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Original Contribution

Predicting Yellow Fever Through Species Distribution Modeling of Virus, Vector, and Monkeys

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Abstract: Mapping yellow fever (YF) risk is often based on place of infection of human cases, whereas the circulation between nonhuman primates (NHP) and vectors is neglected. In 2008/2009, YF devastated NHP at the southern limit of the disease in the Americas. In view of the recent expansion of YF in Brazil, we modeled the environmental suitability for YF with data from 2008/2009 epizootic, the distribution of NHP (*Alouatta* spp.), and the mosquito (*Haemagogus leucocelaenus*) using the maximum entropy algorithm (Maxent) to define risk areas for YF and their main environmental predictors. We evaluated points of occurrence of YF based on dates of confirmed deaths of NHP in three periods, from October 2008 to: December 2008, March 2009, and June 2009. Variables with greatest influence on suitability for YF were seasonality in water vapor pressure (36%), distribution of NHP (32%), maximum wind speed (11%), annual mean rainfall (7%), and maximum temperature in the warmest month (5%). Models of early periods of the epizootic identified suitability for YF in localities that recorded NHP deaths only months later, demonstrating usefulness of the approach for predicting the disease spread. Our data supported influence of rainfall, air humidity, and ambient temperature on the distribution of epizootics. Wind was highlighted as a predicting variable, probably due to its influence on the dispersal of vectors infected with YF in fragmented landscapes. Further studies on the role of wind are necessary to improve our understanding of the occurrence of YF and other arboviruses and their dispersal in the landscape.

Keywords: *Alouatta*, Disease modeling, Epizootic, Maxent, *Haemagogus leucocelaenus*, Nonhuman primates

INTRODUCTION

Yellow fever (YF) is a viral disease caused by a flavivirus of the Flaviviridae family (Monath and Vasconcelos 2015). Endemic to the tropical regions of Africa and South America, the disease presents periodic expansions and

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retractions of its area of occurrence (Jentes et al. 2011). In the Americas, the virus is maintained in the wild in cycles involving nonhuman primates (NHP) and hematophagous mosquitoes (mainly *Haemagogus* and *Sabethes*) and has a relatively narrow range of hosts capable of productive infection (Monath and Vasconcelos 2015). Given its recent introduction (ca. 400 years ago) in the Americas via the slave trade (Bryant et al. 2007), the virus is deadlier to neotropical NHP than to the original hosts in Africa with whom it shares a longer period of coevolution (Hanley et al. 2013). In addition to acquiring the virus through blood feeding on infecting vertebrates, the vectors can also become infected by transovarial transmission, an important mechanism of virus maintenance (Reiter 2001; Carrington and Auguste 2013). In a jungle cycle, humans are sporadically infected by mosquito bites, which typically occur in forested areas (Monath and Vasconcelos 2015). In the urban cycle, humans are the only source of the virus, and human–human transmission occurs via the vector *Aedes aegypti* in or near dwellings (Monath and Vasconcelos 2015).

The clinical manifestation of YF in humans varies greatly, resulting in disease in only a low proportion of infected individuals. Severe cases characterized by jaundice, hemorrhage, and death are good indicators of an outbreak, but represent only approximately 12% (95% CI 5–26%) of the total infected population (Johansson et al. 2014). A vaccine available for 80 years has not prevented major epidemics in areas with long periods without the disease (without natural immunity) or without adequate vaccine coverage (Monath and Vasconcelos 2015).

Although human populations with low vaccine coverage are a key factor in the occurrence of outbreaks, the multifactorial causes of virus dispersal are unclear due to the scarcity of longitudinal field studies (Monath and Vasconcelos 2015). These causes involve complex interactions between deterministic (density and vector competence, virus virulence) and stochastic (environmental impacts, movement of human populations) factors (Monath and Vasconcelos 2015). Spatial expansions of the circulation of YF can be associated with the occurrence of a new strain of the virus (Souza et al. 2010; Bonaldo et al. 2017), but information is lacking on how biological changes derived from genetic alterations influence such expansions to confirm causality (Monath and Vasconcelos 2015). Prolonged rainfall and high temperatures have been associated with YF outbreaks in Africa and South America (Monath and Vasconcelos 2015). In fact, the risk of occurrence of YF in a region relates to human presence, mosquito vectors, and vertebrate hosts under the influence of the climate and the biotic environment (Briand et al. 2009).

Among the climatic factors that affect the occurrence of YF, rainfall is generally considered the most important. Rainfall plays a central role in the multiplication and density of vectors, since breeding sites are scarce during dry periods (Reiter 2001). Given the accumulation of eggs during these periods, heavy rains after long droughts favor the emergence of a generation of mosquitoes infected by transovarial transmission (Reiter 2001; Carrington and Auguste 2013). On the other hand, temperature increases decrease the time elapsed between the ingestion of blood infected with the virus and the possibility of the mosquito transmitting it by biting (Shope 1991).

In addition to the influence on vectors, biotic and abiotic environmental factors also affect the NHP in their geographical distribution, group composition, territorial boundaries, horizontal and vertical movements in the canopy, life span, birth rate, activity period, sleeping sites, and other characteristics that affect the maintenance of the YF cycle in a region (Rodhain 1991). Some variations in these characteristics include the hosts' dispersal ability in continuous or fragmented landscapes; daytime behavior that coincides with the activity of the vector; and the arboreal stratum occupied by NHP, which facilitates the encounter with mosquitoes that inhabit the tree canopy, among others. An association of these factors determines the nature and frequency of contact between NHP and mosquitoes, the way the virus circulates, and how it is maintained between epizootics (Rodhain 1991).

A better understanding of the ecoepidemiological factors that determine the mode of transmission and influence the geographical distribution of YF is essential to define the sites and times with greater risk of transmission (Dégallier et al. 1992), thus allowing to trigger surveillance actions that include preventive immunization in unvaccinated human populations (Romano et al. 2014). This definition has been a constant challenge in risk analysis for the establishment of vaccination strategies (Hill 2012). The first risk analyses for YF considered only the detection of human cases. With the advent of more specific diagnostic techniques, the analyses have evolved to an approach that seeks evidence of the virus in vectors and NHP (Hill 2012) integrated with advanced geoprocessing tools (Hamrick et al. 2017), mapping of YF (and other arboviruses) risk of transmission by *Ae. aegypti* and *Ae. albopictus* (Kraemer et al. 2015; Leta et al. 2018), worldwide modeling of YF risk based on 1155 human cases from 1970 to 2016 and environmental and biological covariates and vaccination coverage (Shearer et al. 2018) and seasonal influence of climate and environment on the transmission of YF in Africa (Hamlet et al. 2018). In Brazil, the state of São Paulo illustrates one of the rare attempts to define risk areas based on the evaluation of environmental variables and the analysis of multiple corresponding factors (Moreno and Barata 2012). In 2018, the spatiotemporal spillover risk of yellow fever in Brazil, from demographic and environmental covariates using a monthly aggregation by municipality, was modeled (Kaul et al. 2018).

In this sense, species distribution models (SDMs) are useful tools because they evaluate the relationship between the occurrence of a species and a set of spatially explicit environmental variables to estimate its niche, which can be projected in geographical space (Franklin 2009). In an epidemiological context, SDMs allow mapping the risk areas to a disease, that is, a geographical projection of the ecological distribution of the pathogen (Peterson 2008). Consequently, SDMs serve to define areas of interest for risk monitoring and management, to simulate scenarios resulting from control actions, to predict outcomes of these actions under different environmental conditions (e.g., climate change-related temporal forecasting) and to identify new areas under risk of disease occurrence (spatial prediction) (Stevens and Pfeiffer 2011).

Examples of the use of SDMs in epidemiology include (1) the analysis of the effect of environmental variables and the occurrence of potential bat reservoirs of the Ebola virus in Africa (Pigott et al. 2014); (2) the modeling of the distribution of NHP hosts and malaria mosquito vectors together with coverage and forest use data in Southeast Asia, delimiting areas of risk in the absence of information from human cases (Moyes et al. 2016); (3) modeling the vector of Chagas disease as an indicator of risk areas for the disease in Brazil and Mexico (Peterson et al. 2002; Gurgel-Gonçalves et al. 2012); and (4) the role of bats in the dissemination of rabies virus in Chile (Escobar et al. 2013). Regarding vector-borne viruses, the distribution of outbreaks of Oropouche, Saint Louis, Mayaro, and Rocio in humans has been modeled in Brazil (Lorenz et al. 2017), and the distribution of NHP was modeled in Colombia to assess its coincidence with the distribution of human cases of YF (Piedrahita-Cortés and Soler-Tovar 2016). Additional models of yellow fever risk at national (Brazil) or international levels have been recently published (Kraemer et al. 2015; Kaul et al. 2018; Shearer et al. 2018).

The last 10 years in Brazil have been marked by the reemergence of YF with significant numbers of human cases and NHP deaths. Between 2007 and 2009, 50 human cases with 20 deaths and 207 confirmed NHP deaths were reported (Cardoso et al. 2010; Moreno et al. 2011; Almeida et al. 2012, 2014; Moreno et al. 2013; Romano et al. 2014). The most affected region, the state of Rio Grande do Sul (RS) in the extreme south of Brazil, has detected an epizootic of unprecedented magnitude (Bicca-Marques and Freitas 2010; Cardoso et al. 2010; Almeida et al. 2012, 2014) through its official public health surveillance system. More than 2000 *Alouatta caraya* and *A. guariba clamitans* (204 confirmed as being of YF) died in 9 months during a disease circulation that also affected the state of São Paulo (Moreno et al. 2011, 2013) and northeastern Argentina (Holzmann et al. 2010). However, the largest outbreak of YF recorded in Brazil has been underway since 2015 in the West-Central and Southeast regions of the country. As of October 2018, 2155 human cases had been recorded, with 745 deaths and 2523 epizootics (Bicca-Marques et al. 2017; Bonaldo et al. 2017; Brasil 2017, 2018a; Fernandes et al. 2017), reaching areas without circulation of the virus for several decades and a progression that defies understanding based on current knowledge (Possas et al. 2018; Rezende et al. 2018).

In this study, we used our database of NHP, vector, and YF occurrence points during the 2008 and 2009 epizootics in RS and data on climatic, topographic, and vegetation variables to model the potential geographic distribution of *Alouatta* spp., the vector *Haemagogus leucocelaenus,* and YF in the extreme south of its occurrence in the Americas. Our objective was to identify the risk areas for the disease and the variables of the biotic and abiotic environments that best explain the occurrence of the virus in the study region.

METHODS

We estimated the YF virus distribution as a function of abiotic and biotic environmental variables to identify areas of disease risk (i.e., environmentally appropriate areas for its occurrence) within the polygon of the state of Rio Grande do Sul (RS). We limited our analysis to RS for two reasons. First, our dataset is composed of records of epizootics made by the personnel of the municipal health secretariats that were sent to the State's Center for Health Surveillance and data collected via passive surveillance by the authors who work at the State's Center. Second, there is no comparative data from the same period from nearest Brazilian state (Santa Catarina in the north) because there were no records of the disease there by both public health and environmental protection authorities.

We generated models with the use of the maximum entropy algorithm—Maxent 3.4.0 (Phillips et al. 2006; Phillips and Dudík 2008). Maxent requires (1) presence data of a species to represent its occurrence pattern in geographic space and to identify environmental variables that are potentially predictive of occurrence and (2) random background points that are not assumed to be "absences" and that also do not represent pseudo-absences. These background points represent the available environmental conditions within the species' extent of occurrence that are used together with the conditions available at the presence locations to assess the response curve of each variable. Maxent's robustness and usefulness have grown since the explanation of their algorithm, model settings and how (and why) to choose proper model settings (Merow et al. 2013; Phillips et al. 2017).

We began by modeling the distribution of host monkeys (*Alouatta caraya* and *A. guariba clamitans*) and the mosquito vector of the disease in RS (*Haemagogus leucocelaenus*). Subsequently, we used the projections generated in these models as predictors of the occurrence of YF in 2008/2009. Although hosts and vectors occur beyond RS boundaries and the YF outbreak has also been recorded in other regions (not in the neighboring Brazilian state of Santa Catarina to the north), we limit our analysis to RS because we do not have accurate information on outbreak locations outside RS's borders, thereby ensuring greater quality and accuracy of the models.

Distribution of Host Monkeys

The occurrence points of *A. caraya* and *A. guariba clamitans* were obtained from the literature, from our database of NHP death points reported by the Municipal Health Secretariats of RS between October 2008 and June 2009, and from sites where the staff of the State Health Surveillance Center of the RS Health Department captured NHP between 2004 and 2009 during active YF surveillance (Almeida et al. 2012, 2014) (Supplementary material/Table A). We merged the occurrence data of both taxa because they are ecologically equivalent (Agostini et al. 2010) and because there is no empirical basis to suspect that they show different susceptibilities to the YF virus. We randomly removed duplicate records within a radius of 10 km to avoid bias arising from spatial clusters (Boria et al. 2014; Renner et al. 2015). Thus, we used 307 records of occurrence from the original database of 971 records in the construction of the models.

We chose 40 environmental variables (31 climatic, 5 vegetational, and 4 topographic) available in WorldClim version 2 (Fick and Hijmans 2017), spatially explicit in the form of raster layers with a spatial resolution of approximately 1 km, as potential predictors of species distribution (Supplementary material/Table B). Monthly estimates of solar radiation, water vapor pressure, and wind speed were also taken from WorldClim version 2. For each variable, we calculated the annual maximum, minimum, mean, and the variation (seasonality) at each pixel to represent the predictable variable. We removed highly correlated variables of the occurrence locations ($VIF > 10$ and $r > |0.7|$) to avoid overfitting of the models, leaving nine potentially predictive variables: (1) elevation, (2) percentage of forest cover, (3) percentage of deciduous forest, (4) mean rainfall in the coldest quarter, (5) mean rainfall in the warmest quarter, (6) minimum temperature in the coldest month, (7) maximum solar radiation, (8) minimum solar radiation, and (9) seasonality in water vapor pressure (air humidity).

We generated 15,000 random points representing background records to implement the model. We validated the model with a cross-validation technique by dividing the occurrences of NHP into 10 groups. We used 10% of the records for training the model and the remaining 90% for testing it. We used the ENMevaluate function of the ENMeval R (Muscarella et al. 2014) package to evaluate and select the best model parameterization (Supplementary material/Text 1).

Distribution of the Mosquito Vector

The modeling of the distribution of *Haemagogus leucocelaenus* was based on field collections by different methods, mainly using entomologic hand nets (Supplementary material/Table C). We used 33 records of occurrence from the original database of 61 records in the construction of the models after removing duplicated ones.

We removed highly correlated variables as described previously, leaving 11 variables potentially predictive of the patterns of mosquito distribution (Supplementary material/Table B): (1) elevation, (2) vertical distance to the nearest drainage, (3) topographic humidity index, (4) net primary productivity (NPP), (5) mean temperature in the wettest quarter, (6) mean temperature in the driest quarter, (7) rainfall seasonality, (8) mean rainfall in the wettest quarter, (9) seasonality in water vapor pressure (air humidity), (10) minimum wind speed, and (11) aridity index.

We also used 15,000 random background records and the cross-validation procedure to validate the vector model. We split mosquito occurrences into three groups (~ 33% for training and ~ 67% for testing) to validate the model. We also selected the best model parameterization using the ENMevaluate function (Supplementary material/Text 2).

Distribution of YF Virus

We modeled the YF distribution based on the points with NHP deaths confirmed of YF between October 2008 and June 2009 (Cardoso et al. 2010; Almeida et al. 2012, 2014). Given that the records can be biased because of their spatial clustering in surveyed areas, we removed duplicate records within a 5-km radius and included the distance to roads as a bias control layer, indicating suitability for disease independent of such proximity. We used 91 out of the 173 YF records in the modeling (Supplementary material/Table D).

In contrast to the modeling of hosts and vectors, we used data from the climatic variables only for the months of the epizootic (October–June). We used the mean, minimum, maximum, and coefficient of variation of the variables temperature, rainfall, solar radiation, water vapor pressure, and wind speed during the following periods: 1 (October–December 2008), 2 (October 2008–March 2009), and 3 (October 2008–June 2009). We divided the modeling into these three cumulative periods to test the predictive power of the modeling of each period relative to the actual points of occurrence of the subsequent period(s), that is, to determine whether the model generated with data from period 1 would predict the area of occurrence for periods 2 and 3, and whether the model of the period 2 would predict the area of occurrence for period 3. In addition to the climatic, topographical, and vegetation variables, we also included the modeled distributions of hosts and vectors to form the set of variables potentially predictive of YF distribution. The removal of the highly correlated variables yielded a set of 11 variables: (1) distribution of hosts, (2) distribution of the vector, (3) leaf area index, (4) percentage of forest cover, (5) terrain slope, (6) minimum temperature in the coldest month, (7) maximum temperature in the warmest month, (8) annual mean rainfall, (9) rainfall seasonality, (10) seasonality of water vapor pressure (air humidity), (11) maximum solar radiation, (12) maximum wind speed, and (13) seasonality of wind speed. We modeled the distribution of the disease during periods 1, 2, and 3 by dividing the occurrences of YF between them. We used 15,000 background records for all YF models. We cross-validated each period's model by dividing its occurrences into three subsets (one for training and two for testing). We also tested whether there was a difference between the randomized cross-validation for the third period (i.e., with all YF records) and the indexing of the subsets of data according to the three periods. We also evaluated the effect of the inclusion of biotic variables (hosts and vectors) among the predictors using an AIC selection procedure to choose the best set of predictors. We also evaluated model parameterization using the ENMevalate function. We prioritized simpler response curves (linear and quadratic) for this model to facilitate the biological interpretation of the effects of the predictor variables (Supplementary material/Text 3).

We chose a threshold of habitat suitability above which we considered that the virus is present to evaluate model accuracy. We accomplished this task by finding the threshold of the receiver operating characteristic (ROC) curve that has maximum sensitivity and specificity. Sensitivity is the proportion of observed presences that are predicted as such. Therefore, sensitivity measures errors of omission or false negatives, i.e., when the model predicts the absence of the species where it is present or predicts inadequate habitats in an appropriate area (Allouche et al. 2006; Franklin 2009; Merow et al. 2013). The specificity of the model is the proportion of observed absences that are predicted as such. Therefore, specificity evaluates commission errors or false positives, i.e., when the model predicts presence where the species is absent (Franklin 2009; Merow et al. 2013). We then evaluated the model's accuracy with the true skill statistic (TSS), an effective and well-accepted measure of accuracy for binary predictions (Allouche et al. 2006). TSS is obtained from sensitivity and specificity (TSS = Sensitivity + Specificity − 1). It ranges from − 1 to + 1. Values close to + 1 indicate accurate predictions, whereas values equal to or lower than zero are not better than random predictions. We used the R 3.3.3 software (R Development Core Team 2016) for data processing and modeling.

We also compared the environmental conditions found at all NHP locations and those environmental conditions found at the infected NHP's locations, i.e., the environmental difference between the niches of NHP and the virus. We used the occurrences of infected NHP obtained during the YF surveillance and those of putatively noninfected NHP from our database to accomplish this task. We then obtained the values of the 11 environmental predictors at the locations of NHP occurrences, scaled all of them to mean zero and one standard deviation, and ordered all occurrences of infected and noninfected NHP in a multidimensional environmental space using a principal component analysis (PCA). The first two PCA axes provided a high-quality measure of the environmental space. They explained 68% of the accumulated variation of environmental predictors. We used this bi-dimensional space to calculate the observed environmental space occupied by all NHP, by infected NHP, and the difference between them. We performed PCA ordination for environmental dissimilarity analysis with the "prcomp" function from the "vegan" R package. Finally, we randomized the "infections" across all NHP 99,999 times to test whether the observed environmental difference was larger than expected by the null distribution.

Data Availability

Our datasets are available from the corresponding author on reasonable request.

RESULTS

The environmental suitability for host NHP is higher in the northwestern, central, and northeastern portions of Rio Grande do Sul State (Fig. 1). Four variables contributed 71% of the model gain in all interactions: higher minimum temperature in the coldest month (20%), lower minimum solar radiation (18%), high percentage of forest cover (17%), and low mean rainfall in the warmest quarter (16%).

The areas with the highest probability of occurrence of the mosquito vector are located in the northern half of RS, especially in the northwestern and eastern limits (Fig. 2). Three variables contributed with a gain of 78% to the model in all interactions: lower seasonality in water vapor pressure (most stable air humidity) (46%), higher mean rainfall in the wettest quarter (22%), and higher mean temperature in the driest quarter (10%).

The epizootic of YF in the populations of *Alouatta* spp. started in the northwest and advanced to the central and northeastern regions of RS (Fig. 3a). The distribution of the hosts (28% contribution in the model) and the vector (24%) and the variation in wind speed (16%) directly influenced the distribution of the disease in period 1 (October 2008–December 2009). The suitability map generated with the occurrence points in this period indicated a region in northeastern RS, approximately 600 km from the first occurrence points, which would register YF in period 2 (Fig. 3). The distribution of the hosts (32%) and the seasonality in the water vapor pressure (20%) positively influenced the distribution of YF in period 2 (October 2008–March 2009), whereas the variation in wind speed (15%) had a negative effect. The model of period 2 also indicated areas of greater suitability, especially in the northeastern and eastern-central regions, which would register the disease only in the following period (Fig. 3b). Finally, considering all records of the disease in period 3 (October 2008–June 2009, Fig. 3c), the most important variables in the model were seasonality in water vapor pressure (annual variation in air humidity) (36%), distribution of hosts (32%), and maximum wind speed (11%). The annual mean rainfall (7%) and the maximum temperature in the warmest month (5%) were important at a lesser extent. All three models had a high accuracy according to TSS metrics: period 1 (0.80 ± 0.01), 2 (0.56 ± 0.01), and 3 (0.55 ± 0.01).

The model including environmental layers and the distribution of hosts among the predictor variables was the best model (Table 1). On the other hand, no difference existed in the performance of the validated models with randomized or cross-validation indexed by the epizootic months (randomized and indexed validation, AIC = 2817.50) (Supplementary material/Text 3 and Figure N). In addition, we found that the inclusion of the distance to the nearest road as a disease predictor, instead of as a sampling bias control layer, generated a model with better fit and performance (bias control, AIC = 2817.50; predictive variable, AIC = 2804.28) (Supplementary material/Text 3 and Figure O). Finally, we found that the observed environmental difference between the niche of NHP and the niche of the virus was much larger than the difference expected by chance, i.e., there are specific environmental conditions within the NHP's range which are appropriate for virus occurrence (Fig. 4).

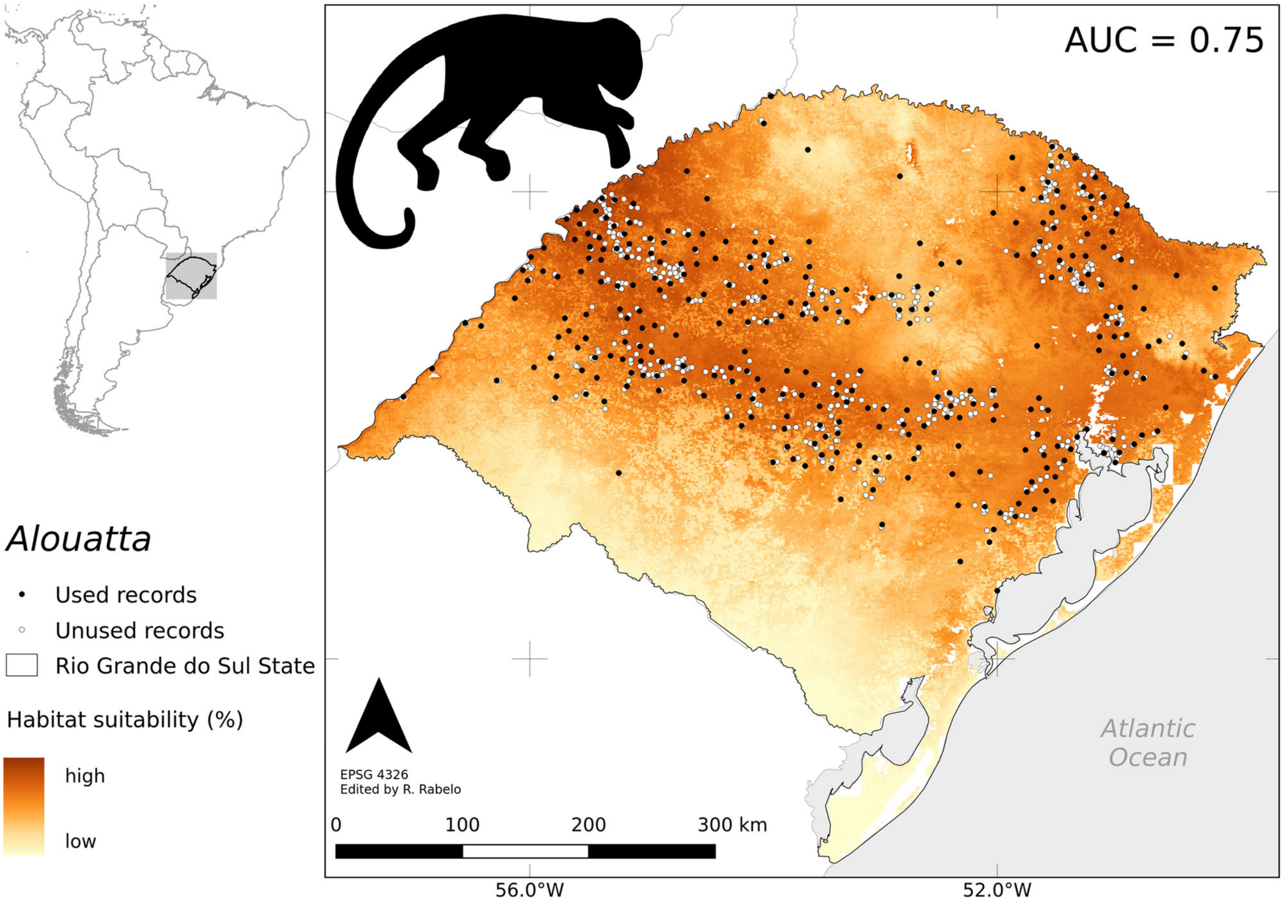

Figure 1. Predicted distribution for *Alouatta* spp. in Rio Grande do Sul State, Brazil. Maps and drawings created specifically for this study. (Made with Natural Earth. Free vector and raster map data @ naturalearthdata.com)

DISCUSSION

In this study, we modeled the distribution of YF using a maximum entropy algorithm based on a large database of accurately recorded geographic coordinates of sites with confirmed YF circulation in NHP to create models of the occurrence of YF and to identify areas of risk in the southern limit of the distribution of the disease in the Americas, where it is not considered endemic. We based the modeling on the potential distribution of host NHP and the mosquito vector as well on abiotic and other biotic environmental variables. The models of the initial periods of the epizootics adequately predicted areas where the YF would occur in the next quarter or semester. The complete model (the entire epizootic period) identified variations in air humidity, the occurrence of *Alouatta* spp., and the maximum wind speed as the most important variables for the distribution of the virus in the landscape. Mean rainfall and maximum temperature were of secondary importance in this prediction.

The participation of the host in the occurrence of YF in the models of the three periods was expected, in part because we used data on the occurrence of YF from confirmed epizootics in NHP. The distribution of *Alouatta* spp. and the variation in humidity accounted for 2/3 of the distribution pattern of jungle YF at the southern limit of its distribution in the Americas.

Abiotic variables related to air humidity, rainfall, and temperature have a strong influence on the reproduction of vectors given their need of natural breeding sites with accumulated water. Therefore, reproduction is favored in environments with higher and more stable humidity, maintained by higher rainfall indexes and higher temperatures (Consoli and Lourenço-de-Oliveira 1994; Reiter 2001; Dégallier et al. 2006). Consequently, these conditions promote an increase in the density of vectors (Dégallier et al. 2006), whose dispersal may be influenced by wind speed and direction (Causey et al. 1950; Moreno and Barata 2012), and facilitate an increase in virus density and dispersal that modulate the transmission dynamics of the

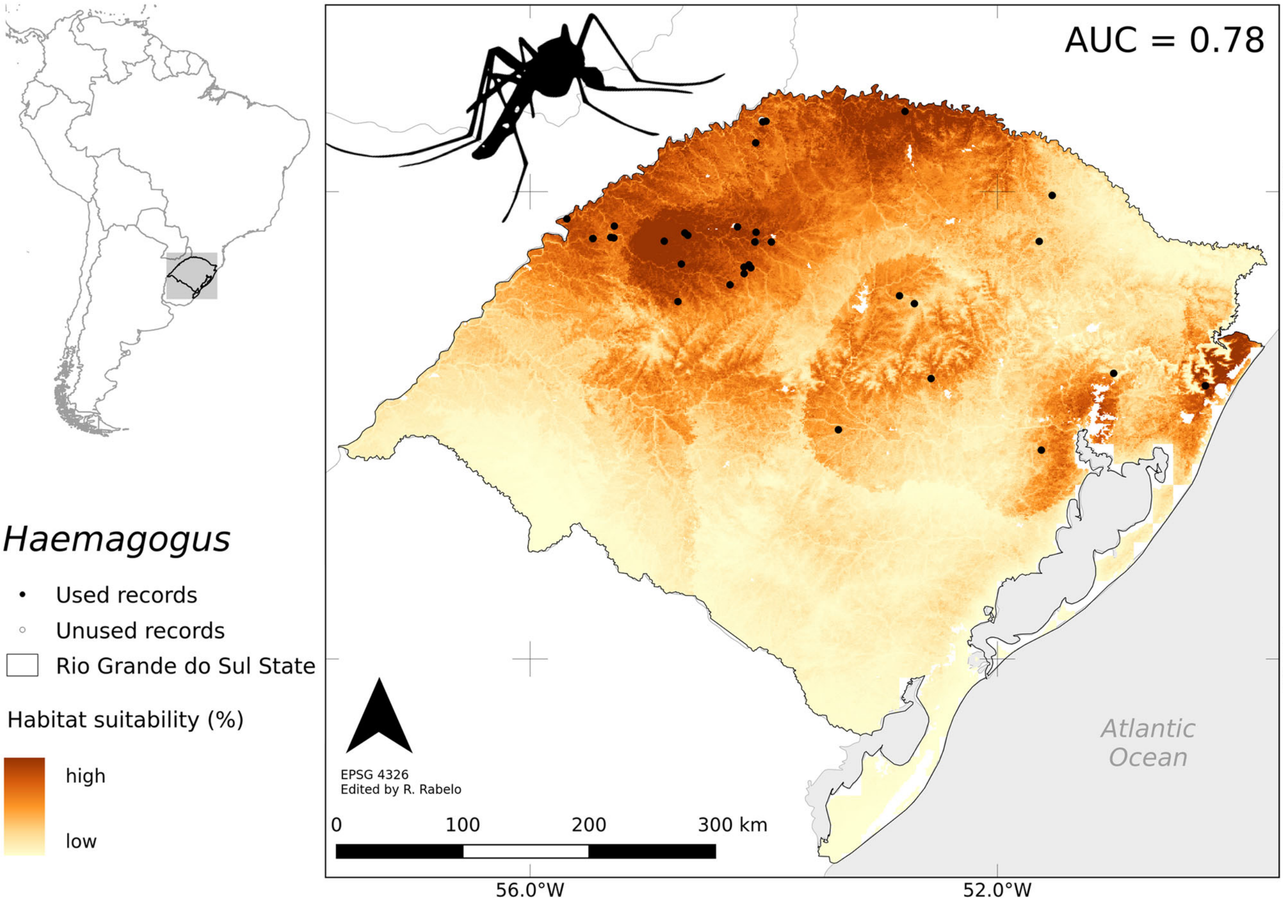

Figure 2. Predicted distribution for *Haemagogus leucocelaenus* in Rio Grande do Sul State, Brazil. Maps and drawings created specifically for this study. (Made with Natural Earth. Free vector and raster map data @ naturalearthdata.com)

disease. The relationship between rainfall and the occurrence of epizootics and outbreaks of YF had been suggested (Dégallier et al. 1992; Vasconcelos et al. 2001a, 2001b; Alencar et al. 2010; Cardoso et al. 2010; Gomes et al. 2010; Vasconcelos 2010; Souza et al. 2011; Lira-Vieira et al. 2013).

Peaks of abundance of the vector *Hg. leucocelaenus* coincide with the rainiest months (October–March) in RS (Gomes et al. 2010). The beginning of the epizootic of 2008 and 2009, for which we generated the models, occurred exactly in the rainiest month (October). Changes in rainfall were recorded during this month in two meteorological stations near the areas with the highest number of YF records during period 1. Rainfall was three times higher than the 30-year mean after 10 months below or near this historical mean in one area (Supplementary material/Figure P) and twice the mean after 5 months below the mean in another area (Supplementary material/Figure Q). Such an increase in rainfall might have triggered an explosive increase in mosquito populations resulting from months of drought and egg accumulation. *Haemagogus janthinomys* eggs, for example, resist desiccation for up to one year (Hervé et al. 1986) and start to hatch when rains resume. Maximum egg hatching in this genus occurs after many submersions in rainwater (Alencar et al. 2008; Marcondes and Alencar 2010). Consequently, periodic immersion-desiccation cycles generate adults throughout the year, whenever the meteorological conditions are favorable for egg hatching (Alencar et al. 2014). The association between a severe and prolonged rainy season and a high abundance of vectors was proposed to explain an increase in the circulation of YF in Nigeria in 1987 and in Brazil in 2000 (Vasconcelos et al. 2001a), where in addition to higher rainfall, the beginning of the year was characterized by a higher mean temperature. The mean temperature of that period was 2°C warmer than the mean of the previous 20 years, while the rainfall in January and February was 25% higher.

The mean temperature in the driest quarter influenced the distribution of the vector. The higher mean winter temperatures probably favored the maintenance of adult

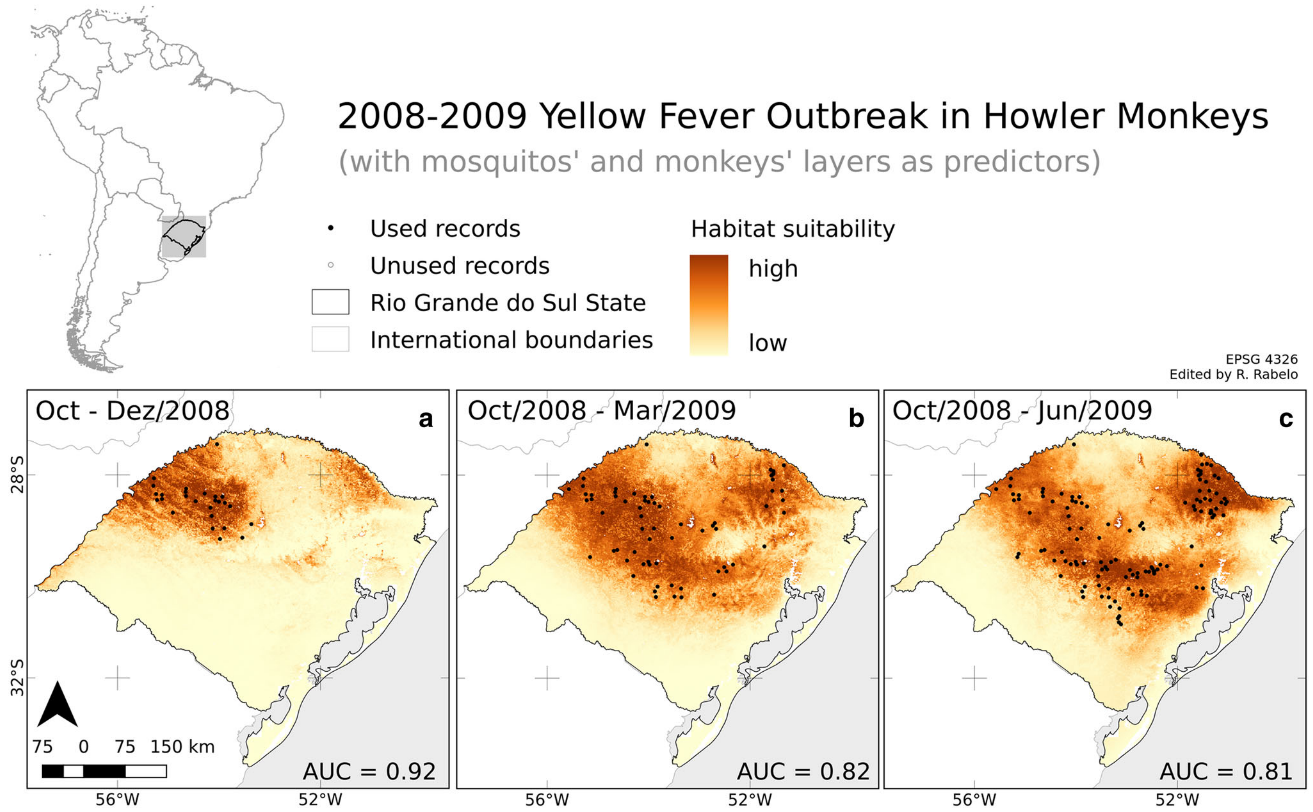

Figure 3. Map of habitat suitability for the occurrence of yellow fever in Rio Grande do Sul State, Brazil, from three cumulative sets of disease occurrence records in nonhuman primates: **a** October–December 2008, **b** October 2008–March 2009, and **c** October 2008–June 2009. Maps and drawings created specifically for this study. (Made with Natural Earth. Free vector and raster map data @ naturalearthdata.com)

Table 1. Ranking of Yellow Fever Models With and Without the Inclusion of Biotic Predictors, According to AIC. In All Four Models, Yellow Fever is the Response Variable as a Function of Combinations of Environmental Variables (Env), Nonhuman Primates (Host) and Mosquitoes (Vector) Distribution.

Model	#par	AICc	ΔAICc	AIC weight	AUC
YF ~ Env + host	17	2814.98	0.00	0.98	0.82
YF ~ Env + host + vector	21	2823.27	8.29	0.02	0.82
YF ~ Env	16	2879.17	64.19	0.01	0.77
YF ~ Env + vector	18	2886.93	71.95	0.00	0.75

mosquitoes laying eggs before the onset of rains. The temperature also plays a role in virus development, which is faster under higher temperatures, resulting in the acceleration of the onset of the infective stage of the vectors (Shope 1991). Both the maximum temperature and its duration have an important role in the extrinsic incubation period of the virus, that is, its incubation in the mosquito vector (Whitman 1951). The virus showed the shortest incubation period in *Haemagogus* mosquitoes under laboratory conditions when the ambient temperature was kept constant at 30°C (Whitman 1951). Interestingly, temperatures reaching above 30°C were recorded in ca. 50% of the days during the period of yellow fever transmission (October 2008–June 2009) at two meteorological stations near the areas with the highest numbers of YF records during the first quarter of the outbreak (Brasil 2018b).

The contribution of wind to the dispersal of vectors (and their viruses) can be significant, particularly in fragmented landscapes characterized by isolated habitat patches surrounded by a matrix of pastures and fields, where

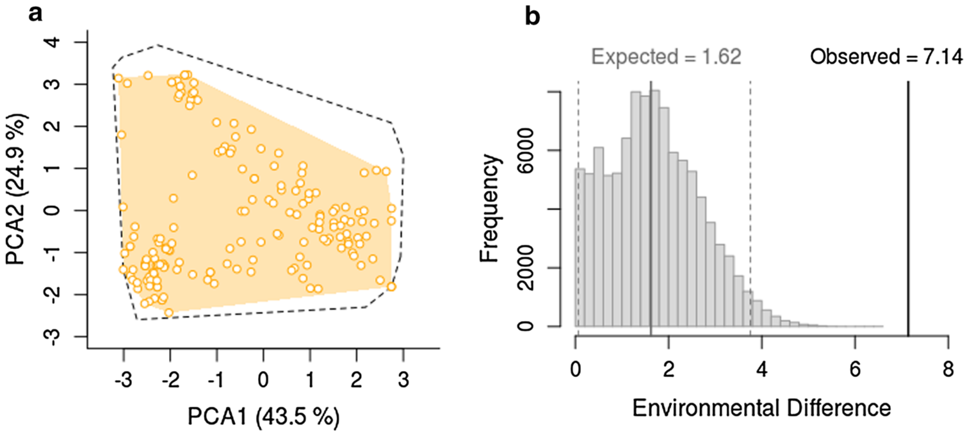

Figure 4. Observed and expected environmental difference between the niche of nonhuman primates and the yellow fever virus. **a** Bi-dimensional space of environmental conditions used by nonhuman primates (i.e., environmental niche of nonhuman primates) represented by the first two axes of a principal component analysis (PCA). The dotted line represents the environmental volume occupied by all nonhuman primates. Points correspond to infected nonhuman primates and the internal polygon (in orange in the online version) represents the volume of the environmental space occupied by infected nonhuman primates. The unfilled area within the dotted line represents the observed environmental difference between the niche of nonhuman primates and virus. **b** Histogram of expected environmental difference between the niche of nonhuman primates and virus according to the null distribution. Gray dotted lines represent the 95% confidence interval for the estimated expected difference.

mosquitoes can move up to 11.5 km (Causey et al. 1950). Some of the species with the greatest potential of dispersal, according to experimental capture/mark/recapture studies (Lira-Vieira et al. 2013), are proven or likely vectors of YF, such as *Hg. Spegazzini* (Causey et al.1950), *Hg. leucocelaenus* (Vasconcelos et al. 2003; Cardoso et al. 2010), *Ae. serratus* (Cardoso et al. 2010), *Ae. terrens* (Berti et al. 2015), and *Psorophora ferox* (Moreno et al. 2011). Therefore, the predominant direction of the winds in a region is a variable with great potential for the definition of priority areas for vaccination (Moreno and Barata 2012). The difference in the predictive power of the wind between the vector distribution models (minor importance) and the YF virus (major importance) probably results from differences in residence time of the respective taxa in the study region. The model of the vector identified that variations in other abiotic variables are more critical in determining the distribution of YF and, consequently, in locating its potential or long-term habitat areas. On the other hand, the YF model highlighted that the wind was an important predictor of the occurrence of the virus during its relatively short stay, although lethal to the NHP, in the RS forested areas. The progression of epizootics in the west–east direction is compatible with the prevailing direction of the wind currents in the state (Rio Grande do Sul 2014) and their possible role in the dispersal of vectors (Causey et al. 1950; Taylor 1951).

The inclusion of the distance to the nearest road as a potential predictor improved the performance of the model and allowed detecting that the highest probabilities of occurrence of YF were concentrated in the vicinity of roads. Most likely, this result reflects a bias in the collection of biological samples from dead NHP by professionals from Municipal Health Secretariats because of accessibility differences among affected areas (Taylor 1951; Oliveira et al. 2016). However, we cannot reject the possibility that roads play a role in the dispersal of infected vectors either via transport in vehicles or the influence of wind “tunnels.” Biodiversity sampling bias in the vicinity of rivers and roads has been demonstrated (Oliveira et al. 2016) and cannot be neglected in SDM studies (Warton et al. 2013). Consequently, we used a layer to control this bias, which did not restrict the environmental suitability of the disease to the vicinity of roads.

As expected, the inclusion of the distribution of hosts and vector as predictors also improved the performance of the model, especially the inclusion of host, which was ranked as the best model. Modeling without these biotic variables predicted a much broader suitable area for the virus. This high commission error rate (overprediction) for jungle YF has important implications for the identification of risk areas for the occurrence of urban YF. According to the niche concept proposed by Soberón (2007), the distribution of a species (i.e., its area of occurrence) is limited by abiotic and biotic factors and by the species' capacity of dispersal and colonization of suitable environments. Although not exclusively dependent on this variable, high infestation rates with the urban vector *Ae. aegypti* within this "enlarged" area detected by the model can indicate regions with greater possibility of YF reurbanization due to a higher proximity to possible foci of wild circulation.

The distribution of hosts stood out as the main predictor of YF distribution, containing most useful information by itself and most information that is not present in the environmental predictors. We found that the observed environmental difference between the niche of NHP and that of the virus is greater than that expected by the null distribution. This finding shows that there is a strong environmental bias between NHP and infected monkeys and suggests that the virus has an environmental niche that is restricted with respect to that of NHP. The environmental niche of NHP, represented by the PCA ordination, was not driven by a few dominant variables, but by different variables that were highly correlated with the two first axes (Supplementary material/Text 3–Table K). It shows that all environmental variables are complementary to each other to determine the environmental niche of NHP and that these environmental predictors may act together for producing this environmental bias between NHP and YF virus.

In summary, our approach covered the three uses of spatial modeling in animal and public health (Stevens and Pfeiffer 2011). First, we used the geographic coordinates of sites with occurrence of YF in NHP to describe the affected areas more precisely than previous modeling based on human cases located in geopolitical boundaries (Hamrick et al. 2017; Hamlet et al. 2018; Kaul et al. 2018; Leta et al. 2018; Shearer et al. 2018) or on the intersecting pattern of occurrence of NHP with human cases (Piedrahita-Cortés and Soler-Tovar 2016). Second, we identified the abiotic variables that best explained the distribution of YF during the epizootic under analysis. Finally, we highlighted the importance of including host and vector models in predicting the path traveled by the virus during the epizootic and identified regions outside the expected range of jungle YF at risk of reurbanization of the disease.

Despite technological advances that include novel detection techniques and complex modeling, more than 80 years after the discovery of the jungle cycle of YF (Soper et al. 1933), our understanding of the driving forces of disease re-emergence after long periods of silence remains limited (Hill 2012). Although the climatic factors frequently indicated as drivers of disease spread still need to be better assessed, we confirmed the important role of rainfall. Likewise, the presence of NHP was important for the occurrence of the disease. However, we need further field studies to elucidate the role of vectors and human and nonhuman hosts on disease occurrence and dispersal in fragmented environments. The support for the influence of the wind as a dispersal agent of the virus, although previously suggested, reinforces its potential as a predictor of disease spatial progression.

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