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**Contribution of multiple  
syndromic surveillance  
components in the FBD  
surveillance**

**JRP6 - NOVA - FBZ1 - 1<sup>st</sup> Call**

NOVA D3.5

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# CONTRIBUTION OF MULTIPLE SYNDROMIC SURVEILLANCE COMPONENTS IN THE FBD SURVEILLANCE

## 1. INTRODUCTION

The general objective of the task 3.3 of the NOVA project was to assess whether the combination of surveillance results from different syndromic surveillance components for Foodborne Diseases (FBD) in animals, food or the environment could lead to an improvement of the surveillance of FBD outbreaks in humans. In task 3.2, three case studies of FBD surveillance with a One Health perspective were explored: *Campylobacter* surveillance in Sweden, *Campylobacter* surveillance in Norway and *Salmonella* surveillance in France. The three case studies represented different states of development of a surveillance system, from an explorative state (proof of concept, France) to the improvement of an operational surveillance system (Norway). The deliverables 3.3 and 3.4 reported the development of several surveillance components for the three case studies, based on a common methodology (use of a set of temporal aberration detection algorithms) and discussed their potential interest for the surveillance of human outbreaks. The present deliverable reports the results of different attempts to combine the univariate surveillance components developed previously into a multivariate surveillance system.

## 2. SURVEILLANCE OF SALMONELLA ALONG THE FOOD CHAIN IN FRANCE

*Salmonella* is the leading cause identified in human foodborne outbreaks in France, causing more than one third of the reported outbreaks (Santé Publique France, 2021). Along with poultry, cattle production is recognized as an important source of human infections. While the prevalence of *Salmonella* excretion does not exceed 2% in broiler and layer flocks, a recent study estimated that the intestinal carriage of *Salmonella* was about 3% in cattle at the abattoir in France (Bonifait et al., 2021). Various surveillance systems already monitor animal health and microbial hazards or hygiene indicators in food in France. A few number of these systems are dedicated to the surveillance of *Salmonella* in animal and food (e.g. Salmonella network) while the majority of them are focused on animal health, as livestock mortality monitoring. The question posed in our work in WP3 was to explore whether the data already collected could be of interest for *Salmonella* surveillance along the food chain in France. In task 3.1., we inventoried the potential sources of data useful for that objective. Twenty-two data sources were identified at first. Due to restriction of access to certain databases and to data quality issues for other sources, a restricted number of data bases could be used in NOVA (see below). In particular, identified data sources in poultry and pig sectors could not be used. Therefore, the case study was limited to the dairy and beef sectors.



## Univariate Sys

Based on a comprehensive mapping of the food-chain surveillance network in France (deliverable 3.2), we solicited the coordinators of several operational surveillance systems to identify existing monitoring data. Considering data accessibility, data quality and monitored species, three animal health databases were relevant: the National Cattle Register (NCR) database for the registration of cattle mortality at farm; the Surveillance network of antimicrobial resistance in pathogenic bacteria from animal (RESAPATH network) database for the report of digestive, mastitis and reproductive syndromes in cattle; and the Salmonella network database for the isolation of *Salmonella* in cattle (animals and their environment, feed) and food (dairy product and beef). In addition, two human health databases were investigated: the coordinated health surveillance of emergency (OSCOUR) database and the General practitioner house call network (SOS Médecins) database. These two databases were aggregated into a single time series depicting the number of reports for gastrointestinal syndromes per week.

Weekly time series (TS) at national scale were extracted from these datasets from 2011 to 2018. A retrospective anomaly detection analysis was performed on the last three years of the time series. It consisted in identifying statistical anomalies within time series, potential outbreaks, by five main algorithms (Holt-Winters, Historical Limits, EWMA, Shewhart and CUSUM). For each TS, we implemented a classical approach consisting of: i) preparing the calibration period to get a baseline cleaned from outbreaks, ii) predicting the expected value for the test week and iii) detecting a potential excess events (anomaly) by comparing observed and predicted values during the test week. For each TS, the baseline was obtained using a generalized linear model (GLM) adjusted for over-dispersion, testing Poisson, Generalised Poisson, Quasi-Poisson and Negative Binomial distributions. We also tested trends (none and linear), seasonality (annual, bi-annually), and auto-regressive components over the last four weeks. Best-fitting model was selected using the Akaike Information Criterion (AIC) while the best-fitting distribution was determined with coefficient of dispersion and assessment of residual plots. The five algorithms for anomaly detection were parametrized as described by Sala et al. (2020).

The selected datasets revealed a wide range of characteristics: considering cattle mortality (NCR data) and human health (OSCOUR and SOS Médecins data), TS depicted regular patterns with distinct seasonality (annual or bi-annual), trend and limited noise; regarding laboratory analyses (RESAPATH and Salmonella data), TS showed yearly seasonality, little to no trend and high noise. Considering time series individually, some statistical anomalies were reported simultaneously by numerous algorithms (fig 1). Likewise, several temporal anomalies were measured concurrently in time series from either multiple animal datasets or both animal and human health datasets. As an example, several anomalies were detected simultaneously in both human health dataset (OSCOUR and SOS Médecins) and laboratory datasets (RESAPATH and Salmonella) (e.g. W32-2017) or human health dataset and cattle mortality (NCR) (e.g. W44-2016).

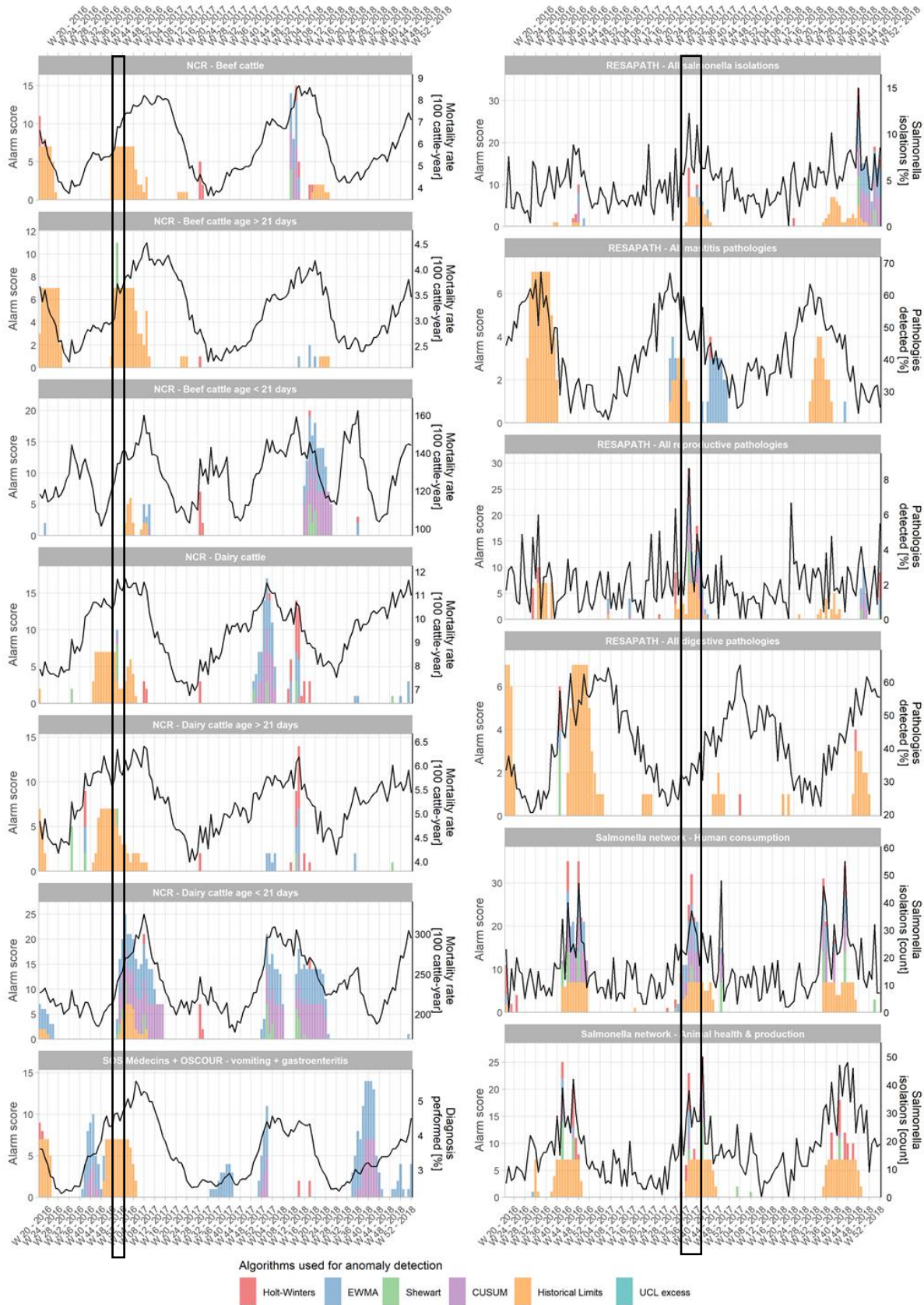


Figure 1. Weekly observed data and model-predicted anomalies per week, for each algorithm. On the left y-axis, the cumulated alarm scores with colors corresponding to algorithms. On the right y-axis, the observation units. The black frames highlight alarms common to several TS



## Multivariate SyS

Due to the diversity of the datasets explored (animal, food, human), we chose to adopt a combined multivariate surveillance strategy. We aimed to identify anomalies in multiple time-series simultaneously. This strategy is a complement to the control charts and the heat maps generated by aggregating several univariate components (see “univariate analysis”). The main hypothesis under a combined multivariate analysis is that TS are independent when there is no epidemic. The aim of the alarm detection is to detect the point when the TS start to be correlated when a common outbreak occurs. Three methods for multivariate detection anomalies were tested: one method based on dimension reduction which summarizes each component at a time point into a single statistic (Hotelling’s  $T^2$ ) and two methods based on vector accumulation, in which information from each TS is accumulated and transformed into a scalar alarm statistic (MEWMA, MCUSUM). MEWMA and MCUSUM are the equivalent of EMWA and CUSUM algorithms (used in univariate analysis) but suitable for the multivariate approach.

For the multivariate analysis, we considered the TS derived from the previous datasets: NCR, RESAPATH, Salmonella network and OSCOUR-SOS Médecin. We used the “clean” TS (i.e. baseline free from outbreaks) to suppress trends and seasonality over the whole time period (2011-2018). First, we checked for collinearity between TS as multivariate algorithms for temporal anomaly detection do not deal with strongly correlated TS (fig 2). Then, we checked the normality of the multivariate TS because it is an assumption to be respected for the application of multivariate control charts as MCUSUM and MEWMA. We considered a 3-years historic as the better compromise between the respect of the normality assumption and the use of a long historic period. The 3-year historic period was used for the first step of the multivariate analysis (Tab 1). This step consisted in calculating the covariance matrix and the vector of means over the 3 year-period. The covariance matrix and the vector of means were calculated for each week between 01-01-2016 and 31-12-2018, resulting in 140 correlation matrix and 140 vectors of means.

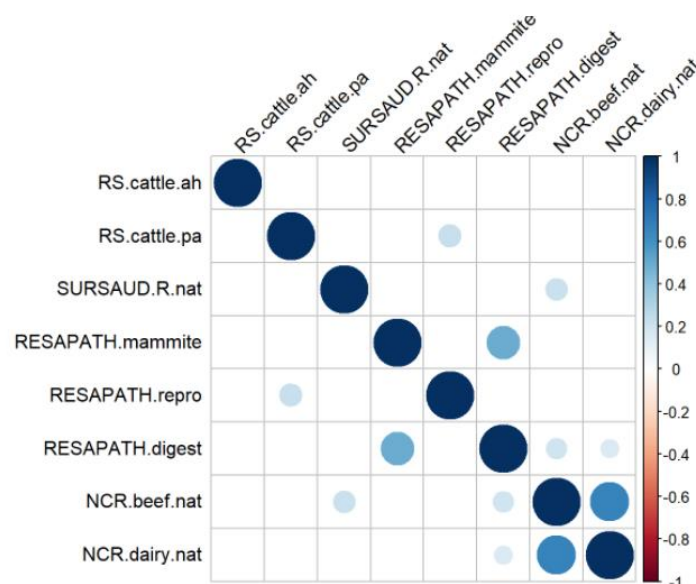


Fig2: Correlogram for the 8 TS considered in the multivariate analysis from 2011 to 2018



subset	hist.1.year	hist.2.years	hist.3.years	hist.4.years	hist.5.years
RS.cattle.ah	100%	96%	93%	100%	96%
RS.cattle.pa	71%	49%	31%	17%	16%
SURSAUD.R.nat	94%	77%	39%	24%	1%
RESAPATH.mammite	100%	100%	100%	100%	100%
RESAPATH.repro	91%	91%	86%	24%	9%
RESAPATH.digest	86%	86%	45%	15%	4%
NCR.beef.nat	100%	100%	100%	89%	40%
NCR.dairy.nat	68%	33%	22%	1%	0%
<b>All subsets - Multivariate Normality</b>	<b>96%</b>	<b>91%</b>	<b>82%</b>	<b>56%</b>	<b>21%</b>

Tab 1: Proportion of TS (2016-2018) showing a normal distribution in univariate analysis (Shapiro-Wilk test) and in multivariate analysis (Hense-Zickler test) according to the historic period (from 1 to 5 years)

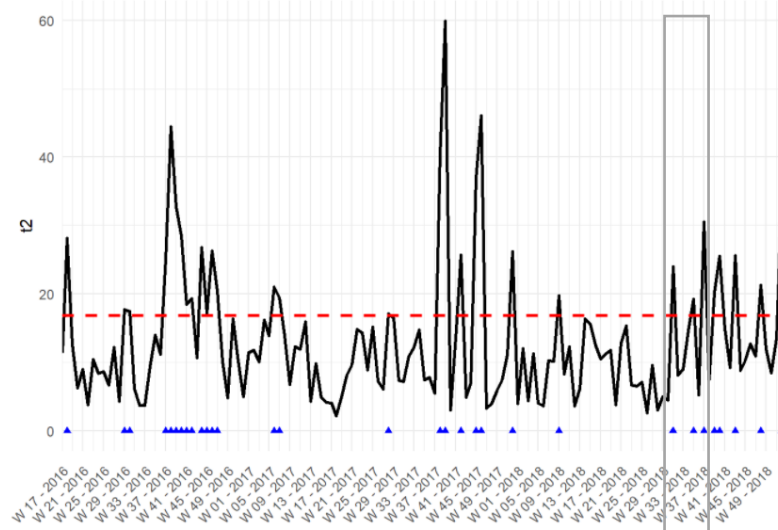
On the second step of the multivariate analysis,  $T^2$  were calculated on the control charts resulting from the previous step (MCUSUM, MEWMA) or directly applied on the raw value to the last week of observation (Hotelling's  $T^2$ ). For generating MCUSUM and MEWMA control charts, an historic of one year and a guard-band of 7 weeks were taken into account. The parametrization of the methods was based on Faverjon et al. 2019.

We observed that the anomalies detected were very different according to the method used (Fig 3). Hotelling's  $T^2$  detected very sharp peaks on a short time-period because this method did not take the vector of the past means into account. Conversely, MEWMA and MCUSUM integrated a one-year history and alarms were triggered when of a progressive shift in the mean baseline was observed. These observations demonstrated that a set of different algorithms is needed to detect different types of anomalies. We observed that anomalies were detected with the three methods from W37-2018 to W41-2018. On the univariate analysis, this period also triggered alarms for the human TS (OSCOURS Médecin), for the Salmonella network – food TS and, to a lesser extent, for the Salmonella network – animal health TS but not for the cattle mortality TS or the RESAPATH TS. It is of interest to highlight that the W37-2018/W41-2018 period was not the most striking period of simultaneous alarms when comparing univariate heat maps.

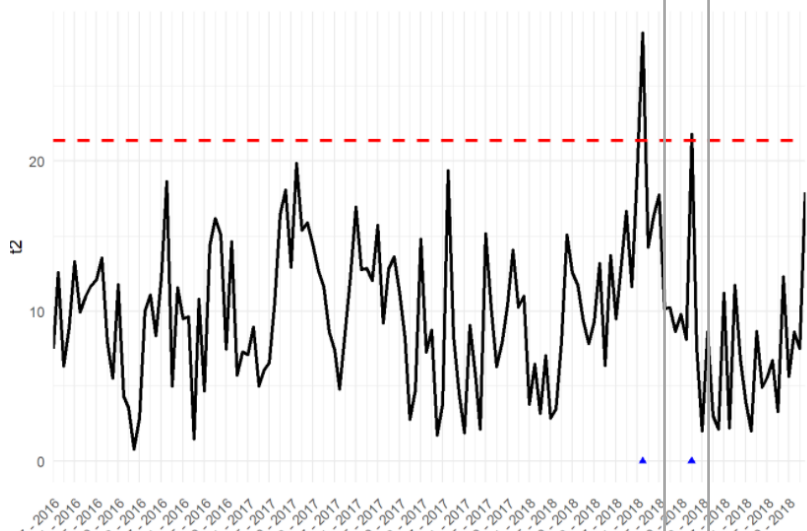
It turned out that the anomalies detected by MEWMA and MCUSUM were very dependant from the algorithm parametrization. For MEWMA, increasing  $\lambda$  from 0.2 to 0.9 increased the proportion of weeks with alarms from 1.5% to 12.5%. High values of  $\lambda$  (near 1, the higher limit) limited the influence given to the historical means in the detection process of alarms. In that cases, MEWMA tended to detect the same alarms than the Hotelling's  $T^2$  method, i.e. sharp peaks on a short-period. Parametrization of MCUSUM was more difficult. The h parameter could be easily set because it directly determine the proportion of weeks with alarms. It defines the upper limit control of the MCSUM control chart (fig 4). The value of k was more difficult to set because it is dependant from the magnitude of the distance between the observed and the expected means. We tested a range of values for k from 0.1 to 1.5. Values of 0.4 and 0.5, associated respectively with h=11 and h=10, rendered around 20 % of weeks in alarms (10 weeks). This was considered as the maximal proportion of weeks in alarm that could be taken into account when running an operational surveillance system.



a



b



c

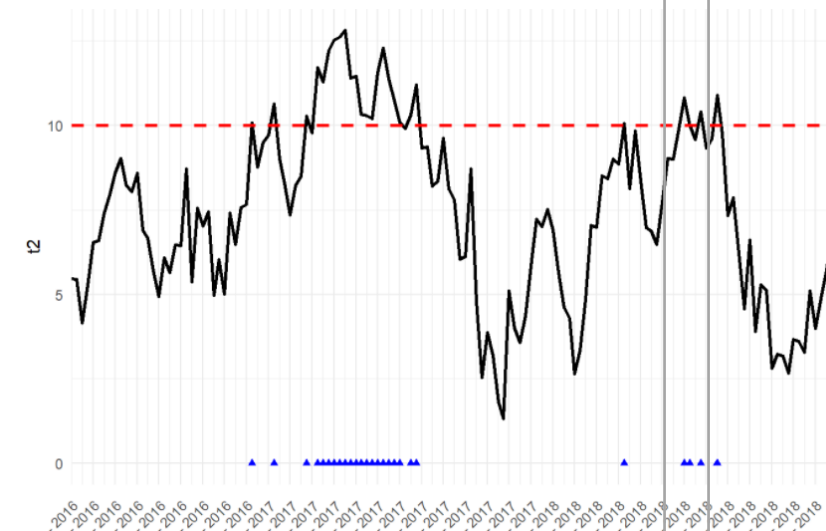


Fig 3: Weekly data and model-predicted anomalies per week over 2016-2018, for each algorithm: a) Hotelling's  $T^2$ , b) MEWMA ( $\lambda=0.3$ ) and c) MCUSUM ( $h=11$  and  $k=0.5$ ).



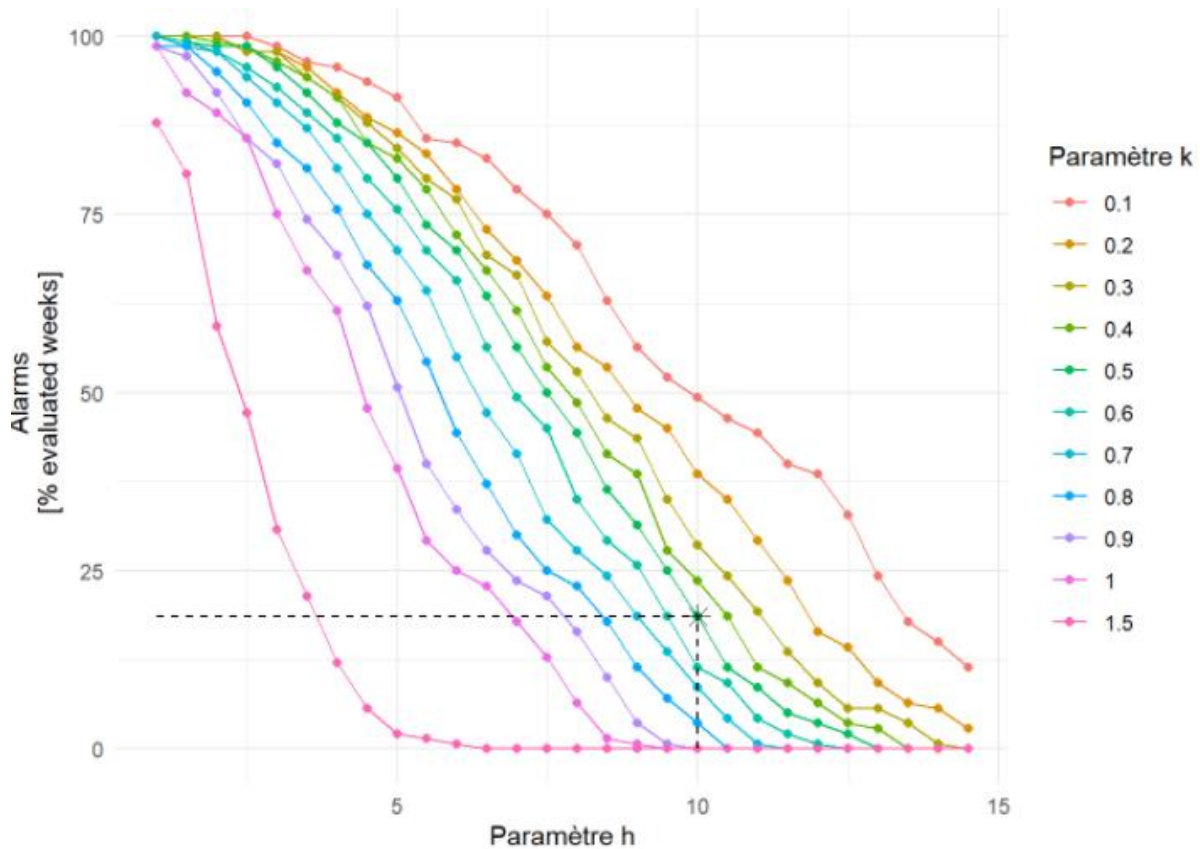


Fig 4. Proportion of weeks with alarms according to the  $h$  parameter for different values of  $k$  in the MCUSUM method

### Conclusion & future direction

We did not assess the sensitivity and specificity of the alarm detection process in the multivariate analysis. As no documented outbreaks occurred during the studied period, the only solution to assess the system performance would have been to simulate multivariate outbreaks. This assessment could not be carried out during the NOVA project. Nevertheless, we proposed for the first time parallel univariate analysis and combined multivariate analysis for several dataset that have been never explored with a One Health surveillance approach. In addition to challenges previously addressed in deliverable 3.4 (data accessibility, data quality, timeliness and geographical aggregation scales), developing a multivariate analysis also raised the problematic of the dependencies between TS investigated. We considered that the TS described a same underlying phenomena: circulation of *Salmonella* along the Food Chain, causing clinical events both in cattle and in humans but also leading to isolations of the bacteria in the food and the environment of the animals. This combined multivariate approach rendered alarms that were not the same than those which were detected by parallel monitoring of the TS. The main advantage of the combined surveillance is to summarize all the TS analysis into a single statistic which is easy to interpret, although the parametrization of the algorithms may need serial adjustments to optimize the system. The combined analysis offered a standardized way of analysing several TS simultaneously, while parallel monitoring with charts or heat maps might be more subject to subjective interpretations. However, combining information of all TS into a single statistic raised issues for the interpretation of the alarms: it was not possible to identify individual TS that contributed the most to the alarms and it was necessary to go back to the univariate



TS analysis to identify the alarms. Another option would have been to restart the multivariate analysis after deleting one (or two) TS in turn and checking if any alarms were still generated without the deleted TS.

This first attempt to develop both univariate and multivariate TS analysis showed that the two strategies are of interest for surveillance. Because TS anomaly detection algorithms are relatively straightforward to implement, it could be possible to perform both univariate and multivariate analysis in an operational surveillance system, after a period of calibration of the methods. The most demanding part would be the parametrization of the algorithms, in order to obtain early detection (adequate timeliness in detection of potential outbreaks) but to avoid false alarms. Indeed, each alarm leads to checks, firstly by in-depth analysis of the TS in question and then, if necessary, by cross-checking with the on-field operators. Ultimately, alarms lead to epidemiological on-field investigations. Under the conditions, time and financial burden caused by false alarms must be carefully taken into account in the algorithms parametrization. Currently, we lack documented epidemiological data to be able to estimate the sensitivity of the methods developed and optimize parametrization. A regional analysis based on documented *Salmonella* outbreaks in dairy cattle and in raw milk cheese consumers in south eastern France in 2018 is currently being developed to allow a first validation based on past episodes.

Since 2011, several networks dedicated to the surveillance of health hazards in animal, plant and food have been developed in France. These networks involve all surveillance stakeholders in each sector. Our work in NOVA is of interest for the animal health surveillance network (plateforme ESA) and the food-chain surveillance network (plateforme SCA). *Salmonella* is a common subject for the two collaborative structures but this is the first time that data from animal, food and environment, produced by different sources, are combined for surveillance in France. Our work is of interest both platformsto both networks, which provide an optimal structure and environment to further develop the One Health surveillance approach.

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### 3. SURVEILLANCE OF HUMAN CAMPYLOBACTERIOSIS IN SWEDEN

Considering the continuous high incidence and subsequent impact on the society, relatively straightforward food chain, and the availability of data (Fig.5), *Campylobacter* was chosen as the target pathogen in Sweden. As the first step, we applied different temporal aberration detection algorithms (TADAs) to the time-series of weekly number of broiler slaughter batches positive for *Campylobacter*, which showed a high potential of the data to be used for detecting outbreaks with syndromic surveillance approach (SyS)(NOVA D3.3). In 2020, we started a collaboration with the Public Health Agency of Sweden (FOHM) on the topic, and got access to the weekly number of clinical campylobacteriosis cases in humans that were known to have no foreign travel history (domestic cases). Meanwhile, we also acquired more knowledge about the broiler data - structure of broiler industry in relation to *Campylobacter* surveillance (NOVA D3.4), more correct estimation and use of sample collection date (slaughter date) – in addition to developing a script to download and aggregate the weather data (temperature, precipitation) from the Swedish Meteorological and Hydrological Institute (SMHI), in collaboration with NOVA WP4 (SVA).

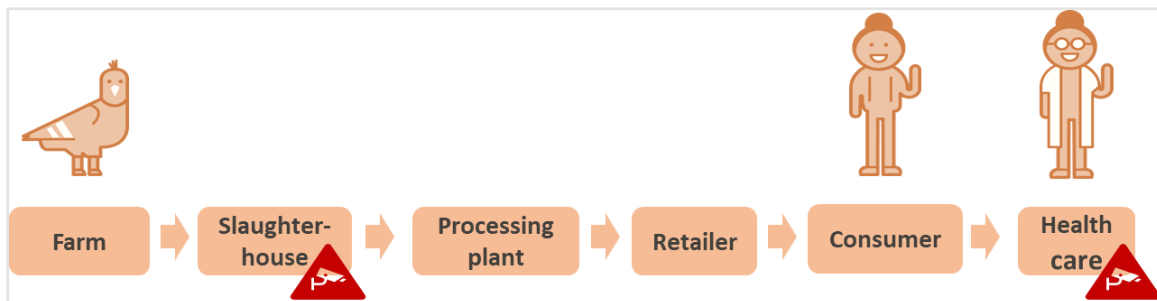


Figure 5. Mapped food chain for *Campylobacter* transmission. There is a national monitoring system at major slaughterhouses in Sweden and human campylobacteriosis cases are reported to FOHM through SMI-net (red surveillance camera signs).

In this deliverable, we report the findings and discussion from **1)** univariate SyS, applying TADAs to the time-series of weekly number of *Campylobacter*-positive broiler slaughter batches (broiler data) and weekly number of clinical campylobacter cases in humans (human data) using data from 2009 to 2019 (The broiler data is re-done with more correct estimation of the date and extended time frame than the previous report in NOVA D3.3), **2)** univariate SyS with the actual weather data to model the seasonality for both broiler and human data, **3)** univariate and multivariate SyS of the broiler data broken down by slaughterhouse, **4)** multivariate SyS of broiler and human data and finally, **5)** discussion on how we can exploit the current surveillance program in broilers to support and enhance the surveillance in humans, with the focus on early detection/decision for further action.

#### Univariate Sys

##### Broiler data

Due to the highly seasonal pattern of the data, regression methods based on global behavior – such as the Farrington algorithm and Poisson regression – performed well in learning the seasonal pattern in the data, while still generating alerts for seasonal peaks that were exceedingly high (Figure 6). Among the two, EWMA consistently alerted during an outbreak period known to have occurred in 2016-2017 (Livsmedelsverket, 2017). The Holt-Winters algorithm, which is a local data-driven regression method, adjusted too well to the high seasonal peaks and failed to provide consistent alarms in known outbreak periods.

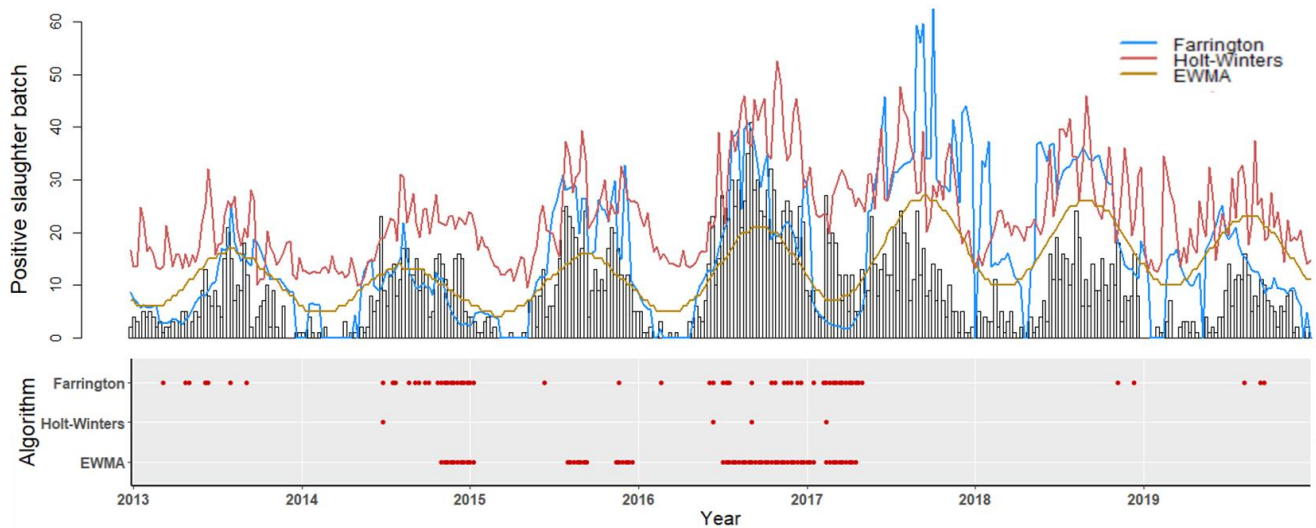


Figure 6. Weekly number of *Campylobacter*-positive broiler slaughter batches (bars) and upper control limits (colored lines) for three temporal aberration detection algorithms (TADAs) evaluated. In the bottom of the figure the red dots represent each week in which the respective TADA generated an aberration detection alarm.

### Human data

Similar results were observed when applying TADAs to the time-series of weekly reported campylobacteriosis cases in humans – global regression methods performed better, and the EWMA performed best in signaling when seasonal peaks exceeded the expectation, while not generating an excessive number of extra alarms overall (Figure 3).

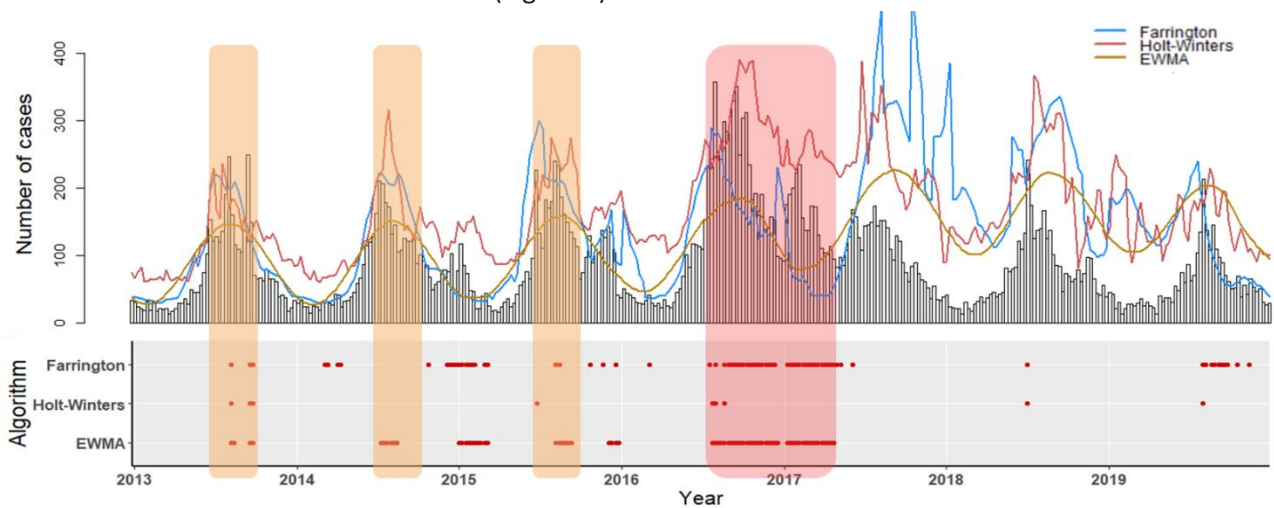


Figure 7. Weekly number of domestic *Campylobacteriosis* cases reported to the Public Health Agency in Sweden (bars) and upper control limits for three temporal aberration detection algorithms (TADAs) evaluated (colored lines). In the bottom of the figure the red dots represent each week in which the respective TADA generated an aberration detection alarm.

The human data also reflected the big outbreak reported in 2016-2017, and all algorithms applied made alarms for the abnormal increase in case numbers during the outbreak period (red-highlighted in Figure 7). However, as highlighted in orange (Figure 7), there were alarms generated nearly every year when the number of cases exceeded the expected seasonal peak, warranting further improvement of the system and assistance in interpreting the generated alarms.



Based on the univariate SyS of broiler and human data, combined with more knowledge and better understanding of the data including weather data, following questions were generated, which are addressed in the same order.

- 1) Can we improve the performance of univariate SyS by modeling the seasonal variation – in both broiler and human data– based on actual weather data (temperature, precipitation)?**  
Temperature and rain fall has been found to be significantly associated with *Campylobacter* both in broilers and humans (Jore S. et al., 2010, Jorgensen F. et al., 2011). The seasonal patterns were modelled using sine and cosine waves in the previous univariate SyS, rather than actual weather data. We wanted to explore whether adding true weather data can potentially capture further noise.
- 2) Can we reduce the number of false alarms or improve the sensitivity of temporal monitoring in the broiler data by breaking down the numbers by slaughterhouse of origin?**  
There are seven major slaughterhouses for broilers in Sweden. We wanted to explore whether implementing monitoring in each of the slaughterhouses individually in parallel could increase the sensitivity, while combining the seven time-series using multivariate SyS methods could improve the confidence in the alarms.
- 3) How can the current surveillance program in broilers complement and assist the surveillance activity in humans for campylobacteriosis?**  
Campylobacteriosis is a zoonosis with broilers (chicken meat) as the main source of infection, strongly warranting a statistical and practical set up of joint analysis for an effective One Health Surveillance. Specifically, an investigation is needed to examine if the broiler data can serve as a predictor of the campylobacteriosis cases in humans, or at least the simultaneous monitoring of broiler data using TADAs can give the relevant support for public health authorities to make more timely decisions to declare an outbreak.

### Weather data in univariate SyS

As previously described, the best TADAs for monitoring both broiler and human data were the Farrington algorithm and regression followed by detection using EWMA in the residuals. However, as shown in Figure 6, the presence of a large outbreak in 2016-2017 caused baseline “contamination”, making all algorithms to incorporate the increased number of cases in their baseline moving forward, which resulted in outbreak signal detection in weeks after the outbreak to deteriorate.

For this reason, for all further univariate SyS, we chose to use regression + EWMA as coded in the freely available package {vetsyn} (Dórea et al. 2015) in statistical programming language R (R Core Team, 2020), which provides users with the option of setting automated correction of the baseline.

To evaluate the effect of incorporating weather as a predictor of *Campylobacter* incidence in both broilers and humans, the EWMA implementation of the {vetsyn} package was adapted to model seasonality based on provided precipitation and temperature data (daily observations from all the weather stations available in 2009-2019 transformed to the weekly average), and the results for the broiler data and human data are shown in Figures 8 and 9, respectively.

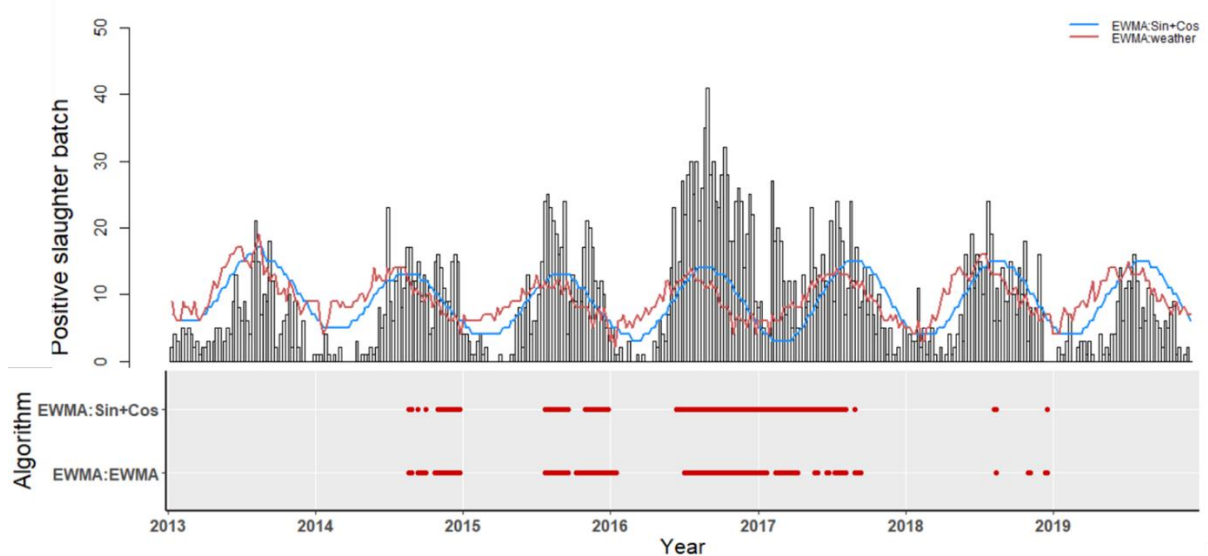


Figure 8. Outbreak signal detection applied to the broiler data using regression + EWMA with automated baseline correction. Seasonal modeling based on sine and cosine waves is compared to modeling using average weekly precipitation and temperature.

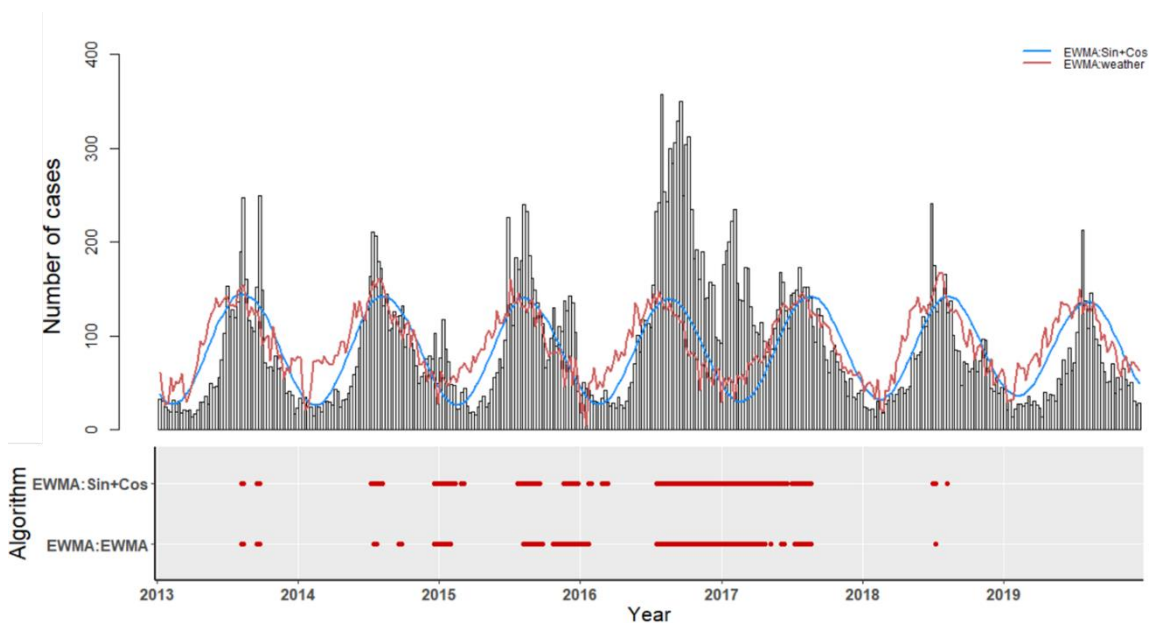


Figure 9. Outbreak signal detection applied to the human data, using regression + EWMA with automated baseline correction. Seasonal modeling based on sine and cosine waves is compared to modeling using average weekly precipitation and temperature.

In both cases the use of baseline correction was effective in preventing the upper detection limits from increasing after the outbreak in 2016-2017. Also, in both cases the use of sine and cosine waves resulted in detection of seasonal peaks that exceeded expectation at least one week before the first aberration signal in the model using weather data, thus outbreak detection was *not* improved by using weather data.



The weather data is explanatory, and therefore its use as a predictor variable in the regression models adjusts our expectation of that season's number of cases. This can be beneficial if the goal is to reduce the number of false alarms. However, if we just want surveillance officials to be alerted when seasonal peaks are starting to appear, the sine + cosine option may be better. The third option could be to have both in use. In that way, surveillance officials will get an early warning based on the sine + cosine model, knowing "the season is really in full speed now". Then they can watch the alarms generated with weather data to see whether it looks like it will be a heavy season, and weather alone explains that, or not, in which case they should get prepared for a possible continued increase. In this proposed scenario, sine + cosine model will be used to generate the alarm, and the weather model as an explanatory rather than detection model.

### Univariate & Multivariate SyS of the broiler data by slaughterhouse

Univariate SyS of counts aggregated over large geographical areas can lead to dilution of outbreak signals (Dórea et al. 2013). We aimed to investigate whether sensitivity for detection of localized outbreaks could be increased by breaking down the weekly counts of positive slaughter batches by the seven different major slaughterhouses in Sweden. Monitoring all the seven time-series individually in parallel can, however, increase the false alarm rate (false discovery problem). Therefore, we wanted to investigate if the problem could be avoided by applying multivariate SyS methods.

As we had been performing univariate analyses using EWMA, the natural choice for the multivariate SyS was the use of multivariate control charts – also preceded by regression to remove seasonal patterns. The multivariate cumulative sums (MCUSUM) and the multivariate EWMA implementations (MEWMA) from the R package {MSQC} (Santos-Fernandez, 2016) were tested and the results are shown in Figure 10. For comparison, the broiler data (total counts) and the alarms generated by regression based on sine + cosine is also shown in the figure.

As shown in Figure 10, the application of multivariate SyS methods (MEWMA, MCUSUM) did not offer advantage over the univariate SyS counterparts – whether applied to the summed count series of all slaughterhouses or to all seven independently. The statistic for the MCUSUM grew to such a high value during the outbreak in 2016, that it stayed on "out of control state", or alarm state, for over one year after the outbreak. This MCUSUM behavior has been repeatedly observed in different MCUSUM implementations we tested (results not shown), and a manual reset of the algorithm would be needed in case of outbreaks. The MEWMA first alerted for an outbreak signal in week 29, five weeks after the EWMA applied to the total counts for all of Sweden generated an alarm.

Meanwhile, particularly in the case of the known outbreak in 2016-2017, the separation of counts by slaughterhouse of origin made it clear that the problem was localized to slaughterhouse F. The aberration detection applied to that slaughterhouse data individually would have signaled for the first time on week 23, and consistently signaled every week after that, while the first signal in the time-series of counts for all of Sweden was in week 24. From this example, we can conclude that having a parallel univariate SyS implemented for all seven slaughterhouses, *in complement* to the time series of the total counts in Sweden, could lead to more timely alert with more information on the source.

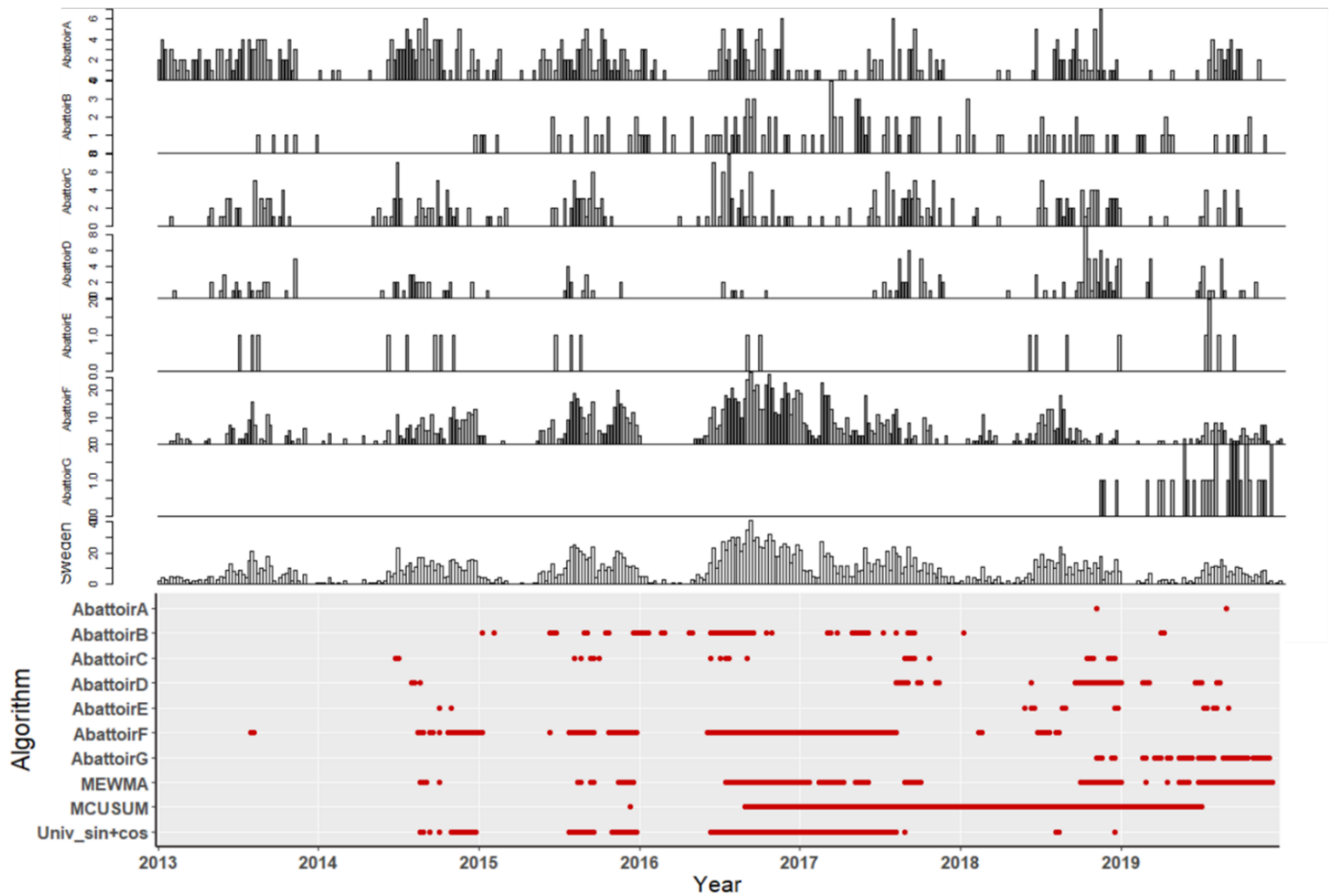


Figure 10. Weekly number of *Campylobacter*-positive broiler slaughter batches in each of 7 major slaughterhouses in Sweden, as well as the total counts (bars). The bottom panel shows the alarms generated when applying syndromic surveillance with regression followed by EWMA independently in each of the slaughterhouses, combining all 7 time-series in multivariate control charts (MEWMA and MCUSUM) and, for comparison, the alarms previously described for the total counts in Sweden.

### Multivariate Sys of broiler and human data

We further investigated whether the broiler and human data could be incorporated into the same temporal monitoring system to improve the timeliness of detection of outbreaks in humans. Based on the assumption that the presence of *Campylobacter* in chicken meat is the leading cause of campylobacteriosis in humans, we included the broiler data as a predictor in the regression model applied to the human data as a pre-processing step to remove temporal patterns before applying EWMA as a TADA. Two settings were tested: using the weekly number of positive slaughter batches directly, week by week aligned with the human data; applying a two-week lag, where the model prediction of the number of cases in humans in a given week is based on the number of broiler batches positive for *Campylobacter* two weeks prior. The time lag of two weeks was based on the preliminary result from an on-going national project in Sweden, which coincides with a similar study in Switzerland (Wei et al., 2015). The results are shown in Figure 11.



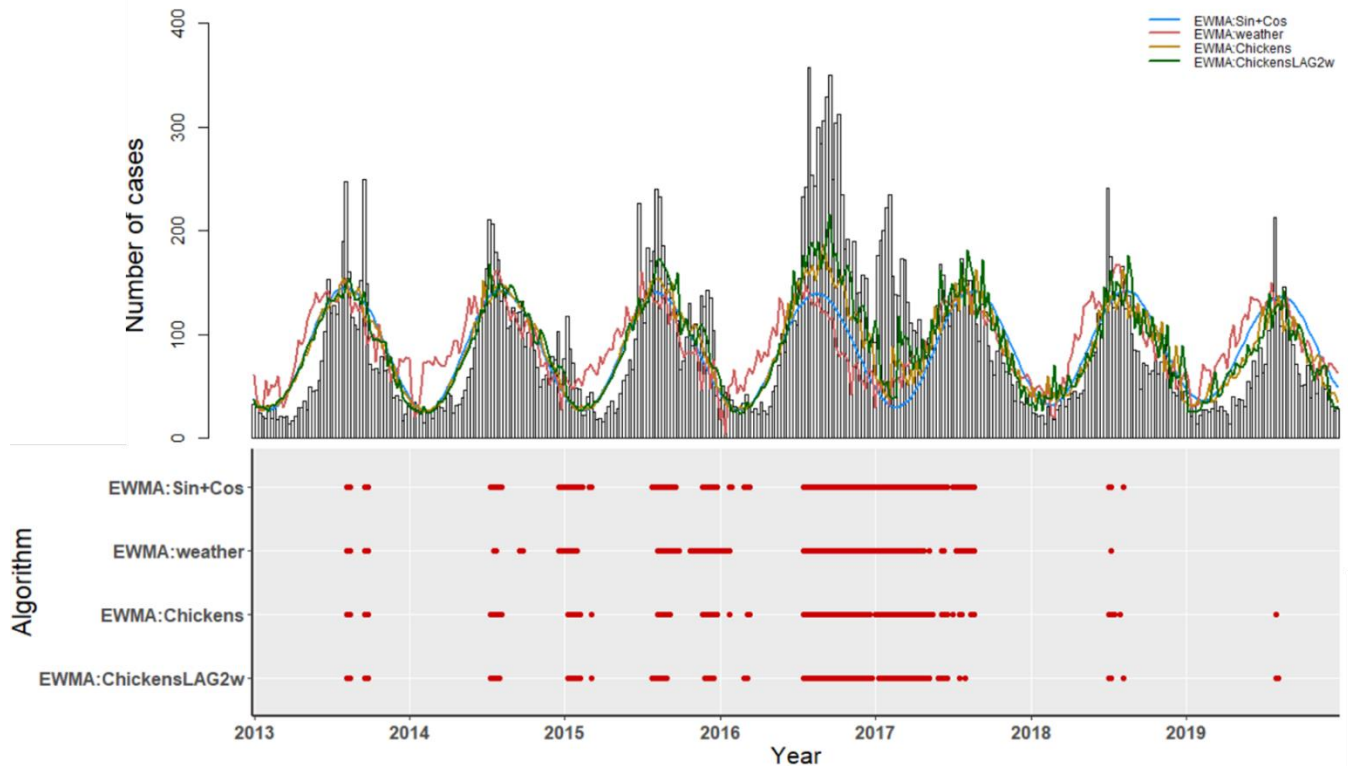


Figure 11. Outbreak signal detection applied to human data using regression + EWMA with automated baseline correction. Seasonal modeling alternatives previously presented are compared to the use of the broiler data as a predictor variable: first directly based on counts in the same week, and second with a two-week lag in-between.

None of the settings used provided earlier detection compared to simply modeling the human data independently based on sine and cosine. First to scrutinize the behavior of the TADA settings in Figure 11, we focused on other years and some smaller simulated outbreaks and concluded that the statistical behavior of the frameworks accurately reflects the biological expectation: the chicken data can serve as a better *explanatory* variable for the number of cases in humans, which is true in non-outbreak weeks as well as outbreak weeks. However, if we are focusing alarm detection only on the human data, this means that the pre-processing model is doing a better job of *explaining* a sudden increase in humans, if a sudden increase in broilers was also observed - an increase in human cases which follows a previous increase in broilers is *expected* by the model, and therefore the residuals delivered to the TADA “discount” that increase to whatever extent it has already been expected by the correlation learned between the two time-series.

The implication is then that if the broiler data is used to *retrospectively explain* behavior in the human data, it *reduces* the number of alarms that the system generates. Instead, we should aim to use the broiler data in a *prospective, predictor* model. Thus, as best exemplified in the outbreak in 2016-2017, where an aberration could be already detected in week 24 in broiler data, while it was week 29 for human data, the One Health Sys should aim to use the broiler data independently to *predict* the weekly counts ahead for human cases.



### Bayesian decision framework

We also investigated using a Bayesian decision framework to combine broiler and human data, which outputs a “Value of evidence” that can be easily combined with a decision theory framework (Andersson et al., 2014). In collaboration with the original author (M.G. Andersson), we extended the original work to accommodate multiple time-series in parallel and examined two different scenarios – one by using the broiler data and human data in parallel, the other by using “posterior probability” of an outbreak from broiler data as a “prior probability” for human data. However, the first scenario also showed the same limitation as the previous explanatory model, as trend in humans were “explained” by the broiler data, thus reducing the sensitivity of alerts. Meanwhile, the second scenario (sequential) warranted further work, particularly in understanding the exact relationship between the two time-series under outbreak and no-outbreak phases, so correct conversion of posterior probability (from broiler data) to prior probability for human data can be performed. However, even if further progress is made on this end, based on the work so far we conclude this approach will not add to the previous approaches in the sensitivity or timeliness. Still, as the extension of Andersson’s previous work to multiple time-series is an important research result of NOVA, we plan to make the statistical framework publicly available in shared code repositories in near future.

### Conclusion & future direction

In this task (Task 3.3 Evaluation of multivariate syndromic surveillance for FBD), we used different SyS approaches to explore three datasets – broiler, human, and weather – separately and also in relation with each other, in search for the most optimal SyS for *Campylobacter* outbreak detection. While no framework investigated so far to statistically combine two sources of data (weather + broiler, weather + human, broiler + human) offered a practical advantage over simply monitoring broiler and human data separately with univariate SyS, breaking down the broiler data into seven major slaughterhouses in Sweden showed a high potential of making more timely alerts when monitored with the total counts. Currently, the One Health surveillance for *Campylobacter* in Sweden relies on regular verbal meetings between authorities, mostly SVA and FOHM, without any automatic alert system in operation at either institution. And while there is delay in reporting for human cases at FOHM to sort out the domestic cases, there is data governance issue around the broiler data with the broiler industry (Svensk Fågel) that blocks SVA from sharing the slaughterhouse-level data (which is restricted to only a few surveillance officials even within SVA). Along with these hindrances, our result shows that there is no benefit of combining the two datasets in a statistical framework. Thus, one proposed way to use the outputs from this work for better One Health surveillance is to set up a separate SyS of *Campylobacter* at SVA and FOHM. At SVA, the SyS can be set up as shown in figure 10, where parallel univariate SyS for each slaughterhouse is shown along with one for the total counts, in addition to one with actual weather data. We expect having a parallel univariate SyS for individual slaughterhouse will be also beneficial to the broiler industry, as they are required to control the prevalence of *Campylobacter* in their premises (farm, slaughterhouse) and early notification of something abnormal in the counts for each slaughterhouse can facilitate more timely and effective control measures at the possible “source”. And if the system makes alert 2-3 weeks in a row, driven by one slaughterhouse (especially with high slaughter batch numbers), then the information could be relayed to the surveillance officials at FOHM that they need to monitor the human cases with increased alertness. At FOHM, the SyS could be set up like Figure 5, showing alerts from both sine + cosine and the actual weather data, so better



understanding of the temporal trend can be easily achieved. If the alert continues both in the broiler and human data in the subsequent week(s), then sample collection can be started at the human side from the regional clinical laboratories, so a joint investigation on the WGS data of *Campylobacter* isolates from humans and broilers can be initiated, along with epidemiological investigations. The exact parameters, like time between steps, will have to be further adjusted based on continuous dialogue between surveillance officials at SVA and FOHM, but overall, we strongly believe that the outputs from this task will promote more effective One Health surveillance and better control of *Campylobacter* in Sweden.

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## 4. SURVEILLANCE OF CAMPYLOBACTERIOSIS IN NORWAY

In Norway, we made a One Health surveillance based on the use of gastrointestinal consultations in human (NorSySS) and Campylobacter surveillance data from broiler flocks. This was based on the availability of the data and the Campylobacter status of chicken flocks is associated with Campylobacter occurrence in humans in the same geographical area (Jonsson M.E. et al, 2010; Jore S. et al., 2010). Also, the NorSySS data was already in daily use for syndromic surveillance for people in Norway and any improvements found can be implemented in the day to day surveillance activities. We combined the data sources with weather data to improve detection and prediction of outbreaks (Jonsson M.E. et al, 2012). We did both univariate and multivariate analysis of the data and we made a dashboard so that the stakeholders could get access to the surveillance data and the results of the models.

### Data sources

#### Gastrointestinal consultations

The Norwegian System for Syndromic Surveillance (NorSySS) was used for the number of outpatient consultations for gastrointestinal symptoms as classified by ICPC-2 diagnosis codes. We included weekly aggregated numbers of consultations per municipality in 5 age groups. The modelling parts discussed in the multivariate section focuses on the 30-65 age group, which is the largest age stratum and avoids the noise potentially introduced by gastrointestinal symptoms in younger age strata. 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 little missingness and mean reporting time is 12 days. NorSySS data was chosen as it is already in daily use for syndromic surveillance for people in Norway. Any improvements in univariate or multivariate surveillance can be implemented in NorSySS and will be of importance for the stakeholders in the day to day surveillance activities.

#### Campylobacter data from broiler flocks

The Campylobacter surveillance data includes the results from the Norwegian surveillance programme for Campylobacter spp. in broiler flocks from 2006 to 2021. From 2006 to 2008 all broiler flocks that were slaughtered before 50 days of age should be sampled. From 2009 and onwards all broiler flocks that were slaughtered between 1 May and 31 October were sampled. The sample is collected by the owner and one sample consists of ten pooled swabs from fresh faecal/caecal droppings. The samples are analysed for Campylobacter spp. by real-time PCR at the Norwegian Veterinary Institute. The data is extracted from the Laboratory Information System at the Norwegian Veterinary Institute. The data is cleaned for registrations where the municipality of the broiler flock is unknown (n = 12) and samples originating from flocks where the species and/or production type were not specified (n = 141). Altogether 39,872 samples from 2006 to 26.06.2021 were included in the data. The samples are aggregated on year, week and municipality. The municipality borders of 2020 was used for aggregating on municipality. For each year, week, municipality, the total number of chicken farms and the number of samples categorized into positive, negative, rejected, and received are reported.



Transfer of data to the Norwegian Public Health Institute once a week is automatized. At the end of each week, data is extracted from the Norwegian Laboratory Information System, cleaned, aggregated and sent automatically from the Norwegian Veterinary Institute to the Norwegian Public Health Institute. Routines to detect if the report fails have been established.

### Weather data

Daily high/low/average temperature and total amount of rain in each municipality from gridded data are 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. We calculate additional transformations of these data including precipitation variation within a week, temperature variation within a week, temperature range within a week, and presence of freezing temperatures. Average weekly temperatures and precipitation are calculated to model the weekly gastrointestinal consultations outcome.

### Univariate Sys

In Norway univariate surveillance is used in the NorSySS to 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 12, 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 model 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.

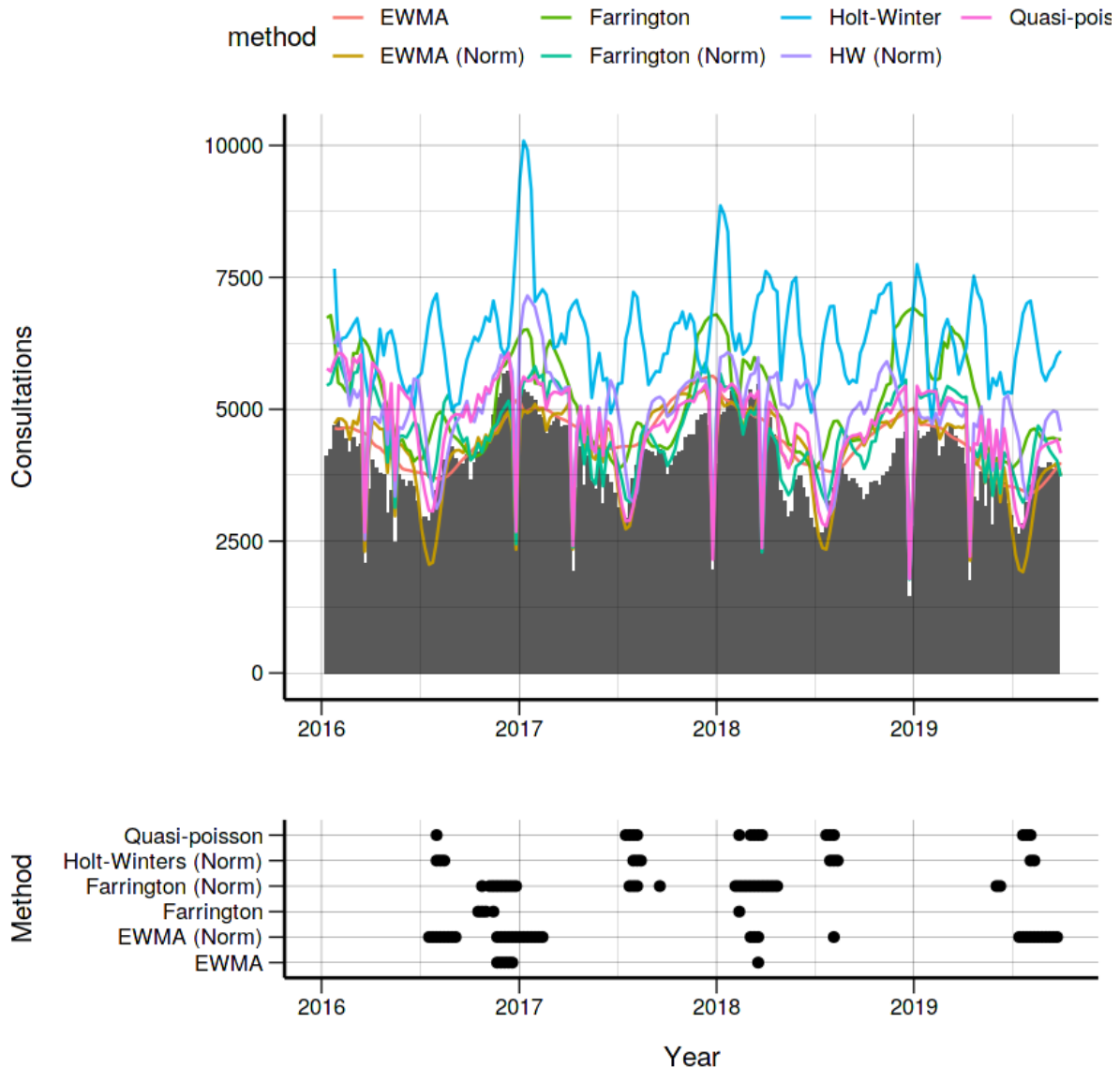


Figure 12: The top chart shows weekly gastro-intestinal consultations and detection thresholds for a range of surveillance algorithms. The second chart shows where the algorithms would raise an alarm due to the number of consultations being above the detection threshold.

### Multivariate Analysis

Two main approaches to multivariate surveillance were identified, we call them explanatory 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.



In certain circumstances 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. We implemented such a risk score using a two-stage approach, whereby we partition variation in the outcome into a “baseline”, or first stage model, and a “deviation”, or second stage model, which are described as follows.

#### First stage model

NorSySS weekly gastrointestinal consultations are used as a proxy indicator for *Campylobacter* case burden, while the total number of weekly physician consultations is the denominator for preliminary adjustment for seasonality, variation due to holidays, etc. From a statistical perspective, gastrointestinal consultations are the negative-binomial distributed outcome with offset of total consultations, explained in a first-stage model by (linear) time, (linear) time since beginning of the corona “era” (approximately week 9 2020), indicator for pre/post corona era, seasonality on 6 degrees of freedom, an indicator for residual holiday variation not explained by the offset formulation, and a municipality-specific random intercept to account for the tendency of some municipalities to have higher gastro proportions than others. Recent iterations of the first-stage model have included 1 week lag autoregressive term, which has been excluded for multiple reasons including a lack of fully populated data within the timeframe needed for the forecast. The holiday status indicator variable has also been dropped because of non-significance in the model—the offset term likely fully controls for gastrointestinal variation due to holiday status for any week being modelled.

#### Second stage model

Two second stage logistic regression models are used to model extreme deviations of the proportion of gastrointestinal consultations from the first-stage, baseline model, where the threshold is variable but currently chosen between 2.1 and 2.3 standard deviations higher than expected, where deviations are calculated municipality-specific. These models are used to predict “outbreak” events on a weekly basis, though deviations at the thresholds we examine should not necessarily be considered outbreaks. The two different models are oriented around 1-week and 2-week forecasts, respectively. The 1-week forecast model uses only 1 or greater (up to 5) week lagged variables, while that for the 2-week model uses only 2 or greater week lagged variables. Variables searched and optimized over via AIC minimization in a variation on backwards-stepwise search included the proportion of farms within a municipality testing positive for *Campylobacter*, total number of farms positive with *Campylobacter*, total number of farms in the municipality, average temperature over the week, average rainfall, within-week temperature variation and range, and an indicator of below freezing temperatures. Variables which showed statistically significant in the forecast models included 2 weeks lagged *Campylobacter* municipality proportion, temperature and precipitation data, and depending on the time frame of the particular forecast model, number of farms in the municipality.

#### Output of the *Campylobacter* prediction model

The first stage model produces a one week forecast of the proportion of gastro consultations (the count of consultations cannot be forecast, because the offset is not known in advance), while the 1- and 2-week second stage models produce a probability of an outbreak event. Both first and second



stage models have strong season trends either because it is explicitly modelled or because of the influence of temperature, precipitation, and *Campylobacter* surveillance covariates, the latter being not monitored in winter. These forecasts currently are made for 43 municipalities in Norway that have regular *Campylobacter* surveillance, but will be expanded as weather-only models are developed which also leverage spatial information.

## Dashboard

The surveillance data and model results are being displayed on a closed R Shiny dashboard.

This surveillance platform contains visualisations of the raw data used for the models (Fig. 13), as well as model results, in the form of a graph of the forecasted ratio of gastro-intestinal consultations and a map of the risk of outbreak per municipality (Fig. 14 and Fig. 15). It also hosts background information on the nature of the project, the data sources and the forecasting process.

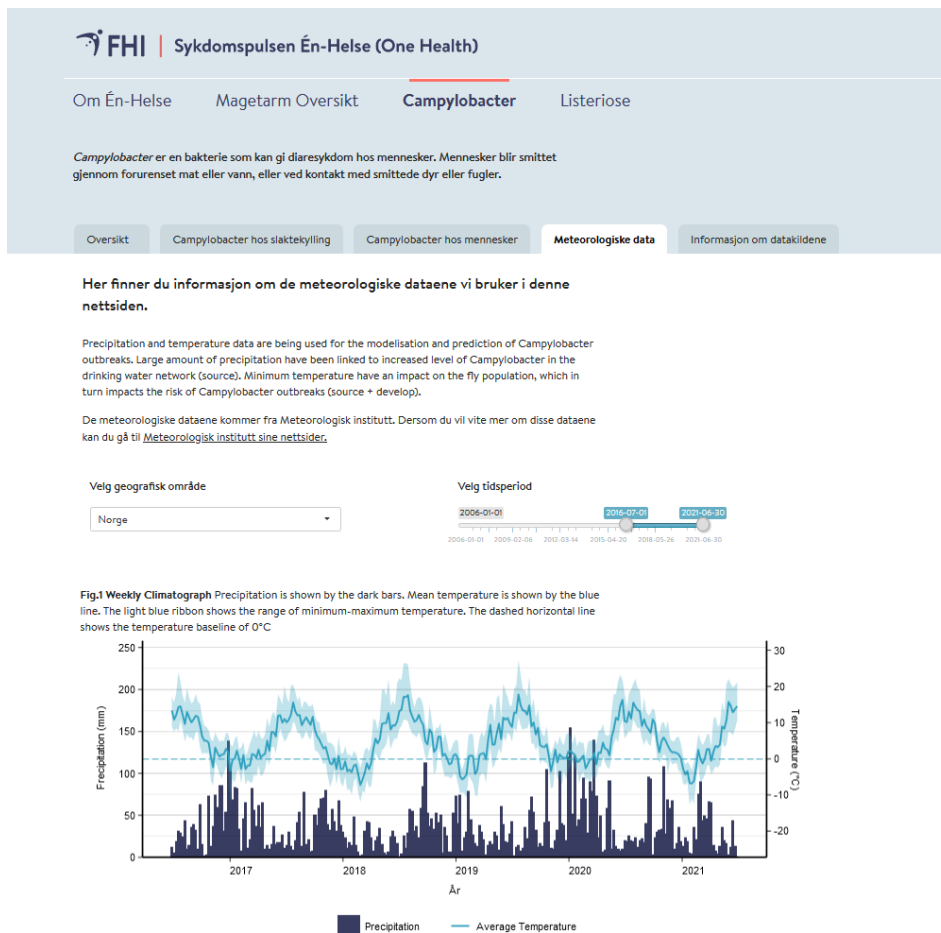


Fig 13. Precipitation and temperature graph as an example of an interactive visualisation of the raw data on the website. The user can choose the location and the time frame of the graph.



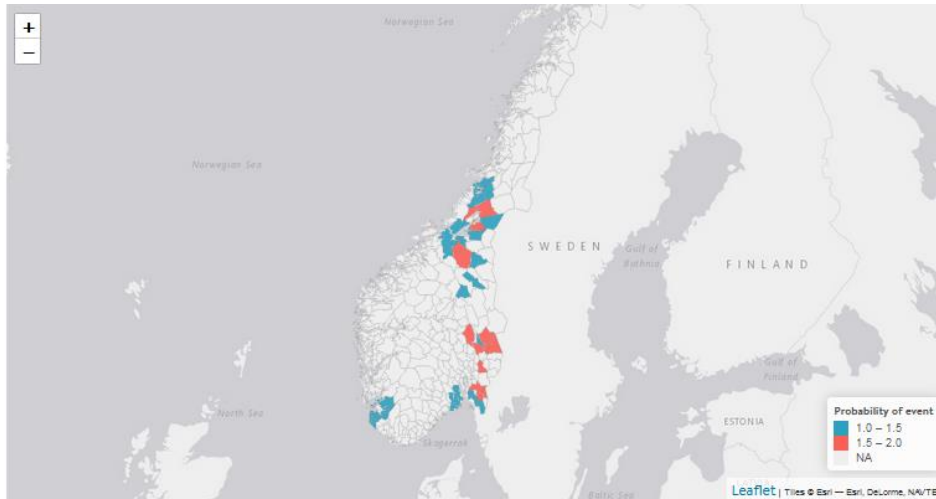


Fig 14. Municipality map of the risk of a gastro-intestinal event occurring one week ahead. These forecasts currently are made for 43 municipalities in Norway that have regular *Campylobacter* surveillance, but will be expanded as weather-only models are developed which also leverage spatial information.

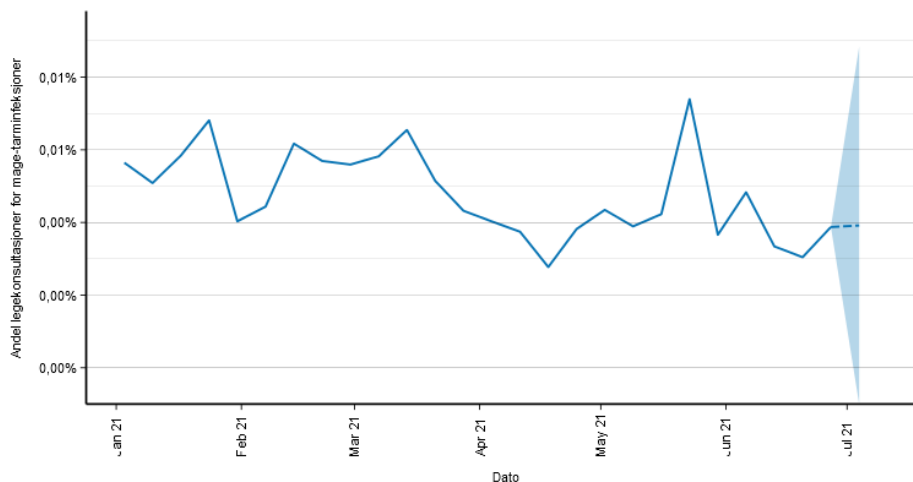


Fig 15. Forecasted ratio of doctor consultations linked to gastro-intestinal symptoms in a given municipality, one week ahead. The user can choose the municipality they wish to display.

### Conclusion & future direction

In Norway, we think the work done in the NOVA project has been very fruitful. The data from the veterinary, meteorological and human side has been explored and there has been development of models and a website for the stakeholders. We had a presentation of the One Health infrastructure and the website in the ASM Sattelite workshop in June 2021.

The covid-19 pandemic has unfortunately delayed the NIPH part of the project a lot. This is because the NIPH team in the NOVA project is the ones also responsible for the Sykdomspulsen infrastructure and website (Including NorSySS) which is one of the main surveillance infrastructures in the NIPH. Therefore, we needed to put a lot of effort into the national Covid-19 surveillance.



The pilot website was originally planned to be accessible to the stakeholders (Norwegian Veterinary institute, The Norwegian Food Safety Authority and The Norwegian Institute of Public Health) in early May 2020, but because of Covid-19 it was postponed to early May 2021. However, due to difficulties regarding the sharing of sensitive data on this platform and the validation of a ROS analysis, and some technical difficulties regarding the implementation of a log-on system, we are currently planning for the website to be accessible and usable by the relevant institutions in August 2021.

The website and the models will continue to live beyond the OHEJP NOVA project and also be extended further in the OHEJP MATRIX project. We have sent an abstract to the One Health in the 21st Century 2021 Conference who is going to be held the 3rd of November 2021 (not received feedback yet) and we are planning to write an article about the One Health surveillance and website.

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