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Title: Taking the inner route: spatial and demographic factors affecting vulnerability to COVID-19 among 604 cities from inner São Paulo State, Brazil.

Running head: COVID-19 in inner São Paulo State, Brazil

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Objectives: The impact of COVID-19 in metropolitan areas has been extensively studied. The geographic spread to smaller cities is of great concern and may follow hierarchical influence of urban centers. With that in mind, we investigated factors that affect vulnerability of inner municipalities in São Paulo State, Brazil, an area with 24 million inhabitants.

Methods: Surveillance data for confirmed COVID-19 cases and admissions for severe acute respiratory disease (SARD) up to April 18th were recorded for each of 604 municipalities that lay outside São Paulo metropolitan area. Vulnerability was assessed in Multivariable models, including sociodemographic indexes, road distance to the State Capital and the municipalities classification proposed by the Brazilian Institute of Geography and Statistics. Municipalities of great regional relevance were used as reference category for that classification. The outcome of interest for Cox regression was having COVID-cases, with time counting from the first report in São Paulo State. For binomial negative regression models, the outcomes of interest were rates of confirmed COVID-19 cases and admissions for SARD.

Results: A total of 198 (32.8%) municipalities had autochthonous COVID-19 cases. In Cox models, affected municipalities were likely to have greater population density (Hazard Ratio[HR] for each 100 inhabitants per square kilometer, 1.07; 95% Confidence Interval [CI], (1.05-1.10)), proportion of inhabitants in urban area (HR, 1.02; 95%CI, 1.00-1.04), higher human development index (HDI, HR for 1%, 1.06; 95%CI, 1.00-1.13) and Gini Index for Inequality of income (HR for 1%, 1.04, 95% CI, 1.00-1.07). On the other hand, distance from the Capital was protective (HR for each 100Km, 0.82; 95%CI, 0.74-0.90). The HR95%[95%CI] also varied negatively according to the categories of influence of major centers (0.41 [0.22-0.77], 0.16 [0.09-0.32], 0.07 [0.03-0.15]). The binomial negative regression models for COVID-19 incidence also detected positive association with population density (Incidence Rate Ratio[IRR], 1.13; 95%CI, 1.07-1.18) and proportion of urban population (IRR, 1.04; 95%CI, 1.01-1.05), protection for cities distant to the Capital (IRR=0.73; 95%CI, 0.68-0.81) and increasing negative association for categories of influence (0.19 [0.09-0.42], 0.07 [0.03-0.15] and 0.03 [0.02-0.08]). Similar findings were detected when we used SARD incidence as outcome.

Conclusion: Municipalities with greater population, density and regional influence were more likely to be affected earlier and more intensely by COVID-19. Non-pharmacological measures should be strengthened in those areas of greater risk.

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Introduction

In the context of the COVID-19 pandemic, public health officials have been forced to make decisions based on scarce evidence (Lv et al, 2020; Tobias, 2020). This is a major challenge for countries such as Brazil, with are both huge and highly heterogenous in socioeconomic indexes, demography and access to health care (de Andrade et al, 2015). São Paulo is the most populous and richer State in Brazil, with a population of 44 million inhabitants. Half of those people live in São Paulo Metropolitan area, A cluster of conurbated cities with high population density. The impact of COVID-19 in that area was predicted by mathematical models (Rocha Filho et al, 2020), which lead to the implementation of a social distancing strategy for the whole state since March 23rd, 2020.

Preliminary studies demonstrated that this strategy lowered SARS-Cov-2 transmission and reproductive number of COVID-19 in the metropolitan area (Ganen et al, 2020). However, monitoring mobility of mobile phones (data available in São Paulo State Government site, https://www.saopaulo.sp.gov.br/coronavirus/isolamento/) has detected lower adherence to social distancing in inner municipalities of the State. Also, the same system has demonstrated a trend towards neglecting governmental recommendations all over the state.

Many countries are now facing the exhaustion of lockdown measures and planning the return of social e economic activities (Hoseinpour Dehkordi et al, 2020; Thomson, 2020). In a State that is more populous than many countries, such as São Paulo, any strategy for loosening social distancing measures must be carefully guided by epidemiological data and a rigorous assessment of regional risk. Therefore, we conducted a study aimed at identifying factors that affect vulnerability to COVID-19 among 605 municipalities in São Paulo State that are located outside the capital metropolitan area metropolitan area. We also aim at providing a methodological approach that is useful for other countries.

Methods

Study setting, design and exclusion criteria.

São Paulo State has 645 municipalities and 46 million inhabitants. We conducted enrolling 605 municipalities from inner São Paulo State, Brazil, with aggregate population of circa 24 million inhabitants. As of April 18th, 2020, 198 of those municipalities reported a total of 2,008 confirmed cases of COVID-19, of whom 152 died. All cities and data from the capital metropolitan area were excluded from the study.

Data collection and analysis

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Data on notifications of confirmed COVID-19 cases and deaths, as well as total admissions for severe acute respiratory diseases (SARD), were obtained from the Center for Epidemiological Surveillance from São Paulo State Health Department (CVE, www.cve.saude.sp.gov.br). Sociodemographic data for each municipality were obtained from the São Paulo State Foundation for Data Analysis (SEADE, https://www.seade.gov.br/). Those data included population density, percentage of persons living in urban area, human development index (HDI) and Gini Index for inequality of income. We also identified 13 municipalities which are centers of greater regional influence. The remaining municipalities were classified according to criteria from the Brazilian Institute for Geography and Statistics (2017): [a] urban municipalities with major influence from regional centers; [b] urban municipalities with minor influence from regional centers; [c] rural municipalities (**Figure 1**). In all models ther 13 regional centers were used as reference category. Finally, we identified the road distance from each municipality to the State capital, São Paulo City (http://www.cidadespaulistas.com.br/prt/cnt/distancias.html)

Statistical analysis

A descriptive analysis of data was performed to identify differences for major categories of municipalities. In the following step, used multivariable Cox regression models with presence of at least one autochthonous case of COVID-19 as the outcome of interest, and days from the first report in São Paulo State as time variable. All those factors cited above were simultaneously included in the model. Finally, we used multivariable models of binomial negative regression, with rates confirmed COVID-19 cases or admissions for SARD as outcomes. The same variables were assessed as risk factors. All analysis were performed using STATA 14 (Statacorp, College Station, TX, USA) or SPSS22 (IBM, Armonk, NY, USA).

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Figure 1. Maps of São Paulo State, Brazil, highlighting the different categories of municipalities outside the metropolitan area.

Results

The categories of regional relevance or influence of regional center impact both the timing of COVID-19 introduction and the on total of confirmed cases, deaths and admissions for SARD (**Table 1**). In Cox regression models of predictors of presence of at least on COVID-19 confirmed case in the municipality, we found that likelihood increased with the population density, proportion of people living in urban areas, HDI and Gini index. On the other hand, it decreased according to distance from the state capital and varied negatively according to the influence of great urban centers (**Table 2** and **Figure 2**). Interestingly, results of Binomial regression models for incidence rates of COVID-19 or SARD were similar (**Tables 3** and **4**).

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Table 1. Characteristics of municipalities from inner São Paulo State, Brazil

Types of Municipalities	Number	Total population	Days until 1rst Case	COVID-19 Incidence*	COVID-19 Mortality*	SARD incidence*
Regional Centers	13	5,953,766	22	15.4 (6.1-51.2)	0.796 (0.5-1.4)	37.6 (31.2-47.0)
Municipalities under major influence	87	6,993,951	31	3.6 (1.1-11.8)	0.0 (0.0-1.1)	26.7 (13.9-38.3)
Municipalities under minor Influence	194	8,346,815	34	0.0 (0.0-.53)	0.0 (0.0-0.0)	23.6 (10.5-39.5)
Rural municipalities	308	2,797,404	55	0.0 (0.0-0.0)**	0.0 (0.0-0.0)**	11.5 (0.0-28.2)

Note. SARD, Severe Acute Respiratory Diseases.

*Per 100,000 inhabitants

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**Though 75th percentiles were zero, upper values for COVID incidence and mortality in rural municipalities were 134.3 and 14.3 per 100,000 inhabitants, respectively. Those were obvious outliers.

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Table 2. Multivariable Cox regression results for likelihood of inner São Paulo State municipalities presenting at least one confirmed case of COVID-19 as of Apri 18th, 2020.

Predictors	**HR (95%CI)**	**p**
Classification of municipalities		
Regional centers (Reference)	...	...
Municipalities under major influence of regional centers	0.41 (0.22-0.77)	0.006
Municipalities under minor influence of regional centers	0.16 (0.09-0.32)	<0.001
Rural municipalities	0.07 (0.03-0.15)	<0.001
Population density (x 100)	1.07 (1.05-1.10)	<0.001
Urbanization rate (%)	1,02 (1.00-1.04)	0.04
Human Development index (%)	1.06 (1.00-1.13)	0.03
Gini index of income inequality (%)	1.04 (1.00-1.07)	0.03
Distance from the State Capital (per 100 Km)	0.82 (0.74-0.90)	<0.01

Note. Urbanization rate is the measure of proportion of inhabitants living in urban area.

HR, Hazard Ratio; CI, Confidence Interval.

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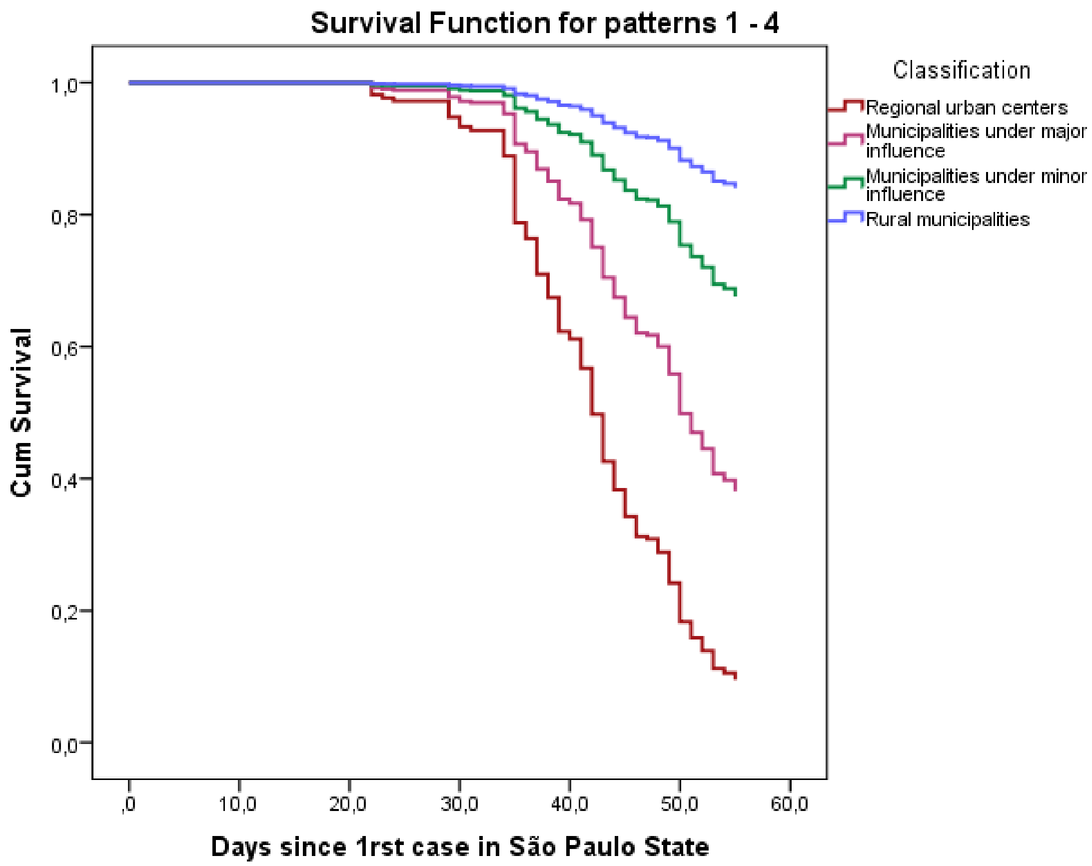

Figure 2. Cox regression graphics for time until introduction of COVID-19 in municipalities from inner São Paulo State, Brazil (based on surveillance data up to April 18th, 2020).

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Table 3. Multivariable negative binomial regression results for rates of confirmed COVID-19 cases in inner São Paulo State municipalities, as of April 18th, 2020.

Predictors	IRR (95%CI)	p
Classification of municipalities		
Regional centers (Reference)	...	...
Municipalities under major influence of regional centers	0.19 (0.09-0.42)	<0.001
Municipalities under minor influence of regional centers	0.07 (0.03-0.15)	<0.001
Rural municipalities	0.03 (0.02-0.08)	<0.001
Population density (x 100)	1.13 (1.07-1.18)	<0.001
Urbanization rate (%)	1.04 (1.01-1.05)	<0.001
Human Development index (%)	1.07 (1.00-1.13)	0.05
Gini index of income inequality (%)	1.05 (1.01-1.08)	0.006
Distance from the State Capital (per 100 Km)	0.73 (0.68-0.81)	<0.01

Note. Urbanization rate is the measure of proportion of inhabitants living in urban area.

IRR, Incidence Rate Ratio; CI, Confidence Interval.

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Table 4. Multivariable negative binomial regression results for rates of admissions for severe acute respiratory disease in inner São Paulo State municipalities, as of April 18th, 2020.

Predictors	IRR (95%CI)	p
Classification of municipalities		
Regional centers (Reference)	...	...
Municipalities under major influence of regional centers	0.54 (0.29-1.01)	0.05
Municipalities under minor influence of regional centers	0.35 (0.19-0.64)	0.001
Rural municipalities	0.16 (0.08-0.29)	<0.001
Population density (x 100)	1.07 (1.03-1.10)	<0.001
Urbanization rate (%)	0.99 (0.98-1.00)	0.18
Human Development index (%)	1.21 (1.17-1.26)	<0.001
Gini index of income inequality (%)	1.05 (1.02-1.07)	<0.001
Distance from the State Capital (per 100 Km)	0.75 (0.70-0.79)	<0.001

Note. Urbanization rate is the measure of proportion of inhabitants living in urban area.

IRR, Incidence Rate Ratio; CI, Confidence Interval.

Discussion

The COVID-19 pandemic has imposed to epidemiologists the performance rapid analyses to guide political decisions. In developing countries, such as Brazil, the challenges range from access to healthcare to the devastating effects of recession (Andrade et al, 2020; Hotez et al, 2020). Up to the present date, two thirds of COVID-19 confirmed cases in São Paulo State occurred in the capital (São Paulo City) metropolitan area. This has created a feeling of safety in the inner cities, with local authorities questioning the measures of social distancing. Our study was conducted to provide findings that can guide public health authorities, by understanding the routes of spread and the vulnerability of municipalities to COVID-19.

One must notice that inner São Paulo State is highly heterogenous, comprising cities that range from one thousand to 1.2 million inhabitants. Our findings highlight the importance of regionally relevant urban centers, some of which are located far from the capital. Interestingly, both the classification of regional relevance and the population density were independently associated with early introduction and higher incidence rates. In order to avoid bias from access to diagnostic tests, we also studied the admissions for SARD, with similar findings.

It is worth noting that, besides regional relevance and other indexes of urbanization, proximity to the state capital (i.e., the State epicenter of COVID-19) was also independently associated with early and greater impact of the pandemic. Therefore, we detected two patterns of epidemic spread into the inner state. In one pattern, the disease spreads by contiguity into areas neighboring the capital and its metropolitan area. In the another, it disseminates rapidly to great cities located in central and western areas of the state, from which it spreads into smaller municipalities. The greater the connectiveness of those municipalities with their regional centers, the greater their vulnerability to COVID-19. This explains the apparent paradox of some high-risk cities being located far from the state capital, and vice versa.

Our study may have inaccuracies inherent to the analysis of partial data in an ongoing pandemic. However, despite its limitations, the ecological design provides the appropriate results to guide public health decisions (Morgestern, 1995). If we are to enter a "post-lockdown" period, it must be planned considering the routes of COVID-19 spread into inner areas of the countries. Late introduction and lower (up to date) incidence may be erroneously interpreted as absence of risks. In our perspective, the findings of this study should be interpreted in the opposite way, i.e., highlighting the necessity of strengthening disease control through social distancing in the urban areas of great social and economic influence, and secondarily in municipalities with major connections with those cities. By identifying target areas for interrupting transmission, countries and states may find safer ways out of the quarantines.

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