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Author summary

The Oropouche, Mayaro, Saint Louis, and Rocio viruses are neglected emerging mosquito-borne viruses that are spreading and causing wide-scale epidemics in South America. However, under-reporting of these cases is possible, as the symptoms are shared with other endemic diseases. Moreover, little is known regarding environmental conditions that favor these tropical outbreaks of arboviral diseases. This study examined the association of environmental factors with the probability of occurrence of Oropouche, Mayaro, Saint Louis and Rocio fever outbreaks (present and future) and finds that temperature is a central variable that determines the distribution of high-risk areas. This fact is very worrying, because the average temperature of some areas has increased significantly over the time. Results from this study strongly suggest that these four diseases have the potential to become important public health problems or become increasingly relevant in Brazil and other tropical areas in the coming years and should be monitored as part of effective control programs.

Introduction

Arboviruses have become important and constant threats in tropical regions, due to rapid climate change, deforestation, population migration, disorderly occupation of the urban areas, and precarious sanitary conditions that favor viral amplification and transmission [1]. Climate fluctuations produce conditions that accelerate arbovirus epidemics, directly affecting global public health [2]. Abnormally high temperatures, for example, affect populations of insect vectors, and arboviral diseases by influencing: the survival and replication of the virus, susceptibility of the vector to viruses, distribution of vectors, extrinsic incubation period of a virus in the insect, and seasonality of virus transmission patterns [3,4]. Besides that, arboviruses are highly spreadable because their vectors can be carried long distances, and even between countries or continents, which can lead to pandemics.

Brazil is the largest South American country and has a population of approximately 207 million in an area of 8,514,215 km^2 [5]. More than >30% of Brazil remains covered by rainforests and other natural ecosystems, despite the high rate of deforestation [5]. These natural environments can harbor many arboviruses that are maintained in different zoonotic cycles. For example, approximately 200 different arbovirus species have been isolated in Brazil, including 40 species that can cause human diseases [6,7]. Although it is acknowledged that dengue, zika, chikungunya, and recently, yellow fever, are today the most important emerging and re-emerging arboviral diseases in Brazil, in this study we focused on others that have been neglected and consequently, are less discussed in medical literature. These include Oropouche (ORO), Mayaro (MAY), Saint Louis (SLE), and Rocio (ROC). Besides the lack of specific tests to identify these diseases, the similarities among the symptoms are very high; fever, for example, is common to all of them. This makes the correct diagnosis very difficult and in most cases may have been underreported.

Oropouche (ORO)

The Oropouche virus (Orthobunyavirus genus) was first isolated in 1955 from a febrile human patient and mosquitoes in Trinidad and Tobago [8]. Five years later, the virus was detected in a Brazilian territory in a sloth ( ) and in mosquitoes [9]. Since then, ORO has been a common cause of explosive urban epidemics in the Amazon region, affecting large cities such as Belem and Manaus.

This virus is transmitted among vertebrate hosts, such as marsupials, sloths, primates, and birds, through a generally wild transmission cycle by the and mosquitoes. Notably, this arbovirus has adjusted to an urban transmission cycle with humans as the main reservoir and (Ceratopogonidae) as the main vector. Thus, there is a worrisome risk of ORO emergence in the densely populated coast of Brazil, which cover the northeastern and southeastern regions, considering that vector . is present in low-altitude areas of the entire Brazilian territory [7,10]. Moreover, . mosquitoes are spread throughout the Brazilian cities, suggesting the need to pay more attention to this mosquito species too.

ORO is one of the most important arboviral diseases in the Americas, especially in the Brazilian Amazon region. However, because ORO fever is not considered a reportable disease, it is difficult to estimate its incidence during outbreaks, although serological surveys are useful in this setting. Thus, research has indicated that approximately 500,000 people in the Amazon region may have been infected with the ORO virus since the early 1960s [6].

Most epidemics of ORO fever typically occur during the rainy season. However, some epidemics have also extended into the dry season, although with less intensity. The seasonal nature of the ORO is most likely linked to the higher density of the populations of the vector . in months with higher levels of rainfall, combined with a higher concentration of exposed hosts. Unfortunately, the diagnosis of ORO can be confused with other acute febrile diseases that are endemic in the Amazon region, such as malaria and dengue [11].

Mayaro (MAY)

The MAY virus, belonging to the Alphavirus genus, has been responsible for outbreaks of acute febrile illness and arthralgia syndrome in northern and midwestern Brazil, as well as Peru, Bolivia, and Venezuela [7,12]. This virus was first detected and isolated in 1954, from rural workers in Trinidad [13].

Human cases of MAY are sporadic and mainly involve people who live in rainforests, as the main vector is the mosquitoes that are common in those forests. Vertebrate hosts are mainly mammals, although there is some evidence of bird infections in southern Brazil. mosquitoes can also transmit the virus in rural, suburban, and urban areas [14]. The course of 3±5 day of illness is characterized by fever, headache, myalgia, rash, and pain, mainly in the large joints, and less often, arthritis [15,16]. The spread of this virus can extend to cities through an infected human or through birds that can travel long distances in a short time, and adapt to a new cycle that involves humans as reservoirs.

This febrile illness occurs throughout the year, more frequently in the rainy season, as with dengue and ORO, and affects people of both sexes, of all ages. The estimated transmission of the virus in Manaus, state of Amazonas, is about 2 million people. This is a public health problem because there is no vaccine, and vector control is not feasible [12].

Saint Louis Encephalitis (SLE)

The SLE virus belongs to the Japanese encephalitis virus complex, which is within the genus, and Flaviviridae family [17]. The virus was first isolated in 1933 from suspensions of human intracerebral brain samples that had been inoculated postmortem with tissues from rhesus monkeys and white mice (Saint Louis, Missouri, USA) [18]. Currently, the SLE virus is broadly distributed throughout all Americas (from Canada to Argentina), and has neurotropic characteristics [12]. It causes an acute disease in humans, with manifestations that range from febrile syndrome to fatal meningoencephalitis [19]. Reports of fatal cases vary from 5% to 20%; however, the numbers are even higher among the elderly population [20].

Transmission of the SLE virus occurs through mosquitoes, and migratory birds spread the virus and other forms of encephalitis along their migratory routes [12]. Despite rare cases of the isolation of SLE virus in humans in Brazil, the antibodies of this virus were found in approximately 5% of the populations of the Northern and Southeastern Regions [12]. Recently, there was an outbreak of SLE in the country, which occurred simultaneously with that of dengue in S o JosÂ do Rio Preto (Sao Paulo) [21]. During this outbreak, some patients with SLE exhibited hemorrhagic manifestations, such as a positive tourniquet test, petechiae, and bleeding [21].

Rocio (ROC)

The ROC virus was first isolated in 1975 from a fatal case of encephalitis in a restricted area of the Atlantic Forest (Ribeira River Valley Sao Paulo) [7]. The case was detected during the 1973±1980 outbreak which caused an estimated 1,000 cases of encephalitis in more than 20 municipalities. The mortality rate was 10%, and among the survivors, about 200 suffered balance or mobility sequelae [7]. It is unclear how the ROC virus spread to this region and why it subsequently disappeared 7 years later, although antibodies have been detected in rural residents of southeastern and northeastern Brazil. [22,23]. Based on the viral isolation and serological data, it is believed that the ROC virus is maintained in a transmission cycle that involves wild birds, including some migratory species, as the reservoirs, and and mosquitoes, as the vectors.

Despite the availability of a comprehensive record in the literature for these relevant diseases, to the best of our knowledge, no predictive models have been developed in this context. In this study, we analyze and illustrate how these four mosquito-borne diseases can have serious public health implications, or increase their relevance in the future. Thus, the study's goals were: (a) to obtain the probability of occurrence of ORO, MAY, ROC and SLE in Brazil, based on environmental conditions corresponding to the periods of occurrence of the outbreaks (b) to describe the macroclimatic scenario in Brazil in the last 50 years, evaluating any detectable tendency to increase temperatures and (c) to predict future expansion of ORO, MAY, SLE and ROC in Brazil, based on future temperature projections for 2046±2065 and 2071±2100, using two different scenarios of greenhouse gas emissions.

Methods

Study area and data source

The approximate locations of human ORO, MAY, SLE, and ROC cases were determined using sites that were identified in the literature between 1961 and 2012 (Table 1). Data were exhaustively collected using searches of the PubMed and Google Scholar databases (search term: ªOropoucheº OR ªMayaroº OR ªSaint Louisº OR ªRocioº AND ªBrasilº OR ªBrazilº) and the library of University of Sao Paulo, Brazil. We have included all records of diseases in Brazilian municipalities reported in epidemiological bulletins since the very first record up until 2012. The criterion for inclusion of a municipality in the analysis was presence 1 of ORO, MAY, SLE or ROC case. This is because the World Health Organization has stated ª

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To determine the ecological and climatic conditions associated with ORO, MAY, SLE, and ROC mosquito-borne disease outbreaks, we examined the relationships between the locations

Table 1. Brazilian municipalities that have presented arbovirus outbreaks in the 1961–2012 interim. (Data from Google Scholar and Pubmed databases. Searching topics = “Oropouche” OR “Mayaro” OR “Saint Louis” OR “Rocio” AND “Brasil” OR “Brazil”). The acronyms next to each municipality indicate the State.

Virus	Municipality	Epidemic Year	References
Oropouche	Belém (PA)	1961, 1968, 1979, 1980	[25–29]
	Bragança (PA)	1967, 1979–1980	
	Baião (PA)	1972	
	Santarém region (PA)	1974–1975	
	Itupiranga (PA)	1975	
	Tomé-Açu (PA)	1978	
	Portel (PA)	1979	
	Bragantina region (PA)	1979–1980, 2006	
	Mazagão (PA)	1980	
	Barcelos (AM)	1980	
	Manaus (AM)	1980–1981	
	Tocantinópolis (TO)	1988	
	Porto Franco (MA)	1988	
	Ouro Preto d'Oeste (RO)	1991	
	Ariquemes (RO)	1991	
	Serra Pelada (PA)	1994	
	Brasil Novo (PA)	1996	
	Novo Airão (AM)	1996	
	Oriximiná (PA)	1996	
	Vitória do Xingu (PA)	1996	
	Xapuri (AC)	1996	
	Parauapebas (PA)	2003	
	Porto de Moz (PA)	2004	
Mayaro	Belterra (PA)	1977–1978	[30–36]
	Conceição do Araguaia (PA)	1981	
	Itaruma (GO)	1987	
	Benevides (PA)	1991	
	Peixe (TO)	1991	
	Acrelândia (AC)	2004	
	Manaus (AM)	2007–2008	
	Santa Bárbara (PA)	2008	
	Sinop (MT)	2011–2012	
	Cuiabá (MT)	2012	
	Sorriso (MT)	2012	
	Várzea Grande (MT)	2012	
	Nossa Senhora do Livramento (MT)	2012	
Saint Louis	São Pedro (SP)	2004	[37–39]
	Ribeirão Preto (SP)	2006	
	São José do Rio Preto (SP)	2007	
Rocio	Cubatão (SP)	1975	[40–43]
	Guarujá (SP)	1975	
	Itanhaém (SP)	1975	
	São Vicente (SP)	1975	
	Mongaguá (SP)	1975	

(Continued)

Table 1. (Continued)

Virus	Municipality	Epidemic Year	References
	Praia Grande (SP)	1975	
	Santos (SP)	1975	
	Cananéia (SP)	1975±1976	
	Iguape (SP)	1975±1976	
	Itariri (SP)	1975±1976	
	Jacupiranga (SP)	1975±1976	
	Juquiá (SP)	1975±1976	
	Miracatu (SP)	1975±1976	
	Pariquera-Açu (SP)	1975±1976	
	Pedro de Toledo (SP)	1975±1976	
	Peruíbe (SP)	1975±1976	
	Registro (SP)	1975±1976	
	Sete Barras (SP)	1975±1976	
	Barra do Turvo (SP)	1976	
	Eldorado Paulista (SP)	1976	

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of the outbreaks and seven variables annual rainfall (RAIN, mm), annual temperature (TEMP, ÊC), elevation (ELEV, m), seasonality of temperature (SEA-TEMP), seasonality of precipitation (SEA-RAIN), thermal amplitude (THER-AMP), and daytime temperature variation (DTV). The SEA-TEMP value was calculated as the standard deviation of the average monthly temperatures. The THERM-AMP value was calculated by subtracting the minimum temperature during the coldest month from the maximum temperature during the hottest month. The SEA-RAIN value was calculated as the coefficient of variation for average monthly precipitation. The mean DTV value was calculated by subtracting the mean minimum temperature from the mean maximum temperature. All weather data were obtained in ASCII-raster format files and using the "LAT/LONG" geodetic coordinate system (Datum WGS-84). These data were obtained from the WorldClimÐGlobal Climate Data database, which contains representative observational data for 1950±2000 that were interpolated to a resolution of 30 arc-seconds (approximately 1 km). As the environmental variables were expressed in various units, the principal components analysis (PCA) was performed after standardizing the variables using a Pearson correlation matrix. The temperature layers for 1970±2010 were obtained from the National Institute of Meteorology [44], and data regarding other variables were obtained from the AMBDATA [45] and WorldClim [46] databases.

Data analysis

Our analysis included all probable (clinically diagnosed) and confirmed (serological) cases of persons with the onset of the disease from 1961 through to 2012. For each disease, the environmental variables analyzed were those that corresponded with the years of outbreaks: ORO (between 1961 and 2006), MAY (between 1977 and 2012), SLE (between 2004 and 2007) and ROC (1975 and 1976). The database was developed based on the presence and absence of arboviroses. We considered value 1 for years with at least one case (or more) of ORO, MAY, SLE or ROC, and value zero for other years (no occurrence), during the period studied (1961 to 2012). Table 1 shows the municipalities that had cases of these arboviruses and the years in which they occurred.

The PCA was performed using R software to preselect the environmental variables that had the greatest influence on the distributions of each disease [47]. The PCA approach was used for two reasons. First, PCA facilitates the identification and elimination of covariant variables, which is a key procedure for avoiding analytical artefacts. Second, PCA has been widely used in equivalent studies and then facilitates comparisons, reproducibility, and future meta-analysis. After the PCA, we selected the four most representative eigenvectors of the variables for each disease, which were used for Maxent analysis (version 3.3.3k: a machine learning algorithm for modeling species distributions based on existing data and environmental variables) [48,49]. The data selection was performed according to the criterion of maximum entropy, with the original variables that reached maximum and minimum values within the ordered ranking of each principal component, because they describe the full range of data variation. The Maxent model may be expressed as:

$$p[f_j] = \frac{1}{N}\sum_{i=1}^{N} f_i(x_i)$$

Where: X = the geographical region of interest; $x = \{x_1, x_2, \ldots, x_N\}$ with $x \in X$; $x \rightarrow$ observed points at X; $f_j = f_1, f_2, \ldots, f_m$ (environmental variables); N = the number of observed cases; and p = the probability of disease occurrence. The model was run 25 times, while withholding a difference of 10% of the localities for each run to estimate the parameters and its precision. The potential distribution maps were created by interpolating the occurrence points and the similarity measures of the environmental variables in each pixel (i.e., a known observation probability value can be assigned to each pixel by calculating a probability whose exponent is a quadratic function). To describe the temperature change patterns in Brazil during the sampled 50 years, we used the kriging method [50,51] and data from approximately 250 monitoring stations throughout Brazil. This approach generated a map by estimating the value at each node of a regular grid, which was superimposed over the area of interest, and then a contouring program was applied to draw iso-level curves. We used a 250 × 250 grid of Brazil map, which provides 62,500 sections, because it was the maximum map resolution with a minimum required amount of computational time. R software [47] was also used to evaluate the temporal trend in temperature during the last five decades.

Future climate data were integrated using two global climate models (GCMs): the HadGEM2-ES [52] and MIROC-5 [53], which were selected for their different strengths. The HadGEM2-ES model is a stable model that represents a realistic state of the climate, vegetation, and oceanic biology, without the need for artificial corrections. On the other hand, the MIROC-5 model also includes components of the Earth's system and climate change, in relation to anthropogenic radiation. The advantage of using this model is that it increases the accuracy of short-term climate prediction, as it can be affected by both anthropogenic and intrinsic fluctuations of the climate system. The spatial resolution of the GCMs was the same as that of the environmental variables (30 arc-seconds, approximately 1 km). The comparison method was the same as for the Maxent model, although the probability calculation for the GCMs incorporated a comparison of the present and future environmental conditions. To obtain future climate scenarios using GCMs, it is also necessary to choose a condition for evolution of the greenhouse gas emissions (GGE), during the period when the future climate is projected. In our prediction we used two different scenarios: low emission (RCP2.6) and very high emission (RCP8.5), detailed in the Special Report on Emissions Scenarios by the Intergovernmental Panel on Climate Change [54]. In the first case, the global temperature tends to increase by 1.0°C and can reach a temperature anomaly ranging from 0.4 to 1.6°C and 0.3 to 1.7°C between 2046–2065 and 2081–2100, respectively [55]. In the second scenario, with high GGE, the global temperature tends to increase 2.0 to 3.7ÊC and can reach to a thermal anomaly ranging from 1.4 to 2.6ÊC and 2.6 to 4.8ÊC between 2046±2065 and 2081±2100, respectively [56,57].

The models of future expansion of ORO, MAY, SLE and ROC in Brazil were then projected into the timeline, and the two future climatic conditions (2046±2065 and 2071±2100), to identify areas suitable for those diseases. A map of raw temperature projections from the GCMs used to drive the disease models can be seen at S1 Fig. The default Maxent autofeature setting was used (linear, quadratic, product, threshold, and hinge). The maps were edited using QGis software 2.10.1.

Results

Through PCA of climatic factors, it was possible to identify three main groups: ROC, SLE and ORO + MAY (Fig 1). It is important to note that both diseases ORO and MAY occurred more in the North and Midwest of the country. The first two components (F1 and F2) were able to explain 82.96% of the variation.

Analyzing each disease separately (Fig 2), according to PCA it was possible to perceive that the most influential factors were distinct for each arbovirus. With respect to ORO cases, the most important variables were TEMP and SEA-TEMP; for MAY: THERM-AMP and SEA-TEMP, which was similar to ORO; for SLE: RAIN and DTV, and finally for ROC, the most important variables were THERM-AMP and ELEV. Details are described in Table 2.

As some variables co-varied (Fig 2), we selected only the non-covariant variables as input for analysis in Maxent software. The cut-off was four variables and was based on ROC, which presented the lowest number (four) of non-covariant variables. After selecting the four most important variables for each disease, we constructed a predictive model in Maxent (Fig 3), in order to determine what areas were most likely to present outbreaks. The contribution of each variable for each model is described in Table 3. The final model for ORO, MAY, SLE and ROC had an area under the curve of 0.79, 0.76, 0.85 and 0.99, respectively, significantly better than the random prediction ($p = 0.001$), indicating good performance of the model. The Maxent outputs and receiver operating characteristic curves [58] for all arboviruses are shown in S2 Fig. We observed that there is a concentration of ORO and MAY in the Northern region of Brazil, while SLE and ROC are mainly present in the South region and coastal region.

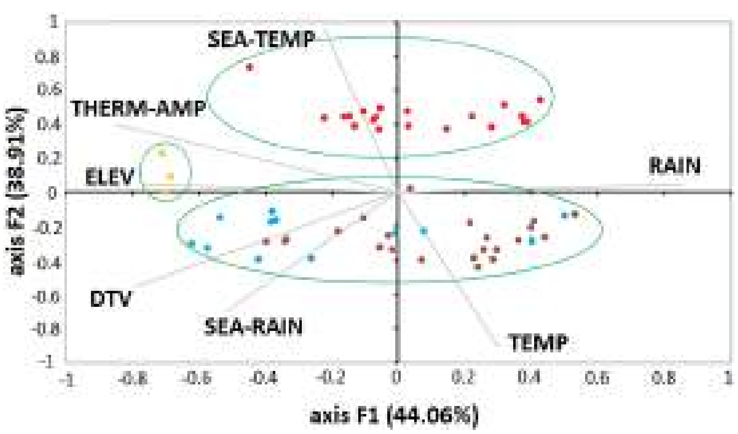

Fig 1. PCA of arboviruse s. This PCA showing the distribution of ORO (brown), MAY (blue), SLE (yellow) and ROC (red) cases according to environmental variables. The green ellipses show the main clusters: ROC, SLE and ORO+MAY.

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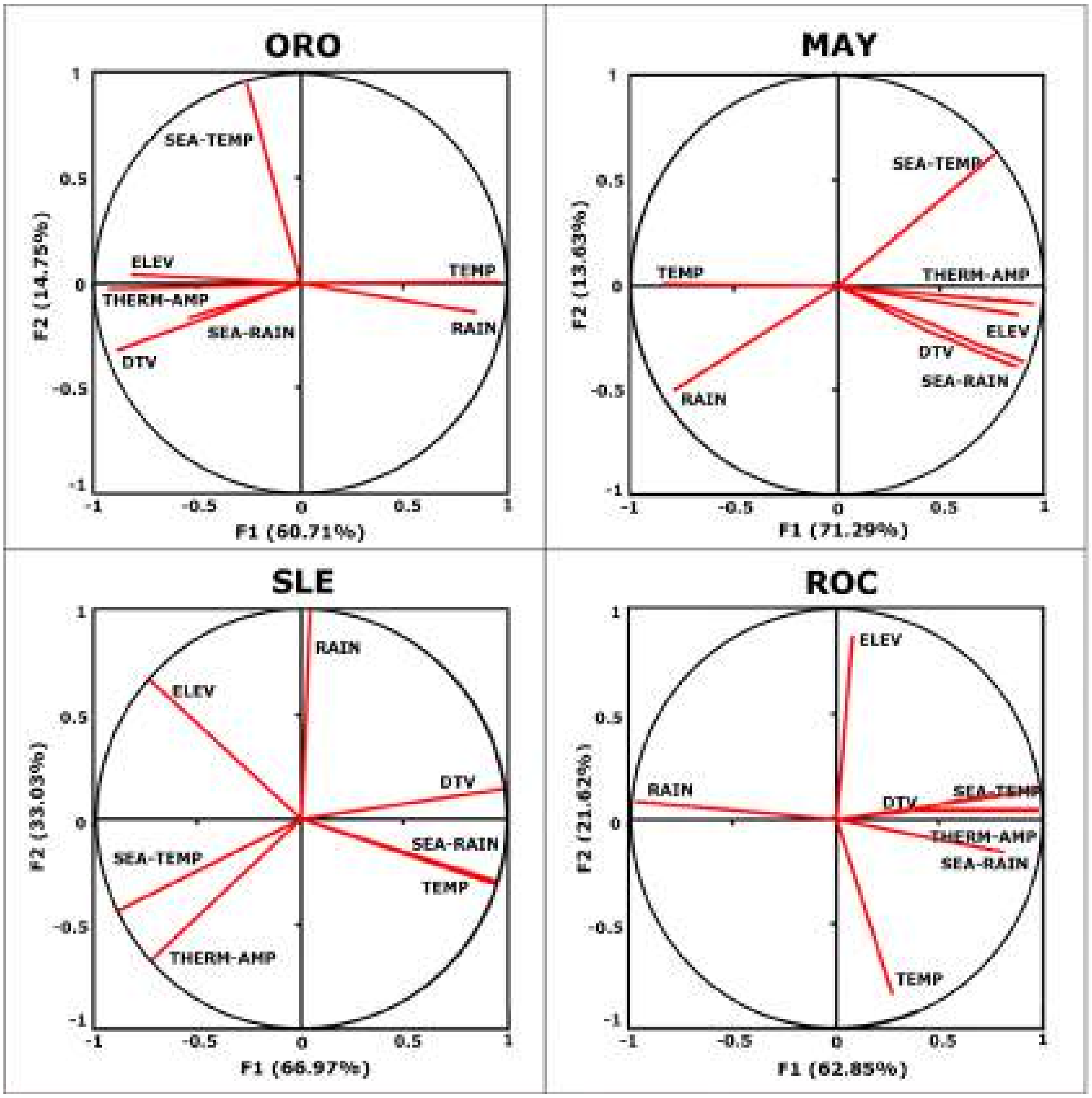

Fig 2. The most influential environmental variables. PCA of each disease showing which environmental variables are the most influential.

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Most of the important variables for the distribution of all four diseases are temperature-related (TEMP, SEA-TEMP), so we analyzed the temperature situation in Brazil in the last 50 years. After analyzing the historical temperature series, and using the kriging method, we realized that there has been an increase in temperature over the decades (Fig 4), especially in the North of the country.

In the case of continuity of this scenario of temperature increase, we generated probability maps with two different climate future projections (Fig 5). The results reveal a progressively expanding areas with an increased likelihood of ORO, MAY, SLE and ROC cases, especially at the edges of the transmission areas. In scenario of high GGE it was possible to observe the increase of high risk areas for ORO and MAY, while for SLE and ROC there were no drastic changes. This fact is in agreement with our observations of temperature increase (Fig 4),