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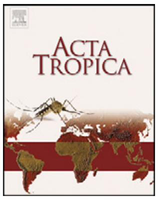

Environmental factors affecting transmission risk for hantaviruses in forested portions of southern Brazil

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ABSTRACT

Using ecological niche modeling approaches, we assessed suites of environmental factors to identify areas of transmission risk in forested regions of southern Brazil. We studied all officially confirmed cases from the Epidemiological Surveillance System of the Brazilian Health Ministry from Atlantic Forest and Araucaria forest areas of southern Brazil ($n = 264$), during 1993–2008. Among climate-related influences associated with hantavirus cases, winter precipitation and high photosynthetic mass (EVI) were particularly closely related to case distributions. Models identified broad risk areas for hantavirus transmission, extending along the coastal Atlantic Forest region from São Paulo to Rio Grande do Sul, eastern Paraguay, and Argentina. Host distribution maps indicate overlap of several species of *Oligoryzomys* in the transmission area, showing the necessity of more detailed reservoir-based studies to detect finer-scale infection foci.

1. Introduction

Hantaviruses belong to the virus family *Bunyaviridae*. In nature, these viruses appear to cause asymptomatic and persistent infections in rodents, and may be transmitted to humans via inhalation of aerosols from urine, feces, and saliva of the rodents, or through direct contact with skin lesions, abrasions, or rat bites (Pan American Health Organization, 1999). Although Eurasian hantaviruses are generally associated with renal complications, American hantavirus infections are related to cardiopulmonary manifestations (Jonsson et al., 2010). American hantaviruses were first reported in the southwestern United States in 1993 (Nichol et al., 1993). In the same year, 3 cases were reported in rural area surrounding Juquitiba, in the state of São Paulo, Brazil (Iverson et al., 1994). By December 2008, given greatly increased and improved surveillance, 1119 cases had been confirmed from all regions of the country (Ministério da Saúde, 2009). In all, 126 cases were reported in São Paulo (of which 22 were in forested areas), 174 in Paraná, 1981 in Santa Catarina, and 68 in Rio Grande do Sul; these southern Brazilian occurrences account for 50% of the known cases in Brazil.

Juquitiba virus (JUQV) is the dominant hantavirus in the forested portions of southern Brazil, occurring both in the Atlantic Forest region and in the temperate *Araucaria* forests farther to the south. These ecosystems hold considerable diversity of rodents in the subfamily Sigmodontinae. Of particular importance among these species is *Oligoryzomys nigripes*, which is known to be associated closely with hantavirus transmission in the region (Suzuki et al., 2004; Figueiredo et al., 2009; Pereira, 2006; Souza et al., 2002)—indeed, analyzing a sample of 4069 sigmodontine rodents from southern and southeastern region of Brazilian Atlantic Forest sites, Souza et al. (2002) detected the highest seroprevalence (7.8%) in this species, followed by that in *Bolomys* sp. (2.0%) and *Akodon* sp. (1.6%) (Souza et al., 2002). *O. nigripes* is a generalist, ecologically speaking, with considerable capacity for adaptation to human-dominated environments, including agricultural areas, plantations, and forestry areas (Püttker et al., 2008; Dalmagro and Vieira, 2005). This species is abundant in Atlantic Forest and *Araucaria* forest areas across southern Brazil, extending into the pampas systems of Rio Grande do Sul. (Dalmagro and Vieira, 2005; Trott et al., 2007)

Pathogen distributions frequently relate directly (if not absolutely) to the geographic distributions of their reservoir hosts (Mills and Childs, 1998), which in turn may be limited by climate, seasonality, substrate, anthropogenic disturbance, and land use (Mills et al., 2010). For this reason, environmental factors can be used to develop a predictive understanding of potential distributional areas of species (Engelthaler et al., 1999; Soberón and Peterson, 2005). Nonetheless, in Brazil, few studies have explored environmental

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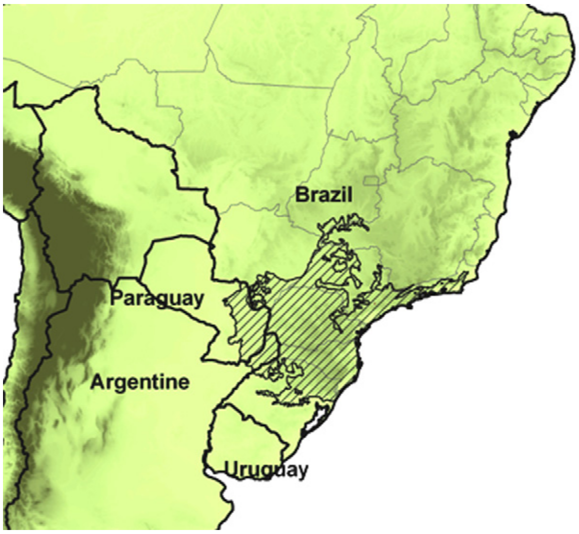

Fig. 1. Atlantic Forest and *Araucaria* forest biomes in southern Brazil, eastern Paraguay and Argentina.

correlates of hantavirus transmission (Donalisio et al., 2008). As a result, to improve understanding of the role of these environmental factors in hantavirus transmission in Brazil, we use ecological niche modeling (ENM) techniques to assess suites of environmental factors and identify areas of transmission risk in the forested regions of southern Brazil. Our analysis are, of necessity for lack of broad sampling to detect viruses in reservoir hosts, based on human case occurrences, and for that reason to some degree mix the ecological situations of infected hosts with those of human populations.

2. Materials and methods

2.1. Input data

Our analyses are based on sites of probable hantavirus transmission, including all officially confirmed cases from the Epidemiological Surveillance System of the Brazilian Health Ministry from forested areas in São Paulo, Paraná, and Santa Catarina ($n = 264$), during 1993–2008, as well as cases from Rio Grande do Sul from 2006 to 2008 ($n = 24$). Each human case residence was visited by epidemiological and vector surveillance teams at the time of notification to confirm the details of hantavirus transmission to the extent possible. Occurrences were plotted as the centroids of the municipalities in which transmission likely occurred (in this region of Brazil, municipalities average 300 km^2, such that a circular municipality would have a diameter on average of 9.8 km).

We focused analyses in southern Brazil, in the states of São Paulo, Paraná, Santa Catarina, and Rio Grande do Sul (Fig. 1). We further restricted analyses to the approximate footprint of Atlantic Forest and *Araucaria* forests, as these biomes appear to correspond closely to the area of transmission of Juquitiba virus and to the range of *Oligorizomys*. Cases from western São Paulo in the cerrado biome were excluded from analysis, because they appear to be connected to Araraquara virus, which is hosted by *Bolomys lasiurus*, and likely have a very different transmission system and ecological regime (Suzuki et al., 2004; Figueiredo et al., 2009).

We assembled diverse raster geographic information system (GIS) data layers to provide a rich characterization of environmental variation across the study region. In particular, we used climatic data from the WorldClim climate data archive (WorldClim, 2010), including monthly precipitation, monthly minimum and maximum temperatures, and various "bioclimatic" parameters (which combine monthly precipitation and temperature data to produce variables that may be more directly relevant to limiting geographic distributions of species). Climatic data were obtained at a spatial resolution of 30" (approximately 1 km^2). To summarize aspects of land cover and vegetation phenology, we used Normalized Difference Vegetation Index (NDVI) and Enhanced Vegetation Index (EVI) summaries of data from the MODIS satellite (500 m resolution) (NASA, 2010a). We also included topographic data sets summarizing elevation, aspect, slope, and compound topographic index (tendency to pool water) from the U.S. Geographic Survey's Hydro-1K data set (NASA, 2010b).

Table 1
Number of independent occurrences of hantavirus infections in humans predicted and proportion of area predicted by Maxent model ($E = 10\%$ threshold) in Atlantic and *Araucaria* forest in portions of southern Brazil.

Regions	Success (%)	Prop. predicted area (%)	Cumulative binomial (p)
São Paulo and Paraná predict *Santa Catarina*	97.2 (71/73)	91.1	0.0091
São Paulo and Santa Catarina predict *Paraná*	93.1 (27/29)	45.7	0.0212
Santa Catarina predicts *São Paulo and Paraná*	70.6 (36/51)	46.9	0.0002
Paraná predicts *São Paulo and Santa Catarina*	64.3 (63/98)	45.7	0.0001

2.2. Model development and interpretation

To identify areas of infection risk across the study region, we used ecological niche modeling (ENM) routines as implemented in Maxent (Phillips et al., 2006). These approaches in general relate points of known occurrence of species or phenomenon to digital maps of a landscape to discover associations between occurrence patterns and environments, an analog of the Grinnellian ecological niche (Soberón and Peterson, 2005).

To identify most relevant environmental parameters for predicting hantavirus infections, we used a jackknife procedure which measured the effects on predictions of each environmental variable (e.g., aspects of climate, landscape, and topography) alone and when omitted from the model (Phillips et al., 2006). We established appropriate thresholds for separating prediction of presence *versus* absence based on the least training presence threshold approach (Pearson et al., 2006), but modified the procedure to take into account the expected error parameter E, which summarizes the approximate proportion of input data likely to be erroneous (Peterson et al., 2008). That is, instead of setting a threshold at the predictive value that includes 100% of the training occurrence data, we used the threshold that includes $(100 - E)\%$ of the training occurrence data, which is thus a more restricted area, but takes into account the possible presence of noise in the occurrence data.

Predictive accuracy of the models was evaluated based on spatially stratified subsets of the available occurrence sites, basically challenging models to use niche patterns estimated on one landscape to anticipate patterns of occurrence on another. We used three states in southern Brazil as the basis for this subsetting exercise—São Paulo, Paraná, and Santa Catarina: we used each pairwise combination of two regions to calibrate models, testing the predictions in the third region, and similarly each region alone to predict each pair of regions (São Paulo was not used to calibrate or test model predictions alone owing to small sample sizes), thus creating a total of four tests of model predictions (Table 1). Such models of ecological niches used to predict geographic have generally been tested using the receiver operating characteristic (ROC) (Elith et al., 2006) which summarizes the accumulation of predictive ability of known presences as more and more area is predicted as suitable with ever-broader thresholds.