

Related factors, time trend and spatial association of abandonment of treatment for tuberculosis in Ribeirão Preto-SP

Fatores relacionados, tendência temporal e associação espacial do abandono de tratamento para tuberculose em Ribeirão Preto-SP

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ABSTRACT

The objective was to identify related factors, classify the time trend and identify areas with spatial association of abandonment of treatment for tuberculosis in Ribeirão Preto, São Paulo. Ecological study; population composed of the cases notified between 2006 and 2017. The chi-square test was performed to identify related factors. For the time trend, the Prais-Winsten method was used to classify the time trend of the event and calculate its percentage of annual variation. To verify spatial association the G and G_i^* techniques were used. In the period, 146 cases of abandonment of the disease treatment were notified; as risk factors, people without education, retreatment after abandonment, and previous failure were identified; as protection, new cases were identified by active search, no Tuberculosis-HIV co-infection, and no alcohol or drug use. The abandonment rate shows an increasing trend (APC=1.6%; 95%CI 0.02–3.48). The study evidences the increase of abandonment of treatment, contradicting the policies directed by the End TB Strategy.

Descriptors: Tuberculosis; Treatment Adherence and Compliance; Public Health; Spatial Analysis.

RESUMO

Objetivou-se identificar fatores relacionados, classificar a tendência temporal e identificar áreas com associação espacial do abandono de tratamento para tuberculose em Ribeirão Preto, São Paulo. Estudo ecológico; população composta pelos casos notificados entre 2006 a 2017. Realizou-se o teste qui-quadrado para identificar fatores relacionados. Para a tendência temporal, utilizou-se o método de *Prais-Winsten* para classificar a tendência temporal do evento e calculada sua porcentagem de variação anual. Para verificar associação espacial, utilizaram-se as técnicas *G* e G_i^* . Foram notificados 146 casos de abandono do tratamento da doença no período; como fatores de risco foi identificado pessoas sem escolaridade, retratamentos pós-abandono e falência prévia; como proteção casos novos identificados pela busca ativa, não ter coinfeção Tuberculose-HIV e não fazer uso de álcool ou drogas. A taxa de abandono apresenta tendência crescente (APC=1,6%; IC95% 0.02–3.48). O estudo evidencia o aumento do abandono de tratamento, contrariando as políticas direcionadas pelo *End TB Strategy*.

Descritores: Tuberculose; Cooperação e Adesão ao Tratamento; Saúde Pública; Análise Espacial.

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INTRODUCTION

Tuberculosis (TB) is one of the main public health problems worldwide. According to the World Health Organization (WHO), in 2015 about 10.4 million people became ill and 1.4 million died of the disease, becoming the world's leading cause of death by a single infectious agent⁽¹⁾. Brazil ranks 20th in this ranking, with an incidence of 33.5 cases per 100,000 inhabitants and mortality equal to 2.1 deaths per 100,000 inhabitants, with an average annual decrease of 2.0% from 2007 to 2016⁽²⁾.

Although the country has succeeded in detecting cases (above 70%), the critical node regarding the elimination of the disease (<1 case per 100,000 inhabitants) refers to the completion of treatment (around 70%, when the minimum expected is 85%)⁽¹⁾.

The low adherence to the treatment, evidenced by high rates of abandonment, contributes to the high incidence of the disease, besides being a risk factor for the appearance of multidrug-resistant bacilli⁽¹⁾.

Abandonment of treatment is considered when the patient, after having started treatment for TB, has stopped turning up to the health unit for more than 30 consecutive days, after the date determined for his return. Among its precursors, the side effects of drugs, social determinants, non-inclusive and/or unwelcoming health service policies, non-individual therapeutic projects, and no link with the health professional stand out⁽³⁾.

The own characteristic of Directly Observed Therapy (ODT), a strategy recommended by the WHO, has been highlighted as a treatment-related aspect, if flexible/inclusive/universal and/or normative/selective, which impose requirements and obligations, which they are not always able to meet⁽³⁾.

Abandonment of treatment has often been described as an important factor for the quality evaluation of health services in the context of "hard to reach populations"; highlighting territories at risk is thus advancing policies aimed at eliminating the disease⁽³⁾.

In the scientific literature, there is a large number of studies that analyzed the abandonment of TB treatment; however, few studies have utilized spatial analysis to understand the dynamics of this event in an endemic community⁽⁴⁾, being important to support decision making and implementation of measures of different magnitudes in light of the predisposing factors of the occurrence of the event addressed.

Another knowledge gap refers to the time trend, with no evidence that this event is on the rise, declining or remains stationary, which would be an important indicator to help evaluate the effectiveness and/or impact of the measures adopted so far in the territories.

That way, with the present study, it was proposed to identify related factors, classify the time trend of abandonment of

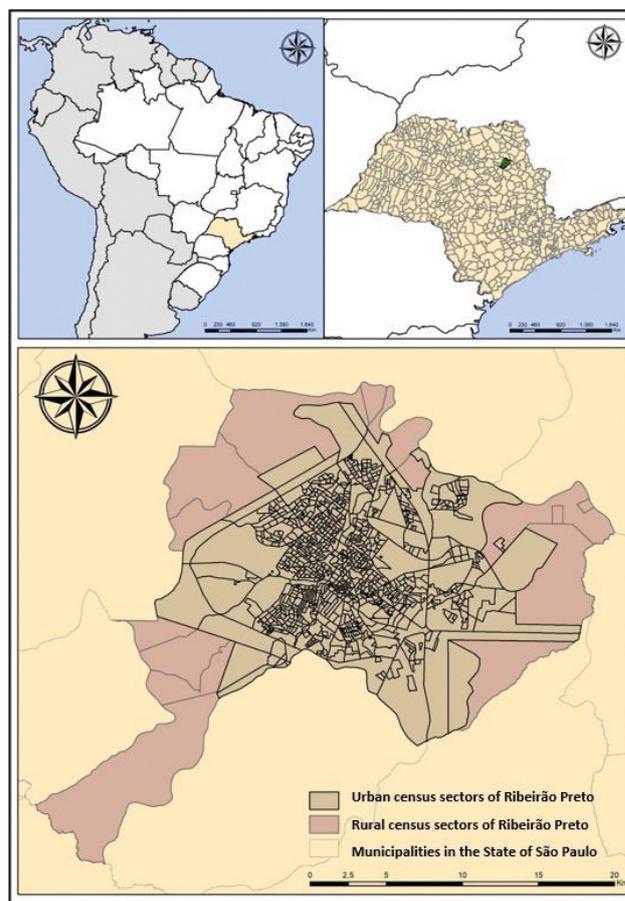
treatment for TB and identify areas with spatial association of this phenomenon in Ribeirão Preto, an endemic municipality in the interior of São Paulo state.

METHOD

This is an ecological study conducted in Ribeirão Preto, interior of São Paulo, 314km from the capital of São Paulo (Figure 1). It has an area of approximately 650km² and a high demographic density of 995.3 inhabitants per km². It also has an estimated population of 647,862 inhabitants in 2010, 99.7% of which live in urban areas⁽⁵⁾.

Regarding the Health Care Network, the municipality has five Health Care District Units (DS) that are divided into North, South, East, West and Central, totaling 49 Primary Health Care (PHC) establishments, being five District Health Care Units (UBDS), 18 Family Health Units (USF) and 26 Basic Health Care Units (UBS)⁽⁶⁾.

Concerning the attention to the TB patient in the city, where the Basic Health Units are responsible for actively searching for respiratory symptoms, with collection of



Source: author's archive.

Figure 1. Geographic location of the municipality. Ribeirão Preto, SP, Brazil, 2019.

smear and/or request for X-ray. However, the treatment and follow-up of TB cases are carried out in the specialized infectology outpatient clinics, not occurring in a decentralized way. Therefore, after confirmation of the diagnosis of TB, the patient is referred to one of the specialized outpatient clinics, which perform the medical follow-up and supervised treatment, as recommended by the Municipal Tuberculosis Control Program⁽⁶⁾.

It should be highlighted that the census sector was used as a unit of ecological analysis, as it presents the advantage of being the most disaggregated level of population and socioeconomic groups collected systematically, periodically and with a standardization of national scope⁽⁷⁾. The cartographic base of the census sectors in Ribeirão Preto was obtained from the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* – IBGE) website free of charge.

Ribeirão Preto is divided into 972 census sectors, but for this study we chose to use only the urban census sectors of the municipality, corresponding to 956 units of analysis.

The study population was composed of all TB cases reported in the Tuberculosis Patient Control System (TBWeb) from 2006 to 2017 of the Epidemiological Surveillance Service in Ribeirão Preto Municipal Health Secretariat that were abandoned as a treatment outcome. All confirmed cases of TB, residents of the urban area of Ribeirão Preto, were considered. As a selection criterion, only one registry per person was adopted.

After consistency analysis of the database, exploratory analyses were performed to characterize the profile of cases of abandonment of treatment for TB and then an association of the variables with the variable of interest (having abandoned treatment for TB) was verified by means of Pearson's chi-square analysis and for the variables that were statistically significant (value $p < 0.05$), the Odds Ratio (OR) and 95%CI were calculated using IBM SPSS software version 25.

After, the TB discontinuation rate was determined from the number of cases diagnosed per year (from 2006 to 2017) and subsequently these rates were logged (\log_{10}) for subsequent steps.

For the time trend analysis, the self-regression method known as Prais-Winsten was used⁽⁸⁾. This method considers and corrects the first-order time autocorrelation in the analysis of time organized value series⁽⁹⁾. The annual change (Annual percent change – APC) of the abandonment rate for the treatment of TB and its respective 95% confidence intervals (95%CI) were also calculated^(9,10). A significance level of 5% was adopted where non-significant value will be classified as stationary or significant value will be classified as increasing or decreasing according to its 95%CI.

In order to verify the spatial association of abandonment of treatment for TB, the Getis-Ord General G and Getis-Ord

G_i^* techniques were used, using the rates calculated previously. The Getis-Ord General G technique, based on Moran's Global Index and, as in the inferential statistics, the results are based on the null hypothesis that there is no spatial grouping. If the p-value is significant, the null hypothesis can be rejected and the z-score value becomes important, where its values of ± 3 represent a confidence level of 99%^(11,12). If the z-score value is positive, the observed G Index is higher than expected, indicating high event indices grouped in the study area. If the z-score value is negative, the observed G Index is smaller than the expected index, indicating that low values are grouped in the study area⁽¹⁰⁾.

The Getis-Ord G_i^* technique, in turn, indicates local association, considering the values for each census sector of the municipality from a neighborhood matrix. In this analysis a z-score is also generated for the statistically significant census sectors. The higher the z-score, the more intense is the grouping of high values (Hotspot), while the lower the value, the more intense is the grouping of low values or the lower occurrence of the event (Coldspot)⁽¹⁰⁾.

In addition to the z-score, the p-value and significance level (Gi-Bin) is provided. Gi-Bin values identify statistically significant hot and cold points. Values vary from ± 3 and reflect statistical significance with a 99% confidence level, ± 2 95% confidence level, ± 1 90% confidence level and zero is not statistically significant⁽¹⁰⁾.

Posteriorly, all health units in the municipality were geocoded to verify the existence of patterns between the number of health units and the areas with spatial association identified by the Getis-Ord G_i^* technique.

The study was approved by the Research Ethics Committee of the Ribeirão Preto School of Nursing, with the Certificate of Presentation for Ethical Appreciation (CAAE) no. 87696318.3.0000.5393 and Protocol no. 3.294.221.

RESULTS

In the period 2006 to 2017, 2,115 cases of TB in Ribeirão Preto were notified, of which 6.9% ($n=146$) abandoned treatment. Table 1 presents the epidemiological profile of cases that have withdrawn from treatment for TB.

With Pearson's chi-square analysis (χ^2), it was possible to find an association with the studied outcome, in which people who do not have any year of study present 1.63 times (95%CI 1.03–2.57) more chance of abandoning treatment, new cases present 1.87 times more chance (95%CI 1.11–2.02), retraction after abandonment (OR=0.05; 95%CI 0.038–0.092) and retreatment after failure or resistance (OR=0.16; 95%CI 0.05–0.54).

As protective factors for abandonment of treatment, new cases were identified by active search (OR=0.67; 95%CI 0.45–0.99), not having TB-HIV co-infection (OR=0.57;

Table 1. Characteristics and factors related to cases that abandoned the treatment of Tuberculosis. Ribeirão Preto, SP, Brazil (2006–2017)**.

Variables	N (146) (%)	Pearson Chi-square (χ^2)	p-value	Odds Ratio (95%CI)
Age (years)				
0 to 14	3 (2.0)	1.31	0.25	–
15 to 30	40 (27.3)	345	0.06	–
31 to 59	85 (58.2)	0.01	0.96	–
Above 60	17 (11.6)	0.68	0.13	–
Ignored	1 (0.6)	–	–	–
Sex				
Male	105 (71.9)	0.83	3.36	–
Female	41 (28.1)	–	–	–
Race				
Yellow	1 (0.7)	0.80	0.36	–
White	60 (41.1)	0.10	0.75	–
Brown	25 (17.1)	0.07	0.78	–
Black	13 (8.9)	0.45	0.49	–
Ignored	47 (32.2)	–	–	–
Years of Study				
From 1 to 3	9 (6.2)	1.77	0.18	–
From 4 to 7	42 (28.8)	0.04	0.83	–
From 8 to 11	27 (18.5)	1.09	0.29	–
From 12 to 14	4 (2.7)	0.14	0.70	–
15 and over	1 (0.7)	1.11	0.29	–
None	3 (2.1)	4.58	0.03	1.63 (1.03–2.57)
Ignored	60 (41.1)	–	–	–
Profession/Employment Relationship				
Unemployed	8 (5.4)	2.22	0.13	–
Formal Work	7 (4.7)	1.21	0.27	–
Informal Work	25 (17.0)	0.03	0.84	–
Retired/Beneficiary	1 (0.6)	0.04	0.83	–
Ignored	105 (71.9)	–	–	–
Type of Case				
New	86 (58.9)	101.14	p<0.01	1.87 (1.11–2.02)
Recurrence	12 (8.2)	0.01	0.95	–
Retreatment after abandonment	45 (30.8)	260.19	p<0.01	1.05 (1.03–1.09)
Retreatment after failure or resistance	3 (2.1)	11.47	P<0.01	1.16 (1.05–1.54)

Continue...

Table 1. Continuation.

Variables	N (146) (%)	Pearson Chi-square (χ^2)	p-value	Odds Ratio (95%CI)
Classification				
Extrapulmonary	18 (12.3)	–	–	–
Pulmonary	128 (87.7)	6.30	0.01	0.55 (0.35–0.88)
Discovery				
Active Search	1 (0.7)	3.64	0.05	0.67 (0.45–0.99)
Outpatient Demand	71 (48.6)	0.05	0.82	–
Diagnostic Elucidation in Hospitalization	34 (23.3)	0.06	0.79	–
Urgence	30 (20.5)	0.01	0.98	–
Ignored	10 (6.9)	–	–	–
TB-HIV Coinfection				
No	99 (67.8)	9.93	p>0.01	0.57 (0.40–0.81)
Yes	47 (32.2)	–	–	–
TB-Diabetes Coinfection				
No	142 (97.3)	1.56	0.21	–
Yes	4 (2.7)	–	–	–
Alcoholism				
No	104 (71.2)	11.29	p<0.01	0.54 (0.37–0.77)
Yes	42 (28.8)	–	–	–
Mental illness				
No	141 (96.6)	1.22	0.26	–
Yes	5 (3.4)	–	–	–
Drug addiction				
No	102 (69.9)	59.42	p<0.001	0.25 (0.17–0.36)
Yes	44 (30.1)	–	–	–
Smoking				
No	137 (93.8)	0.56	0.45	–
Yes	9 (6.2)	–	–	–

Notes: **Calculated the measure of association only for those variables with p<0.05.

Source: research database.

95%CI 0.40–0.81) besides not using alcohol (OR=0.54; 95%CI 0.37–0.77) and drugs (OR=0.25; 95%CI 0.17–0.36).

Through the Prais-Winsten autoregression in the period between 2006 to 2017, it was possible to observe that the abandonment rate of treatment for TB in the municipality of Ribeirão Preto shows an increasing trend, with APC=1.6% (95%IC 0.02-3.48).

Figure 2A shows the local spatial association of treatment abandonment rates for TB using the Getis-Ord G_i^* technique, allowing the identification of hotspots or hot areas (high-clusters) in the central, western and northern regions of the municipality with confidence levels of 90, 95 and 99%, i.e., in these areas there was a grouping of high values or higher occurrence of the analyzed event. It also allowed

the identification of coldspots or cold areas (low-clusters) in the eastern region of Ribeirão Preto, areas with a grouping of low values or lower occurrence of the analyzed event, with confidence levels of 90, 95% and 99%. With the Getis-Ord General G technique presented in Figure 2B, a z-score of 2.73 was obtained and through the pseudo-significance test it was possible to confirm the non-randomness of the clusters ($p < 0.01$), thus it is possible to verify that in the municipality there is formation of clusters, identified by G_i^* .

As to the Figure 3 shows the areas with spatial association previously identified with the geocoding of all 49 health units in the municipality, including the reference centers for TB care according to the area of coverage of each health unit. The Eastern district has seven health facilities, the Southern district has five, the Western district has 20, the Northern district has 11, and finally the Central district has six health units.

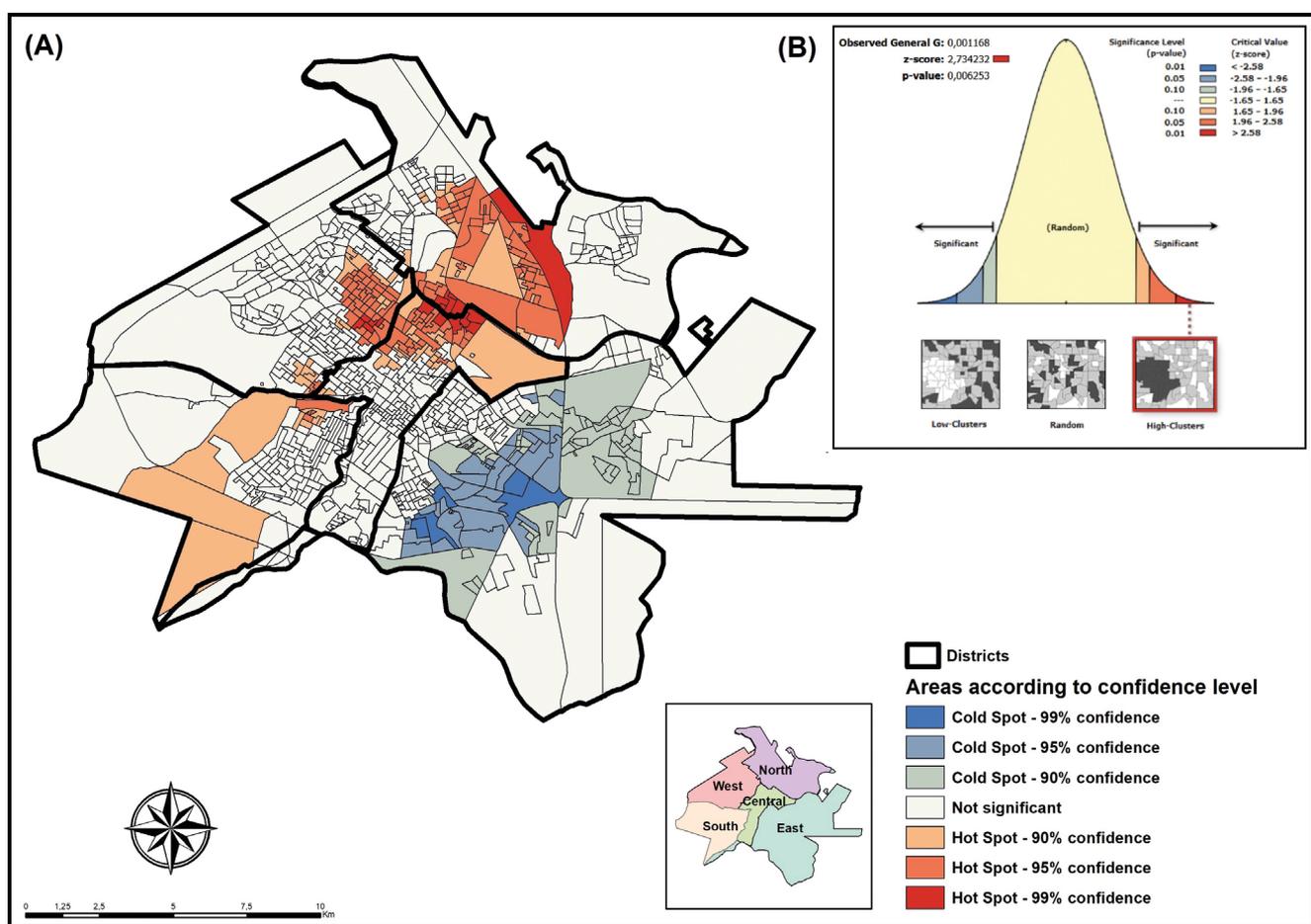
As to the areas where there was the lowest occurrence of abandonment of treatment in the areas where the highest incidence of abandonment of treatment has occurred, are the areas of coverage of six health units in the Northern District;

five units in the Western District; three units in the Southern District and one health unit in the Central District. As to the areas where there was grouping of lowest occurrences of abandonment of treatment, are the areas of coverage of six health units, all in the Eastern District.

DISCUSSION

The main results of this study were: associated to risk factors such as low education, new cases of the disease identified through active search, cases of retreatment after abandonment, failure or drug resistance; as to the pulmonary clinical form, new cases through active search, not having HIV and the patient not making use of alcohol and illegal drugs, were protective factors for abandonment. The time trend of treatment abandonment was classified as increasing and areas with spatial association of the event in the municipality were identified.

In this study, it was found that patients with low education present a higher risk of treatment abandonment, which may



Source: Author's archive.

Figure 2. High-clusters and Low-clusters for the abandonment of treatment for Tuberculosis. Ribeirão Preto, SP, Brazil, 2006–2017.

be related to the difficulty in understanding about the disease and its form of treatment⁽¹¹⁾. In this sense, it is a fundamental role of health professionals, with emphasis on nurses, to question the patient on the understanding of his/her situation and reinforce the aspects related to the disease and treatment transmissibility, always providing clear information and reinforcing all aspects that may generate doubts, thus trying to minimize unfavorable outcomes^(12,13).

New cases of TB present 1.87 times more chance of abandoning TB treatment. An integrative review of the literature⁽¹⁴⁾ points out that being in the initial phase of therapy, suffering from adverse effects of medication and presenting rapid symptomatic improvement contribute to treatment abandonment.

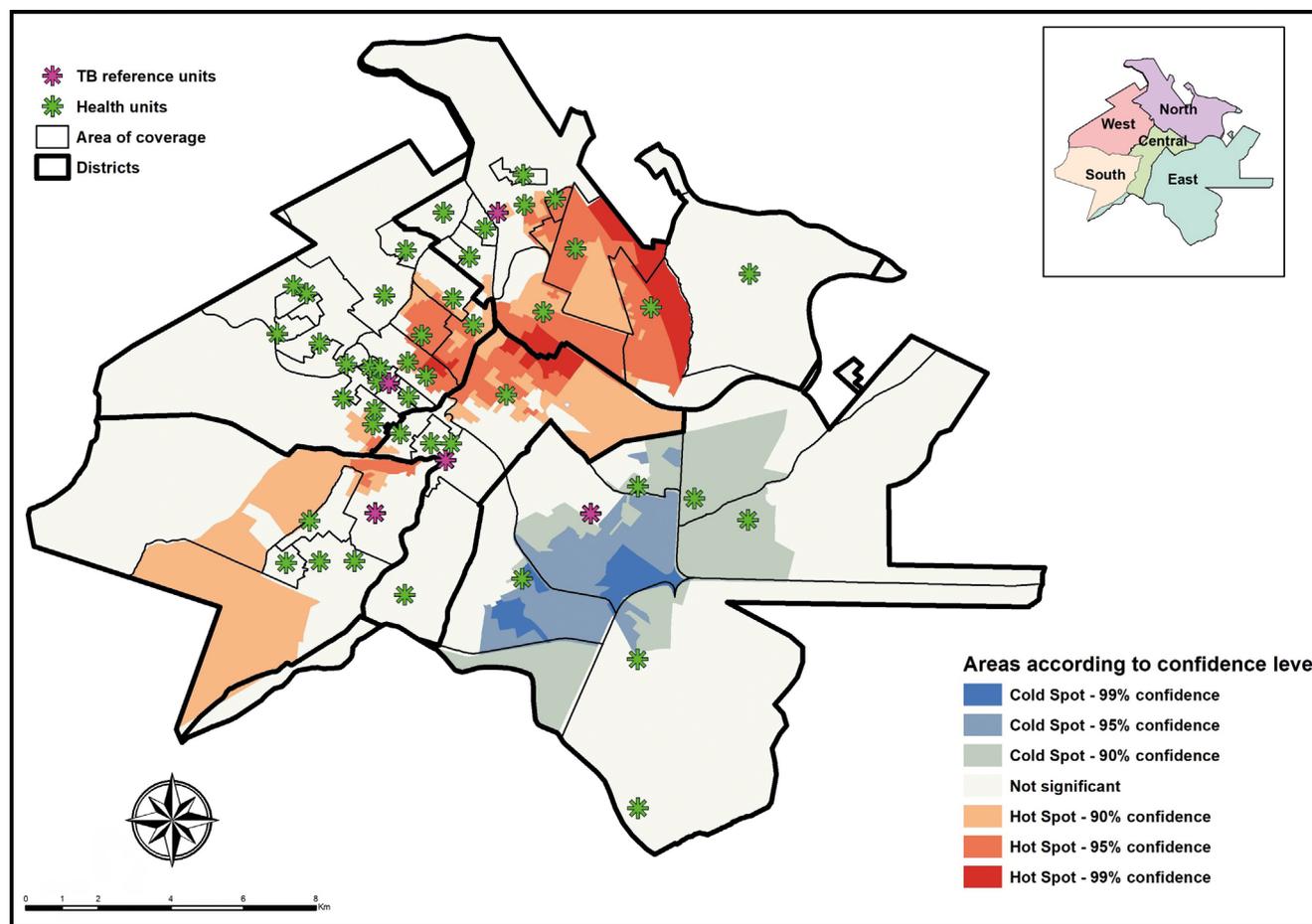
Cases of retreatment after previous abandonment and retreatment after failure or drug resistance presented 1.05 and 1.16 times more chance to abandon treatment, respectively. Investigators⁽³⁾ reported that patients with previous abandonment, the chance of a new interruption in therapy is three times higher. Thus, these patients should have greater

attention from health professionals in order to emphasize and make the patient aware of the importance of adherence to the treatment and its conclusion.

The factors that motivated prior abandonment should be investigated in order to avoid unfavorable outcomes and selection of resistant bacilli, which makes it a challenge for the health system and TB control, considering the impact on costs in relation to treatment time and aggravation of cases for hospitalization⁽¹⁴⁾.

The pulmonary clinical form presented itself as a protective factor against abandonment of treatment when compared to extrapulmonary TB. The extrapulmonary form of TB has a treatment time of 12 months and generally consists of cases of greater complexity according to the organ affected by the disease. The invasive diagnosis, low probability of bacillus culture and uncertain clinical evaluation are reasons why abandonment of treatment is greater in extrapulmonary cases, making pulmonary TB a protective factor⁽¹⁴⁾.

The identification of new cases through active search is a protective factor for abandonment in this study, which may be



Source: author's archive.

Figure 3. Relationship of the municipality's health units with the areas of spatial association for the abandonment of treatment of Tuberculosis identified according to area of coverage. Ribeirão Preto, SP, Brazil, 2006–2017.

associated with initial contact with the patient and appropriate guidance on the importance of treatment, through the link established between the team, patient and family, favoring co-responsibility and humanized welcome. When patients are cared for by the same professional, the creation of a bond is favored, so that patients see these professionals as a reference in their health care. The accompaniment of the patient by this professional considered as a reference allows the strengthening of the bond created, benefits the participation of the patient as a protagonist of his treatment and facilitates the evaluation of problems encountered in previous consultations, thus providing a more effective assistance. A study carried out shows that when the same professional care for the patients, it is easier to identify those at risk for abandonment and to pay special attention to such cases^(16,17).

It was possible to identify that not having HIV associated with TB is also a protective factor against abandonment of treatment. In cases of TB/HIV co-infection, a study identified that treatment for both diseases has a significant impact, with increased drug burden and side effects⁽¹⁴⁾.

A qualitative study⁽¹⁸⁾ that sought to analyze the reasons that lead TB-HIV co-infected patients to abandon TB treatment identified that factors related to patients that contribute to abandonment are low socioeconomic status, adverse effects of the drugs, drug use and low personal motivation. In addition, factors related to health services that also contribute to abandonment of treatment were identified, such as physical structure, work process organization, and access.

Finally, also as a protection factor against abandonment of treatment is the fact that the patient does not use alcohol or drugs. The use of illegal or licit drugs, such as alcohol, presents as a poor prognosis for the treatment of TB, commonly when it does not contribute to abandonment, generating a delay and/or prolongation of treatment⁽¹⁹⁾. Drug use and consequent abandonment of treatment may be related to the concomitant process of chemical dependence, which, together with the responsibility for taking medication and regular visits to health services, hinders the continuity of treatment, in addition to implying in the forgetfulness of drug taking and potentiation of hepatotoxic effects⁽¹⁴⁾.

Through the Prais-Winsten self-regression technique for time series classification, it was possible to observe that the abandonment rate for TB treatment in the municipality of Ribeirão Preto shows an increasing trend in the period between 2006 and 2017, with 1.6% annual growth.

Considering that the rate of abandonment of treatment for TB presents an increasing trend in the municipality, health education strategies regarding the disease and its treatment are necessary, in order to minimize stigma and misconceptions, in addition to the awareness of the importance of performing the complete treatment, explaining in detail the long duration of treatment and the possible side effects of the drugs, this

empowerment of the patient makes them co-responsible for the success or failure of the treatment, motivates them to an increased adherence and increases the chance of positive outcomes⁽¹⁴⁾.

With the identification of hot and cold areas for abandonment of treatment, it was possible to confirm that clusters do not form randomly in the space, and cases of abandonment of treatment for TB are unequally distributed in the municipality. A hot area was identified that encompasses the central regions (high rate of street dwellers), west and north (regions with the highest amount of subnormal clusters in the municipality, coinciding with areas with high concentration of poverty and intermediate living conditions)⁽⁷⁾ that, in general, correspond to areas with higher social vulnerability and also higher incidence and prevalence of TB, as already evidenced in other studies^(20,21). PHC plays a determining role in social protection and equity, despite the fact that the districts present differences in terms of social vulnerability⁽²⁰⁾.

It was also possible to identify coldspots in the eastern region of Ribeirão Preto (one of the most valued regions), thus, once again, the unequal distribution of TB cases in the municipality is highlighted. These identified cold areas should be analyzed with caution, as they may be indicating underreporting or poorly filled information with respect to the treatment outcome.

In Ribeirão Preto, all basic health units should perform active search for respiratory symptoms. However, after the decentralization of the attention to the TB patient in the city, it was opted for its treatment and follow-up with the specialized infectology outpatient clinics. Thus, after the diagnosis of TB, the patient is referred to one of those outpatient clinics, where they perform medical follow-up and supervised treatment, in accordance with the recommendations of the Municipal Tuberculosis Control Program⁽⁶⁾.

Thus, the service should be organized and offered in such a way as to supply the demand of that area, and according to the principle of equity, in places with fewer social opportunities or with a population with more vulnerable socioeconomic characteristics should present PHC in a stronger and more effective manner⁽²⁰⁾.

For the success of TB treatment, the conduct of health care teams in the care for the patient is extremely important, because it is mainly the role of health professionals to clarify any questions the patient has about his condition, in addition to all information about the treatment and its duration, the importance of regularity and non-interruption in the use of medications and the possible consequences of abandonment of treatment.

Thus, the determination of an organized flow aiming the early diagnosis and also ensuring the continuity of care brings users closer to the health service, strengthening the link and expediting the resolution of the presented health needs⁽²²⁾.

CONCLUSION

The use of spatial analysis tools has allowed the identification of hot and cold areas for the abandonment of treatment for TB, and adherence to treatment is one of the greatest challenges in the control of the disease and, in this sense, the link of the patient with the professional and also with the health service becomes fundamental.

The study also shows a growing trend of abandonment of treatment for TB in the municipality, as it goes against the policies aimed at eliminating TB through the End TB Strategy, thus requiring the attention of health authorities, since the policies and actions are not being effective, especially with regard to the completion of treatment, mainly with regard to the hot areas identified in the study; although the municipality may have advanced in terms of time of diagnosis from the implementation of the molecular rapid test, there are still shortcomings in ensuring patient follow-up and adherence to treatment.

It is reinforced that community involvement can be an effective mechanism to promote treatment completion, since raising awareness and educating populations at risk, involving family and community as a whole can improve the indicators of the scenario under study.

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