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.R2
Manuscript Type:	Original Research
Date Submitted by the Author:	05-Feb-2016
Complete List of Authors:	Faverjon, Céline; INRA UR 0346, VetAgro Sup, Andersson, Mats; SVA, Chemistry, Environment and Feed Hygiene Decors, Anouk; Office National de la Chasse et de la Faune Sauvage, Direction des études et de la recherche Tapprest, Jackie; ANSES, Laboratory for Equine Diseases Tritz, Pierre; RESPE, collège syndrome nerveux; AVEF, Commission maladies infectieuses Sandoz, Alain; Centre de recherche pour la conservation des zones humides méditerranéennes, Fondation Tour du Valat; UFR Sciences, Aix-Marseille University, Kutasi, Orsolya; Hungarian Academy of Sciences - Szent Istvan University, Hungarian Academy of Sciences - Szent Istvan University Sala, Carole; ANSES, Epidemiology Unit Leblond, Agnès; INRA UR 0346, VetAgro Sup, Département Hippique
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 outputs are either not quantitative and/or do not take into account all available information. Our study aimed to test a multivariate syndromic surveillance system in order to evaluate if the sensitivity and the specificity of detection of WNV could be improved. 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.

TITLE: Evaluation of a multivariate syndromic surveillance system for West Nile virus.

AUTHORS: C. Faverjon[1], M.G. Andersson[2], A. Decors[3], J. Tapprest[4], P. Tritz[5], A. Sandoz[6,7], O. Kutasi[8], C. Sala[9], A. Leblond[10]

(1) INRA UR0346 Animal Epidemiology, VetagroSup, F-69280 Marcy l'Etoile, FRANCE; celine.faverjon@vetagro-sup.fr

(2) Department of Chemistry, Environment and Feed Hygiene. The National Veterinary Institute, SE- 751 89 Uppsala, SWEDEN; gunnar.andersson@sva.se

(3) Office National de la Chasse et de la Faune Sauvage, Direction des études et de la recherche, 5 rue de Saint Thibaud, 78610 Auffargis, France. Anouk.decors@oncfs.gouv.fr

(4) ANSES Dozulé Laboratory for Equine Diseases, FRANCE. Jackie.Tapprest@anses.fr

(5) Clinique vétérinaire, 19 Rue de Créhange, 57380 Faulquemont, collège syndrome nerveux du RESPE et Commission maladies infectieuses de l'AVEF, ,6 avenue du Maréchal Montgomery 14000 Caen, France. pitritz@wanadoo.fr

(6) Centre de recherche pour la conservation des zones humides méditerranéennes, Fondation Tour du Valat, Arles F-13200, FRANCE. sandoz@tourduvalat.org

(7) UFR Sciences, Aix-Marseille University, Marseille F-13003, France. alain.sandoz@univ-amu.fr

(8) Hungarian Academy of Sciences - Szent Istvan University (MTA-SZIE) Large Animal Clinical Research Group, 2225 Ullo, Dóra major, HUNGARY. Kutasi.orsolya@gmail.com

(9) ANSES-Lyon, Epidemiology Unit, 69364 Lyon, France ; carole.sala@anses.fr

(10) INRA UR0346 Animal Epidemiology et Département Hippique, VetAgroSup, F-69280, Marcy L'Etoile, FRANCE; and Réseau d'EpidémioSurveillance en Pathologie Equine (RESPE), Caen, FRANCE. agnes.leblond@vetagro-sup.fr

ABSTRACT

Background: Various methods are currently used for the early detection of West Nile virus (WNV) but their outputs are not quantitative and/or do not take into account all available information. Our study aimed to test a multivariate syndromic surveillance system in order to evaluate if the sensitivity and the specificity of detection of WNV could be improved.

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 zoonotic mosquito-borne arbovirus mainly transmitted by mosquitoes from the genus *Culex* (family Culicidae). Main reservoir 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, and more specifically in France, WNV lineage I emerged in the 1960s and several outbreaks have been documented since that time (Calistri et al., 2010). Even if this lineage 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).WNV lineage II has been introduced in Europe in 2004 and spread in several parts of Europe. This lineage induces more cases and more severe symptoms than lineage I in humans, horses, and birds (Bakonyi et al., 2006; Calzolari et al., 2013; Hernández-Triana et al., 2014). As an example, in Greece, 197 neuroinvasive human cases and 35 deaths were reported in 2010 with lineage II (Danis et al., 2011). All these elements contribute to make WNV a growing concern in Europe. Currently, in France and in most of countries, the surveillance of WNV is mainly passive i.e., based on the vigilance of owners and veterinary practitioners who declare the cases. 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., 2014a).

Syndromic surveillance is defined as “the (near) real-time collection, analysis, interpretation and dissemination of health-related data to enable the early identification of the impact – or absence of impact – of potential threats. Syndromic surveillance is based not on the laboratory-confirmed diagnosis of a disease but on non-specific health indicators including clinical signs, symptoms as well as proxy measures” (Triple S Project, 2011). In Europe, the surveillance of nervous syndromes in horses is considered as one of the most cost-effective surveillance systems in the European context (Chevalier et al., 2011) and has been shown to detect an outbreak of WNV 3 weeks prior to laboratory identification in the South of France (Leblond et al., 2007a; Saegerman et al., 2014). 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 II 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, 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. Considering that horses and birds should be affected by WNV before humans (Kulasekera et al., 2001; Leblond et al., 2007a), a surveillance system based on the analysis of these data could be especially useful in serving as early warning for possible human viral infections.

Multivariate syndromic surveillance combines different syndromic data sources available (Frisén et al., 2010; Sonesson and Frisén, 2005) and should give better results for outbreak detection in terms of specificity and sensitivity 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. Mortality will be considered in our study as a syndrome. 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 according to the last outbreaks occurring in 2000, 2004, 2006 and 2015 (Anonymous, 2007; Autorino et al., 2002; Bahuon et al., 2015; Kutasi et al., 2011; Leblond et al., 2007a; Murgue et al., 2001). This French region is especially at risk because mammalian and avian hosts, bridging vectors, and large protected wetlands with numerous migratory birds are all present.

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. In the RESPE database, nervous symptoms in horses are defined as any signs of impairment of the central nervous system, i.e. ataxia, paresis, paralysis and/or recumbency, and/or behavioral disorder. Nervous disorders with evidence of traumatic or congenital

origins are excluded. All the samples sent for laboratory diagnosis are systematically tested for two diseases, WNV and equine herpes virus-1, and results are registered in the RESPE database. Currently, the collected data are mainly used to produce alerts when cases with positive laboratory diagnoses are identified. 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 2011 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 2011 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 modeling

All time series were aggregated weekly. Using visual examination, abnormal peaks were observed only in *DeadBird* due to health troubles occurring in wild birds' population (i.e., intoxication). 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 negative binomial distribution (see Appendix I) 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 (see Appendix I). 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.

2.2. Baselines simulation

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).

2.3. WNV outbreaks modeling

The weekly counts of cases of five real European WNV outbreaks (Anonymous, 2007; Autorino et al., 2002; Kutasi et al., 2011; Leblond et al., 2007a; 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., 2007a; 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's opinions to be $\mathcal{NB}$(mean=2.23, theta=3.34). Experts were European diplomates in equine internal medicine and persons involved in SAGIR network, RESPE network, and reference laboratories. They based their estimation on data available in the literature (Bakonyi et al., 2013); (Del Amo et al., 2014a, 2014b; Dridi et al., 2013; Sotelo et al., 2011; Ziegler et al., 2013) and their personal knowledge acquired during the observation of real WNV outbreaks in Hungary, France, Italy and Spain during the last decade and their knowledge of equine and wild birds diseases in general.

2.4. WNV outbreaks simulation

Data on real WNV outbreaks are scarce, so we 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 of 8 weeks were simulated by randomly sampling the corresponding distribution. All the weeks within an epidemic time period have thus the same probability to have a high (or low) number of cases.

2.5. Simulated WNV outbreaks insertion in simulated baselines

One simulated outbreak was inserted in each year of 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 according to (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). A summary of time lag between nervous symptoms in horses, horses mortality and wild birds mortality is available in Appendix II figure 1.

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 event 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* in a particular week.

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 $$P(E \mid H_1) = \sum_{i=0}^{n} \left[P_{base}(i) \times P_{out}(n-i) \right]$$

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.

To detect outbreaks, several values for O_{post} were tested to serve as alarm thresholds.

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 conditionally independent given outbreak status and seasonality of baselines, 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 II figure 2.

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

This is the first time that a real assessment of sensitivity and specificity has been implemented for WNV syndromic 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 (Bellini et al., 2014b; Brown, 2012; Chaskopoulou et al., 2013; El Adlouni et al., 2007; Gosselin et al., 2005; Rosà et al., 2014; Shuai et al., 2006; Valiakos et al., 2014). Only two attempts to assess the sensitivity and specificity of surveillance have been made (Andersson et al., 2014; Leblond et al., 2007a) 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. 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).

In our study, we have refrained from assessing timeliness as there is currently little or no data to support assumptions on the temporal course on WNV outbreak in Europe especially in wild birds. Indeed, we are currently only able to estimate the number of cases expected during an epidemic time period, but not the difference between the number of expected cases at the start of an outbreak and later on. All the weeks within an epidemic time period are thus independent and have the same probability to have a high (or low) number of cases. In this situation, assessing which one is detected first would be not informative about the timeliness of our detection. However, further studies should be conducted on that point to rule on the efficiency of such surveillance in serving as early warning system for possible human viral infections.

Our results indicated that 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. To implement such surveillance system on the field, it would be necessary to assess the cost-effectiveness of the system in order to define, in close collaboration with decision-makers, the best balance between sensitivity and specificity. In addition, the real representativeness of datasets are still unknown and should be assessed as they might have a great impact on systems performances. However, it is hoped that our promising results will promote the timely collection and analysis of relevant data and the implementation of such studies.

The best detection performance was obtained using multivariate syndromic surveillance based on reports of nervous symptoms in horses (*NervSy*) and wild bird mortality (*DeadBird*). It is complicated to know how different datasets complement one another. However, we can expect that dead birds would be mainly used to signal the start of an outbreak and that horses confirm the occurrence. To our knowledge, this is the first time that multivariate syndromic surveillance has been implemented for WNV detection. Our results offer a wide range of opportunities but raise also questions regarding practical implementation on the field of such multivariate system. In the model, the value of evidence compares the probability of observing syndromes under baseline conditions and during a WNV outbreak and the calculation of specificity refers to false alarms from random aberrations. Consequently peaks in the syndromic data streams due to other causes such as (i.e.,

equine herpes virus-1 for *NervSy* or Avian Influenza or intoxication for *DeadBird*) will be presented as evidence in favor of WNV. The Bayesian framework offers the possibility to include differential diagnoses and specify their prior probability and expected impact on the distribution of counts in each data-stream. Doing so would enable us to estimate the posterior probability and evidence in favor of a WNV outbreak. However, such a model would be very complicated and hard to support with data. Instead we explicitly define our hypothesis of interest. When the model triggers an alarm, the distinction between WNV and other diagnoses will be made using field investigations.

The Bayesian framework is a comprehensive and logical way to combine syndromic data from several data-streams and it seems well adapted for multivariate WNV detection using three indicators for WNV outbreak detection. This framework provides a means of weighting the results from syndromic surveillance and thus, additional information can be easily added. 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). In addition, the Bayesian approach could be easily adapted to spatiotemporal analysis. Such approach could be especially relevant for WNV surveillance as there are strong links between environment and WNV outbreaks and as we expect local clusters of cases (e.g., (Leblond et al., 2007b; Mostashari et al., 2003)). Without integrating a spatiotemporal approach, the usefulness of a multivariate syndromic approach could be limited especially for vector-borne diseases surveillance, and thus the next step would be to develop and test a spatiotemporal model. However, the quality of geographical information of reported cases used in our study are currently insufficient to implement spatiotemporal analysis. In future studies, it would be interesting to improve data quality in order to test if spatiotemporal analysis could also improve WNV detection and to rule on the usefulness of *Deadhorse* time series. Indeed, using another spatiotemporal scale, local clusters of deaths in horses might be used as a signal of a WNV outbreak.

CONCLUSION

The proposed approach gives promising results for improving surveillance of WNV in France, and maybe also more generally in Europe. It offers a comprehensive and logical way to combine syndromic data from several

data-streams which can be relevant to improve the surveillance of many other diseases (e.g., Bluetongue virus combining data from milk yield and stillbirths, or Japanese encephalitis combining data on nervous symtoms in horses and reproductive losses in swine). However, questions remain on the practical implementation on the field of such multivariate system especially regarding interpretation of combined signal, and detection's timeliness to serve as an early signal for possible human WNV infections in Europe. It is hoped that our results will support the implementation of further studies to solve these questions and that they will contribute to develop more collaborative work between existing surveillance networks.

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

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

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

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

295 Bahuon C, Marcillaud-Pitel C, Bournez L, Leblond A, et al. West Nile Virus epizootics in Camargue, France, 2015
296 and reinforcement of West Nile Virus surveillance and control networks. Rev Sci Techn OIE. 2015 (submitted)

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

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

301 Beck C, Jimenez-Clavero M, Leblond A, Durand B, et al. Flaviviruses in Europe: Complex Circulation Patterns and
302 Their Consequences for the Diagnosis and Control of West Nile Disease. Int. J. Environ. Res. Public. Health.
303 2013;10(11):6049–83.

304 Bellini R, Calzolari M, Mattivi A, Tamba M, et al. The experience of West Nile virus integrated surveillance
305 system in the Emilia-Romagna region: five years of implementation, Italy, 2009 to 2013. Euro Surveill.
306 2014a;19(44).

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

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

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

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

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

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

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

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

325 Calzolari M, Monaco F, Montarsi F, Bonilauri P, Ravagnan S, Bellini R, et al. New incursions of West Nile virus
326 lineage 2 in Italy in 2013: the value of the entomological surveillance as early warning system. Vet. Ital.
327 2013;49(3):315–9.

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

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

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

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

334 Chaintoutis SC, Dovas CI, Papanastassopoulou M, Gewehr S, et al. Evaluation of a West Nile virus surveillance
335 and early warning system in Greece, based on domestic pigeons. Comp. Immunol. Microbiol. Infect. Dis.
336 2014;37(2):131–41.

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

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

Danis K, Papa A, Theocharopoulos G, Dougas G, et al. Outbreak of West Nile Virus Infection in Greece, 2010. Emerg. Infect. Dis. 2011. 17, 1868–1872.

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

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.

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

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

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.

El Adlouni S, Beaulieu C, Ouarda T, Gosselin P, and 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, 1–7.

Frisén M, Andersson E, and Schiöler L. Evaluation of multivariate surveillance. J. Appl. Stat. 2010. 37, 2089–2100.

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. 2007a;7(3):403–10.

Leblond A, Sandoz A, Lefebvre G, Zeller H, and Bicout DJ. Remote sensing based identification of environmental risk factors associated with West Nile disease in horses in Camargue, France. Prev. Vet. Med. 2007b. 79, 20–31.

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

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.

Sonesson C, and Frisén M. Multivariate Surveillance. In Spatial and Syndromic Surveillance for Public Health, A.B. Lawson, and K. Kleinman, eds. (John Wiley & Sons, Ltd). 2005. pp. 153–166.

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.

Triple S Project. Guideline for designing and implementing a syndromic surveillance system. 2011.

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.

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.

CORRESPONDENCE ADDRESS

FAVERJON Céline, cfaverjon@gmail.com, INRA UR0346 Animal Epidemiology, VetagroSup, F-69280 Marcy l'Etoile, FRANCE

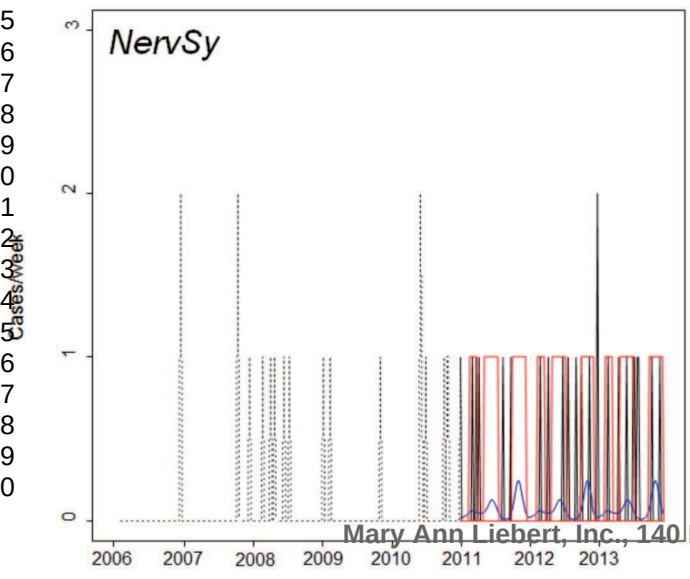
ILLUSTRATIONS

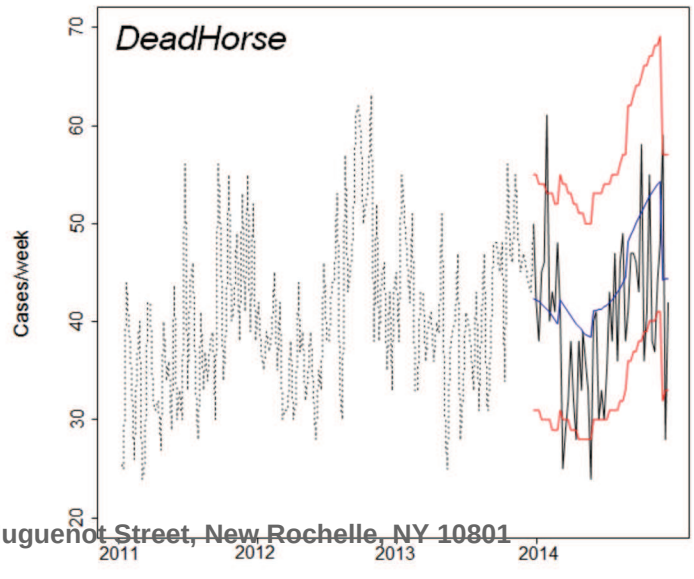
Figure 1: Three time series considered. *NervSy*: number of declaration of nervous syndrome in horses without positive lab result. *DeadHorse*: number of dead adult horses collected by French fallen stock companies. *DeadBird:* number of dead wild birds autopsied with values above the 95% confidence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

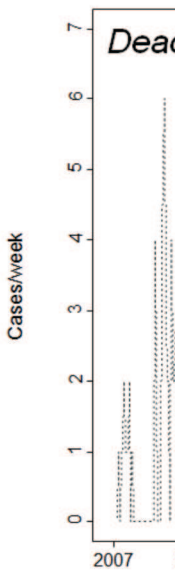
Figure 2: Value of evidence and probabilities of observing n cases during a non-outbreak (Base) and an outbreak (Out) situation. Base= distribution of distribution into the baseline, Out = distribution of cases related

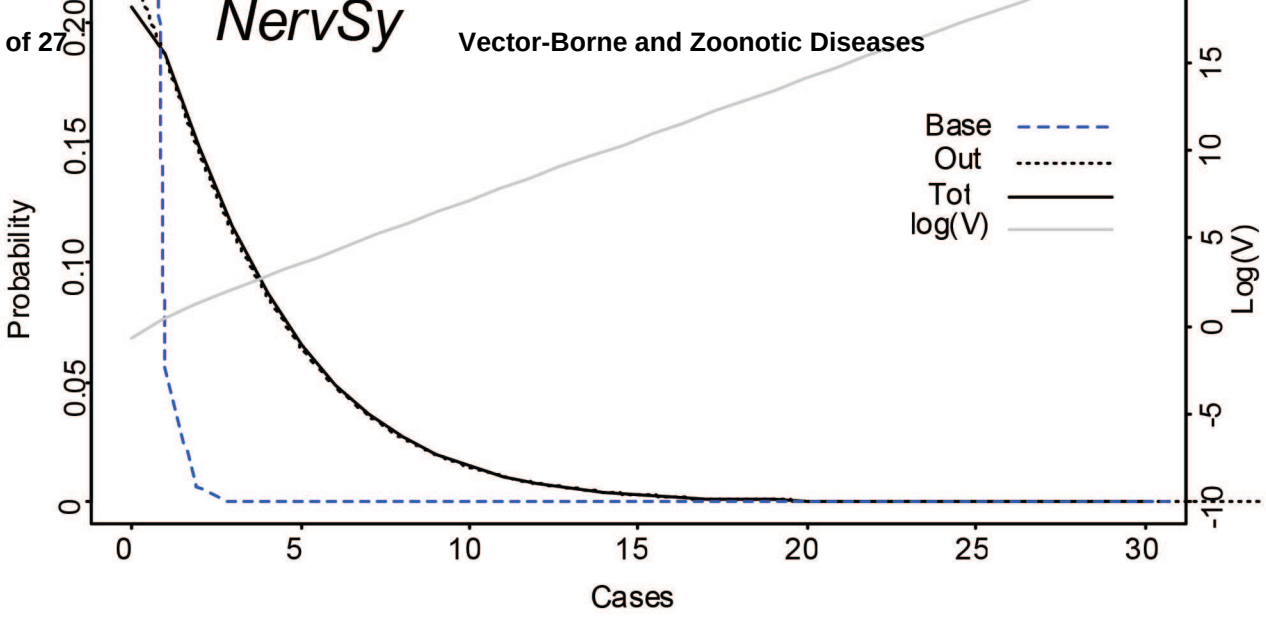
to a WNV outbreak, Tot= distribution of cases during an outbreak (Base + Out), Log(V)= $\log_{10}$(p(n|outbreak)/p(n|baseline)). Out was estimated with *fitdistr* function of the package {fitdistrplus} and was based for *NervSy* on NB(mu= 3.12, theta =1.150), for *DeadHorse* on NB(mu= 3, theta =2.005), and for *DeadBird* on NB(mean= 2.23, theta=3.34).

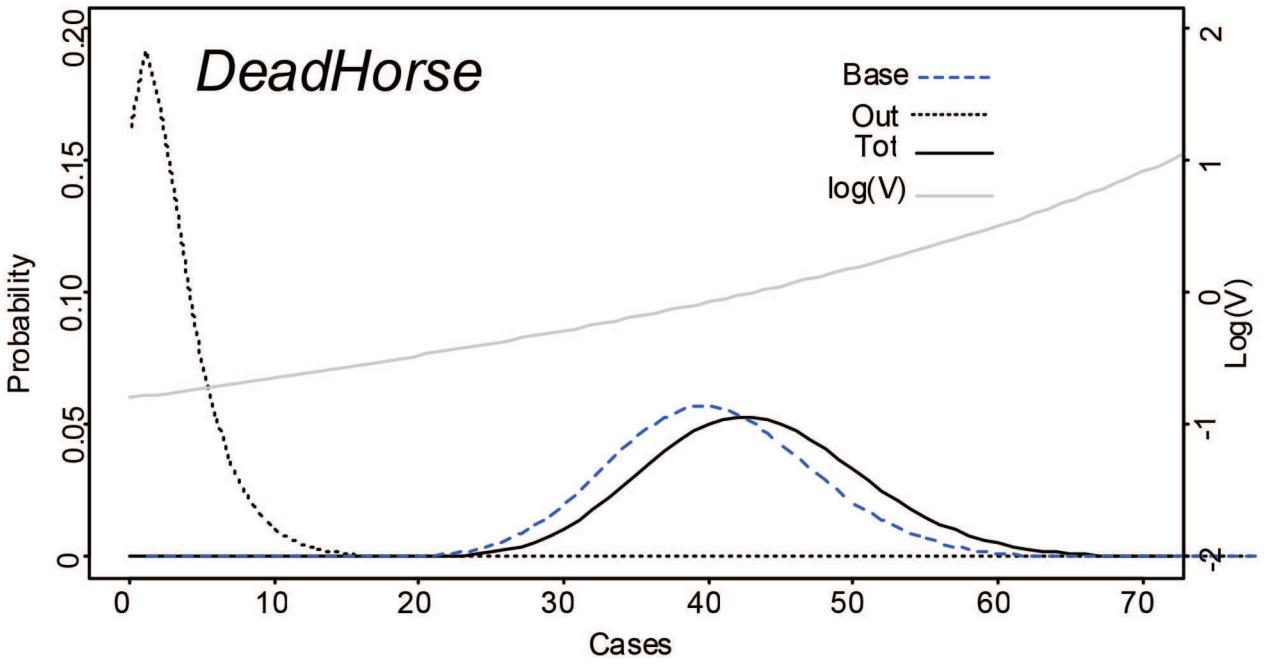
Figure 3: ROC curves for univariate and multivariate outbreak detection using *NervSy*, *DeadHorse* and *DeadBird*.

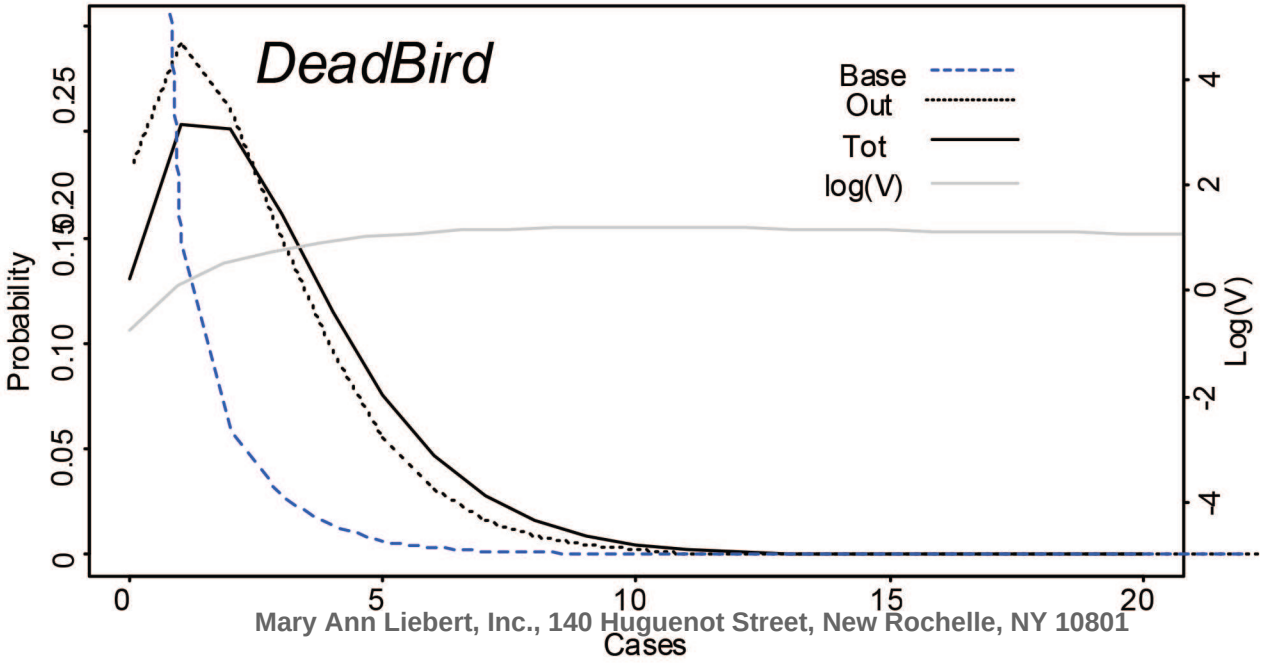


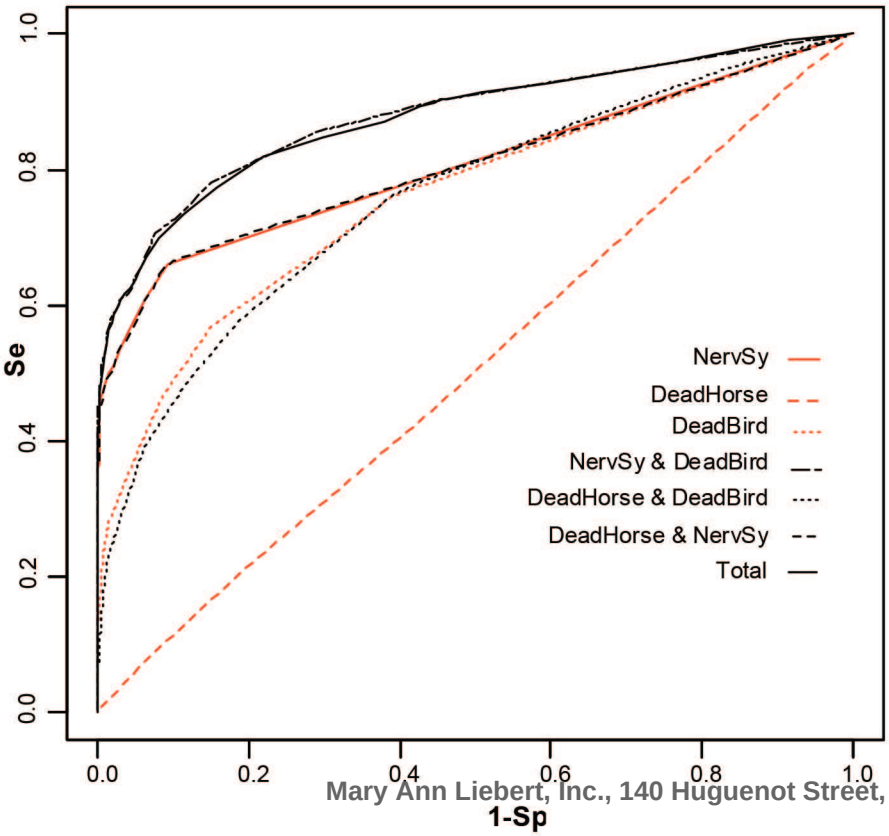





NervSy
Base
Out
Tot
log(V)
Probability
Log(V)
Cases


DeadHorse
Base
Out
Tot
log(V)
Probability
Log(V)
Cases


DeadBird
Base
Out
Tot
log(V)
Probability
Log(V)
Cases



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

Table 1: Models and models parameters obtained for the three time series. Theta is the dispersion parameter as defined in the function *glm.nb* (package {MASS}) in R x64 version 3.0.2.

	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:

Table 1: Variables tested for each time series available and for Poisson and negative binomial distributions

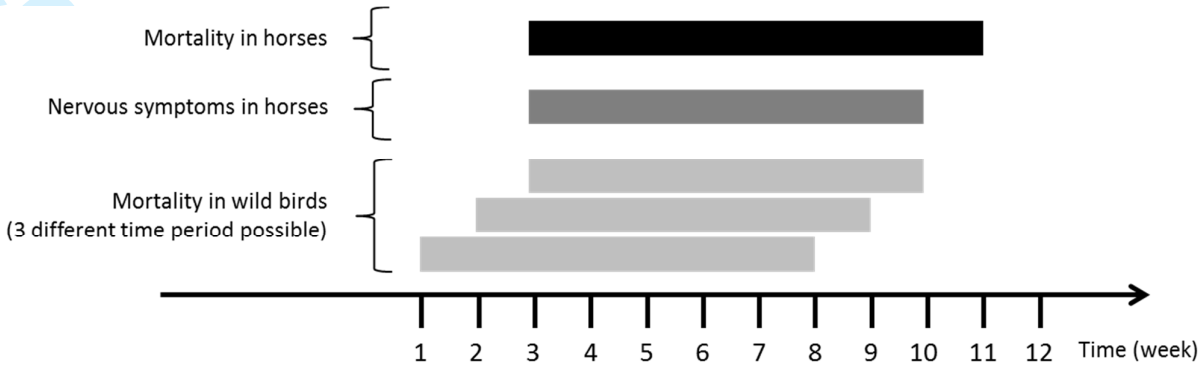
Variable name	Variable description
year	Year considered
week	Week of the year considered
time	Week number according to the total number of weeks available in the dataset
season	Season of the year considered
month	Month of the year considered
sin	sin(2*pi*(week/53))
cos	cos(2*pi*(week/53))
period8	Round(week*8/52)
period8shift	Round((3+week)*8/52)
season.shift2	Round((week-4)*4/52)
sinX2	sin (2*pi* week/26.5)
sinX2.shift	sin (2*pi*(week-6)/26.5)
sinminus6	sin (2*pi*(week-6)/53)
sinminus12	sin (2*pi*(week-12)/53)
sinminus18	sin (2*pi*(week-18)/53)
sinX4.shift	sin (2*pi*(week-3)/13.25)
sinX4	sin (2*pi*(week)/13.25)
sinX3.shift	sin (2*pi*(week-4)/18.33)
sinX3	sin (2*pi*(week)/18.33)
histmean	mean of the 53 previous weeks (and guard band of 4 weeks)

Table 2: Negative binomial model used to remove extreme values from *DeadBird* using Tsui et al. approach

Negative binomial distribution			*AIC*	*GOF*	$RMSE_c$
Formulae	*theta*	*mean*			
$\text{DeadBird} \sim 8 \times (3+t)/52 + \sin(2\pi t/26.5)$	0.22	0.79	819	0.65	1.84

Appendix II:

Supplementary figure 1: Course of WNV outbreak considering mortality in wild birds, nervous symptoms in horses and mortality in horses: duration of syndromes and time lag between them.



Supplementary figure 2: 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)