D-JRP6-4.4 Assessment of the spatio-temporal infection dynamics model of Salmonella in low prevalence regions – Evaluation of optimal surveillance strategies

JRP6 - NOVA - FBZ1 - 1st Call

Responsible Partner: SVA

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Contents

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Evaluation of Optimal Surveillance Strategies

1. Background

Salmonella Dublin (*S.* Dublin) is a cattle-adapted *Salmonella* serotype. Infections usually cause clinical disease, increased calf mortality and decreased milk production (Nielsen, 2012a), resulting in substantial economic losses for the farmer (Nielsen, 2013a). *S.* Dublin also has a zoonotic potential, but infection in humans is uncommon. However, when it occurs, consequences are often more severe than those caused by other serotypes (Jones, 2008).

S. Dublin is one of the most common *Salmonella* serotypes infecting cattle populations in Europe (EFSA, 2018). Some European countries have started control programs to reduce the prevalence, or even eradicate it (Bergevoet, 2009; Nielsen 2009). In Sweden, legislated *Salmonella* control was initiated already in the 1960s, including all serotypes and all animal species along the entire chain from feed to food. The program has resulted in a progressive reduction of *Salmonella* prevalence in Swedish cattle, but since the mid-1990s, the number of cattle herds detected within the control program has remained at a low but steady level (SVA, 2018). A national bulk milk screening in 2013 showed that only 1% of dairy herds were positive for *S.* Dublin antibodies, but the occurrence of the infection was strongly clustered. Most of the positive herds were, in fact, located on Öland (an island in the south-east), where the proportion of bulk milk positive dairy herds was as high as 15% (Ågren, 2016).

Species-adapted *Salmonella* serotypes have been shown to be possible to eradicate. However, the sensitivity of the Swedish surveillance system in cattle, which consists mainly of clinical passive surveillance, is considered too low to achieve eradication of *S*. Dublin. One possible way to increase the sensitivity of the surveillance for *S*. Dublin detection could be to perform repeated bulk milk samplings in dairy cattle (Warnick ,2006; Ågren, 2016)

In order to evaluate potential surveillance strategies, both the within- and between-herd transmission dynamics of *S.* Dublin infection need to be taken into account. Previous work in this work-package has resulted in a disease spread model achieving probable results at either regional level or within herd level, but not for both levels at the same time. The reason for this is the combination of an overall low prevalence of *S.* Dublin in Sweden and a pronounced cluster of positive herds in one region.

2. Objective

The aims of the project were:

a) To complete the disease spread model in the Swedish context.
b) To evaluate different surveillance options.
c) To find direct risks for human salmonellosis using Danish data.

3. Material and methods

A) SimInf framework

The disease spread modelling was performed in the R package SimInf (Widgren, 2019). The SimInf framework is designed to efficiently simulate stochastic disease spread models in a large network of interconnected farms. The framework integrates infection dynamics in each farm as continuous-time Markov chains (CTMC) using the Gillespie stochastic simulation algorithm (Gillespie, 1977) and incorporates available data such as births, deaths or movements as scheduled events.

B) Within-herd spread

The spread of infection among the animals in a herd was modelled as a compartmental Susceptible-Infected-Carrier-Recovered model based on environmental transmission ($SICR_E$). These compartments stratify the population into four health states: healthy individuals capable of acquiring the infection (Susceptible, S); infected individuals capable of transmitting the infection (Infected, I); long term persistently infected individuals capable of transmitting the infection at a low rate (Carrier, C); healthy recovered individuals who developed immunity against the infection (Recovered, R). The four health states were further subdivided into three age groups: calves (< 6 months), young stock (6 - 30 months) and adults (> 30 months), to capture age-related differences in infection dynamics within the host (Nielsen, 2012b; Nielsen 2013a; Nielsen 2013b).

The faecal-oral route of transmission of Salmonella, where susceptible individuals get the infection from the environment contaminated by faeces of infectious and carrier animals, was modelled by means of a time dependent environmental infectious pressure variable, uniformly distributed within each herd. It represents the number of bacterial cells per m^2 at any point in time and depends on the bacterial load shed by infected and carrier animals per surface area, and on the rate of bacterial decay (i.e., decimal reduction time) in the environment. Based on the results of Ågren et al. (2016) on the risk factors for a dairy herd to be infected by S. Dublin, the environmental infectious pressure was further set to increase proportionally to the number of infected holdings in the neighbourhood.

Disease seasonality was incorporated into the model by using the approach described by Widgren (2018). Briefly, meteorological data with the average temperature at the geographical location of each holding was used to incorporate four seasons (spring, summer, fall and winter) and adjust the rate of the bacterial decay in the environment by season.

C) Between-herd spread

The spread of infection between the cattle herds was modelled deterministically based on the recorded event data described above. The raw data was converted into four categories of events – exit, enter, ageing and transfer – as described elsewhere (Widgren, 2016). The exit event happens when animals leave a holding due to slaughter, euthanasia or export. The enter event includes births and imports. The ageing event happens the day animals change age group (i.e., from calf to young stock or young stock to adult). The transfer event occurs when animals are moved from one holding to another. Another, albeit minor, transmission route is via local spread between holdings. To capture that most of the positive herds were located on Öland, an "Öland effect" was included in the model by increasing the local spread in all holdings located on this island.

Simulations started the first day of recorded data (01/07/2005) and ended on the last one (31/12/2013). After every day of the simulation, the number of animals in each health compartment of each age group and herd was updated according to the event database. In the case of enter events, the reported number of animals were added to the susceptible compartment of the relevant age group. In case of ageing events, calves or young animals were removed from their current health compartment and added to the same health state in the next age group (i.e., young stock or adult, respectively) of the same herd. In case of exit events, animals were removed from the herd according to the reported age of the animal in the exit event, and randomly selected health states. In the case of transfer events, animals were removed from the sending herd according to the same procedure as an exit event and added to the receiving herd in the corresponding age-specific health compartments.

D) Evaluation of surveillance strategies

The detection of dairy herds infected with *S*. Dublin in Sweden currently mainly relies on passive surveillance (i.e., mandatory investigation of clinical symptoms with reporting of positive cases), meaning that there is no historical data about the disease status of most herds, except a national screening performed on 2013. Therefore, the aforementioned disease spread model was used to generate data for quantitative assessment of surveillance performance. The simulation produced a series of datasets consisting of the number of individuals in the age-specific disease compartments in each holding at weekly intervals. A dairy herd was considered to be infected when it hosted at least one infectious animal.

Two alternative surveillance options were then explored: one conventional and one risk-based. The risk definition was based on the geographical location of the cattle herds, as the occurrence of *S*. Dublin is strongly clustered in Sweden. The high-risk area included all the farms located in the island of Öland and in two municipalities of Skåne county (Figure 1), where herd outbreaks constantly happen since 2008 (Ågren et al., 2015). The remaining herds in all other parts of Sweden were considered at a lower risk. Conventional surveillance involved a high intensity blanket sampling, where all dairy herds were sampled every third month, as currently done in Denmark (Nielsen, 2009). In the risk-based design, three strategies with different coverage and intensity were explored. In risk-based strategy 1, dairy herds in the high-risk stratum were sampled every third month while those in the low-risk stratum were sampled once a year, during the 3rd quarter (i.e., at the peak of infection). Strategy 2 was equal to strategy 1 with the exception that the sampling of herds in the low-risk stratum happened during the 4th quarter (i.e., at the peak of seroconversion). Strategy 3 included quarterly bulk milk sampling of all dairy herds in the high-risk area only. A summary of the surveillance strategy under evaluation is provided in table 1.

The surveillance activities of the different strategies were simulated deterministically on top of the stochastically simulated disease transmission data. At specific sampling points, it was checked whether the proportion of recovered adults (i.e., representing the bulk milk pool) in each herd exceeded the detection threshold of 15% (Nielsen, 2003). When > 15% of the cows have antibodies the bulk milk sample is likely to test positive. Therefore, whenever this happened, it was considered to be a positive bulk milk test result. It was assumed that a perfect confirmatory test was applied in bulk-milk positive herds to confirm or rule out the infection. If the detection happened in truly infected holdings, i.e., at least one infectious animal present in the herd, then they were considered to be true positive. Truly infected herds were considered to be put under control and further removed from the population

under surveillance four weeks after the initial detection (i.e., to allow time for confirmatory testing and restrictions). If the detection happened in non-infected holdings, then they were considered to be false positive and further subjected to surveillance activities.

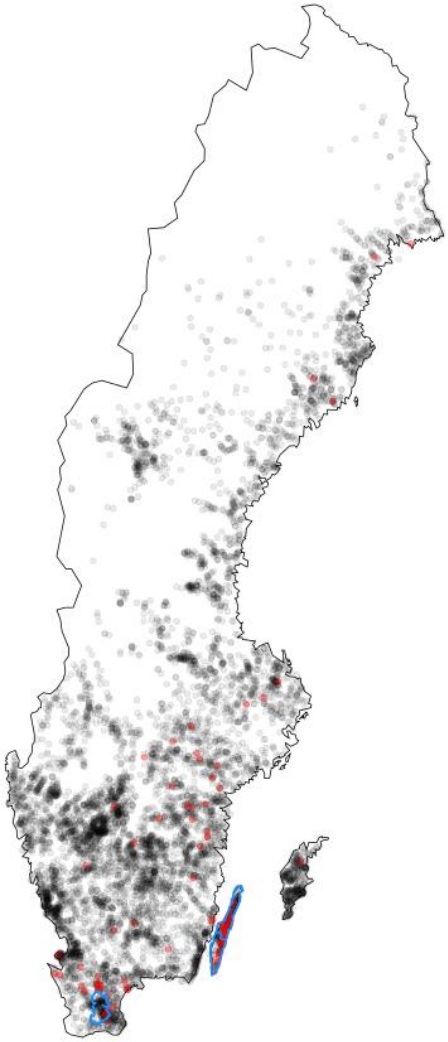


Figure 1. Geographical location of the Swedish dairy farms that were active in 2013. Red dots represent infected farms, while black dots represent uninfected farms. Intensity of shade reflects farm density. Blue contours indicate the high-risk area as defined in the risk-based surveillance approach.

Table 1. Brief description of the surveillance strategies under evaluation.

Surveillance option	Brief description
A) Traditional	All dairy herds are sampled once every quarter of the year
B.1) Risk-based strategy 1	All dairy herds in the high-risk area are sampled once every quarter of the year. All dairy herds in the low-risk area are sampled once a year, during the third quarter.
B.2) Risk-based strategy 2	All dairy herds in the high-risk area are sampled once every quarter of the year. All dairy herds in the low-risk area are sampled once a year, during the fourth quarter.
B.3) Risk-based strategy 3	Only dairy herds in the high-risk area are sampled once every quarter of the year.

The effectiveness of the alternative surveillance strategies was estimated in terms of the detection fraction, i.e., the proportion of truly infected herds detected by surveillance, whereas their efficiency was estimated in terms of the number of samples required to detect one infected herd.

4. Results and discussion

A) Disease spread model

Simulation model code is available from https://github.com/SVA-SE/NOVA.

The modelled proportion of infected dairy herds over the study period is shown in **Fel! Hittar inte referenskälla.**. After an initial adjustment of the artificially seeded infections (i.e., burn-in period), the herd level prevalence stabilizes around 1%, mimicking the current prevalence in Sweden since 1995 (SVA, 2013). The inclusion of the "Öland effect" allowed to reproduce the higher herd-level prevalence (around 15%) in this part of the country (Figure 3). Despite previous attempts, no specific risk-factors explaining the endemic occurrence of *S.* Dublin at Öland have been identified (Ågren et al., 2017). However, there are still indications that the risk of disease spread is higher in Öland than in other regions. Öland is a region with a particular geology, vegetation, history and culture, which may affect management procedures in the cattle herds. For example, shared pastures with mixing of animals from several herds is frequently occurring in Öland, but not in other regions (Ågren et al., 2017). And when pastures are not shared, they may constitute of long strips of land next to each other, as a result of non-shifted land in this region. This is uncommon in other regions and allows for over the fence contacts between animals. Pastures often border to the sea (Baltic Sea), which probably provides an opportunity for efficient disease spread when animals drink from shallow water contaminated with manure. The long shallow shores also enable animals to move around the outer end of the fence, resulting in mixing of animals from different herds. The theory that there a specific risk-factors for disease spread present on Öland is also supported by the fact that other infections than *S.* Dublin have been shown to be more common in cattle in Öland than in cattle in other regions (Winsö et al., 1980; Åsenius et al., 2005; Nusinovici et al., 2015). Based on this, we find it reasonable to add an Öland factor in our disease spread model for *S.* Dublin.

The within-herd infection dynamics by age group is summarized in **Fel! Hittar inte referenskälla.**. It clearly shows a seasonal trend, as a consequence of the different rate of bacterial decay in different seasons. In particular, the within-herd prevalence peaks in the third quarter of the year, and is higher for calves than for young and adult animals (**Fel! Hittar inte referenskälla.**, top row). On the other hand, the seroprevalence peak is shifted by three to five months, depending on the age (**Fel! Hittar inte referenskälla.**, bottom row). While the between-herd disease dynamics is mostly driven by animal movement, and therefore depends on the data, the within-herd dynamics depends on the parameters chosen for the model. Most of the parameters were considered age-specific and all except the uptake rate (i.e., the indirect transmission rate of the contaminated environment) were derived from literature. Given that our model did not assume direct transmission, it was not possible to translate the value of the *infection rate* parameter found in literature into our uptake rate. We then fixed all the other parameters in the model and derived the uptake rate by trial and error, assuming herd level endemic equilibrium.

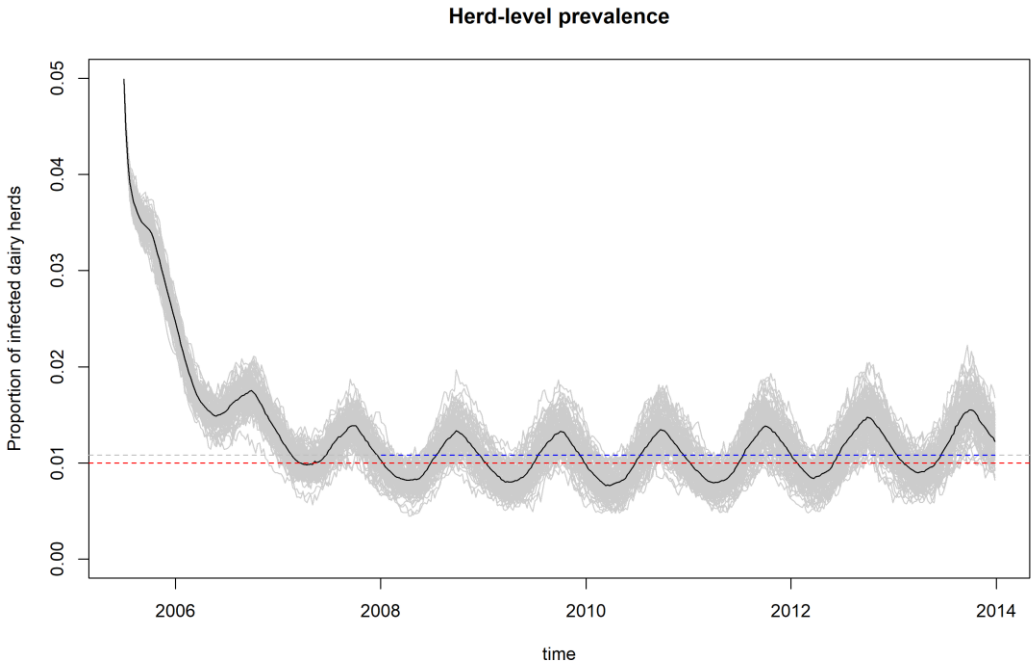


Figure 2. Simulated proportion of infected dairy herds over the years. Grey solid lines represent each simulation (n=100). The black solid line represents their average. The blue dashed line represent the average from 2008 onwards (the first years were excluded from the calculation as burn-in phase). The red dashed line represents the expected value for herd level prevalence.

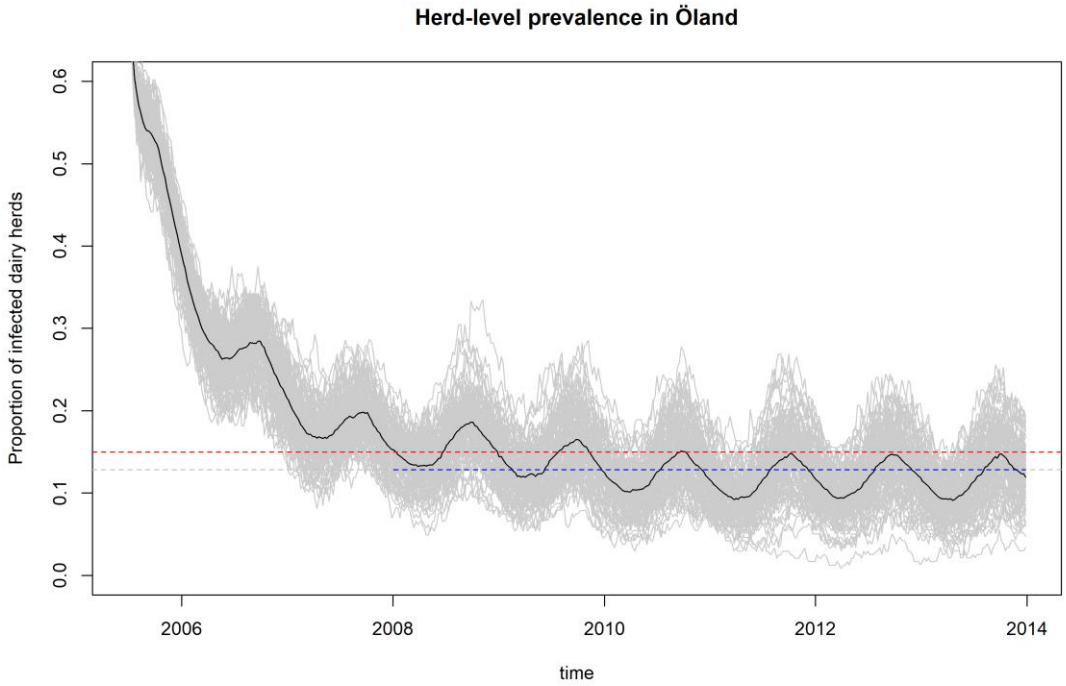
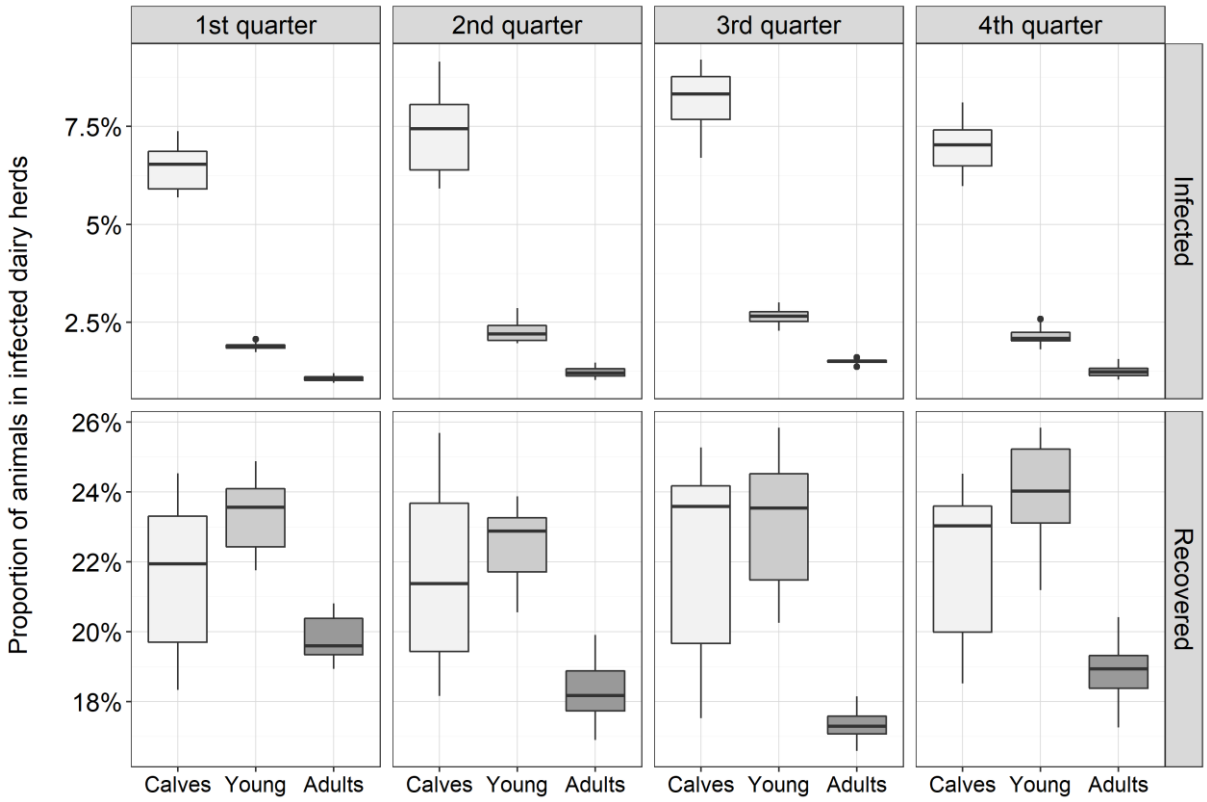


Figure 3. Simulated proportion of infected dairy herds in the Öland island over the years. Grey solid lines represent each simulation (n=100). The black solid line represents their average. The blue dashed line represent the average from 2008 onwards (the first years were excluded from the calculation as burn-in phase). The red dashed line represents the expected value for herd level prevalence.

Figure 4. Proportion of infected animals (i.e., prevalence) and recovered animals (i.e., seroprevalence) in infected dairy herds by age group and quarter of the year. Mean of 100 simulations using data from 01-01-2008 to 31-12-2013.



B) Evaluation of surveillance

Results of simulated surveillance activities are summarized in Table 2 and Figure 5. The proportion of infected dairy herds was around 1%, with seasonal variations (Figure 5, black line). The conventional surveillance involved 29,095 bulk milk samples for one year, detecting 25% [20-29%] of the truly infected herds (Table 2). The risk-based surveillance strategies where all dairy herds were sampled once a year in addition to quarterly samples of the high-risk stratum (strategies 1 and 2) achieved a detection fraction of 14% [10-19%] with 8260 samples and 18% [14-23%] with 8403 samples, depending whether the blanket sampling happened during the third or the fourth quarter of the year, respectively. The risk-based surveillance strategy targeting only at herds in the high-risk area achieved a detection fraction of 11% [6-15%] exploiting 1274 samples.

The detection fractions achieved by the various surveillance strategies were lower than expected, especially for the conventional surveillance. For comparison, in Denmark, where a surveillance system like our conventional surveillance scenario is currently in place, the sensitivity of the testing strategy in infected herds has been estimated to around 95% (Warnick et. al., 2006). When all herds, as in this scenario is tested, the detection fraction and sensitivity can be expected to be comparable. One explanation could be that the disease spread model failed to properly mimic the within-herd infection dynamics. The proportion of infected adults in the simulated data was rather low and consequently the proportion of recovered adults contributing to the bulk milk pool was also low. This could have negatively impacted the outcome of the bulk milk test, which was deemed to be positive when at least 15% of the adult cows had recovered at the sampling occasion. Therefore, we can consider this evaluation as a worst-case scenario. Nevertheless, for the purpose of comparing surveillance

strategies, the precision of the simulated within-herd infectious dynamics is of minor importance, as it is the same for all strategies. We can thus consider the relative comparison among strategies unbiased.

While the conventional approach allowed the detection of more infected herds, it involved 3.5 times the number of samples used by the risk-based approach with less intense sampling of the population at lower risk (strategies 1 and 2). This resulted in a lower efficiency, as it required on average 353 samples to detect one infected herd, versus the 136 samples/detection of the risk-based strategy 2 (Table 2).

Figure 5 shows that at the end of one year of surveillance activities the proportion of infected herds is 0.65% when traditional surveillance is adopted (blue line) and 0.69% in case of risk-based surveillance with different sampling intensity according to the risk (strategy 2) (yellow line). For comparison, if no surveillance activities aimed at detecting and removing infected herds is in place, the proportion of infected herds after one year would be 1.22% (black line). Risk-based surveillance sampling the low-risk stratum during the third quarter of the year (strategy 1) was less efficient the counterpart where the blanket sampling happened during the fourth quarter (strategy 2). A possible explanation could lie in the delayed onset of antibody peak compared to the peak of infection, resulting in a higher proportion of false negative test results. Risk-based surveillance targeting only the herds in the high-risk area, although it was associated to the lowest number of samples required to detect one infected herd (i.e., 42), only detected a small proportion of the infected herds, as it completely missed a substantial part of the population.

Other aspects, in addition to the above mentioned, will be important to consider when deciding on surveillance strategy. For example, the consequences of delayed detection in an endemic region may not be as severe delayed detection of infected herds in a cattle dense area where the infection has not previously been present.

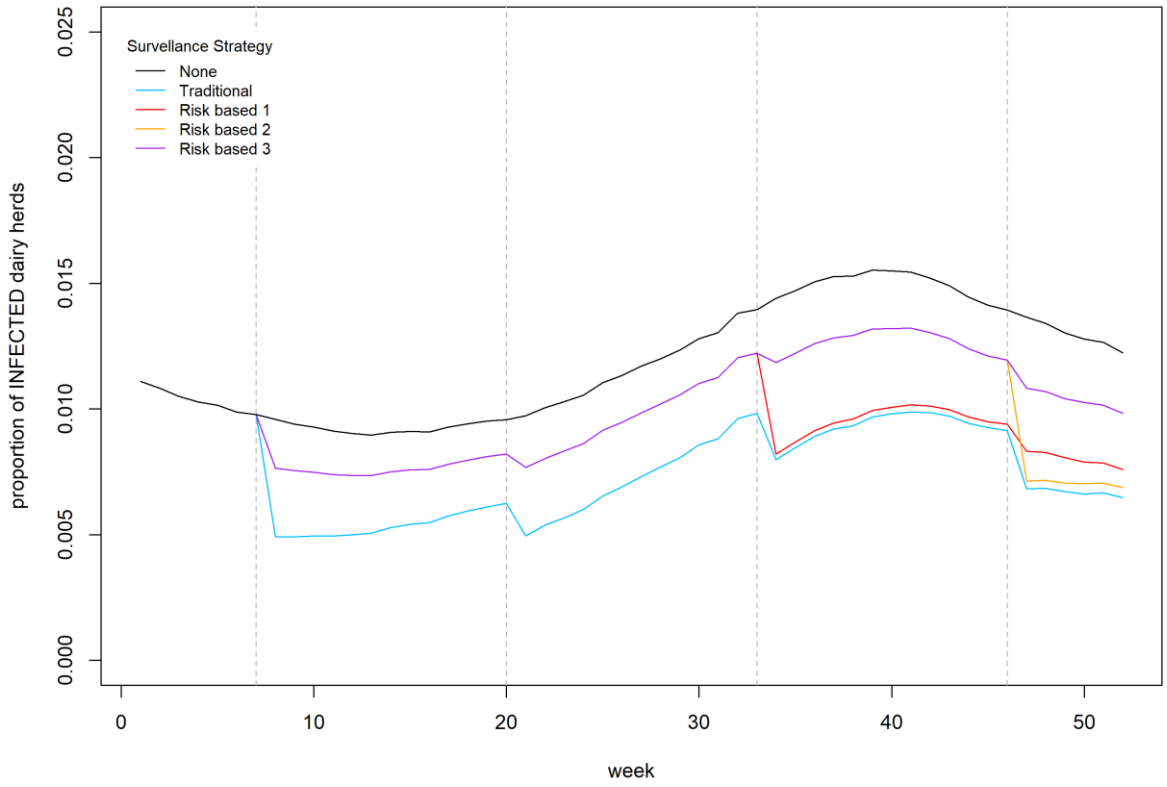


Figure 5. Proportion of infected dairy herds when no surveillance is in place (black line) and after successful detection and removal due to surveillance activities (other lines). Average of 100 simulations.

Table 2. Comparison of the performance of traditional and-risk based surveillance strategies over one year.

	Traditional surveillance		Risk based surveillance					
			Strategy 1		Strategy 2		Strategy 3	
	median	95%CI	median	95%CI	median	95%CI	median	95%CI
Active herds	7448	[7448 - 7448]	7448	[7448 - 7448]	7448	[7448 - 7448]	7448	[7448 - 7448]
Infected herds	336	[264 - 400]	336	[264 - 400]	336	[264 - 400]	336	[264 - 400]
Sampled herds	29095	[29044 - 29143]	8260	[8223 - 8297]	8403	[8367 - 8435]	1422	[1386 - 1455]
Test+ herds	220	[166 - 263]	113	[83 - 146]	136	[97 - 167]	80	[50 - 109]
True Positive (TP)	82	[58 - 110]	47	[30 - 69]	62	[40 - 84]	34	[19 - 51]
False Positive (FP)	97	[72 - 120]	50	[32 - 69]	64	[45 - 83]	38	[21 - 52]
False Negative (FN)	171	[129 - 211]	92	[65 - 123]	101	[74 - 141]	64	[40 - 93]
True Negative (TN)	28705	[28590 - 28841]	8052	[7982 - 8140]	8168	[8096 - 8250]	1274	[1211 - 1358]
Sensitivity (Se)	0.33	[0.28 - 0.38]	0.33	[0.26 - 0.43]	0.38	[0.3 - 0.45]	0.35	[0.27 - 0.44]
Specificity (Sp)	1	[1 - 1]	0.99	[0.99 - 1]	0.99	[0.99 - 0.99]	0.97	[0.96 - 0.98]
Detection fraction[1]	0.25	[0.2 - 0.29]	0.14	[0.1 - 0.19]	0.18	[0.14 - 0.23]	0.11	[0.06 - 0.15]
Samples per detection[2]	353	[264 - 498]	176	[120 - 277]	136	[100 - 211]	42	[27 - 77]

[1] proportion of truly infected herds that are detected over one year

[2] average number of samples needed to detect one infected herd over one year

C) Risk factors for human salmonellosis

It takes a lot of time and effort to apply disease models developed for one region to another region or to apply disease data collected in the region to the other regions with different environmental settings. Sometimes it may not be appropriate. In addition, sharing disease data that contains sensitive information between institutions is challenging. Therefore, SVA and SSI tried to find a disease that both institutes have a common interest and can collect human cases and other relative data (e.g., VTEC/EHEC), instead of sharing human case data. In the revised research plan, the main objective for the study of direct risks to human cases is to exchange research methods rather than direct data exchange between the two institutes, which will be carried out the third year.

5. Conclusion and future direction

The results showed that the conventional surveillance would lead to a higher detection fraction than the risk-based design. This can be explained by the fact that (i) the only difference between the two strategies (strategy A vs. B1 and B2) laid in the frequency of sample collection, which was higher in the conventional approach, resulting therefore in a higher chance of case detection, and (ii) high-risk stratum in the risk-based approach was associated to a high-risk ratio, but the risk fraction (i.e., the proportion of the population in the high-risk stratum) was very low (5%), making the high performance of the surveillance in such stratum to contribute only minimally to the overall performance of the surveillance component. However, a risk-based strategy sampling herds at high risk every third month and herds at low risk once a year during the fourth quarter could be a good compromise. In fact, it would allow to detect a slightly lower proportion of infected herds (18 vs. 25%) at a substantially lower cost (136 vs. 356 samples/detection). Also, the purpose of detection needs to be considered when deciding on which strategy to use.

For the study of direct risks to human cases, the disease of interest is replaced from salmonella to VTEC/EHEC while maintaining the large frame ‘spatial mapping/spatial analysis.’ The main direction of the work task will be to explore methods to examine the relationship between EHEC human case and cattle farm location. The methodology can be applied to other diseases or other countries.

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