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THE 2016-2019 WILD YELLOW FEVER EPIDEMIC IN SAO PAULO, BRAZIL: ASSOCIATED FACTORS BEYOND VACCINE COVERAGE

A EPIDEMIA EM 2016-2019 DE FEBRE AMARELA SILVESTRE EM SAO PAULO, BRASIL: FATORES ASSOCIADOS ALÉM DA COBERTURA VACINAL

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ABSTRACT

Objectives: To describe the occurrence of yellow fever (YF) in the Brazilian state of Sao Paulo between 2016 and 2019, and after adjustment for vaccination coverage, evaluate associations with environmental and demographic variables. Methods: This ecological study on confirmed autochthonous cases of YF in SP between April 2016 to May 2019 considered latent Bayesian Gaussian models, spatial random effects at the municipality level, and zero-inflated and non-zero-inflated Poisson and negative binomial probability distributions where the incidence rate per 100,000 inhabitants were also considered. Results: Between 2016 and 2019, there were 648 human cases of YF, with lethality of 35.5%. Among the covariates considered in the models, native vegetation cover and total rural population were associated with YF occurrence, after adjustment for vaccine coverage. As expected, vaccine coverage was shown to have a protective effect: an increase in one standard deviation (SD) of coverage in a given municipality resulted in 82% fewer cases (relative risk [RR]=0.18; 95% credibility interval (CI): (0.11–0.27). Vegetation cover rate and rural population were shown to be risk factors, regardless of vaccination coverage. A one-SD increase in the values for these variables represented a 109% increase (RR= 2.09; 95% CI: 1.60–2.73) and 99% (RR=1.99; IC 95%: 1.41–2.87) in the number of YF cases, respectively. Conclusions: This study demonstrated that besides vaccination coverage, local factors such as vegetation cover and rural population size are involved in the occurrence of YF in affected municipalities. Since vaccine stocks are limited and large portions of the population are still unvaccinated, this information can help identify risk areas for increased vaccine coverage and broaden epidemiological and entomological surveillance activities.

Keywords: Yellow fever. Ecological study. Bayesian models. Vegetation cover. Rural population.

RESUMO

Objetivos: Descrever a ocorrência de febre amarela (FA) no estado de São Paulo (SP) entre 2016 e 2019 e, após ajuste para cobertura vacinal, avaliar associações com variáveis ambientais e demográficas. Métodos: Este estudo ecológico de casos autóctones confirmados de FA em SP entre abril de 2016 a maio de 2019, considerou modelos gaussianos bayesianos latentes, efeitos aleatórios espaciais em nível de município e distribuições de probabilidade binomial negativa e Poisson inflado e não inflado por zero, onde foram considerados também a taxa de incidência por 100.000 habitantes. Resultados: Entre 2016 e 2019, ocorreram 648 casos humanos de FA, com letalidade de 35,5%. Entre as covariáveis consideradas nos modelos, a cobertura vegetal nativa e a população rural total foram associadas à ocorrência de FA, após ajuste para cobertura vacinal. Como esperado, a cobertura vacinal mostrou ter um efeito protetor: o aumento de um desvio padrão (DP) da cobertura em um determinado município resultou em 82% menos casos (risco relativo [RR] = 0,18; intervalo de credibilidade (IC) de 95% (0,11 – 0,27). A taxa de cobertura vegetal e a população rural mostraram-se fatores de risco, independentemente da cobertura vacinal. Um aumento de um DP nos valores

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dessas variáveis representou um aumento de 109% (RR= 2,09; IC 95%: 1,60 – 2,73) e 99% (RR=1,99; IC 95%: 1,41 – 2,87) no número de casos de FA, respectivamente. Conclusões: Este estudo demonstrou que além da cobertura vacinal, fatores locais como cobertura vegetal e tamanho da população rural são envolvidos na ocorrência da FA nos municípios afetados. Como os estoques de vacinas são limitados e grande parte da população ainda não foi vacinada, essas informações podem ajudar a identificar áreas de risco para aumento da cobertura vacinal e ampliar as ações de vigilância epidemiológica e entomológica.

Palavras-chave: Febre Amarela. Estudo ecológico. Modelos Bayesianos. Cobertura vegetal; População rural.

INTRODUCTION

Yellow fever (YF) is an infectious disease caused by an arbovirus in the Flaviviridae family, which includes other viruses responsible for diseases that affect humans including dengue and Zika. The disease remains endemic and enzootic in tropical regions of the Americas and Africa, and epidemics of varying magnitudes are recorded in these localities from time to time (de Rezende *et al.*, 2018).

In the Americas, there are two known cycles of transmission for the YF virus, differing only from an epidemiological point of view. The wild cycle involves circulation of the virus in different mosquito species (such as *Haemagogus* spp. and *Sabethes* spp.), with non-human primates (NHP) participating in this cycle as amplifiers (Cavalcante and Tauil, 2017). Humans entering forest areas can be infected after being bitten by a wild mosquito that previously fed on an infected primate (Hamrick et al., 2017). In the urban cycle, humans are the hosts, and the virus circulates in a human-mosquito-human cycle in which *Aedes aegypti* is the main vector (Cavalcante and Tauil, 2017; Giovanetti *et al*, 2020). This cycle can cause mass epidemics that are difficult to control, due to the presence of this mosquito in large urban areas and a greater chance that infected humans will move from place to place compared to NHP (Giovanetti *et al*, 2020).

The virus incubates for 3–6 days; in symptomatic cases, this is followed by fever, weakness, headache, nausea, and muscle pain. However, 70–85% of YF infections are asymptomatic or have mild symptoms (Zhao *et al.*, 2018). Lethality is high in symptomatic cases, according to Brazilian data. The cases reported between 2000 and 2012 in Brazil indicated average lethality of 47% (Cavalcante and Tauil, 2017). The main prevention measure for YF in humans is vaccination, since an effective vaccine is available (Garske *et al.*, 2014a). The 17D vaccine has been used for decades and provides effective immunization within 10 days. A single dose is sufficient to provide life-long immunization (WHO, 2014)

In Brazil, there have been reports of YF since 1685, and the last record of the urban cycle of this disease was in 1942 in Sena Madureira, in the state of Acre (Cavalcante and Tauil, 2017). Since then, only cases of wild YF (WYF) have been recorded (Lacerda *et al*, 2021). The North and Center-west regions of the country are considered endemic areas. From 1999, most cases were recorded in the Center-West, Southeast, and South, mainly during the rainy season (de Rezende *et al*., 2018). Several episodes of WYF have occurred in the state of Sao Paulo since the 2000s, particularly the Northwest of this state in southeastern Brazil. In 2008 and 2009, the Northwestern and Center-South regions of Sao Paulo registered autochthonous cases (Saad and Barata, 2016; Tauil, 2010) and the Brazilian Ministry of Health consequently recommended vaccination for residents in more than 70% of the municipalities in this state (MS, 2015).

Epidemic occurrences of WYF in Brazil have followed a cyclical pattern lasting approximately three to seven years (Hill *et al*., 2020; Saad and Barata, 2016). After the 2009 epidemic, the country was affected by a new cycle that began in 2014 and still continues (Figueiredo *et al*., 2020), also affecting Sao Paulo. In this new cycle, the first autochthonous and epizootic cases in NHP were detected in the northwest and north of this state in 2016, and transmission extended until 2019 (Mares-Guia *et al*., 2020). This new ongoing epidemic process was responsible for a 2,100 cases and more than 700 deaths from YF between 2016 and 2019 in Brazil's Center-West, Southeast, and South regions (de Thoisy *et al.*, 2020; Ministério da Saúde, 2020).

Recent studies (Hill *et al*., 2020; Kallas *et al.*, 2019; Sacchetto *et al*., 2020) indicate that a combination of factors may have contributed to the severity of the epidemic that began in 2016. First is the proximity of rural populations to the natural habitats of YF vectors and hosts, which may have intensified as new spaces were converted for agriculture and other land use activities, usually linked to burning and deforestation (Sacchetto *et al*., 2020). This proximity makes the rural population, especially the non-vaccinated population, more likely to contract YF.

Climatic factors as well as climate change can also be considered important variables to be analyzed in the epidemic process of YF. This is because the transmission cycles of arbovirus diseases are inherently dependent on changes in precipitation and temperature that directly influence the proliferation, distribution, density, and physiology of mosquitoes (Gomes *et al*., 2010; Possas *et al*., 2018; Weber and Wollmann, 2016). Another factor is vegetation cover, which can contribute to the spread of the YF virus since the main reservoirs and viral amplifiers of the wild cycle (the vectors *Haemagogus* and *Sabethes* and NHP, respectively) are found in forests and surrounding areas (Sacchetto *et al*., 2020).

A favorable combination of these factors may have contributed to the extent of the epidemic that began in 2016 and could determine similar processes in the future. Since there is a vaccine against yellow fever and this vaccine is effective and immunizes the individual against the virus, our purpose was to quantify how much the other variables interfere in the spread of the disease, considering who is susceptible to the disease and who is not. The objective was to describe the occurrence of YF in Sao Paulo state between 2016 and 2019 in spatial and temporal terms and evaluate associations with environmental and demographic variables after adjustment for vaccine coverage.

More information about the factors involved in this epidemic process also contributes to a better understanding of the risk that YF will urbanize. Many of the remaining forest fragments in Sao Paulo are located near cities with medium and high population densities that are infested with *A. aegypti*. This is a cause for great concern, given the risk these areas pose for the occurrence of this disease in urban areas (De Abreu *et al*., 2019) especially as vector control activities undertaken by the municipalities have not been effective.

MATERIALS AND METHODS

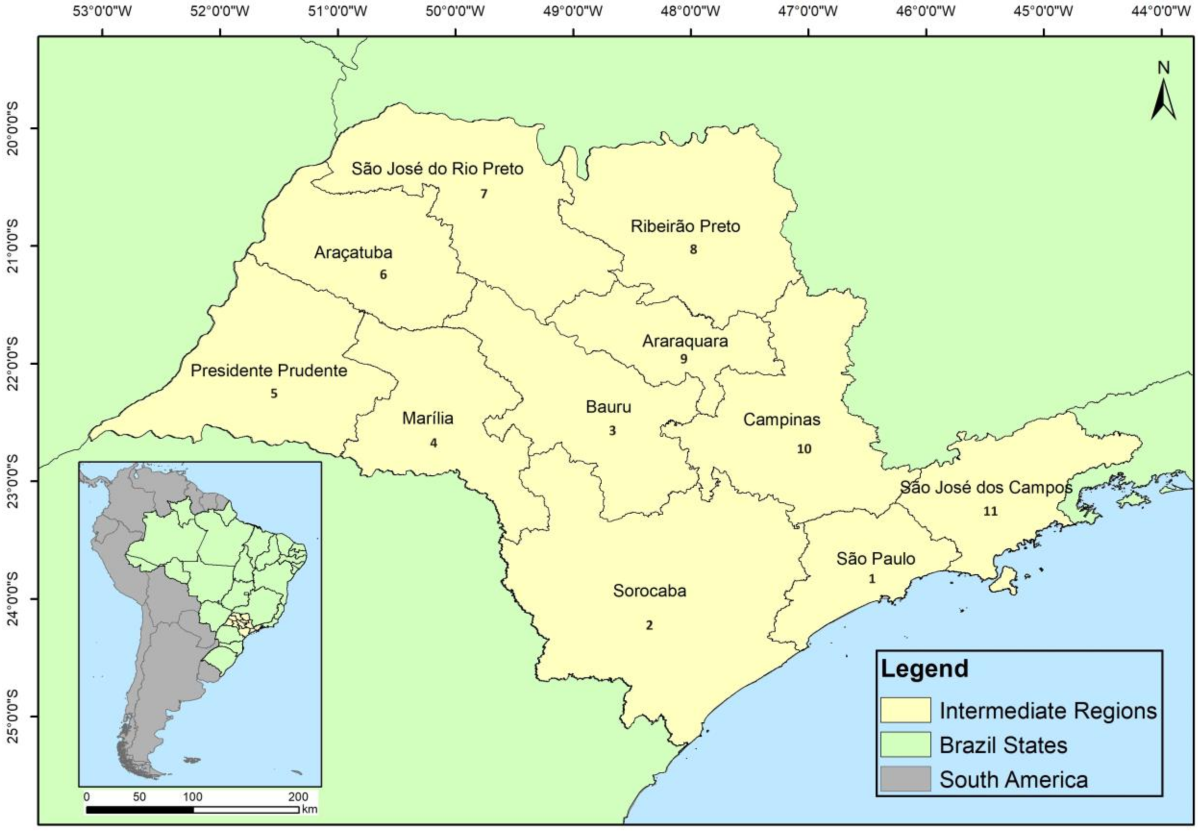
Type, area, and period of study

This present study uses an ecological design to analyze the occurrence of autochthonous human cases of YF between 2016 and 2019 in Sao Paulo State. This state contains 645 municipalities and is subdivided into 11 intermediate regions by the Brazilian Institute of Geography and Statistics (IBGE). We chose to use this division because it gives us support to explain the distribution of human cases in the present YF epidemic. It is the country's main financial center, accounting for 30.9% of national GDP, and is the most populous state with more than 44 million inhabitants. Almost half of this population resides in the metropolitan region that encompasses its capital city, Sao Paulo, and comprises 39 municipalities (EMPLASA, 2017). Geographically, this state has relatively elevated terrain, with 85% of its area at 300–900 m altitude.

The climate in Sao Paulo is quite diverse. In mountainous areas where remnants of Atlantic Forest are present, temperatures are milder, and frost may occur in winter. The interior of the state is predominantly hot due to continentality and can reach 40°C in summer. In terms of vegetation, Atlantic Forest biomes are found in the South of the state, along its entire coast, and in its north and northeast.

Sao Paulo is the most important of Brazil's states because it concentrates a wide range of activities involving trade, industry, sophisticated services, and research and higher education institutions. But although it is the largest economy in the country, the state also exhibits a series of deficiencies in urban and social infrastructure related to a lack of housing units and public services and a need to expand sanitation.

Figure 1 – Location of Sao Paulo state in Brazil and South America, and subdivisions into intermediate regions and municipalities



Source: Maps created using ArcGIS 10.4 by the authors.

Dependent Variable

Cases of YF

Information on autochthonous human cases of YF from April 2016 to May 2019 was collected from the Sao Paulo State Epidemiological Surveillance Center (Centro de Vigilância Epidemiológico, CVE) and aggregated by municipality.

Data on YF cases in SP are available on the CVE website (CVE, 2019) from weekly Epidemiological Bulletins issued during the epidemic periods. This information is publicly available; records are divided into autochthonous and imported human cases and epizootics in NHPs. In both cases, the information is aggregated by municipality and month and does not provide personal information that can identify individuals. For this reason, approval by the institutional ethics review board was not required.

Numbers of autochthonous YF cases were presented, and the incidence rates for YF were calculated according to space (by municipality) and time (months and years). The rural population of the municipality was obtained from IBGE and used as a denominator to calculate rates. Although all autochthonous cases of YF have been classified as wild by CVE and the Brazilian Ministry of Health (SVS/MS, 2017; CVE,2019), it cannot be said that only the rural population was at risk of acquiring YF; residents in the urban areas of these municipalities were also at risk, since they frequented rural and wild areas of their own or neighboring municipalities. Given this limitation, we considered the rural population of the municipalities as a proxy for the population at risk of acquiring YF. In the modeling, the number of autochthonous cases of YF, according to municipalities and throughout the study period, was considered the response variable of this study.

Covariates

Considering that NHP amplify the YF virus and move through regions with green areas (ecological corridors), the percentage of native vegetation cover per municipality was obtained for use as a variable in the modeling. The map of native vegetation cover in SP was obtained via 2010 Landsat 5 satellite images from its Thematic Mapper sensor, using object-based classification and subsequent visual correction and generated by the authors (Secretaria do Meio Ambiente, 2010).

The total rural population and percentage of this population per municipality (both obtained from IBGE, 2017) were also considered as covariates. A high rural population can lead to greater human exposure in forest areas where vectors and NHP are found.

Monthly mean precipitation and temperature data were collected from the Brazilian Integrated Center for Agrometeorological Information (Centro Integrado de informações Agrometeorológicas, CIIAGRO). Data from meteorological stations with over 10 years of data were selected, totaling 120 municipalities within the state. For each station, the monthly average was calculated and then the average per season of the year, since rainfall and temperature varied significantly during winter and summer, impacting vector proliferation (Torres *et al*., 2017). Kriging was performed to obtain temperature and precipitation values for each of the 645 municipalities, and considered the latitude, longitude, and attitude of each municipality. Kriging is an interpolation method similar to the weighted mobile mean, but differs in the weight calculation, which is defined from a spatial analysis based on an experimental semivariogram (Camara and Medeiros, 1998).

Because the vaccine is the main control measure for YF, vaccine coverage data is important to provide an estimate of the population's protection against the virus. Vaccine coverage data available from the Brazilian National Immunization Program (Programa Nacional de Imunização, PNI) and the Department of Information Technology at the Brazilian Unified Heath System (DATASUS 2020) refer only to doses applied in infants (9 months, first dose) and children (4 years of age, booster dose). Since vaccination coverage data was only available for children under five years old, they were used as a proxy for vaccine coverage throughout the population. In order to represent mean vaccination coverage prior to the epidemic, annual coverage data was obtained for each of the municipalities in Sao Paulo state for 2007–2016, and mean values for this data were calculated. The year 2016 was included in the calculation of this average coverage, since during that year YF occurred entirely in areas with high vaccine coverage (Cunha *et al*., 2019). Vaccine coverage data for 2018 were also obtained from PNI to show the advance of vaccine coverage in municipalities in the state during the epidemic.

Statistical Analysis

Bayesian Modeling

A database was initially constructed containing information on each municipality in Sao Paulo, the number of YF cases that occurred between 2016 and 2019, and the respective co-variable values described above. Exploratory analysis of the variables was conducted to identify outliers, evaluate the relationship between the number of YF cases in a preliminary manner, and identify collinearity between covariates (Zuur *et al.*, 2010).

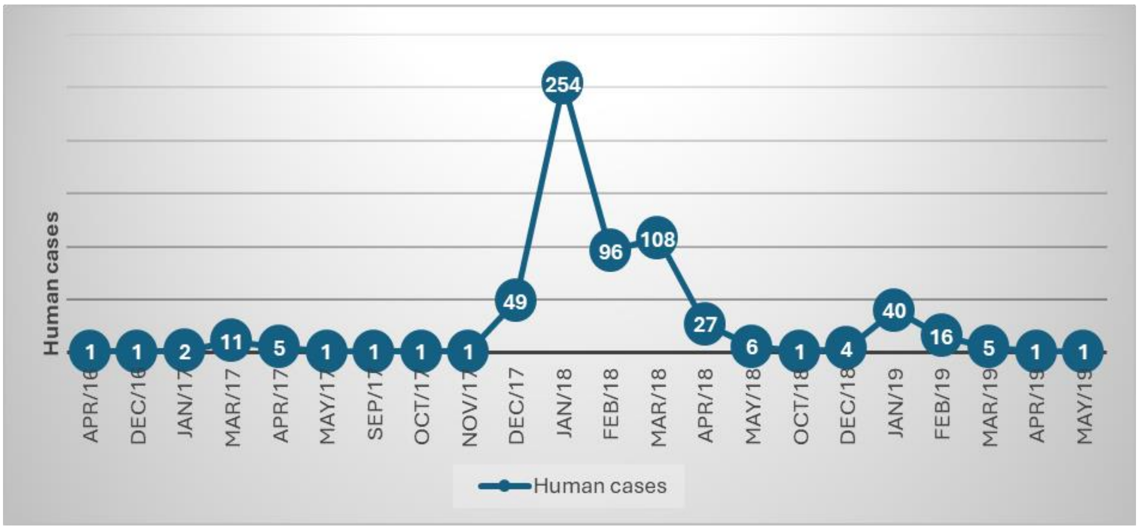
The modeling was performed using latent Bayesian Gaussian models, considering structured and unstructured spatial random effects at the municipal level. These were modeled according to Besag *et al.*, (1991) and the modification proposed by Riebler *et al.* (2016). Neighborhood between municipalities was constructed using the criterion of contiguity. Zero-inflated and non-zero-inflated Poisson and negative binomial probability distributions were considered. Modeling began with intercept-only models and spatial random effects; covariates were then included, with mean vaccination coverage from 2007 to 2016 considered as an adjustment variable. These were standardized by subtracting the mean and dividing by the standard deviation (SD). When it was necessary to select models, those with the lowest deviance information criterion (DIC) (Blangiardo & Cameletti 2015) values were used.

The Bayesian models were made using the Integrated Nested Laplace Approximation (INLA), which obtains the posterior distribution of the parameters of interest (Rue *et al*., 2009). Because of its speed and ease of use, INLA is a successful alternative to other Bayesian methods such as the Markov Chain Monte Carlo (MCMC), and is more computationally efficient (Blangiardo & Cameletti, 2015). Priors with penalized complexity were considered in the modeling, as proposed by Simpsons *et al*. (2017). The maps were made using ArcGIS 10.4 software. The statistical analysis was carried out with R 3.5.3 software (R Core Team, 2019), using the devtools (Wickham *et al*., 2019), sf (Pebesma, 2018), spdep (Bivand & Wong, 2018), INLA (Rue *et al*., 2009), INLAOutputs (Baquero, 2018), and lattice (Sakar, 2008) packages*.*

RESULTS

From 2016 to 2019, 648 autochthonous human cases of YF and 230 deaths were recorded in Sao Paulo State, with lethality of 35.5%. The periods spanning December 2016 to April 2017, November 2017 to April 2018, and November 2018 to March 2019 had the highest case numbers (Fig. 2). During the analysis period, there were months in which no cases of YF were recorded, on January 2018 was recorded the highest number of cases (254). Adding to the previous month (December 2017) and the two subsequent months (February and March 2018), the number of cases is more than 500 in São Paulo State. The median was 4,5 cases per month.

Figure 2 – Autochthonous human cases of yellow fever in the state of Sao Paulo by month, 2016 – 2019

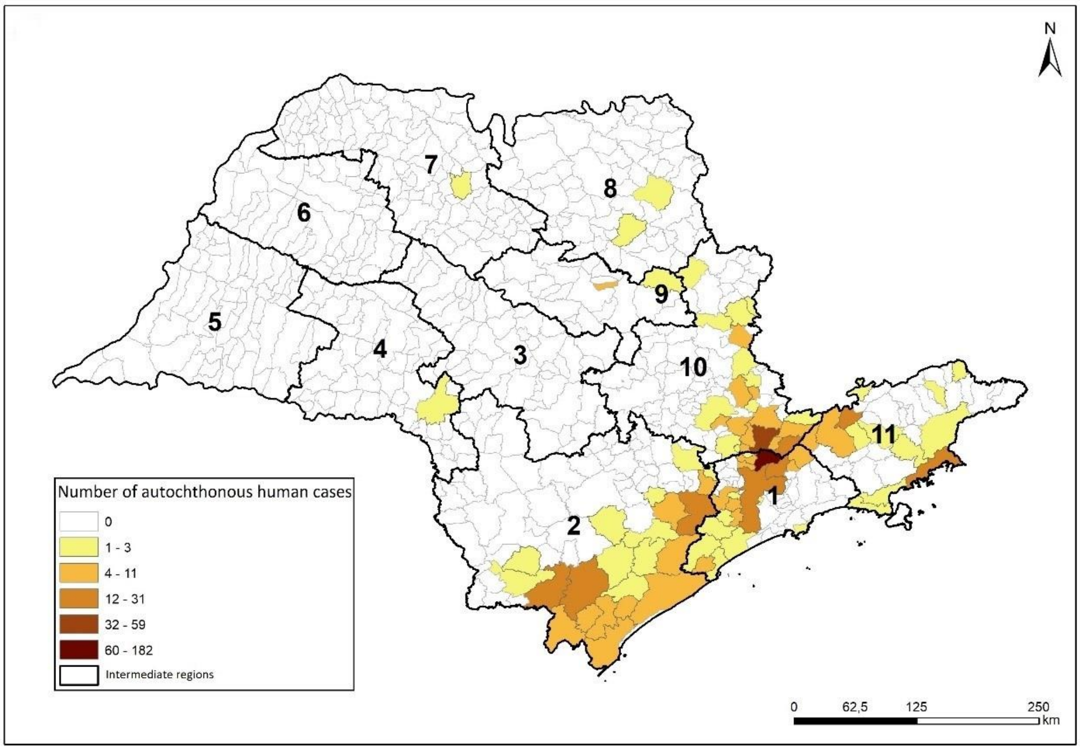


Source: Information on autochthonous human cases from CVE. By the authors.

Figure 3 shows the municipalities of Sao Paulo according to the number of autochthonous human cases of YF) and their respective incidence rates (Figure 4) between 2016 and 2019. The two maps show that transmission of YF occurred almost entirely in the municipalities within the Sao Paulo, Campinas, Sorocaba, and Sao José dos Campos intermediate regions, in the Eastern, Northeastern, Southeastern, and Southern portions of the state.

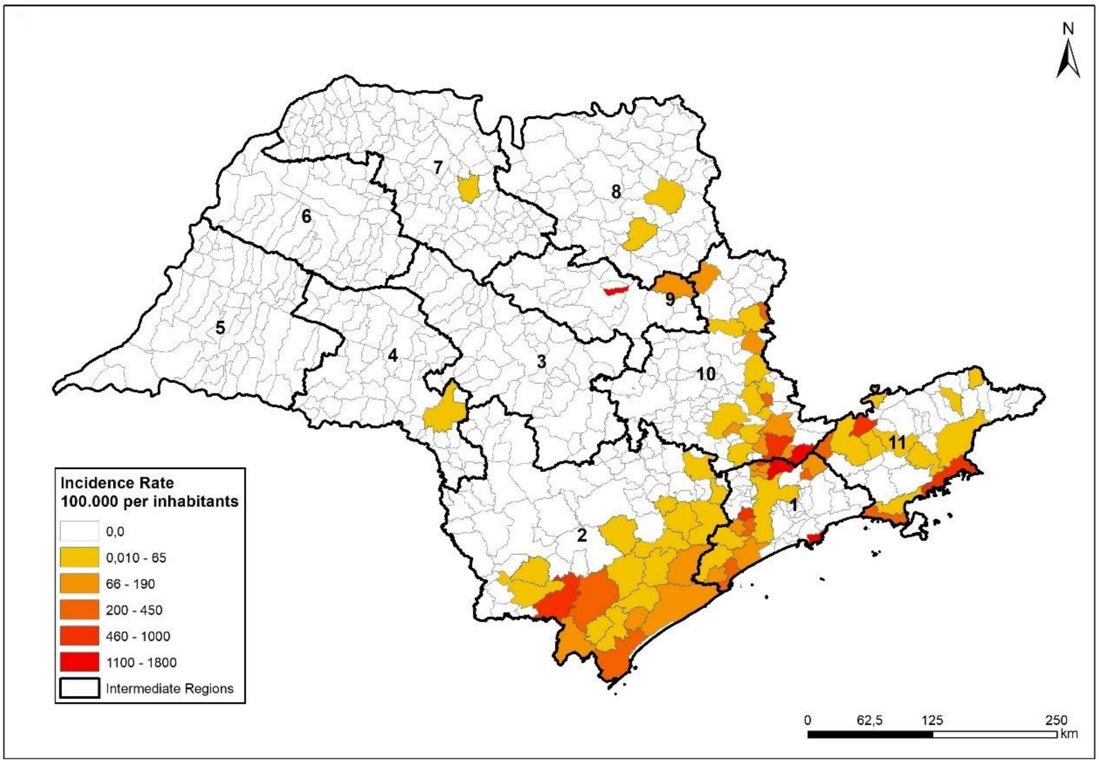
The municipalities with the highest case numbers were Mairiporã, Atibaia, Nazaré Paulista, and Guarulhos in the Sao Paulo intermediate region, and Ubatuba in the Sao José dos Campos intermediate region (Figure 3). The difference between the case and incidence curves between November 2018 and March 2019 (Figure 2). The incidence cases were calculated based on the rural population of each municipality since it was observed from epidemiological surveillance that the registered cases occurred, in their majority in rural areas (Figure. 4). Results from the fact that transmission during this period was more intense in the Sorocaba intermediate region and in municipalities with smaller rural populations than those located in the Sao Paulo, Campinas, and Sao José dos Campos intermediate regions (Figures 3 and 4).

Figure 3 – Numbers of autochthonous human cases of yellow fever for municipalities and intermediate regions in the state of Sao Paulo, 2016–2019



Source: Maps created using ArcGIS 10.4 by the authors.

Figure 4 – Incidence rate for municipalities and intermediate in the State of São Paulo, 2016-2019



Source: Maps created using ArcGIS 10.4 by the authors.

Of the covariates initially considered for modeling, winter temperature, summer temperature, and winter precipitation demonstrated collinearity with mean vaccine coverage between 2007 and 2016 (r=0.77; 0.70 and -0.55, respectively); because this is our model adjustment variable, the meteorological variables mentioned above were removed. After collinearity was eliminated, the following factors remained for modeling: native vegetation cover, total rural population, summer precipitation and mean vaccine coverage 2007–2016 (presented in Figures 5A, B, C and D, respectively), . Note that outliers were identified in the total rural population, which was transformed for modeling purposes using the root elevated to the fourth power.

The models that used Poisson probability distribution showed variance below the mean and were consequently discarded. Modeling was then conducted with zero-inflated (ZIP) and zero-inflated negative binomial distribution (ZINB), given the high number of zeros in the response variable (87%). Table 1 shows the model using only the intercept and random spatial effects and negative binomial (NB) distribution yielded a DIC of 939. When the covariates were added, this criterion dropped to 736. In these same models, but using negative binomial distribution inflated from zeros, DIC values of 945 and 740 were obtained, respectively. Considering the smaller DIC values, we chose to use non-zero-inflated negative binomial distribution.

Table 1 – Deviance information criterion (DIC) results from the Negative Binomial and zero inflated negative binomial models only with intercept and explanatory variables

	Neg Binomial (Intercept)	Neg Binomial (Covar)	ZINB (Intercept)	ZINB (Covar)
DIC	939	736	945	740

Source: Result of the models performed by the authors.

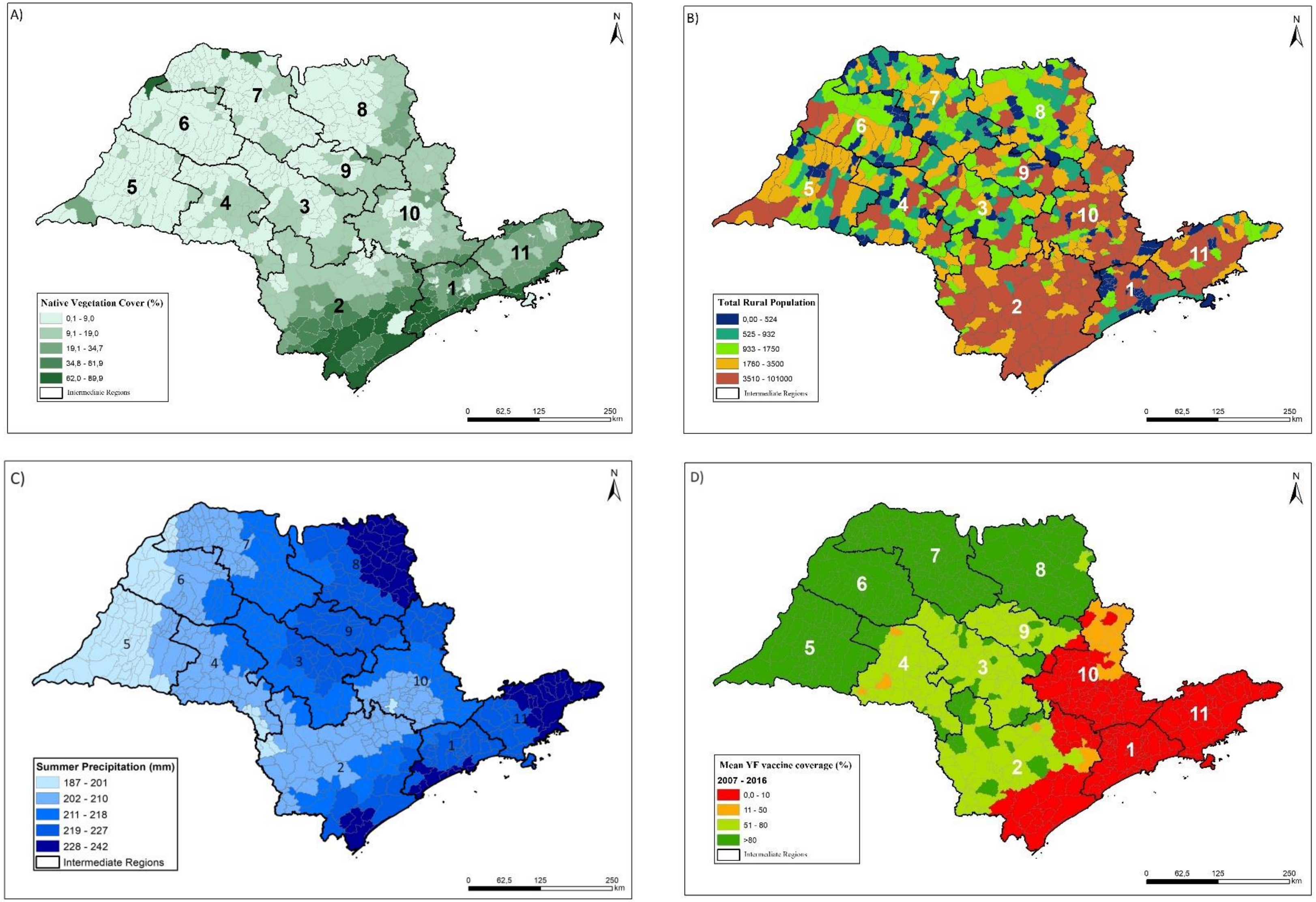
Table 2 shows the posterior means of relative risk (RR) obtained as a result of spatial modeling for the covariates considered, and their respective 95% credibility intervals (95% CI). After adjustment for mean vaccination coverage between 2007 and 2016, native vegetation cover and total rural population emerged as statistically significant risk factors. An increase of one SD in the values for these variables in a given municipality represented an increase of 109% (RR=2.09; 95% CI: 1.60–2.73) and 99% (RR=1.99; IC 95%: 1.41–2.87) in the number of YF cases, respectively.

Table 2 – Posterior means of relative risk (RR) and their 95% credibility intervals (95% CI) for the covariates considered in the modeling of yellow fever cases in municipalities in the state of Sao Paulo, 2016–2019

Covariates	**RR**	**95% CI**
Intercept	0.04	0.01–0.07
Native vegetation cover	2.09	1.60–2.73
Total rural population	1.99	1.41–2.87
Percent of rural population	0.95	0.71–1.24
Summer precipitation	1.14	0.76–1.67
Mean vaccination coverage, 2007–2016	0.18	0.11–0.27

Source: Result of the models performed by the authors.

Figure 5 – Mosaic of maps of native vegetation cover (**A**); total rural population (**B**); Summer precipitation (**C**); mean vaccination coverage, 2007–2016 (**D**); municipalities and intermediate regions in the state of Sao Paulo



Source: Maps created using ArcGIS 10.4 by the authors.

Native vegetation cover (Figure 5A) varied widely in SP, ranging from less than 1% to 90%; the average value was 15%. The highest percentage is concentrated along the coast and in the Sorocaba, Sao Paulo, and Sao José dos Campos intermediate areas, where it varies from 60 to 90%. These same areas, along with the Campinas intermediate area, recorded the highest numbers of YF cases. Figure 5B shows the distribution of the total rural population in the state of São Paulo. The lowest rural population values were seen for the regions of Aracatuba, Araraquara, Presidente Prudente, Ribeirao Preto, and Sao José do Rio Preto, and the highest values in the Sorocaba, Campinas, Sao Paulo, and Sao José dos Campos intermediate regions, where many cases of YF occurred.

Mean vaccination coverage between 2007 and 2016 had a protective effect for YF occurrence, as expected; an increase of one SD in coverage in a given municipality resulted in an 82% decrease (RR=0.18; 95% CI: 0.11–0.27) in the number of cases. The relationship between this variable and the occurrence of YF is clear when comparing the maps in Figure 3 and 4D. Note that the municipalities with YF transmission were generally located in areas where vaccine coverage was less than or equal to 10%.

DISCUSSION

The transmission dynamics of YF encompass multiple factors, both human and environmental in origin, and are consequently complex to understand and require a range of variables to analyze the factors responsible for the YF epidemic in Sao Paulo state in recent years.

The YF virus circulates permanently in the Amazon region (where it is endemic), while in Sao Paulo outbreaks occur in cycles at intervals of 3–7 years when conditions are favorable; these include infestation of vectors and the population of wild primates (Hill *et al.*, 2020; Saad and Barata, 2016). The 2016–2019 epidemic was the result of a combination of factors that allowed viral circulation in areas with no history of acquired immunity or no vaccine recommendation, as well as reintroduction of the virus into areas where it was already known to circulate in the past (Sacchetto *et al*., 2020).

To better understand why the present epidemic reached proportions not seen in decades, we used covariates to explain the pattern of virus diffusion in Sao Paulo, especially in the Sao Paulo, Bauru, Campinas, and Sao José dos Campos intermediate areas. For this purpose, data on native vegetation cover and summer precipitation were used, along with total values and percentages for rural populations in each municipality, and mean vaccination coverage from 2007 to 2016 as an adjustment variable. These covariates were selected based on studies (Cavalcante and Tauil, 2017; De Abreu *et al*., 2019; Possas *et al*., 2018; Sacchetto *et al*., 2020) listing the main factors that could explain the atypical displacement of YF cases to Southeastern and Southern Brazil.

Considering environmental factors, the remaining forest areas are where the main vectors (*Haemagogus* and *Sabetes*) are found, and are also home to the NHP that are the main amplifiers of the YF virus (Possas *et al*., 2018). These areas of forest are often close to urban and periurban areas with higher human densities (De Abreu *et al.*, 2019). Human interventions in nature involving deforestation and burning are among the main reasons YF risk areas have expended, since they culminate in new areas for the vectors, altering the interactions between vectors and amplifiers of particular species (Sacchetto *et al*., 2020). These new altered areas can be considered problematic because the wild transmission structure is moving increasingly closer to the cities as humans enter wild areas, which may increase the risk of anthropogenically reintroducing urban YF (Hill *et al*., 2020). In our study we found that the percentage of native vegetation in each municipality was the factor with the highest impact when analyzing YF cases, since an increase of 1 standard deviation in vegetation would result in a 109% increase in YF cases.

We also found that the rural population of each city is also an important indicator for YF cases,because total rural population of a municipality demonstrates how much of the local population was in contact with the YF vector, since the epidemic transmission cycle was classified as wild by the CVE and the Ministry of Health (SVS/MS, 2017; CVE, 2019). In this study, baysian models showns an increase of 1 standard deviation in rural population increase the RR for YF cases in 99%.

We can consider infections in the urban population “accidental” since human penetration into the environment is increasingly frequent. In a recent descriptive, ecological, and observational study, Torres *et al*., (2017) used data from autochthonous cases of YF throughout the state of Goiás from 2007 to 2017, totaling 108 cases confirmed by testing. This study found that most cases (77%) occurred in men between 21 and 40 years of age (61%). These authors also determined that in nearly 50% of the cases of YF, the probable site of infection was linked to these people's employment (as farmers, security staff, caretakers, and travel agents) which takes place in rural and forest areas or their surroundings. Cavalcante and Tauil (2016) conducted an epidemiological study of YF throughout Brazil from 2000 to 2012 and also found that rural workers predominated (45%) among confirmed cases of the disease.

Vaccination against YF is certainly the main way to prevent this disease. The 17D vaccine has been used for decades and provides effective immunization within 10 days, with a single dose enough for life-long immunization (Garske *et al.*, 2014b; WHO, 2016). In this present study, mean vaccination coverage from 2007 to 2016 was used to adjust our model as well as to understand the scale of its role in protecting against the YF virus (de Thoisy *et al.*, 2020; Kallas *et al*., 2019; Sacchetto *et al*., 2020; Torres *et al*., 2017). In Sao Paulo State. In the period from 2007 to 2016, 190 municipalities in the State had vaccination coverage below 10% for yellow fever. Analyzing the registered cases, we observed that the municipalities with the highest incidence were located in these areas with low vaccination coverage.

For this reason, the Sao Paulo State Health Department (SES-SP) adopted a vaccination strategy to cover the most vulnerable populations, since there were not enough vaccines for all inhabitants and the side effects of the vaccine (viscerotropic disease) are correlated with the number of vaccines applied (Fioravante, 2018). The vaccine strategy was based on the circulation of the virus in NHP via ecological corridors rather than considering the municipality as a whole, thus identifying priority areas for vaccination (Fioravante, 2018). It is important to emphasize that this strategy averted many more cases and deaths because vaccination campaigns were carried out before the virus arrived (as determined by the prediction model).

Although temperature did not enter the model because it was collinear with vaccine coverage and precipitation did not have a significant result, these variables were significant in other relevant studies on the epidemic (Possas *et al*., 2018; Sacchetto *et al*., 2020; Torres *et al*., 2017). The mosquito life cycle and viral replication are directly related to temperature and rainfall (Torres *et al*., 2017). Average temperatures between 24 and 28°C are ideal for mosquito proliferation (Weber and Wollmann, 2016). When the temperature is very low for several days, proliferation and transmission by the mosquitoes are interrupted. Precipitation exceeding 150 mm combined with high average temperatures are optimal conditions for YF vector proliferation (Urbinatti *et al*., 2007).

Recently, Figueiredo *et al*., (2020) discussed the challenges, lessons learned, and perspectives of the YF epidemic. These authors highlight the lack of effective surveillance of the vector population and control strategies to prevent new outbreaks, not only of YF but also all arbovirus diseases, as major challenges to be overcome throughout Brazil. Epizootic control and surveillance are another challenge, and effective and constant monitoring could reduce the number of human cases by knowing when the virus arrives via NHP.

This study has some limitations; first, the spatial data is granular. We could have obtained more precise results if data from the YF cases had included the address of the probable site of infection. This would have allowed us to group the cases by census tracts, for example, in turn permitting the use of sociodemographic and environmental information from areas within the municipalities and closer to the phenomenon being investigated. Another limiting factor was the lack of information about infected patients; for example, access to information on their professions and home addresses could explain whether they lived or worked near forests or wild areas. Another issue that we could not take into account is asymptomatic humans, for obvious reasons of lack of records, which may be transmitting agents. The lack of data on vector infestation and underreporting of the presence of NHP potentially infected with the YF virus are also limiting factors in this study. We understand that this lack of detailed information about registered cases does not only occur with yellow fever, but it is important to highlight that the lack of this data limits scientific research from obtaining a more accurate and precise result, which would result in more accurate and effective surveillance actions and prevent deaths.

Strong points of this study include its extent, covering the entire epidemic process of YF in SP between 2016 and 2019. Use of Bayesian modeling as a spatial analysis method is also a strength, since this methodology effectively adjusts complex models that consider spatial dependence in the data correlation structure (Zuur *et al*., 2017).

In conclusion, this study demonstrated that in addition to vaccination coverage, local factors such as vegetation cover and rural population size are involved in the occurrence of wild YF. Because the stock of vaccines is limited and large portions of the Brazilian population are still unvaccinated, these results make it possible to identify risk areas for increased vaccine coverage as well as to amplify epidemiological and entomological surveillance activities.

DECLARATION OF COMPETING INTEREST

There are no conflicts of interest.

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