**Evaluation of a multivariate syndromic surveillance system for West Nile virus**

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**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.

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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 (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 NB distribution and the resulting distribution of the additional number of nervous cases due to WNV during an outbreak was 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 $\mathcal{NB}(\text{mean}=2.23, \theta=3.34)$.

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 $H_0$, “there is an ongoing outbreak of WNV (or another event with similar
"symptoms)," and H₀, "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:

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

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

$$O_{post} = \frac{P(H_1 | E_x)}{P(H_0 | E_x)}$$

where $P(H_1 | E_x)$ is the probability of $H_1$ given the evidence $E$ observed in time series $x$ and $P(H_0 | E_x)$ 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:

$$O_{post} = V_x \times O_{pri} = \frac{P(E_x | H_1)}{P(E_x | H_0)} \times \frac{P(H_1)}{P(H_0)}$$

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:

$$P(E_x | H_1) = \sum_{i=0}^{n} [P_{base}(i) \times P_{out}(n-i)]$$

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.

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

### 3.2. Combining time series

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When the three time series were combined, $V_{\text{tot}}$ incorporated evidence from NervSy, DeadHorse, and DeadBird, respectively denoted as $E_{\text{NervSy}}$, $E_{\text{DeadHorse}}$, and $E_{\text{DeadBird}}$. Assuming that the three sources of evidence were conditionally independent given outbreak status and seasonality of baselines, $V_{\text{tot}}$ was calculated as:

$$V_{\text{tot}} = \frac{P(E_{\text{NervSy}}, E_{\text{DeadHorse}}, E_{\text{DeadBird}} | H_1)}{P(E_{\text{NervSy}}, E_{\text{DeadHorse}}, E_{\text{DeadBird}} | H_0)} = V_{\text{NervSy}} \times V_{\text{DeadHorse}} \times V_{\text{DeadBird}}$$

and $O_{\text{post_tot}}$ was calculated as:

$$O_{\text{post_tot}} = \frac{P(H_1 | E_{\text{NervSy}}, E_{\text{DeadHorse}}, E_{\text{DeadBird}})}{P(H_0 | E_{\text{NervSy}}, E_{\text{DeadHorse}}, E_{\text{DeadBird}})} = V_{\text{tot}} \times \frac{P(H_1)}{P(H_0)}$$

### 4. Performance assessment

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

$$Se = \frac{TP}{TP + FN}$$

$$Sp = \frac{TN}{TN + FP}$$

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 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 \textit{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 symptoms 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.

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DISCLOSURE STATEMENT

No competing financial interests exist.

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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)=

\[
\log_{10}\left(\frac{p(n|\text{outbreak})}{p(n|\text{baseline})}\right)
\]

Out was estimated with \texttt{fitdistr} function of the package \texttt{fitdistrplus} and was based for \textit{NervSy} on NB(\(\mu=3.12, \theta=1.150\)), for \textit{DeadHorse} on NB(\(\mu=3, \theta=2.005\)), and for \textit{DeadBird} on NB(\(\text{mean}=2.23, \theta=3.34\)).

Figure 3: ROC curves for univariate and multivariate outbreak detection using \textit{NervSy}, \textit{DeadHorse} and \textit{DeadBird}. 
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.

<table>
<thead>
<tr>
<th>Formula</th>
<th>theta</th>
<th>mean</th>
<th>AIC</th>
<th>GOF</th>
<th>RMSE_2</th>
<th>RMSE_v</th>
</tr>
</thead>
<tbody>
<tr>
<td>NervSy ~ sin(2π(t − 4)/18.33) + sin(2πt/26.5)</td>
<td>0.413</td>
<td>0.077</td>
<td>143</td>
<td>0.279</td>
<td>0.30</td>
<td>0.39</td>
</tr>
<tr>
<td>DeadHorse ~ 4 × (t − 4)/52 + t + sin(2π(t − 12)/53)</td>
<td>176</td>
<td>40.3</td>
<td>1063</td>
<td>1.016</td>
<td>7.06</td>
<td>8.57</td>
</tr>
<tr>
<td>DeadBird ~ 4 × (t − 4)/52 + sin(2πt/26.5)</td>
<td>0.373</td>
<td>0.520</td>
<td>497</td>
<td>0.675</td>
<td>1.03</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>NervSy</td>
<td>DeadHorse</td>
<td>DeadBird</td>
<td>NervSy &amp; DeadBird</td>
<td>NervSy &amp; DeadHorse</td>
<td>DeadHorse &amp; DeadBird</td>
</tr>
<tr>
<td>----------------</td>
<td>--------</td>
<td>-----------</td>
<td>----------</td>
<td>-------------------</td>
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<td>----------------------</td>
</tr>
<tr>
<td>AUC</td>
<td>0.80</td>
<td>0.50</td>
<td>0.75</td>
<td>0.87</td>
<td>0.80</td>
<td>0.75</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.0082</td>
<td>0.0097</td>
<td>0.0089</td>
<td>0.0068</td>
<td>0.0081</td>
<td>0.0089</td>
</tr>
</tbody>
</table>

Table 2: Area under the ROC curve (AUC) and standard error for univariate and multivariate outbreak detection using NervSy, DeadHorse and DeadBird.
## Table 1: Variables tested for each time series available and for Poisson and negative binomial distributions

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

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

<table>
<thead>
<tr>
<th>Negative binomial distribution</th>
<th>AIC</th>
<th>GOF</th>
<th>RMSE&lt;sub&gt;c&lt;/sub&gt;</th>
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</thead>
<tbody>
<tr>
<td>Formulae</td>
<td>theta</td>
<td>mean</td>
<td></td>
</tr>
<tr>
<td>DeadBird ~ 8 x (3 + t)/52 + sin(2πt/26.5)</td>
<td>0.22</td>
<td>0.79</td>
<td>1.84</td>
</tr>
</tbody>
</table>
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)