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An African West Nile virus risk map for travellers and clinicians

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ABSTRACT

International travellers are exposed to pathogens not commonly found in their countries of residence, including West Nile virus (WNV). Due to the difficulty of its diagnosis, little is known about its distribution in Africa. Understanding the geographic extent of risk of WNV infections is a necessity for both travellers and clinicians who advise and treat them, since there is no human vaccine. To date, there is no risk map for WNV infections in humans in Africa. Having a high-resolution risk map for the virus could be of relevance before the trip, to take preventive measures, and after the trip, for appropriate diagnosis of the disease. Virus detection in humans along the African continent were collected from official reports, and published scientific research for the period 1940 to 2020, and then geo-referenced in order to use biogeographical modelling for WNV. Models were based on fuzzy logic and machine learning algorithms and were designed to identify the environmental drivers that explain the distribution of human cases and to locate favourable areas for infections. We elaborated a high-resolution risk map for WNV infections that highlights favourable areas for infections in Africa. Although WNV infections are widely spread across Africa, the risk of the disease is not homogenously distributed. Popular tourist destinations such as Morocco, Tunisia, and South Africa, are high-risk areas for WNV infection.

1. Introduction

West Nile virus (WNV) is a re-emerging zoonotic mosquito-borne Flavivirus maintained in a bird-mosquito-bird cycle. The virus is incidentally transmitted to humans and other mammals, which are dead-end hosts, by the bite of infected mosquitoes *Culex* sp. Although the majority of infected humans are asymptomatic, some infections (~20%) can lead to febrile disease (West Nile fever [WNF]) and less than 1% will develop neurologic disease (West Nile neurologic disease [WNND]). Approximately 0.1% will result in a fatal neurologic infection [1,2]. Serious illness can occur in people of any age. However, people over the age of 50 and some immunocompromised persons (for example, transplant patients) are at the highest risk of getting severely ill when infected with WNV [3]. No specific prophylaxis or treatment exists against the disease in humans [4]. Migratory birds can transport the virus between different countries [5]. However, environmental characteristics determine if the virus remains in a certain area [6]. Although at the moment, the virus is widely spread, being present in Africa, Europe, the Middle East, America, and even Oceania [7–9], it is widening its distribution and the prevalence of the disease may vary significantly between adjacent areas.

While natural processes, such as bird migration, can spread the virus from its original areas to new ones, globalization can accelerate contact between people and the virus by facilitating the transport of infected mosquitoes, trade in birds, or the contact of travellers with endemic areas of the disease [10,11]. Flavivirus infections, such as those of WNV, have become not only a public health concern, but also a global health issue [10]. Africa is the continent where WNV is most widely spread and the second continent, behind Asia, that has experienced the greatest annual increase in the number of tourists [12]. In addition, the arrival of tourists is expected to double in the period from 2010 to 2030 in the African continent [13]. However, given the non-specific clinical signs produced by WNV, and the lack of surveillance in some African countries, it is difficult to ascertain the real African distribution of WNV at a continental scale. Although the risk of WNV infection in Africa has been studied through the animal components involved in the cycle (Garcia--Carrasco et al., 2022), there are knowledge gaps in the continent regarding the real disease burden for humans [14]. To date, there is no

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risk map for the human infection that can be used by clinicians and travellers to be aware of the risk. In order to develop the first risk map for WNV infection in humans in continental Africa, we have conducted a literature review of the distribution of known cases of WNV infection in humans in Africa. Based on this information, and applying distribution-modelling techniques, we aimed to construct a high-resolution risk map that would visibly represent the WNV-infection risk areas, which would be useful for clinicians and travellers visiting Africa. Given the weak surveillance and the difficulty of diagnosing this disease, this approach is useful and necessary.

2. Methods

2.1. Data collection

We used GIDEON (Global Infectious Diseases and Epidemiology Network) database [15], which compiles reports and articles related to infectious diseases worldwide, to elaborate a literature search using "West Nile fever", as a disease, and the names of the 48 continental countries and territories of Africa. We complemented the GIDEON database with an electronic literature search. It was made through Web of Science, Scopus and Google Scholar for the African countries using different combinations of the following keywords "West Nile virus"; "WNV"; "West Nile Fever"; "WNF"; "West Nile" and the name of each African country. The search comprised the period 1940–2020.

We geo-referenced every locality where the virus was detected among humans in the revised articles and reports. The occurrences of WNV infections were only geo-referenced when the location of the site was precise at the village, town or city level. The place name and all the contextual information provided were used to determine the latitudinal and longitudinal coordinates using Google Maps (https://www.google.es/maps), Google Earth (https://www.google.com/intl/es/earth), Geonames (http://www.geonames.org) and Google searches.

2.2. Analysis and downscaling

The African continent was divided into hexagonal units of the same size, 7742 km^2, which were built using Discrete Global Grids for R [16]. Those hexagons were our operational geographic units (OGU). Each geographic location from the literature search was intersected with the hexagonal grid. We considered WNV infections in humans to occur in a hexagonal unit if at least one geographic location was within its area. In this way, we avoided the excessive weight of the oversampled areas with respect to the undersampled ones.

A set of environmental variables related to three explanatory factors (anthropic, ecosystemic and climatic) that could influence the distribution of WNV cases or the components of the WNV cycle (bird, mosquitoes and population) were used to identify the favourable areas for WNV human infections in Africa (Table 1). We performed univariate logistic regressions of the presence and absence of reports of disease cases in each hexagon on each explanatory variable, and the significance of the relationship with the variables was assessed according to score tests. Multicollinearity among variables was controlled using Spearman correlation. If two variables related to the same explanatory factor were correlated over 0.8, the least explanatory one, according to the score tests, was deleted. The type II error of null hypotheses were controlled with the score test ($p < 0,05$) and the type I error of the alternative hypotheses were controlled with the False Discovery Rate ($q < 0,05$) [17]. The variables that overcame these previous filters were used in an multivariate stepwise logistic regression, a machine learning algorithm [18]. It began with a null model with no explanatory variables. Then, at each step a new variable was added, resulting in a new regression model. If the new variable significantly improved the model fit, the variable was maintained. The process continued till no new variable improved the model fit. We tested the model goodness-of-fit according to Chi-square test. The result of the multivariate logistic regression was a probability

Table 1
Explanatory variables used in the West Nile virus models.

Type	Subtype	Name	References
Human	Human concentration	Population density	[1]
		Distance to population center	[2]
	Livestock	Poultry density	[3]
		Farmed duck density	[3]
		Horse density	[3]
		Buffalo density	[3]
		Goat density	[3]
		Cattle density	[3]
		Sheep density	[3]
		Pig density	[3]
	Infrastructure	Distance to roads	[4]
		Distance to railway tracks	[4]
	Agriculture	Irrigated croplands	[5]
		Rainfed croplands	[5]
		Mosaic cropland (>50%)/ Vegetation(<50%)	[5]
		Mosaic vegetation(>50%)/ Cropland (<50%)	[5]
		Percentage of areas equipped for irrigation	[6]
Non-human	Ecosystem	Broadleaved evergreen and/or semi-deciduous forest	[5]
		Closed broadleaved deciuous forest	[5]
		Open broadleaved deciuous forest	[5]
		Closed needleleaved evergreen forest	[5]
		Open needleleaved deciuous or evergreen forest	[5]
		Closed to open mixed broadleaved and needleleaved forest	[5]
		Mosaic Forest/Shrubland/Grassland	[5]
		Mosaic Grassland/Forest/Shrubland	[5]
		Shrubland	[5]
		Grassland	[5]
		Sparse vegetation	[5]
		Broadleaved forest regularly flooded	[5]
		Broadleaved semi-deciduous and/or evergreen forest regularly flooded	[5]
		Vegetation on regularly flooded or waterlogged soil	[5]
		Desert	[5]
		Forest loss	[7]
		Distance to Ramsar sites	[8]
	Hydrographic	Distance to rivers	[9]
	Topographic	Altitude	[10]
		Slope	[11]
	Climatic	Annual Mean Temperature	[12]
		Max Temperature of Warmest Month	[12]
		Min Temperature of Coldest Month	[12]
		Temperature Annual Range (Bio5-Bio6)	[12]
		Annual Precipitation	[12]
		Precipitation Seasonality (Coefficient of Variation)	[12]

1. LandScanTM 2008 High Resolution Global Population Data Set (copyrighted by UT-Battelle, LLC, operator of Oak Ridge National Laboratory), excluding any areas less than 2-km far from urban areas (as delimited by the MODIS 500 -m Map of Global Urban Extent for 2001–2002 (Schneider et al., 2009; 2010).
2. Administrative Centers & Populated Places shapefile at the Relational World Database II (RWDB2) updated in 2000 (http://www.fao.org/geonetwork).
3. Global FAO 2010 livestock (http://www.fao.org/livestock-systems/en/).
4. Vector Map Level 0 at the Digital Chart of the World (DCW, http://worldmap.harvard.edu), updated in 2002.
5. GlobCover (GC) Land Cover version 2.1 database for 2005–2006 (Bicheron et al., 2008).
6. Global Map of Irrigation Areas (version 4.0.1) around the year 2000 (http://www.fao.org/nr/water).
7. Global Forest Change 2000–2019 (http://earthenginepartners.appspot.com/science-2013-global-forest/download_v1.7.html). Downloaded in 2020.

8. Ramsar Sites Information Service (https://rsis.ramsar.org/). Downloaded in 2020.
9. Global Drainage Basin Database GDBD. Released Version 1.0: May 29, 2007 (http://www.cger.nies.go.jp/db/gdbd/gdbd_index_e.html).
10GTOPO30 (US Geological Survey 1996).
11. Elaborated from DEM (Digital Elevation Model) using the altitude variable (GTOPO30; US Geological Survey 1996), using the Geographic Information Sistem ArcGIS Desktop 10.3.
12. Chelsa (http://chelsa-climate.org).

value of WNV infection. Finally, each probability value was transformed into a favourability value, representing the degree of risk of WNV outbreaks, using the Favourability Function [19]. In that way, if the probability value represents the probability of each OGU to show WNV infection records, the favourability represents the degree to which environmental conditions favour the occurrence of the WNV in humans [20,21]. We downscaled the model from 7742 km^2 of each hexagon (OGU) to 100 km^2 squares using the direct downscaling approach [22], that is, using the logistic regression equation to get favourability values for 100 km^2 squares according to variable values at the same spatial resolution, to increase the potential utility of our cartographic model. In this way the precision of the risk map was increased, being more useful for travellers and clinicians.

3. Results

Three hundred twenty-eight articles were identified during the literature search, 120 of which were included in the database (**Supplementary Table**). The remaining ones were excluded for the elaboration of the risk map due to any of the following reasons: the survey for WNV was negative for the virus, the survey for WNV was positive for the virus, but the research was conducted to a country level without identifying specific places; the survey detected WNV, but not in human populations. Only Cameroon and Zambia had cases of human WNV infection reported, but these could not be used for modelling as the information was at the country level and not at specific locations.

This database is the first developed in Africa that includes the detection of WNV in humans throughout the continent. The database contains 461 geo-referenced locations of the virus throughout the entire Africa (Fig. 1). Twenty-eight countries reported WNV cases compared to 18 which did not report WNV cases. The largest number of human cases were located in North Africa, with 179 locations, 90% of them in Tunisia and Egypt, followed by Eastern Africa with 144 locations. In West Africa

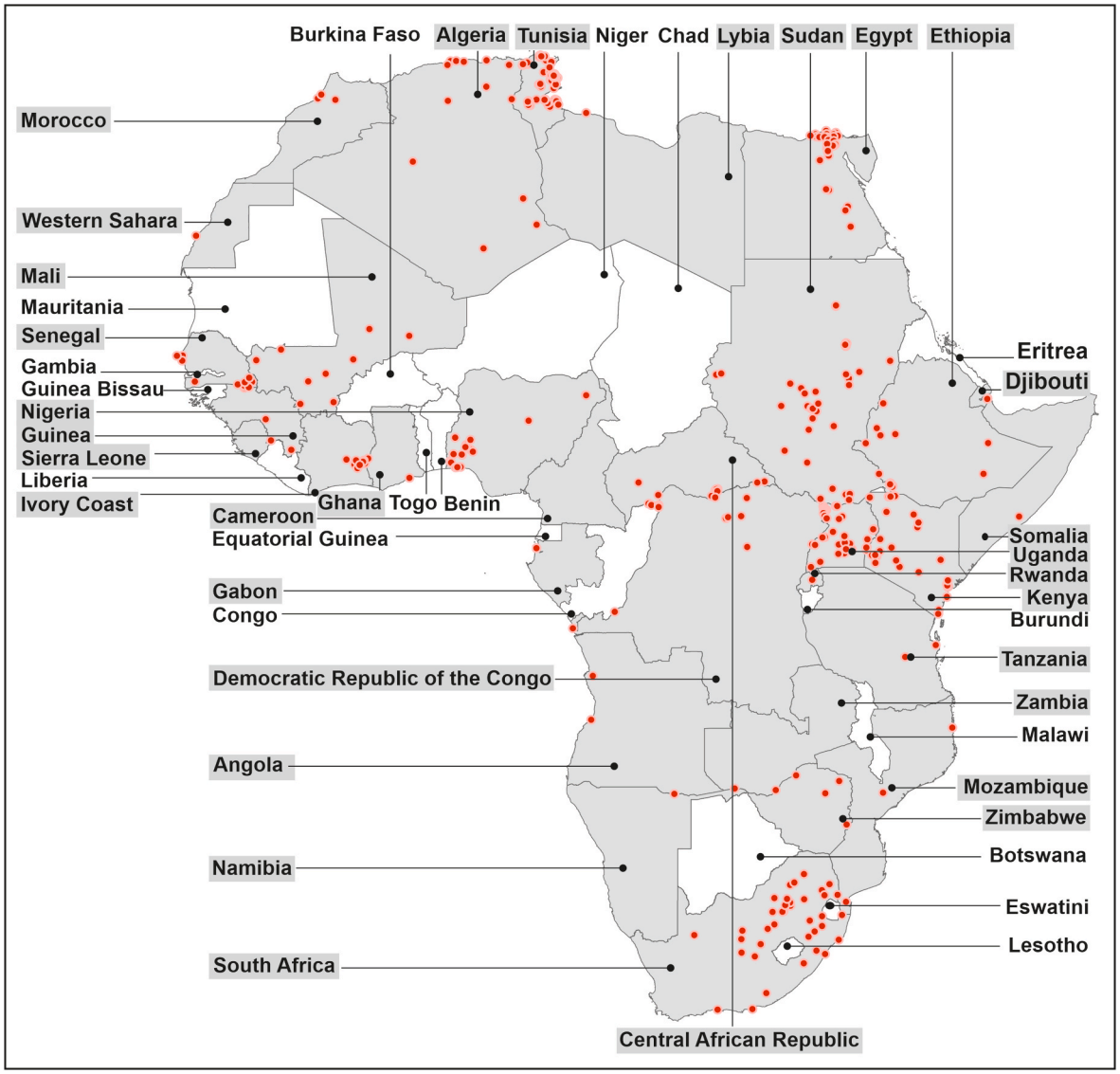

Fig. 1. African countries with WNV infections reported (gray countries) and geo-referenced (red dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

62 human locations were geo-referenced, 51 in Southern Africa (78% of them in South Africa) and 25 in Central Africa. Within a country, WNV cases were not homogeneously distributed. In North African countries, cases were clustered in the coastal areas, with very few cases in the drier areas. In the case of Egypt, the distribution of cases was closely linked to the course of the Nile, with a high concentration at the mouth of the river. In East Africa, cases were more evenly distributed within a country, but were generally concentrated near Lake Victoria and in the proximity of the Nile River. In South Africa, cases were more concentrated in the eastern part of the country, with large areas unrecorded in the west.

High temperature and low average annual precipitation characterized the areas where people are more prone to infection by WNV. Types of land cover also influenced the risk of WNV infection, such as the presence of shrub formations and soil floodability. Human-related variables such as population density, proximity to population centers and roads contributed to explain the distribution of WNV among humans. Other human activities, such as livestock (buffalo, cattle and chicken) and agricultural areas also played a role as explanatory variables. The list of explanatory variables is shown in Table 2.

According to the risk model (Fig. 2), the areas with risk of WNV infections in humans are widely spread across Africa, but not homogenously. Uganda, where WNV was firstly discovered, and countries around the Lake Victoria, constitute areas of high risk. South Africa has a large proportion of its area at risk, with the higher risk zone in its capital, Johannesburg. The Nile delta, including Cairo, in Egypt, is also a high-risk area, with a narrow strip of high risk along the entire length of the Nile. The Maghreb is also an area of high risk, especially the Mediterranean coast (Morocco, Tunisia and Algeria). The Atlantic coast of West Africa also stands out as a risk-area, particularly the Ivory Coast, Ghana, Togo, Benin and Nigeria. In Ethiopia, Algeria, Nigeria, and South Africa cases of WNV infections have been locally reported, but in large areas at risk no cases have still been detected.

Table 2
Predictor variables included in the risk model. X^2 is the model goodness of fit according to Chi-square test is given with its statistical significance. B is the value of the coefficient that multiplies the variable value in the logit of the multivariate logistic regression. The Wald parameter quantifies the relevance of every variable in the model. Sig. is the significance of the Wald test. Variable abbreviations are given in Table 1.

	$X^2 = 393.576$ ($p < 0.05$)		
	B	Wald	Sig.
Precipitation Seasonality	−1.76E-02	32.45	1.22E-08
Annual Precipitation	−9.72E-04	25.109	5.42E-07
Mosaic vegetation (>50%)/Cropland (<50%)	1.742	17.595	2.73E-05
Distance to population center	−3.14E-05	15.434	8.54E-05
Buffalo density	1.87E-03	13.38	2.54E-04
Cattle density	1.17E-04	12.703	3.65E-04
Mean Temperature	8.81E-03	11.596	6.61E-04
Mosaic Forest/Shrubland/Grassland	1.651	8.603	3.36E-03
Poultry density	8.05E-06	8.527	3.50E-03
Distance to railway tracks	−1.70E-06	7.026	8.03E-03
Population Density	9.71E-04	5.573	1.82E-02
Vegetation on regularly flooded soil	3.475	5.387	2.03E-02
Distance to roads	−3.20E-05	5.216	2.24E-02
Shrubland	1.268	4.866	2.74E-02
Constant	−1.816	11.702	6.24E-04

4. Discussion

To this day, there is no human vaccine or antiviral treatment for WNV [4], making identification of risk areas for the disease a priority for prevention. If we also consider that WNV is becoming a global health issue [10], it is clear that anticipating the risk of human cases occurring, either in the local population or in travellers moving to endemic areas, is increasingly important. Africa has experienced a rise in the number of tourists that annually travel to the continent [12], and this tendency is expected to increase in the coming years [13]. Morocco, South Africa and Tunisia are major tourist destinations [12] and are also the African countries hosting the areas with the highest risk to be infected by WNV (Fig. 2). In fact, there have been cases of infections imported to Germany by tourists returning from Tunisia and from Egypt, specifically from Cairo [23], both of them identified as high risk areas according to our model. These countries hold abundant populations of *Culex pipiens*, the most effective vector of the disease [24]. Other countries, such as Belgium and the United Kingdom, have also reported imported cases of WNV via tourists that were infected during stays in African (sub)tropical regions or in South Africa [25,26]. Furthermore, Asian tourists have also acquired WNV during their stay in Africa [27], as well as African travellers within the continent, such as documented cases of Guineans travelling to Senegal [28] or Zambians visiting Angola [29].

The risk map highlights countries and regions at high risk of WNV infection where no WNV infections have yet been reported, such as Burundi, Eswatini, Gambia, Guinea-Bissau, Togo, Benin, Equatorial Guinea, Malawi or the South of the Republic of the Congo. Even so, the risk map could have some limitations, underestimating the impact of the virus. WNV is a neglected disease and the lack of resources in most countries to detect WNV hinders the ability to obtain a robust database that is as close to reality as possible. This, coupled with the fact that WNV infections often present with nonspecific symptoms and signs [29], can cause WNV infections to be misdiagnosed, and thus underestimate the presence of the virus [8,14]. Many of the countries in sub-Saharan Africa are endemic for malaria and typhoid fever, making cases of acute febrile illness associated with one of these two diseases. Added to this is the lack of diagnostic capacity of arboviruses, whose diseases are usually diagnosed as fevers of unknown origin. Seroprevalence studies in Ghana and Nigeria have shown that WNV is endemic [30] with WNV infections probably asymptomatic in childhood. Twenty-five percent of Nigerian patients were WNV seropositive, many of whom were infected with *Plasmodium falciparum* or *Salmonella* Typhi, suggesting that WNV infection may be confounding with these diagnoses or with other co-circulating arboviruses. This is the main reason why having a risk model may be a great advance when it comes to filling knowledge gaps in certain regions.

Scientists and travel medicine physicians emphasize the importance of performing a complete travel history, including route, season and purpose of travel, even when travellers are returning from non-tropical countries, to better understand what types of infectious diseases travellers may have been exposed to Ref. [23]. A map like the one shown in Fig. 2 may be of great help when diagnosing potential diseases based on the places visited by travellers.

Malaria is nowadays perceived as an important risk when travelling to Africa [31]. However, the current relative unfamiliarity with WNV infection still facilitates a perception of low risk of this disease. This occurs in Europe, where Italian occupational physicians had a relative unfamiliarity even in high-risk areas of WNV infection [32], and we could say that in Africa it is happening at a higher level. Malaria is transmitted by *Anopheles* mosquitoes, which have similar habits to *Culex* mosquitoes, with the difference that *Culex* mosquitoes are active both indoors and outdoors [33]. Being aware of malaria risk protects

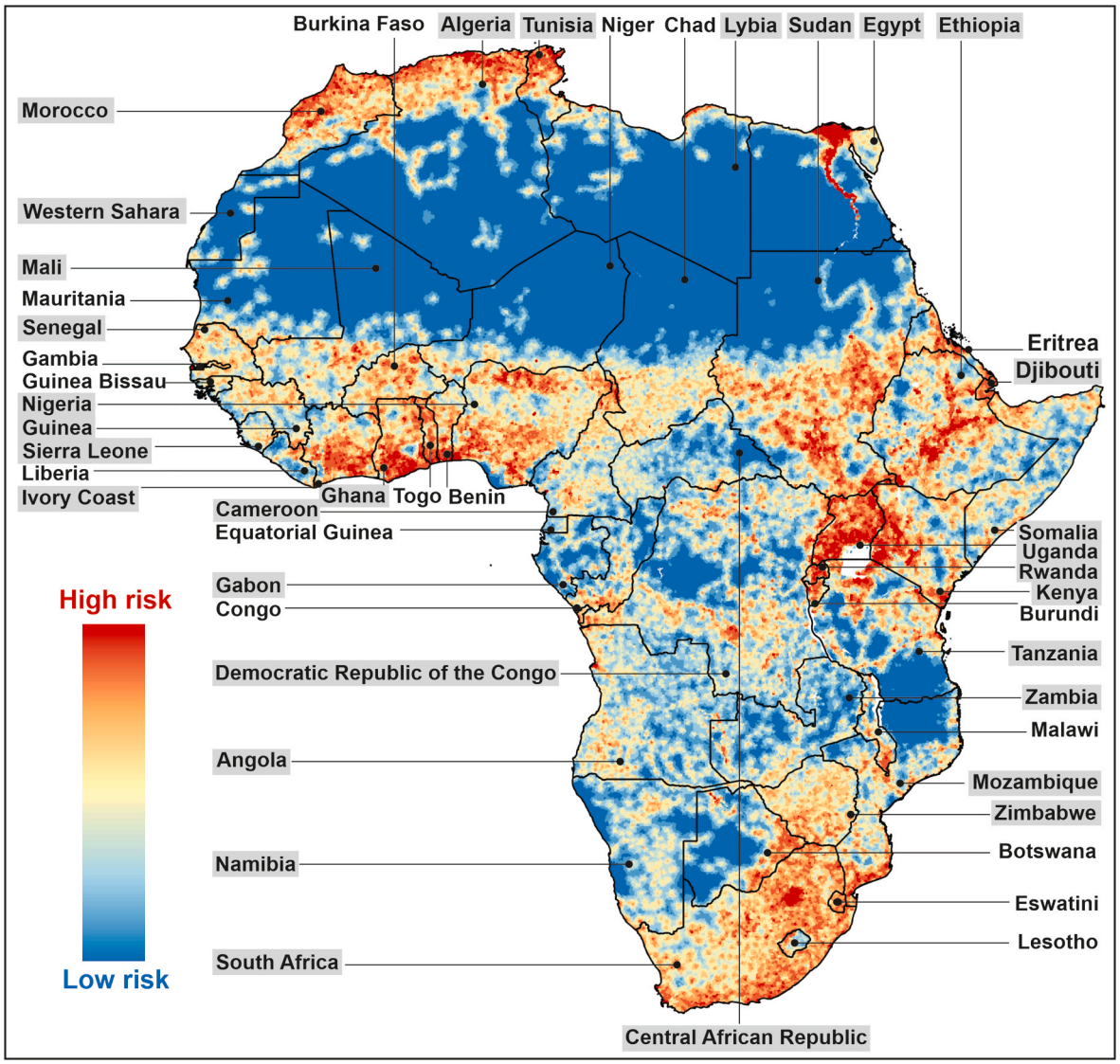

Fig. 2. Risk model of WNV outbreak in Africa. Favorability values, shown from blue to red, represent the degree of risk of **WNV** outbreaks at a 100-km^2 resolution. Countries' name in gray are those which reported WNV detection. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

travellers against WNV infection, but in malaria-free areas it is common to lower the guard in terms of protection against mosquitoes, although the risk of WNV infection may persist. This is the case in Northern Africa, where Morocco, Tunisia and Egypt are important tourist destinations, receiving travellers mostly during spring and summer, when WNV outbreaks typically occur. In countries of the Sahel, like Senegal, which are highly visited by nature tourists and birdwatchers during the dry season, the risk of WNV infection may be high, because tourists tend to relax preventive measures against mosquito-borne diseases due to the low risk of malaria infection. At that season, West Africa hosts millions of migratory birds, which could act as WNV amplifiers. In other subtropical areas such as Namibia and South Africa, the risk of WNV transmission is higher from October to May [34], when both temperature and precipitation are higher, accelerating mosquito breeding conditions. Moreover, this period overlaps with the return of migratory birds, further increasing the risk of WNV transmission. Therefore, prevention measures against arthropod-borne diseases should increase during this period, especially in natural areas of particular interest for tourists, such as the Kruger National Park.

The countries around Lake Victoria are popular nature-based tourism destinations. These areas include the Serengeti National Park in Tanzania and the Maasai Mara in Kenya, and pose a high risk of WNV infections. In these areas travellers engaged in activities such as hiking or bird watching are more exposed to this disease, given the exophagic behaviour of *Culex* and the fact that in natural areas the enzootic cycle of the virus (mosquito-bird-mosquito) may predominate. These tropical regions concentrate a higher risk of WNV transmission at the end of the rainy season, when there is a higher density of mosquitoes.

A continental perspective of the distribution of risk zones represents an opportunity to update the current view of the distribution of WNV infections in Africa. Disease risk mapping facilitates the diagnosis and allows a better understanding of this re-emerging infectious disease. It may also help physicians to advice travellers on preventive measures against mosquitoes in WNV endemic areas, perhaps of particular relevance in non-malaria-endemic areas where the travellers tend to relax protection against mosquitoes, such as North Africa and South Africa. Therefore, extending the use of preventive measures against mosquitoes, such as insecticide-treated nets, repellents and protective clothing, not only will avoid the exposure to malaria (*Anopheles*), but also to WNV vectors (*Culex*) [35,36]. There is an increasing number of travellers with risk factors associated with the possible development of severe neurological disease due to WNV, such as advanced age, immunosuppression

and chronic diseases, where preventive measures against the virus are especially important [37].

It is not the first time, nor will it be the last, that a re-emerging virus has affected people from different regions, naturally by bird migration or bringing people into contact with disease-endemic areas through international travel. A coordinated local and international surveillance system, such as control of epizootic outbreaks and vector control and surveillance, would help improve the public health of the local population. The risk map provided in this study will help medical professionals tailor appropriate preventive recommendations to international travellers, as well as facilitate proper diagnoses of sick travellers returning from their destinations in Africa.

5. Conclusions

Travellers, and clinicians who advise and treat them, need to understand the geographic extent of risk of WNV infections and other re-emerging arboviral diseases. Despite the wide distribution of cases in Africa, there is currently no human risk map for the continent. Using the different grades of risk of WNV-infection, travellers can be advised by clinicians on sanitary measures prior to travel in order to prevent mosquito bites in areas of high risk. It is important to be aware of the existence of this disease in non-malaria-endemic areas, where travellers tend to relax protection measures against mosquitoes. We recommend the use of anticipatory measures focused on preventing mosquito bites in high and medium risk areas. Moreover, the profile of travellers has changed a lot in recent years, with a travelling population increasingly at risk of suffering from this disease with a serious clinical picture. We highlight the importance of biogeography as a relevant and useful tool at the service of travel medicine. Similarly, this approach could be used for other diseases, particularly those without vaccine or chemoprophylaxis for prevention.

CRediT authorship contribution statement

José-María García-Carrasco: Conceptualization, Resources, Methodology, Data curation, Formal analysis, Visualization, Writing – original draft. **Antonio-Román Muñoz:** Writing – review & editing, Supervision. **Jesús Olivero:** Methodology, Writing – review & editing. **Marina Segura:** Conceptualization, Writing – review & editing. **Raimundo Real:** Writing – review & editing, Supervision.

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Appendix A. Supplementary data

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