



Univariate syndromic  
surveillance development for  
FBD JRP6 - NOVA - FBZ1 - 1<sup>st</sup>  
**Call**

NOVA D3.3

Responsible Partner: ANSES, SVA, NIPH,  
NVI



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# Development of data-driven surveillance components for the surveillance of FBD outbreaks

## Introduction

The objective of the task 3.1 in the NOVA project was to identify potential data sources (in Member states contributing to WP3) suitable for the development specific surveillance components for FBD based on “secondary data” (data-driven surveillance). Secondary data are already available information, sometimes collected for other purposes than health surveillance, which may be of interest for health surveillance. We identified 27 data sources in Member states contributing to WP3 that may be used for the data-driven surveillance of FBZ. Analysis of the identified data sources showed that data availability and quality were potentially appropriate for the surveillance of human gastrointestinal syndromes. In particular, data on major food-poisoning agents as Salmonella and Campylobacter were available at various points of the food chain (from feed to human).

The objective of Task 3.2. is to evaluate statistical approaches and potential of the data sources identified in Task 1 to detect FBD outbreaks. The surveillance components are developed in parallel for each data source selected from the inventory in task 3.1 (univariate surveillance).

For Task 3.3 we want to evaluate a framework for multivariate one-health surveillance where we combine surveillance data from testing in animal health with data from syndromic surveillance and from laboratory confirmed cases with weather data.

The progress of tasks 3.2 and 3.3 differs between partners. This difference is related to the initial state of access and knowledge of the data: the data used by NVI and NIPH in Norway were already partly used in surveillance systems while SVA and Anses used data sources not yet used for surveillance. Tasks 3.2 ("univariate") and 3.3 ("multivariate") are presented separately in the following sections of the document.

## Data sources

The data sources selected as a result of Task 3.1.2 for the national case studies are presented below.

### Sweden

Among the five data sources identified in Sweden through Task 3.1 (JRP6-NOVA D3.2), SVALA was evaluated to be the most relevant for FBZ detection, considering the accessibility and availability for implementation of a nearly real-time monitoring system, and the information that can be extracted. SVALA is SVA's Laboratory Information Management System (LIMS), in which management of all the samples submitted to SVA is handled, from sample registration to results. Data exists for approximately 400,000 samples per year in SVALA, covering both domestic and wild animal species (SVA, 2019).



We selected *Campylobacter* as the pathogen since 1) SVA is the national and EU reference laboratory for *Campylobacter*, which ensures accuracy of the data, 2) with the recent large outbreaks in Sweden in 2016-2017, consensus on the need for One Health Surveillance (OHS) for *Campylobacter*, including an early warning system, has already been established between national authorities of animal health (SVA) and public health (FOHM) sectors, and 3) there is a monitoring system in broilers for *Campylobacter* since 1991, ensuring the completeness and continuity of the data in the future.

In the monitoring program, sampling is performed by collecting intact caeca from 10 birds from each slaughter batch at the major abattoirs. The caeca are pooled into one composite sample per batch, and further analyzed according to ISO 10272 part1. The program covers 99% of the broilers slaughtered in Sweden (SVA, 2019), and as the analyses are performed at SVA all the results are available in SVALA. As for the timeliness, there is approximately 1-5 days of delay in data centralization after sample collection. Assuming the meat processing time, and the incubation period of *Campylobacter* cases in humans (2-5 days), we determined that this data has potential to serve as an early warning alarm for human outbreaks.

We also reviewed the quality and quantity of data from other animal species that were available in SVALA for *Campylobacter*, but they were either sampled only periodically for research projects or had little clinical relevance for human cases, e.g. *C. helveticus* from dogs.

#### **Norway (data from 2006-2018)**

- Norwegian System for Syndromic Surveillance (NorSySS) – Number of outpatient consultations for gastrointestinal symptoms as classified by ICPC-2 diagnosis codes. Weekly aggregated numbers of consultations per municipality in 5 age groups. This data was chosen as it is already in daily use for syndromic surveillance for humans in Norway. Any improvements in univariate or multivariate surveillance can be implemented in NorSySS and will be of importance for day to day surveillance activities. In later stages of the project we will also consider laboratory confirmed human cases of different gastro-intestinal infections including *Campylobacter* and compare with the syndromic cases. All GPs and out-of-hours GPs are required to submit all consultations with ICPC-2 codes within two weeks of the consultation to receive compensations from the Ministry of Health (note that the amount of reimbursement is independent of the diagnostic code). The data has good completeness and mean reporting time is 12 days.
- *Campylobacter* surveillance in chickens. We selected *Campylobacter* data as we hypothesise that the *Campylobacter* status of chicken flocks may be associated with *Campylobacter* occurrence in humans (Jonsson et al., 2010, Jore et al., 2010). The data are owned by the Norwegian Food Safety Authority and all examinations have been performed by the Norwegian Veterinary Institute (NVI), making the data easily accessible for the project and ensuring completeness and continuity of the data in the future. Since April 2001, chicken flocks that are slaughtered before 50 days of age have been examined for *Campylobacter*. Until 2008, the sampling was performed all year, since 2009 only flocks slaughtered between May and October have been sampled. The samples are collected maximum four days before slaughter by the owner. The sample consisted of ten pooled swabs from fresh faecal droppings. The samples were submitted to the NVI, where they were analysed for *Campylobacter* spp. by real-time PCR. As for timeliness, the result is available as soon as the analysis have been performed.



The test outcomes are aggregated by municipality and week. Therefore the data will be included on a weekly basis.

- Weather data – Weekly average temperature and total amount of rain in each municipality from gridded data provided by the Norwegian meteorological institute. Based on measurements and models the meteorological institute creates a daily raster with 1x1km resolution of rain and temperature. We then aggregated this to the municipality geographic level.

## France

- For France, Salmonellosis has been selected as study case because of the multiple monitoring systems in place throughout the food chain. Among the 19 data sources identified as having an interest or potential for FBD surveillance, eight are currently available for the project, and two are still under negotiation (Appendix 1).
- The amount of data is large and the variable sources cover different points in the food chain, from the farm to the processing and consumer. The data are of varying accuracy and completeness. To take into account these different levels of precision, analyses with weekly and monthly (eventually quarterly) time steps will be explored and three spatial aggregation levels will be used: national, regional in four zones (northwest, southwest, southeast and northeast) and departmental (if the data by department are sufficient). The data will also be separated by syndrome (gastroenteritis, vomiting and food poisoning in humans, digestive diseases, abortion, septicemia and other diseases in animals, no clinical sign), Salmonella strain according to their zoonotic potential and/or production type (dairy/beef cattle, meat poultry/laying poultry, reproduction/fattening pigs). The description of the datasets is in progress. The first results of the descriptive analysis are available in Appendix 1.

## Univariate Surveillance

### Sweden

We extracted all the sample data from SVALA that were part of the broiler *Campylobacter* monitoring program from January 1<sup>st</sup> 2009 to May 28<sup>th</sup> 2019. A total of 37,170 samples (slaughter batches) were identified and included for further analysis. After importing and cleaning the data in R, we assessed the temporal trends of the data by visualizing the total number of samples, number of positive samples and percentage positive (proportion of tested samples that are positive) by week (Figure 1).

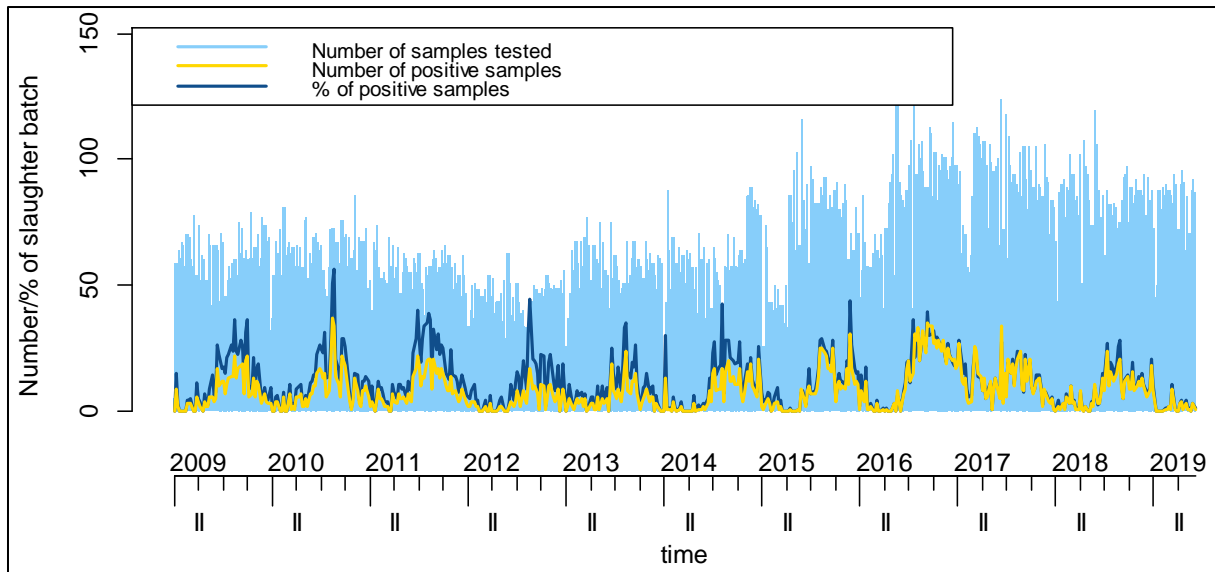


Figure 1. Time series graph showing results of the *Campylobacter* monitoring program in broilers since 2009 in Sweden

As the number of positive samples showed a very similar trend to the percentage of positives, we selected the count data (number of *Campylobacter* positive batches) for application of three different algorithms to detect aberrations as shown in Table 1. Also, considering the variation in total number of samples submitted each week (Figure 1), we assessed the effect of taking the total numbers into account for each algorithm. For the Farrington algorithm, this was done by activating the “population offset” parameter. For the Holt-Winters (HW) and exponentially weighted moving average (EWMA) algorithms, we normalized the count data by differencing the observed data from a centered statistic based on the total number of samples tested per week. Thus, in total, 6 different univariate analyses were performed on the weekly number of *Campylobacter* positive batches. Functions and packages used are listed in Table 1.

Table 1. Aberration detection algorithms applied to the weekly number of *Campylobacter* positive broiler slaughter batches in Sweden.

Data	Dealing with temporal effects directly		Removing temporal effect & using control charts	
	Algorithm	R package	Algorithm	R package
Count (weekly number) of <i>Campylobacter</i> positive batches	1) Farrington	{surveillance}[2]	5) GLM regression & EWMA	{vetsyn}
	2) Farrington with population offset			
	3) Holt-Winters	{vetsyn}[3]		
Normalized count of <i>Campylobacter</i> positive batches by the center statistic (R package {qcc}[4])	4) Holt-Winters	{vetsyn}	6) GLM regression & EWMA	



As the aim of the univariate analyses was to investigate the potential and feasibility of the identified time series data as a syndromic surveillance indicator for human outbreaks, we did not assess the performance of any algorithm in particular nor optimize the algorithms settings at this stage. All the algorithms were applied with their default settings as listed in Table 2. A population parameter ('parameter=total number of samples tested') was added to the default setting of Farrington for activating the "population offset", and the same settings were used when using normalized counts for Holt-Winters and EWMA. In all cases detection was applied from the first week of 2015 to the last week of data available (week 22 in 2019).

Table 2. Parameters setting for the 3 aberration detection algorithms evaluated.

Algorithm	Parameters settings
Farrington	Baseline = 2 years Window of evaluation size = 4 weeks at a time Reweight = TRUE Detection limit = 95% Trend = TRUE No power transformation Regression fit option = fitGLM.fast
Holt-Winters	Baseline = 104 time points (2 years) Detection limits= 2.5, 3, and 3.5 standard deviations* Steps-ahead in prediction = 2 Seasonal effect = additive Baseline correction = TRUE Alpha, beta and gamma default values (assuming convergence)
EWMA	Baseline = 104 time points (2 years) Lambda = 0.2 Detection limits= 2.5, 3, and 3.5 standard deviations* Steps-ahead in prediction = 2 Baseline correction = FALSE Remove temporal effects based on a gaussian generalized linear model (GLM) regression, using sin and cos as covariates (based on retrospective analysis of the data available – $y \sim \sin + \cos$ )

\* The default settings for algorithms in the {vetsyn} package includes an assessment of multiple detection limits.

Figure 2 shows the results of applying six aberration detection algorithms/settings. The weekly upper bounds are shown in the top graph, and detected alarms are shown in the bottom. For the HW and EWMA algorithms, alarms reflect when the middle detection limit was applied.

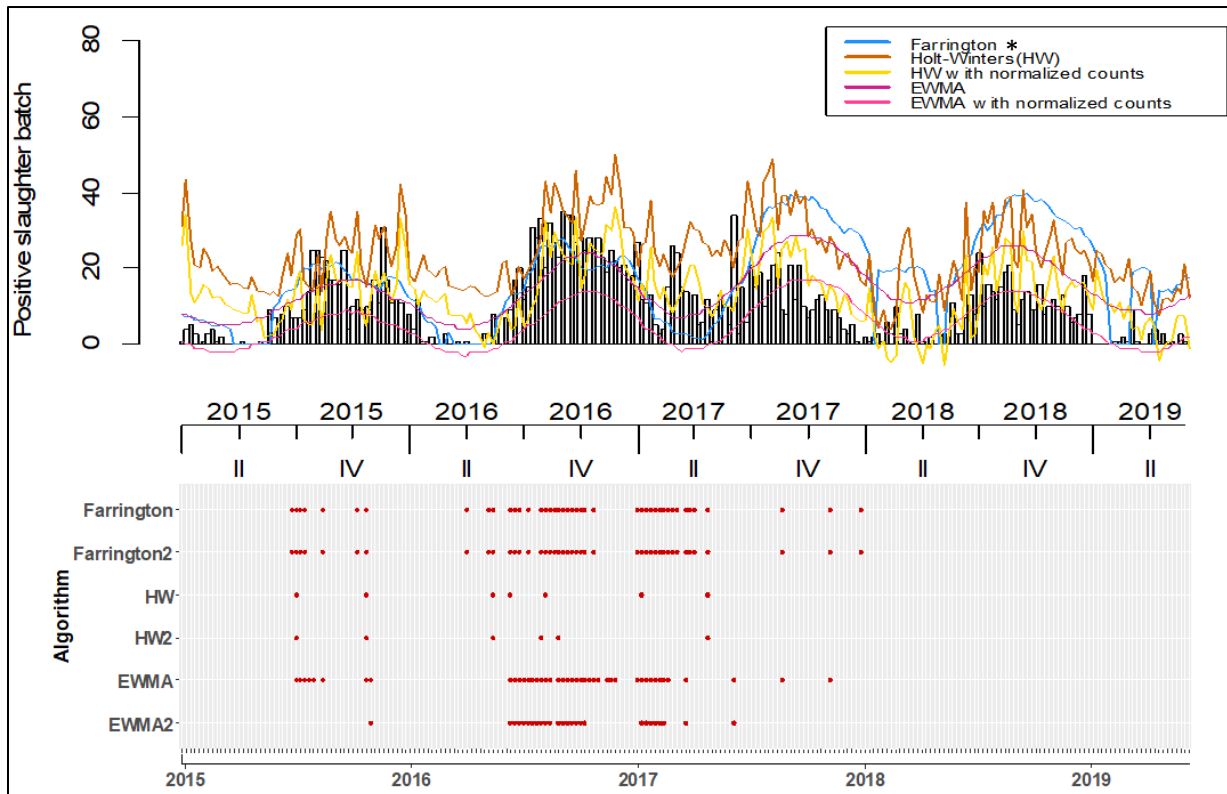


Figure 2. Upper bounds and alarms generated by 6 different algorithms/settings applied to the time series of the weekly number of broiler slaughter batches positive for *Campylobacter* in Sweden from 2015.

\* Farrington with/without population offset had the same upper bounds.

*Campylobacter* is endemic in the Swedish broiler population, from 8.7% to 15.4% of the total annual slaughter batches testing positive for *Campylobacter* (2009-2018). As the natural reservoir of *Campylobacter* (*C. jejuni*, which accounts for approximately 90% of human infections), there is no indication of the infection dynamics, e.g., clinical symptoms, outbreak data, from the broiler population. For this reason, rigorous evaluation of each algorithm for outbreak-signal detection will be performed in a multivariate syndromic surveillance system at the next phase of the project, in which the broiler testing data will be used as a potential explanatory or predictive time series for the occurrence of *Campylobacter* outbreaks in humans.

For this task, we aimed to investigate the potential of the identified time-series data for temporal analyses and outbreak detection by trying different algorithms, and to identify the characteristics, i.e., total number of samples tested, that may need to be explicitly handled during the process. The analyses so far, summarized in Figure 2, allowed us to conclude that:

- 1) There are obvious temporal patterns in the weekly number of *Campylobacter* positive slaughter batches that must be taken into account in the analyses. No statistically significant trend was found, but temporal effects could be successfully modelled using a sin/cos regression model in EWMA algorithm.
- 2) All algorithms were able to identify a long period of increase (alarms) in the number of positive samples in 2016, which coincides with the human outbreaks reported in the year (National Public Health Authority). This shows a high potential of the data as an indicator for human





outbreaks, but a thorough comparison with actual human case data and examination of the time lag is warranted.

- 3) The Farrington algorithm was very sensitive to detect increases during the 2016 outbreak. However, the detection limits after that were clearly “contaminated” (shown by the upper bounds in Figure 2), as the aberration periods themselves became the baseline of detection. If used in further development of the system, the algorithm should be applied in a loop of systematic baseline correction, such as those implemented inside the {vetsyn} package.
- 4) There were only marginal differences in the number of alarms generated when the total number of slaughter batches tested was explicitly taken into account. This indicates that the absolute count of positive samples may serve as a direct indicator, but further validation using simulated data may be needed in the next steps.

This year, we also established a connection with FOHM to collaborate on the next phase of this project. We are still in the discussion process of how the work will be carried out, but the current aim is to conduct a rigorous evaluation of each algorithm assessed in this task to actual human outbreak data, and also to the alarms generated by the automated outbreak detection system (CASE; Computer Assisted Search for Epidemics) at FOHM (Cakici et al., 2010). We will also assess other time-series data that may affect the infection dynamics of *Campylobacter* in both broilers and humans, e.g., temperature, length of daytime, humidity, to consider all the explanatory time-series data available for developing the multivariate syndromic surveillance system for human *Campylobacter* outbreaks.

### **Norway**

In Norway univariate surveillance is used in the NorSySSto detect signals in the number of consultations with gastro-intestinal symptoms reported from GPs and out-of-hours GPs. The data used in this report is for the whole of Norway, while the surveillance system also raises signals on the county and municipality level. The main method used in this surveillance system is a quasi-poisson (QP) regression model. This model takes into account seasonality, time trends and holidays and uses the total number of consultations as a population offset. To reduce the effect of previous outbreaks a reweighting scheme similar to the Farrington method is used. Here we show an alarm threshold corresponding to a z-value of 2.

In Figure 3, we compare the alarms generated by this method with the set of surveillance algorithms used for *Campylobacter* in Sweden as described above. It seems like taking into account the total number of consultations lead to better alarm thresholds. This is likely due to differing reporting practises throughout the year and especially during holidays. There are clear similarities in which weeks alarms are raised for the different algorithms, but also clear differences. For example the Holt-Winter approach without normalisation seem to give a significantly higher threshold than the other algorithms. One interesting finding is that there seems to be an increase in consultations in early autumn every year that gives alarms in the quasi-poisson method that we do not see in the Farrington methods. The main difference between them is that the QP method models the seasonality explicitly, while the Farrington method implicitly models seasonality by restricting the data used to derive the threshold. For this specific increase every year, it would seem that the Farrington methods perform better and that the alarms raised by the QP method might be spurious.



Further evaluation of surveillance methods for potential use in NorSySS need to take into account that the current surveillance system is multivariate since we do surveillance in each of 435 municipalities for each disease. This gives multivariate surveillance problem even if we only consider one data source. Due to likely correlations between data from different municipalities, issues of multiple testing and it being likely that better performance can be reached using partial pooling, it is important that algorithms, and optimisation criteria are chosen such that the multivariate nature is taken into account.

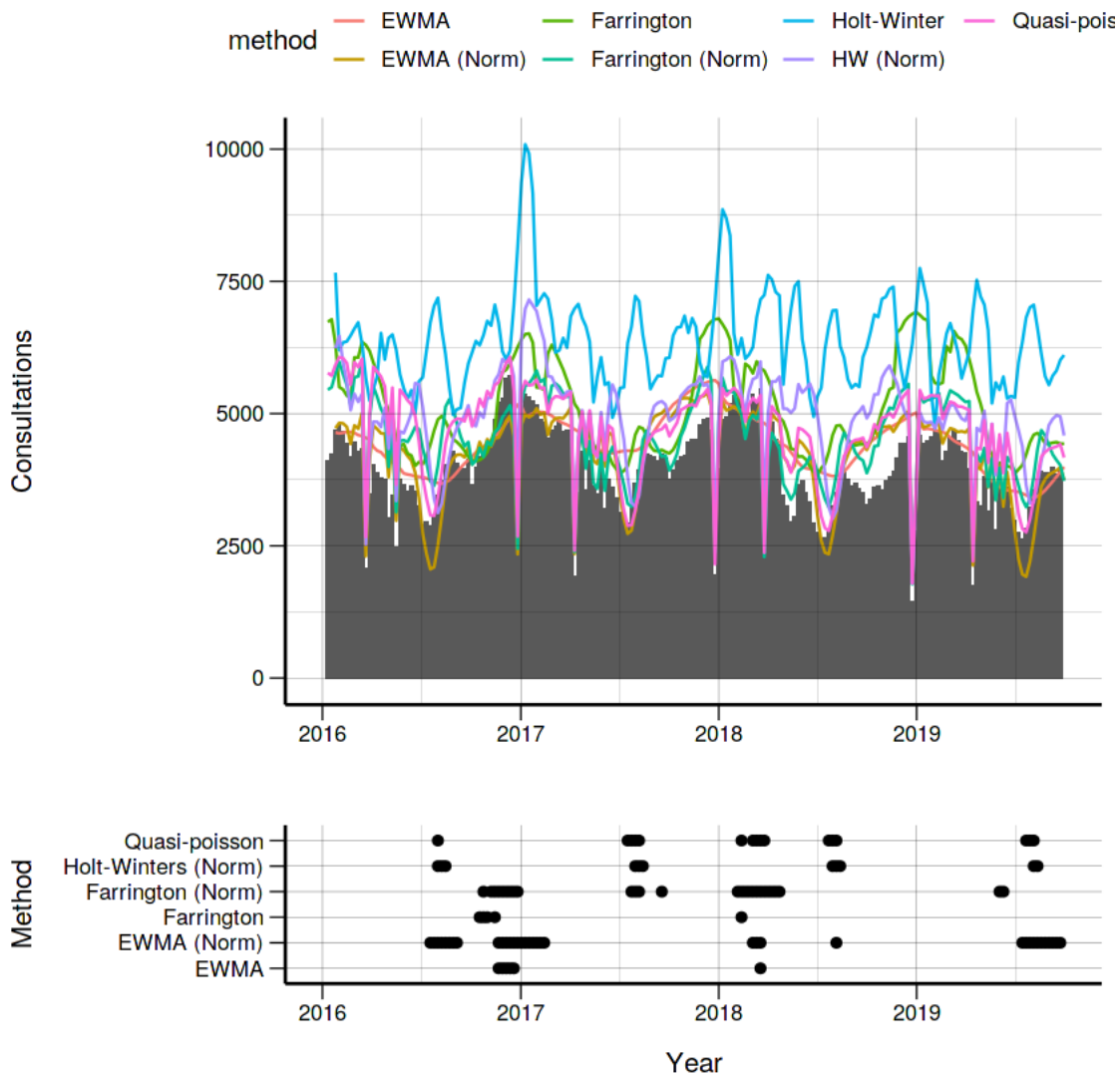


Figure 3: The top chart shows weekly gastro-intestinal consultations and detection thresholds for a range of surveillance algorithms. The second chart shows where the algorithms would raise an alarm due to the number of consultations being above the detection threshold.

### France

French data will be analysed using a modified VetSyn R package and count models. We adapted Rcode to analyse the data at monthly and quarterly time steps. We also will implement detection algorithms used by other countries and compare results to evaluate the potential of each method for detection anomalies depending on data sets. Analyses are in process.



Table 3. Detection algorithms applied to French data sources.

Time series data	Data type	Cleaning the baseline	Dealing with temporal effects directly		Removing temporal effect & using control charts	
			Algorithm	R package	Algorithm	R package
Weekly Monthly Quarterly Number of X	Count	Automated GLM (modified VetSyn codes)	Holt-Winters	Surveillance	GLM regression & EWMA	modified VetSyn codes
			Historical limits	None (manual coding)	GLM regression & Shewhart	
					GLM regression & EARS	

The parametrisation of the algorithms comes from the OMAR project (Sala et al. 2019) and allows to automatic or semi-automatic parametrisation.

Table 3. Parameters setting for detection algorithms applied in French datasets.

Algorithm	Parameters settings*
Holt-Winters	Baseline <=5 years Steps-ahead in prediction = 4 to 8 Detection limit = 7 limits from 95% to 99.99% $\alpha$ , $\beta$ and $\gamma$ default values; in case of convergence failure, using default value for $\alpha$ and $\gamma$ and $\beta = 0.1$ or removed if no trend detected by the GLM; in case of failure of semi-automatic parametrization, $\alpha = \beta = \gamma = 0.1$ Seasonal effect = additive
Historical limits	Baseline = no limit Detection limits= 1.65,1.96,2.33,2.58,2.75,3, and 3.25 sd Prediction based 12-units periods (three blocks of 4 units) centered on the index of the units of interest over the last Y complete years
Shewhart**	Baseline <=5 years Std.dev = 'SD' Detection limits= 2.33,2.58,2.75,3,3.25,3.5 and 3.755 sd Guard band = 4 to 8
EWMA**	Baseline <=5 years Lambda = 0.4 Detection limits= 2.33,2.58,2.75,3,3.25,3.5 and 3.755 sd Guard band = 4 to 8
CUSUM**	Baseline <=5 years se.shift = 2 Detection limits= 2.33,2.58,2.75,3,3.25,3.5 and 3.755 sd Guard band = 4 to 8

\*For each evaluation at time  $t_{w/m}$ , baseline is corrected from  $t_0$  to  $t_{w-1/m-1}$  using a GLM including cos+sin and tested for trend and autocorrelation (see VetSyn package)

\*\* For control charts, the temporal effects are removed from the GLM used to correct the baseline



## Multivariate surveillance

Three main approaches to multivariate surveillance were identified, we call them explanatory, combined and predictive approaches. The explanatory approach aims to include covariates to “explain” variation in the main time-series of interest. This would allow us to de-prioritise outbreak signals that seem to be explained by known covariates. In our example, it might be less important to investigate a signal in gastrointestinal symptoms if it can be explained by an increase in cases from animal surveillance. Since we aim to maximise the probability of detecting real outbreaks while keeping the false positive rate low this can lead to a better surveillance system. The “explanatory” approach can also provide significant insight into the epidemiology of the disease or symptoms.

With combined multivariate surveillance we are looking for anomalies in multiple time-series simultaneously. We are interested in large changes in individual time-series or a changes in the whole system over multiple series. For surveillance purposes this form of multivariate surveillance is often important even with only one data-source since data is often aggregated in smaller geographic areas and we want to detect outbreaks in each area. The simplest solution is to evaluate each time-series independently and set the signal threshold such that the rate of false positives is manageable. From a one-health perspective we can also consider combined surveillance using surveillance time-series from both the animal and the human side.

In certain circumstance such as in Norway, the context means that we are mainly interested in improving the surveillance of human cases since any positive tests in chickens are dealt with locally. Therefore we want to use the data from campylobacter testing in chicken to predict future number of human cases. This would allow the construction of risk scores and potentially provide opportunities to intervene before an outbreak and not just detect the outbreak. Following Gneiting et al. (2008), we will use probabilistic forecasts that provide both point predictions and estimates of their own uncertainty. We aim to produce calibrated forecasts with maximum sharpness and we will use proper scoring rules (Gneiting et al 2007) that provide consistent rules for ranking forecasts. Proper scoring rules for predictions can also be used to evaluate some univariate surveillance algorithms since a subset of such algorithms depend on detecting large observed deviations from the predicted or normal number of cases. The prediction models are under development, but will likely hierarchical structures and spatial information. If successful prediction algorithms are developed, they will be included in the routine automated surveillance in NorSSys.

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Appendix 1 : French datasets available for the NOVA project

Information collected				Information available for NOVA project							
Database name	Target	Type recod	Frequency of colletion	Period available	Spatial coverage	Geographical level	Temporal level	Indicator	Covariates	Aggregation for analysis	no. of observations (total count)
	Cattle							no. of dead animals			12685676
EDI-SPAN	Poultry	clin	daily	2011-2019	national	municipality	day	weigth of dead animals	production	week/month* dep/reg* production	1557682 t for 1557682 removes
	Pigs							no. of dead animals			4274469
LNR Salmonella in poultry	Poultry	lab	monthly to yearly	2011-2018	national	department	day	no. of Salmonella isolates	serovar;production	month* dep/reg* serovar* production	19136
RESAPATH pathogen	Cattle							no. of Salmonella isolates	production		3764
	Poultry								production	month* reg* species	689
	Pigs	lab-clin	monthly to yearly	2011-2018	national	department	day		production		469
RESAPATH syndrom	Farmed animal							no. of syndrom (digestive, abortion, septicemia)	production	under evaluation	
RNOEA	Poultry	clin	monthly	2010-2015	national	national	month	no. of Salmonella reports	serovar;production	month* nat* serovar* production	20482
Salmonella	Animal, food, feed, envt	lab	daily	2010-2017	national	department		no. of Salmonella isolates - reports	serovar;production; type of surveillance	week/month*dep/reg*Production*Serovar	43898 reports 67593 isolates
								no. of consultationsfor gastro-enteritis			1384417
OSCOUR (SURSAUD)	Human	clin	daily	2011-2018	national	department	week	no. of consultations for vomiting	none	week/month*syndrome*dep/region	68138
								no. of consultations for food poisoning			44746



Information collected				Information available for NOVA project								
									no. of consultations for gastro-enteritis		1487825	
									no. of consultations for vomiting		281671	
SOS medecin	Human	clin	daily	2011-2018	national (83%)	department	week		no. of consultations for food poisoning	none	week/month*syndrome*dep/region	4553
									no. of consultations for diarrhea			216038
National control plan in poultry	Poultry	lab	daily							upon request		
OQUALIM	Feed	lab	monthly							upon request		