Acta Tropica 169 (2017) 163–169

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Risk mapping of West Nile virus circulation in Spain, 2015

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ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form 10 February 2017
Accepted 13 February 2017
Available online 16 February 2017

Keywords:
West Nile virus
Risk assessment
Spain

ABSTRACT

West Nile fever is an emergent disease in Europe. The objective of this study was to conduct a predictive risk mapping of West Nile Virus (WNV) circulation in Spain based on historical data of WNV circulation. Areas of Spain with evidence of WNV circulation were mapped based on data from notifications to the surveillance systems and a literature review. A logistic regression-based spatial model was used to assess the probability of WNV circulation. Data were analyzed at municipality level. Mean temperatures of the period from June to October, presence of wetlands and presence of Special Protection Areas for birds were considered as potential predictors. Two predictors of WNV circulation were identified: higher temperature [adjusted odds ratio (AOR) 2.07, 95% CI 1.82–2.35, $p < 0.01$] and presence of wetlands (3.37, 95% CI 1.89–5.99, $p < 0.01$). Model validations indicated good predictions: area under the ROC curve was 0.895 (95% CI 0.870–0.919) for internal validation and 0.895 (95% CI 0.840–0.951) for external validation. This model could support improvements of WNV risk- based surveillance in Spain. The importance of a comprehensive surveillance for WNF, including human, animal and potential vectors is highlighted, which could additionally result in model refinements.

1. Introduction

West Nile virus (WNV) is a zoonotic flavivirus that is maintained in an enzootic cycle primarily through transmission between birds and ornithophilic (bird-biting) mosquitoes (Rossi et al., 2010). Mammals such as humans and horses are accidental dead-end hosts, as viremia resulting from WNV infection is insufficient to contribute to the amplification cycle (Jiménez-Clavero, 2012). Although up to 80% of human infections are asymptomatic, neuroinvasive disease occurs in less than 1% of the infections (Pérez-Ruiz et al., 2011).

West Nile fever (WNF) is an emergent disease in Europe, under surveillance in the European Union. Although serological surveys have pointed to WNV circulation in Europe since 1950s (Bardos et al., 1959), human outbreaks were relatively rare until recently. Since 2010, the WNV affected areas with confirmed human cases have further spread and the number of cases has increased markedly in Europe (ECDCD, 2011a, 2011b). Besides WNV lineage 1 that has traditionally circulated in Europe, lineage 2 has been recently detected in several European countries, including Greece (Papa et al., 2011) and Italy (Bagnarelli et al., 2011). In Spain, two cases of human WNF were confirmed in 2010 in Andalucía (southern Spain) (García-Bocanegra et al., 2011b). In the same area, outbreaks in horses have been detected since 2010–2014 (World Organisation for Animal Health, 2015).

Risk assessment (RA) is a systematic process for gathering, assessing and documenting information to assign a level of risk. This supports decision-making to reduce the negative consequences of public health risks (World Health Organization, 2012). Its importance has been particularly highlighted for assessing risks posed by emerging or re-emerging infections (Morgan et al., 2009). Determining spatial patterns is of particular interest to identify at risk territories. The objective of this study was to conduct a predictive risk mapping of WNV circulation in Spain based on historical data of WNV circulation, in order to support risk-based surveillance.

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http://dx.doi.org/10.1016/j.actatropica.2017.02.022
0001-706X/

2. Materials and methods

A predictive suitability map for WNV circulation in Spain was developed by following the next steps: (a) identification of areas with evidence of WNV circulation, (b) identification of suitability factors for WNV circulation, (c) logistic regression model to identify the predictors and estimate the probability of WNV circulation at municipality level, (d) generation of a predictive risk map.

2.1. Identification of areas with evidence of WNV circulation

Areas with evidence of WNV circulation were identified through a review of the notifications of WNF outbreaks to the Animal Health Alert Network of the Spanish Ministry of Agriculture, Food and Environment (MAGRAMA) and to the National Network of Epidemiological Human Surveillance (without temporal limits) as well as a literature review of scientific papers published in PubMed in which sampling was conducted between 2000 and 2015, using the search terms "West Nile virus"[Mesh] and Spain.

Evidence of WNV circulation in mosquitoes, birds or mammals was defined as (a) serological evidence confirmed by micro virus neutralization test (VNT) or plaque reduction neutralization test (PRNT); (b) WNV detection by polymerase chain reaction (PCR); (c) clinical compatible symptoms and IgM positive for WNV in horses or humans.

Areas with evidence of WNV circulation were mapped at municipality level, using ArcGis 10.2.

2.2. Suitability factors for WNV circulation

WNV is a complex disease that is influenced by multiple environmental and climatic factors. A literature review was conducted to identify conditions favoring WNV circulation. Four factors were considered as the most influential: abundance of competent vectors, temperature, presence of wetlands and existence of avian hosts.

Regarding competent vectors, *Culex* mosquitoes are considered the main vectors of WNV (Zeller and Schuffenecker, 2004). In Spain, species such as *Culex pipiens* have been found to be widely distributed in places where entomological studies have been conducted (Lucientes and Molina, 2014; Muñoz et al., 2012). Other factors such as temperature or presence of areas with seasonal or permanent water accumulations can influence mosquito abundance, so they were used as a proxy for spatial modeling.

Ambient temperature plays an important role in viral replication rates and transmission of WNV (Paz and Semenza, 2013). Optimal temperatures (up to 30–32 °C) increase growth rates of vector populations, decrease the interval between blood meals and accelerate the virus replication cycle (Dohm et al., 2002; Kilpatrick et al., 2008). Above-average summer temperatures have been associated with WNF outbreaks in United States and in Europe (Paz et al., 2013; Reisen et al., 2006). Higher temperatures in July and August were predictive of high-risk areas for WNV infection in Canadian horses (Epp et al., 2011).

Landscape features are influential factors for vector activity and virus endemization. Aquatic habitats are required for *Culex pipiens* females to oviposit and larvae to survive (Wynn and Paradise, 2001). Rural wetlands and river deltas provide ideal conditions, as serve as bird-nesting areas and favor the maintenance of the bird-mosquito cycle (Paz and Semenza, 2013). Most WNF outbreaks in Europe have occurred in wetland areas, such as the Rhone delta (Camargue region) in southern France (Murgue et al., 2001), the Volga delta in southern Russia (L'vov et al., 2004) and the Danube delta in Romania (ECDC/WHO Regional Office for Europe, 2011). The Po plain in Italy and the lowland plains between and around the Aliakmonas and Axios rivers in Greece have been identified as epicenters of recent outbreaks (Angelini et al., 2010; ECDCD, 2010). In a recent model of human WNF risk in Europe, the presence of wetlands was identified as risk factor of WNV infection (Tran et al., 2014). In Greece, proximity to water was an important predictor of appearance of both human and wild bird cases of WNV infection (Valiakos et al., 2014).

WNV outbreaks are driven by the ongoing presence of infected avian hosts since elevated viremia is critical for establishing infections in *Culex* mosquitoes (Paz and Semenza, 2013). The role of migratory birds in WNV dispersion into Europe has been supported by serological findings and phylogenetic studies (Charrel et al., 2003). Spanish sites serve as rest areas or destinations within flyways coming from WNV endemic areas, such as the African continent or Northern Europe. Migratory birds bring together with resident birds, which may contribute to the maintenance of local viral transmission (Calistri et al., 2010).

2.3. Statistical model

Data were analyzed at municipality level, including Spanish municipalities of the Iberian Peninsula and the Balearic Islands (n = 8209 spatial units). Logistic regression (LR) was used to estimate the probability of WNV circulation according to the following predictor variables:

- Temperatures: Data regarding temperature values were extracted from the digital cartographic database of the MAGRAMA for the period 2008–2010 (MAGRAMA: [Veterinary Health Alert Network]). Mean monthly values were computed in ArcGIS® software through the Spline interpolation function for each municipality's centroid. We used the mean temperature of the period from June to October (the period of WNV transmission in Spain), as continuous variable, for our logistic regression model.
- Wetlands: Wetlands included in the list of the Ramsar Convention (Ramsar official website: The Ramsar Convention and its mission), considered as wetlands of international importance, were used for spatial modelling, due to its particular relevance as waterfowls habitats. Cartographic information from Spanish wetlands included in the List of the Ramsar Convention was obtained from the Ramsar Sites Information Service and from the MAGRAMA's digital cartographic database (MAGRAMA:[Spanish wetlands included in the Ramsar Convention list]). Presence or absence of wetlands in each municipality was calculated using ArcGIS® software.
- Special Protection Areas (SPA) for birds: Many avian species could potentially act as WNV reservoirs, with evidence suggesting that passeriform birds (an order which includes more than half of all bird species) tend to be the most competent hosts (Ezenwa et al., 2006). As a proxy for modelling, we used cartographic information from SPA for birds, designated under the Directive 2009/147/EC of the European Parliament and of the Council of 30 November 2009 on the conservation of wild birds. These are habitats of wild birds, including many migratory species, which congregate not only in aquatic but also in terrestrial and mountainous environments. Data regarding SPA for birds was obtained from the MAGRAMA. Presence or absence of SPA for birds in each municipality was calculated using ArcGIS® software.

The existence or not of evidence of WNV circulation in a municipality was the dependent variable in the logistic regression model. We used data from sampling conducted between 2000 and 2013 to fit the model and data from 2014 and 2015 for external validation. We used likelihood-ratio-test-based backward stepwise model selection to select the final model, which retained variables with significant associations at 5% level. The Nagelkerke's R squared