Vector-Borne and Zoonotic Diseases

Vector-Borne and Zoonotic Diseases: http://mc.manuscriptcentral.com/vbz

Evaluation of a multivariate syndromic surveillance system for West Nile virus

Journal:	*Vector-Borne and Zoonotic Diseases*
Manuscript ID:	VBZ-2015-1883
Manuscript Type:	Original Research
Date Submitted by the Author:	09-Aug-2015
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Keyword:	West Nile, Surveillance, Modeling, Time Series Analysis
Abstract:	Background: Various methods are currently used for the early detection of West Nile virus (WNV) but their output is either not quantitative or does not take into account all available information. Our study aimed to test a multivariate syndromic surveillance system in order to improve early detection of WNV. Method: Weekly time series data on nervous syndromes in horses and mortality in both horses and wild birds were used. Baselines were fitted to the three time series and used to simulate 100 years of surveillance data. WNV outbreaks were simulated and inserted into the baselines based on historical data and expert opinion. Univariate and multivariate syndromic surveillance systems were tested in order to gauge how well they detected the outbreaks; detection was based on an empirical Bayesian approach. The systems' performances were compared using measures of sensitivity, specificity, and area-under-ROC-curve (AUC). Result: When data sources were considered separately (i.e. univariate systems), the best detection performance was obtained using the dataset of nervous symptoms in horses compared to those of bird and horse mortality (AUCs respectively equal to 0.80, 0.75, and 0.50). A multivariate outbreak detection system that used nervous symptoms in horses and bird mortality generated the best performance (AUC = 0.87). Conclusion: The proposed approach is suitable for performing multivariate

	syndromic surveillance of WNV outbreaks. This is particularly relevant given that a multivariate surveillance system performed better than a univariate approach. Such a surveillance system could be especially useful in serving as an alert for the possibility of human viral infections. This approach can be also used for other diseases for which multiple sources of evidence are available.

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ABSTRACT

Background: Various methods are currently used for the early detection of West Nile virus (WNV) but their output is either not quantitative or does not take into account all available information. Our study aimed to test a multivariate syndromic surveillance system in order to improve early detection of WNV.

Method: Weekly time series data on nervous syndromes in horses and mortality in both horses and wild birds were used. Baselines were fitted to the three time series and used to simulate 100 years of surveillance data. WNV outbreaks were simulated and inserted into the baselines based on historical data and expert opinion. Univariate and multivariate syndromic surveillance systems were tested in order to gauge how well they detected the outbreaks; detection was based on an empirical Bayesian approach. The systems' performances were compared using measures of sensitivity, specificity, and area-under-ROC-curve (AUC).

Result: When data sources were considered separately (i.e. univariate systems), the best detection performance was obtained using the dataset of nervous symptoms in horses compared to those of bird and horse mortality (AUCs respectively equal to 0.80, 0.75, and 0.50). A multivariate outbreak detection system that used nervous symptoms in horses and bird mortality generated the best performance (AUC = 0.87).

Conclusion: The proposed approach is suitable for performing multivariate syndromic surveillance of WNV outbreaks. This is particularly relevant given that a multivariate surveillance system performed better than a univariate approach. Such a surveillance system could be especially useful in serving as an alert for the possibility of human viral infections. This approach can be also used for other diseases for which multiple sources of evidence are available.

Key words: West Nile, syndromic surveillance, Bayes, horses, multivariate detection

INTRODUCTION

West Nile virus (WNV) is a mosquito-borne arbovirus mainly transmitted by mosquitoes from the genus *Culex* (family Culicidae). Its main hosts are birds but the virus also affects various non-avian species including horses and humans, with dramatic consequences for public health and for the equine industry, i.e. potentially fatal encephalitis in humans and horses (Campbell et al. 2002; Castillo-Olivares and Wood 2004). In Europe, WNV emerged in the 1960s and several outbreaks have been documented since that time (Calistri et al. 2010). Even if the virus is now considered endemic in a large part of Europe, the number of reported outbreaks is presently increasing in southern and eastern Europe, particularly in Italy, Greece, and Bulgaria (Di Sabatino et al. 2014). This increasing number of outbreaks, combined with the recent introduction and spread in Europe of WNV lineage 2, which induces severe symptoms in humans, horses, and birds (Bakonyi et al. 2006; Calzolari et al. 2013; Hernández-Triana et al. 2014), has resulted in growing concern about WNV in Europe. In addition, the implementation of prevention plans for WNV outbreaks is difficult (Zeller 2010) because the environmental factors and meteorological interactions underlying the increase in WNV circulating in mammals are still poorly understood. To improve early detection of WNV outbreaks, then, the major challenge is to develop more integrated and quantitative approaches (Beck et al. 2013; Bellini et al. 2014b).

Syndromic surveillance is currently a popular approach for the early detection of health-related phenomena (Dórea et al. 2011) and has already been implemented for WNV. In Europe, the surveillance of nervous syndromes in horses has been shown to detect early indicators of WNV outbreaks (Leblond et al. 2007; Saegerman et al. 2014) and is one of the most cost-effective surveillance systems in the European context (Chevalier et al. 2011). In the USA, instead, increased mortality in wild birds is one of the most timely indicators of virus activity (Brown 2012). Mortality in wild birds had rarely been reported in Europe until the recent explosive spread of lineage 2 in 2008-2009 in Hungary and Austria, which suggests that this parameter could be also incorporated into future monitoring systems in Europe (Bakonyi et al. 2013). This is consistent with recent experimental infections of European wild birds with various WNV strains, which generated an average mortality rate of 43% (Del Amo et al. 2014a; Del Amo et al. 2014b; Dridi et al. 2013; Sotelo et al. 2011; Ziegler et al. 2013). Apart from mortality in wild birds and nervous symptoms in horses, WNV is also associated with mortality in horses, which could constitute another signal of a WNV outbreak. Combining all available information in a multivariate algorithm should give better results for outbreak detection than univariate

methods alone. However, at the time of writing, multivariate syndromic surveillance has never been implemented for the detection of WNV outbreaks.

The aim of our study was to evaluate the performance of a multivariate syndromic surveillance system in detecting WNV using three datasets: nervous syndromes in horses and mortality in horses and wild birds. We focused on the French Mediterranean coast, which is a particularly high-risk area for WNV outbreaks. Indeed, in France, WNV has only ever been identified in this area, which is home to mammalian and avian hosts, bridging vectors, and large protected wetlands with numerous migratory birds.

MATERIALS AND METHODS

1. Data sources

1.1. Nervous syndromes in horses

Data on nervous syndromes in horses are collected through the passive surveillance system "RESPE". This French network for the surveillance of equine diseases (http://www.respe.net/) collects standardized declarations from veterinary practitioners registered as sentinels. All the samples sent for laboratory diagnosis are systematically tested for WNV and equine herpes virus, and results are registered in the RESPE database. To obtain an outbreak-free baseline dataset, we used data from 2006 to 2013 that included only the 44 declarations without positive laboratory test results from the region of the French Mediterranean coast. The time series of nervous syndromes in horses is designated *NervSy* in subsequent sections.

1.2. Mortality in horses

Data on mortality in horses have been centralized since 2010 in the "EDI-SPAN" database, managed by all the French fallen stock companies and the French Ministry of Agriculture (Perrin et al. 2012). As WNV does not produce perinatal mortality, we only considered the 8 742 dead adult horses collected around the French Mediterranean coast between 2010 and 2014. The time series of mortality in adult horses is designated *DeadHorse* in subsequent sections.

1.3. Mortality in wild birds

Data on mortality in wild birds are collected through the event-based surveillance system "SAGIR", the national French surveillance network of diseases in wild birds and mammals, which collects declarations from field workers (e.g., hunters, technicians from departmental hunting federations, and environmental inspectors from

the French National Hunting and Wildlife Agency (ONCFS)). Surveillance relies on diagnosis at a local veterinary laboratory (Decors et al. 2014). Between 2007 and 2013, 292 dead wild birds were collected and necropsied around the French Mediterranean coast. The time series of the number of necropsied wild birds is designated *DeadBird* in subsequent sections.

2. Data modeling and simulation

2.1. Baselines

All time series were aggregated weekly. Using visual examination, abnormal peaks were observed only in *DeadBird.* These extreme values were removed based on a method adapted from Tsui *et al.* (Tsui et al. 2001): the entire dataset was first fitted to a Poisson distribution and then values above the 95% confidence interval were deleted and replaced with the average value of the four previous weeks.

To calibrate the models, we used *NervSy* data from 2006 to 2010, *DeadHorse* data from 2011 to 2013, and *DeadBird* data from 2007 to 2011. Instead, to validate the quality of predictions, we used *NervSy* data from 2011 to 2013, *DeadHorse* data from 2014, and *DeadBird* data from 2012 to 2013. To define the background noise of the time series without outbreaks, we fitted alternative regression models based on Poisson and negative binomial ($\mathcal{NB}$) distributions. Models were implemented in R x64 version 3.0.2. Dynamic regression was performed with the functions *glm* (package {stats}) and *glm.nb* (package {MASS}). The expected number of counts at time *t* was estimated with the *predict* functions of the respective packages.

Models were evaluated using the Akaike information criterion (AIC) (Bozdogan 1987), and the adjusted deviance (deviance/degree of freedom) was used as a measure of goodness-of-fit (GOF). The agreement between predicted and observed values was assessed according to the root-mean-squared error (Chai and Draxler 2014). The criterion was assessed within the calibration period ($RMSE_c$) and within the validation period ($RMSE_v$). In either case, the lower the value, the better the predictive performance of the model.

For each time series, the best regression model was used to predict the expected value of each week of the next simulated year. Distribution of cases for each week was defined as a Poisson distribution with lambda equals to the predicted value for the same week. Weekly samples from 100 fictive years were generated by random sampling from the previous distributions as proposed by Dórea *et al.* (Dórea et al. 2013).

2.2. WNV outbreaks

Data on real WNV outbreaks are scarce, so we thus used simulated outbreaks to evaluate our detection system. For each syndrome, the distribution of the number of cases during an outbreak was estimated with the *fitdist* function of the package {fitdistrplus}. Time series for each syndrome during 100 fictive outbreaks were simulated by randomly sampling the corresponding distribution. One simulated outbreak was inserted in each simulated baseline. The outbreaks related to nervous cases in horses were randomly inserted, followed by the corresponding outbreaks related to wild bird mortality, such that the time lag between the first dead bird and the first nervous case in horses due to WNV was 0, 1, or 2 weeks (Kulasekera et al. 2001). The corresponding horse mortality outbreaks were inserted such that half of the affected horses died the week of onset of clinical signs and half died the week after (Bunning et al. 2002; Cantile et al. 2000; Trock et al. 2001; Ward et al. 2006).

The weekly counts of cases of five real European WNV outbreaks (Anonymous 2007; Autorino et al. 2002; Kutasi et al. 2011; Leblond et al. 2007; Murgue et al. 2001) were fitted to the $\mathcal{NB}$ distribution and the resulting distribution of the additional number of nervous cases due to WNV during an outbreak was $\mathcal{NB}$(mu=3.12, theta=1.150). The mortality among horses clinically affected by WNV was fitted to a normal distribution (mean=0.384, standard deviation=0.128) based on (Autorino et al. 2002; Leblond et al. 2007; Murgue et al. 2001; Ward et al. 2006). The *NervSy* dataset did not provide the real number of clinically affected horses, so we assumed that only 50% of horses with nervous symptoms were declared to RESPE. To estimate the real number of clinically affected horses, we simulated RESPE declarations of nervous symptoms associated with 100 WNV outbreaks and doubled the counts of horses obtained. The related weekly count of dead adult horses was then deduced and fitted to the $\mathcal{NB}$ distribution $\mathcal{NB}$(mu=3, theta=2.005). The distribution of the weekly number of dead birds was estimated by expert opinion to be $\mathcal{NB}$(mean=2.23, theta=3.34).

3. Outbreak detection

3.1. Bayesian framework

Bayesian hypothesis testing is based on two mutually exclusive hypotheses which can be expressed in the syndromic surveillance context as H_1, "there is an ongoing outbreak of WNV (or another disease with similar symptoms)", and H_0, "there is no ongoing outbreak" (Andersson et al. 2014). The relative probability of the two hypotheses can be expressed as a ratio (O_{pri}) which represents our *a priori* belief about the disease status:

Eq.1 $$O_{pri} = \frac{P(H_1)}{P(H_0)}$$

When evidence in favor (or not) of each hypothesis is observed, we can build the *a posteriori* belief about the disease's status (O_{post}):

Eq.2 $$O_{post} = \frac{P(H_1 \mid E_x)}{P(H_0 \mid E_x)}$$

where $P(H_1 \mid E_x)$ is the probability of H_1 given the evidence E observed in time series *x* and $P(H_0 \mid E_x)$ is the probability of H_0 given the evidence E observed in time series *x.*

Using this general framework with the application of Bayes' theorem, O_{post} can be calculated as:

Eq.3 $$O_{post} = V_x \times O_{pri} = \frac{P(E_x \mid H_1)}{P(E_x \mid H_0)} \times \frac{P(H_1)}{P(H_0)}$$

where V_x is the value of evidence, $P(E_x|H_1)$ is the probability of observing the number of reported cases of syndrome *x* in a particular week given that H_1 is true, and $P(E_x|H_0)$ is the probability of observing the number of reported cases of syndrome *x* in a particular week given that H_0 is true.

In order to estimate $P(E_x|H_1)$ and $P(E_x|H_0)$, information on the probability distribution for the number of reported cases in non-outbreak and outbreak situations is used. The probability of E_x (observation of *n* cases in time series *x*) during an outbreak is calculated as:

Eq.4 $$P(E_x \mid H_1) = \sum_{i=0}^{n} P_{base}(i) \times P_{out}(n-i)$$

where $P_{base}(i)$ is the probability of drawing *i* cases from the baseline distribution in time series *x* and $P_{out}(i)$ is the probability of drawing *i* cases from the outbreak distribution in time series *x* based on the shape of the outbreak, as previously simulated.

3.2. Combining time series

When the three time series were combined, V_{tot} incorporated evidence from *NervSy*, *DeadHorse,* and *DeadBird*, respectively denoted as E_{NervSy}, $E_{DeadHorse}$, and $E_{DeadBird}$. Assuming that the three sources of evidence were independent, V_{tot} was calculated as:

Eq.5 $$V_{tot} = \frac{P(E_{NervSy}, E_{DeadHorse}, E_{DeadBird} \mid H_1)}{P(E_{NervSy}, E_{DeadHorse}, E_{DeadBird} \mid H_0)} = V_{NervSy} \times V_{DeadHorse} \times V_{DeadBird}$$

and O_{post_tot} was calculated as:

Eq.6 $$O_{post\_tot} = \frac{P(H_1 \mid E_{NervSy}, E_{DeadHorse}, E_{DeadBird})}{P(H_0 \mid E_{NervSy}, E_{DeadHorse}, E_{DeadBird})} = V_{tot} \times \frac{P(H_1)}{P(H_0)}$$

4. Performance assessment

Sensitivity (Se) and specificity (Sp) were calculated as:

Eq.7 $Se = TP / (TP + FN)$

Eq.8 $Sp = TN / (TN + FP)$

where TP is the number of true positive alarms, TN the number of true negative alarms, FP the number of false positive alarms, and FN the number of false negative alarms.

The receiver operating characteristic (ROC) curve was generated in R by testing various alarm thresholds, and the areas under the curves (AUC) were calculated with the *auc* function of the package {flux}. A larger AUC represented a better detection performance.

RESULTS

1. Modeling time series and simulating data

For all time series the best fits were obtained for $\mathcal{NB}$ distributions. The resulting models' parameters are summarized in table 1 and corresponding baselines and predictions are shown in figure 1. The probabilities of observing *n* cases and the resulting value of V ($p(E|H_1)/ p(E|H_0)$) during a non-outbreak ($p(E|H_0)$) and an outbreak ($p(E|H_1)$) situation for each time series are summarized in figure 2.

2. Outbreak detection

We estimated the respective performance of each univariate system (*NervSy*, *DeadHorse*, and *DeadBird*) in detecting WNV outbreaks without considering any *a priori* values for disease status (O_{pri}=1). Examples of simulated baselines with inserted outbreaks and associated variations in log10(V) are presented in Appendix I.

The best results for univariate outbreak detection were obtained for *NervSy*, which outperformed analyses using *DeadHorse* and *DeadBird* (figure 3 and table 2). *DeadBird* models yielded intermediary detection performances whereas models using *DeadHorse* were not able to discriminate between outbreak and non-outbreak situations (AUC≈0.50).

The best results for multivariate outbreak detection were obtained for analyses that combined *NervSy* with *DeadBird* data, which gave similar results to a combination of the three time series (figure 3 and table 2). The results of using *NervSy* combined with *DeadBird* were also better than those obtained with each time series alone. For example, for a specificity set at 0.80, the sensitivity of the detection reached 0.80 with the combined *NervSy* and *DeadBird* series whereas it was 0.67 with *NervSy* and 0.60 with *DeadBird* alone.

DISCUSSION

Our results indicated that the best detection performance was obtained using multivariate syndromic surveillance based on reports of nervous symptoms in horses (*NervSy*) and wild bird mortality (*DeadBird*). To our knowledge, this is the first time that multivariate syndromic surveillance has been implemented for WNV detection. However, when using a univariate detection method, *NervSy* was the best indicator of WNV outbreaks. This is consistent with the number of expected cases during an outbreak compared to the baseline of each time series considered (i.e. high number of case for *NervSy*, moderate number of cases for *DeadBird*, and low number of cases for *DeadHorse*). Indeed, models based only on the *DeadHorse* data resulted in poor detection performance at the regional level because mortality in horses is mainly due to causes other than WNV. However, before ruling on the usefulness of this datasource for WNV surveillance, it would be interesting to test whether an outbreak generates local clusters of deaths in horses that may be used as a signal of a VNW outbreak. However, the quality of geographical information of reported cases are currently insufficient to test this hypothesis.

This is the first time that a real assessment of system performance has been implemented for WNV surveillance. Previous early warning systems developed for WNV only identified risk factors of WNV outbreaks, but did not evaluate the detection performances of those systems (Adlouni et al. 2007; Bellini et al. 2014a; Brown 2012; Chaskopoulou et al. 2013; Gosselin et al. 2005; Rosà et al. 2014; Shuai et al. 2006; Valiakos et al. 2014). Timeliness has occasionally been evaluated but only based on a limited number of real WNV outbreaks, and has not been associated with a further evaluation of system performance (Calzolari et al. 2013; Chaintoutis et al. 2014; Eidson et al. 2001; Johnson et al. 2006; Mostashari et al. 2003; Veksler et al. 2009). Only two attempts to assess the sensitivity and specificity of surveillance have been made (Andersson et al. 2014; Leblond et al. 2007) but the parameters of interest were only evaluated based on a limited number of outbreaks, which did not allow any conclusions to be drawn regarding overall system performance.

To assess the surveillance systems and compare them, we simulated baselines and outbreaks using parameters from data observed in Europe (Anonymous 2007; Autorino et al. 2002; Bakonyi et al. 2013; Leblond et al. 2007; Ward et al. 2006). To expand upon this, patterns of outbreaks in other locations should be tested in order to evaluate the performance of multivariate syndromic surveillance in more varied situations. Particular attention should be paid to patterns of mortality of wild birds, as the dynamics of wild bird mortality during a WNV outbreak have only been poorly investigated in Europe.

The Bayesian approach seems well adapted for multivariate WNV detection and can be used for other diseases. Indeed, Bayesian hypothesis testing is based on two mutually exclusive hypotheses which can be expressed in the syndromic surveillance context as: H_1, “there is an ongoing outbreak of WNV or of another disease with similar symptoms”, and H_0, “there is no ongoing outbreak”. It would be theoretically possible to include every possible differential diagnosis for every syndrome (or group of syndromes) considered; however, such a system would be difficult to implement and maintain. It would thus be interesting to first examine the evidence from each time series individually and then together in order to identify which combination of datasets results in the strongest signal. It would be up to the relevant decision maker in a given situation to consider appropriate differential diagnoses and the actions that should be implemented for further investigation.

In our study, we considered three sources of evidence for WNV outbreak detection. Nevertheless, additional information can be utilized with Bayesian approaches, as it is easy to add such information. Then, a next step in

the early detection of WNV outbreaks should be to test the efficiency of the method with other data, such as the predicted abundance of mosquitoes (Calistri et al. 2014; Rosà et al. 2014), environmental risk factors (Tran et al. 2014), and risk of introduction (Bessell et al. 2014; Brown et al. 2012).

CONCLUSION

The proposed approach is suitable for performing multivariate syndromic surveillance of WNV outbreaks. Indeed, we found that a multivariate surveillance system using this approach performed better than a univariate approach in detecting WNV outbreaks in southern France. In particular, a combination of data regarding nervous symptoms in horses and wild bird mortality was the most efficient in detecting outbreaks. Such multivariate surveillance systems could be especially useful in serving as early warnings for possible human viral infections, considering that horses and birds are affected by WNV before humans (Kulasekera et al. 2001; Leblond et al. 2007). We propose that this methodology is generally applicable to other diseases for which multiple sources of evidence are available.

ACKNOWLEDGMENTS

Data on mortality in horses were provided by the French Ministry of Agriculture. Data on mortality in wild birds were provided by the event-based surveillance system “SAGIR”, the French surveillance network for wild birds and mammals. Data on nervous symptoms in horses were provided by ‘RESPE’ (Réseau d’Epidémio-Surveillance en Pathologie Equine). The authors wish to thank all persons involved in these networks (hunters, technicians of FDC and environmental inspectors of ONCFS, local veterinary laboratories, veterinarians, and fallen stock companies) for collecting these data and all these institutes for providing them.

This research was carried out as part of the VICE project funded under the FP7 EMIDA ERA-NET initiative. National funding within ERA-Net was provided by the Dutch Ministry of Economic Affairs (Project nr. BO-20-009-009) and by the Swedish research council Formas. This work was also partially financially supported by IFCE (Institut Français du Cheval et de l’Equitation) and Vetagro Sup (National Veterinary School of Lyon).

DISCLOSURE STATEMENT

No competing financial interests exist.

REFERENCES

Adlouni S El, Beaulieu C, Ouarda T, Gosselin P, Saint-Hilaire A. Effects of climate on West Nile Virus transmission risk used for public health decision-making in Quebec. Int. J. Health Geogr. 2007;6(1):1–7.

Del Amo J, Llorente F, Figuerola J, Soriguer RC, et al. Experimental infection of house sparrows (Passer domesticus) with West Nile virus isolates of Euro-Mediterranean and North American origins. Vet. Res. 2014a;45(1):33.

Del Amo J, Llorente F, Pérez-Ramirez E, Soriguer RC, et al. Experimental infection of house sparrows (Passer domesticus) with West Nile virus strains of lineages 1 and 2. Vet. Microbiol. 2014b;172(3–4):542–7.

Andersson MG, Faverjon C, Vial F, Legrand L, Leblond A. Using bayes' rule to define the value of evidence from syndromic surveillance. PloS One. 2014;9(11):e111335.

Anonymous. Programme de surveillance vétérinaire de la fièvre West-Nile. Direction générale de l'alimentation; 2007. Report No.: DGAL/SDSPA/N2007-8136. Available from: http://agriculture.gouv.fr/IMG/pdf/dgaln20078136z.pdf

Autorino GL, Battisti A, Deubel V, Ferrari G, et al. West Nile virus Epidemic in Horses, Tuscany Region, Italy. Emerg. Infect. Dis. 2002;8(12):1372–8.

Bakonyi T, Ferenczi E, Erdélyi K, Kutasi O, et al. Explosive spread of a neuroinvasive lineage 2 West Nile virus in Central Europe, 2008/2009. Vet. Microbiol. 2013;165(1–2):61–70.

Bakonyi T, Ivanics É, Erdélyi K, Ursu K, et al. Lineage 1 and 2 Strains of Encephalitic West Nile Virus, Central Europe. Emerg. Infect. Dis. 2006;12(4):618–23.

Beck C, Jimenez-Clavero M, Leblond A, Durand B, et al. Flaviviruses in Europe: Complex Circulation Patterns and Their Consequences for the Diagnosis and Control of West Nile Disease. Int. J. Environ. Res. Public. Health. 2013;10(11):6049–83.

Bellini R, Calzolari M, Mattivi A, Tamba M, et al. The experience of West Nile virus integrated surveillance system in the Emilia-Romagna region: five years of implementation, Italy, 2009 to 2013. Euro Surveill. 2014a;19(44).

Bellini R, Zeller H, Bortel WV. A review of the vector management methods to prevent and control outbreaks of West Nile virus infection and the challenge for Europe. Parasit. Vectors. 2014b;7(1):323.

Bessell PR, Robinson RA, Golding N, Searle KR, et al. Quantifying the Risk of Introduction of West Nile Virus into Great Britain by Migrating Passerine Birds. Transbound. Emerg. Dis. 2014;

Bozdogan H. Model selection and Akaike's information criterion (AIC): The general theory and its analytical extensions. Psychometrika. 1987;52(3):345–70.

Brown EBE, Adkin A, Fooks AR, Stephenson B, et al. Assessing the Risks of West Nile Virus-Infected Mosquitoes from Transatlantic Aircraft: Implications for Disease Emergence in the United Kingdom. Vector-Borne Zoonotic Dis. 2012;12(4):310–20.

Brown G. California Mosquito-borne Virus Surveillance & Response Plan. Mosquito & Vector control Association of California, University of California at Davis; 2012 p. 57. Available from: http://www.cdph.ca.gov/HealthInfo/discond/Documents/CAResponsePlanMay2012.pdf

Bunning ML, Bowen RA, Cropp CB, Sullivan KG, et al. Experimental infection of horses with West Nile virus. Emerg. Infect. Dis. 2002;8(4):380–6.

Calistri P, Giovannini A, Hubalek Z, Ionescu A, , et al. Epidemiology of West Nile in Europe and in the Mediterranean Basin. Open Virol. J. 2010;4:29–37.

Calistri P, Savini L, Candeloro L, Di Sabatino D, et al. A Transitional Model for the Evaluation of West Nile Virus Transmission in Italy. Transbound. Emerg. Dis. 2014; Available from: http://doi.wiley.com/10.1111/tbed.12290

280 Calzolari M, Monaco F, Montarsi F, Bonilauri P, Ravagnan S, Bellini R, et al. New incursions of West Nile virus
281 lineage 2 in Italy in 2013: the value of the entomological surveillance as early warning system. Vet. Ital.
282 2013;49(3):315–9.

283 Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ. West Nile virus. Lancet Infect. Dis. 2002;2(9):519–29.

284 Cantile C, Di Guardo G, Eleni C, Arispici M. Clinical and neuropathological features of West Nile virus equine
285 encephalomyelitis in Italy. Equine Vet. J. 2000;32(1):31–5.

286 Castillo-Olivares J, Wood J. West Nile virus infection of horses. Vet. Res. 2004;35(4):467–83.

287 Chaintoutis SC, Dovas CI, Papanastassopoulou M, Gewehr S, et al. Evaluation of a West Nile virus surveillance
288 and early warning system in Greece, based on domestic pigeons. Comp. Immunol. Microbiol. Infect. Dis.
289 2014;37(2):131–41.

290 Chai T, Draxler RR. Root mean square error (RMSE) or mean absolute error (MAE)? – Arguments against
291 avoiding RMSE in the literature. Geosci. Model Dev. 2014;7(3):1247–50.

292 Chaskopoulou A, Dovas CI, Chaintoutis SC, Kashefi J, et al. Detection and Early Warning of West Nile Virus
293 Circulation in Central Macedonia, Greece, Using Sentinel Chickens and Mosquitoes. Vector-Borne Zoonotic Dis.
294 2013;13(10):723–32.

295 Chevalier V, Lecollinet S, Durand B. West Nile virus in Europe: a comparison of surveillance system designs in a
296 changing epidemiological context. Vector Borne Zoonotic Dis. 2011;11(8):1085–91.

297 Decors A, Hars J, Faure E, Quintaine T, et al. Le réseau Sagir: un outil de vigilance vis-à-vis des agents
298 pathogènes exotiques. Bull. Épidémiologique Santé Anim. Aliment. 2014;(66):35–9.

299 Dórea FC, McEwen BJ, McNab WB, Revie CW, Sanchez J. Syndromic surveillance using veterinary laboratory
300 data: data pre-processing and algorithm performance evaluation. J. R. Soc. Interface. 2013;10(83):20130114.

301 Dórea FC, Sanchez J, Revie CW. Veterinary syndromic surveillance: Current initiatives and potential for
302 development. Prev. Vet. Med. 2011;101(1-2):1–17.

Dridi M, Vangeluwe D, Lecollinet S, van den Berg T, Lambrecht B. Experimental infection of Carrion crows (Corvus corone) with two European West Nile virus (WNV) strains. Vet. Microbiol. 2013;165(1–2):160–6.

Eidson M, Kramer L, Stone W, Hagiwara Y, Schmit K. Dead bird surveillance as an early warning system for West Nile virus. Emerg. Infect. Dis. 2001;7(4):631–5.

Gosselin P, Lebel G, Rivest S, Douville-Fradet M. The Integrated System for Public Health Monitoring of West Nile Virus (ISPHM-WNV): a real-time GIS for surveillance and decision-making. Int. J. Health Geogr. 2005;4(1):1–12.

Hernández-Triana LM, Jeffries CL, Mansfield KL, Carnell G, et al. Emergence of West Nile Virus Lineage 2 in Europe: A Review on the Introduction and Spread of a Mosquito-Borne Disease. Front. Public Health. 2014;2(271). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4258884/

Johnson GD, Eidson M, Schmit K, Ellis A, Kulldorff M. Geographic Prediction of Human Onset of West Nile Virus Using Dead Crow Clusters: An Evaluation of Year 2002 Data in New York State. Am. J. Epidemiol. 2006;163(2):171–80.

Kulasekera VL, Kramer L, Nasci RS, Mostashari F, et al. West Nile virus infection in mosquitoes, birds, horses, and humans, Staten Island, New York, 2000. Emerg. Infect. Dis. 2001;7(4):722–5.

Kutasi O, Bakonyi T, Lecollinet S, Biksi I, et al. Equine Encephalomyelitis Outbreak Caused by a Genetic Lineage 2 West Nile Virus in Hungary: Lineage 2 West Nile Virus Encephalomyelitis. J. Vet. Intern. Med. 2011;25(3):586–91.

Leblond A, Hendrikx P, Sabatier P. West Nile Virus Outbreak Detection Using Syndromic Monitoring in Horses. Vector-Borne Zoonotic Dis. 2007 Sep;7(3):403–10.

Mostashari F, Kulldorff M, Hartman JJ, Miller JR, Kulasekera V. Dead Bird Clusters as an Early Warning System for West Nile Virus Activity. Emerg. Infect. Dis. 2003;9(6):641–6.

Murgue B, Murri S, Zientara S, Durand B, et al. West Nile outbreak in horses in southern France, 2000: the return after 35 years. Emerg. Infect. Dis. 2001;7(4):692–6.

Perrin J-B, Ducrot C, Vinard J-L, Morignat E, et al. Assessment of the utility of routinely collected cattle census and disposal data for syndromic surveillance. Prev. Vet. Med. 2012;105(3):244–52.

Rosà R, Marini G, Bolzoni L, Neteler M, et al. Early warning of West Nile virus mosquito vector: climate and land use models successfully explain phenology and abundance of Culex pipiens mosquitoes in north-western Italy. Parasit Vectors. 2014;7(269). Available from: http://www.biomedcentral.com/content/pdf/1756-3305-7-269.pdf

Di Sabatino D, Bruno R, Sauro F, Danzetta ML, et al. Epidemiology of West Nile Disease in Europe and in the Mediterranean Basin from 2009 to 2013. BioMed Res. Int. 2014;2014(ID 907852):10.

Saegerman C, Alba-Casals A, García-Bocanegra I, Dal Pozzo F, van Galen G. Clinical Sentinel Surveillance of Equine West Nile Fever, Spain. Transbound. Emerg. Dis. 2014; Available from: http://doi.wiley.com/10.1111/tbed.12243

Shuai J, Buck P, Sockett P, Aramini J, Pollari F. A GIS-driven integrated real-time surveillance pilot system for national West Nile virus dead bird surveillance in Canada. Int. J. Health Geogr. 2006;5(1):1–14.

Sotelo E, Gutierrez-Guzmán A, del Amo J, Llorente F, et al. Pathogenicity of two recent Western Mediterranean West Nile virus isolates in a wild bird species indigenous to Southern Europe: the red-legged partridge. Vet. Res. 2011;42(1):1–8.

Tran A, Sudre B, Paz S, Rossi M, et al. Environmental predictors of West Nile fever risk in Europe. Int. J. Health Geogr. 2014;13(1):26.

Trock SC, Meade BJ, Glaser AL, Ostlund EN, et al. West Nile virus outbreak among horses in New York State, 1999 and 2000. Emerg. Infect. Dis. 2001;7(4):745.

Tsui FC, Wagner MM, Dato V, Chang CC. Value of ICD-9 coded chief complaints for detection of epidemics. Proc. AMIA Symp. 2001;711–5.

Valiakos G, Papaspyropoulos K, Giannakopoulos A, Birtsas P, et al. Use of Wild Bird Surveillance, Human Case Data and GIS Spatial Analysis for Predicting Spatial Distributions of West Nile Virus in Greece. PLoS ONE. 2014;9(5):e96935.

Veksler A, Eidson M, Zurbenko I. Assessment of methods for prediction of human West Nile virus (WNV) disease from WNV-infected dead birds. Emerg. Themes Epidemiol. 2009;6(1):1–10.

Ward MP, Schuermann JA, Highfield LD, Murray KO. Characteristics of an outbreak of West Nile virus encephalomyelitis in a previously uninfected population of horses. Vet. Microbiol. 2006 Dec 20;118(3–4):255–9.

Zeller H. West Nile virus: the need to strengthen preparedness in Europe. 2010;15(34). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19647

Ziegler U, Angenvoort J, Fischer D, Fast C, et al. Pathogenesis of West Nile virus lineage 1 and 2 in experimentally infected large falcons. Vet. Microbiol. 2013;161(3-4):263–73.

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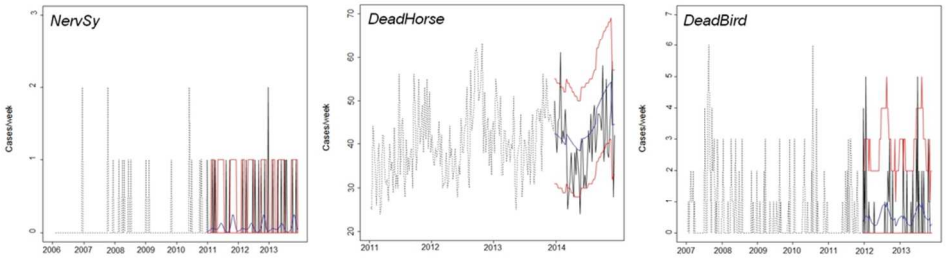
ILLUSTRATIONS

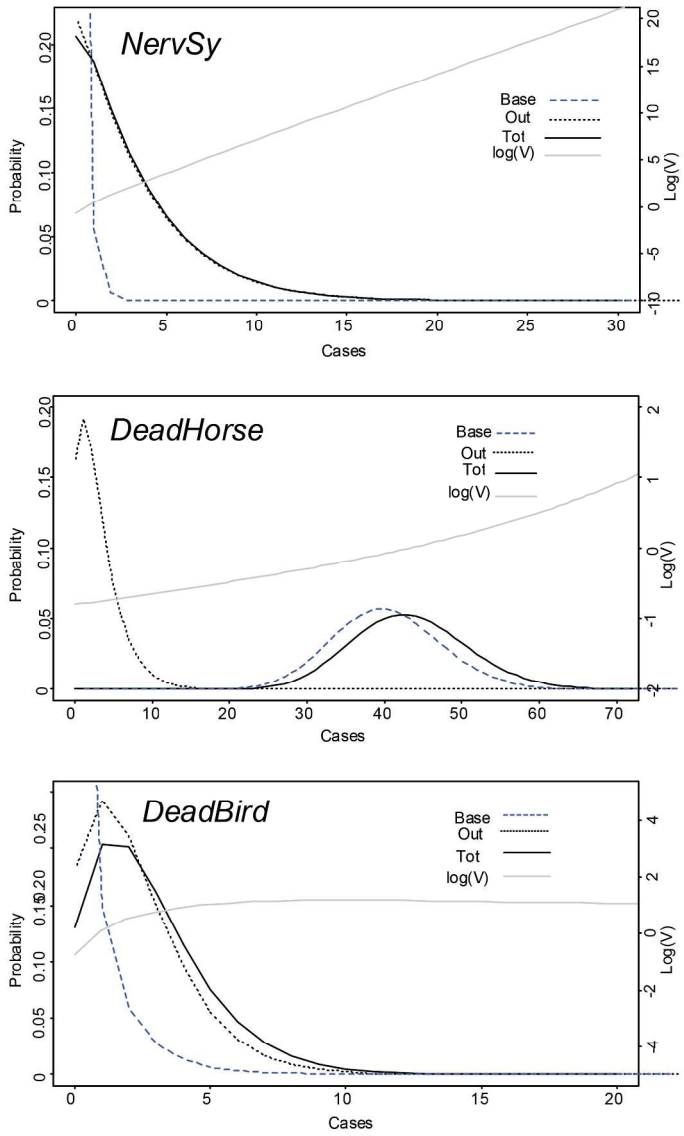
Figure 1: Three time series considered. *NervSy*: number of declaration of nervous syndrome in horses without positive lab result. *DeadHorse*: number of dead adult horses collected by French fallen stock companies. *DeadBird:* number of dead wild birds autopsied with values above the 95% confidence interval deleted. Dotted lines = training data, solid black lines = test data, solid blue lines = predicted value, solid red lines = 95% Confidence interval.

Figure 2: Value of evidence and probabilities of observing n cases during a non-outbreak (Base) and an outbreak (Out) situation. Base= distribution of distribution into the baseline, Out = distribution of cases related to a WNV outbreak, Tot= distribution of cases during an outbreak (Base + Out), Log(V)= $\log_{10}(p(n|\text{outbreak})/p(n|\text{baseline}))$. Out was based for *NervSy* on NB(mu= 3.12, theta =1.150), for *DeadHorse* on NB(mu= 3, theta =2.005), and for *DeadBird* on NB(mean= 2.23, theta=3.34).

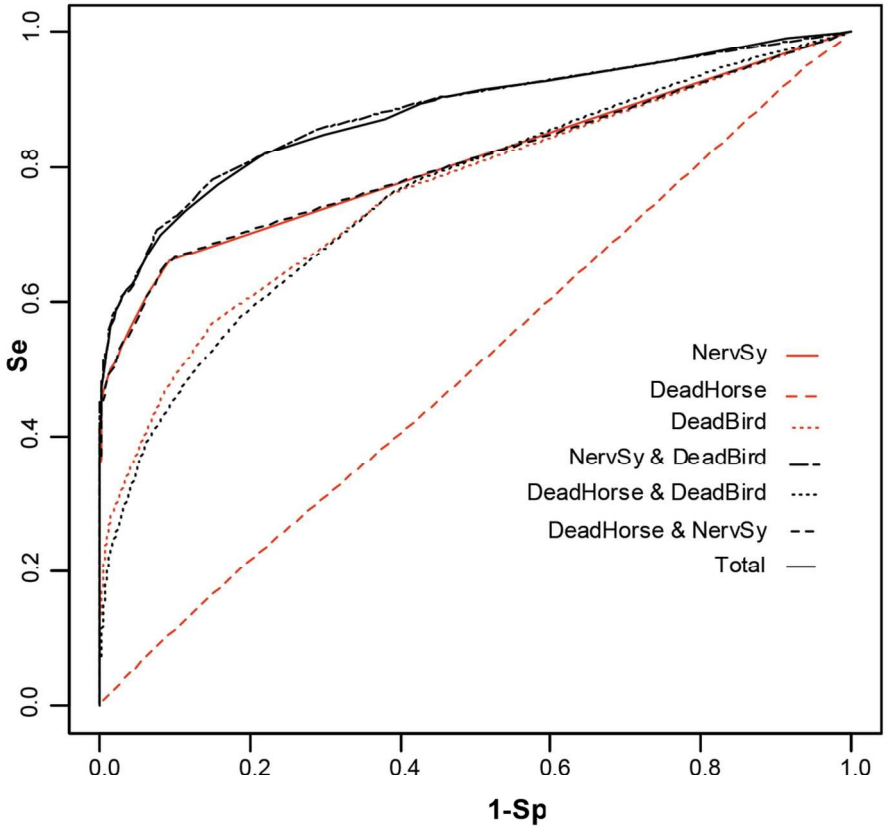
Figure 3: ROC curves for univariate and multivariate outbreak detection using *NervSy*, *DeadHorse* and *DeadBird.*



Three time series considered. NervSy: number of declaration of nervous syndrome in horses without positive lab result. DeadHorse: number of dead adult horses collected by French fallen stock companies. DeadBird: number of dead wild birds autopsied with values above the 95% confidence interval deleted. Dotted lines = training data, solid black lines = test data, solid blue lines = predicted value, solid red lines = 95% Confidence interval.
95x30mm (300 x 300 DPI)



Value of evidence and probabilities of observing n cases during a non-outbreak (Base) and an outbreak (Out) situation. Base= distribution of distribution into the baseline, Out = distribution of cases related to a WNV outbreak, Tot= distribution of cases during an outbreak (Base + Out), Log(V)= log10(p(n|outbreak)/p(n|baseline)). Out was based for NervSy on NB(mu= 3.12, theta =1.150), for DeadHorse on NB(mu= 3, theta =2.005), and for DeadBird on NB(mean= 2.23, theta=3.34).
297x420mm (300 x 300 DPI)



ROC curves for univariate and multivariate outbreak detection using NervSy, DeadHorse and DeadBird.
124x115mm (300 x 300 DPI)

Negative binomial distribution			*AIC*	*GOF*	$RMSE_c$	$RMSE_v$
Formulae	*theta*	*mean*				
NervSy $\sim \sin(2\pi(t-4)/18.33) + \sin(2\pi t/26.5)$	0.413	0.077	143	0.279	0.30	0.39
DeadHorse $\sim 4 \times (t-4)/52 + t + \sin(2\pi(t-12)/53)$	176	40.3	1063	1.016	7.06	8.57
DeadBird $\sim 4 \times (t-4)/52 + \sin(2\pi t/26.5)$	0.373	0.520	497	0.675	1.03	1.05

Table 1: Models and models parameters obtained for the three time series.

	NervSy	*DeadHorse*	*DeadBird*	*NervSy & DeadBird*	*NervSy & DeadHorse*	*DeadHorse & DeadBird*	*Total*
AUC	0.80	0.50	0.75	0.87	0.80	0.75	0.87
Standard error	0.0082	0.0097	0.0089	0.0068	0.0081	0.0089	0.0068

Table 2: Area under the ROC curve (AUC) and standard error for univariate and multivariate outbreak detection using *NervSy*, *DeadHorse* and *DeadBird*.

Appendix I:

Supplementary figure 1: Examples of simulated baseline with inserted outbreak and corresponding variation of the value of evidence (V). solid black line = simulated data, solid blue line = predicted value, solid red line = 95% confidence interval, Dotted lines = log10(V)