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Evaluation of a multivariate syndromic surveillance system for West Nile virus

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Keyword:	West Nile, Surveillance, Modeling, Time Series Analysis
Abstract:	<p>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.</p> <p>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).</p> <p>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).</p> <p>Conclusion: The proposed approach is suitable for performing multivariate</p>

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	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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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 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

1 INTRODUCTION

2 West Nile virus (WNV) is a mosquito-borne arbovirus mainly transmitted by mosquitoes from the genus *Culex*
3 (family Culicidae). Its main hosts are birds but the virus also affects various non-avian species including horses
4 and humans, with dramatic consequences for public health and for the equine industry, i.e. potentially fatal
5 encephalitis in humans and horses (Campbell et al. 2002; Castillo-Olivares and Wood 2004). In Europe, WNV
6 emerged in the 1960s and several outbreaks have been documented since that time (Calistri et al. 2010). Even
7 if the virus is now considered endemic in a large part of Europe, the number of reported outbreaks is presently
8 increasing in southern and eastern Europe, particularly in Italy, Greece, and Bulgaria (Di Sabatino et al. 2014).
9 This increasing number of outbreaks, combined with the recent introduction and spread in Europe of WNV
10 lineage 2, which induces severe symptoms in humans, horses, and birds (Bakonyi et al. 2006; Calzolari et al.
11 2013; Hernández-Triana et al. 2014), has resulted in growing concern about WNV in Europe. In addition, the
12 implementation of prevention plans for WNV outbreaks is difficult (Zeller 2010) because the environmental
13 factors and meteorological interactions underlying the increase in WNV circulating in mammals are still poorly
14 understood. To improve early detection of WNV outbreaks, then, the major challenge is to develop more
15 integrated and quantitative approaches (Beck et al. 2013; Bellini et al. 2014b).

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

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

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

36 MATERIALS AND METHODS

37 1. Data sources

38 1.1. Nervous syndromes in horses

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

46 1.2. Mortality in horses

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

52 1.3. Mortality in wild birds

53 Data on mortality in wild birds are collected through the event-based surveillance system “SAGIR”, the national
54 French surveillance network of diseases in wild birds and mammals, which collects declarations from field
55 workers (e.g., hunters, technicians from departmental hunting federations, and environmental inspectors from
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3 56 the French National Hunting and Wildlife Agency (ONCFS)). Surveillance relies on diagnosis at a local veterinary
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5 57 laboratory (Decors et al. 2014). Between 2007 and 2013, 292 dead wild birds were collected and necropsied
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7 58 around the French Mediterranean coast. The time series of the number of necropsied wild birds is designated
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9 59 *DeadBird* in subsequent sections.

10 11 12 60 **2. Data modeling and simulation**

13 14 61 *2.1. Baselines*

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16 62 All time series were aggregated weekly. Using visual examination, abnormal peaks were observed only in
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18 63 *DeadBird*. These extreme values were removed based on a method adapted from Tsui *et al.* (Tsui et al. 2001):
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20 64 the entire dataset was first fitted to a Poisson distribution and then values above the 95% confidence interval
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22 65 were deleted and replaced with the average value of the four previous weeks.

23
24 66 To calibrate the models, we used *NervSy* data from 2006 to 2010, *DeadHorse* data from 2011 to 2013, and
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26 67 *DeadBird* data from 2007 to 2011. Instead, to validate the quality of predictions, we used *NervSy* data from
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28 68 2011 to 2013, *DeadHorse* data from 2014, and *DeadBird* data from 2012 to 2013. To define the background
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30 69 noise of the time series without outbreaks, we fitted alternative regression models based on Poisson and
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32 70 negative binomial (\mathcal{NB}) distributions. Models were implemented in R x64 version 3.0.2. Dynamic regression was
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34 71 performed with the functions *glm* (package {stats}) and *glm.nb* (package {MASS}). The expected number of
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36 72 counts at time t was estimated with the *predict* functions of the respective packages.

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39 73 Models were evaluated using the Akaike information criterion (AIC) (Bozdogan 1987), and the adjusted
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41 74 deviance (deviance/degree of freedom) was used as a measure of goodness-of-fit (GOF). The agreement
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43 75 between predicted and observed values was assessed according to the root-mean-squared error (Chai and
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45 76 Draxler 2014). The criterion was assessed within the calibration period ($RMSE_c$) and within the validation period
46
47 77 ($RMSE_v$). In either case, the lower the value, the better the predictive performance of the model.

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49 78 For each time series, the best regression model was used to predict the expected value of each week of the
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51 79 next simulated year. Distribution of cases for each week was defined as a Poisson distribution with lambda
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53 80 equals to the predicted value for the same week. Weekly samples from 100 fictive years were generated by
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55 81 random sampling from the previous distributions as proposed by Dórea *et al.* (Dórea et al. 2013).

56 57 58 82 *2.2. WNV outbreaks*

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83 Data on real WNV outbreaks are scarce, so we thus used simulated outbreaks to evaluate our detection
84 system. For each syndrome, the distribution of the number of cases during an outbreak was estimated with the
85 *fitdist* function of the package {fitdistrplus}. Time series for each syndrome during 100 fictive outbreaks were
86 simulated by randomly sampling the corresponding distribution. One simulated outbreak was inserted in each
87 simulated baseline. The outbreaks related to nervous cases in horses were randomly inserted, followed by the
88 corresponding outbreaks related to wild bird mortality, such that the time lag between the first dead bird and
89 the first nervous case in horses due to WNV was 0, 1, or 2 weeks (Kulasekera et al. 2001). The corresponding
90 horse mortality outbreaks were inserted such that half of the affected horses died the week of onset of clinical
91 signs and half died the week after (Bunning et al. 2002; Cantile et al. 2000; Trock et al. 2001; Ward et al. 2006).
92
93 The weekly counts of cases of five real European WNV outbreaks (Anonymous 2007; Autorino et al. 2002;
94 Kutasi et al. 2011; Leblond et al. 2007; Murgue et al. 2001) were fitted to the \mathcal{NB} distribution and the resulting
95 distribution of the additional number of nervous cases due to WNV during an outbreak was $\mathcal{NB}(\mu=3.12,$
96 $\theta=1.150)$. The mortality among horses clinically affected by WNV was fitted to a normal distribution
97 (mean=0.384, standard deviation=0.128) based on (Autorino et al. 2002; Leblond et al. 2007; Murgue et al.
98 2001; Ward et al. 2006). The *NervSy* dataset did not provide the real number of clinically affected horses, so we
99 assumed that only 50% of horses with nervous symptoms were declared to RESPE. To estimate the real number
100 of clinically affected horses, we simulated RESPE declarations of nervous symptoms associated with 100 WNV
101 outbreaks and doubled the counts of horses obtained. The related weekly count of dead adult horses was then
102 deduced and fitted to the \mathcal{NB} distribution $\mathcal{NB}(\mu=3, \theta=2.005)$. The distribution of the weekly number of
103 dead birds was estimated by expert opinion to be $\mathcal{NB}(\text{mean}=2.23, \theta=3.34)$.

104 3. Outbreak detection

105 3.1. Bayesian framework

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

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

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

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

115 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
116 probability of H_0 given the evidence E observed in time series x .

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

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

120 where V_x is the value of evidence, $P(E_x | H_1)$ is the probability of observing the number of reported cases of
121 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
122 reported cases of syndrome x in a particular week given that H_0 is true.

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

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

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

130 3.2. Combining time series

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

$$134 \quad \text{Eq.5} \quad V_{tot} = \frac{P(E_{NervSy}, E_{DeadHorse}, E_{DeadBird} | H_1)}{P(E_{NervSy}, E_{DeadHorse}, E_{DeadBird} | H_0)} = V_{NervSy} \times V_{DeadHorse} \times V_{DeadBird}$$

135 and O_{post_tot} was calculated as:

$$136 \quad \text{Eq.6} \quad O_{post_tot} = \frac{P(H_1 | E_{NervSy}, E_{DeadHorse}, E_{DeadBird})}{P(H_0 | E_{NervSy}, E_{DeadHorse}, E_{DeadBird})} = V_{tot} \times \frac{P(H_1)}{P(H_0)}$$

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138 4. Performance assessment

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

$$140 \quad \text{Eq.7} \quad \text{Se} = \text{TP} / (\text{TP} + \text{FN})$$

$$141 \quad \text{Eq.8} \quad \text{Sp} = \text{TN} / (\text{TN} + \text{FP})$$

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

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

147

148 RESULTS

149 1. Modeling time series and simulating data

150 For all time series the best fits were obtained for \mathcal{NB} distributions. The resulting models' parameters are
151 summarized in table 1 and corresponding baselines and predictions are shown in figure 1. The probabilities of
152 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
153 outbreak ($p(E|H_1)$) situation for each time series are summarized in figure 2.

154 2. Outbreak detection

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3 155 We estimated the respective performance of each univariate system (*NervSy*, *DeadHorse*, and *DeadBird*) in
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5 156 detecting WNV outbreaks without considering any *a priori* values for disease status ($O_{pri}=1$). Examples of
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7 157 simulated baselines with inserted outbreaks and associated variations in $\log_{10}(V)$ are presented in Appendix I.

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10 158 The best results for univariate outbreak detection were obtained for *NervSy*, which outperformed analyses
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12 159 using *DeadHorse* and *DeadBird* (figure 3 and table 2). *DeadBird* models yielded intermediary detection
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14 160 performances whereas models using *DeadHorse* were not able to discriminate between outbreak and non-
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16 161 outbreak situations ($AUC \approx 0.50$).

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18 162 The best results for multivariate outbreak detection were obtained for analyses that combined *NervSy* with
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20 163 *DeadBird* data, which gave similar results to a combination of the three time series (figure 3 and table 2). The
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22 164 results of using *NervSy* combined with *DeadBird* were also better than those obtained with each time series
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24 165 alone. For example, for a specificity set at 0.80, the sensitivity of the detection reached 0.80 with the combined
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26 166 *NervSy* and *DeadBird* series whereas it was 0.67 with *NervSy* and 0.60 with *DeadBird* alone.

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30 31 168 **DISCUSSION**

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34 169 Our results indicated that the best detection performance was obtained using multivariate syndromic
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36 170 surveillance based on reports of nervous symptoms in horses (*NervSy*) and wild bird mortality (*DeadBird*). To
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38 171 our knowledge, this is the first time that multivariate syndromic surveillance has been implemented for WNV
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40 172 detection. However, when using a univariate detection method, *NervSy* was the best indicator of WNV
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42 173 outbreaks. This is consistent with the number of expected cases during an outbreak compared to the baseline
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44 174 of each time series considered (i.e. high number of case for *NervSy*, moderate number of cases for *DeadBird*,
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46 175 and low number of cases for *DeadHorse*). Indeed, models based only on the *DeadHorse* data resulted in poor
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48 176 detection performance at the regional level because mortality in horses is mainly due to causes other than
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50 177 WNV. However, before ruling on the usefulness of this datasource for WNV surveillance, it would be interesting
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52 178 to test whether an outbreak generates local clusters of deaths in horses that may be used as a signal of a VNV
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54 179 outbreak. However, the quality of geographical information of reported cases are currently insufficient to test
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56 180 this hypothesis.

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3 181 This is the first time that a real assessment of system performance has been implemented for WNV
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5 182 surveillance. Previous early warning systems developed for WNV only identified risk factors of WNV outbreaks,
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7 183 but did not evaluate the detection performances of those systems (Adlouni et al. 2007; Bellini et al. 2014a;
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9 184 Brown 2012; Chaskopoulou et al. 2013; Gosselin et al. 2005; Rosà et al. 2014; Shuai et al. 2006; Valiakos et al.
10
11 185 2014). Timeliness has occasionally been evaluated but only based on a limited number of real WNV outbreaks,
12
13 186 and has not been associated with a further evaluation of system performance (Calzolari et al. 2013; Chaintoutis
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15 187 et al. 2014; Eidson et al. 2001; Johnson et al. 2006; Mostashari et al. 2003; Veksler et al. 2009). Only two
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17 188 attempts to assess the sensitivity and specificity of surveillance have been made (Andersson et al. 2014;
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19 189 Leblond et al. 2007) but the parameters of interest were only evaluated based on a limited number of
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21 190 outbreaks, which did not allow any conclusions to be drawn regarding overall system performance.

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23 191 To assess the surveillance systems and compare them, we simulated baselines and outbreaks using parameters
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25 192 from data observed in Europe (Anonymous 2007; Autorino et al. 2002; Bakonyi et al. 2013; Leblond et al. 2007;
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27 193 Ward et al. 2006). To expand upon this, patterns of outbreaks in other locations should be tested in order to
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29 194 evaluate the performance of multivariate syndromic surveillance in more varied situations. Particular attention
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31 195 should be paid to patterns of mortality of wild birds, as the dynamics of wild bird mortality during a WNV
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33 196 outbreak have only been poorly investigated in Europe.

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36 197 The Bayesian approach seems well adapted for multivariate WNV detection and can be used for other diseases.
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38 198 Indeed, Bayesian hypothesis testing is based on two mutually exclusive hypotheses which can be expressed in
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40 199 the syndromic surveillance context as: H_1 , "there is an ongoing outbreak of WNV or of another disease with
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42 200 similar symptoms", and H_0 , "there is no ongoing outbreak". It would be theoretically possible to include every
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44 201 possible differential diagnosis for every syndrome (or group of syndromes) considered; however, such a system
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46 202 would be difficult to implement and maintain. It would thus be interesting to first examine the evidence from
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48 203 each time series individually and then together in order to identify which combination of datasets results in the
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50 204 strongest signal. It would be up to the relevant decision maker in a given situation to consider appropriate
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52 205 differential diagnoses and the actions that should be implemented for further investigation.

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55 206 In our study, we considered three sources of evidence for WNV outbreak detection. Nevertheless, additional
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57 207 information can be utilized with Bayesian approaches, as it is easy to add such information. Then, a next step in
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3 208 the early detection of WNV outbreaks should be to test the efficiency of the method with other data, such as
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5 209 the predicted abundance of mosquitoes (Calistri et al. 2014; Rosà et al. 2014), environmental risk factors (Tran
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7 210 et al. 2014), and risk of introduction (Bessell et al. 2014; Brown et al. 2012).
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10 211 **CONCLUSION**

11
12 212 The proposed approach is suitable for performing multivariate syndromic surveillance of WNV outbreaks.
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14 213 Indeed, we found that a multivariate surveillance system using this approach performed better than a
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16 214 univariate approach in detecting WNV outbreaks in southern France. In particular, a combination of data
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18 215 regarding nervous symptoms in horses and wild bird mortality was the most efficient in detecting outbreaks.
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20 216 Such multivariate surveillance systems could be especially useful in serving as early warnings for possible
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22 217 human viral infections, considering that horses and birds are affected by WNV before humans (Kulasekera et al.
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24 218 2001; Leblond et al. 2007). We propose that this methodology is generally applicable to other diseases for
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26 219 which multiple sources of evidence are available.
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31 222 **ACKNOWLEDGMENTS**

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35
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37
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39
40 225 and mammals. Data on nervous symptoms in horses were provided by 'RESPE' (Réseau d'Epidémiologie-Surveillance
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45
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234 **DISCLOSURE STATEMENT**

235 No competing financial interests exist.

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237 **REFERENCES**

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44 366 **ILLUSTRATIONS**

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47 367 **Figure 1: Three time series considered.** *NervSy*: number of declaration of nervous syndrome in horses without
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49 368 positive lab result. *DeadHorse*: number of dead adult horses collected by French fallen stock companies.

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51 369 *DeadBird*: number of dead wild birds autopsied with values above the 95% confidence interval deleted. Dotted
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53 370 lines = training data, solid black lines = test data, solid blue lines = predicted value, solid red lines = 95%
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55 371 Confidence interval.

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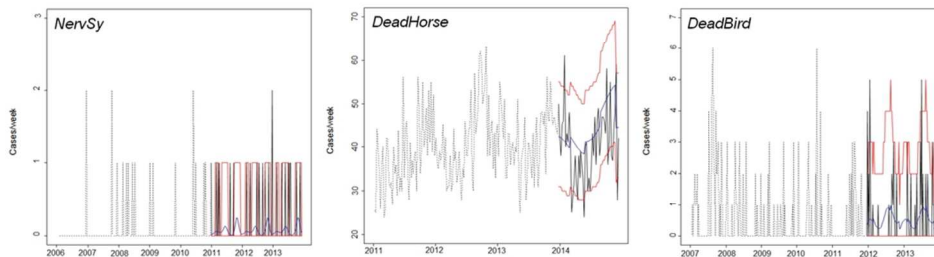
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373 **Figure 2: Value of evidence and probabilities of observing n cases during a non-outbreak (Base) and an**
374 **outbreak (Out) situation.** Base= distribution of distribution into the baseline, Out = distribution of cases related
375 to a WNV outbreak, Tot= distribution of cases during an outbreak (Base + Out), $\text{Log}(V) =$
376 $\log_{10}(p(n|\text{outbreak})/p(n|\text{baseline}))$. Out was based for *NervSy* on NB($\mu = 3.12$, $\theta = 1.150$), for *DeadHorse*
377 on NB($\mu = 3$, $\theta = 2.005$), and for *DeadBird* on NB($\text{mean} = 2.23$, $\theta = 3.34$).

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

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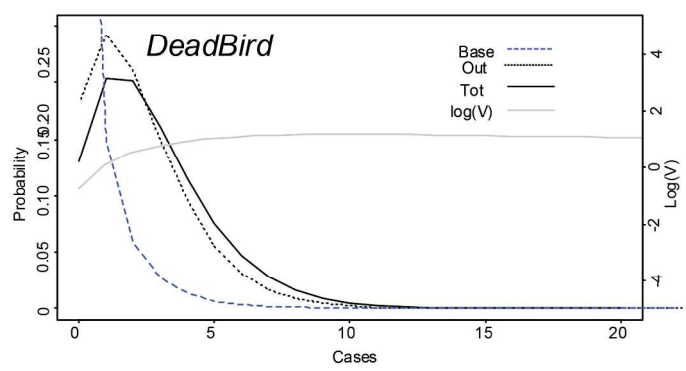
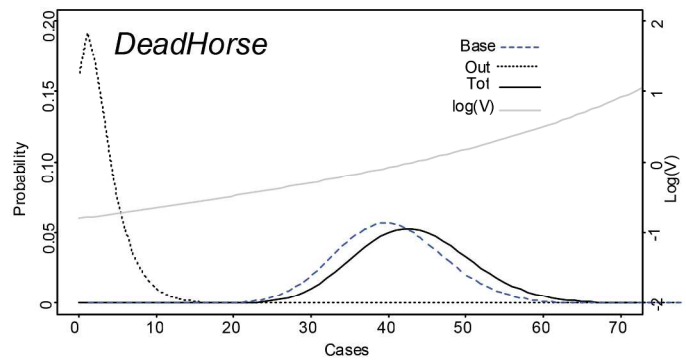
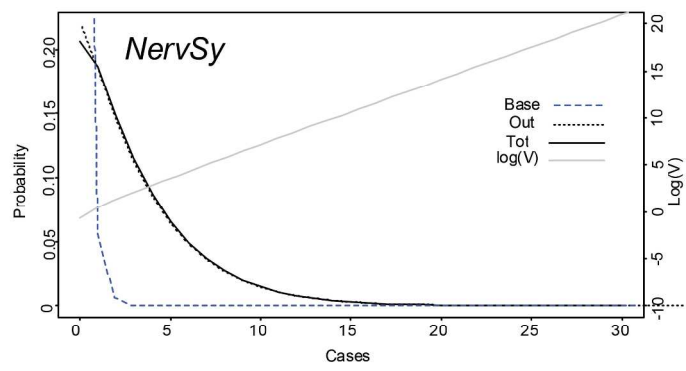


Three time series considered. NervSy: number of declaration of nervous syndrome in horses without positive lab result. DeadHorse: number of dead adult horses collected by French fallen stock companies. DeadBird: number of dead wild birds autopsied with values above the 95% confidence interval deleted. 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)

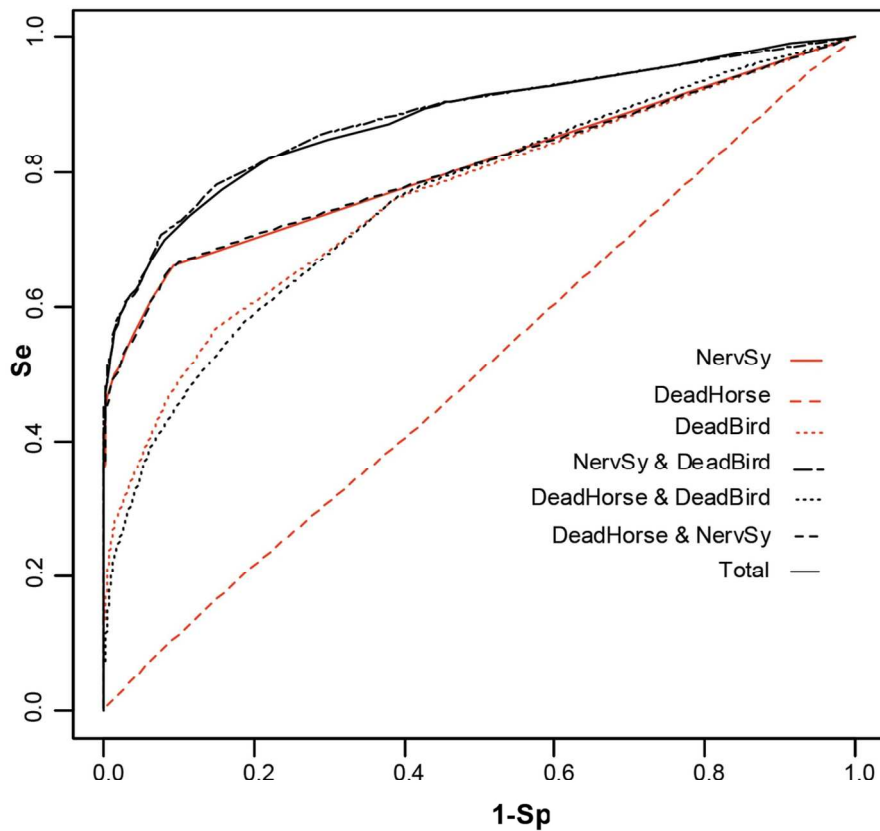
Only/Not for Distribution

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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), $\text{Log}(V) = \log_{10}(p(n|\text{outbreak})/p(n|\text{baseline}))$. 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, $\theta = 3.34$).
297x420mm (300 x 300 DPI)





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

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

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

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	<i>NervSy</i>	<i>DeadHorse</i>	<i>DeadBird</i>	<i>NervSy & DeadBird</i>	<i>NervSy & DeadHorse</i>	<i>DeadHorse & DeadBird</i>	<i>Total</i>
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 = $\log_{10}(V)$

