

## Statistical methods in veterinary epidemiology

Titre: Méthodes statistiques en épidémiologie animale

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**Abstract:** The main aim of veterinary epidemiology is to increase knowledge on both i) the dynamics and impact of diseases on animal production, health and welfare and on ii) the risk of animal-acquired (i.e. zoonoses) and food-borne diseases in humans. Because animals and animal products are the source of income for a large sector of society, the emphasis on economic aspects is much more important in veterinary epidemiology than in human epidemiology. Typical research questions deal with the identification of risk factors for a disease, the estimation of the impact of a disease on production, the evaluation of the efficacy of a treatment or the timely identification of disease occurrence. For these purposes, a wide range of statistical techniques are used and several types of data sources exist. One peculiarity in animal productions is the collection of large production related data such as daily milk productions, live weights or reproduction data for example. These extremely large databases are both an asset and a challenge for statistical modelling. To illustrate the data sources and statistical methods used in veterinary epidemiology, we present part of the work conducted following the emergence of the bluetongue virus in cattle in 2006. First, we show how the impacts of the disease on milk production and reproduction were estimated. Then, in order to improve the timeliness of detection of such emergences, the application of syndromic surveillance methods to the bluetongue emergence is presented. Finally, some knowledge gaps and directions for future work are presented.

Résumé : L'objectif principal de l'épidémiologie animale est de faire progresser les connaissances à la fois sur i) la dynamique et l'impact des maladies sur les productions, la santé et le bien-être des animaux ii) les risques pour la santé humaine associés aux maladies animales transmissibles à l'homme (zoonoses) et aux toxi-infections alimentaires. Parce que les animaux et les produits animaux sont une source de revenus majeure pour une partie de la population, une place plus importante est accordée aux aspects économiques en épidémiologie animale qu'en épidémiologie humaine. Pour un trouble de santé, des questions de recherche classiques auront trait à l'identification de facteurs de risque de survenue du trouble, l'estimation de son impact sur la production, l'évaluation de l'efficacité d'un traitement ou encore la détection précoce de sa survenue. A ces fins, un large éventail de méthodes statistiques est utilisé et de nombreuses sources de données existent. Une particularité des productions animales consiste en la collecte de grands volumes de données en lien avec la production tels que des productions laitières quotidiennes par vache, des poids vifs ou des données de reproduction. Ces grands volumes de données disponibles représentent à la fois un avantage et une difficulté pour la modélisation statistique. Pour illustrer les sources de données et les méthodes utilisables en épidémiologie animale, nous présentons des travaux effectués suite à l'émergence de la fièvre catarrhale ovine en 2006. Dans un premier temps, nous montrons comment les impacts de la maladie sur la production laitière et la reproduction ont été estimés. Puis, dans l'objectif d'améliorer la précocité de la détection de telles émergence, l'application des méthodes de surveillance syndromique est présentée. Enfin des besoins de connaissances et des perspectives pour de futures recherches sont présentés.

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*Keywords:* animal, disease, data, model *Mots-clés :* animal, maladie, données, modèle *AMS 2000 subject classifications:* 92-01, 92D30

## 1. Introduction

The World Health Organization (**WHO**) defines epidemiology as *the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems*<sup>1</sup>. As a science, epidemiology relies importantly on statistics, but also on medicine and biology as well as on economics and other scientific disciplines.

Veterinary epidemiology has similar although slightly different aims in animals. In order to briefly draw the contours of veterinary epidemiology, scientific articles published in this discipline were analysed. Our aim here was not to conduct a comprehensive analysis of the articles published in veterinary epidemiology, but to provide the reader unfamiliar with the discipline with a brief overview of the research themes, journals and methods. To this end, on the Pubmed and Science Direct websites, all the fields were searched for the expression *veterinary epidemiology*. The titles, keywords and abstracts of the 2 722 identified articles were downloaded and analysed. The first 2 occurrences of the expression veterinary epidemiology were in 1978. One article was published by a group called Veterinary Epidemiology and Preventive Medicine Unit (Hawkins and Morris, 1978) indicating that the expression was in use before its appearance in print. The other one contained the expression in the abstract Hayes Jr. (1978). The first identified occurrence of the expression veterinary epidemiology in the title of an article was in 1979. This article, published in Spanish, was entitled Research methods in veterinary epidemiology and their use by government services (Saiz Moreno, 1979). But veterinary epidemiology really started to be an area of active research from the mid-1980s (See Figure 1). This coincides with the launching in 1982, of the leading journal in veterinary epidemiology: Preventive Veterinary Medicine (Riemann, 1982). This journal accounts for almost 40% (1 032/2 722) of the retrieved articles (Figure 2). Between the mid 1980s and the end of 2014, the number of articles published per year has increased steadily. Overall, between the early 1980s and the early 2000s, the number of articles published in *veterinary epidemiology* increased faster than the number of articles published in *veterinary* sciences. This trend reversed after 2000, although the number of articles published in veterinary epidemiology increased (See Figure 1 for details). Considering that most articles published in Preventive Veterinary Medicine were about veterinary epidemiology, all the articles published in this journal were added to the list of references described above, giving a total of 5 209 articles. The wordcloud presented in Figure 3 represents the word frequencies in the titles and keywords of these articles. The most frequent words relate to health, disease and their measure (e.g. prevalence, sensitivity), disease agents, animal species or categories of animals. Most of the articles are on farm animal species (*cattle*, *bovine*, *dairy*, *swine*, *pig*, *sheep* or *goat*). In these productions, the most important difference with human epidemiology is the strong economic element (economic, impact, production). Public and collective health aspects, both in humans and animals, are also very much present (population, surveillance, H5N1, program). Words related to statistics include

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<sup>&</sup>lt;sup>1</sup> http://www.who.int/topics/epidemiology/en/

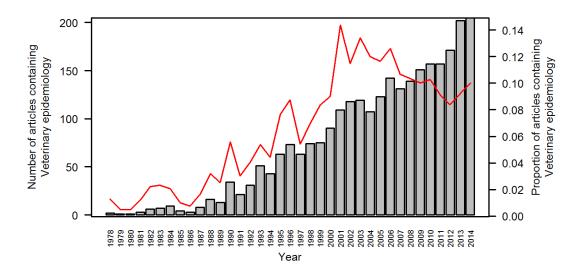


FIGURE 1. Articles referenced by Pubmed or Science Direct containing the expression veterinary epidemiology as a number (bars) and as a proportion of the articles containing the expression veterinary science (red line) by year. The expressions could be present in the title, abstract, keywords or name of the publishing group.

*model, stochastic, Bayesian* or *network.* Another feature which is important to understand the interaction between statistics and veterinary epidemiology is the hierarchical nature of most of the data. Typically, animals are clustered within farms, herds or flocks. Within a herd, there can be several pens or batches. Animals can be followed at multiple points in time, giving rise to longitudinal data. This has resulted in the extensive use of multilevel models, also called mixed or random effect models.

In the remainder of this article, we show how veterinary epidemiology and statistics can interact through work conducted following the emergence of the bluetongue virus (BTV) in Northern Europe in 2006. Section 2 introduces the basic biological and epidemiological characteristics of the BTV and relates the 2006 emergence. Section 3 describes some of the data sources that can be used in veterinary epidemiology. We then present estimations of the impact of i) BTV-8 on milk production (section 4), ii) BTV-8 on reproduction (section 5) and iii) vaccination against BTV-8 on reproduction (section 6). Section 7 shows how syndromic surveillance methods can be used for the detection of vector-borne emerging diseases. Finally, in the discussion, we present some of the challenges and problems facing veterinary epidemiology that would benefit from deepening the collaborations between veterinary epidemiologists and statisticians.

#### 2. The Bluetongue virus emergence in cattle in France as a case study

Bluetongue (**BT**) is a non-contagious, insect-transmitted disease of domestic and wild ruminants caused by the bluetongue virus. Before the emergence of BTV serotype 8 (**BTV-8**) in northern Europe in 2006, five different BTV serotypes had been spreading in Mediterranean Europe, mainly since 1998 (Mellor et al., 2008; Mellor and Wittmann, 2002; Saegerman et al., 2008). BTV-8 and BTV serotype 1 (**BTV-1**) emerged in 2006 and 2008 respectively. In France, only a few clinical

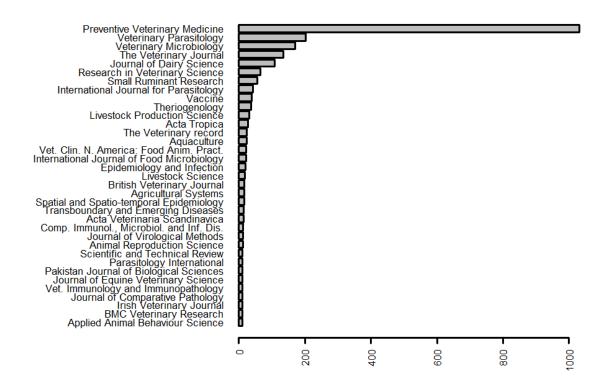


FIGURE 2. Journals that published  $\geq$  10 articles referenced by Pubmed or Science Direct containing the expression 'veterinary epidemiology' between 1979 and 2014. The expression could be present in the title, abstract, keywords or name of the publishing group.

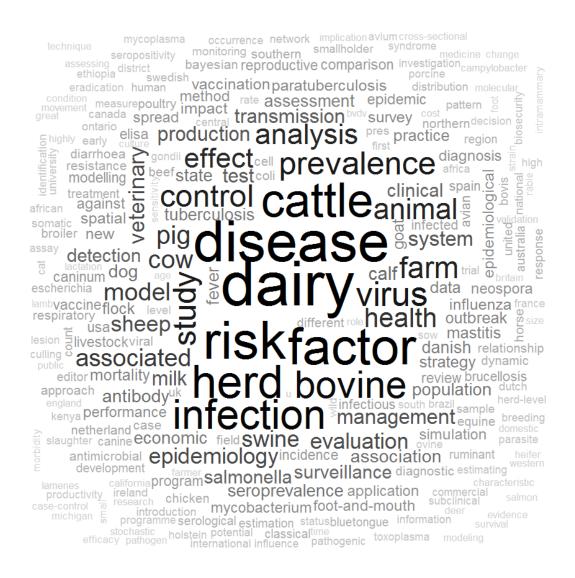


FIGURE 3. Wordcloud of the frequency of words in titles and keywords. From articles referenced by Pubmed or Science Direct either containing the expression 'veterinary epidemiology' or published in Preventive Veterinary Medicine, between 1979 and 2014.

cases of BTV-8 were reported in 2006. The first of these cases occurred in August, near the border with Belgium. Subsequently, the disease re-emerged in 2007 and 2008 (Durand et al., 2010), resulting in a respective 10,500 and 26,500 herds officially reported with clinical signs.

BT has a heavy economic impact, mostly due to the disease effects on animals and to the disruption of international animal trade (Saegerman et al., 2008). Production losses include mortality, decreased milk production, weight loss, and decreased reproductive performance (Velthuis et al., 2010). When the disease emerged, regulations were in place and decisions had to be made regarding the best ways to mitigate the disease consequences. The main tools that were available to control disease propagation were restriction of animal movements and vaccination. During the emergence, animal movements were restricted in and around affected areas. Annual vaccination campaigns, voluntary in 2008 against BTV-8 and compulsory in 2009 and 2010 against BTV-8 and BTV-1, were implemented. But the efficiency of these control measures was largely unknown.

An important step in understanding the impact of such control measures is to understand how the disease spreads. BTV is transmitted by midges of the *Culicoides* genus, which feed on ruminants. For the disease to spread, midges carrying the virus and able to transmit it need to be present around ruminants. The distance and speed at which the midges can carry the disease are important to determine, in order to define the movement restriction zones and areas in which it is necessary to vaccinate. Furthermore, since the midges are not active during winter, the ability of the virus to persist from one year to the next was unknown. Another way to spread the disease is through the movements of infected animals. The role of cattle movements in the spread of the disease needs to be evaluated. A preliminary analysis consists in exploring the intrinsic characteristics of the cattle trade network (Dutta et al., 2014). This could have important practical implications regarding the decision to vaccinate and movement restrictions. Several studies have looked at disease dynamics. These studies, most of which used mathematical models, will not be described further in this article which focuses on statistical models.

A reason to vaccinate is to alter the disease dynamics in the hope of preventing its spread to untouched areas as well as its re-emergence in subsequent years (Charron et al., 2011). A further reason is the mitigation of disease impacts on production. In this case, the benefits of vaccination must outweigh its cost. In order to estimate the potential benefits of vaccination, and more generally of all prevention and control measures against BTV, the effects of the disease on production in cattle must be estimated. Since dairy farmers derive most of their revenue from the sale of milk, losses of milk production resulting from the infection must be investigated. Furthermore, lactation is initiated by the birth of a calf and aging animals need to be replaced. As a consequence reproduction is also central to dairy farming. In sections 4 and 5, we present some work that was published on the effect of BTV-8 on milk production and reproduction in dairy cattle. But vaccination can be associated with adverse effects in the vaccinated animals, which could result from the stimulation of the immune system or from the stress induced by the manipulation of animals. In section 6, we present a study on the effect of vaccination against BTV on reproductive performance in dairy cows.

Although the notification of clinical suspicion of BTV was mandatory between 2006 and 2008, it is possible that some herds had disease cases that were not reported. There are several reasons for this: the symptoms could have been mild and gone undetected by farmers; farmers knowing that there were no treatments could have waited that the disease resolved; farmers could have

wanted to avoid the burden associated with vet visit and notification. As a consequence, losses associated with the disease quantified from notified herds alone could have been underestimated. In section 5, we present some work by Nusinovici et al. (2014) who evaluated whether a decrease in fertility could be used to evidence the under-reporting and to quantify the extent to which non-reported cases contribute to the total burden of the epizootic.

After BT, another vector borne disease, due to a virus called Schmallenberg, emerged in 2011 in Northern Europe. Looking at the instances recorded between 1940 and 2004, Jones *et al.* Jones et al. (2008) estimated that the frequency of infectious disease emergences was increasing over time. It has been suggested that climate change could favour these emergences (Guis et al., 2012; Purse et al., 2008). Surveillance systems able to detect this type of events should be in place. In such case, screening for specific diseases in animals at risk or in a sentinel population will be impossible since it is impossible to test for all known and unknown etiological agents. This has led to the development of a family of approaches broadly labelled syndromic surveillance (Dupuy et al., 2013). Syndromic surveillance consists in the real-time collection and analysis of health related data for the early detection of emerging diseases (Henning, 2004; Hoinville et al., 2013). These data are usually collected for purposes other than disease surveillance. In section 7, we present some work on the use of production and reproduction data for syndromic surveillance in dairy cattle.

#### 3. Data sources

The sources of data that can be used to answer research questions in veterinary epidemiology are different from the data sources used in human epidemiology. An important distinction can be made between data that are collected specifically for research and routinely collected data. Since farmers' revenue depends on the sale of animals or animal products, large amounts of data related to production are routinely collected in farm animals. These data are paid for and used by farmers to evaluate the performance of their herd and/or of individual animals within the herd. A further use of these data is the evaluation of the genetic (breeding) value of breeding animals. For the latter purpose, in cattle, all the data collected are centralised in large databases that can be used for epidemiological studies. In order to be able to compare data across countries, guidelines are written and maintained by the International Committee for Animal Recording (ICAR)<sup>2</sup>. In the next sections, we list some of the data sources we have used in our own research and provide a non-exhaustive list of other data sources.

## 3.1. Cattle identification

In France as well as in most European countries, cattle identification is mandatory. Farmers have to notify all cattle births, movements and deaths within a few weeks after their occurrence. These data are centralised in national databases. Unique animal IDs ensure that every bovine can be uniquely identified through all the other databases. Animals are implanted with ear tags with these national IDs so that they can be used on farm and in epidemiological studies. Since farms also have unique identifiers and that their location is known, cattle movements between holdings

<sup>&</sup>lt;sup>2</sup> http://www.icar.org/

(farms, markets and assembly centres) and to slaughter houses, within and between countries can be followed. These data allow the quantification of the role of movements in the spread of diseases (Brooks-Pollock et al., 2014) or the investigation of mortality (Perrin et al., 2010).

## 3.2. Routinely collected production data

**Milk recording** Milk recording consists in the regular recording of milk quantities and the measure of milk constituents from all the lactating cows of a herd. The measures are usually performed once a month on two consecutive milkings. In France, it is estimated that around 60% of dairy herds participate to the program. In North America, a similar scheme exists and is usually called Dairy Herd Improvement (DHI).

**Artificial insemination data** On most French dairy farms artificial insemination (AI) is used. When a cow is detected on heat, semen from a selected bull is introduced in the cow's reproductive tract. This is usually performed by technicians from the breeding companies. The date, cow ID and bull ID are recorded and centralised. These data are used for genetic selection.

**Other routinely collected data in cattle** There are important differences between the data recorded in dairy herds and in beef herds. For obvious reasons, there is no milk recording in beef herds. Beef performance recording exists and guidelines are provided by ICAR. It mostly consists in weighing animals at regular intervals. But performance recording is far less common in beef herds than milk recording in dairy herds. Part of the reason is that beef cows spend on average more time at pasture and that few farms have the facilities to gather the animals to perform the necessary measures. This also explains why artificial insemination is only performed in 15% to 30% of French beef herds.

**Production data in species other than cattle** Different types of data are collected depending on the type of production. In poultry and pig productions for example, given the numbers of individuals, it is impossible to identify every single animal. The data that are kept and stored are batch level aggregated data such as mortality rates, feed efficiency.

## 3.3. Health related data

**Laboratory data** Laboratory test results are also generated and stored following vet requests for the investigation of health problems. However, the way these data are collected is not standardised across labs which makes large scale studies complicated. In some instances such as when BTV emerged in France in 2006, notification was mandatory so that the data could be used. However, even in this case, only herd level data were kept so that individual cow data could not be used. In this area, there is a need for standardised data collection practises to be developed and implemented.

**Epidemiological data** In order to investigate a specific disease, it is necessary to diagnose this disease either by performing clinical diagnosis on farm or by collecting samples that will be analysed as well as to gather data on factors and treatments explaining or preventing its

occurrence. This is especially suited for production diseases for which experimental reproduction is not always easy and the range of risk factors and preventive measures cannot be reproduced in a laboratory. An example in dairy cattle is the investigation of digital dermatitis (Relun et al., 2013). The disease is multifactorial, but always involves bacteria of the genus *Treponema* belonging to various species. The experimental reproduction of the disease is possible but limited to a small number of animals (Gomez et al., 2012). In these conditions, it is necessary to collect data from farms. In such cases, production data are often used in parallel, for example, to evaluate the impact of the disease of interest on production or reproduction (Amory et al., 2008).

**Entomological data** Another type of data worth mentioning is entomological data. Following the emergence of BT and of the Schmallenberg virus, several countries have started to collect data on culicoides (Balenghien et al., 2014). These data should help to better understand the epidemiology of vector-borne diseases, to better evaluate the risk of emergence and to design better control strategies.

**Surveillance data** For some diseases, that are either important to the industry because of their consequences on animal health and production or that pose a risk to human health, data are collected on a regular basis. In France, this is the case with bovine tuberculosis and brucellosis for which systematic surveillance programs are in place. At regular intervals, animals or herds are tested for the presence of specific diseases. In the case of syndromic surveillance, which will be developed in section 7, routinely collected data are used for surveillance purposes.

#### 4. Quantification of the impact of a disease on milk production in cattle

#### 4.1. Study design

We present how the impact of BTV-8 infection on milk production was evaluated in affected herds by Nusinovici et al. (2013). The objectives of the study were to quantify the mean effect of exposure to BTV-8 on milk yield for all cows in herds previously naive and to determine the duration of these effects before and after the time when the disease first detected in the herd.

Information regarding exposure to BTV-8 was obtained from the official surveillance system. This information was only available at herd level: the status of individual cows was unknown. A herd was considered exposed if at least one animal showing clinical signs tested positive for BTV-8. Selected exposed herds will be referred as case herds. The dates of clinical suspicions were used as the estimated exposure dates. The same date of exposure was assigned to all cows from the same case herd. There were 8 279 case herds located in 19 *départements*<sup>3</sup> (French administrative units). The dates of exposure ranged from the 31<sup>st</sup> of July to the 28<sup>th</sup> of December 2007.

Milk yields of cows belonging to exposed herds were compared with those of cows in unexposed herds. Dairy herds exposed to the virus during the 2007 French epizootic were selected to quantify the effect of exposure in a population of naive cows, unvaccinated against BTV-8. Performances recorded between 2004 and 2006 for cows in case herds were used as the unexposed reference

<sup>&</sup>lt;sup>3</sup> http://en.wikipedia.org/wiki/Departments\_of\_France

population. This enabled the comparison of cows within the same herd, thereby controlling for farming and climatic conditions.

From milk recording, individual cow milk yields were available as daily milk productions collected once a month in all cows from a dairy herd. The statistical unit was therefore the herd milk recording date called test-day (**TD**). For a given cow, milk yield varies with the time elapsed since the previous calving (stage of lactation or days in milk) and with the number of calvings (parity). Added to that, feeding and management practices within a herd influence the level of milk production. Therefore, as is common in veterinary epidemiology, milk production has both an animal as well as a herd level components that need to be accounted for when modelling disease impact (Madouasse et al., 2012).

## 4.2. Statistical model

The relationship between milk yield and exposure to BTV-8 was estimated using mixed linear models to account for the non-independence of (i) cows from the same herd, and (ii) TD from the same lactation (repeated measures). These data characteristics have been taken into account by including (i) a random variable corresponding to herd number and an (ii) autocorrelation structure of order 1 between TD. Furthermore, factors known to affect milk yield must be considered when assessing the effect of BTV-8 (Bareille et al., 2003; Beaudeau et al., 2007; Fourichon et al., 1999). Because of differences in the shape of the lactation curves and the amount of milk produced between parities, the analyses were stratified by parities (parity 1, 2,  $\geq$  3). The equation below describes the model used for parity 2 cows:

$$Y_{ijt} = \beta_0 + EXP_{ijt}\beta_1 + SL_{ijt}\beta_2 + MO_{ijt}\beta_3 + BV_{ijt}\beta_4 + v_j + \varepsilon_{ijt}$$

$$v_i \sim Normal(0, \sigma_v^2)$$
(1)

where  $Y_{ijt}$  is the milk yield of cow *i* in herd *j* at time *t*,  $EXP_{ijt}$  is a variable measuring the exposure/time since exposure to BTV-8 (78 classes, corresponding to the time periods considered before and after the date of exposure),  $SL_{ijt}$  is the stage of lactation (41 classes with different time length depending on the stage of lactation: 5 days in early lactation, 10 days in mid-lactation and 15 days in late lactation),  $MO_{ijt}$  is the month of TD (12 classes),  $BV_{ijt}$  is the estimated breeding value for milk (quantitative, after having checked the linearity with milk yield),  $v_j$  is the random effect for herd *j*. Herd random effects follow a normal distribution with mean 0 and variance  $\sigma_v^2$ .

An autocorrelation structure, known as autoregressive, adjusts for the fact that milk yield for a given TD is correlated with the milk yield of the previous TD (Gröhn et al., 1999). The correlation structure of order 1 between the measures of milk yield from a single cow during her lactation requires the estimation of 2 parameters,  $\Phi$  and  $\sigma_n$ :

$$\begin{aligned} \varepsilon_{ijt} &= \Phi \varepsilon_{ij(t-1)} + \eta_{ijt} \\ \eta_{ijt} &\sim Normal(0, \sigma_n^2) \end{aligned}$$
 (2)

where  $\varepsilon_{ijt}$  is the residual from  $TD_t$  for cow *i* from herd *j*,  $\varepsilon_{ijt(t-1)}$  is the residual from  $TD_{t-1}$ ,  $\Phi$  is the correlation parameter and  $\eta_{ijt}$  is the residual error from  $TD_t$ .

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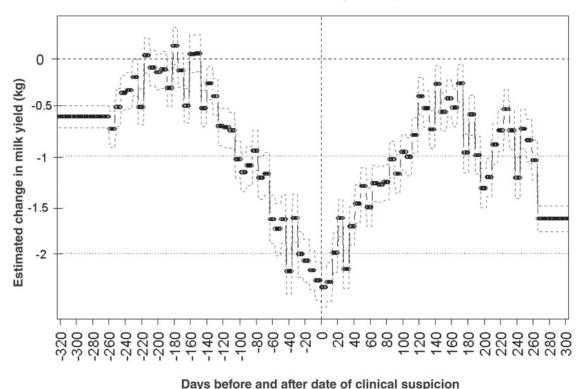


FIGURE 4. Estimated changes in milk yield (kg) by milk yield test-day and 95% confidence intervals around the herds

dates of clinical suspicions for parity 2 cows in herds located in exposed districts (exposed population: 15 754 cows in 873 herds; unexposed population: 164 854 cows in 2 974 herds). Each point corresponds to milk yield changes estimated by the model between exposed population and the reference population for each class of the exposure variable. (From Nusinovici et al., 2013)

## 4.3. Effect of BTV-8 exposure on milk yield

A sharp decrease in individual cow milk yield was observed around the time of herd exposure to BTV-8. The estimated variations in milk yield per TD as a function of the time interval between TD and time of case herd exposure for cows in their second lactation in the most exposed *départements* are shown in Figure 4. Each point corresponds to milk yield changes estimated by the model between exposed population and the reference population for each class of the exposure variable. The negative and positive abscissas correspond to TD that happened before and after the date of clinical suspicion, respectively. The decrease in milk yield continued long after the date of clinical suspicion in the herd. The maximum decrease in milk yield per TD was 2.3 kg and occurred 1 week after the herd exposure.

## 5. Evidence of underreporting of BTV-8 cases using fertility data

## 5.1. Study design

As fertility deteriorates, the proportion of unsuccessful inseminations increases. The association between BTV-8 exposure and fertility was quantified using AI data. The occurrence of an AI following a previous AI (as opposed to an AI following calving), which is called return to service, can be used as a proxy for fertility problems. Therefore, a decrease in fertility will be characterised by an increase in returns to service, or equivalently, by a shorter interval between consecutive AIs. In this piece of work, the hypothesis that exposure to BTV-8 could have altered dairy cow fertility was tested.

In *départements* exposed to the virus in 2007, cattle case herds were selected (n=4 392) as well as herds that were not reported during 2007 and located in these *départements*. In the latter case, herds were considered to have an uncertain infectious status, and were thus referred as *herds with uncertain BTV-8 status* (n=13 804). A date of exposure to BTV-8 was either estimated from recorded data for cows in case herds, or interpolated for cows in herds with uncertain BTV-8 status. This interpolation was based on the spatio-temporal dynamics of detection of confirmed case herds that reported clinical signs in 2007. Decreases in fertility in both case herds and herds with uncertain BTV-8 status were quantified around the date of exposure (observed or predicted).

The criterion used to quantify the impact of BTV-8 exposure on fertility was a return-to-service occurring between 18 and 90 days after AI (binary variable). The study population was composed of 122 079 cows with a first AI performed in 2007 (43 786 cows in case herds and 78 293 in herds with uncertain BTV-8 status) in 7 883 herds located in the epizootic area (2 646 case herds and 5 237 herds with uncertain BTV-8 status). A reference population was used to quantify the decrease in fertility of both cows in case herds and cows in herds with uncertain BTV-8 status. It was composed of cows located in two French regions unexposed to BTV-8 during 2007: Brittany and a South-western area. This comparison limited the impact of any possible confounding factors due to variations of herd management over time. The reference population was composed of 211 578 cows in 9 485 herds located in regions unexposed to BTV-8.

## 5.2. Interpolation of a date of detection of clinical signs for herds not reported and located in exposed areas

A date of exposure to BTV-8 for each cattle herd with uncertain BTV-8 status during 2007 was interpolated. Kriging (Chilès and Delfiner, 2012; Gaetan and Guyon, 2008), a geostatistical interpolation method, was used to estimate a date of detection of clinical signs for herds with uncertain BTV-8 status. Dates were expressed as a number of days since the first case herd reported in 2007. Kriging uses a data sample, i.e. cattle case herds with a recorded notification date, to predict values at unsampled locations, i.e. in herds with uncertain BTV-8 status. This method is based on assumptions regarding the form of the trend of the sample data, its variance and spatial correlation. The first step consisted in analysing spatial variations of the data through an experimental semivariogram. Semivariograms allow to characterize spatial correlation by plotting semivariance as a function of distance. Two models (Gaussian and exponential) fitting the spatial dependence were compared. A cross-validation process with observed data was used to determine

each model's goodness of fit and to compare their predictions. Spatial variation in detection dates were modelled using a Gaussian semivariogram - for smooth long-range propagation waves - and an exponential semivariogram - for short-range random propagation between neighbouring herds - models. To account for the non stationarity of the BTV-8 spreading process, the gradient of the viral diffusion was also included in the model by the use of Universal Kriging in place of Ordinary Kriging. For the final interpolation of detection dates, only the Gaussian-model spatial component was kept in order to filter the random local component within municipality range.

#### 5.3. Interpolated date of clinical signs detection for herds with uncertain BTV-8 status

Figure 5 shows the experimental semivariogram of the observed dates of clinical sign detections in case herds. Some case herds located in the same municipality were detected at different periods of the epizootic. These point pairs had thus a large semivariance, giving a pure random term (nugget effect) of 640 day<sup>2</sup> and a fitted exponential semivariogram model with a semi-variance of 127 day<sup>2</sup> and a range of 9.9 km. The fitted Gaussian semivariogram model had a semi-variance of 243 day<sup>2</sup> for a scale parameter (sd) of 82 km that is equivalent to an effective range of about 160 km. The fitted nested semivariogram model, plotted in black, shows the suitability of the fitted model for all distances larger than 10 km. The Gaussian component of the variogram model, in red dashed line, was used to map mid-to-long-range variation by Universal Kriging, filtering short range variation (5 to 10 km) and semivariance due to location uncertainty inside the municipality level.

Figure 6 shows the location of the 8 313 cattle herds used as the data sample and the predicted values of the kriging model for the dates of clinical detection of the disease in the outbreak area. Predicted dates of clinical suspicion were expressed as a number of days since the first clinical case detected the 31<sup>st</sup> of July 2007 among cattle herds. The virus first affected the north-eastern part of France and then progressed in the south-west direction. As a result of the nugget effect quantified in the semivariogram, kriging model predicted within neighboring areas values corresponding both to early and mid/late infections.

## 5.4. Statistical model for fertility

The relationship between exposure and occurrence of a possible return-to-service was assessed with multivariable Cox models. To account for factors likely to influence the probability of return-to-service, the association between BTV-8 exposure and occurrence of return-to-service was adjusted for several independent variables already described as risk factors for fertility traits in the literature (Hillers et al., 1984; Malher et al., 2006; Marcé et al., 2009; Robert et al., 2004) as described by the following equation:

$$\lambda_{ij}(t|X_{ij}, \mathbf{v}_j) = \lambda_0(t) \times exp(X_{ij}\boldsymbol{\beta} + \mathbf{v}_j) \mathbf{v}_j \sim Normal(0, \boldsymbol{\sigma}_{\mathbf{v}}^2)$$
(3)

where  $\lambda_{ij}$  is the hazard function at time *t* for the probability of 90-day-return-to-service following the first AI for the *i*<sup>th</sup> cow in the *j*<sup>th</sup> herd.  $X_{ij}$  is a matrix containing, for each cow, the 6 following variables: exposure status (36 classes corresponding to 12 periods of 2 weeks for 3 populations); lactation number (4 classes); maximum milk production in kg at the 3 first milk

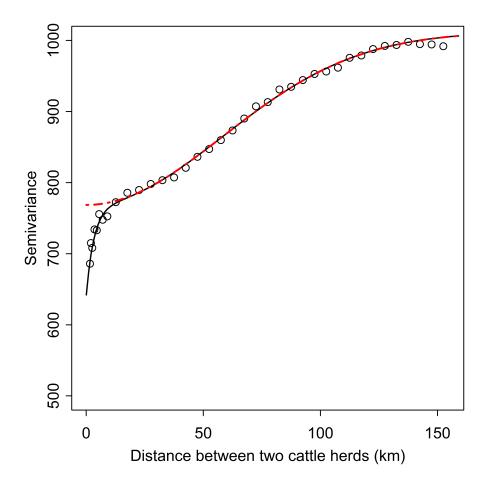


FIGURE 5. Experimental variogram of the observed dates of detection of Bluetongue virus serotype 8 clinical signs of reported case herds (dots) and the fitted nested model of semivariogram (solid black line) which is the sum of a nugget effect, an exponential and a Gaussian variogram model. The Gaussian component which is kept for kriging is shown in red dashed line. (From Nusinovici et al., 2014)

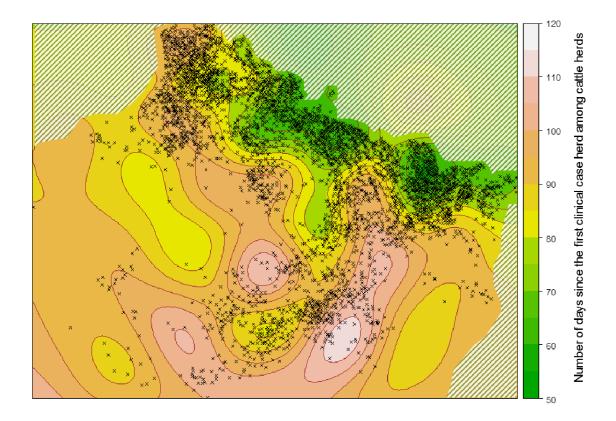


FIGURE 6. Kriging map of the dates of detection of Bluetongue virus serotype 8 clinical signs, expressed as a number of days since the first clinical case herd during the 2007 epizootic in France (31st July 2007), and location of reported case herds (black crosses). The hatched areas correspond to regions with no data.(From Nusinovici et al., 2014)

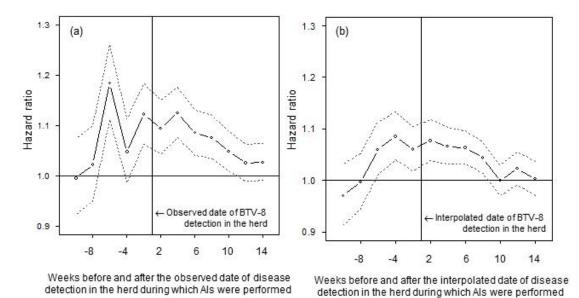


FIGURE 7. Hazard Ratio (HR), with 95% confidence intervals, of 90-day-return-to-service before and after (a) the date of Bluetongue virus serotype 8 (BTV-8) clinical detection for case herds reported during the 2007 epizootic, (b) the interpolated date of BTV-8 clinical detection for non-reported herds located in the 2007 outbreak area, France. (From Nusinovici et al., 2014)

recordings in the lactation used as a proxy for peak milk yield (5 classes); minimum of milk protein to fat ratios out of the first 3 milk records (5 classes); calving-to-AI interval (7 classes) and month of AI (8 or 10 classes).  $\beta$  is the vector of coefficients associated with these 6 variables and  $v_j$  is a herd random effect which follows a normal distribution with mean 0 and variance  $\sigma_v$ . The random effect term made it possible to adjust for clustering within the data using a frailty model. The effects in percentage points of return rate were calculated from estimated hazard ratio (HR).

## 5.5. Under-reporting evidenced using performance data

As expected, exposure to BTV-8 at the time where clinical signs were observed was associated with an increase in the 90-day-return-to-service rate for cows in case herds (Figure 7-a). The period of fertility decrease corresponded to AIs performed between 6 weeks before to 10 weeks after the date of clinical detection (HR between 1.05 and 1.18). More interestingly, for cows in herds with uncertain BTV-8 status, an increase of the 90-day-return-to-service rate was also found (Figure 7-b). The period of decreased fertility corresponded to AIs performed between 6 weeks before and 8 weeks after the interpolated date (HR between 1.04 and 1.08). These fertility decreases corresponded to an increase of 5.2 and 3.0 percentage points of 90-day-return-to-service for cows in case herds and cows in herds with uncertain BTV-8 status, respectively.

#### 6. Side effect on fertility associated with vaccination against BTV-8

#### 6.1. Study design

The objective of this study by Nusinovici et al. (2011) was to quantify a possible side effect of vaccination against BTV-8 using inactivated vaccines on the fertility of dairy cows in field conditions. The general design involved the comparison of the fertility of vaccinated and unvaccinated dairy cows, none of which had been exposed to BTV-1 or BTV-8 during 2008. Cows were selected from herds located in Brittany. Overall, 150 891 cows in 3 360 herds not exposed to BTV were selected. Reproductive performance was assessed by the occurrence of a repeat AI (return-to-service) after a first or a second AI. There are three causes of return-to-service before the implantation of an embryo: conception failure, early embryonic death (before 16 days) and late embryonic death (after 16 days). Both conception failure and early embryonic death lead to a new heat 3 weeks after AI, and, if the heat is detected, a 3-week-return-to-service. A 3-week-return-to-service was defined as a return-to-service occurring between 18 and 26 days after AI.

It was assumed that if vaccination had a side effect on cattle fertility, the effect would occur within a few days. In order to test an effect of vaccination on conception failure or early embryonic death, a comparison of 3-week-return-to-service rates was performed between cows vaccinated between 3 days before and 16 days after the AI and unvaccinated cows (3-week-return-to-service model). The vaccinated cows were divided into three categories according to the time interval between when they underwent AI and vaccination. Categories were constituted as follows: from 3 days before to 1 day after AI (assuming an effect on conception failure), from 2 to 7 days after AI (assuming an effect on the embryo viability in its first week) and from 8 to 16 days after AI (assuming an effect on the embryo viability in its second week). Two analyses were conducted separately for the first and the second vaccine injection.

Unvaccinated cows were selected according to the date of AI so that both vaccinated and unvaccinated cows underwent AI during the same period in 2008. Moreover, unvaccinated cows were selected so that vaccinated and unvaccinated cows had the same length of return-to-service observation periods to allow an unbiased comparison.

#### 6.2. Statistical model

The relationship between vaccination and occurrence of a possible return-to-service was assessed using multivariable statistical models. To assess the risk of 3-week-return-to-service, a mixed effect logistic regression model was used. To account for factors likely to influence the probability of return-to-service, the association between vaccination status and occurrence of return-to-service was adjusted for several independent variables already described as risk factors for fertility traits in the literature (Hillers et al., 1984; Malher et al., 2006; Marcé et al., 2009) as described by the following equation:

$$Y_{ij} \sim Bernoulli(p_{ij})$$

$$\ln(\frac{p_{ij}}{1-p_{ij}}) = \beta_0 + VAC_{ij}\beta_1 + SR_{ij}\beta_2 + PAR_{ij}\beta_3 + MY_{ij}\beta_4 + PF_{ij}\beta_5 + CAII_{ij}\beta_6 + MO_{ij}\beta_7 + EN_{ij}\beta_8 + \nu_j$$

$$\nu_i \sim Normal(0, \sigma_{\nu}^2)$$
(4)

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Vaccination status	Vaccination timing (days since AI)	3-week-return-to- service (%)	Number of AIs	RR	95% CI	р
Unvaccinated	NA	22.1	10,298	1	Ref	
Receiving a first injection	-3 tot +1	21.1	973	0.98	[0.95-1.05]	0.70
	+2 to +7	21.1	1,022	0.97	[0.95-1.04]	0.67
	+8 to +16	21.8	1,440	1.00	[0.95-1.05]	0.98
Unvaccinated	NA	22.1	10,594	1	Ref	
Receiving a second vaccine injection	-3 to +1	23.1	996	1.08	[0.94-1.21]	0.25
	+2 to +7	25.8	1,112	1.19	[1.07-1.33]	0.002
	+8 to +16	22.2	1,672	1.03	[0.93-1.14]	0.55

TABLE 1. Relative risk of 3-week-return-to-service depending on the interval between AI and BTV-8 vaccination, and the rank of vaccine injection in Holstein dairy herds unexposed to BTV in 2008; Brittany; France (two separate models for each vaccine injection).

where the outcome  $Y_{ij}$  is a binary variable denoting the occurrence of a 3-week return to service following a first or a second AI in cow *i* from herd *j*, with a probability of occurrence  $p_{ij}$ ;  $\beta_0$  is the intercept;  $VAC_{ij}$  is the vaccination status (2 or 4 categories according to the model considered);  $SR_{ij}$  is the service rank (2 levels);  $PAR_{ij}$  is the lactation number (4 levels);  $MY_{ij}$  is the peak milk yield expressed as the maximum of the three first milk records in the lactation (continuous);  $PF_{ij}$ is the minimum of Protein:Fat ratio out of the first three milk records (3 levels);  $CAII_{ij}$  is the calving-to-AI interval (6 levels);  $MO_{ij}$  is the month of AI (between 3 and 5 categories according to the model considered);  $EN_{ij}$  is the proportion of exposed neighbouring cantons (3 levels) and  $v_j$  is a composite (random) variable combining herd ID and inseminator ID. Odds-ratios were converted into risk ratios using Beaudeau and Fourichon's method (Beaudeau and Fourichon, 1998).

# 6.3. Effect associated with a vaccine injection administered between 3 days before and 16 days after AI on 3-week-return-to-service rate

After a first vaccine injection Selection of AI from cows receiving a first vaccine injection between 3 days before and 16 days after that AI resulted in 3 435 selected AIs. These AIs were compared to 10 298 AI from unvaccinated cows in the time period from the  $2^{nd}$  of August 2008 to the  $27^{th}$  of November 2008. After adjustment, the 3-week-return-to-service rates of vaccinated cows did not differ significantly from unvaccinated cows whatever the time interval between AI and vaccination (Table 1).

After a second vaccine injection Selection of AI from cows receiving a second vaccine injection between 3 days before and 16 days after that AI resulted in 3 780 selected AIs. These AIs were compared to 10 594 AIs from unvaccinated cows in the time period from the  $1^{st}$  of September 2008 to the  $17^{th}$  of December 2008. After adjustment, the 3-week-return-to-service

rate was significantly higher for cows vaccinated for the second time between 2 days and 7 days after AI compared to unvaccinated cows (Table 1). This difference corresponded to an increase of 4.2 percentage points of 3-week-return-to-service rate.

## 7. Detection of emerging diseases

#### 7.1. Statistical methods for the detection of disease emergences

When estimating the impact of a disease, the statuses of the animals or herds studied are known and health parameters or productions are compared between affected and unaffected entities. In syndromic surveillance, the problem is reversed. Whether a disease is present needs to be determined from the data on health or production. The individuals investigated are a mix of animals uninfected and varying proportions of animals infected at different stages of the disease. The different families of statistical methods used aim at detecting outbreaks, anomalies, changes or ruptures in time series. Classically, statistical methods for outbreak detection are divided into 3 stages: i) evaluation or modelling of historical data in order to predict expected values in the absence of disease, ii) comparison of expected and observed values at each time/location and iii) alarms triggered based on the detection of abnormal deviations between observed and predicted. A wide range of methods can be used. The choice of a particular method depends on the type of disease that could emerge as well as on the type of indicator(s) and its (their) distribution(s) (univariate or multivariate time series, rare or frequent events, count or continuous data), and the availability of historical data. Control charts (cumulative sums, exponentially weighted moving average ...), regression models (Farrington method, ARIMA model, ...), spatial or spatio-temporal model (Scan statistics) are a few examples of the methods available (Unkel et al., 2012). For some diseases, it is possible to work with aggregated time series since adding spatial information requires more complex models and should not improve detection timeliness. On the other hand, vector-borne diseases such as BTV, from an introduction location, spread by contiguity and are introduced to new places through cattle movements. In this case, the incorporation of spatial information to models can help to accelerate disease detection. In the following section, we explore both types of approaches (See also the article by Britton and Giardina in this issue).

## 7.2. Detection of the BTV-8 emergence in France using production and reproduction data

#### 7.2.1. AI data for the detection of vector borne disease emergences

Using all the AI data collected between 2003 and 2009 in French dairy herds enrolled in the national milk recording scheme, it was possible to test indicators for the detection of the BTV emergence (Marceau et al., 2014). Five indicators aiming at measuring infertility, embryonic and foetal losses and shortened gestations were constructed from AI and calving dates. Three indicators were based on the interval between the first and a second AI in lactation and 2 were based on the interval between the last known AI date in lactation and a subsequent calving. The indicators were daily numbers of event occurrences over daily numbers of cows at risk, i.e. rates. These rates were averaged per week. As a unit of spatial aggregation, the French

administrative *département* was chosen. The indicators analysed were therefore weekly time series. Simple periodic linear regressions were performed on each spatial unit separately to remove seasonal variation and values above the upper bound of the 95% confidence intervals were used as indications of abnormal events:

$$\lambda_{t} = \mu + \sum_{n=1}^{3} \left[ \alpha_{n} . cos(\frac{2\pi tn}{52}) + \beta_{n} . sin(\frac{2\pi tn}{52}) \right] + \varepsilon_{t}$$

$$\varepsilon_{t} \sim Normal(0, \sigma_{\varepsilon}^{2})$$
(5)

where  $\lambda_t$  is the mean daily rate of occurrence of a given indicator on week *t*, which is the number of weeks since the 1<sup>st</sup> of January 2003, and  $\varepsilon_t$  is the residual error with mean 0 and variance  $\sigma_{\varepsilon}^2$ . The annual seasonal pattern of 52 weeks was modelled by 3 harmonics (n = 1, 2, 3) chosen based on the AIC to best fit all observed patterns. A model was fitted for each *département* on the data collected between 2003 and 2005, period without any major epidemic event. Then, expected values were predicted for the period between 2006 and 2009. Four out of the 5 indicators showed an elevation during the BTV emergence with median times between notification and elevation ranging from 20 to 71 days. The most timely and specific indicator was the proportion of cows calving between the 1<sup>st</sup> and the 25<sup>th</sup> percentiles of the normal gestation length. This was not expected as a shortening of gestation associated with BTV infection had never been documented. It could be either a specific consequence of the infection by this virus or a side effect of the fever induced that could be associated with any infectious agent causing fever. In this case, this indicator would be a very good candidate for any syndromic surveillance system.

A potential area of improvement regards the optimum level of space-time aggregation. In the above described work, it was chosen to work at the *département*-week level. These levels were chosen for empirical reasons, based on the need to have sufficiently precise levels of detection while maintaining high enough numbers at the denominators and numerators. But regarding spatial aggregation, it would have been possible to aggregate at some lower spatial level, starting from municipality until a sufficient number of cows at risk is reached. This minimum number of animals at risk can be based on sample size calculations using the baseline rate and the minimum intensity of the change to detect as inputs.

## 7.2.2. Milk recording data for the detection of vector borne disease emergences

Madouasse et al. (2014) evaluated monthly collected milk yields for the detection of the BTV emergence. Disease detection was based on the identification of clusters of low milk production using a scan statistic. The scan statistic was run on the difference between observed and predicted milk productions. The analyses were conducted for the year 2007, using milk yields collected between 2003 and 2006 as reference historical data.

**Prediction of milk production** Herd TD milk productions per cow were predicted with linear mixed models accounting for past herd production. Herd specific seasonal effects were incorporated into the model by linearly interpolating individual days of year between pre-specified change points that were modelled at the herd level. The model specification was as follows:

$$Y_{ij} = \sum_{k=1}^{8} \left[ (\beta_k + \mathbf{v}_k^j) \frac{d - \tau_k}{\tau_{k+1} - \tau_k}) + (\beta_{k+1} + \mathbf{v}_{k+1}^j) (1 - \frac{d - \tau_k}{\tau_{k+1} - \tau_k}) \right] + \varepsilon_{ij}$$

$$v_k^j \sim MVN(0, \Sigma_v^2)$$

$$\varepsilon_{ij} \sim Normal(0, \sigma_\varepsilon^2)$$
(6)

where  $Y_{ij}$  is the milk production per cow in herd *j* on TD *i*, *d* is the day of year at  $TD_j$ . *d* is mapped onto 8 time intervals defined by 8 change points labelled  $\tau_1$  to  $\tau_8$ . For 8 time intervals, there should be 9 change points, but because the data are periodic, days from the last interval are mapped onto  $\tau_8$  and  $\tau_1$ .  $I_k$  takes the value 1 if *d* is between  $\tau_k$  and  $\tau_{k+1}$ , 0 otherwise. The mean and herd specific milk productions estimated for  $\tau_k$  are  $\beta_k$  and  $v_k$  respectively.  $v_k$  follows a multivariate normal distribution with mean 0 and a variance-covariance matrix  $\Sigma_v^2$ .  $\varepsilon_{ij}$  is the residual error which follows a normal distribution with mean 0 and variance  $\sigma_{\varepsilon}^2$ . The model was fitted to data collected between 2003 and 2006. The estimated parameters were used to predict expected milk productions in 2007.

**Cluster detection** For each TD that occurred in 2007, the differences between observed and predicted milk productions were calculated. These differences were analysed with a space time scan statistic as implemented in the SaTScan software (Kulldorff, 2011). For the detection of purely spatial clusters, the program creates a random circle and calculates the likelihood of the data observed within the circle given the distribution of the data lying outside the circle used as the null hypothesis. This is repeated thousands of times, varying the size and location of the circles. In the case of space-time clusters, cylinders are used instead of circles, but the idea remains the same. Our assumptions were that if milk production followed a herd specific seasonal pattern, the differences between observed and predicted should be random noise but if a disease emerged, there should be clusters of lower than expected milk production. The analyses were repeated on a weekly basis, as if the data were acquired in real time. The coordinates of the municipality in which each individual herd was located were used as spatial information.

**Detection of the BTV-8 emergence** Some events, for example climatic events such as droughts, can produce clusters of low milk production which are not related to disease occurrence. These would lead to false alarms, lowering the performance of the system. On the other hand, when a disease emerges, the objective is to detect it within the shortest possible delay. Based on the log likelihood ratios of the clusters identified by the algorithm, a threshold was chosen to define alarms. This threshold was a trade-off between the number of false alarms and the timeliness of BTV-8 detection. This allowed detecting BTV-8 within 9 weeks after its emergence in France, with a mean of 0.8 false alarms per week.

#### 7.3. Evaluation of syndromic surveillance systems through simulation

Although it was possible to detect the emergence of BTV-8 using production and reproduction data, the work presented above gives only limited indications on the ability of the indicators and methods presented to detect other emergences. In this section, we show how simulation can be used to evaluate syndromic surveillance systems.

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Syndromic surveillance systems can be considered as tests for the detection of disease emergences. In epidemiology, disease detection tests are compared using sensitivity (Se) and specificity (Sp) as performance measures. Se is the probability of a test detecting a disease if the disease is present (p(T+|D+)) and Sp is the probability of the test returning a negative result when the disease is absent (p(T-|D-)). These are based on the assumption that the distributions of the disease indicators (parameters measured) are different between diseased and healthy individuals. If there is no overlap in the distributions, then the test is perfect with a Se of 100% and a Sp of 100%. However, in nearly all cases, the distributions overlap and a threshold value that best discriminates diseased from healthy individuals has to be identified. Different objectives can lead to different thresholds being used.

When there are a vast number of diseases that could emerge, most of which are unknown, it is impossible to determine what effect an emergence would have on a given indicator. If syndromic surveillance systems can be considered as disease detection tests, their performances cannot be evaluated by calculating Se and Sp. A solution consists in reversing the problem by evaluating the performance of an indicator through the simulation of disease spread and its consequences on the indicator, as if a disease were emerging. For specific diseases such as BTV, existing spatio-temporal spread models can be used to simulate disease spread (Charron et al., 2013; Szmaragd et al., 2009). However, for a more general evaluation a range of plausible disease spread and effect scenarios should be considered. This was done in Madouasse et al. (2013) where the performance of monthly collected milk yields for the detection of vector borne emerging diseases was evaluated.

## 7.3.1. Simulation of vector borne disease emergences

Vector borne disease emergences and their effects on cow milk production were simulated. For the simulations, individual cow milk recording data collected in 2006, before the 2007 BTV-8 emergence, were used. At each TD date each herd and recorded cow were assigned an infected or uninfected disease status. Recorded milk productions were either left unchanged or decreased by a certain amount if a cow was infected.

The parameters of the simulation that were varied were disease starting location, disease starting date, disease front wave speed, probability for a herd of getting the disease, probability for a cow of getting the disease and disease impact on milk production. Disease introduction was simulated in both a high and a low cattle density area, starting either on the 1<sup>st</sup> of March or on the 1<sup>st</sup> of September. Disease front wave was made to progress as a circle with speeds of 1, 5 or 10 km/day, based on work by Pioz et al. (2011). Once the front wave had reached a given herd, this herd could get the disease with daily probabilities of 0.005, 0.01, 0.05 or 0.1. Once a herd was infected, each cow from this herd could get the disease with daily probabilities of 0.005, 0.01, 0.05 or 0.1. By the end of these steps, each cow had been assigned a date of infection or was uninfected. From the day she was infected, the milk production recorded on a TD was decreased by x%, with x varied between 0.35 and 0.9, between 0 and d1 days after infection and was made to go back to normal linearly between d1 and d1 + d2 days after infection. d1 and d2 varied between 5 and 21 days. Mean milk productions per cow were calculated for each herd TD.

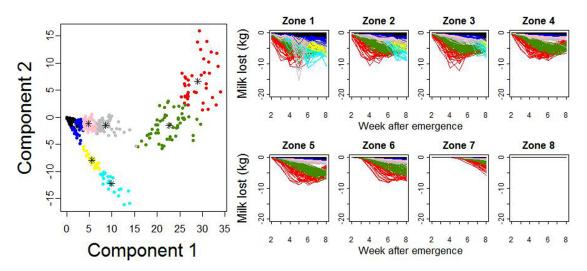


FIGURE 8. Projections of 576 disease spread scenarios on the first 2 components of a principal component analysis. On the left-hand side plot, each dot represents a scenario and each color represents one of the 8 retained scenario groups. The plot on the right-hand side represents the mean quantity of milk lost per cow in each of 8 geographical area and during the first 8 weeks after emergence. (From Madouasse et al., 2013)

#### 7.3.2. Definition of families of scenarios

All combinations of parameters were simulated which resulted in 576 scenarios. Since it would have been impossible to undertake disease detection on all scenarios, families of scenarios were defined based on the simulated drop in mean herd TD milk production per cow in 8 circular zones centred on the disease emergence location for 8 weeks after the simulated date of emergence. Therefore, for each simulated scenario a matrix of 64 values (8 zones x 8 weeks) summarising the impact of disease emergence on milk production was available. Principal component analysis (PCA) was used to reduce the number of values required to describe a scenario. The first 2 dimensions of the PCA explained over 92% of the variability. From these 2 components, 8 families of scenarios were created with the K-means algorithm. The scenario which was the closest to each family's centroid was used for cluster detection (Figure 8).

## 7.3.3. Performance of milk yield as an indicator for syndromic surveillance

As in section 7.2.2, herd TD milk productions were predicted from historical data using linear mixed models. Clusters of low milk production were detected using a space time scan statistic. Alarms were defined as clusters with an associated p-value smaller or equal to 0.05. Depending on the scenario, clusters of low milk production were detected between 1 and 3 weeks after emergence. The simulated parameters that had the strongest association with the timeliness of detection were the daily probabilities of infections for herds behind the front wave and for cows within infected herds. This makes sense because as these probabilities increase, the proportion of cows with a decreased milk production within an affected area increase, thereby increasing the signal to noise ratio. Adding random noise to the simulated milk production losses tended

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to deteriorate the timeliness of detection. The main limitation to the use of milk yield for the detection of vector borne disease emergence was the elevated number of false alarms. This number could have been lowered by selecting clusters with lower p-values (as was done in the work presented section 7.3.2), which would have delayed detection of true disease clusters. This number of false alarms depended more on bias in predicted values than on random noise. There were clusters of low milk production that were not predicted by the model and which were mimicking disease emergences. The interesting aspect of this work was to highlight the factors that were important for an emerging disease to be detected. Timeliness of detection seems to be mostly influenced by the speed of disease propagation within infected areas. Further work should focus on better predicting milk production in the absence of disease in order to decrease the number of false alarms.

## 7.4. Multivariate methods for syndromic surveillance

Most of the statistical methods used for early detection of anomalies are used in their univariate variant: statistical control process methods as cumulative sums algorithm (CuSum), exponentially weighted moving average algorithm (EWMA) (De Vries and Conlin, 2003; De Vries and Reneau, 2010), temporal regression (Bronner et al., 2015; Farrington et al., 1996), scan statistics (Kulldorff, 1999), space-time scan statistics. In the case of BTV-8, although the short gestation indicator was the most promising, other indicators, both reproductive and related to milk production, were affected by the emergence. Therefore, there would be an added value to monitor multiple indicators simultaneously. This would allow capturing different and complementary biological phenomena thereby improving the timeliness of detection. A way of improving the system would be to use multivariate time series methods which would account for the correlation, spatial and possibly lagged, between the different indicators. The most important challenge with these methods is to maintain a low false alarm rate, which grows with the number of monitored indicators, at an acceptable level.

Few multivariate methods have already been proposed to monitor multiple indicators. They can be classified into three categories: parallel and consensus monitoring methods, joint modelling methods and dimension reduction methods. The parallel and consensus monitoring methods consist in univariate monitoring of separate series followed by the combination of the results of anomaly detection of each series (first date of alarm, function of p-values obtained by statistic tests on each series for example). The joint modelling methods are a multivariate extension of statistical control process methods (multivariate cumulative sum algorithm, multivariate exponential weighted moving average Lowry et al., 1992). Kulldorff et al. (2007) also developed a multivariate space-time statistics. The last group of multivariate methods, the reduction dimension methods, consist in first reducing multivariate data at each time point to a scalar and then in applying univariate surveillance method (Unkel et al., 2012).

Most of these methods are based on the detection of anomalies on expectation of multivariate time series. However, detection of abnormal phenomena in a system can be viewed as detection of equilibrium breakdowns between several indicators. We can make the hypothesis that, in a normal situation, a system is in a state of equilibrium. When an abnormal phenomenon occurs, this equilibrium is disrupted. An analysis of time dependence between indicators could permit to monitor this equilibrium between indicators. This state of equilibrium can be expressed as a

global indicator of health status in a cattle population. Latent variable models such as the factor analysis model and its extensions to dynamic situation could be used to analyse and monitor this global indicator of health status of the cattle population (Anderson, 1963; Bollen, 2002; Hasson and Heffernan, 2011; Skrondal and Rabe-Hesketh, 2007).

Preliminary analysis of data collected during BTV epidemic in 2007 in France showed that during the epidemic, not only expectation but also dependence between indicators are modified. These first results show that the use of a latent variable model for multiple time series could be a promising tool to improve syndromic surveillance systems.

## 8. Discussion

Since its emergence as a discipline in the mid-1980s, veterinary epidemiology has always made an extensive use of statistical methods. Furthermore, both veterinary epidemiology and statistics have undergone tremendous changes with the massive increases in computation power and data storage capacity since the early 21<sup>st</sup> century. Despite the important progresses made, there remain challenges that only collaborations between researchers from both disciplines can overcome. In this section, we outline some of the most pressing questions that would benefit from joint work by epidemiologists and statisticians.

With the increase in computer speed, it is now possible to carry out simulations either to check model fit as is the case with cross validation or posterior predictive simulations (Green et al., 2009) or to test the performance of a method as was done in Madouasse et al. (2013). On the other hand, as discussed in section 3, large amounts of data are collected in farm animals. These data, whether they are collected or simulated, can now be stored at a small cost. The challenge is to analyse the large volumes of data available. This requires the development of efficient methods and algorithms. The solution adopted in Madouasse et al. (2013) was to analyse a subset of the data that captured most of the variability present in the entire dataset. This was possible thanks to an initial dimension reduction step followed by the identification of groups with similar characteristics. Another stream of research is concerned with the identification of patterns in large datasets. This is known as data mining and knowledge discovery. This represents both an opportunity for methodological developments (Reshef et al., 2011) that can lead to new discoveries as well as the danger of identifying patterns and associations that have no biological significance or that are misleading. In this sense, the concern raised by Ioannidis (2005) that most published research findings are false can only be exacerbated, because more data leads to an increase in the absolute number of false associations that can be uncovered. It is therefore essential for novice veterinary epidemiologists to conduct question-driven research, to know about the difference between association and causation, to be aware of both the meaning of p-values as tests of pre-specified hypotheses and of the dangers associated with multiple comparisons. Furthermore, the teaching of statistics to undergraduate veterinary students is of prime importance since, even if they do not work as researchers, they should be readers of scientific research. Therefore, veterinarians and veterinary epidemiologists can only benefit from deepening their statistical culture.

Another common and important challenge in veterinary epidemiology is to make inference or predictions for events that cannot be measured perfectly from a high number of variables and with missing observations. Furthermore, these data generally have a hierarchical structure whereby animals are clustered within farms. For example, with the advances in farming techniques, there are a growing number of sensors on farm that aim at measuring and predicting a range of diseases or reproductive events and which generate large amounts of data. The aims of these sensors are to detect the events of interest early in order to get a better treatment outcome and to prevent unnecessary treatments (Timsit et al., 2011). There are several problems associated with these data which may benefit from better statistical analyses. The first of these problems is the measurement of a high number of variables, which can be highly correlated, to predict the occurrence of an event. This is usually resolved by using dimension reduction methods (Garcia et al., 2014). The second problem associated with these sensors is that measurements can be missing, at random or not. In this case data imputation can be undertaken or, more commonly, the missing data are excluded. The last of these problems is due to the multiplicity of sensors on the market that, for a same biological phenomenon, produce outputs that are not strictly comparable either because they do not measure the same indicator, or because they vary in the way the measured indicators are treated. This makes the performance of these sensors hard to compare. This is analogous to the evaluation of test characteristics in the absence of a gold standard which has traditionally been dealt with using latent class Bayesian models (Branscum et al., 2005; Clegg et al., 2011). When the true health status of an animal is hard to measure and when it is measured by several tests and sensors, this true status can be modelled as a latent variable.

Latent variable modelling can also be used to uncover causal relationships. The representation of causal pathways using directed acyclic graphs lends itself to structural equation modelling or Bayesian modelling (Greenland et al., 1999). Several pieces of work that explore the causal structure of biological phenomena have been published in veterinary epidemiology (Detilleux et al., 2012; Jensen et al., 2009). But linear and generalised linear models remain the rule while it seems that models incorporating a structure could be more powerful.

Since the seminal work by John Snow who showed that an 1854 cholera outbreak in London was centred on a particular water pump, space has always played an important role in epidemiology. As discussed in the introduction, this role has been growing steadily during the past 20 years in veterinary epidemiology. On the other hand, there are a vast number of methods that allow modelling time in epidemiology. But there seems to be a lack of methods that account for both space and time.

We hope that this quick overview of what is veterinary epidemiology and the challenges it faces will inspire people from both statistics and veterinary epidemiology to collaborate on methodological developments.

## Acknowledgements

This work was carried out with the financial support of the French Research Agency (ANR), Program Investments for the Future, project ANR-10-BINF-07 (MiHM $\Sigma$ S), by the European fund for the regional development (FEDER Pays-de-la-Loire), and by INRA & Oniris.

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