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Tuberculosis space-temporal distribution from 2011 to 2016 in the municipality of Maputo, Mozambique

Distribución espacio-temporal de la tuberculosis de 2011 al 2016 en el municipio de Maputo, Mozambique

Antonio C. Titosse¹, Marcus Vinícius Pimenta Rodrigues², Ana Paula Marques Ramos³, Lucas Prado Osco⁴, Rogério Giuffrida⁵, Elivelton da Silva Fonseca⁶ y Alba Regina Azevedo Arana⁷

ABSTRACT: Objective: Carry out a spatial-temporal characterization of the incidence of tuberculosis (TB) in Maputo, Mozambique. **Method:** a descriptive ecological study of tuberculosis cases reported in an information system. The annual mean incidence rate and the number of TB notification cases in the municipality of Maputo from 2011 to 2016 were analyzed. Descriptive statistics were used with calculations of measures of central tendency (mean) and an application of the Poisson linear regression model. Trimester notifications were stratified by district, clinical form, and age group. The quarterly average temperature of the evaluated area was added as a covariate in the model seasonal. **Results:** 34,623 TB cases were notified from 2011 to 2016, with a trimester average of 1,443 cases. The average annual incidence was higher in the Kampfumo district, with 909.8 per 100 thousand inhabitants (95% CI 854.1 - 968.2); almost twice as much as the incidence of the municipality of Maputo, 527.8 (95% CI 514, 3-541.6), and the country of Mozambique, 551 (95% CI 356 - 787). The clinical diagnosis of the tested cases was higher concerning the bacteriological diagnosis; 44%, and 35%, respectively. **Conclusion:** Maputo had similar incidence rates to the country of Mozambique, however, there was a heterogeneity rate by district and a reduction in the number of TB cases in both the general population (not co-infected with HIV) and those over 15 years old, being higher in the first trimester.

Keywords: Epidemiology, spatial-temporal analysis, public health, Mozambique.

RESUMEN: Objetivo: realizar una caracterización espacio-temporal de la incidencia de tuberculosis (TB) en Maputo, Mozambique. **Método:** estudio ecológico descriptivo de casos de tuberculosis reportados en un sistema de información. Se analizó la tasa de incidencia media anual y el número de casos de notificación de TB en el municipio de Maputo entre 2011 y 2016. Se utilizó estadística descriptiva para calcular las medidas de tendencia central (media) y la aplicación del modelo de regresión lineal de Poisson. Las notificaciones trimestrales se estratificaron por distrito, forma clínica y grupo de edad. **Resultados:** se notificaron 34,623 casos de TB entre 2011 y 2016, con un promedio trimestral de 1,443 casos. La incidencia anual promedio fue mayor en el distrito de Kampfumo, 909.8 por cada 100 mil habitantes (IC 95% 854.1 - 968.2), casi el doble que la incidencia del municipio de Maputo, 527.8 (IC 95% 514, 3-541.6), y el país de Mozambique, 551 (95% CI 356 - 787). El diagnóstico clínico de los casos fue mayor en relación al diagnóstico bacteriológico, 44% y 35%, respectivamente. **Conclusión:** Maputo tuvo tasas de incidencia similares a las del país, sin embargo, hubo

una heterogeneidad en las tasas por distrito y una reducción en el número de casos de TB en la población general (no coinfectados con VIH) y en los mayores de 15 años, siendo mayores en el primer trimestre.

Palabras clave: Epidemiología, análisis espacio-temporal, salud pública, Mozambique.

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1. Introduction

Since the World Health Organization (WHO) declared Tuberculosis (TB) as a global health emergency in 1993, there has been a 2% decline in the annual rate of disease worldwide; and, from 2000 to 2017, a worldwide reduction of 42 % in overall TB mortality (WHO, 2018). However, Mozambique showed an increase in the incidence rate until 2012, reaching approximately 551 cases for every 100 thousand inhabitants, and is currently remaining at that rate (The World Bank, 2018), despite the progress achieved in recent years in indicators such as the treatment success rate, surveys about HIV diagnosis, TB / HIV patients on Prophylactic Treatment with cotrimoxazole (CPT) and detection rates for new TB cases (WHO, 2018; Ministry of Health of Mozambique, 2013).

As in many countries where the population has a low income, in Mozambique, TB remains a serious public health problem, being one of the top 10 causes of mortality in all age groups. The epidemic of HIV and resistant multidrug TB (MDR TB) have a high incidence of the disease in the country, which has an estimated HIV prevalence of 13.2%, of which 40% are co-infected with TB and 3.7% are associated with strains of HIV TB MDR (Ministry of Health of Mozambique, 2018; WHO, 2018).

TB incidence rates usually have an important seasonal pattern in countries on Asian and African continents, which together with the temporal trend allows for planning strategies regarding the prevention control (Narula et al. 2019; Wubuli et al. 2017). The peaks in notified TB records vary according to the study design, the time intervals considered, and the region. In most countries, seasonality peaks in spring-summer (Fares, 2011). In Xinjiang, China, the peak is observed in March and October (Zheng et al. 2015), while in Shenzhen, in the same country, it occurred in April, May, and June (Zhu et al. 2018).

Tuberculosis is an infectious and contagious disease, which has *Mycobacterium tuberculosis* (MTB) as a causative agent. It is estimated that a transmitting individual can infect between 10 to 15 people annually (WHO, 2018). Several researchers emphasize the importance of detecting and reporting TB cases for controlling the disease. (Oshi et al. 2016 Avilov et al. 2015). The increase in lung disease depends on the ability of the bacilli to survive the phagocytosis processes and to multiply in the intracellular environment, as well as from the development of the latent phase contained in the infection and active pulmonary infection, which culminate in different clinical situations (Wubuli, et al. 2017). Individuals infected with MTB have a 5 to 15% lifetime risk of developing the disease. Immunosuppressed people, such as those who are positive for malnourished immunodeficiency virus (HIV), malnourished, diabetic, or smokers, are at higher risk of becoming ill (WHO, 2018).

The mortality rate and prevalence of TB across the world decreased between the years 1990 to 2015 by 47% and 42%, respectively (WHO, 2018). But TB is, still, among the top ten causes of death in the world. In 2017, ten million people (between 9 and 11.1 million) developed the disease, of which 5.8 million were men, 3.2 million women, and 1.0 million children. Studies emphasize the detection and reporting of cases in certain specific groups, such as children, inmates, and people living in rural areas. Regardless, no study explores and reports TB cases by district or area (Oshi et al. 2016; Avilov et al. 2015; Van't et al. 2016). Other investigations indicate that not only social as also environmental factors are associated with the hospitalization of patients with TB (Oliveira and Gonçalves, 2013; Freitas et al. 2015; Abebe et al. 2010).

Geographic Information System (GIS) data and processing adopted in health studies refers to a strategic tool for supporting research and planning actions in TB programs. Maps of disease rates, populations at risk, identification of regions with disease outbreaks, or even verification of socio-environmental risk factors are some of the cartographic products generated in the GIS environment. Munch et al. (2003) used a GIS to analyze spatial patterns of TB transmission in a high-incidence area in South Africa. In China, the Spatial-temporal analysis of tuberculosis was evaluated for Chongqing, between 2011 and 2018 (Yu et al. 2020). Kumar et al. (2014) analyzed a time-series to discover the seasonality of tuberculosis in Delhi, India. Wubuli et al. (2017) performed a time-series analysis to assess the trend and seasonality of notification of active TB in Xinjiang, China. Gashu et al. (2018) conducted a six-year trend analysis in Ethiopia, Africa, to determine seasonal variations in tuberculosis case reporting.

In the Mozambican municipalities and regions, García-Basteiro et al. (2017) analyzed the TB notification time-series (1997 to 2012) to assess the evolution of incidence rates and other key indicators of the disease in the district of Manhica. In this sense, the analysis of the Spatio-temporal of diseases by GIS can support the development of public intervention actions aiming to contain the disease proliferation, being a strategy adopted by many countries (Munch et al. 2003; Kumar et al. 2014; García-Basteiro et al. 2017; Gashu et al. 2018; Wardani and Wahono, 2020; Wang et al. 2020; Yu et al. 2020).

However, to the best of our knowledge, no study evaluated the spatial-temporal distribution of TB in Maputo's municipalities, which present a high TB rate. In the southern region of Mozambique, where Maputo is located, almost 70,000 people migrate annually to work in the mines of South Africa, a country that holds 3% of the TB load in the world (Southern Africa Tuberculosis and Health Systems [SATBHSS], 2017; WHO, 18; Mathema et al. 2015). In Mozambique, in the district of Manhica, TB notifications from 1997 to 2012 are three times higher than in other areas, being higher for men than for women (Nguenha et al. 2018). Despite data being available at the regional level, the temporal trend of TB in the capital Maputo has been little explored to support intervention measures aimed at TB prevention and control. In this regard, determining the TB cases reporting patterns may

introduce relevant information about the restrictions of detecting and reporting cases in a country with a high rate of this disease. Our study can contribute to the formulation of policies that improve the detection and notification of TB events. Here we verified the spatial-temporal distribution of tuberculosis notification cases in the municipality of Maputo - Mozambique between 2011 and 2016.

2. Method

2.1 Experimental design

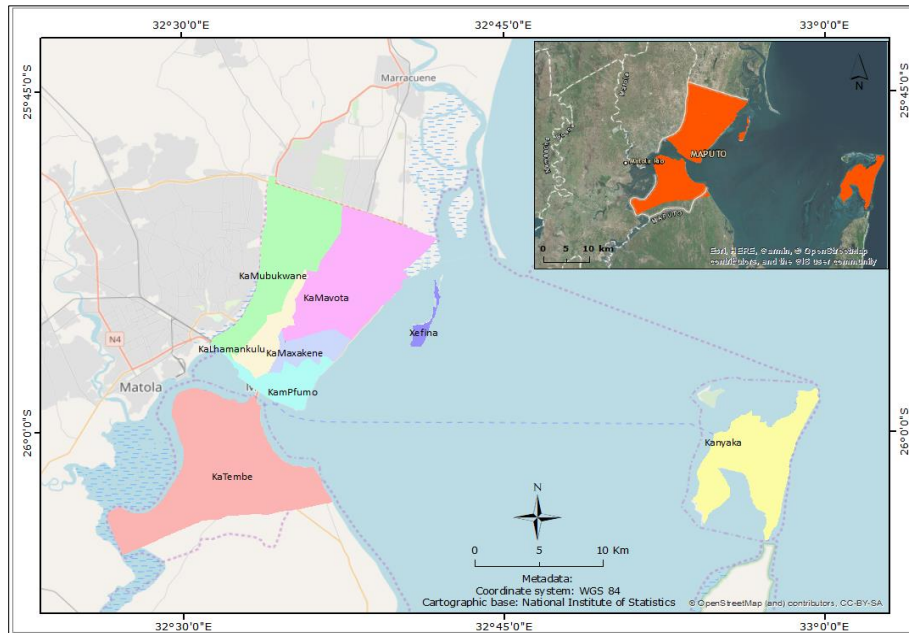
The experimental design refers to an ecological and descriptive study, using secondary data that present certain conditions associated with TB (age and clinical form). These data came from the database of the Tuberculosis control program in the municipality of Maputo between 2011 and 2016, and they were provided by the National Statistics Institute of Mozambique (INE). As they are secondary, anonymous, collective, and public data, the consent term or the confidentiality commitment form was not necessary.

2.2 Characteristics of Maputo Municipality

The Municipality of Maputo is a city-province with the same name, located in the extreme south of Mozambique and the capital of the country. It is located on the western bank of Maputo Bay, close to the national border with South Africa (120 km) and Swaziland (80 km). It is limited to the West by the Influence Valley, which separates it from the Municipality of Matola to the East by the Indian Ocean, to the South by the Matutuine district, and to the North by the Marracuene district. It has a population of 1,094,628 inhabitants (National Institute of Statistic, 2007), distributed in seven districts (Municipal Administrative Unit) (Figure 1) and 64 neighborhoods. The districts are KaMpfumo, NIhamakulu, KaMaxakeni, KaMubukwana, KaMavota, KaTembe, and KaNyaka (National Institute of Statistic, 2007, 2011).

Figure 1

Maputo city administrative division.



Source: The authors have created this map using Geographic Information System (GIS) software.

2.3 TB rate incidence by districts and subgroups

In this study, the people of interest are residents in Maputo (Mozambique) capital, being distributed in seven districts (Figure 1) and 64 neighborhoods. These districts are named KaMpfumo, Nihamakulu, KaMaxakeni, KaMubukwana, KaMavota, KaTembe, and KaNyaka. Our dataset is composed of recordings taken from a total of 29 health units that carry out the Directly Observed Short-Term Treatment (DOTS) of Tuberculosis and is available in the Ministry of Health Mozambique. We organized the data by year, districts, bacteriologically confirmed pulmonary tuberculosis, clinically diagnosed pulmonary TB, extrapulmonary TB, and age group.

Based on TB recordings per quarter, the quarterly rate of cases for every 100 thousand inhabitants was determined using the direct method. Additionally, from these data, the annualized rates of standardized TB incidence were calculated, according to the subgroup of interest. We used point estimates and intervals with 95% confidence, applying the Wilson method to compare the incidence rates between the subgroups. Subgroups with incidences that generated non-overlapping confidence intervals were considered statistically different. Quarterly data was expressed in timeline graphs, separately for each district, clinical form, and age.

From the reported cases of TB per trimester, the trimester rate of cases for every 100 thousand inhabitants was determined using a direct method. From these data, the annualized rates of standardized TB incidence were calculated, according to the subgroup analyzed, with estimates and intervals with 95% confidence. They were used to compare the incidence rates between the subgroups (Fay and Feuer, 1997). Trimester data was expressed in timeline graphs, separately for each district, clinical form, and age groups. Box-plot graphs were also constructed to assess the distribution and dispersion of TB cases in the municipality of Maputo, separately for each trimester.

2.4 Spatial analysis

The cartographic data for creating the maps was provided by the National Statistics Institute of Mozambique. Climatic data related to the average monthly temperature was obtained with the Meteorological Institute of Mozambique (INAM), via Maputo Station / Observatory, from 2011 to 2015. Data on the municipality's population and respective districts were obtained from the III General Population and Housing Census 2007, made available by the National Statistics Institute of Mozambique (INE). The notified cases of Tuberculosis were provided by the Ministry of Health in Mozambique.

2.5 Regression-temporal models

For the time models, the trimester incidence rate between 2011 and 2016 was displayed with line graphs, in which the occurrence of predominant seasonal peaks in the first trimester of each year was noted. A seasonal pattern was also suggested when the standardized rates of quarterly incidence of TB cases were plotted on box-plot graphs. Thus, it was decided to model the data in a time-series that capture the seasonal components, which were capable of explaining the trimester oscillation of TB cases in Maputo. The model chosen was the generalized linear (GLM), based on the Poisson probability distribution, adjusted by a sinusoidal function with terms composed of pairs of sines and cosines (Bhaskaran et al. 2013).

The Poisson distribution is based on count data from model instances in fixed time intervals, suitable for modeling incidence rates. This model has some limitations, as the assumption of independent observations is generally violated since observations close to the timeline are likely to be more similar than those distant over time. However, this serial autocorrelation is usually associated with the predictive variables of the model. Thus, the quarterly average temperature was included as a covariate in the final model, to verify and reinforce the investigation about the variables capable of predicting Tb cases in Maputo. Another limitation is the overdispersion of data, when the variance

of the result counts is greater than the average. This problem was minimized by adjusting the data with the logarithmic transformation (Bhaskaran et al. 2013).

This method is considered adequate to capture the seasonality of communicable diseases when compared to other methods and has been used to model the seasonal occurrence of tuberculosis in developing countries (Liao et al. 2012; Lundbye et al. 2009; Narula et al. 2015). Models were adjusted for TB rates per 100 thousand inhabitants for both the entire municipality of Maputo and the age stratification (> 15 years and ≤ 15 years).

For modeling, a logarithmic link function was applied. The final model selected for each subgroup was composed of:

$$\text{Log}(Y_t) = 1 + \alpha_0 + \alpha_1 T + \alpha_2 \text{Temp} + \cos(2\pi T/4) + \text{sen}(2\pi T/4) + \varepsilon,$$

Where:

Y_t = Standardized TB rate for every 100 thousand inhabitants;

T = time unit (Trimester, being $T = 1, 2, 3, \dots, 24$);

Temp = Trimester average temperature;

ε = model's error

sen = sine

cos = cosine

From the models proposed for each subgroup, scatter plots were constructed in which the original data was inserted as points, and the data series predicted by the model as a continuous line. Spearman's non-parametric correlation analysis was used to assess the relationship between the trimester average temperature and the rate of cases reported in the period considered. All analyzes were developed with mathematical functions available in the open-source program R and additional packages (Ginestet, 2011; Nunes et al. 2020).

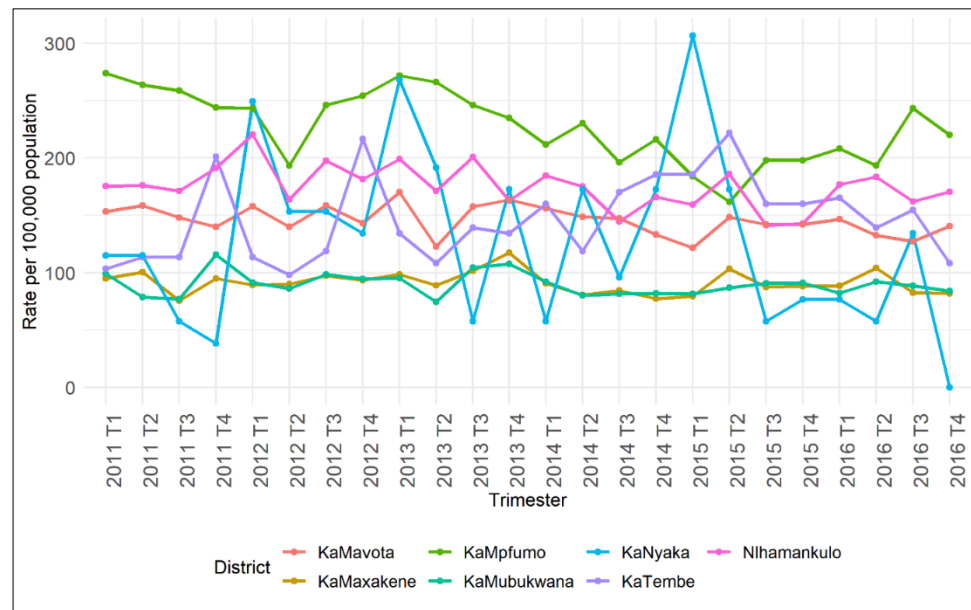
3. Results

A total of 34,623 new TB cases was notified from 2011 to 2016, with an average annual incidence rate of 527.8 cases (95% CI 514.3-541.6) per 100 thousand inhabitants. The trimester distribution of cases showed heterogeneity between the districts (Figure 2). The KaNyaka district showed

heterogeneity in the standardized incidence, with prominent fluctuations over the trimester compared to others. KaMpfumo showed a higher incidence than the other districts throughout the same period, while KaMubukwana and KaMaxakene showed the lowest incidences.

Figure 2

Standardized rates notified cases of TB per trimester (T) in the districts of the municipality of Maputo (2011-2016).

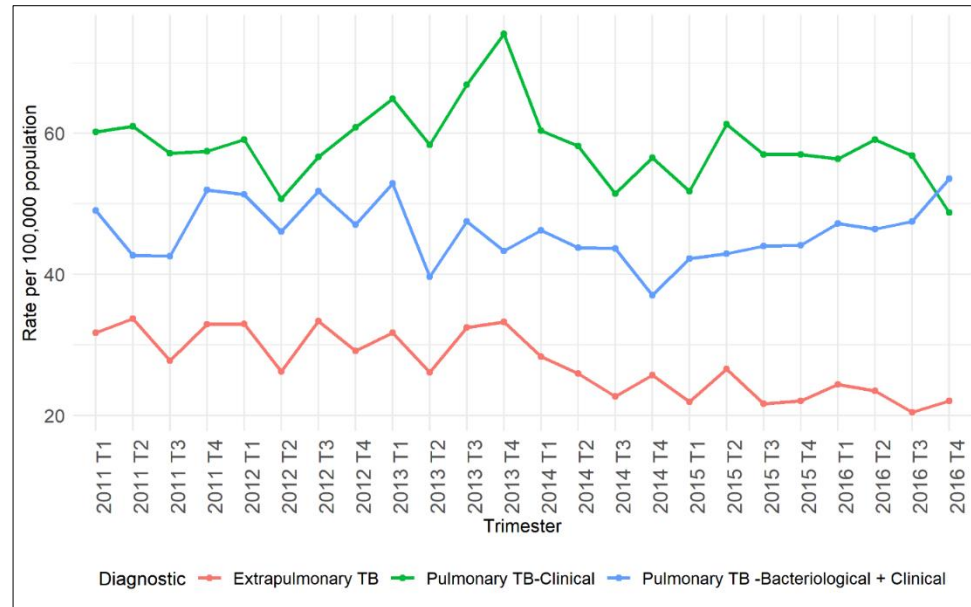


Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018).

When the incidence per diagnosis cases is observed (Figure 3), it appears that the rates of pulmonary TB in patients with disease confirmed only by clinical examination exceeded those observed for patients with clinical + bacteriological diagnosis. This pattern slightly reversed in the last trimester. The incidence of pulmonary forms exceeded the extrapulmonary, which showed a decrease in standardized rates throughout the study.

Figure 3

Standardized rates of notified TB cases per trimester according to diagnosis in the municipality of Maputo, (2011-2016).

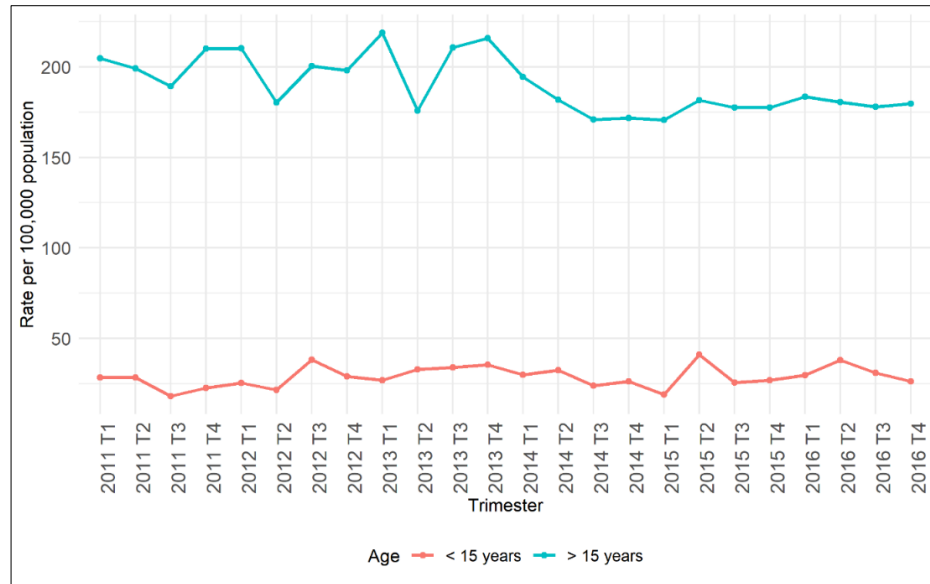


Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018).

The rates of trimester notification of TB in those older than 15 years exceeded the ones observed in those younger than 15 years; both of which showed little variation during the study period (Figure 4).

Figure 4

Standardized rate of notified TB cases per trimester by age group (less than or over 15 years), in the municipality of Maputo (2011-2016).

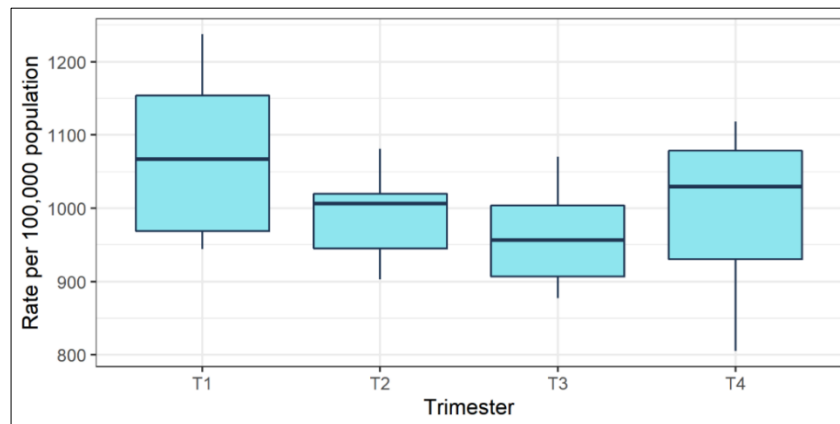


Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018).

The Box-Plot type graph (Figure 5) suggests that the incidence of TB in Maputo peaked in the first trimester, subsequently declining in the 2nd and 3rd trimesters, to rise again in the 4th trimester.

Figure 5

Standardized average rates of notified cases of TB per trimester in the municipality of Maputo, Mozambique, between the years 2011 to 2016.

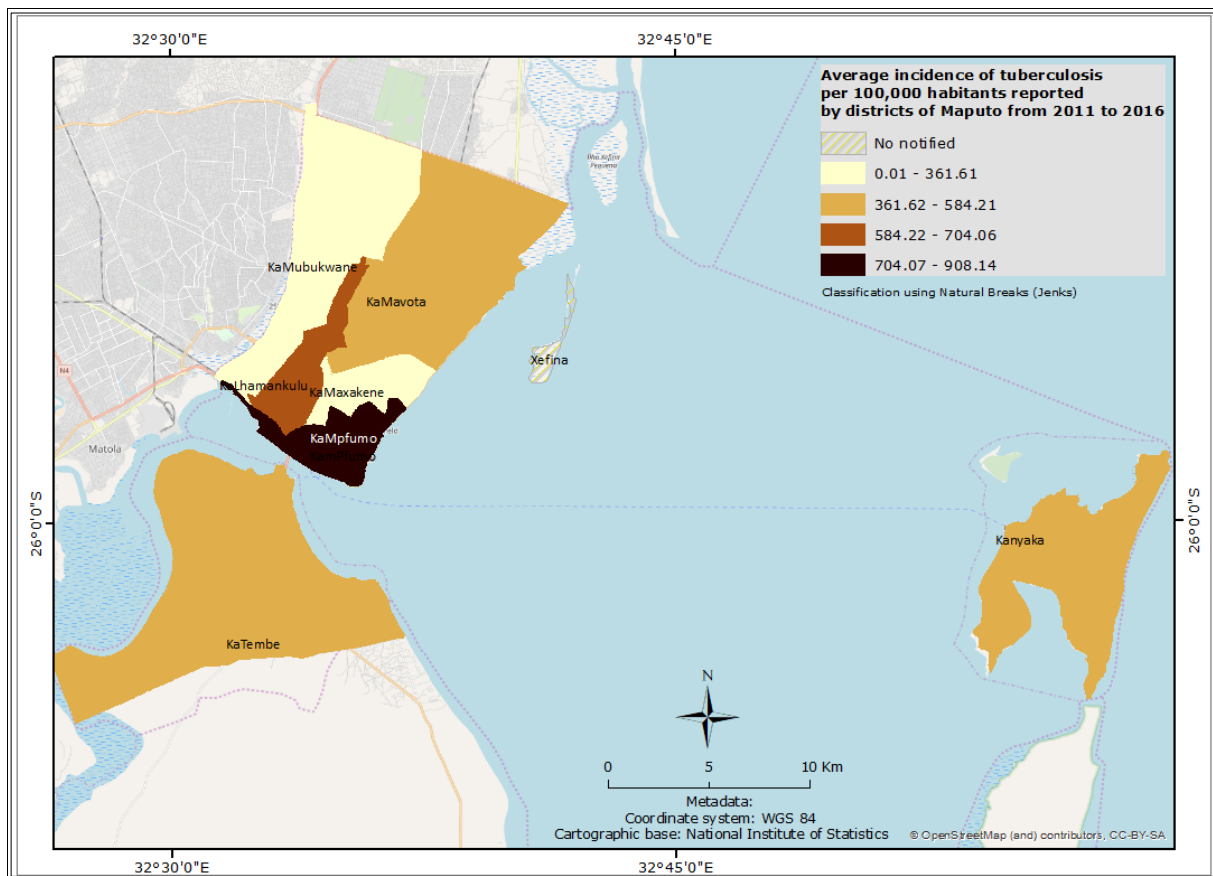


Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018).

The spatial distribution of average notification rates (Figure 6) showed that the district of KaMpfumo has the highest TB case reporting rate in the municipality, followed by the districts of Nlhamankulo, Katembe, and KaNyaka.

Figure 6

Spatial-temporal distribution of the average incidence rates of TB cases per 100 thousand inhabitants in the Municipality of Maputo, (2011 - 2016).



Source: The authors have created this map using Geographic Information System (GIS) software.

Table 1 describes the average annual incidence rates of TB by subgroups (districts, diagnosis, and age). Considering the overlay of confidence intervals for the incidence estimates in the districts, KaMpfumo had a higher incidence than the other areas, followed by Nhamankulo and KaTembe. The lowest rates were observed in KaMubukwana and KaMaxakene. The average annual notification rate for pulmonary TB was higher than for extrapulmonary TB. There were 233.7 cases of pulmonary TB with a negative bacteriological diagnosis in every 100 thousand inhabitants. The age group under 15 years had the lowest incidence below the age group over 15 years of age (Table 1).

Table 1

Distribution of standardized rates of average annual incidence by the district of Maputo municipality.

Subgroups	Average Annual Incidence *	IC95%
	(cases x 100 thousand habs.)	
District		
KaMubukwana	359.2 (a)	337.8 - 381.7
KaMaxakene	365.2 (a)	340.7 - 391.1
KaNyaka	514.4 (abc)	338.8 - 748.5
KaMavota	583.3 (b)	556.1 - 611.6
KaTembe	587.6 (bc)	484.9 - 705.6
NIhamankulo	700.7 (c)	659.7 - 743.6
KaMpfumo	909.8 (d)	854.1 - 968.2
General (Maputo)	527.8	514.3 - 541.6
TB Pulmonar		
Positive Bacteriological	184.1 (a)	176.1-192.3
Negative Bacteriological	233.7 (b)	224.7-242.0
General	417.8	405.7-430
Extrapulmonary	109.4	103.3-115.8
Age Group		
< 15 years	115.0 (a)	104.7-126.1
> 15 years	760.0 (b)	739.8-780.7

* Values in the same column followed by different letters indicate significant differences between standardized annual incidence rates

Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018)

Table 2 describes the parameters of the Poisson linear regression models for the TB rate in Maputo, stratified by age. In this table, the regression coefficients related to time (quarter), seasonality (sin and cos), and temperature can be observed in each subgroup. The regressors for seasonal components and temperature were not significant in all subgroups. There was a negative and significant trend only for TB incidence rates in the general population of Maputo and at children under 15 years old. The seasonality component of the model did not significantly influence the incidence rates.

Table 2

Parameters of Poisson linear regression models for Maputo and stratified in the age range from 2011 to 2016

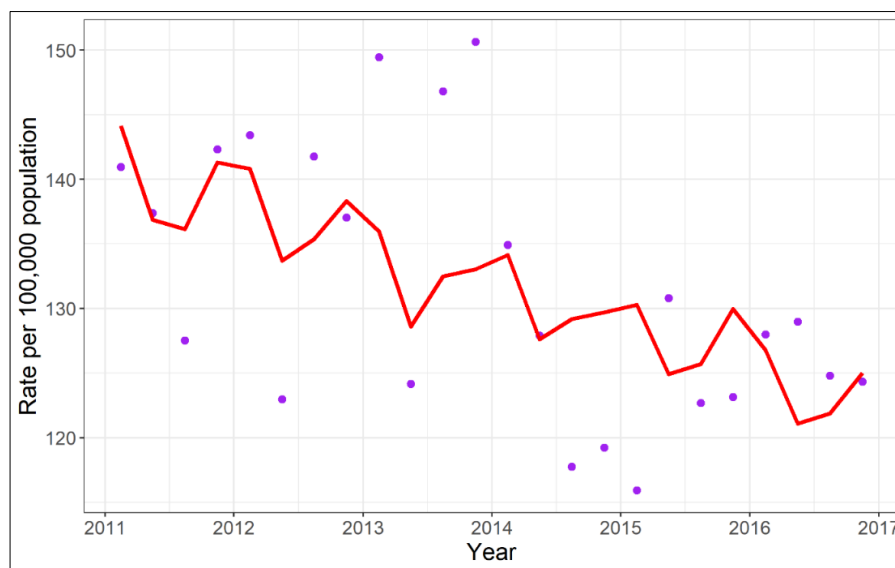
Subgroup	Coefficient	Estimation	Standard Error	Statistic Z	P
Maputo	Interceptor	4.5059	0.998	4.511	<0.001
	Trimester	-0.0063	0.002	-2.353	0.018*
	Sen	-0.0372	0.115	-0.321	0.748
	Cos	0.00275	0.048	0.056	0.955
	Temperature	0.01947	0.043	0.45	0.652
Over 15 Years	Interceptor	3.337504	2.157022	1.547	0.122
	Trimester	0.007	0.005	1.319	0.187
	Sen	-0.017	0.248	-0.072	0.943
	Cos	-0.084	0.106	-0.788	0.431
	Temperature	-0.003	0.093	-0.035	0.972
Under 15 Years	Interceptor	4.840	0.831	5.822	< 0.001
	Trimester	-0.007	0.002	-3.358	< 0.001*
	Sen	-0.039	0.096	-0.404	0.685
	Cos	0.010	0.040	0.252	0.800
	Temperature	0.021	0.036	0.596	0.551

Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018); 3) Temperature: National Meteorological Institute of Mozambique (INAM)

Figures 7 to 9 show the trimester incidence rates observed in the municipality (represented by points) and the lines applied corresponded to the values predicted by the models described in Table 2. The purple points represent the data observed in the timeline and the sinuous red curve represents the values predicted by each model. There was no significant seasonal trend in any subgroup. Concerning the trend, cases dropped significantly over the trimesters for the subgroup "Age under 15 years", denoted by the negative and significant coefficient of the model's temporal term, as shown in Table 2.

Figure 7

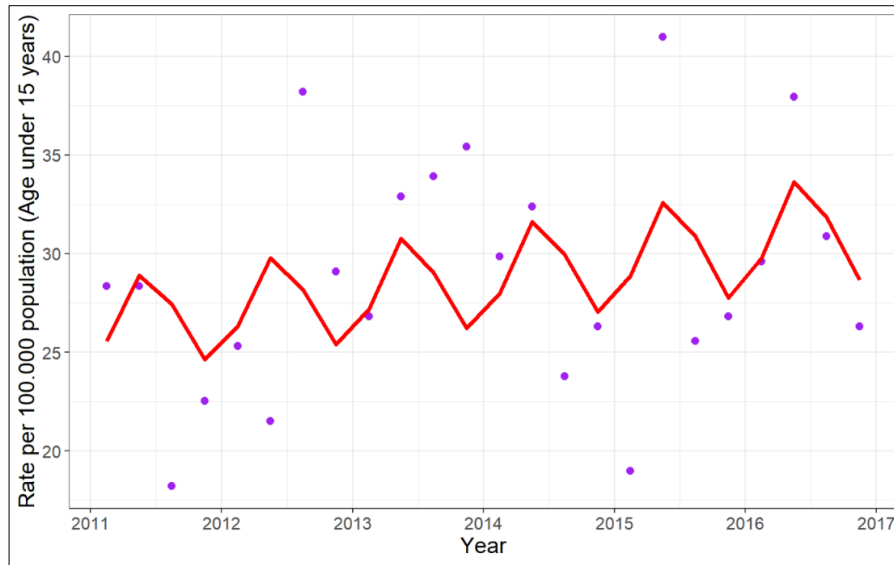
Time series for the number of TB cases per 100 thousand inhabitants in the municipality of Maputo, Mozambique, from 2011 to 2016



Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018).

Figure 8

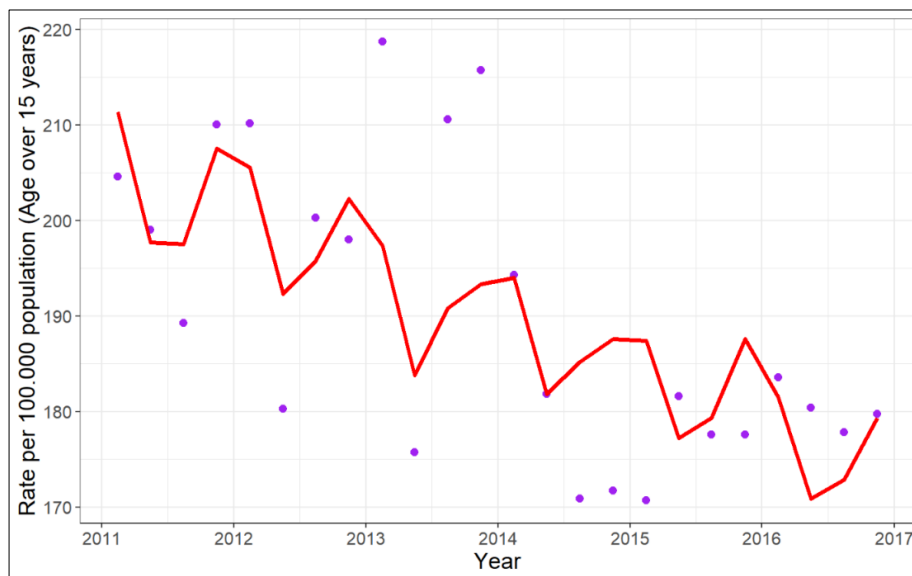
Time series for the number of TB cases per 100 thousand inhabitants for the age group “less than or equal to 15 years” in the municipality of Maputo, Mozambique from 2011 to 2016.



Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018).

Figure 9

Time series for the number of TB cases per 100 thousand inhabitants for the age group over 15 years-old in the municipality of Maputo, Mozambique from 2011 to 2016.



Data source: 1) Population: National Statistics Institute - INE (2007); 2) notified cases: National Program to Combat Tuberculosis - PNCT (2018).

4. Discussion

The present study demonstrates the variation of temporal changes in TB incidence rates in the municipality of Maputo, capital of Mozambique. The average annual incidence rate of notified cases per 100,000 inhabitants is one of the parameters recommended by the WHO to guide TB control worldwide. In Maputo, the rate observed is similar to that of the rest of the country (501 cases / 100 thousand inhabitants), with Mozambique being recognized as the third country in the world with the highest rate of the disease, behind Lesotho and the Philippines (WHO, 2019). Faced with this worrying scenario, the country must recognize this disease as a serious public health problem and prioritize combat policies based on the recommendations of the World Health Organization.

The high incidence of observed cases suggests that the capital Maputo concentrates the most important centers of infection in the country. A retrospective study (1997 - 2012) carried out in the district of Manhiça, Southern Mozambique in 2017, found results superior to ours (573 cases per 100 thousand inhabitants), confirming the disease epidemic in the country (García-Basteiro, 2017). The high rates observed may be closely related to high HIV prevalence in the country, as the region's TB / HIV co-infection was estimated at 72% in 2017 (Ministry of Health of Mozambique, 2015). The country ranks 4th in the world with high HIV rates, despite the prevalence being higher in rural than in urban areas (Muleia et al. 2020).

The southern provinces of Mozambique have the highest levels of TB and HIV recorded in the world. Cross-border migration to work in ore mines, in particular from South African miners co-infected with HIV / TB (Baleta, 2012; Sema-Blatazar et al. 2020), contributes significantly to the high levels of TB observed in the region. In addition to migration and the high prevalence of HIV, flaws in control policies are recognized, which include delays in tracking positive individuals' contacts and delay in starting treatment for individuals with confirmed cases (García- Basteiro et al. 2016).

The districts have variable incidence rates over the period, which suggests that regional determinants directly influence the distribution of the disease. It cannot be said, however, that the incidence rates are due exclusively to these local determinants since there is the possibility of underreporting cases and/or notification of alien cases within a district as also as differences between them concerning access to health services (De Schaccht et al. 2019). The district of Kampfumo was the most affected, with almost twice as many cases of the municipal incidence. The rate, of almost 1,000 cases per 100 thousand inhabitants, is possibly one of the highest in the world as it concentrates a serious epidemic of the disease. However, these districts have more favorable social indicators than the others,

including the lowest illiteracy rate among the population aged 15 or over (2.2%), the lowest level of poverty (28%), and the highest inequality rate (64%) of the municipality. Regardless, it has a better structured sanitary infrastructure, sanitation, and other support services for the population, as well as an economically favorable population (National Institute of Statistic, 2017). Thus, the observed incidence rates may be due to neighborhoods belonging to other districts with a lower structure, which leads the inhabitants to seek the services of the district of Kampfumo with a better structure to support the population. Another explanation for this phenomenon may be the presence of the prison unit, with a high HIV infection rate, and the underreporting that may have influenced the outcome (Telisinghe et al. 2016).

The districts of Nihamankulo, Katembe, and Kanyaka had the second-highest notification rate in the municipality (Table 1). These districts are characterized by a similar inequality rate, with a poverty rate above 50%. The district of Nihamankulo has the highest population density in Maputo, while Katembe and Kanyaka have the lowest population density in the municipality (National Institute of Statistic, 2017). The districts of Kamavota, Kamubukwana, and Kamaxaquene had the lowest incidence rates in the municipality, but they are high compared to some countries in Africa and the world. These districts are characterized by, united, having 57% of the population of Maputo. The KaMaxaquene district also has a high population density. These characteristics make districts vulnerable to infectious diseases such as TB.

Despite the high rates observed in Maputo, the incidence showed a significant downward trend between 2011 and 2016 (Table 2), denoted by the negative coefficient of the observed regression model for the overall rate. Although we do not rule out problems with underreporting, the results suggest that the official tuberculosis control program established in 2014 recommended by the government may be sensitive to the detection of cases, resulting from massive search campaigns and encouraging the population to seek health services when the disease is suspected. The early referral of presumptive tuberculosis patients, the intensification of tuberculosis on campaign days in all health units, and the involvement of volunteers, can justify TB notifications in all districts of Maputo (Ministry of Health of Mozambique, 2014).

Variations in TB notification were observed in the municipality of Maputo in different trimesters of the year. The box-plot suggests that the case notification rate was higher in the first trimester (summer predominates) and lower in the second (winter predominates). These results corroborate the findings in studies from other countries, where the notification of TB cases was high in the summer (Gashu et al. 2018; Ana-Anyangwe et al. 2007; Narula et al. 2015). However, the regression model did not detect a significant influence of temperature on the incidence rate, both in the municipality as a whole and in the subgroups. Furthermore, the Fourier terms inserted to model the fluctuations in incidence rates were not significant (Table 2).

Several studies have corroborated the association between TB and seasonality (Gashu et al. 2018; Gelaw et al. 2019; Tedijanto et al. 2018). The seasonality may be related to other comorbidities, such as vitamins D (Martineau et al. 2011). In the present study, the absence of a seasonal pattern associated with atmospheric temperature may be the result of several factors that were not possible to be explored here. Notifications in the municipality are quarterly, which can skew seasonal peaks since in each year are only four moments registered for the event of interest (Vynnycky, 2000). Another explanation is the long incubation period of the disease, so the moment of TB notification hardly corresponds to the moment when the infection occurred. Moreover, some patients may take a long time to seek medical care, adding the time to process diagnostic tests (Borgdorff et al. 2011). These factors can be minimized with a long-term study (Fox et al. 2013), but they can have a low efficiency when notifications are quarterly instead of monthly.

It was observed that the average incidence rate of notification of pulmonary TB was predominant (417.8 cases per 100 thousand inhabitants) concerning extrapulmonary TB (109.4 cases per 100 thousand inhabitants). It is estimated that approximately one-fifth of the cases notified in the municipality is for extrapulmonary forms. This percentage is above the average estimate for the African continent, which is 15% of extrapulmonary cases (WHO, 2019). However, this form of tuberculosis presents difficulties in being diagnosed, since sputum tests do not detect them. Besides, case tracking is neglected by the National TB Control Programs due to the less important role of extrapulmonary forms in the spread of TB (Wang et al. 2014). Despite the less important role of extrapulmonary forms in the spread of the disease, they must be closely monitored because they may be related to cases of food transmission of TB, especially when considering the intake of raw milk or individuals in contact with cattle with *M. bovis*, a highly prevalent agent in cattle raised in the country (Berg et al. 2015; Moiane et al. 2014). The tracking of cases associated with *M. bovis* is difficult since the clinical signs are indistinguishable from *M. tuberculosis*. In Maputo, a substantial fraction of cases is diagnosed only by clinical examination (Figure 3). Therefore, it is not possible to determine which microorganism is associated with the disease, except for cases diagnosed by rapid molecular tests.

High TB incidence rates were observed in confirmed cases with clinical diagnosis (bacteriologically negative TB) around 233.7 per 100 thousand inhabitants. These cases refer to individuals clinically and epidemiologically compatible with TB, but that has been negative in sputum smear microscopy or in molecular techniques (GeneExpert), which is used only in 36 primary health care units. The sputum smear method has a low sensitivity limitation for the diagnosis of extrapulmonary TB, pediatric TB, and HIV co-infected patients (Orlando et al. 2018). Thus, the rate of TB / HIV co-infection in Maputo, above 60%, and patients with HIV in the advanced stage often present themselves at the health unit in an advanced stage of infection (Orlando et al. 2018) which may have influenced the negative smear. Delays, on an average of 28 days, in the diagnosis and treatment of TB estimated

from negative smear microscopy in co-infected patients should also be considered (Lisboa et al. 2019). Other possibilities that may explain the high rates of clinical diagnosis with negative bacteriology is the increase in pediatric cases since there is difficulty in establishing an accurate diagnosis, mainly because of the difficulty in collecting samples and due to the problems in differentiating TB from others childhood respiratory infections (Dodd et al. 2014). A study carried out in the district of Manhiça, Southern Mozambique, in 2015, reported greater bacteriological confirmation among the sputum smear of TB / HIV negative cases than HIV positive (Garcia- Basteiro et al. 2015):

As for the analysis by age group, the notification of cases was higher in those over 15 years of age when compared to those younger than or equal to 15 years, with a rate of 760 cases per 100 thousand inhabitants. This corresponds to 92% of all cases, suggesting that TB notification in Maputo is predominant in the population over 15 years old. In 2015, WHO estimated that 90% of TB had occurred in individuals over the age of 15 and 10% in ≤ 15 years (WHO, 2019). Although tuberculosis showed a significant tendency to decrease, according to the proposed model, in the subgroup aged ≤ 15 years, the non-significant coefficient indicates that the infection remained stable throughout the study period. This suggests that control measures may not be having the desired effect to control TB in this subgroup. This is troublesome, as Mozambique has a relatively young population since the 0-15-year-old age group constitutes approximately 50% of the population (National Institute of Statistic, 2017). It is expected that the contribution of TB in this range is greater.

The low detection and notification of TB cases, mainly for children, leads to an obstacle for both the notification system and treatment. There is a lack of professionals, long distances traveled by patients in search of treatment, lack of adequate means for TB detection, and little information or campaigns that recommend health practices in the public for contributing to the TB control (Boss et al. 2016; Brouwer et al. 2014).

A study of child TB modeling in endemic countries suggested that the magnitude of the disease could be greater for this group (Dodd et al. 2014). Children are often infected with *M. tuberculosis* at home, and the diagnosis depends on exposure to an infectious source, along with findings of TB on chest radiography (X-ray). Due to the non-specific nature of its symptoms, the difficulties in obtaining samples for microbiological examination, and often paucibacillary nature of the disease (García-Basteiro et al, 2015). it is possible to raise the hypothesis of an underdiagnosis of pediatric cases in Maputo. Although, in recent years, there has been an improvement in the tracking and diagnosis of these cases, resulting from the qualification and training of clinicians in the field of pediatric TB (Ministry of Health of Mozambique, 2014; Nguenha et al. 2018).

In summary, our study has some limitations. Firstly, the registration of quarterly cases, instead of monthly, can mask the seasonality of TB in the municipality. Moreover, the quarter of registration of cases may not correspond to the quarter in which the transmission occurred. Finally, the data are secondary records, subject to bias of the inaccuracy of the data record and the underreporting of cases.

5. Conclusion

It was demonstrated herein the spatial-temporal distribution of tuberculosis incidence rates in the municipality of Maputo, capital of Mozambique, between 2011 and 2016. Maputo presents similar values of TB incidence compared to the rest of the country, but it should be remembered that Mozambique has one of the highest reporting rates of TB in the world. Therefore, our study reinforces the importance of monitoring the TB epidemic in this municipality of Maputo. The high incidence rates of TB can be associated with high values of HIV that exist in Mozambique since it occupies the 4th position in the world-rank. Although Kamphumo presented the highest levels of TB, it is also the more developed district in Maputo, which may imply that people can drive to this region for obtaining a more appropriate treatment against the disease.

Even though there are high rates of TB in Maputo, we verified that the TB incidence is down within the evaluation period (2011 and 2016), both in general and in age groups (over 15 years old) analysis. This reduction may indicate an underreporting due to poor implementation of TB prevention and control campaigns. In contrast, the rate in children under 15 years of age remained stable, which suggests that measures to control and prevent childhood tuberculosis have been inefficient in the municipality. The pulmonary TB incidences were superior to the extrapulmonary rates.

We conclude that tuberculosis, still, represents a serious public health in African countries. Because it is a chronic disease, the control measures take effect only in the long run. In Maputo, where the transportation system is a serious problem and the TB cases reported annually are less than estimated, mobilizing various sectors like education, health, and transport to control TB rates can help increase the detection and reporting of cases. It is recommended that improvements take place in the frequency of notification for early detection of outbreaks, and also the active case finding and improvement of information systems, as the seasonality effect may be masked by quarterly intervals notification.

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