

# Human leptospirosis in the municipality of São Paulo, SP, Brazil: distribution and trend according to sociodemographic factors, 2007–2016

*Leptospirese humana no município de São Paulo, SP, Brasil: distribuição e tendência segundo fatores sociodemográficos, 2007–2016*

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**ABSTRACT: Objectives:** This study aimed to describe the incidence and proportional lethality of human leptospirosis in the municipality of São Paulo, between 2007 and 2016, according to sociodemographic factors and characteristics of the disease, and to assess the temporal trends of incidence, according to age group and region of residence. **Methods:** Proportional distributions of leptospirosis cases of residents in the municipality were built and regression models with a Binomial Negative response were adjusted. **Results:** 2,201 cases of leptospirosis were registered, most of them being males (82%), aged between 20 to 59 years (64.6%), white (39%) or brown (32.8%), residing in the South (27.8%), East (23.8%) and North (18.5%) regions. The overall lethality was 15.1%. The risk was higher in the 20 to 59 age group. There was a downward trend in incidence in all age groups and regions, estimated at 5.6% per year. **Conclusions:** Despite the downward trend in incidence, leptospirosis is a serious disease with high lethality, affecting mainly male individuals in the age groups considered economically active and living in the peripheral regions of the municipality.

**Keywords:** Leptospirosis. Time series studies. Incidence. Regression analysis.

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**RESUMO:** *Objetivos:* O presente estudo teve como objetivos descrever a incidência e a letalidade proporcional de leptospirose humana no município de São Paulo, entre 2007 e 2016, segundo fatores sociodemográficos e características da doença e, avaliar a tendência temporal da incidência, conforme a faixa etária e a região de residência. *Métodos:* Foram construídas distribuições proporcionais dos casos de leptospirose de residentes no município e ajustados modelos de regressão com resposta binomial negativa. *Resultados:* Foram registrados 2.201 casos de leptospirose, a maioria do sexo masculino (82%), com idades entre 20 e 59 anos (64,6%), de raça/cor branca (39%) ou parda (32,8%), residentes nas regiões sul (27,8%), leste (23,8%) e norte (18,5%). A letalidade geral foi de 15,1%. O risco da doença foi maior nas faixas etárias de 20 a 59 anos. Houve tendência de queda na incidência, em todas as faixas etárias e regiões, estimada em 5,6% ao ano. *Conclusões:* Apesar de apresentar tendência de queda na incidência, a leptospirose continua sendo uma doença grave e de alta letalidade, acometendo sobretudo indivíduos do sexo masculino, nas faixas etárias consideradas economicamente ativas e residentes nas regiões periféricas do município.

*Palavras-chave:* Leptospirose. Estudos de séries temporais. Incidência. Análise de regressão.

## INTRODUCTION

Leptospirosis is a zoonosis of worldwide importance that is consolidated as a public health problem, due to the damage resulting from its high incidence in certain areas and high lethality in isolation or in seasonal epidemic outbreaks<sup>1</sup>. It is caused by the bacteria *Leptospira*, present in the urine of synanthropic rodents. Climatic factors such as rainfall, temperature and humidity play a decisive role in the occurrence of the disease. Heavy rains, when causing floods, provide a favorable condition for the spread of the bacteria and can cause epidemics of leptospirosis through the contact of mucous membranes and excoriated skin, or even skin macerated by prolonged exposure, with contaminated water<sup>2</sup>. The situation is aggravated in regions with precarious housing and irregular waste disposal practices that favor the spread of rodents<sup>2</sup>.

According to the World Health Organization, in temperate countries, where the occurrence of leptospirosis is lower, the incidence per 100 thousand inhabitants/year varies from 0.1 to 1. In the humid tropics, where it is more frequent, this rate can vary from 10 to 100. When outbreaks occur in groups with high exposure to risks, this rate can exceed 100 per 100 thousand inhabitants/year<sup>3</sup>. According to Costa et al.<sup>4</sup>, only severe cases, which represent 5 to 15% of all clinical cases, are reported by surveillance systems, and, after a systematic review of 80 studies published from 1970 to 2008 in 34 countries, 1.03 million serious clinical cases are estimated to occur annually, with 58,900 deaths.

In Brazil, leptospirosis is endemic, with epidemic peaks in the months with the highest rainfall. The occurrence is greater in specific areas of capitals and metropolitan regions, due to the high density of low-income population, poor housing, insufficient basic sanitation, and infestation by rodents. Most cases happen among people who live or work in these areas<sup>5</sup>. The average annual incidence in the country, between 2007 and 2016, was 2 per 100

thousand inhabitants, with an average annual lethality of 8.9%. Leptospirosis cases were recorded in all Brazilian states, with the largest numbers in the South and Southeast regions.

Between 2007 and 2016, 7,891 confirmed cases were recorded in the state of São Paulo, with an average annual incidence of 1.8 per 100 thousand inhabitants and an average lethality of 12.2%. In the municipality of São Paulo, as well as in the state of São Paulo and in Brazil, leptospirosis is endemic for most of the year and epidemic in the summer, when the population is exposed to contaminated water and mud during the floods, which are frequent in periods of intense rains. The disease usually affects people who live in risk areas with poor basic sanitation, in precarious conditions, with the presence of garbage and close to streams<sup>6</sup>. Thus, it is plausible to state that its incidence is epidemiologically related to socioeconomic factors.

Few studies have been conducted to assess the trend of leptospirosis around the world, and different results have been achieved. Costa et al.<sup>4</sup> did not detect significant temporal trends in the reviewed studies. There was a decrease in incidence in France<sup>7</sup> between 1920 and 2003, in the Netherlands<sup>8</sup> between 1925 and 2008, in northeastern Thailand<sup>9</sup> between 2001 and 2012, in China<sup>10</sup> between 2007 and 2018, and in Brazil, in Belém (PA)<sup>11</sup>, between 2007 and 2013. On the other hand, studies have pointed out an increase in incidence in Croatia<sup>12</sup> between 2009 and 2014, and in Malaysia<sup>13</sup> between 2004 and 2014.

This study aimed to describe the incidence and proportional lethality of leptospirosis in the city of São Paulo between 2007 and 2016, according to sociodemographic factors and some characteristics of the disease. In addition, we aimed to assess the temporal trend in incidence of leptospirosis in the period, according to age group and region of residence. The intention is to expand the knowledge about the behavior of the disease in the municipality and to identify sub-populations at higher risk, providing information that can help in surveillance, control and prevention.

## METHODS

This is an ecological time-series study.

## STUDY AREA

São Paulo (Figure 1A) is the most populous city in the country, with about 12 million inhabitants<sup>14</sup> and an area of 1,523.3 km<sup>2</sup>. Located at an average altitude of 760 meters, it has a humid subtropical climate and an average rainfall of 1,700 mm annually, mainly concentrated in the summer, a period in which the city is subject to constant flooding<sup>15</sup>. Its administrative division comprises 32 regions, governed by sub-municipalities, distributed in six Regional Health Coordinators (RHC) which are responsible for the implementation of municipal health policies in their territory, among other duties. The RHC, from this point onwards referred to as “regions” only, are: Center, East, North, West, Southeast and South (Figure 1B).

## LEPTOSPIROSIS CASES

Information about all notified and confirmed cases of leptospirosis in residents of the municipality was obtained from the Information System for Notifiable Diseases (SINAN), with onset of symptoms between 2007 and 2016. Based on these data, the number of cases was collected for each year, according to sex, age group, race/skin color and region of residence of individuals. The age groups (in years) were defined as: 0 to 19, 20 to 39, 40 to 59 and 60 and more.

## POPULATION DATA

Data on population size between 2007 and 2016 per year, sex, age group and region of residence were obtained through the TabNet program (<https://www.prefeitura.sp.gov.br/cidade/secretarias/saude/tabnet>), from the Municipal Health Secretariat of São Paulo.

## STATISTICAL ANALYSIS

The proportional distribution of cases and the incidence rate was performed during the period, according to sex, age group, race/skin color and region of residence. The lethality

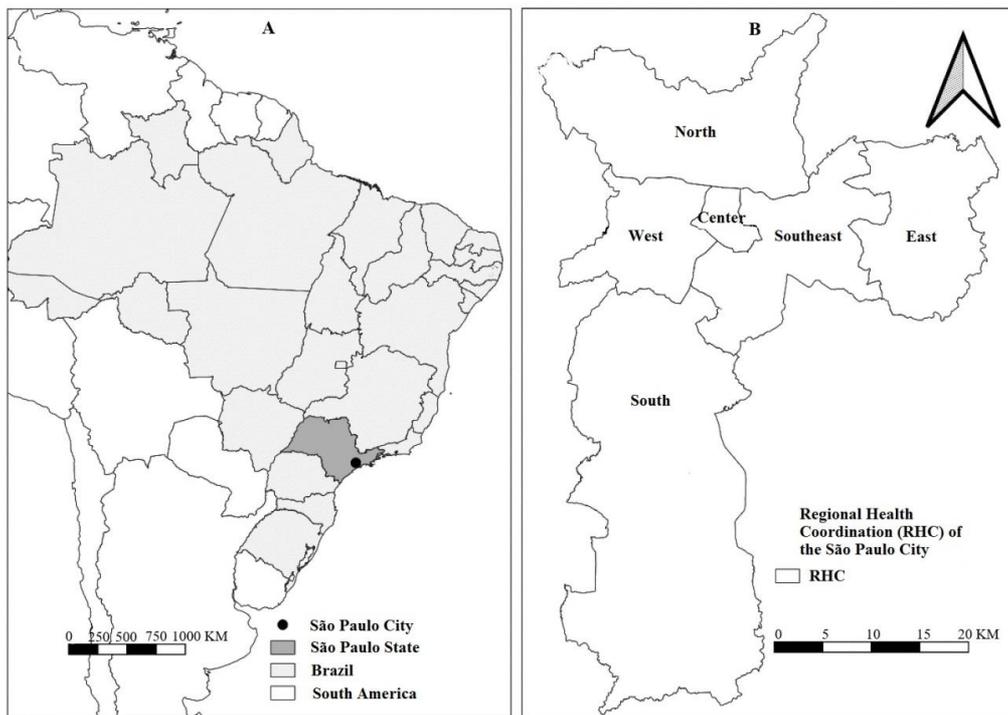


Figure 1. (A) Location of the municipality of São Paulo and (B) Regional Health Coordinators (RHC).

was calculated according to the same variables added to the characteristics of the area and environment of infection, signs and symptoms, and hospitalization.

To investigate the trend in incidence of leptospirosis over time, two types of generalized linear models (GLM) with negative binomial response were adjusted.

In the first model, the incidence trend in the municipality of São Paulo as a whole was assessed. The variable response was the annual number of cases, and the explanatory variable was the time, in years. The size of the population each year was used as a control (offset).

In the second model, the trend was assessed according to age group and region of residence. We decided not to include the variables sex and race/skin color in this analysis, although they are of great interest, because of the small number of cases among females (especially when evaluated year by year and in different age groups) and the large percentage of incomplete information on race/skin color. The variable response was the annual number of cases, and the explanatory variables were time, in years, and indicator variables for age groups and regions of residence. All interactions between the explanatory variables were also included in the model, but only the significant ones remained. The size of the population each year was used as a control (offset).

Based on the estimates of the adjusted models, the annual percentage (APC) of the incidence was calculated, obtained through the coefficient estimated for the variable year (Equation 1):

$$APC = (e^{\beta_{ano}} - 1) * 100 \quad (1)$$

The level of significance of tests was set at 0.05.

The analysis was performed with the aid of the software R for Windows.

## RESULTS

2,201 confirmed cases of leptospirosis were recorded during the study period. All of them presented complete information about sex and age. Information about the region of residence and race/skin color was incomplete in 5 and 18% of cases, respectively.

Regarding race/skin color, most cases were in white (39%) or brown people (32.8%). The indigenous people had the highest incidence (per 100 thousand inhabitants) of the disease (3.1), however there were only four cases. The incidences among black (2.8) and brown (2.1) people, which are greater than in the white (1.3) people, stand out. Yellow individuals had the lowest incidence (0.6). Lethality was high among the yellow (20%, total of three deaths), white (17%), black (12.8%) and brown (12.2%).

Table 1 shows the proportional distribution of number of cases and deaths from leptospirosis in the municipality of São Paulo, from 2007 to 2016, in addition to incidence and lethality rates of the disease, according to sociodemographic characteristics.

Most individuals were males (82%), aged between 20 and 59 years (64.6%), living in the southern (27.8%), eastern (23.8%) and northern regions (18, 5%).

Of the total cases, 333 ended up in obit (15.1%). The lethality rate was similar between men (15.2%) and women (14.6%) and, in general, increased with age. The highest lethality rates were reported in the Center (19.7%), North (16.9%) and Southeast (16.8%) regions, and the lowest was in the West (6.7%).

The incidence (per 100 thousand inhabitants) of the disease in the municipality was 1.9, being higher in males (3.4) than in females (0.7). Thus, the gross risk of the disease (without controlling for other variables) for males was 4.9 times the risk for females.

The incidence increased with age up to 59 years old and decreased thereafter. The age groups that had the highest incidence were 20 to 39 years old (2.3) and 40 to 59 years old (2.8). The lowest incidences occurred among the aged 0-19 years (0.9) and 60 years and over (1.4). Thus, the gross risk of the disease among individuals aged 20 to 59 years was more than 2.8 times the risk for individuals aged 0 to 19 years.

The south, east and north regions had the highest incidences (2.4, 2.2 and 1.8, respectively). The gross risk in these regions was more than 1.6 times that of the central region.

Table 1. Distribution of cases and deaths from leptospirosis, lethality, coefficient of incidence and relative risk according to sex, age group and region. Municipality of São Paulo, 2007 to 2016.

Variable	Cases		Obits		Lethality	Incidence	RR
	N	%	N	%	%	100,000 inhabitants	
Total	2,201	100	333	100	15.1	1.9	
Sex							
Feminine	396	18	58	17.4	14.6	0.7	1
Masculine	1,805	82	275	82.6	15.2	3.4	4.9
Age group (years)							
0-19	283	12.9	25	7.5	8.8	0.9	1
20-39	917	41.7	79	23.7	8.6	2.3	2.6
40-59	804	36.5	157	47.1	19.5	2.8	3.2
60+	197	9	72	21.6	36.5	1.4	1.6
Region							
Center	66	3	13	3.9	19.7	1.5	1.1
East	523	23.8	76	22.8	14.5	2.2	1.7
North	408	18.5	69	20.7	16.9	1.8	1.4
West	149	6.8	10	3	6.7	1.4	1.1
Southeast	333	15.1	56	16.8	16.8	1.3	1
South	611	27.8	93	27.9	15.2	2.4	1.8

RR: relative risk.

The lowest incidence occurred in the west and southeast regions (1.4 and 1.3, respectively), where the risk of the disease was similar to that of the Center.

Table 2 lists the proportional distribution of number of cases and deaths from leptospirosis in the city of São Paulo, from 2007 to 2016, in addition to lethality rate according to the characteristics of area and environment of infection, as well as signs and symptoms.

The vast majority of cases occurred in an urban area (85.6%), and the most reported likely infection environments were the patients' household (55.4%) and workplace (12.4%).

The most common signs and symptoms were fever (89.7%), myalgia (82.8%), jaundice (62.1%), headache (61.6%) and calf pain (53.6%). The vast majority of cases (84.3%) required hospitalization.

The lethality rate was higher among patients who had pulmonary hemorrhage (40.2%), cardiac disorders (37.9%), respiratory disorders (32.8%), other hemorrhages (27.9%), renal failure (25.2%) and jaundice (19.3%).

The proportional distribution of number of cases of leptospirosis was also obtained according to exposure to risk situations. The most frequently recorded were contact with

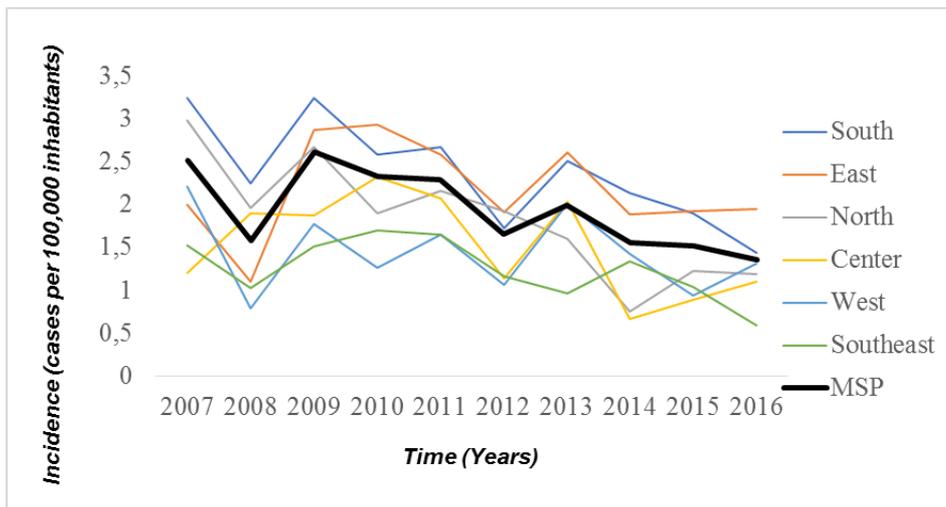
Table 2. Distribution of cases of leptospirosis, deaths and lethality, according to characteristics of the area and environment of infection, as well as and signs and symptoms. Municipality of São Paulo, 2007 to 2016.

Variable	Cases		Obits		Lethality
	N	%	N	%	%
Total	2,201	100	333	100	15.1
Area of infection					
Urban	1,884	85.6	299	89.8	15.9
Rural/periurban	80	3.6	9	2.7	11.2
Environment of infection					
Household	1,219	55.4	185	55.6	45.2
Work place	273	12.4	46	13.8	16.8
Leisure/other	246	11.2	32	9.6	13
Signs and symptoms					
Fever	1,974	89.7	287	86.2	14.5
Myalgias	1,823	82.8	259	77.8	14.2
Jaundice	1,367	62.1	264	79.3	19.3
Headache	1,356	61.6	155	46.5	11.4
Calf pain	1,180	53.6	175	52.6	14.8
Renal failure	785	35.7	198	59.5	25.2
Respiratory changes	606	27.5	199	59.8	32.8
Pulmonary hemorrhage	239	10.9	96	28.8	40.2
Other bleedings	219	10	61	18.3	27.9
Cardiac changes	140	6.4	53	15.9	37.9

flood water and/or mud (38.7%) and contact with or cleaning of a place with signs of rodents (35.9%).

Figure 2 details the annual leptospirosis incidence rates in the municipality according to region of residence (Figure 2A) and age group (Figure 2B). In general, the southern, eastern and northern regions had the highest incidences in the period. The lowest were observed in the west and southeast regions. Both in the municipality and in regions, there is a downwards trend of the incidence over the years. The age groups with the highest incidences

#### A. According to region



#### B. According to age

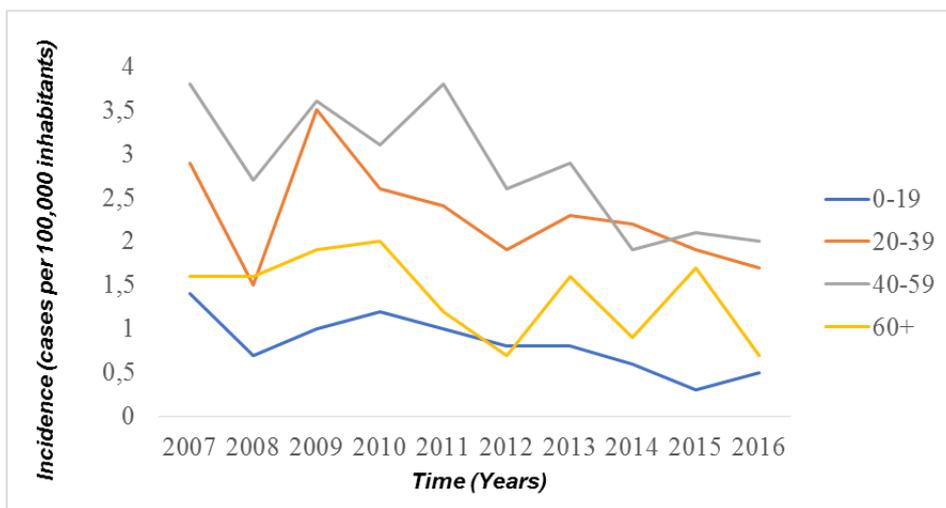


Figure 2. Leptospirosis incidence rates over time. Municipality of São Paulo, 2007 to 2016.

were 40 to 59 years old and 20 to 39 years old. The lowest were reported in the range of 0 to 19 years. In all age groups, the incidence tends to drop over the years.

According to the estimates of the regression model, which assessed the trend in the municipality of São Paulo as a whole, the incidence of leptospirosis showed a downward trend during the period (relative risk – RR = 0.9;  $p < 0.01$ ), estimated at 5.6% per year (95% confidence interval – 95%CI 2.4 - 8.8). The adjusted incidence (per 100,000 inhabitants) fell from 2.5 in 2007 to 1.5 in 2016.

Table 3 shows the estimates of the final regression model for the incidence of leptospirosis over time per age groups and regions. None of the interactions involving these three variables was significant. Therefore, they did not remain in the model. After adjusting for region and age group, the downward trend remained significant (RR = 0.95,  $p < 0.001$ ) and was similar in all age groups and regions, estimated at 5.5% per year (95%CI 4.1 - 6.9).

The relative risks for each region were estimated using the central region as a reference. The risk of disease was higher in the south (RR = 1.67,  $p < 0.001$ ), east (RR = 1.55,  $p = 0.001$ ) and north (RR = 1.27,  $p = 0.068$ ) regions than in the center. The southeast (RR = 0.85,  $p = 0.233$ ) and west (RR = 0.97,  $p = 0.853$ ) regions had risks similar to those in the center.

The RRs for each age group were estimated using the 0 to 19 age group as a reference. The greatest risks occurred in the economically active age groups, from 20 to 39 years (RR = 2.68,  $p = 0.001$ ) and from 40 to 59 years (RR = 3.38,  $p = 0.001$ ). In the age group of 60 and over, the risk was greater than in the age group from 0 to 19 years (RR = 1.79,  $p = 0.001$ ), but slightly lower than in the age group of 20 to 59 years.

Table 3. Estimates of the regression model for incidence according to regions and age groups. Municipality of São Paulo, 2007 to 2016.

Explanatory variables	RR	95%CI (RR)	p	APC	95%CI (APC)
				%	%
Time (years)	0.95	(0.93 – 0.96)	< 0.001	5.5	(4.1 – 6.9)
Region					
Center	1				
East	1.27	(0.98 – 1.65)	0.068		
North	1.55	(1.20 – 2.01)	0.001		
West	0.85	(0.65 – 1.11)	0.233		
Southeast	1.67	(1.30 – 2.16)	< 0.001		
South	0.97	(0.73 – 1.30)	0.853		
Age group (years)					
0-19	1				
20-39	2.68	(2.33 – 3.07)	< 0.001		
40-59	3.38	(2.94 – 3.89)	< 0.001		
60+	1.79	(1.49 – 2.16)	< 0.001		

RR: relative risk; 95%CI: 95% confidence interval; APC: annual percentage change.

## DISCUSSION

The highest incidences of leptospirosis in the city of São Paulo, between 2007 and 2016, were found in males and in economically active age groups, which may be associated with work activities carried out in unhealthy conditions or situations, or practices that provide contact with the agent etiological. Examples of such activities are: civil construction, handling of waste and recyclables, work in sewage cleaning, salvage of goods in floods, among others<sup>1,11,16</sup>.

Other studies have reported similar results, with the disease more prevalent in males and in economically active age groups in Brazil<sup>11,17-19</sup> and abroad<sup>20-24</sup>, but the type of exposure and the risk factors associated with the disease varied around the world. In general, in more developed countries, the disease is linked to occupational activities, recreational activities and international trips to endemic areas, mainly for adventure tourism<sup>25,26</sup>. In the least developed countries, however, it is linked to poverty. Routine activities, high population density, lack of sanitation and climatic conditions are determining factors<sup>3,16,25</sup>.

The average incidence rate (per 100 thousand inhabitants) observed in the municipality in the study was similar to those registered in the state of São Paulo and in Brazil in the same period (respectively, 1.9 and 2) and in Latin America<sup>27</sup> (2), in 2014, however this rate is much higher than in more developed countries. In these places, leptospirosis is relatively uncommon and has low incidence rates. The European Union, in 2014, reached an incidence of 0.2328. In studies in Europe, incidence rates of 0.06 were found in Germany<sup>29</sup>, 0.20 in France<sup>7</sup>, 0.25 in the Netherlands<sup>8</sup> and 0.34 in Denmark<sup>21</sup>.

The lethality found in the municipality was higher than in the state of São Paulo and Brazil for the same period – 11.6 and 8.9%, respectively. In general, lethality above 10% is considered high<sup>30</sup>, and it was similar for both sexes, with a gradual increase according to the aging of individuals, as observed for the state of São Paulo<sup>30</sup>. However, for individuals who presented pulmonary hemorrhage, the lethality was 40%, in accordance with a report by the Ministry of Health that states that lethality can reach 50% in these cases<sup>31</sup>. This manifestation is increasingly recognized as important, often resulting in death<sup>32</sup>.

The fact that almost two thirds of patients with leptospirosis have experienced jaundice may mean that suspicions about the condition only occur when there are more severe forms. According to the São Paulo State Department of Health, percentages greater than 10% of patients with jaundice are considered high, meaning that health services are not suspecting mild and moderate cases without jaundice, with less specific clinical conditions<sup>33</sup>. The large number of hospitalizations for the disease reinforces this hypothesis. According to the literature, approximately 90% of leptospirosis cases go unnoticed or are confused with simple viruses<sup>19,34</sup>.

The fact that most cases were reported in an urban area and/or in a home environment corroborates results observed in numerous Brazilian studies<sup>6-16,17,19,35-39</sup>. In addition, the most frequent exposures—involving water, flood mud and the presence of synanthropic rodents—were also reported in studies carried out in developing countries<sup>16,17,40</sup>.

The downward trend in the incidence of leptospirosis in the analyzed period, both in the municipality and regions, could be a reflection of the investment in the construction of detention reservoirs (swimming pools), linear parks, cleaning of galleries, desilting of river gutters, among others. These improvements were implemented by the Macrodrainage Master Plan of the Alto Tietê Basin, by the Department of Water and Electricity (DAEE), and by the Drainage Master Plan of the Municipality of São Paulo, in 1998.

The drop in incidence may also be associated with the improvement in the Municipal Human Development Index (MHDI) of the peripheral regions in the municipality, which grew above 10% between 2000 and 2010, indicating a general improvement in the population's living conditions<sup>41</sup>.

Another factor that could have contributed to the drop in incidence is the increase in immunity. Tassinari et al.<sup>42</sup> point out that people residing in slums, places with a lack of basic sanitation and garbage collection or areas susceptible to flooding can acquire immunity through repeated episodes of mild exposure to the etiologic agent, leading to a decrease in disease manifestation and, consequently, in the incidence. Seroprevalence studies could be conducted to investigate this hypothesis.

Finally, it is important to consider that leptospirosis is a disease that is known to be underreported<sup>43</sup>, since it can be confused with other seasonal diseases. It is possible that, in part, an increase in underreporting over the years, due to outbreaks of other diseases such as dengue, may have contributed to the decrease in incidence.

The differences seen between the various regions of the municipality of São Paulo may be associated with socioeconomic and environmental-profile variances. The south, east and north regions may be more vulnerable to the disease, as there are more administrative districts with high demographic density, low housing standard, precarious basic sanitation and disposal of solid waste, high level of social vulnerability, scarcity of public services and facilities, among other factors<sup>44</sup>. In fact, Pelissari et al.<sup>35</sup>, Soares et al.<sup>6</sup> and Lara et al.<sup>17</sup> pointed out that leptospirosis is linked to low socioeconomic levels and environmental factors. On the other hand, the southeastern, western and central regions have administrative districts with higher per capita income, low levels of social vulnerability, good housing standards, water supply, sewage and solid waste collection practically in their entirety<sup>44</sup>.

The lowest incidences were found in the western region, probably due to better environmental and socioeconomic conditions. For example, in the west, eight districts have per capita income between five and ten minimum wages, while most peripheral districts in the municipality have per capita income below one minimum wage<sup>45</sup>.

In a study in the municipality of São Paulo from 1998 to 2006, Soares et al.<sup>6</sup> reported an increased incidence in districts close to dams (south zone) and peripheral ones in rainy periods and in southern and eastern districts in dry periods. They reported that, in the dry period, cases occurred in areas with the worst housing conditions and, in the wet period, also in other districts, perhaps related to the proximity of rivers and streams. The incidence was low in the central region (which included some districts in the west and southeast regions of our study), with the exception of the Sé and Brás districts, which had a high incidence.

The main limitations of this work are inherent to ecological studies and the use of secondary data. Studies with secondary data are restricted to the available data.

The ages and places of residence of the cases were considered in statistical models and, in order not to incur an ecological bias or fallacy, we cannot infer for an individual what we observed in groups or clusters.

Despite these limitations, with a long period of study and an adequate statistical methodology for data analysis, taking into account its temporal autocorrelation, this study was able to provide important information regarding leptospirosis in the municipality of São Paulo that may be useful for improving the surveillance and control the disease.

The municipality of São Paulo has great social, housing and environmental diversity, which is very challenging. Although there has been a downward trend in the incidence of leptospirosis, it remains a serious disease with high lethality, and investments to meet the basic needs of the population are needed, mainly in peripheral regions.

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