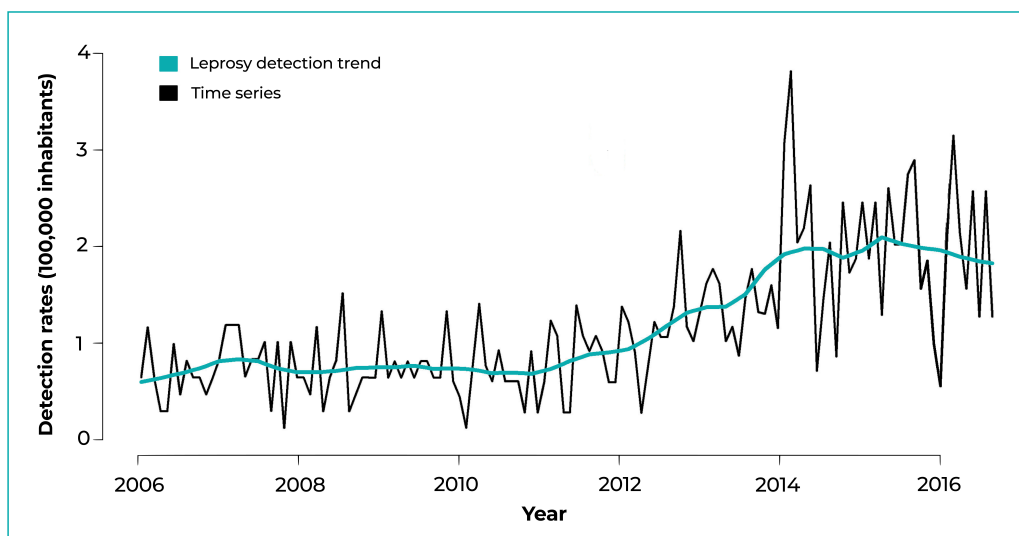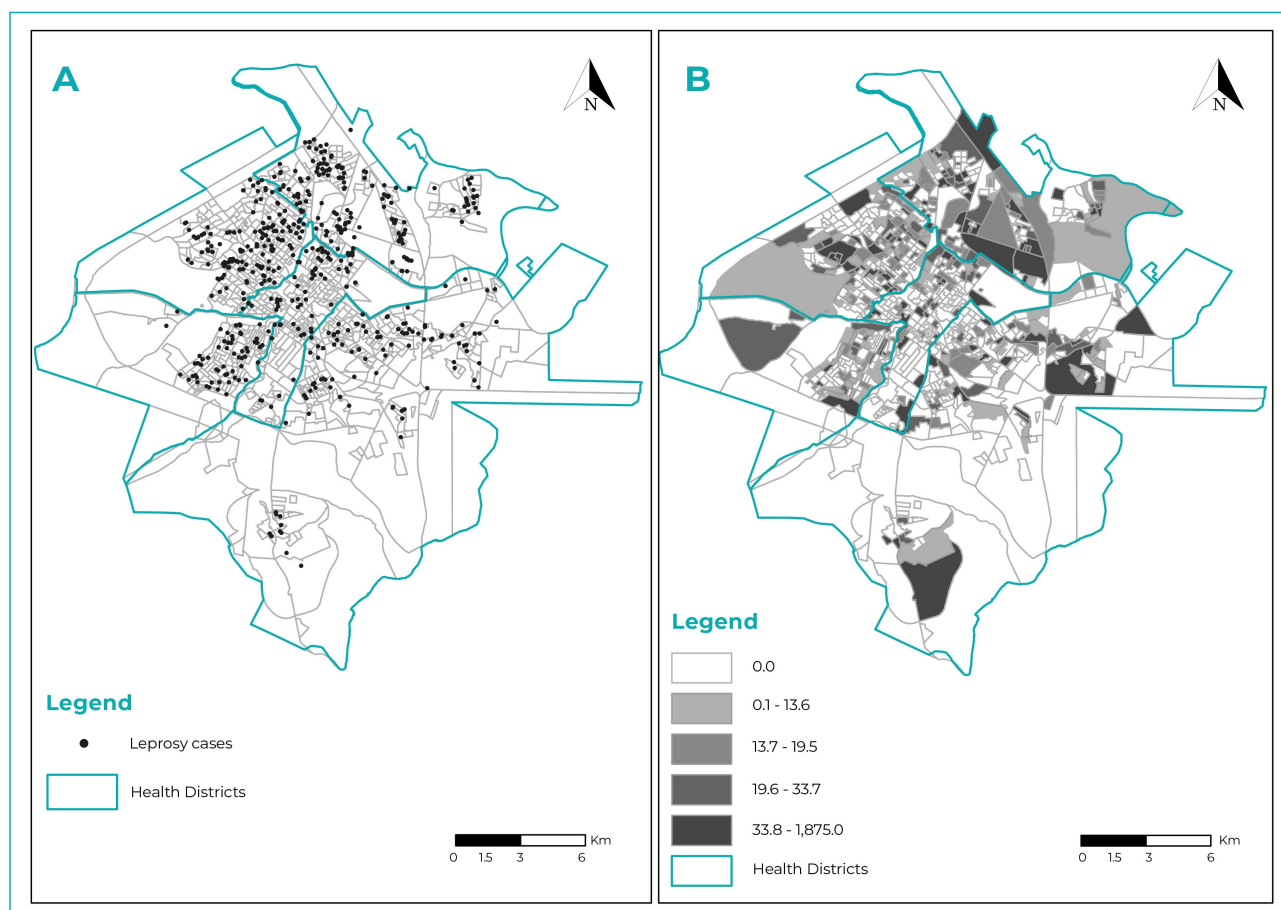
Figure 2 – Time series and temporal trend of leprosy detection rates, Ribeirão Preto, state of São Paulo, Brazil, 2006-2016

A) Spatial distribution of leprosy cases according to census tracts; B) Leprosy case detection rates per 100,000 inhabitants, distributed according to census tracts.

Figure 3 – Leprosy cases georeferenced according to census tracts, Ribeirão Preto, state of São Paulo, Brazil, 2006-2016

to multibacillary cases, with a higher proportion of G1D at the time of diagnosis. Despite the predominance of G1D, it is noteworthy that 16.4% of total cases had G2D, and together G1D and G2D accounted for about 50% of notified cases. The predominance of multibacillary cases together with GD suggests the occurrence of active transmission of the disease, and the high proportion of G2D among new cases may be an indication of failures in case access to diagnosis and follow-up in Ribeirão Preto.[21]

The 30-59 age group was the most affected by leprosy. This is an age range that includes a large portion of the economically active population, among whom the disease can affect job performance, result in limitations and time off work due to the disabilities caused by leprosy and, as a consequence, lead to workers facing sick leave, early retirement and decreased quality of life.[22]

Besides the 30-59 age group, high proportions of cases were found in those aged 60 and over, this being the second most affected age group. The elderly constitute an important group for the control of leprosy, since the disabilities resulting from the disease are more frequent in this age group, which together with the aging process and other comorbidities, contribute to greater vulnerability and loss of autonomy in this group age.[23]
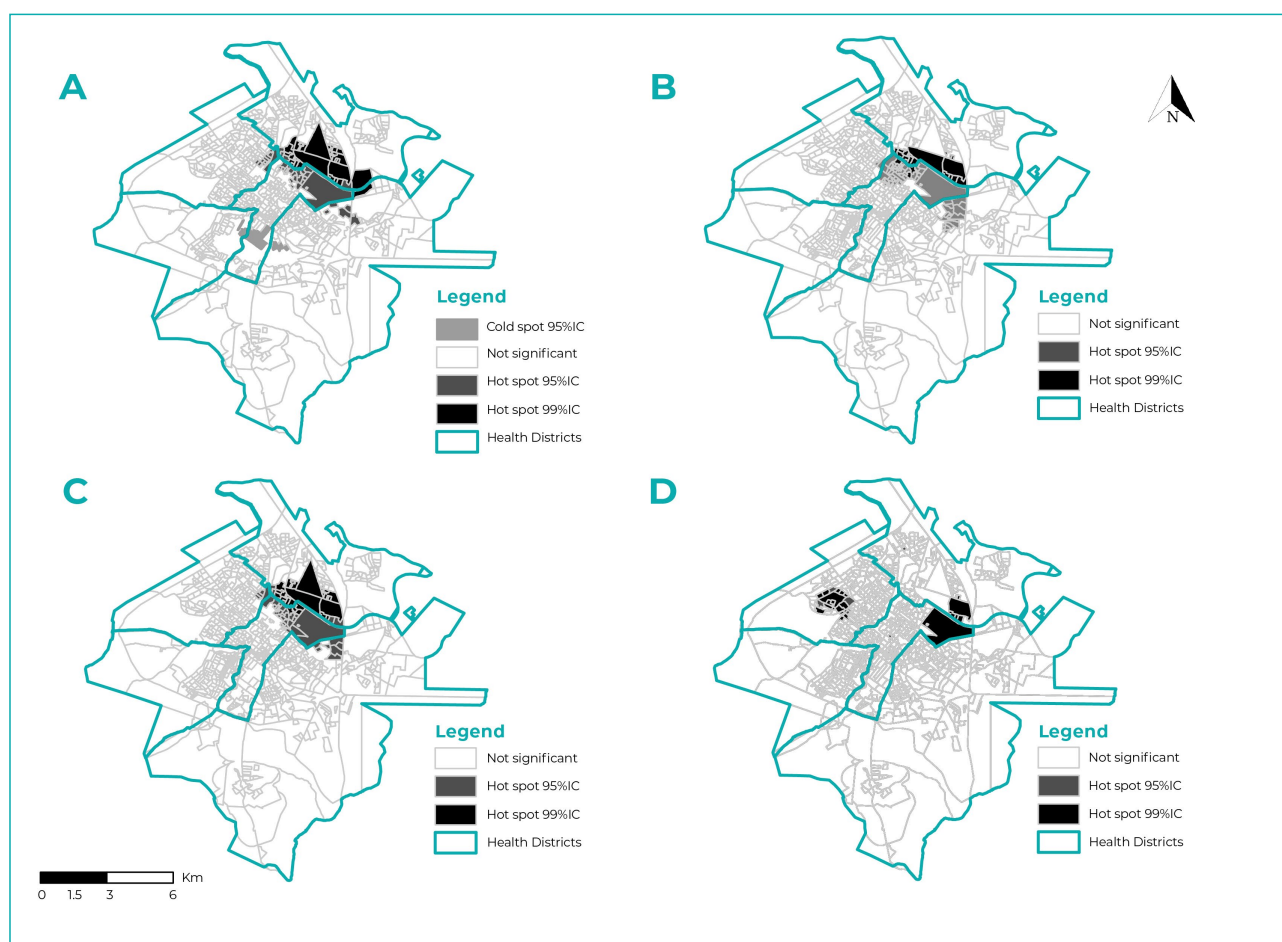
A) 2006-2016; B) 2006-2009; C) 2010-2013; D) 2014-2016; CI: confidence interval.

Figure 4 – Clusters of high and low leprosy detection rate values, distributed according to census tracts, Ribeirão Preto, state of São Paulo, Brazil, 2006-2016

Surveillance actions aimed at early diagnosis and prevention of disabilities should be targeted at all ages and reinforced in the most affected groups, in order to reduce transmission of the disease and prevent disabilities in the population as a whole.

In Ribeirão Preto, most of the cases reported were male, a result that is in keeping with the literature.[24] Occurrence of leprosy is more frequent in males, who are also more vulnerable when compared to females.[25] The higher occurrence of the disease in men may be related to a greater exposure to *M. leprae* due to individual vulnerabilities, such as low demand and/or late demand for health services when compared to women, due to difficulties in accessing health services, which increase the risk of developing disabilities.[26] The finding that males were more affected by leprosy in Ribeirão Preto contributes to the planning of health practices that minimize the risk of leprosy transmission in this population, such as developing public campaigns.

Regarding education levels, most of the notified cases had only elementary schooling, with an average of less than ten years of study. The association between education and leprosy has been studied and has revealed evidence of the following association: low levels or absence of education are related to increased transmission of the disease, and may contribute to an up to twofold increase in its incidence and, consequently, to an increase in physical disabilities.[25,27] Populations with little or no schooling also have greater difficulty in accessing health services and less understanding of the meaning of health actions.[28]

The time series analysis of leprosy identified a rising trend in the detection rate from 2006 to 2016. Although a slight falling trend was seen at the end of the study period, it is noteworthy that the detection rate values were higher at the end of the series than at the beginning. During the study period, leprosy diagnosis and treatment actions were mainly carried out in municipal Reference Centers for leprosy care, so they were not fully decentralized to Primary Health Care.

Despite this characteristic, professional training and active searching for cases are regularly carried out in the municipality, especially with effect from 2011 and 2012, coinciding with the sharp increase in the detection rate trend curve.[29]

While the present study did not directly evaluate the impact of decentralized care and active case-finding actions, following professional training and community outreach measures, studies carried out in low-endemicity leprosy settings identified a significant increase in the number of reported cases, with a clear impact on the increase in detection rates, evidencing that such low-endemicity settings may harbor "hidden leprosy endemicity".[6,7]

The analysis of the time series indicated that the leprosy detection rate showed a rising trend over the study period as a whole, providing evidence that, even in a scenario of low endemicity, in which occurrence of the disease presents stability, there may be active transmission of *M. leprae*. This finding reinforces the importance of the need for constant actions involving active searching for and detection of new cases.

By using the Getis-Ord Gi* technique it was possible to identify areas of high and low occurrence of leprosy in Ribeirão Preto, over the period of time observed, showing that the disease is heterogeneously distributed in the city. In all analyzed periods, the areas of higher occurrence were located in the northern region of Ribeirão Preto, while the areas of low risk were located in the southern region of the city (identified here only on the map of the complete period, from 2006 to 2016). There was an exception in the final period of investigation, from 2014 to 2016, when hot spots were present in the Western Health District. Some Health Districts shared both hot spots and cold spots (Central and Eastern), although these are in opposite areas of these regions.

The Northern Health District, which had the highest occurrence of clusters of cases in all periods, is composed of the neighborhoods with the lowest social indicators among the five Health Districts, with the highest percentage of

people with no income or income below one minimum wage, the lowest municipal human development index (HDI-M), the lowest school attendance rates and the highest number of crowded substandard living conditions (slums) in the municipality.[30]

The Central Health District, composed of both high-risk (to the north) and low-risk (to the south) clusters, is made up of the city's oldest neighborhoods, with a high percentage of residents over 60 years old.[30] The Central Health District has the main referral center for leprosy cases, although it has low Family Health Strategy coverage.[30] Although the Central Health District has both hot spots and cold spots, they are geographically opposite to each other, so that its hot spots have similar characteristics to those of the Northern Health District, while its cold spots are similar in their characteristics to those of the Eastern and Southern Health Districts.

The Western Health District, which had hot spots in the period 2014-2016, is characterized by having a complex health service network, with a greater number of Primary Health Care centers. Regarding social indicators, in this district there is a predominance of households with families whose income is between one and five minimum wages and crowded substandard living conditions.[30] The hot spots found in Western Health District in the final years of the study may reflect increased case detection in this region, thus influencing spatial distribution of the disease.

The high-risk clusters in the Eastern Health District comprise few census tracts and border the Central Health District tracts, so they may share similar characteristics with this region.

In the southern region of the city, besides the Central Health District cold spots, cold spots are also found in a small number of census tracts in the Eastern and Southern Health Districts; the latter Health District did not have hot spots, and is therefore the region in which occurrence of leprosy is lowest. The Eastern and Southern Health Districts are characterized by better socioeconomic indicators, better HDI-M, a population with higher levels of education and a low proportion of people with no income. Another characteristic of these Health Districts is that they have the highest concentration of neighborhoods where real estate speculation is more active.[30]

In Ribeirão Preto, analysis of the spatial association of the occurrence of cases and their distribution over time reinforces the fact that leprosy is a social disease: the areas with the highest concentration are located predominantly in the northern region of the city of Ribeirão Preto, historically characterized by great social inequality. These results can support the formulation of intervention strategies in these territories, especially actions involving active searching for cases, which should impact indicators and contribute to reducing transmission of the disease.

The main limitation of this study refers to its ecological design, which does not allow its results to be generalized to the individual level. Another limitation of the study is the use of secondary data, which are sometimes unavailable or incomplete. Finally, the time series rates were calculated based on population estimates, which may not fully reflect the size of the population in the period.

In conclusion, the time series analysis in Ribeirão Preto identified a rising trend in the leprosy detection rate during the study period, raising the hypothesis that, even in a scenario of low endemicity, existence of high transmission of the disease remains. The spatial-temporal analysis made clear that the disease is heterogeneous in Ribeirão Preto, with well-defined behavior over time, and that the north of the city is the region with the greatest social inequalities and areas with the highest rates of the disease.

The results of this investigation can inform health surveillance actions aimed at leprosy control. The understanding of aspects related to the profile, time trend and spatial distribution of cases in the municipality of Ribeirão Preto, São Paulo, can serve as a guide to where its main leprosy control actions should be focused.

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