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Present and future situation of West Nile virus in the Afro-Palaearctic pathogeographic system

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West Nile virus (WNV) is a globally widespread arthropod-borne virus that poses a significant public health concern. Mosquitoes transmit the virus in an enzootic cycle among birds, which act as reservoirs. Climate plays a crucial role in these outbreaks as mosquitoes are highly influenced by climatic conditions, and bird migrations are also affected by weather patterns. Consequently, changes in climate can potentially impact the occurrence of WNV outbreaks. We used biogeographic modelling based on machine learning algorithms and fuzzy logic to analyse and evaluate separately the risk of WNV outbreaks in two different biogeographic regions, the Afrotropical and the Western Palaearctic region. By employing fuzzy logic tools, we constructed a comprehensive risk model that integrates the Afro-Palaearctic system as a unified operational unit for WNV spread. This innovative approach recognizes the Afro-Palaearctic region as a pathogeographic system, characterized by biannual connections facilitated by billions of migratory bird reservoirs carrying the disease. Subsequently, we forecasted the effects of different climate change scenarios on the spread of WNV in the Afro-Palaearctic system for the years 2040 and 2070. Our findings revealed an increasing epidemic and epizootic risk south of the Sahara. However, the area where an upsurge in risk was forecasted the most lies within Europe, with the anticipation of risk expansion into regions presently situated beyond the virus' distribution range, including central and northern Europe. Gaining insight into the risk within the Afro-Palaearctic system is crucial for establishing coordinated and international One Health surveillance efforts. This becomes particularly relevant in the face of ongoing climate change, which disrupts the ecological equilibrium among vectors, reservoirs, and human populations. We show that the application of biogeographical tools to assess risk of infectious disease, i.e. pathogeography, is a promising approach for understanding distribution patterns of zoonotic diseases and for anticipating their future spread.

Keywords: climate change, infectious diseases, vector-borne diseases, disease ecology, one health

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Introduction

Transmission of infectious diseases is mostly conditioned by socioeconomic, ecological and climatic factors. Current climatic conditions, as well as meteorological aspects, are able to influence the risk of disease (Brugueras et al. 2020). Many prevalent human diseases, such as cardiovascular, respiratory, malnutrition and infectious diseases, are consequences of climate fluctuations (Patz et al. 2005). Anthropogenic climate change had already claimed more than 150 000 lives per year during the last 30 years of the last century (Patz et al. 2005), a figure that is expected to rise to 250 000 deaths per year during 2030–2050 (World Health Organization 2014, Karn and Sharma 2021).

The relationship between climate change and infectious diseases can also influence the periods of the transmission season, change ecological balances, as well as modify the geographical distribution of vectors, reservoirs and human populations (Lafferty 2009, Semenza and Menne 2009). In zoonotic diseases, global warming can affect the different animal components that are involved in the pathogen cycle, with climatic factors greatly influencing the risk of pathogen transmission.

West Nile virus (WNV) is a highly prevalent arthropod-borne virus of global significance (Paz 2015). This Flavivirus is primarily transmitted among birds (acting as reservoirs) through blood-feeding mosquitoes (serving as vectors) (Vogels et al. 2017). When an infected mosquito bites a mammal, the virus can deviate from its usual enzootic cycle, leading to epidemic events in humans, causing West Nile fever (WNF) episodes, or epizootic events in non-human mammals (Hubálek 2000). These epidemic and epizootic events may be driven by the same processes (García-Carrasco et al. 2023a). Since its initial detection in Uganda in 1937 (Smithburn et al. 1940), the virus was extensively detected across the African continent (Chauhan et al. 2020, García-Carrasco et al. 2022, 2023b), entering Europe through migratory bird populations (Calistri et al. 2010, Burki 2018). Presently, the virus has a widespread presence in the Americas (Komar 2003, Komar and Clark 2006), West Asia (Eybpoosh et al. 2019), and Oceania (Frost et al. 2012).

Arthropod-borne viruses, such as WNV, are particularly sensitive to climate as these vectors are cold-blooded (Semenza and Menne 2009). The typical seasonal nature of WNV incidence in Europe is linked to the ecology of the vectors (Zeller and Schuffenecker 2004, Parker et al. 2011). However, not only are mosquitoes particularly sensitive to climate conditions, but also birds and the virus itself (McMichael and Lindgren 2011). The abundance of birds, the type of migration (short – inside a biogeographic region – or long-distance movements – reaching a different biogeographic region) is mainly influenced by the search for better climatic conditions (Herrera 1978, Newton 2010). Therefore, providing input about how climate change could condition the incidence of this disease is useful to take concerted action focused on addressing public health issues.

Understanding the potential influence of climate change on the incidence of the WNV is crucial for taking coordinated action and addressing public health challenges. Our objective is to provide an intercontinental perspective on the current status of the disease in the Afro-Palaearctic system, comprised of two biogeographic regions: the Afrotropical (Sub-Saharan Africa) and the Western Palaearctic region (Europe up to the Urals Mountains, and northern Africa). These two biogeographic regions are inherently interconnected through the migratory patterns of birds, the primary reservoirs of the virus. By examining the environmental, anthropic, and biological factors contributing to disease transmission in different regions, we employ the emerging field of pathogeography (Murray et al. 2018). Through mapping present and future disease patterns and identifying potential risk factors, our study aims to inform public health policies and interventions that can effectively prevent and control the spread of this infectious disease.

Methodology

Study area and data collection

The study area consisted of the Afro-Palaearctic system, made up of the Western Palaearctic, which comprises Europe, the northern and central part of Arabia, and North Africa; and the Afrotropical region, i.e. sub-Saharan Africa. This includes African, European, Caucasian and Middle East countries (Supporting information). Africa and Europe have been considered together for the first time as a pathogeographic unit for the study of the disease since the Afro-Palaearctic migration system comprises billions of birds travelling between Europe and Africa twice each year (Hahn et al. 2009, García-Carrasco et al. 2023c), forming strong links between the two continents and acting as transport vehicles for diseases and parasites.

We first created a database for all recorded WNV outbreaks in Europe and Africa, which we considered spillover events, i.e. reports of pathogen transmission from the enzootic cycle to mammals (humans and not humans, mainly equines given the ease of detection of the virus in these species). This database was built using GIDEON (2021). In it we selected 'West Nile Fever' as the target disease, and every African and European country chosen for literature search. We complemented the articles and reports hosted in GIDEON, with papers found using an electronic literature search in Web of Science (https://clarivate.com/webof-sciencegroup/solutions/web-of-science), Scopus (https://www.scopus.com), and Google Scholar (https://scholar.google.com) for all countries. We used the following search terms: 'West Nile virus', 'West Nile fever', 'WNV', 'WNF', together with the name of each African country. Moreover, for Europe, we obtained epidemiological data from the European Centre for Disease Control and Prevention (ECDC 2022). Despite the scarcity of information available on WNV in Africa, we compiled all available data from articles and reports on spillover events in

human and non-human mammals from 1937 (when WNV was first described) to 2020. With the aim of gathering comprehensive information regarding WNV cases, we have included spillovers to humans as well as spillovers to non-human species. This enables us to obtain data from regions where only veterinary information is available, rather than medical data. Additionally, considering that the enzootic cycle of WNV may be influenced by similar factors (García-Carrasco et al. 2023a), consolidating information from various components involved provides a more integrated and realistic perspective (García-Carrasco et al. 2022).

Location data were available as geographic coordinates, others at city level, and others at administrative unit level such as the Nomenclature of Territorial Units for Statistics (NUTS) provided by the ECDC (European Commission 2003). To standardise reporting, all disease incidences were transformed to NUTS for Europe, and to similar administrative units for Africa and Western Asia. We projected the administrative units with WNV presences into an equal-sized hexagonal grid of 7742 km². The hexagonal grid was created using Discrete Global Grids for R (Barnes and Sahr 2017), and constituted our system of operational geographic units (OGUs). Thus, the study area was divided into 6338 OGUs (3035 in the Western Palaearctic and 3033 in the Afrotropical region). Using OGUs has several advantages. They gather environmental information from the environment. OGUs with disease cases (regardless of the number of records) are assigned a value of 1, and 0 when there are none. Using binary values helps reduce the excessive influence of over-sampled areas (Europe) compared to under-sampled areas (Africa), thus mitigating spatial autocorrelation. In this way, all presences of WNV cases are contained in units of the same size in the Afro-Palaearctic context.

Selection of variables

We used a set of variables hypothesized to influence the spillover events. Variables were grouped into three factors: anthropic, ecosystemic, and climatic (Supporting information). Anthropic factors included human related variables such as population density or human infrastructures. These variables can influence human exposure to mosquitoes or anthropogenic alterations of the environment that could lead to spillovers into populations (Rochlin et al. 2011, García-Carrasco et al. 2022). Ecosystemic variables included wetlands of international importance (Ramsar sites) known for hosting migratory birds, which can serve as competent reservoirs for WNV (García-Carrasco et al. 2023c) and various land-use patterns that may influence interactions between mosquito, wildlife, and humans (Kilpatrick 2011). Finally, climatic variables comprised temperature and precipitation characteristics, which are key factors on mosquitoes' distribution and WNV outbreaks (Brugueras et al. 2020). We used climatic variables to assess possible future changes in the distribution of disease outbreaks, according to climate projections obtained from the Coupled Model Intercomparison Project Phase 6 (CMIP6) (IPCC 2022a, b). Climatic variables were

obtained from the CHELSA database (Karger et al. 2021) and for future projections we tested two horizons: 2040 and 2070. We used two Global Circulation Models (GCM): GFDL-ESM4 (from National Oceanic and Atmospheric Administration, Geophysical Fluid Dynamics Laboratory) and MPI-ESM1-2-HR (from Max Planck Institute for Meteorology). We used three shared socioeconomic pathway (SSP) scenarios according to different socioeconomic models. SSP1.26, which assumes taking a 'green road' with a low fossil fuel dependence; SSP3.70, where regional rivalry sidelines international priority for environmental problems; and SSP5.85, the most pessimistic scenario, that assumes a high fossil-fuel reliance and high economic growth (Riahi et al. 2017). For each OGU, we computed the mean value for each explanatory variable using the 'Zonal statistics as table' tool within the ArcGIS Desktop 10.8.2 software (ESRI, https://www.esri.com).

Risk modelling

For the elaboration of the models, we used a multivariate stepwise logistic regression, a supervised machine-learning algorithm where the predictive power of each variable (Supporting information) was assessed according to the significance of the score test. Before applying the logistic regression, we used a number of filters to determine the initial pull of variables (Supporting information). We reduced the multicollinearity of the variables by calculating the Spearman correlation coefficients. When two variables, belonging to the same factor, showed a correlation >0.8, we retained the one with highest individual predictive power. To test the true value of a variable with respect to the total model we use the Wald test. With the variables included in the final model, we re-evaluated the effect of multicollinearity by calculating the variance inflation factor (VIF) and ensured that it did not exceed values of VIF > 5 (Zuur et al. 2010). Moreover, we checked the unimodal response of variables to the distribution of the disease. For this purpose, we built binary stepwise logistic regression models for each of the predictor variables separately, using the original form (X) and the quadratic form (X²). We considered that a certain variable presented a unimodal response when the best logistic regression model included the original form in positive and the quadratic in negative form (X–X²), as this was the only biologically plausible unimodal response. Once we identified the predictor variables with unimodal response and multicollinearity, we compensated for the type I error due to multiple tests using the false discovery rate (FDR) (Benjamini and Hochberg 1995). Only variables with an FDR value <0.05 were selected for the logistic regression (Rao 1948).

According to the anthropic, ecosystemic and climatic characteristics of every OGU, the multivariate stepwise logistic regression assigned to it a probability value for the occurrence of a WNV outbreak. The process starts with a null model, with no predictor variables. The null model outputs a constant probability of outbreaks at each OGU. This value is the proportion of OGUs with disease occurrence in the

whole study area. Then, variables are added, and are maintained in the equation if the addition results in a significantly improved regression (Hosmer et al. 2013). Finally, we used the favourability function to transform probability values (P), resulting from the logistic regression, into favourability values (F) (Real et al. 2006):

$$F(OGU) = \left(P(OGU)/\left(1 - P(OGU)\right)\right)/$$
$$\left(\left(n_1/n_0\right) + \left(P(OGU)/\left(1 - P(OGU)\right)\right)\right)$$

where n_1 is the number of OGUs where WNF cases were reported and n_0 is the number of OGUs where n_0 WNF cases were reported in the data set, respectively. For the modelling process, we consider all OGUs with disease cases from 1937 to 2020 as presences, and the remaining ones, which did not show any cases during that period, as absences. In this way, favourability is based on the effect of the environment on the probability of outbreaks to occur, while discounting the effect of proportion of OGUs with disease occurrence on that probability. Favourability values range from 0 to 1, where a favourability of 0.5 indicates that the local probability of an outbreak is the same as the proportion of OGUs with disease occurrence in the study area. Therefore, favourability values serve as a measure of risk, representing the degree to which environmental conditions at an OGU favour the occurrence of an WNV outbreak. The statistical analyses of logistic regression, Spearman's correlation and FDR were performed using the Statistical package for the social sciences (IBM SPSS Statistics ver. 28.0.1.1). The multivariate stepwise logistic regression models were elaborated using the SPSS software (script in the Supporting information).

Fuzzy logic is a form of multi-valued logic that allows for several values of truth. Fuzzy logic and its applications have their origin in the theory of fuzzy sets proposed by Zadeh (1965), which are characterized by a membership function that assigns to each object a degree of membership in each set ranging from zero to one. The favourability function is the membership function in the fuzzy set of OGUs with favourable conditions for the occurrence of WNF. Fuzzy logic has been used to detect favourable areas for species (Real et al. 2008), and to assess the impact of climate change on species' distributions (Real et al. 2010) and for the study of zoonotic diseases (Olivero et al. 2017, Aliaga-Samanez et al. 2021) including WNV (García-Carrasco et al. 2021, 2023a).

We performed this modelling procedure for the entire Afro-Palaearctic region, which we called it the Integrated Model, and also for the Western Palaearctic and the Afrotropical region separately. In this manner we worked with two different areas, which despite forming a connected set, are geographically separated with regards to the disease: spatially separated by the Sahara Desert, and temporally separated by the phenology of bird migrations and outbreak seasonality. Subsequently, the Western Palaearctic and the Afrotropical models were combined into a single cartographic risk model using fuzzy logic. One of the advantages of working with

favourability values rather than probabilities is that they are commensurable, enabling the comparison and integration of different models (Real et al. 2006). This allows for the combination of the Palaearctic and Afrotropical models. This combination is achieved by considering the maximum favourability values (fuzzy union) (Barbosa and Real 2012). Considering the maximum values for the Palaearctic and Afrotropical models:

$$F_{Afrotropical} \cup F_{Palaearctic}(OGU) =$$
$$\max\left(F_{Afrotropical}(OGU), F_{Palaearctic}(OGU)\right)$$

where $\cup$ is the fuzzy union, i.e. the maximum value between favourability values; allows representing the risk zones for the Palaearctic model or for the Afrotropical model, which results in a final distribution of risk across the entire Afro-Palaearctic area. We call this model the Combined model.

Model evaluation

We evaluated the models on the basis of their discrimination and classification capacity. We calculated the area under the receiver operating characteristics curve (or AUC) to evaluate the discrimination capacity (Lobo et al. 2008). On the other hand, classification ability was quantified using several different indices: sensitivity (i.e. the proportion of correctly classified presences), specificity (i.e. the proportion of correctly classified absences), over-prediction (i.e. the proportion of favourable OGUs that coincide with absences), under-prediction (i.e. the proportion of unfavourable OGUs that coincide with presences) (Barbosa et al. 2013), correct classification rate (CCR, that is the proportion of correctly classified presences and absences), Cohen's Kappa coefficient (which takes into account the possibility of random correct classifications) (Fielding and Bell 1997), and true skill statistics (similar to Kappa, but independent of proportion of OGUs with disease occurrence) (Allouche et al. 2006). The 0.5-favourability value was used as a threshold for correct classification, as it defines the point at which the probability due to the explanatory factors is higher than the proportion of OGUs with disease occurrence in the study area. We assessed the calibration of the model using the Hosmer–Lemeshow test (Hosmer and Lemeshow 1980), where non-significant values ($p > 0.05$) indicated a good fit between the predicted and observed probabilities. The probabilities of the model were divided into range 10 bins of equal rank.

Variation partitioning

In order to facilitate the explanation of the current and predicted distributions of spillover events we have grouped the variables considering climate on the one hand, and non-climatic variables (anthropic and ecosystemic), on the other. To take into account the pure and shared effect of climate from the effect of non-climatic factors we used a variance

partitioning analysis (Legendre 1993, Barbosa et al. 2001, Muñoz et al. 2005). The part of the variation accounted for by each factor in the final model, both individually and in combination with the other factor (in this case non-climatic variables grouped into a single factor) was obtained by calculating the square value of the Pearson correlation coefficient between the final model's values and those of a model based solely on that factor. To determine the pure contribution of each factor, we subtracted the variance explained by all other factors from the variance explained by the overall explanatory model. The overlaid effect of two factors was obtained by subtracting the pure effects of each factor from their combined effect (Muñoz et al. 2005). The pure effect of climate together with the overlaid effect of non-climatic factor was called apparent climate effect. In this way, we quantified how much of the variation in favourability was explained by the pure effect of climate, how much was explained by the pure effect of non-climatic variables, and how much was indistinguishably explained by climate and by other factors (i.e. the shared effect or intersection). To reduce the possible over- or under-prediction of the models once they were projected into the future, we used the correction factor (ρ), which was calculated dividing the pure effect of climate by the whole (i.e. pure + shared = apparent) effect of climate, following Real et al. (2013). This analysis was performed for both the Western Palaearctic and the Afrotropical region.

Future projections

To assess the climatic conditions with its inherent variability, it is customary to consider a 30-year average of weather conditions, i.e. the climate normal (Guttman 1989). Thus, the effects of climate on the onset of the WNF at a specific time must be calculated over the previous climate normal. We projected the models into two horizons: 2040 and 2070. For the year 2040, we considered the climate normal of 2011–2040, and for the year 2070 the climate normal of 2041–2070 (Karger et al. 2021). For each period, we generated six projections, resulting from all possible combinations between the two GCMs and the three SSPs scenarios considered (variables selection section above). Future favourability values were calculated by replacing the current climatic values (2010) in the favourability models with those expecting according to each GCM and SSP for those expected in 2040 and 2070.

Assessment of uncertainty

Our aim was that the forecasted impact of climate change on the risk of the disease would be informative for policy planning. This implies a balance between producing unambiguous forecasts and managing the inherent uncertainty of the scientific endeavour. We evaluated different types of uncertainties in our distribution models.

First, we assessed the uncertainty in whether the disease is expected to occur or not at every OGU, implicit in the favourability values used to evaluate the risk. Favourability

entails a measure of uncertainty regarding the risk of disease occurrence. High favourability values (close to 1) and low favourability values (close to 0) imply less uncertainty regarding the associated risk. Values near 0.5 imply high local uncertainty, as the local environmental conditions are neither favourable nor unfavourable for the occurrence of the disease. Thus, the risk maps represent both the risk level and the uncertainty associated to those risks.

Second, entropy is a characteristic of the geographical distribution of species and therefore also of pathogens and cases of diseases caused by them. A distribution with higher entropy implies greater uncertainty, as the environment less restrictively limits its spread across the territory (Estrada and Real 2021). In this sense, the entropy of the disease distribution is an indicator of the overall uncertainty regarding the occurrence of disease. For different models and future projections, we have calculated the entropy of their distribution using fuzzy entropy as a measure (Kosko 1986). Working with favourability values allows the calculation of the fuzzy entropy (R), which is defined as:

$$R = \frac{c\left(F \cap F^c\right)}{c\left(F \cup F^c\right)}$$

where c(x) represents the summation of x across all the OGUs, F is the favourability value in an OGU, F^c is the complement of F, that is $(1 - F)$, $\cup$ is the sign of fuzzy union (the maximum value) of favourability and its complement, and $\cap$ is the sign of fuzzy intersection (the minimum value) of favourability and its complement. Fuzzy entropy values range from 0 to 1. If fuzzy entropy is one, the distribution of the risk is completely disordered, i.e. favourability is equally distributed in the entire Afro-Palaearctic with $F = 0.5$. The smaller the fuzzy entropy, the more orderly the distribution of risk, with areas clearly at risk and clearly not at risk, and lower the uncertainty of it.

Third, we assessed the uncertainty associated with the different GCMs and SSPs, through the calculation of the consistency of circulation models and the coincidence of socioeconomic pathways (Real et al. 2010). Consistence is defined as the agreement between predictions for a given SSP scenario applying two different GCMs, while coincidence is defined as concurrence between predictions according to two SSP scenarios for a given GCM. We calculated consistence and coincidence using the mathematical formulation proposed Real et al. (2010). We chose the GCM that showed the highest coincidence for each pair of SSP scenarios, and the SSP scenario that showed the highest consistence for both GCMs in the period 2040 since uncertainty would be lower in a nearer period. For the period 2070 we kept the same GCM and SSP-scenario.

Finally, to determine whether the area at risk of WNV transmission in the Afro-Palaearctic region could expand or contract according to our projections, we calculated the Increment in favourability according to Real et al. (2010).

Results

Model evaluation

The evaluation of the models for the Western Palaearctic and the Afrotropical regions showed high sensitivity (0.843 and 0.778, respectively) and high specificity (0.727 and 0.676, respectively). Both models also discriminated efficiently between presence and absence of WNV outbreaks (AUC = 0.854 and 0.813, respectively) (Table 1). The Combined model showed higher classification and discrimination abilities compared to the Integrated model (Table 1). In addition, the Combined model had lower under-prediction than the Integrated model. This finding is particularly relevant when dealing with diseases, especially in Africa, where the actual prevalence is generally underestimated. The Hosmer and Lemeshow calibration test also provided support for the Combined model. The differences between expected and predicted values were not significant (p > 0.05) in the Afrotropical region and significant (p = 0.004) in the Western Palaearctic region. When analysed separately, both regions also showed better calibration than the Integrated model (p = 0.000038) (Supporting information). Therefore, we ultimately decided to use the Combined model (Fig. 1A). All variables included in the Western Palaearctic and Afrotropical model exhibited VIF values below 5, signifying minimal correlation among the independent variables (Supporting information).

Current situation of West Nile virus in the Afro-Palaearctic pathogeographic system

The WNV model indicated that high-risk areas were found in parts of the Mediterranean basin, specifically in countries such as Spain, Italy and Greece; the area around the Black Sea; and North African countries such as Morocco, Tunisia and Egypt. In the Afrotropical region, the risk of outbreaks was highest in East Africa, followed by South Africa and West Africa (Fig. 1A).

The risk model of WNV outbreaks in the Western Palaearctic included 15 predictors, of which 4 were anthropic,

9 ecosystemic, and 2 climatic variables (Table 2). The most important explanatory climatic variable in the risk model, showing the highest Wald value, was the maximum temperature of the warmest month (Wald = 60.75). In the Afrotropical region, the outbreak risk model was explained by 9 anthropic variables, 9 ecosystem variables, and 4 climatic variables. In this region, the climatic variable with the greatest explanatory weight was the precipitation seasonality (Wald = 67.04). Livestock and irrigated croplands were good predictors of outbreaks in both continents. Temperature annual range was also a good predictor. However, a high range seems to favour the occurrence of outbreaks in the Western Palaearctic, but to unfavour it in the Afrotropical region.

According to the variation partitioning analysis for the Western Palaearctic, the pure effect of climate explained 8.96% of the total variation in favourability and the combination of climate and non-climatic factors (apparent effect) explained a 64.14% of the total variation (Fig. 1A). Instead, in the Afrotropical region, the pure effect of climate explained 11.78% of the total variation in favourability whereas the apparent effect of climate explained 28.59% of the total variation (Fig. 1A).

Future situation of West Nile virus in the Afro-Palaearctic pathogeographic system

Assessment of uncertainty

The fuzzy entropy of the risk distribution at present was relatively low, with an entropy value of R = 0.315. Regarding the projections in different global circulation models, the GFDL model, on average, had slightly lower entropy (R = 0.295) than the MPI model (R = 0.3). Values of fuzzy entropy for the different future projections are shown in the Supporting information.

The coincidence values showed small differences across various shared socioeconomic pathways, and similarly, consistency values remained highly consistent when different Global circulation models were employed. Nevertheless, the coincidence values exceeded those of the consistencies. The discrepancies in consistency and coincidence are small

Table 1. Classification and discrimination indexes for each of the models made. CCR = correct classification rate; AUC = area under curve; TSS = true skill statistics.

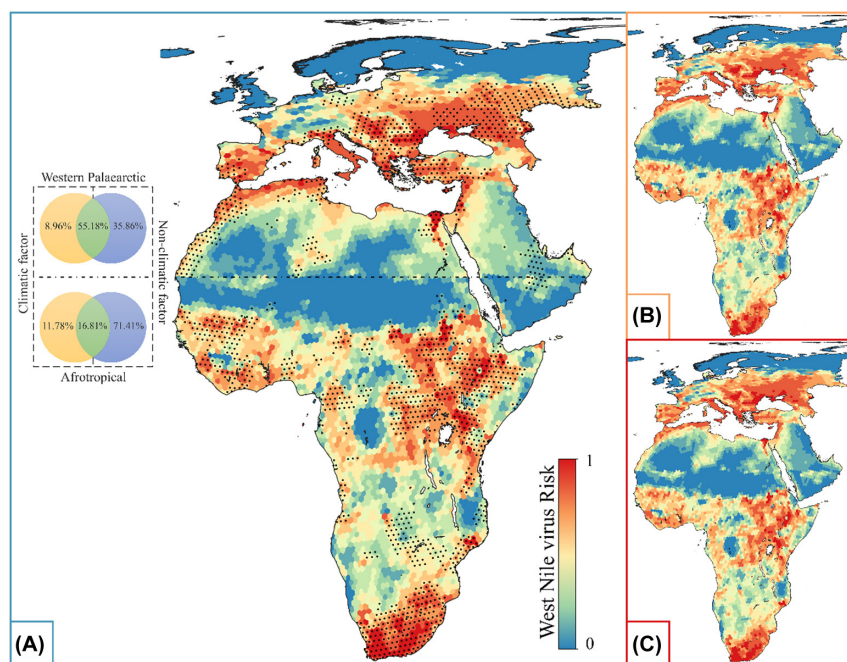|	Western Palaearctic model	Afrotropical model	Combined model	Integrated model
Classification				
Sensitivity	0.843	0.778	0.806	0.792
Specificity	0.727	0.676	0.701	0.627
CCR	0.754	0.706	0.729	0.670
Overprediction	0.514	0.507	0.510	0.569
Infraprediction	0.062	0.117	0.090	0.105
Kappa	0.455	0.388	0.420	0.330
TSS	0.570	0.455	0.507	0.419
Discrimination				
AUC	0.854	0.813	0.833	0.788

Figure 1. West Nile virus risk model (A) and projection for the year 2040 (B) and 2070 (C) in the Afro-Palaearctic system. Yellow areas indicate intermediate risk, and thus higher uncertainty in whether the disease is expected or not to occur, whereas red and blue areas represent higher and lower risk, respectively. Black dots in (A) correspond to WNV cases in the study area. The future models represented in this figure correspond to those that presented the greatest coincidence and consistence (GFDL-ESM4 SSP 3.70) in the year 2040. Venn diagrams in (A) show the variance partitioning analyses performed for the Western Palaearctic (up) and Afrotropical (down) models, respectively. The values shown in the diagrams are the percentages of variation explained exclusively by the climatic factor (yellow), by the non-climatic factor (blue), and by the intersection of these two factors (green). The figure shows the apparent effect of climate (yellow + green). The changes in infection risk for 2040 and 2070 relative to the present can be observed in Fig. 2.

because the variations in the values of the CHELSA climate variables between different SSPs and GCMs are small for the period 2011–2040. Among all model projections to assess the risk of future WNV transmission, considering all possible GCM-SSP combinations, the one with the highest consistence and coincidence combined the GFDL-ESM4 GCM with the SSP3.70 scenario (Supporting information).

Our study revealed that, in the year 2040 and 2070, the risk of WNV transmission in the Western Palaearctic region would increase in Europe compared to the model for the present, whereas it is expected to decrease in much of North Africa and the Near East. In the Afrotropical region, a slight upsurge in risk was observed in areas that have a high favourability in the present time (e.g. in East, South and West Africa). Details of the other cartographic models, categorized by circulation models (GFDL-ESM4 and MPI-ESM1-2-HR) and scenarios (SSP1.26, 3.70 and 5.85), can be seen in the Supporting information.

Degree of increment of the risk

The Western Palaearctic region is expected to experience more pronounced changes in the risk of outbreaks than the Afrotropical region (Fig. 2). In sub-Saharan Africa, countries in the Afrotropical region are predicted to have a slight increase in risk, with a notable rise in coastal areas of Nigeria and Cameroon, as well as in countries such as Mali,

Mauritania, Botswana, Namibia and South Africa. In the year 2040 (Fig. 2A), the risk will increase by 0.98%, and in the distant future (Fig. 2B), by 3.60%. On the other hand, in North Africa, the risk is projected to significantly decrease in the Sahara area and slightly increase along the Mediterranean coast. In the entire northern Africa region, it will decrease by 14.14% and 20.54% in the year 2040 and 2070, respectively. The most significant shifts in the risk of WNV infection are predicted to occur in central European countries. A notable increase is expected to occur in France, Germany, Austria, Switzerland, Poland, Czech Republic and Slovakia. In Europe, the risk will increase by 6.34% in the short term and by 8.38% in the long term (Fig. 2).

When we consider only the pure climatic effect, the increase and decrease of risk is not as marked, as the pure climate effect is 8.96% in the Palaearctic model and 11.78% in the Afrotropical model (Fig. 1A). Thus, for Europe, the increase in risk in the year 2040 future would be 0.89% and for the period 2070 1.18%. For Africa, the decrease in risk would be 0.19% in the year 2040 and an increase of 0.21% in the year 2070 (Supporting information).

Discussion

The Western Palaearctic and the Afrotropical regions are two geographic areas within the same pathogeographic system,

Table 2. Explanatory variables that are part of the models along with their slope (B), standard error of the slope, Wald statistics and significance (P), for the Western Palaearctic and Afrotropical model. Variables with unimodal response are highlighted in bold. Source of the variables can be seen in the Supporting information.

Variable	Western Palaearctic				Afrotropical			
	B	Standard Error	Wald	P	B	Standard error	Wald	P
Climatic								
Maximum temperature of warmest month	**0.525**	**0.067**	**60.75**	**6.480×10^{-15}**	0.004	0.002	6.371	0.012
Temperature annual range	**0.641**	**0.224**	**8.206**	**0.004**	−0.819	**0.177**	**21.293**	**3.941×10^{-06}**
Annual precipitation	–	–	–	–	**0.542**	**0.128**	**17.973**	**2.241×10^{-05}**
Precipitation seasonality	–	–	–	–	−0.002	2.15×10^{-04}	67.044	2.656×10^{-16}
Ecosystemic								
Distance to RAMSAR sites	−0.182	0.034	29.446	5.749×10^{-08}	–	–	–	–
Open needleleaved evergreen forest	−20.127	7.743	6.756	0.009	15.561	3.918	15.772	7.147×10^{-05}
Closed to open shrubland	**−0.926**	**0.201**	**21.147**	**4.255×10^{-06}**	–	–	–	–
River distance	1.039×10^{-06}	4.229×10^{-06}	6.031	0.014	–	–	–	–
Closed to open mixed broadleaved and needleleaved forest	−3.915	1.445	7.345	0.007	–	–	–	–
Closed needleleaved evergreen forest	**0.714**	**0.260**	**7.514**	**0.006**	–	–	–	–
Mosaic forest/shrubland	−5.173	3.242	2.546	0.111	**0.935**	**0.118**	**62.76**	**2.335×10^{-15}**
Closed to open grassland	−22.804	6.861	11.046	8.886×10^{-04}	–	–	–	–
Closed to open vegetation on regularly flooded soil	3.649	2.041	3.196	0.074	2.6	1.259	4.265	0.039
Bare areas	–	–	–	–	−1.518	0.344	19.459	1.028×10^{-05}
Open broadleaved deciduous forest	–	–	–	–	**0.466**	**0.111**	**17.602**	**2.723×10^{-05}**
Slope	–	–	–	–	**0.348**	**0.175**	**3.972**	**0.046**
Sparse vegetation	–	–	–	–	2.906	0.527	30.428	3.465×10^{-08}
Closed to open broadleaved evergreen and/or semi-decidous forest	–	–	–	–	0.954	0.262	13.222	2.767×10^{-04}
Closed broadleaved forest regularly flooded	–	–	–	–	−6.82	1.5	20.66	5.484×10^{-06}
Anthropic								
Mosaic cropland	**0.661**	**0.072**	**83.491**	**6.400×10^{-20}**	–	–	–	–
Goat density	**0.373**	**0.120**	**9.578**	**1.970×10^{-03}**	–	–	–	–
Horse density	–	–	–	–	**0.659**	**0.123**	**28.595**	**8.921×10^{-08}**
Sheep density	–	–	–	–	**0.579**	**0.119**	**23.522**	**1.235×10^{-06}**
Distance to population centers	–	–	–	–	9.925×10^{-06}	2×10^{-06}	23.056	1.574×10^{-06}
Post-flooding or irrigated croplands	**0.424**	**0.139**	**9.323**	**2.264×10^{-03}**	10.066	3.695	7.421	0.006
Distance to highways	$−9.344 \times 10^{-06}$	2×10^{-06}	14.957	1.100×10^{-04}	$−1.278 \times 10^{-05}$	3×10^{-06}	15.397	8.713×10^{-05}
% of irrigation areas	–	–	–	–	**0.549**	**0.115**	**22.875**	**1.729×10^{-06}**
Distance to railway	–	–	–	–	$−2.910 \times 10^{-06}$	3.667×10^{-07}	62.956	2.114×10^{-15}
Mosaic vegetation/cropland	–	–	–	–	**0.391**	**0.096**	**16.469**	**4.945×10^{-05}**
Population density	–	–	–	–	**−0.743**	**0.198**	**14.126**	**1.709×10^{-04}**

each with their own distinct features and characteristics in terms of outbreak seasonality, disease surveillance, and socioeconomic pressure. Because of this it is essential to address them separately and to work within their respective contexts. This becomes evident in the assessments of the different models (classification, discrimination and calibration), with the best models being those that were developed specifically for each biogeographic region, the Combined model (Table 1). However, despite their unique differences, both regions are part of a single pathogeographic unit since billions of birds i.e. potential disease reservoirs continuously connect them, thus shaping the distribution of the disease across both continents. Therefore, a more integrated and intercontinental perspective of outbreaks can be obtained by addressing them jointly. In this study, we present the first intercontinental approach to the study of this disease, both in the present and in the future. At a local scale, the virus may be present and circulating endemically, without the need for the introduction of reservoirs carrying the pathogen. Consequently, outbreaks of the disease might be controlled at this resolution. However, long-distance migratory birds can connect areas with different levels of disease risk, with some of them acting as source zones and others as sink zones for birds carrying the pathogen, thereby impacting differently remotely interconnected areas. Our models included both climatic and non-climatic variables, but other drivers such as mosquitoes and bird distributions have not been considered. This is because, at this large geographic scale, it is difficult to study these elements at microscale levels with different species of vectors and reservoirs amplifying the virus at different localities. Furthermore, mosquitoes of the *Culex* genus, the primary vectors of WNV, are widely distributed species that cover the entire study area with few limitations (Ciota and Kramer 2013, and the Supporting information of García-Carrasco et al. 2023c). On the other hand, it is difficult to assess and quantify future changes in non-climatic variables such as land cover or anthropic variables. However, the pure contribution of climate provides information on the increase in risk based solely on changes in this factor (Supporting information). Social variables, such as those related to the healthcare system or mosquito control efforts, could be of interest for inclusion in the models. However, their unavailability throughout the entire study area has hindered their use.

Current situation of West Nile virus in the Afro-Palaearctic pathogeographic system

The European peninsulas located in the Mediterranean basin, Iberia, Italy and the Balkans, are prominent areas at risk of WNV infection. These areas have experienced numerous outbreaks of the disease throughout history, with the largest outbreak in the Iberian Peninsula occurring recently in 2020 (García San Miguel Rodríguez-Alarcón et al. 2021). Previous studies have highlighted the significance of the main river basins as high-risk areas for the virus (Cuervo et al. 2022). Our Western Palaearctic-scale model has also highlighted the course of the main river basins in the Iberian Peninsula as high-risk areas (Fig. 1A). In the Italian Peninsula, the annual incidence rate of WNV infection has increased over the last decade, with cases mainly clustered in northern Italy, particularly in the Po River Basin (Riccò et al. 2021), which our model also identifies as a high-risk area. The Balkans likewise present high-risk areas, with several WNV outbreaks occurring in recent decades, including the largest outbreak in Greece in 2018 (Pervanidou et al. 2020). Eastern Europe is also an area historically associated with large WNV outbreaks (Napp et al. 2018), including areas such as Romania (Zeller and Schuffenecker 2004), Ukraine (Yushchenko et al.
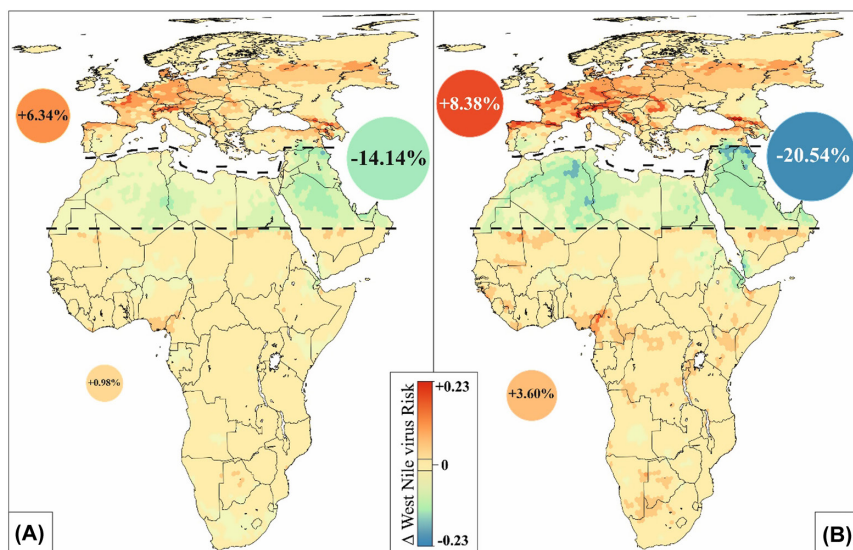

Figure 2. Increased risk of West Nile virus transmission in the year 2040 (A) and in 2070 (B). The coloured circles indicate the increase (warm colours) and decrease (cool colours) of risk in the total area of Europe, North Africa and sub-Saharan Africa, from top to bottom, respectively.

2020) and southern Russia (Hubálek and Halouzka 1999, Malkhazova et al. 2020). These regions have consistently been identified as high-risk areas by various models in the Western Palaearctic (Tran et al. 2014, Semenza et al. 2016). According to our model, the eastern region constitutes one of the largest regions with a high risk for WNV infection in the Afro-Palaearctic, making it a significant WNV risk area at present.

In Africa, the area associated with the Mediterranean basin as well as the entire Nile Delta is a high risk for the development and spread of WNV, as shown by data and outbreaks in recent years (García-Carrasco et al. 2022). As we move deeper into the Sahara Desert the risk decreases significantly, mainly due to extreme temperatures and low rainfall, which hinder the development of mosquitoes (Paz 2019). Only water points in desert areas, i.e. oases, would be at risk of transmission according to both the present model and reported cases (Ayadi et al. 2017, Benbetka et al. 2018, García-Carrasco et al. 2022). However, in the Near East, the risk of WNV transmission depends on the area. On the other hand, countries in the Near Eastern region that are located near the Mediterranean Sea, such as Palestine, Israel, Lebanon and Syria, are particularly notable for their high favourability. This area constitutes a major stopover for migrating birds (Frumkin et al. 1995, Paz 2006), specifically those arriving in or leaving Europe via the eastern migratory route (Briedis et al. 2020), mostly soaring birds (Malkinson et al. 2002, Phipps et al. 2019). Unlike in Europe, where there is a lot of data and monitoring of the disease during seasonal outbreaks, in Africa (especially in the Afrotropical region) the information is very limited (García-Carrasco et al. 2023b). Despite being present in Africa for decades, WNV remains one of the least studied mosquito-borne viruses in the region (Sule et al. 2018). Little is known about its geographic distribution, the rate of infection in humans and animals, and the true impact on public health. Furthermore, many cases of infection can go unnoticed or be misdiagnosed due to the lack of specific diagnostic tests and poor surveillance (Sejvar and Campbell 2006, Mencattelli et al. 2022, Bekele et al. 2023). Thus, caution must be exercised in interpreting the results for this region. Nevertheless, the model highlights areas of high risk, particularly in areas with a historical occurrence of outbreaks, such as in South Africa (Weinbren 1955, Jupp 2001, Venter and Swanepoel 2010) or in countries surrounding Lake Victoria (Henderson et al. 1970, Mease et al. 2011, Sutherland et al. 2011, Sule et al. 2018, Nyaruaba et al. 2019). These areas are linked to water sources and comprise countries along the Great Lakes region such as Uganda, Kenya, Burundi, Tanzania, and the Democratic Republic of Congo; and river basins such as the Nile River, Niger River, Congo River, Zambezi River, Orange River, Limpopo River, and Senegal River. They are also areas associated with tropical (East and West Africa) and temperate (South Africa) environments. In this case, climate and water availability favour the concentration of birds and, therefore, are hot spots for WNV transmission (Paz 2015, Kraemer et al. 2015). Furthermore, the models highlight areas with no outbreaks so far, but

would require special attention, such as northern Libya, the western part of South Africa and Tanzania. It is precisely in these areas highlighted by the model, with no reported cases, where prevention efforts should be most intense, as cases may be occurring but are not being identified due to the ambiguous symptoms associated with the virus being attributed to other illnesses (Eybpoosh et al. 2019). The model has a low under-prediction rate (0.117) and a suitable over-prediction (0.510). A high over-prediction is not usually adequate in distribution modelling. However, when the modelled entity is an infectious disease whose presence is underestimated in certain areas, this indicator could be pointing to the existence of potential risk in underreported locations (Aliaga-Samanez et al. 2021, García-Carrasco et al. 2023b). The aforementioned results exemplify the efficacy of our models, particularly in light of the dearth of disease data on which they were built.

Future situation of West Nile virus in the Afro-Palaearctic pathogeographic system

As WNV is transmitted by arthropod vectors, it is notably susceptible to climate change. The distribution of mosquitoes is influenced by the environmental conditions that allow them to maintain and reproduce (Bellone and Failloux 2020). A decrease in precipitation could negatively affect the survival of larvae, while an increase in temperatures, along with sufficient water availability, could strengthen the mosquito life cycle. Moreover, it's worth noting that droughts can elevate disease prevalence due to increased interactions between vectors and disease reservoirs (Paull et al. 2017). In addition, warmer temperatures favour mosquitoes to become infected with West Nile virus, and also that in warmer environments infection and dissemination rates spread more efficiently and rapidly (Dohm et al. 2002, Vogels et al. 2016). This would lead to an increased risk of infection in areas where these changes are more prominent in the future (Paz 2015) and expand the infection to new areas (Paz 2019). Secondarily, the introduction of the virus into new areas may also be triggered by the large dispersive movements of migratory birds, reservoirs of the virus (Rappole et al. 2000). The regions presenting the highest risk for WNV infections, both in the present and in the future (Fig. 1), largely overlap with the distribution areas of plenty of migratory birds that overwinter in Africa and spend the breeding season in Europe (García-Carrasco et al. 2023c). Climate change could alter the migration patterns of these species, changing their flyways, their phenology and probably favouring the colonization of new areas (Nieto et al. 2018, Whitehorn and Yacoub 2019, Chamorro et al. 2020), which could finally affect the propagation of the virus into new areas, both in latitude and altitude.

As a consequence of climate change, an increase in the risk is foreseen, primarily in central and eastern European countries (Fig. 2) where the disease is currently spreading (Vogels et al. 2017, Chaintoutis et al. 2019). Furthermore, our model allows us to forecast a northward expansion due to climate change, resulting in an increased risk of WNV infections

in countries such as France, Belgium, the Netherlands, Germany, Denmark, Poland, Belarus, Russia, and even southern Great Britain (Fig. 2A). This risk is expected to increase in the year 2070 (Fig. 2B). The virus has been linked to low lands, potentially due to the accumulation of water and the density of vectors and reservoirs (Valiakos et al. 2014, García-Carrasco et al. 2021). However, in the future, it is expected to expand to higher altitudes (Hoover and Barker 2016, Paz 2019). Our model indicates that the risk will increase significantly in the major European mountain ranges, such as the Alps, Pyrenees, Carpathians and the Caucasus. This increase in risk at higher altitudes and latitudes may be associated with the emergence of more favourable environmental conditions for the survival of mosquitoes and other arthropod vectors. Warmer winters are progressively extending the breeding seasons for mosquito vectors, enabling them to survive through the winter, either in the form of eggs or as overwintering female mosquitoes (Watts et al. 2021), and at the same time is expected that warming minimum temperatures could expand the potential range of *Culex pipiens* mosquitoes to higher latitude (Hongoh et al. 2012).

In the African continent, we found significant differences in risk dynamics according to the area. In North Africa, along the Mediterranean coast, the risk would stay stable compared to the present. Increased temperatures accompanied by decreased rainfall in already arid areas may have negative consequences for mosquito larval development, reducing the risk of West Nile virus transmission in areas at risk, as predicted in eastern North America (Keyel et al. 2021, Keyel 2023). Furthermore, an increase in temperature beyond the optimal range of 23–26°C can reduce the efficiency of virus transmission by mosquitoes (Shocket et al. 2020). Therefore, as the distance from the coastline increases, the risk of infection in the future decreases (Fig. 2). On the other hand, in the Afrotropical region, the risk would continue to be stable for the year 2040, although it is expected to increase slightly in the western and southern countries such as South Africa, where the virus is already highly prevalent (Sule et al. 2018, García-Carrasco et al. 2023b). However, the risk of WNV may increase in the year 2070 throughout the Afrotropical region, especially in western, southern and, to a lesser extent, eastern countries (Fig. 2B). In the Near East region, the risk of infection will decrease, probably as a consequence of increased aridity due to climate change. However, in certain areas, disease outbreaks could intensify, such as those hosting wetlands, such as Palestine, Israel, Lebanon and Syria. In these zones, the availability of water would lead to a concentration of birds and mosquitoes, increasing the bird-mosquito interaction, which would accelerate the epizootic cycle and would amplify the virus, resulting in spillover to the human population and the most susceptible livestock (Crowley 2016, Paz 2019).

Climate change has far-reaching implications for ecosystems and the health of both human and non-human animals (McCarty 2001, Costello et al. 2009, Gibb et al. 2020). The re-emergence of diseases like WNV presents a significant public health challenge. Developing countries, with limited resources and healthcare infrastructure, are particularly vulnerable to the spread of such diseases (Paz et al. 2021, Ozili 2022). Furthermore, developed countries may face future challenges due to increased life expectancy and an aging population, as individuals over the age of 60 are at higher risk of severe WNV infection (Montgomery 2017, Marois et al. 2020, Liu et al. 2023).

The expansion of WNV into new areas also poses risks to blood banks, as the virus can be transmitted through blood transfusion, and a substantial proportion of infections are asymptomatic (Frank et al. 2022). Additionally, the burden of disease is expected to increase due to climate change, potentially leading to a rise in the incidence of West Nile Neuroinvasive Disease and an increased probability of mortality.

Distribution modelling, such as mapping and forecasting the risk of WNV in the Afro-Palaearctic system, is valuable and applicable to other regions and diseases. Pathogeography offers a promising approach to understand the distribution patterns of zoonotic diseases and predict their future spread. As global climate mitigation efforts may not be sufficient to prevent significant warming, regional and national adaptation strategies become crucial in safeguarding public health and building resilience against future zoonotic risks (Marotzke 2019, Gibb et al. 2020).

This information serves as a vital climate change adaptation measure, and policymakers and health authorities in high-risk countries should consider implementing surveillance programs and prevention policies based on this knowledge. Such measures can help mitigate the impact of the disease on public health and reduce the exposure of human and animal populations to the virus.

Author contributions

José-María García-Carrasco: Conceptualization (lead); Data curation (lead); Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (lead); Visualization (lead); Writing – original draft (lead); Writing – review and editing (equal). **Lucrecia Souviron-Priego**: Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Visualization (equal); Writing – original draft (equal); Writing – review and editing (equal). **Antonio-Román Muñoz**: Investigation (supporting); Project administration (supporting); Supervision (supporting); Writing – original draft (supporting); Writing – review and editing (supporting). **Jesús Olivero**: Conceptualization (supporting); Formal analysis (supporting); Funding acquisition (supporting); Investigation (equal); Methodology (equal);

Project administration (lead); Supervision (equal); Writing – original draft (supporting); Writing – review and editing (equal). **Julia E. Fa**: Funding acquisition (lead); Supervision (supporting); Writing – review and editing (supporting). **Raimundo Real**: Conceptualization (equal); Formal analysis (supporting); Investigation (equal); Methodology (lead); Supervision (lead); Writing – original draft (supporting); Writing – review and editing (equal).

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Data availability statement

Data are available from the Dryad Digital Repository: https://doi.org/10.5061/dryad.4xgxd25hs (García-Carrasco et al. 2024).

Supporting information

The Supporting information associated with this article is available with the online version.

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