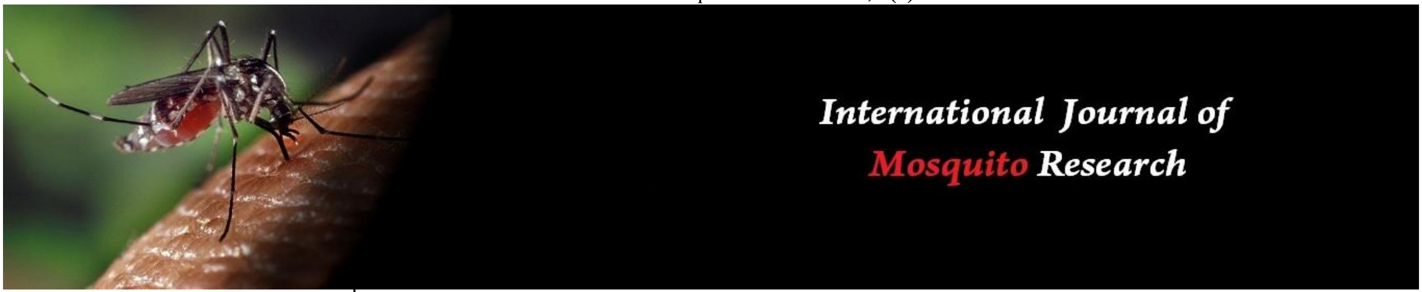

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Predicting current and future distribution of West Nile disease in Tunisia

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Abstract
West Nile Disease (WND) is an emerging infectious vector borne disease. *Culex pipiens* is the most implicated mosquito species in the transmission of WNV in Tunisia. The spatial distribution of this disease has continued to expand in Tunisia since the first epidemic in 1997, while the existing knowledge of environmental factors triggering such events continues to be rather poor. Based on the geographical locations of human WND cases and using ecological factors as predictors, the MaxEnt model was developed to identify environmental factors influencing *C. pipiens* competence. Potential areas at high risk of WND occurrence under current and future climate background are determined. The key environmental factors affecting vector competence and WND occurrence were the minimum temperature of the coldest quarter and precipitation in the warmest and driest quarter. The risk prediction maps suggested that north-eastern, the eastern and southern coast and oasis areas of Tunisia are potential areas at high risk of WND. Identifying potential environmental factors that influence WND occurrence in Tunisia is the first step for the implementation of a statistically rigorous system for real-time alert and prediction of WND. The potential high risk of WND areas are distributed widely in Tunisia. The epidemiological surveillance system should be enhanced in these high risk regions.

Keywords: West Nile disease, ecological niche model, MaxEnt, Tunisia

Introduction
WND is an emerging vector borne disease and is a potentially serious illness in humans. About one out of 150 persons infected with WND will develop a severe illness with long lasting symptoms. Neurological effects may be permanent. Respectively, up to twenty percent and approximately eighty percent of the infected population show milder symptoms and no symptoms at all [1].
It is recognised that the most implicated mosquito species in the transmission of WNV in Tunisia is *C. pipiens*, which is the most widely spread mosquito species [2]. Experimentally, *C. pipiens* populations collected in Tunisia have been shown to be highly susceptible to WNV infection and readily to transmit the virus [3]. The highest densities of *C. pipiens* are found in stagnant waters rich in organic matter located in the outbreak areas [4]. Both forms of *C. pipiens* and their hybrids coexist in the several outbreak sites in Tunisia. This supports the hypothesis that *C. pipiens* is a bridge vector for the WND transmission in Tunisia [5].
In the last decade, Tunisian authority reported two major epidemic of human WND in 2012 (86 suspected cases, 37 confirmed cases and 12 deaths) and in 2018 (65 suspected cases, 49 confirmed cases and 2 deaths) [6]. Sporadic WND human cases are recorded in 2013, 2014 and 2015 [6]**.** Most human infections occur in the summer or early fall in Tunisia [7] with an important increasing of *C. pipiens* densities. It's assumed that the transmission of WNV is determined by the interaction of the pathogen and the vector with the biotic and abiotic environment factors [8]**.** Moreover, the presence of favourable ecological habitats for vectors and hosts, with permissive weather conditions and their appropriate seasonal timing are crucial constituents for a successful transmission cycle [9-10]. But, the existing knowledge of environmental factors associated with the distribution and the dynamic of WND vector continues to be rather poor in Tunisia. Comprehensive and consistent analyses of climatic relationships with *C. pipiens* dynamic and WND occurrence are needed to better distinguish relationships from more localized contingencies.
Modelling tools of species distribution are more frequently used in ecology and in many Ecological applications [11-12].

These models are based on associations between the occurrences of species of *Culex* and the biophysical and environmental conditions in a study area. A variety of modelling methods are available to predict potential suitable habitat of species [13-15]. Most of these methods are sample size sensitive [15] and may not accurately predict habitat distribution patterns of threatened and endangered species. Compared to other model algorithm methods, MaxEnt [16] has proved powerful when modelling rare species with narrow ranges and available scarce presence-only occurrence data [17]. It has been proven to be a powerful tool to characterize the ecological distribution of species, to identify the habitats of undocumented diseases, and thus to anticipate the areas at high risk for disease occurrence. By using the maximum entropy ENM with MaxEnt software version 3.4.1, the initial ENM was first trained based on the locations of human WND occurrence and ecological variables downloaded from WorldClim dataset (www.worldclim.org).

In the present study our objectives were to: (1) identify the environmental factors associated with *C. pipiens* competence and WND occurrence distribution and (2) predict suitable habitat distribution for WND in Tunisia. We used WND occurrence records, QGIS (geographical information system) environmental layers (bioclimatic), and the maximum entropy distribution modelling approach [17] to predict the current and future areas at risk of WND occurrence.

Materials and methods

WND occurrence data and environmental variables used

Data related to 85 neuroinvasive WND human cases recorded in 2012 were georeferenced (suspected and confirmed cases) (Figure 1) [18]. WND human cases recorded in 2018 were used to validate athe model. To determine which environmental variables most influence the distribution of WND human cases, the principle of maximum entropy (MaxEnt) was used. We included in our model 19 bioclimatic variables downloaded from WorldClim dataset (www.worldclim.org) (Table 1). The future climate data for representative concentration pathways (RCPs) for carbon dioxide for 2050 (average of predictions for 2041–2060) is also included. This is the most recent GCM climate projections that are used in the Fifth Assessment IPCC report.

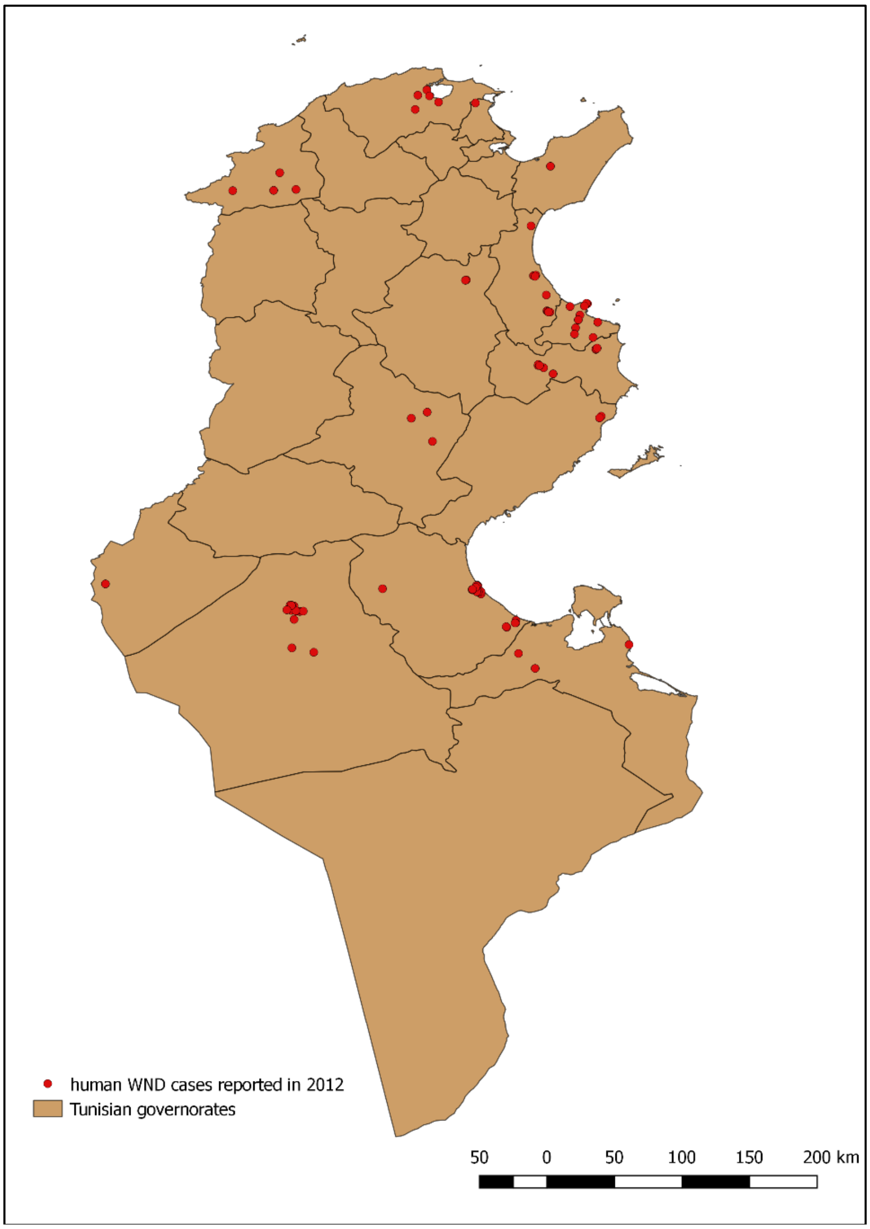


Fig 1: Localisation of WND human cases recorded in 2012 in Tunisia

Table 1: Bioclimatic variables used in the model

Code	Bioclimatic variables
BIO1	Annual Mean Temperature
BIO2	Mean Diurnal Range (Mean of monthly (max temp - min temp))
BIO3	Isothermality (BIO2/BIO7) (* 100)
BIO4	Temperature Seasonality (standard deviation *100)
BIO5	Max Temperature of Warmest Month
BIO6	Min Temperature of Coldest Month
BIO7	Temperature Annual Range (BIO5-BIO6)
BIO8	Mean Temperature of Wettest Quarter
BIO9	Mean Temperature of Driest Quarter
BIO10	Mean Temperature of Warmest Quarter
BIO11	Mean Temperature of Coldest Quarter
BIO12	Annual Precipitation
BIO13	Precipitation of Wettest Month
BIO14	Precipitation of Driest Month
BIO15	Precipitation Seasonality (Coefficient of Variation)
BIO16	Precipitation of Wettest Quarter
BIO17	Precipitation of Driest Quarter
BIO18	Precipitation of Warmest Quarter
BIO19	Precipitation of Coldest Quarter

Modelling procedure

The maximum entropy model (MaxEnt version 3.4.1 [17]; http://www.cs.princeton.edu/wschapire/MaxEnt/) has been used in this study since it is well adapted to the sample size [11, 19]. This model uses presence-only data to predict the distribution of a species based on the theory of maximum entropy. The program attempts to estimate a probability distribution of species occurrence that is closest to uniform despite environmental constraints [20]. Highly correlated variables (r ≥0.85 Pearson correlation coefficient) were eliminated from further models [21] in order to reduce multi-collinearity among the 19 bioclimatic variables. To determine the variables that reduce the model reliability when omitted, Jackknife test was used. The area under the Receiving Operator Curve (AUC) was used to evaluate model performance. The value of AUC ranges from 0 to 1. An AUC value of 0.50 indicates that the model did not perform better than random, whereas a value of 1.0 indicates perfect discrimination [22]. Thus, the model with the highest AUC value was considered the best performer.

To further analyse our data, we imported the results of the MaxEnt models predicting the presence of WND (0–1 range) into Qgis 2.18.

Results

Environmental factors associated with the current situation

The reduction of predictor variables resulted in the inclusion of only height variables for models (Table 2). Table 2 gives estimates of relative contributions of the environmental variables to the MaxEnt model. The MaxEnt model for WND occurrence probability distribution in Tunisia provided satisfactory results, with an AUC value of 0.962 (+/- 0.001) which is higher than 0.5 of a random model (Figure 2). The Minimum Temperature of the Coldest Month (Bio6) contributed most to the model, followed by the Precipitation of Warmest Quarter (Bio18), Precipitation of Driest Quarter (Bio17), Temperature Seasonality (standard deviation *100) (Bio4) and Precipitation of Wettest Month (Bio 13). The cumulative contribution of these five factors is 93.1% (Table 2).

Table 2: Relative contributions of the environmental variables to the MaxEnt model

Variable	Signification	Percent contribution
bio6_a	Min Temperature of Coldest Month	28.3
bio18_a	Precipitation of Warmest Quarter	27
bio17_a	Precipitation of Driest Quarter	16.2
bio4_a	Temperature Seasonality (standard deviation *100)	12.5
bio13_a	Precipitation of Wettest Month	9.1
bio5_a	Max Temperature of Warmest Month	4.6
bio12_a	Annual Precipitation	2.2
bio16_a	Precipitation of Wettest Quarter	0.1

Fig 2: The receiver operating characteristic (ROC) of the predicted model (Note that the specificity is defined using predicted area)

The jackknifed test is used to examine the accuracy of various predictors. The results of the jackknife test of variables' contribution are shown in Figure 3. Bio6 provided very high gains (>1.0) when used independently, indicating that Bio6 contained more useful information by itself than the other variables did. Bio18, Bio17 and Bio4 had moderate to high gain when used independently (0.7>gain <1). Other variables including Bio12, Bio13, Bio16 and Bio 5 had low gains when used in isolation; they did not contain much information by themselves.

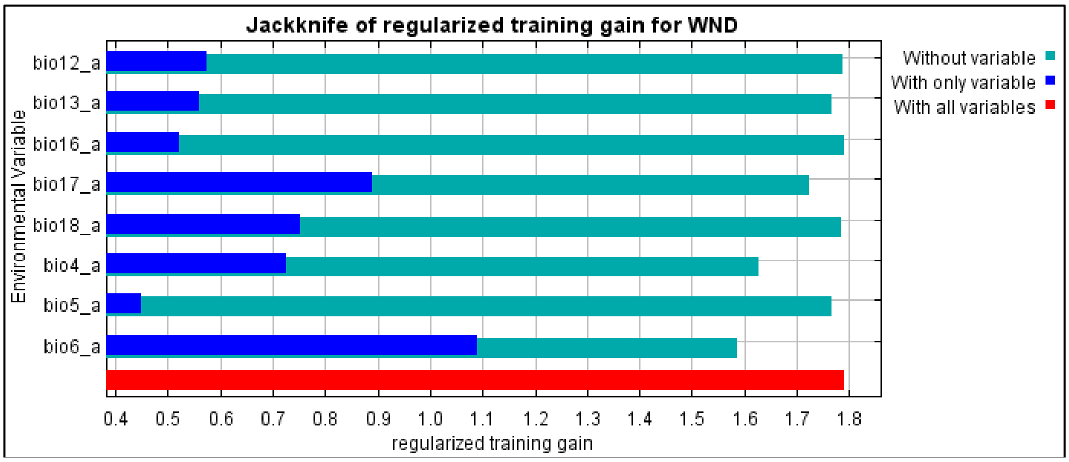
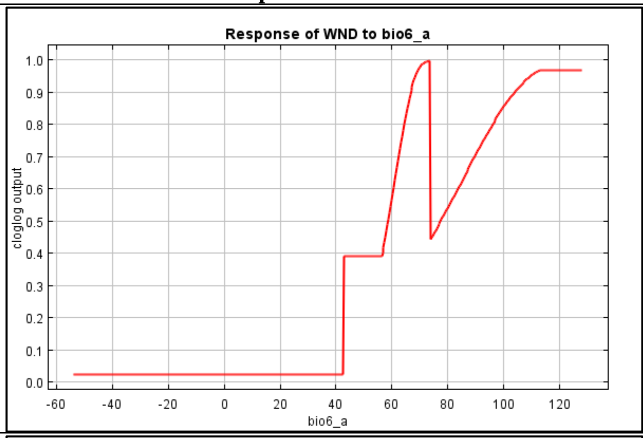
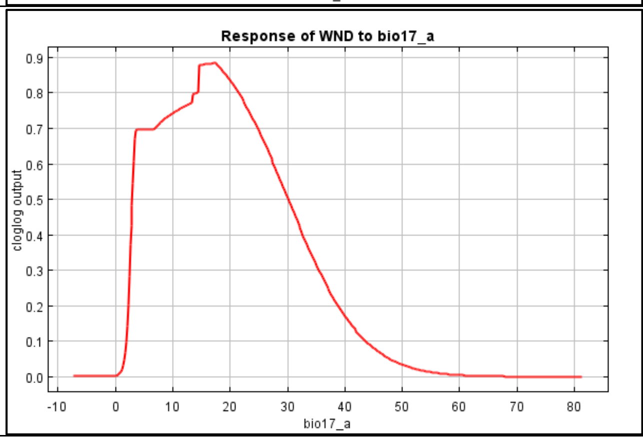


Fig 3: The Jackknife test for evaluating the relative importance of environmental variables for WND occurrence distribution in Tunisia

(The regularized training gain describes show much better the Max Ent distribution fits the presence data compared to a uniform distribution). The dark blue bars indicate that the gain from using each variable in isolation, the light blue bars indicate the gain lost by removing the single variable from the full model, and the red bar indicates the gain using all of the variables.

Based on the individual response curves for the potential bioclimatic variables influencing the probability of WND occurrence (Figure 4), the probability of WND occurrence is positive correlated with level of min temperature of coldest quarters ranged between 10 and 12 °C. A positive correlation is observed with level of precipitation of Driest and warmest quarter ranged between 10 and 40 mm. A negative correlation is observed when the level of precipitation exceeds the 50 mm. Overall; it appeared that winter temperature and summer precipitation were the major factors in determining the probability of WND occurrence in Tunisia.

Bioclimatic variables	signification	individual response to WND occurrence
Bio6	Min Temperature of Coldest Month	
Bio17	Precipitation of Driest Quarter	

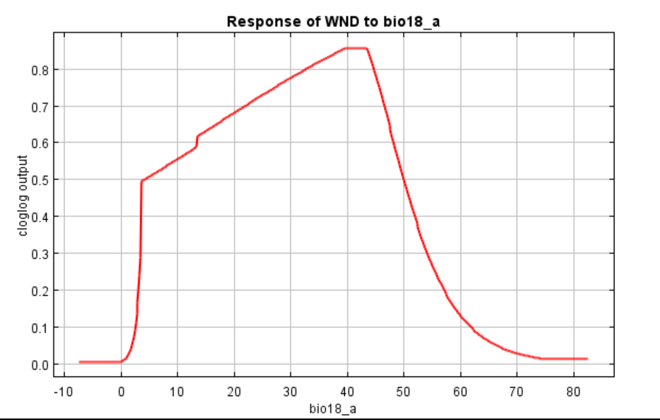
Bio18	Precipitation of Warmest Quarter	

Fig 4: Individual relationships between top bioclimatic variables and probability of WND occurrence.

Predicted Current suitable areas for WND occurrence

Based on the major environmental variables that modulate distribution of WND occurrence suitable habitats were predicted in Tunisia. Figure 5 shows the MaxEnt model for WND occurrence in Tunisia. Warmer colours show areas with better predicted conditions.

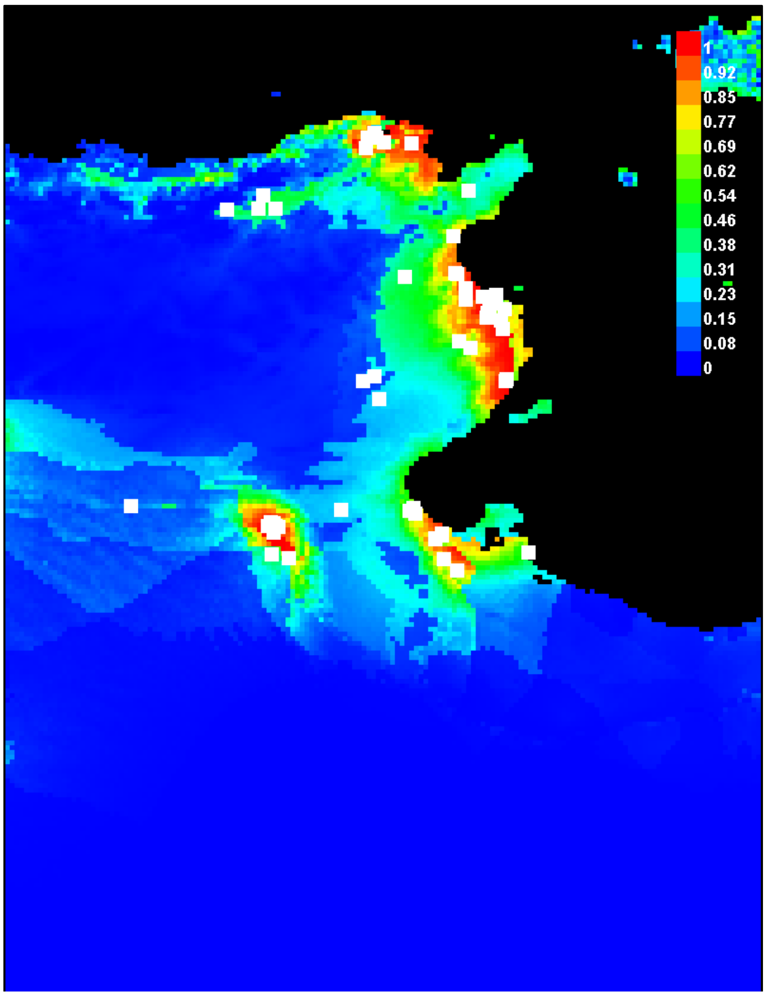


Fig 5: MaxEnt model for WND occurrence in Tunisia (White dots show the presence locations used for training)

For better feasibility, we imported the results of the Max Ent models predicting WND occurrence (0–1 range) into Qgis 2.18, five classes of potential habitats were regrouped: unsuitable habitat (0–0.2); barely suitable habitat (0.2–0.4); suitable habitat (0.4–0.6); highly suitable habitat (0.6–0.8); very highly suitable habitat (0.8–1.0) **(**Figure 6).

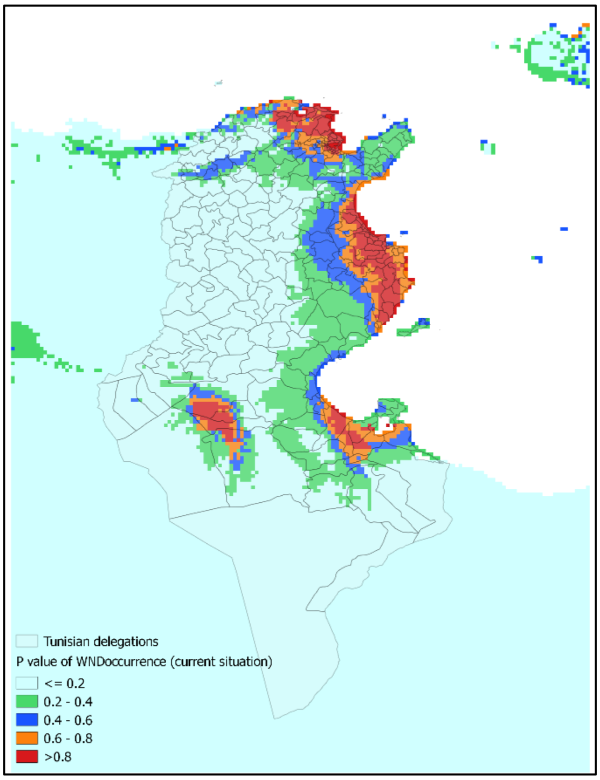


Fig 6: p-value distribution of WND occurrence suitable habitats in Tunisia (current situation)

To further validate the MaxEnt model results, a comparison with human WND confirmed cases recorded in 2018 (49 cases), was performed (Figure 7). The localisation of human cases is obtained by georeferencing of scanned map of WND human cases published online by ONMNE [6]. A leave-one-out cross validation was performed to validate the model. The area was considered well predicted when the mean p-value was higher than 0.05. The cross-validation based on the leave-one-out method identified 44 points of 49 (89.8%) falling in the suitable areas (P-value >0.05).

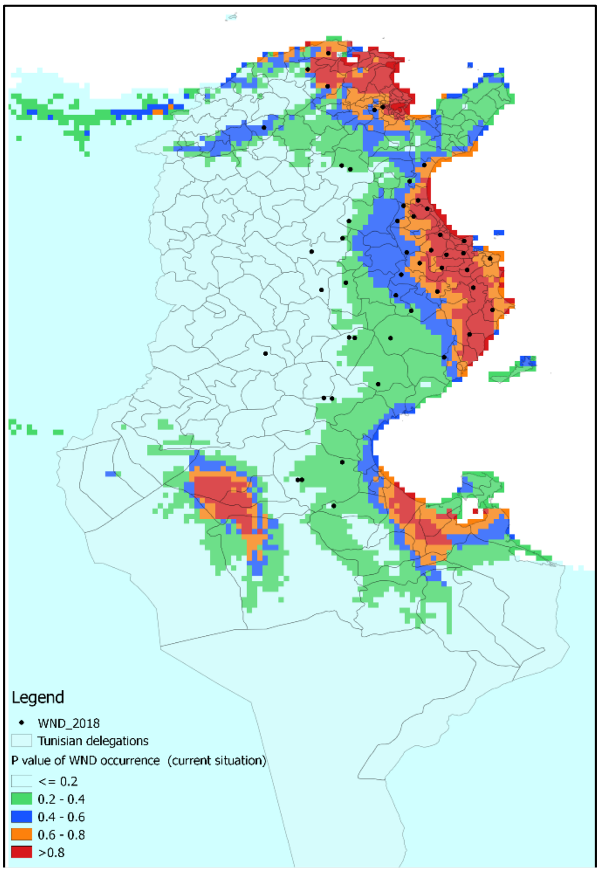


Fig 7: Tunisian delegations reporting WND human cases in 2018 superposed to risk map

Predicted future potential distribution for 2050

Although the location of the future potential distribution of WND is very similar to the current potential distribution (Figure 8), our model results suggest that the geographic distribution would expand under predicted levels of climate change. Compared with the area of the most optimal habitat under current climate prediction, the predictions for 2050 using the Rcp45 climatic models showed almost or slightly more than the present predictions.

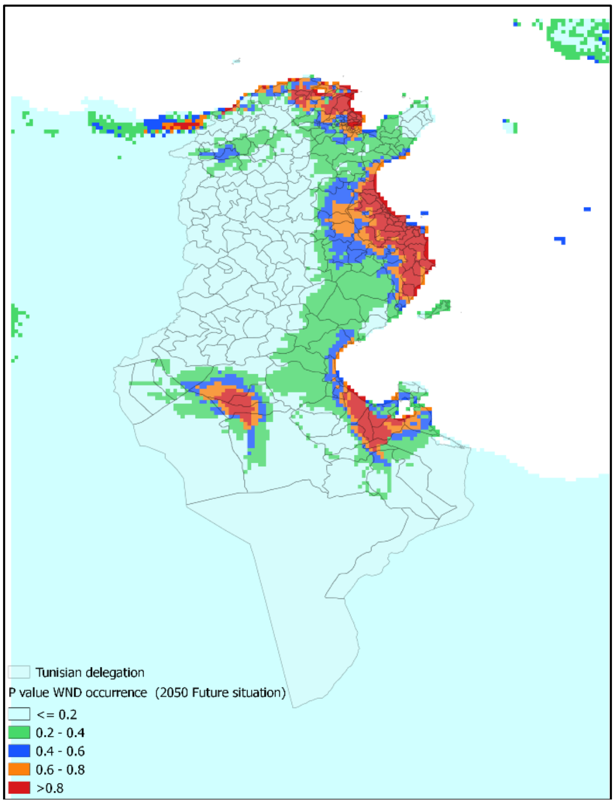


Fig 8: p-value distribution of WND occurrence suitable habitats in Tunisia (Future situation)

Discussion

The most geographically consistent result from this study was the positive relationship between WND occurrence and the minimum temperature recorded during the previous winter months in Tunisia. Warmer winter temperatures may lead to larger summer mosquito populations [23]. This is in accordance with the observations of Mogi (1996) who hypothesized that milder winters may lead to larger populations the following summer [24]**.** Field observations suggest that the overwintering phase of the WNV enzootic cycle is a climatically sensitive period. This phase has the potential to impact virus amplification and to ultimately increase the risk to humans during the subsequent transmission season. In Tunisia, the dynamics of WND may be greatly impeded by the overwintering period. The mosquito mortality caused by low temperature may reduce the survival of infected mosquitoes and limit the potential for virus amplification and transmission to humans in the following year. This hypothesis is supported by the positive association between winter temperature and WND risk. Indeed, high levels of overwintering mortality of diapausing mosquitoes have been reported, and mortality has been shown to increase during periods with particularly low temperatures and relative humidities [25-26]. Similarly, non-diapausing mosquitoes were also shown to have decreased activity during colder weather [27]. This decreased activity could reduce the potential for WNV transmission. In areas with harsh winters, small proportions of *C. Pipiens* can acquire WNV through vertical transmission. Then these infected mosquitoes enter diapause and carry the virus through the winter to infect avian hosts the next year. A better understanding of the specific mechanisms that affect mosquito activity and survival during the overwintering would help to identify with precision the types of climatic anomalies that can influence WNV risk during the subsequent summer in Tunisia.

In relation to precipitations, the results of this study suggest that precipitation of the warmest and driest quarter could explain better the pattern of spatial variability of WND spread in Tunisia. Warmest and driest quarters in Tunisia are generally in summer (June, July, August) and early fall (September, October). Our results suggest a positive correlation between WND occurrence and a level of precipitation ranged between 10 and 40 mm. the amount of precipitation can influence the patterns of disease incidence [28]**.** Above-average precipitation may lead to a higher abundance of mosquitoes, and to an increased potential for disease outbreaks [29]. These precipitations might have increased the standing water availability, an important breeding resource for mosquitoes. The delayed appearance of the disease observed in Gibraltar could be explained by an increase in rainfall later in the season (during August) [8]**.** However, our results demonstrate a negative correlation when the level of precipitation exceeds the 50 mm. Large rain events often negatively impacts the population size of *C. pipiens*, the primary enzootic and epidemic vector, by flushing catch basins, a primary urban larval habitat, and reducing organic content in all ovipositing sites [30]**.** The positive impact of precipitation (10-40 mm) is correlated with high temperature (precipitation of the warmest quarter). Increased temperature is known to increase growth rates of vector populations [31], decrease the length of the gonotrophic cycle (interval between blood meals), shorten the extrinsic incubation period of the virus in the vector and increase the rate of virus evolution [32]. It's clear that precipitation influences the emergence of mosquito populations in temperate climates [33].

Conclusion
Species distribution modelling generates valuable information regarding the influence of various climatic parameters on the occurrence and distribution of WND in Tunisia, which will be useful for preventing the occurrence of outbreaks of VBD. Our findings can be applied in various ways such as developing strategies for monitoring of this disease, which in turn will enable assessment of establishment risk in the presently unaffected regions. This model can be applied to identify environmental risk factors for others potential vector borne diseases in Tunisia.

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