

Mayaro virus distribution in South America

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ABSTRACT

Mayaro virus (MAYV) is a pathogen endemic to South America and some Caribbean islands, with reports of occasional outbreaks. However, its current distribution and high-risk areas are little known. We conducted a modelling study to determine the areas with highest prevalence of MAYV occurrence in South America, based on confirmed cases and serological detection over the last 20 years and socio-environmental variables. We performed our analysis using Maxent software, a machine learning algorithm used for species distribution modeling. Our results showed that the occurrence of MAYV is mainly associated with the biome type, population density, annual rainfall, annual vapor rate, and elevation. Among biome types, the one most related to the occurrence of MAYV is Cerrado, probably related to the lifecycle of the *Haemagogus* vector and human population concentrations. According to our modelling, there is high yet undetectable MAYV concentration in the central region of Brazil and west-coastal region of the continent. A change in virus dispersion patterns was observed. The virus was previously predominantly in forests but now occupied rural areas and was becoming increasingly urbanized, which increases the risk of outbreaks. Our results will serve to identify priority areas in the development of preventive actions and structuring of epidemiological surveillance.

1. Introduction

In recent years epidemic mosquito-borne arboviruses are increasing in frequency, and the current global scenario presents a perfect combination of factors for their expansion: climatic anomalies, deforestation, growing contact of humans with animal reservoirs/vectors, and the rapid evolution of the vector. In South America, a high concentration of native forests and diverse biomes - a biome is a large ecological area on earth's surface with distinctive plant and animal groups which are adapted to that particular environment - allows for great genetic diversity among viruses. One of these viruses is Mayaro (MAYV), a member of the *Alphavirus* genus (family *Togaviridae*). The MAYV is a single-stranded RNA virus, and previous phylogenetics studies propose that it has four different genotypes so far: D, L, N (Auguste et al., 2015) and a recombinant D/L (Mavian et al., 2017). Genotype D contains isolates from Trinidad, Brazil, French Guiana, Suriname, Peru, Bolivia and Venezuela; genotype L was detected in Brazil (Auguste et al., 2015; Powers et al., 2006) and Haiti (White et al., 2018); and genotype N was detected only in Peru so far (Auguste et al., 2015). It is primarily transmitted by mosquitoes of the genus *Haemagogus*, commonly from an infected vertebrate host (monkeys, birds, rodents, sloths, and other small mammals) to a susceptible human (Esposito and Fonseca, 2017).

These tree-dwelling vectors are also associated with the sylvatic cycle of yellow fever, and although MAYV maintenance efficiency in primary reservoirs is not known, it has been detected in other vertebrates (De Thoisy et al., 2003). *Aedes aegypti* mosquitoes have also shown to be competent vectors of MAYV in the laboratory (Long et al., 2011), suggesting that an urban arthropod has the potential to be a vector of this virus and spread it over a wider scale than sylvatic areas. MAYV infection has been detected in tourists returning from the Amazon region (Hassing et al., 2010), highlighting a possible role in global transmission (Halsey et al., 2013).

MAYV was first isolated in Trinidad in 1954 (Anderson et al., 1965), but human cases have primarily been observed in the Amazon and other tropical regions of South America (Powers et al., 2006; Halsey et al., 2013; Auguste et al., 2015). Most cases have been reported in French Guiana, Suriname, Venezuela, Peru, Bolivia, and Brazil (Azevedo et al., 2009; Figueiredo and Figueiredo, 2014). In Brazil, Mayaro fever has been reported in the Amazon region (Azevedo et al., 2009; Mourão et al., 2012) and in Mato Grosso (Zuchi et al., 2014; Pauvolid-Corrêa et al., 2015). More often cases have been reported recently in the Brazilian states of Goiás and Tocantins (MS, 2018). Human infections with MAYV result in an acute febrile illness, with onset of fever, arthralgia/arthritis, and a maculopapular rash. Other

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associated symptoms may occur: headache, myalgia, retro-orbital pain, vomiting and diarrhea (Acosta-Ampudia et al., 2018; Auguste et al., 2015). The clinical manifestation is difficult to distinguish from other arboviruses such as dengue, Zika and chikungunya (Pinheiro et al., 1981; Tesh et al., 1999; Lednicky et al., 2016), possibly resulting in underreporting of MAYV cases. This underreporting has occurred for most vector-borne pathogens, especially for those of neglected tropical diseases. Public health surveillance actions are important for detecting cases and outbreaks and implementing prevention measures, emphasizing the importance of identifying possible high-risk areas. Studies about MAYV are rare, and there is no approach to identifying high-risk areas across South America, which is critical to consider for the formulation of public policies related to control and prevention. In light of this situation, we conducted a modelling study to determine the most probable areas of MAYV occurrence in South America, based on confirmed cases and serological detection of the last 20 years and socio-environmental variables.

2. Materials and methods

2.1. Data source

We included all records of MAYV in South America reported in epidemiological bulletins or scientific papers in the last 20 years (between 1998 and 2018). We used this time period to verify the most recent virus circulation records since the areas in which the virus was detected are probably still the same today. According to the SEDAC (2018) there were no significant spatial changes in the variables considered in this period. Our analysis included all confirmed (serological) autochthonous human cases besides MAYV records in blood samples (IgM), mosquitoes, horses, or monkeys infected (Table 1). To ensure the spatial scale of serological cases, we considered only those who did not travel outside the municipality of residence. The criterion for inclusion of a municipality in the analysis was presence ≥ 1 of MAYV. Data were exhaustively collected using searches of Google Scholar and PubMed databases (search terms: “Mayaro” AND “South America” OR “Argentina” OR “Bolivia” OR “Brazil” OR “Chile” OR “Colombia” OR “Ecuador” OR “Guiana” OR “French Guiana” OR “Paraguay” OR “Peru” OR “Suriname” OR “Uruguay” OR “Venezuela”) and the Ministry of Health, Brazil. The points with presence data are the coordinates of the centroid of the municipality in which the case was registered, or the coordinate of the case itself (when available).

To determine the ecological and climatic conditions associated with MAY distribution, we first examined 16 variables that, according to the literature, could influence the life cycle of the arthropod vector (*Haemagogus*) or the vertebrate host and, consequently, the distribution of the MAY; they are listed in Table 2. All weather data were obtained in ASCII-raster format files and using the “LAT/LONG” geodetic coordinate system (Datum WGS-84). These data came from the AMBDATA (2018) and WorldClim (2018) databases, at a resolution of 30 arc-seconds (approximately 1 km). The NDVI index was obtained from NASA’s Moderate Resolution Imaging Spectroradiometer MODIS (2018). Besides, we also included population density information in our study, as it may interfere with the distribution of MAY cases; this data came from the Socioeconomic Data and Applications Center (SEDAC, 2018).

2.2. Data analysis

The following procedures were based on Rochlin et al (2013). We performed a Pearson correlation coefficient analysis using the software ENMTools v1.3 (Warren et al., 2010), to preselect the environmental variables that most represent the dataset. This approach was used to detect correlation between variables, which is a key procedure for avoiding analytical artefacts. When two variables showed a correlation over 0.75, one variable was excluded from the analysis to avoid

Table 1

South America regions that have presented MAYV detection in the 1998–2018 interim.

Country	Region	Year	Record Type	References
Peru	Iquitos	1998	Human case	Tesh et al., 1999
Peru	Yurimaguás	1998	Human case	
Peru	Tocache	1998	Human case	
Peru	Pucallpa	1998	Human case	
Peru	Huanuco	1999	Human case	
Peru	Quillabamba	1998	Human case	
Peru	Tumbes	1998	Human case	
Peru	Cuzco	2003	Human case	Powers et al., 2006
Peru	Loreto	2003	Human case	
Peru	Madre de Dios	2010	Human case	Auguste et al., 2015
Peru	Chanchamayo	2011	Human case	Halsey et al., 2013
Peru	Puerto Maldonado	2011	Human case	
Peru	Cuzco – Santusaires	2018	Human case	Regional Government of Cuzco, 2019
Peru	Cuzco – San Martín	2018	Human case	
Peru	Cuzco – Pareato	2018	Human case	
Peru	Cuzco - Chirumbia	2018	Human case	
Peru	Cuzco - Lampachaca	2018	Human case	
Peru	Cuzco - Pampa Esperanza	2018	Human case	
Peru	Cuzco - Santa María	2018	Human case	
Bolivia	Nuflo de Chavez	2007	Human case	Long et al., 2011
Bolivia	Rurrenabaque region	2012	Human case	Theilacker et al., 2013
Venezuela	Portuguesa	2010	Human case	Auguste et al., 2015
Brazil	Camapuã/MS	2000	Human case	Coimbra et al., 2007
Brazil	Acrelândia/AC	2004	Human case	Terzian et al., 2015
Brazil	Juruti/PA	2007	IgM human and animals	Cruz et al., 2009
Brazil	Manaus/AM	2008	Human case	Mourão et al., 2012
Brazil	Santa Bárbara/PA	2008	Human case	Azevedo et al., 2009
Brazil	Corumbá/MS	2010	Infected horse	Pauvolid-Corrêa et al., 2015
Brazil	Sinop/MT	2011	IgM and human case	Vieira et al., 2015
Brazil	Cuiabá/MT	2012	Human case and infected mosquito	Zuchi et al., 2014
Brazil	Sorriso/MT	2012	Human case	
Brazil	Várzea Grande/MT	2012	Human case	
Brazil	Nossa Senhora do Livramento/MT	2012	Human case	
Brazil	Jardim/MS	2013	Infected monkey	Batista et al., 2013
Brazil	Pontalina/GO	2014	IgM	Brunini et al., 2017
Brazil	Goiânia/GO	2015	IgM and human case	
Brazil	Hidrolândia/GO	2015	IgM and human case	
Brazil	Aparecida de Goiânia/GO	2015	Human case	Brazilian Ministry of Health, 2018
Brazil	Bela Vista de Goiás/GO	2015	Human case	
Brazil	Belém/PA	2015	Human case	
Brazil	Caldazinha/GO	2015	Human case	
Brazil	Caiapônia/GO	2015	Human case	
Brazil	Orizona/GO	2015	Human case	
Brazil	Piracanjuba/GO	2015	Human case	
Brazil	Professor Jamil/GO	2015	Human case	
Brazil	Rio Quente/GO	2015	Human case	
Brazil	Senador Canedo/GO	2015	Human case	
Brazil	Palmas/TO	2015	Human case	
Brazil	Paraíso do Tocantins/TO	2015	Human case	
Brazil	Itacajá/TO	2015	Human case	
Brazil	Formoso do Araguaia/TO	2015	Human case	

potential bias in the modelling (see Table 2). We used a maximum entropy model analysis through Maxent software (version 3.3.3): a machine learning algorithm based on presence-only data and environmental factors (Phillips and Dudík, 2008). Compared to other available

Table 2
Environmental variables used in the analysis and model selection. Variables included in the final model are indicated in bold.

Variable	Abbreviation	Inclusion in the final model
Type of biome	BIOME	Yes
Normalized difference vegetation index	NDVI	No, highly correlated with POP
Annual frost	FROST	No, highly correlated with VAPOR
Annual cloudiness	CLOUD	No, highly correlated with BIOME
January rainfall	JAN-RAIN	No, not significant based on AIC
April rainfall	APR-RAIN	No, highly correlated with AN-RAIN
July rainfall	JUL-RAIN	No, not significant based on AIC
October rainfall	OCT-RAIN	No, highly correlated with AN-RAIN
Annual rainfall	AN-RAIN	Yes
Maximum temperature	MAX-TEMP	No, highly correlated with VAPOR
Minimum temperature	MIN-TEMP	No, highly correlated with VAPOR
Annual temperature	AN-TEMP	No, highly correlated with VAPOR
Daytime temperature variation	DTV	No, not significant based on AIC
Annual vapor rate	VAPOR	Yes
Elevation	ELEV	Yes
Population density	POP	Yes

algorithms, Maxent performance consistently ranked among the best (Elith et al., 2006). However, Maxent was found to be overly sensitive to the choice of modeling parameters with model over-fitting, multicollinearity, and data-dredging, negatively affecting the prediction's accuracy (Rodda et al., 2011). To address these statistical issues, a model selection procedure based on Akaike information criterion (AIC) was proposed (Rodda et al., 2011; Warren et al., 2010). Comparative analysis of different models generated by Maxent was done using ENMTools v1.3 software. After this procedure, the five best-fitted variables among the set of variables for MAYV were selected (Table 2). The models were run 25 times, with 30% of records being used in the test step and the remainder for validation. Potential distribution maps were built by interpolating the occurrence data and similarity measures of the environmental variables in each pixel. The linear, quadratic e hinge Maxent feature class setting were used. The maps were edited using QGIS software 2.10.1.

3. Results

Among the 16 preselected variables, we selected only those non-correlated as input for analysis in Maxent software (Table 2, see also Supplementary Material 1 for coefficient of Pearson). Model selection using AIC criterion (ENMTools) resulted in the best-fitted model containing biome type, annual rainfall, annual vapor rate, elevation, and population density. The final model had an area under the ROC curve of 0.917 (standard deviation = 0.01), which indicated good performance

of the model (Fig. 1). The omission rate (proportion of test points not predicted) was 0.015, which was significantly better than random prediction at $p = 0.001$ by binomial test. The contribution of each variable for the final model is described in Fig. 2A. Biome type was strongly associated with MAYV occurrence, specifically type 6: grasslands, savannas, and shrublands (Fig. 2B). In Brazil, this ecological region is known as Cerrado.

Modeling analyses identified several potential areas with environmental conditions suitable to MAYV in South America (Fig. 3), including high concentrations in the central region of Brazil and west-coastal region of the continent. The map with standard deviation of the 25 model replications can be visualized in Supplementary Material 2.

4. Discussion

Our analysis showed that the occurrence of MAYV in South America is mainly associated with biome type and population density. Among the biome types, the one most related to the occurrence of MAYV is Cerrado: a tropical savannah that primarily covers 22% of the Brazilian territory (De Lara Pinto et al., 2017). It is considered the second greatest phytogeographic domain in South America and a hotspot of great biodiversity (Klink and Moreira, 2002; Mittermeier et al., 2011). In the Cerrado biome, a variety of vegetation can be found, including riparian forest, gallery forest, dry forest, savanna, classic Cerrado, rough savannah, grassland, wetlands and palms (Brasil, 1982; Sano et al., 2008). This ecoregion has the ideal characteristics for Mayaro

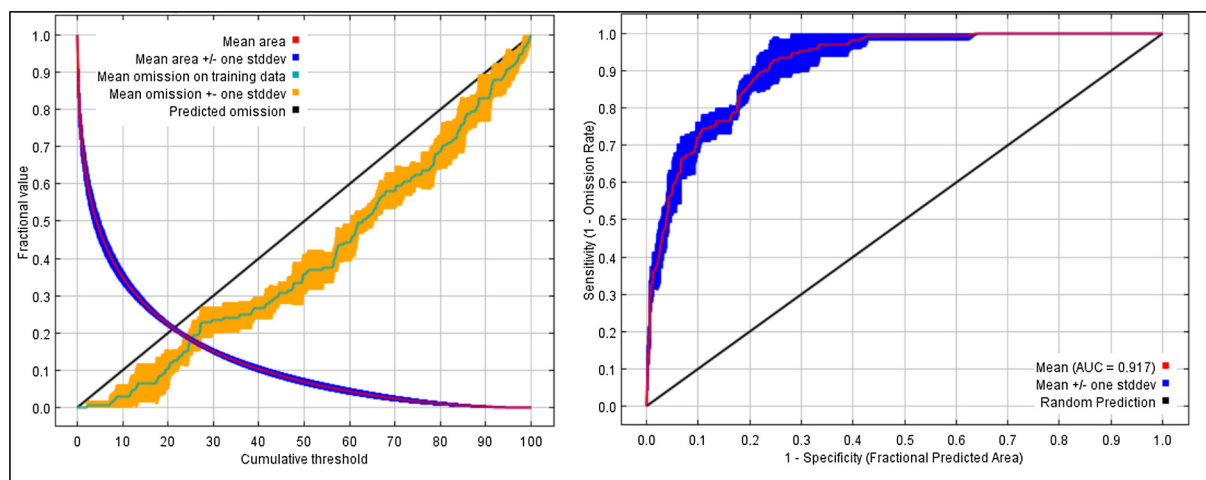


Fig. 1. Left: Average Omission and predicted area for MAYV distribution; Right: Average sensitivity vs. 1 – specificity for MAYV. Data obtained from Maxent software version 3.3.3.

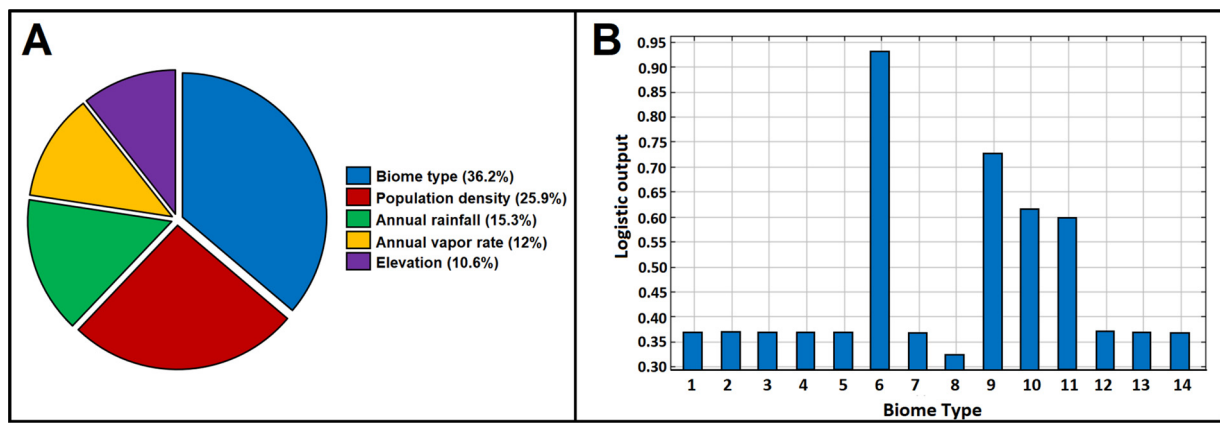


Fig. 2. A) Importance of each variable for the final Maxent model of MAYV. B) All categories for the variable “Biome type”; the category number 6 represents Cerrado biome (grasslands, savannas and shrublands).

fever, due to the diversity of ecosystems and, consequently, large number of vertebrate hosts and mosquito vectors. A large population of residents and workers in rural areas are also susceptible, and with an unknown degree of immunity to MAYV, so the risk of outbreak is a concern (Pilatti et al., 2018). However, human modification due to agriculture, population growth, urbanization, human migration, and deforestation might change this scenario in the future. Burkett-Cadena and Vittor (2018) showed that the association between deforestation

and mosquito-borne disease can be complex and unpredictable, with the presence of forest vectors and non-forest vectors in the same region. In a recent study, Laporta (2019) demonstrated that deforestation can increase or decrease malaria incidence depending on the amount of forest cover; for MAYV incidence the future remains uncertain. Despite their importance, temperature (assigned by variable “vapor rate”) and precipitation (assigned by variable “annual rainfall”) may not be sufficient to define the range of MAYV in our present model; this

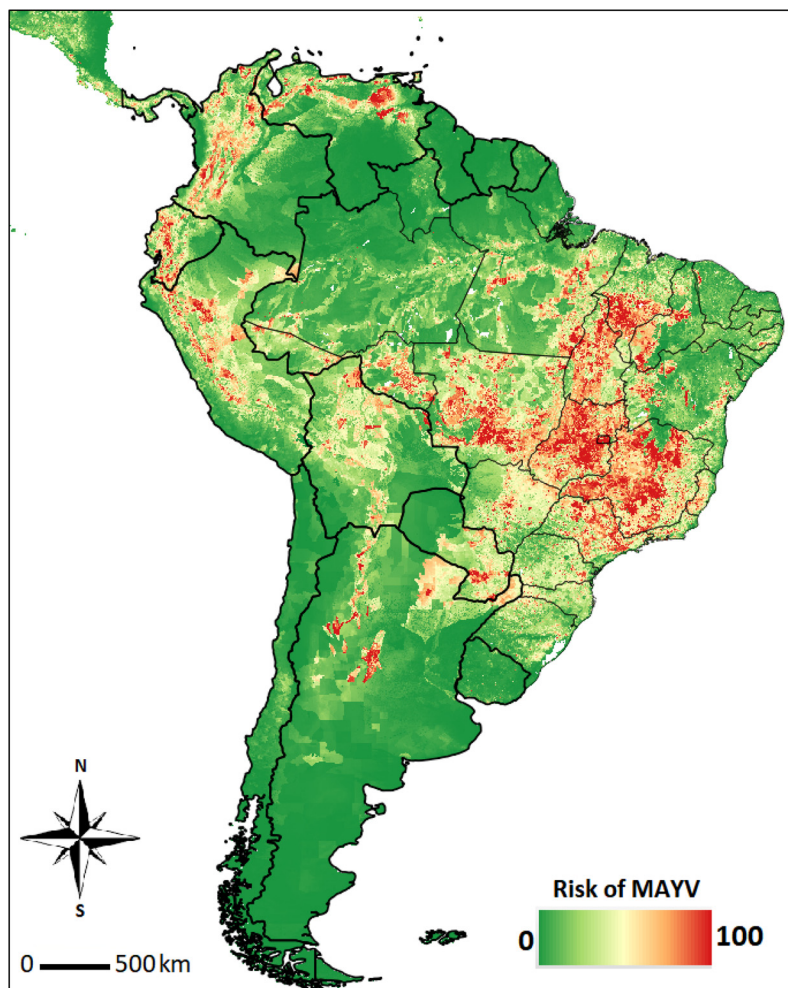


Fig. 3. Current potential risk map for MAYV in South America region based on Maxent modelling. The thick lines represent the boundaries between countries; the fine lines are the boundaries among the Brazilian states.



Fig. 4. Main biomes of South America according to the classification of World Wildlife Fund (WWF) Terrestrial Ecoregions. The circles represent the approximate location of MAYV detection in the last 20 years (modified from Center for International Earth Science Information Network – NASA). *Considering the record of MAYV in the literature up to the present date of our study.

contradicts the model proposed by Lorenz et al (2017), which showed that MAYV risk was particularly influenced by temperature. This may have happened because those authors considered only climate variables and not type of biome and population density in their model; nevertheless, the areas of MAYV distribution predicted in both studies are similar.

It is possible to note a change in the virus dispersion over the last 20 years (Fig. 4): they were previously predominantly in forests but now occupy rural areas and are increasingly urbanized. MAYV is mainly transmitted by *Haemagogus janthinomys* mosquitoes, which live in the forest canopy and spread in a sylvatic cycle predominantly in non-human primates (De Thoisy et al., 2003). Consequently, living or working in the Amazon rain forest was an important risk factor for the acquisition of MAYV infection (Azevedo et al., 2009; Izurieta et al., 2011; Batista et al., 2012). However, our findings demonstrate that living in the Cerrado today is riskier than living in the forest due to population density: another variable that contributes significantly to our modeling. This study result is consistent with the sylvatic/rural character of MAYV and its vectors so far. Studies of the feeding profile of the vector *Haemagogus* by Silva et al (2012) showed that this mosquito is very eclectic regarding its source of blood, including birds, horses, and cows. This attraction for birds is supported by findings of

Alencar et al. (2008), who also considered the abundance of hosts an important risk factor. The high positivity for cow and horse blood evident in the area of Cerrado may be related to the habit of nearby livestock farmers releasing their herds close to forest areas (Dos Santos Silva et al., 2012), facilitating the transmission of MAYV.

In view of this present rural and endemic character of MAYV disease in South America, the possibility of its urbanization is worth considering. One of the characteristic features among the alphaviruses is their ability to infect many mosquito species (Strass et al., 1995); therefore, it is conceivable that MAYV could infect other vectors and cause urban outbreaks. Experimental studies (Aitken and Anderson, 1959; Long et al., 2011) indicate that MAYV can also infect and be transmitted by *Ae. aegypti*; this highly anthropophilic urban mosquito has infested most communities in Tropical America (Tesh et al., 1999). The growth of cities near forest areas in the center-west of Brazil also demonstrate the potential for urbanization of MAYV in these localities (Pauvolid-Corrêa, et al., 2015). The expansion of *Haemagogus* mosquito populations into areas of high human population density generate potential foci for the transmission of MAYV.

According to our findings, potential distribution areas for the MAYV are located mainly in the central region of Brazil and west-coastal region of continent. In these areas the populations are probably

immunologically naïve, since the MAYV was previously restricted to the forest region. This is of particular concern due to the risk of outbreak. In addition, a study investigated febrile patients with dengue and chikungunya negative who visited rural areas near Goiânia, Goiás, Brazil, and found a high proportion of MAYV IgM (Brunini et al., 2017). These findings suggest the presence of a high prevalence of MAYV in some areas of the central region of Brazil, and laboratory investigation of the MAYV as a differential diagnosis with DENV, CHIKV and Zika virus should be considered (Brunini et al., 2017). Acosta-Ampudia et al (2018) point out that the main control measures adopted today to reduce the MAYV transmission depend on interrupting human-vector contact, such as insecticides at breeding sites and residual insecticide treatment of adult resting places. These measures are not usually very effective, since *Haemagogus* is a sylvatic vector. Immunization is the best means of prevention, but no licensed vaccine against MAYV exists yet (Acosta-Ampudia et al., 2018). According to Liang et al (2015), one of the effective strategies would be to develop, at the international level, public health measures to inform and educate citizens in local arboviral disease control measures, including monitoring and reporting. In the current scenario, MAYV infection in humans has essentially been described in rural areas, with few of these cases spreading to urban areas. Given the latest severe outbreaks of Zika, Dengue, and Chikungunya, conscientious supervision of MAYV by implementing lessons learned from previous outbreaks will increase positive public health outcomes.

Although this study has resulted in a better understanding of the current distribution of the MAYV, our study findings must be considered in the context of a number of assumptions and data limitations. Our first limitation was the supposed underreporting of MAYV cases and the difficulty in diagnosis, with a symptomatology similar to other arboviruses prevalent in South America. Mayaro fever is considered a non-fatal disease most often resulting in a mild clinical condition, and many people who become ill do not seek medical care or are incorrectly diagnosed (Pilatti et al., 2018). We also did not take into account the distribution areas of the *Haemagogus* and other possible vectors, which are crucial for the transmission, but very difficult to measure. The lack of available socioeconomic data for entire South America also made it difficult to approach other variables in our model. Like all modeling, there are also the intrinsic problems of each algorithm, such as extrapolation from a limited set of records. Even using all the data available in the literature so far, it is likely that there are much more MAYV records in South America. Despite a number of constraints to our model, it is an important first step in estimating the distribution areas for MAYV in South America and connected many local information of literature, summarizing all the relevant research that has been conducted up to the present. Continual epidemiological and entomological surveillance should be carried out to determine MAYV endemic areas and the risk of infection for human hosts, especially in areas close to regions where the virus has been detected (Acosta-Ampudia et al., 2018). We encouraged further studies regarding the MAYV using other algorithms and other set of variables to improve its distribution model.

5. Conclusions

In conclusion, MAYV probably occurs more frequently than reported in central Brazil and west-coastal region of South America. Improving public health surveillance by increasing the detection and investigation of cases of MAYV and implementing prevention and control measures are priorities. Our analyses showed that biome type and population density, represents the major constraint on the extent of MAYV expansion, because they are related to the lifecycle of the *Haemagogus* vector and spread of virus. Although MAYV is known as a sylvatic disease, there is an increasing rate of MAYV in rural areas, which represents a risk for arbovirus outbreaks and possible urbanization of the virus. Filling the current gaps in geographic distributions of MAYV is necessary to improve our understanding of the evolution and

dispersion of this emerging alphavirus in the Americas. Moreover, the results presented here will be important for the definition of public policies addressing control and prevention of the MAYV in South America.

Author contributions

C.L. and F.C.N. designed the study. C.L. were responsible for literature search and Maxent analysis. C.L., A.F.R. and F.C.N. wrote the draft. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declared that they have no competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.actatropica.2019.105093>.

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