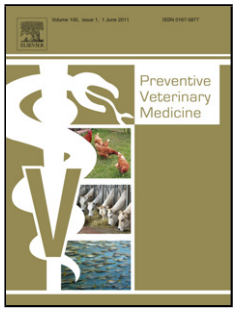

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Multivariate syndromic surveillance for cattle diseases: epidemic simulation and algorithm performance evaluation

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ABSTRACT

Multivariate Syndromic Surveillance (SyS) systems that simultaneously assess and combine information from different data sources are especially useful for strengthening surveillance systems for early detection of infectious disease epidemics. Despite the strong motivation for implementing multivariate SyS and there being numerous methods reported, the number of operational multivariate SyS systems in veterinary medicine is still very small. One possible reason is that assessing the performance of such surveillance systems remains challenging because field epidemic data are often unavailable. The objective of this study is to demonstrate a practical multivariate event detection method (directionally sensitive multivariate control charts) that can be easily applied in livestock disease SyS, using syndrome time series data from the Swiss cattle population as an example. We present a standardized method for simulating multivariate epidemics of different diseases using four diseases as examples: Bovine Virus Diarrhea (BVD), Infectious Bovine Rhinotracheitis (IBR), Bluetongue virus (BTV) and Schmallenberg virus (SV). Two directional multivariate control chart algorithms, Multivariate Exponentially Weighted Moving Average (MEWMA) and Multivariate Cumulative Sum (MCUSUM) were compared. The two algorithms were

evaluated using 12 syndrome time series extracted from two Swiss national databases. The two algorithms were able to detect all simulated epidemics around 4.5 months after the start of the epidemic, with a specificity of 95%. However, the results varied depending on the algorithm and the disease. The MEWMA algorithm always detected epidemics earlier than the MCUSUM, and epidemics of IBR and SV were detected earlier than epidemics of BVD and BTV. Our results show that the two directional multivariate control charts are promising methods for combining information from multiple time series for early detection of subtle changes in time series from a population without producing an unreasonable amount of false alarms. The approach that we used for simulating multivariate epidemics is relatively easy to implement and could be used in other situations where real epidemic data are unavailable. We believe that our study results can support the implementation and assessment of multivariate SyS systems in animal health.

KEY WORDS

Syndromic surveillance, MEWMA, MCUSUM, time series, directional multivariate control charts, epidemic simulation

INTRODUCTION

Syndromic surveillance (SyS) is based on the real-time or near real-time analysis of health related data that are available prior to laboratory confirmation (Triple-S Project, 2011). Since the beginning of the 21st century, SyS has been used to enhance traditional passive disease surveillance, improve early warning systems, and for better control of emerging or re-emerging diseases. Multivariate SyS systems that simultaneously assess and combine information from different data sources have potential value for strengthening systems for early detection of infectious disease epidemics. Diseases often cause a wide variety of symptoms and/or affect different subpopulations. For example, abortion can only affect

breeding age females. A single syndrome time series (TS) cannot capture different types of information. We would not expect to capture information about a disease that causes diarrhea in adult cows by monitoring a TS of cattle abortions. To capture more of this information, SyS systems should be multivariate, because multiple data sources contain more information about the changing disease status of a population (Dorea and Vial, 2016; Wong et al., 2003). Including more data in a surveillance system and combining them in an appropriate way should provide greater event detection sensitivity and more confidence in the information produced by the system (Hopkins et al., 2017; Rolka et al., 2007).

Numerous methods have been proposed for multivariate SyS using spatio-temporal or temporal approaches. Temporal approaches can be classified into three main categories (Sonesson and Frisén, 2005; Vial et al., 2016): parallel monitoring, dimension reduction, and vector accumulation. Parallel monitoring is a method that combines univariate methods. Aberration detection algorithms are applied separately to each TS and an alert is raised depending on how many TS exceed a limit and how the results from individual TS are combined. Different rules or methods for combining results have been proposed. Recent examples in animal health have been reported (Brouwer et al., 2015; Burkom et al., 2011; Dorea et al., 2013). Dimension reduction methods summarize the components for each time point into one statistic. A popular reduction method is the Hotelling T^2 statistic (Hotelling, 1947), but other approaches using Bayesian hypothesis testing have been proposed, see (Burkom et al., 2004; Faverjon et al., 2016) for examples in animal health. Vector accumulation approaches are methods in which information from each TS is accumulated and transformed into a scalar alarm statistic. Multivariate control charts such as Multivariate Cumulative Sums (MCUSUM) and Multivariate Exponential Weighted Moving Average (MEWMA) fall into this category (Frisén, 2011). See (Miekley et al., 2013; Whist et al., 2014) for examples from veterinary public health. Many multivariate control charts can detect change in TS means in any direction (Pignatiello and Runger, 1990). In early disease detection surveillance, the interest is often in detecting a change in only one direction, usually an increase. Occasionally a decrease is important but

rarely are both relevant in the same TS. In SyS, directionally sensitive multivariate control charts have been recommended to improve the aberration detection performance of the algorithms (Fricker, 2007; Joner et al., 2008; Yahav and Shmueli, 2014). Compared to Hotelling T^2, MEWMA and MCUSUM have been reported to detect small shifts in the process mean and should be more effective for detecting an epidemic early in its course, when the number of cases is small, and the shift in the TS mean is minimal.

Despite the strong motivation for implementing multivariate SyS, and numerous methods being available, the number of operational multivariate SyS systems in veterinary medicine is still very small (Dorea and Vial, 2016). One reason could be the gap between research and surveillance practice (Hopkins et al., 2017). This is especially true for methods to evaluate the detection performance of a SyS system, where examples in the public health literature are scarce, and even scarcer in veterinary public health (Colón-González et al., 2018; Dorea and Vial, 2016). Where examples exist, they focus only on a single disease and/or a limited number of syndromic data sources, using real (Brouwer et al., 2015; Burkom et al., 2011; Miekley et al., 2013; Siegrist and Pavilin, 2004; Vial et al., 2016) or simulated epidemic data (Tokars et al., 2009; Xing et al., 2011; Yahav and Shmueli, 2014). Using real multivariate epidemic data for one disease raises the question of how the surveillance system will perform when there is an epidemic with different characteristics (i.e. a different epidemic shape), or if the epidemic were caused by a different disease. When multivariate epidemics are simulated, authors often report comparing algorithm performance under standardized conditions using, for example, a single epidemic peak with the same shape and magnitude, inserted into all the TS being monitored, at the same point in time. These simulated epidemics are far from representative of the behavior of real epidemics, and the results of the corresponding evaluations may not be generalizable in surveillance practice. Some reports have proposed simulating more realistic multivariate epidemics using approaches based on expert opinion, historical epidemic data, or compartment models (Colón-González et al., 2018; Faverjon et al., 2016; Lotze et al., 2007). However,

the number of examples in the literature is still scarce and the simulation of multivariate epidemics remains a challenge.

Strengthening surveillance for early detection of animal diseases is a priority for Switzerland. It has been highlighted as an important component of the 'Swiss Animal Health Strategy 2010'[1] that aims to maintain or improve the high standard of animal health in the country. Switzerland has been officially free from Infectious Bovine Rhinotracheitis (IBR) since 1990 (Ackermann et al., 1990), and started an eradication program for Bovine Virus Diarrhea (BVD) in 2008 which dramatically reduced the number of incident BVD cases in the country (Zimmerli et al., 2009). Being able to detect re-emergences of these diseases quickly and with certainty is of primary importance for maintaining freedom from IBR and achieving freedom from BVD. The last two major cattle epidemics in Europe, Bluetongue virus (BTV) in 2006 (Zientara and Sánchez-Vizcaíno, 2013), and Schmallenberg virus (SV) in 2011 (Doceul et al., 2013), produced only a small number of disease cases in Switzerland. However, the risk of new epidemics of these diseases in Europe is far from negligible, as illustrated by the recent re-emergence of BTV in France (Courtejoie et al., 2018). Diseases such as IBR, BVD, BTV, and SV typically produce clinical cases with nonspecific clinical signs, making early epidemic detection difficult for traditional passive surveillance systems (Doherr and Audigé, 2001). Multivariate SyS may hold promise as a method for strengthening early detection systems for re-emerging cattle diseases in Switzerland.

The purpose of this paper is to demonstrate a practical multivariate event detection method (directionally sensitive multivariate control charts) that can be easily applied in livestock disease SyS. We used real SyS TS from the Swiss cattle population as an example. Epidemics are required to estimate the performance of event detection algorithms. However, since epidemics of important diseases are often rare, we also present a standardized method for simulating multivariate epidemics using four diseases of interest for

[1] See http://www.blv.admin.ch/gesundheit tiere/03007/index.html?lang=en.

Switzerland (BVD, IBR, BTV and SV) as examples. The detection performance of two directionally sensitive multivariate control charts were compared: directionally sensitive MEWMA (Joner et al., 2008), and directionally sensitive MCUSUM (Fricker, 2007). The detection performance of the two algorithms was compared using 12 syndrome TS extracted from two Swiss national databases.

MATHERIAL AND METHOD

1. Data collection and selection

Two databases containing data from the national Swiss cattle population were used: the *Swiss Animal Movement Database* (AMD), and a database owned by the *Association of Swiss Cattle Breeders* (ASR). The AMD has been studied and reported to have potential value for syndromic surveillance because of its relatively high quality in terms of population representativeness and reporting timeliness (Struchen et al., 2015). The ASR database contains clinical data collected by farmers. This database has not been investigated in Switzerland, but similar data have been reported to be of value for SyS in others countries(Dorea and Vial, 2016). The selection of candidate TS was based on the type of data available, organ systems potentially affected by the diseases under surveillance and cattle age groups.

The AMD contains cattle mortality data reported by farmers to the national Swiss system for the identification and registration of cattle. All reported on-farm deaths and stillbirths for the period from January 1st, 2009 to December 31st, 2017 were extracted from the AMD. Four TS were created from this database. One was based on stillbirths (*AMD_stillbirth*) and three were based on categories of on-farm deaths defined according to the age at death: up to six months old (*AMD_mortality_calves*), 6 months to two years (*AMD_mortality_young*), and more than two years *(AMD_mortality_adults*). Beginning in mid-2014, stillbirths in the AMD were defined as non-living fetuses expelled before the end of gestation, or

calves born dead within 24 hours following birth. Before that date, no official definition of a stillbirth existed in Switzerland.

The *Association of Swiss Cattle Breeders (ASR) (http://asr-ch.ch/en/asr/)* is the private umbrella organization of the Swiss cattle breeding organizations. One of objectives of the ASR is coordination of the activities of its members. Since 2013 the ASR has developed and implemented a homogenized database containing cattle illness diagnoses reported by farmers and veterinarians. All cases are reported using a coding system with four levels ranging from least specific (i.e., organ affected) to most specific (e.g., infectious agent isolated). The data were available for the three most common breeds in Switzerland: Braunvieh, Fleckvieh and Holstein, which represent the majority of Swiss dairy cattle. The timeliness of reporting to this database is unknown. Data were available from January 1st, 2014 to December 31st, 2017. In the ASR database calves are defined as cattle up to 6 months of age. All the other animals are defined as adults. Three syndromes based on the most frequent diagnostic classification found in the database were created for each age category: gastrointestinal symptoms (i.e., *ASR_GI_calves* and *ASR_GI_adults*), respiratory symptoms (i.e., ASR_*RESPI_calves* and *ASR_RESPI_adults*), and cattle having a classification of "other" in the ASR classification schema (i.e., *ASR_OTHER_calves* and *ASR_OTHER_adults*). The category "other" encompasses various unspecific symptoms such as fever, anorexia, changing behavior or reduction in production. Two other syndromes based on fertility disorders (*ASR_FERTILITY*), and locomotion disorders (*ASR_LOCO*) were created but the data did not allow the distinction between calves and adults.

In total, data for 12 syndromes were extracted from the two databases and converted to weekly syndrome TS (see figure 1).

2. Data simulation

Detection performance was assessed using simulated data (epidemic-free baselines and multivariate epidemics). Time series modelling was used to create 300 simulated epidemic free baseline TS for each of the 12 TS selected for the study. These were copied 4 times (once for each of the 4 diseases included in the study). Three hundred multivariate epidemics were simulated for each of the 4 diseases included in the study and inserted into the corresponding set of 300 baseline TS. The output was one set of 300 multivariate epidemics for each disease.

2.1. Simulated epidemic-free baselines

The Holt–Winters generalized exponential smoothing (HW) (Chatfield and Yar, 1988; Gardner, 1985) was used to model each syndrome TS and predict the value of the two next years of data. HW is a popular method used to make predictions using TS that contain a trend or seasonality. HW requires only two years of historical data. All the data available from 2013 to 2015 were used for model training and the HW parameters were determined through minimization of the squared prediction error (Kalekar, 2004). The data available from 2016 to 2017 were used for model validation and for the estimation of model prediction performance (see supplementary material 1). To simulate the epidemic-free baselines, we assumed that the number of cases reported on the week t followed a Poisson distribution with mean μ_t, where μ_t was the mean predicted value of the week t obtained with the best HW model. We then randomly sampled from each weekly Poisson distribution to simulate 300 epidemic-free baselines each containing two years of simulated data for each TS.

2.2. Simulated multivariate epidemics

No real epidemics of BTV, SV, IBR or BVD were present in the data, as there were no epidemics of these diseases in Switzerland during the study period. In order to assess detection performance of the

algorithms and to compare their performance for different diseases, we simulated multivariate epidemics based on expert opinion. We aimed at collecting information on the expected duration of a potential epidemic, and the proportion of diseased animals having a given clinical sign at a certain time during the epidemic period. We were not able to find the information we required in the literature at the desired level of detail in a standardized manner for the diseases of interest. Expert elicitation is an accepted method for estimating information when data are unavailable or difficult to collect and it was deemed the most appropriate method to meet our objectives. Three veterinary experts were selected based on their experience, and clinical and scientific knowledge: a) two large animal practitioners and researchers at the University of Bern Farm Animal Clinic, b) one veterinary official from the disease control department of the Swiss Federal Food Safety and Veterinary Office. Questionnaires were administered by personal interviews. Experts were questioned about the proportion of diseased animals showing each of 12 syndromes over the course of an epidemic. The experts suggested that for some of the selected diseases, infected animals would show different disease syndromes during different stages of the epidemic. Based on their recommendations, we divided the simulated epidemics into four consecutive periods (T = 1, T = 2, T = 3, T = 4) of equal length. We asked the experts to estimate the proportion of infected animals that would show each syndrome during each of the four periods of the epidemic. Two age classes were considered – calves and adult cows. This information was used to simulate 300 multivariate epidemics for each of the four diseases in the study (examples of simulated epidemics are presented in supplementary material 2).

The four consecutive steps in the multivariate epidemic simulation process are reported in table 1. Epidemic cases for each disease were added to simulated epidemic free baseline TS at randomly selected times between the first week of the first year of an epidemic free baseline TS and the 16th week of the second year of an epidemic-free baseline TS. Since the epidemics were 36 weeks long, the last 36 weeks

of the second year of the simulated epidemic-free baseline were exculded from the random selection to ensure that all the inserted epidemics had the same duration.

Steps	Parameters	Value or Estimation
Step 1. Simulate the number of newly infected animals for each time step of the epidemic period	1.1 Shape of the epidemic curve	Linear increase for all four diseases
	1.2 Length of the epidemic (*t_max*)	t_max= 36 weeks (based on expert opinion)
	1.3 Total number of animals newly affected during the last week of the epidemic (*cases_max*)	cases_max = 400 (assumption)
	1.4 Number of newly infected animals for each week (t = 1,2, 3…*t_max*) of the epidemic period (Inf_tot_t)	Based on the step 1.1, Inf_tot_t was estimated as follow: • $Inf\_tot_t = \lvert t*cases\_max / t\_max \rvert$
Step 2. Divide the number of newly infected animals between calves and adult cattle for each time step	2.1 Incidence of the disease in calves (*Inc_calves*) and adults cattle (*Inc_adults*)	We assumed that the four diseases would infect calves and adult cattle equally. Therefore we assumed that the incidence of the diseases in the two age groups should equal the proportion of each age group in the Swiss cattle population: • Inc_adults = 0.75 • Inc_calves = 0.25
	2.2 Number of newly infected calves (Inf_calves_t) and adult cattle (Inf_adults_t) for each week *t* of the epidemic period	• $Inf\_calves_t = Inf\_tot_t * Inc\_calves$ • $Inf\_adults_t = Inf\_tot_t * Inc\_adults$
Step 3. Estimate the percent of infected calves and adult cattle showing clinical signs or syndromes in the population at each time step	3.1 Percentage of infected animals showing the syndrome *S* at the time period *T* (S_T) Each epidemic was divided into four equal periods *T* (i.e., first quarter of the epidemic = T1, second quarter of the epidemic = T2, third quarter of the epidemic = T3, last quarter of the epidemic = T4). The percentage of infected animal showing each Syndrome *S* varied by the epidemic period *T*. Examples: • Percentage of infected calves showing respiratory syndrome (*S = RESPIcalves*) at the start of the epidemic (*T=1*) is noted $RESPIcalves_{T1}$ • Percentage of infected calves showing respiratory syndrome (*S = RESPIcalves*) in the middle of the epidemic (*T=2*) is noted $RESPIcalves_{T2}$ • Percentage of infected calves showing respiratory syndrome (*S = RESPIcalves*) at the end of the epidemic (*T=3*) is noted $RESPIcalves_{T3}$ • Percentage of infected calves showing respiratory syndrome (*S = RESPIcalves*) at the end of the epidemic (*T=4*) is noted $RESPIcalves_{T4}$ • Percentage of infected calves showing gastrointestinal syndrome (*S = GIcalves*) at the start of the epidemic (*T=1*) is noted $GIcalves_{T1}$ • Etc.	The minimum, most likely and maximum values of S_T were based on expert opinion (see details in supplementary material 3). Each S_T was then represented as a beta PERT distribution using the values defined by the experts as parameters. For each simulation of a multivariate epidemic, we randomly sampled a value for S_T from the corresponding beta PERT distributions.
	3.2 Number of infected animals showing each syndrome *S* at week *t* of the epidemic (Inf_S_t)	Example of calculation given for the syndrome *S* related to *calves* at the week *t* (with *t* included in the time period *T1*): • $Inf\_S_t = Inf\_calves_t * S_{T1}$

Step 4. Number of infected animals showing clinical signs AND reported in the data at each time step	4.1 Percentage of animals infected, showing clinical signs AND reported in AMD (*$Reporting_{AMD}$*) and ASR (*$Reporting_{ASR}$*)	Expert opinion: • $Reporting_{AMD} = 1$ • $Reporting_{ASR} = 0.5$
	4.2 Number of animals infected, showing clinical signs AND reported in each syndrome *S* during the week *t*, with *t* included in the time period *T* (*N_{St}*)	Example of calculation given for the syndrome S related to calves and ASR data during the week *t* (with *t* included in the time period *T1*): • $N_{St} = Inf\_S_t * Reporting_{ASR}$

Table 1: Consecutive steps used for multivariate epidemic simulation, associated parameters description and estimations

3. Multivariate control charts

The 12 TS in the study were assumed to be conditionally independent. The conditional independence assumption means that we assume that the TS are independent only when there is no epidemic ongoing in the population. This is an important difference as the purpose of the multivariate detection algorithms we used in this study is to detect the point in time when TS start to be correlated. An animal reported in one TS could be reported in another TS. However, we considered this event to be rare and randomly distributed in the data because: i) 98.6% of the cattle reported sick in ASR showed only one clinical sign, ii) endemic diseases in calves are rarely associated with diseases in adult cattle, and iii) we assumed that diseases considered in our study were only occasionally associated with the death of the animal. Conditional independence between TS meets the statistical process control chart assumption that input variables are independent and identically distributed multivariate normal random vectors. To meet the normality assumption, a one week differencing (i.e., computation of the difference between consecutive observations) was used to remove the temporal effects present in the raw data. The differenced residuals were saved as new TS. Multivariate normality of the differenced residuals was assessed and confirmed using the HenzeZirkler's test (Henze and Zirkler, 1990). The two multivariate statistical process control chart algorithms were implemented on the differenced residual TS.

Algorithms were implemented in R x64 version 3.0.2 (R Development Core Team, 2008). Multivariate normality was assessed using the R package {MVN} (Korkmaz et al., 2014). The covariance matrix and the

mean vector were estimated using the historical data available from 2013 to 2015, using the function 'mult.chart' from the R package {MSQC} (Montgomery, 2009; Santos-Fernandez, 2013).

- **Directionally sensitive MEWMA**

The original MEWMA proposed by Lowry (Lowry et al., 1992) is Hotelling T^2 control chart applied to EWMA statistics instead of the original data. The MEWMA is based on cumulative differences between observed data in a time window, and a threshold. Joner (Joner et al., 2008) proposed a directionally sensitive version of the algorithm based on the equation:

$$Z_t = \begin{cases} \max\{0, \lambda(X_t - \mu) + (1-\lambda)Z_{t-1}\} & if\ t > 0 \\ 0 & if\ t = 0 \end{cases} \quad (1)$$

where λ is a smoothing parameter ($0 \leq \lambda \leq 1$) that determines the relative weight of the current observed values (X_t) in relation to past values, and μ is the target mean of the process. Z_t is a vector of the weighted average of the current observations standardized around 0 and it has a covariance matrix $\sum_{Zt}$ at time t equal to $\frac{\lambda(1-(1-\lambda)^{2t})}{2-\lambda}\sum$, with $\sum$ being the covariance matrix of X_t. When $t \to \infty$, then $\sum_{Z\infty}$ equals to $\frac{\lambda}{2-\lambda}\sum$. The inverse of $\sum_{Z\infty}$, $\sum_{Z\infty}^{-1}$, corresponds to the partial correlation of the variables once you condition on all other variables and is used to compute the MEWMA chart statistic: $MEW_t = Z_t' \sum_{Z_\infty}^{-1} Z_t$. Z_t' is the transposed vector of Z_t. Five values of λ were evaluated: 0.1, 0.2, 0.3, 0.4, and 0.5.

- **Directionally sensitive MCUSUM**

Many versions of MCUSUM have been proposed. In this study, we chose the method suggested by Crosier (Crosier, 1988) and adapted for directional sensitivity by Fricker (Fricker, 2007). This directionally sensitive MCUSUM is based on the equation:

$$S_t = \begin{cases} \max\left\{0, (S_{t-1} + X_t - \mu) * \left(1 - \frac{k}{C_t}\right)\right\} & if\ C_t > k \\ 0 & if\ C_t \leq k \end{cases} \quad (1)$$

Where k represents the expected magnitude of the distance between the target mean of the process and the actual mean of the process, μ is the target mean of the process, and $C_t = [(S_{t-1} + X_t - \mu)' \sum^{-1} (S_{t-1} + X_t - \mu)]^{1/2}$ with $\sum^{-1}$ being the inverse of the covariance matrix of X_t. The procedure starts with $S_0 = 0$ and is sequentially calculated. Five different values of k were evaluated: 0.1, 0.2, 0.5, 0.7 and 0.8.

4. Assessing aberration detection performance

Each week of observation was classified as true positive (TP) if a certain upper control limit (UCL) was exceeded on a week that was part of an epidemic. An undetected week of an epidemic was classified as false negative (FN). Each week in a non-epidemic period was considered a true negative (TN) if no alert was generated and a false positive (FP) if an alert was generated. Accuracy was evaluated using: the sensitivity based on the number of epidemics detected out of all inserted epidemics *(Se_out),* the sensitivity based on the number of weeks in an epidemic period in which an alarm was triggered (*Se_wk)*, the specificity (Sp), the positive predictive value (PPV) and the negative predictive value (NPV). Se_out was calculated for all 300 simulated epidemics-baseline TS pairs combined. The parameters Se_wk, Sp, PPV, NPV were calculated for each epidemic-baseline TS pair. These parameters were calculated as follow:

Se_out = epidemics detected /total number of epidemics inserted

Se_wk = TP/(TP+FN)

Sp = TN/(TN + FP)

PPV = TP/(TP + FP)

NPV = TN/(TN + FN)

For disease detection, it was not important for all weeks of an epidemic to be recognized, but it was crucial for an epidemic to be detected at least once and that it should be detected early in the course of the epidemic. Therefore, the Se_out was considered more important than Se_wk. The timeliness of the first

alarm raised during an epidemic was computed (detection timeliness) as the time lag (in weeks) between the start of the epidemic and the first alarm. The average (Tmean), median (Tmed), t minimum and maximum values (Tmin and Tmax), and the standard deviation of the timeliness (Tsd) were computed using the results from all 300 simulated baselines with epidemics.

Because a large number of false positive alarms would quickly become unmanageable in surveillance practice, we set the UCLs at a maximum of 5% false positive alarms. These UCLs were considered the optimal alarm thresholds for each algorithm and named UCL5%. The UCL5% were defined for each algorithm and each set of parameters by using the 300 epidemic-free simulated baselines.

RESULTS

- **Expert opinion and multivariate epidemic simulation**

Experts estimated the proportion of diseased animals showing individual clinical signs or syndromes in different stages of an epidemic. Respiratory syndromes in calves and cows were estimated to be highly prevalent for IBR. Anorexia/weight loss/apathy were more prevalent in diseased animals infected with SV. However, for most clinical signs the differences between the diseases were not very large. Mortality values did not vary greatly between diseases. Stillbirths and abortions in diseased animals were estimated to occur in similar levels for all four pathogens. Milk loss and other productive deficits were present in every disease, although the experts highlighted BVD as the disease where this syndrome was particularly prevalent. Results of the expert opinion survey can be found in supplementary material 3.

- **Overall detection performance using simulated data**

The upper control limits producing 5% false positive alarms (UCL5%) were computed for each algorithm and each set of parameters tested (i.e., k for MCUSUM and λ for MEWMA) by considering all the simulated

diseases epidemics together. The results and their corresponding overall epidemic detection performance are reported in table 2.

For MEWMA, the highest Se_wk and PPV were obtained with smaller values of λ. The timeliness of the detection was lowest for λ equal to 0.3. When λ increased or decreased, the time to the first true alarm (TP) increased. The shortest average time for detection for MCUSUM was obtained with a k value of 0.5. However, for this value of k, PPV was one of the lowest values obtained and Se_wk one of the largest.

At UCL5%, both algorithms were able to correctly detect more than 97% of the epidemics inserted, with PPV varying between 86.9 and 95.0. Se_wk and NPV were low overall and never exceeded 40% and 62% respectively. The mean time of detection (Tmean) varied a lot depending on the algorithm. MEWMA always outperformed MCUSUM. MCUSUM had the shortest average time for detection (Tmean values ranged between 8.6 and 10.6 weeks) compared to MCUSUM (Tmean values ranged between 14.6 and 16.6 weeks) regardless of the parameters used.

Algorithm		UCL5%	Tmean	Se_out	Se_wk	NPV	PPV
MCUSUM	k = 0.1	11	16.6	97.8	34.0	59.3	94.8
	k = 0.2	9.5	15.8	98.2	35.5	59.6	93.0
	k = 0.5	6.5	14.6	99.8	34.6	59.2	91.9
	k = 0.7	5.5	14.9	99.9	30.3	57.9	94.6
	k = 0.8	5.0	15.3	100	25.8	56.4	92.3
MEWMA	λ = 0.1	55.5	10.6	100	39.1	61.2	95.0
	λ = 0.2	35.5	8.9	100	32.3	58.4	91.6
	λ = 0.3	29.5	8.6	100	28.3	57.0	90.0
	λ = 0.4	27.5	9.1	100	25.2	55.9	88.1
	λ = 0.5	27.0	9.5	100	23.6	55.3	86.9

Table 2: Overall detection performance obtained with MEWMA and MCUSUM for different parameter values at the upper control limit producing 5% false positive alarms (UCL5%). detection, Tmean = mean time of detection, Se_out = sensitivity based on the number of epidemics detected out of all inserted epidemics, Se_wk = weekly sensitivity, NPV = negative predictive value, PPV = positive predictive value

- **Individual disease detection performance using simulated data**

Detection performance was computed separately for each simulated disease. Based on the previous results and because our objective was to favor early detection, we set the parameters λ and k of MEWMA and MCUSUM respectively at 0.3 and 0.5 for the rest of the analysis. The results obtained with these parameters at the UCL5% previously defined are reported in table 3.

Algorithm	UCL5%	Disease	Tmin	Tmax	Tmean	Tmedian	Tsd	Se_wk	Sp	NPV	PPV
MCUSUM, K = 0.5	6.5	IBR	1	29	11.4	11	5.5	49.6	96.8	65.1	94.0
		SV	1	24	13.6	15	7.8	44.1	97.0	62.8	93.9
		BTV	1	35	16.3	18	9.3	22.6	96.8	55.7	87.5
		BVD	1	35	16.9	19	9.5	22.1	96.9	54.8	88.0
MEWMA, λ = 0.3	29.5	IBR	1	14	7.2	9	2.8	38.7	96.7	60.5	92.4
		SV	1	22	8.1	7	5.2	35.0	97.0	59.2	92.4
		BTV	1	28	9.0	8	6.1	19.7	96.6	54.7	85.2
		BVD	1	28	10.2	9	6.5	20.0	96.8	54.1	86.5

Table 3: Specific detection performances obtained with MEWMA and MCUSUM for the parameters values minimizing the time for detection and for each disease (i.e., Infectious Bovine Rhinotracheitis (IBR), Schmallenberg virus (SV), Bluetongue virus (BTV), and Bovine viral diarrhea (BVD)). UCL5% = upper control limits producing 5% false positive alarms, Tmin = time minimal of detection, Tmax = time maximal of detection, Tmean = mean time of detection, Tmedian = median time of detection, Tsd = standard deviation of the time of detection, Se_wk = weekly sensitivity, Sp = specificity, NPV = negative predictive value, PPV = positive predictive value

The two algorithms detected 100% of the simulated epidemics. IBR epidemics were detected earlier on average (i.e., shorter average timeliness and higher Se_wk) than epidemics of the other diseases. Epidemics of SV were detected 1 to 3 weeks later than IBR epidemics. Epidemics of BTV and BVD were the most difficult to detect and had similar detection performance.

The MEWMA algorithm always outperformed MCUSUM especially for detection timeliness. The average and median time to detection (Tmean and Tmedian, respectively) were shorter and the standard deviation (Tsd) and maximum time to detection (Tmax) were smaller.

DISCUSSION

To our knowledge, this is the first report of directionally sensitive multivariate control charts being evaluated for animal health surveillance (Dorea and Vial, 2016). The method was easy to implement and the results were easy to interpret because all the information contained in the different TS were combined in one unique statistic. However, combining information from all TS into one statistic is also limitation of the approach. It was not possible to identify which TS contributed the most to the alarms raised. Surveillance practitioners would have to go back to the raw data to identify the TS contributed to an alarm. This is not a major limitation but it is a practical concern that should be considered when implementing multivariate control charts in field settings.

The multivariate control charts evaluated in our study detected all simulated epidemics of BVD, IBR, BTV and SV between 2 and 3.6 months after the start of the epidemic, with 95% specificity. Comparing the detection performance obtained in our study to the current Swiss surveillance system is difficult because there is little data or information available about epidemics of these diseases in the country. With the exception of Schmallenberg, active surveillance systems for the diseases included in this study are in place in Switzerland. Programs to assure freedom from IBR and BVD are in operation. A risk-based selection of farms is performed yearly for IBR. Sampling is conducted in both dairy (through bulk-milk sampling in January and April) and non-dairy farms (blood sample are taken between January and May). For BT, blood samples are collected at slaughterhouses at the end of the vector season (beginning of November). In 2008, an eradication program for BVD was initiated in Switzerland. At the moment, the sampling procedure (including frequency and type of sampling) depends on the type of cattle farm (dairy *versus* non-dairy) and the presence of persistently infected animals on a farm in the previous 36 months (BLV, 2018). Based on expert opinion, we estimated 9 months (the maximum length of simulated epidemics in our study) to be the maximum time needed, on average, to identify an epidemic of IBR, BVD, BTV or SV in Switzerland with the current Swiss active surveillance systems. Using this as a standard for comparison,

the multivariate control charts implemented in our study have the potential to strengthen the early detection surveillance in Switzerland. However, our study is simulation based and more information is needed before definitive conclusions can be made.

The two algorithms had the same overall sensitivity and specificity but performed differently in terms of detection timeliness. The MEWMA always detected epidemics earlier that the MCUSUM. These results are in contradiction to Fricker (Fricker et al., 2008) who reported that the two algorithms had very similar performance. We used a different method for epidemic simulation and this may explain the observed differences between the two studies. Fricker (Fricker et al., 2008) reported using simple simulated multivariate epidemics that had a linear increase in the number of cases and that were inserted at the same time point in all TS. In our study, the simulated epidemics where more subtle. For example, in some of our TS, there were no epidemic cases added because the experts consulted did not expect additional cases to appear in these TS (see supplementary material 3). In addition, the increases in the number of cases were not always inserted at the same time point in all TS because the experts indicated there might be a delay in the appearance of some syndromes. It is well known that multivariate control charts are affected by the so-called inertia problem (Woodall and Mahmoud, 2005). This problem arises because control charts accumulate information over time, and tend to detect changes occurring in the data with some delay especially when only small changes occur. The multivariate control charts tested in this study are reported to be less severely affected by the inertia problem than other multivariate control charts (Joner et al., 2008). Our results suggest that MEWMA is more robust than MCUSUM to the inertia problem. The time to the first true positive alarm using the MCUSUM algorithm was almost double that of the MEWMA. Fricker (Fricker et al., 2008) suggested that the MEWMA should be selected over the MCUSUM because it is easier to develop an intuitive appreciation for how to choose λ than k. We suggest

it should also be selected because it is less sensitive to the inertia problem, especially when subtle changes occur in the TS.

Differences in detection performance were observed between the four diseases. Timeliness of detection was shorter and Se_wk was higher for both algorithms for epidemics of IBR and SV compared to epidemics of BVD and BTV. We expected to see differences, because our experts expected BTV and BVD to produce more subtle clinical signs than the other diseases. For this reason, epidemics of these two diseases were predicted to be more difficult to detect. These results however heavily depend on the approach used to simulate the epidemics of the different diseases. In this study, we assumed that the number of animals infected, differences between adults cattle and calves, the shape and length of the epidemics, and the rate of underreporting were fixed for all diseases and TS. If short simulated epidemics were used, some of them may not have been detected at all and this would have resulted in reduced detection performance. For this reason, we simulated long (9 months) epidemics in order to completely explore the variation in detection timeliness. The rate of underreporting in ASR data was estimated to be 50% and no underreporting was taken into account for the AMD data. These assumptions are probably optimistic especially given the fact that it is known that AMD data have a reporting delay (Struchen et al., 2017) that may affect detection performance to a greater or lesser degree in the case of a real epidemic. These assumptions may have resulted in over- or underestimation of the overall detection performance of the algorithms tested. Most importantly, having fixed the number of animals infected, the shape and length of the epidemics and the prevalence between adult cattle and calves means that the differences of detection performances between the diseases are only due to differences in terms of percentage of infected animals showing certain clinical signs. Choosing a different set of parameters for these assumptions for each disease could have produced different results. We decided to fixe these parameters for the sake of simplicity but it would be easy to modify them using our epidemic simulation approach. In

future studies, it would be interesting to investigate how changes in these parameters would affect the detection performance of the algorithms and especially the difference observed between the four diseases.

We present a standardized approach for simulating multivariate epidemics caused by different diseases. Simulations have the advantage of allowing a full sensitivity analysis and testing multiple epidemic settings, which is essential for SyS assessment. This can rarely be done with real epidemics, as there is seldom enough data (Buckeridge et al., 2004). However, using simulated epidemics always raises questions about the validity and reliability of the results. In our study, the percentage of infected animals showing certain clinical signs was estimated based on expert opinion. Initially we tried to find this information in published literature. We were not able to find much useful epidemic data because there is huge variation in how epidemics are reported. There are no standards for epidemic reporting which is crucial for obtaining descriptive information that can be compiled across epidemics. Information about clinical signs is rare. We were specifically looking for the proportion of diseased animals showing specific clinical signs that would be present in our data. Outbreak reports more commonly contain other denominators such as the number of animals in the farm, region or country. For these reasons, we abandoned the literature search in favor of expert opinion. Expert opinion is an accepted method to obtain information when data are unavailable or difficult to collect and has been previously used for epidemic simulation (Faverjon et al., 2016). It should be pointed out that this process can introduce bias. The information we required is very specialized. It is related not only to diseases studied, but also to the characteristics of each disease within the Swiss cattle population and to the way that data are collected in Switzerland. Because of the uniqueness of the Swiss cattle production system, we expect this information is specific to Switzerland and may not be generalizable to epidemics in other countries. There are few experts who have the knowledge we needed, and their knowledge was likely to have been

influenced by their experience. It is also worth mentioning that due to the length and complexity of the interview, experts were not required to provide an interval of values for their estimates. Therefore, the parameters used in the beta PERT distributions reflect the range of individual estimates. More standardized and detailed outbreak reporting could provide the data required to substitute for expert opinion. Another option would be to use complex disease transmission models to estimate the number of animals infected and those showing symptoms during epidemics of BVD, IBR, Bluetongue or Schmallenberg. For example, Colón-González (Colón-González et al., 2018) proposed a framework based on compartmental models to simulate multivariate epidemics in public health. However, there were no published reports containing data for the 4 diseases used in this study that could be adapted to the Swiss cattle production system, making it impossible to implement a similar approach in our study. Developing compartmental models is quite technical and demands resources, which may limit their use. Eliciting expert opinion for multivariate epidemic simulation is cost-efficient and currently may be the most appropriate way to evaluate multivariate SyS system performance under field conditions where reliable data and other or resources are scarce.

CONCLUSION

The directional multivariate control charts evaluated in this study appear promising for combining information from multiple TS for early detection of subtle changes occurring in a population while maintaining the number of false positive alarms to a reasonable amount. The method was easy to implement and the results were easy to interpret because all the information contained in the different TS were combined in one unique statistic. The approach that we proposed for simulating multivariate epidemics has some limitations but is a solution for assessing the performance of multivariate event

detection in the absence of real multivariate epidemic data. We believe that our results can support the implementation and assessment of multivariate SyS systems in animal health.

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Figure 1