Optisample: Open web-based application to optimize sampling strategies for active surveillance at herd level. Porcine Respiratory Reproductive Syndrome as a working example

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Abstract

Design of efficient active surveillance sampling schemes is challenging because optimum surveillance strategies may differ depending on the epidemiological conditions of the farm including infection status, structure, management, or resources for conducting samplings. Here, we present an open web application, referred as 'Optisample', designed to optimize farm sampling strategies for early detection of pathogens or to substantiate freedom of infection considering also costs of testing. In addition to herd size, estimated prevalence, test sensitivity, and desired level of confidence, the model takes into account the risk of disease introduction at different stages of the production cycle, the structure of the herd, and the procedures used to select the samples over time. We illustrate the functionality and capacity of 'Optisample' through its application to active surveillance of porcine reproductive and respiratory syndrome

virus (PRRSv) in hypothetical swine herds subjected to disparate epidemiological conditions. Diverse sampling schemes for each farm are simulated and the most cost-effective strategy is estimated for each farm based on the outputs of the model. The algorithms evidence the importance of considering both the epidemiological context and the process of sampling selection to demonstrate freedom of disease. This approach demonstrated here for PRRSv may be easily extended to other animal disease surveillance systems.

Keywords

Freedom from disease; Surveillance; Sampling design; Open Web Application; PRRSv

Introduction

The confidence in freedom of infection is often derived from the absence of clinical signs and negative lab results from consecutive samplings conducted at farm level [1, 2].

To implement effective and sustainable systems for animal disease surveillance at farm level it is crucial for the producers to identify cost-effective strategies of sampling. However, there are infinite schemes to conduct these samplings and the optimum strategy may differ between herds depending on their infectious status for a given disease, their structure and management, the epidemiological context and the capability of conducting these samplings. As a result, in order to enhance active surveillance of important animal diseases, practical methods to identify efficient sampling strategies taking into account the context of the herd and costs would be useful. The case of the active surveillance conducted for the porcine reproductive and respiratory syndrome virus (PRRSv) may serve to exemplify this need.

Since its first recognition in 1987 PRRSv has been wide spread in many countries throughout the world, causing a devastating economical impact to the swine industry.

The PRRSv causes important losses due to an increase of mortality, decrease of growth performance in growing pigs, and abortions, stillbirths and premature farrowings in breeding herds. Moreover PRRSv is also associated with respiratory disease, pyrexia, and anorexia at all ages [3]. PRRSv control and elimination at herd and regional level requires important efforts. PRRSv elimination programs require continuous testing and culling of positive animals in breeding herds, whole herd depopulation and repopulation with negative pigs, herd closure and rollover, interrupting the introduction of incoming replacement for at least 6 months with elimination of seropositive pigs over time [4].To facilitate its control and elimination at the regional and national level, the American Association of Swine Veterinarians and the United States Department of Agriculture PRRS-Coordinated Agricultural Project defined a standardized terminology to classify the status of swine herds considering both PRRSv shedding and exposure [5].

The main aim of this work is the creation of 'Optisample', a flexible and accessible modeling tool for stakeholders and veterinarians to identify cost-effective sampling strategies of active surveillance according to the epidemiological context of each herd. We demonstrate its application for active surveillance of PRRSv in different farm types.

Materials and Methods

'Optisample' is an expanded version of the models proposed by Cannon (2002) [6] and Martin (2007, 2008) [7-9] to substantiate freedom of disease at farm level. The innovations incorporated in this model allows also to assess the influence of the sampling selection process and to compare the efficacy of different sampling schemes to demonstrate freedom from infection and costs of testing.

Inputs and outputs of 'Optisample'

The user includes as inputs: the herd size, the probability of being infected at arrival, the risk of incursion between consecutive samplings, the degree of relatedness between sampled groups, the expected prevalence to detect, the sampling scheme, the sensitivity of laboratory tests and the price of each individual test.

'Optisample' provides as outputs: the cost of testing and the probability of being free of disease after each sampling and overall period given that all the tests result negative. This probability is expressed as Area under the Curve (AUC). The model simulates two scenarios for each farm:

1. Where the group sampled is representative of the herd and is always the same group,
2. Where the groups sampled vary over time.

The parameterization used in 'Optisample' is shown in table 1.

	CODE	PARAMETER	RANGE
INPUTS			
Demographic and epidemiologic context			
Herd size	N	Integer	0 - 10000
Initial risk of disease infection	$Pr_{InitInf}$	Pert(min_{Init}, $mode_{Init}$, max_{Init})	0 – 1
Risk of disease incursion between consecutive samplings	$Pr_{InfBw_{Samp}}$	Pert(min_{BS}, $mode_{BS}$, max_{BS})	0 – 1
Degree of relatedness among sampled groups	ICC_{BG}	Pert(min_{BG}, $mode_{BG}$, max_{BG})	0 – 1
Sampling strategy			
Design prevalence	P*	Fixed percentage	0 – 1
Sample size of consecutive samplings	n_T	Sequence of 12 integers	0 – 100
Diagnostic test sensitivity	se_t	Pert(min_t, $mode_t$, max_t)	0 – 1
Unit price for lab test	$Price_t$	Integer	0 – 10000
OUTPUT			
Pr. free of infection after sampling T	$Pr_{Free_{SampT}}$	Pert(min_T, $mode_T$, max_T)	0 – 1
Pr. free of infection over all period sampling on the same group	AUC_S	min_S -md_S -max_S	0 – 1
Pr. free over all period sampling different related groups	AUC_d	min_d - md_d -max_d	0 – 1
Cost of testing	$Cost_t$	Integer	0 – 999999

Table 1. Summary of the inputs and outputs of 'Optisample'

Operation modeling

In this approach we assume that if a positive sample were detected, this result would be investigated further to discard any false positive outcome; on this basis we consider that the specificity will be effectively 100%.

Steps of the calculation process:

1. At the initial moment the user introduces a minimum, most likely and a maximum value for the probability that the animals are infected, abbreviated as $Pr_{InitInf}$.

These values can be determined based on retrospective data available from its origin and the reliability on this information. Accounting for the uncertainty and variability of these values the $Pr_{InitInf}$ is defined as a continuous PERT distribution with possible values within a range between 0 and 1.

$$Pr_{InitInf} = \text{PERT}\,(min_{Init}, mode_{Init}, max_{Init}, \lambda = 4) \quad (1)$$

2. At time T=1 a first sampling (Samp1) is conducted on a number of animals (n1) with a certain diagnostic test.

The probability of detecting at least one infected animal in the Samp1 if the herd was infected (Se_{Samp1}) is estimated taking into account: the expected prevalence (P*), the size of the susceptible population (N), the number of sampled animals at T1 (n_1) and the sensitivity of the diagnostic test (se_t).

The user may define the value of P* between 0 and 1 based on the market-requirements or accreditation purposes. The se_t can be determined based on the information provided by the veterinary diagnostic laboratory that processes the samples or by available scientific references. Frequently, the se_t is estimated from comparative analyses conducted on a panel of samples representative of the population using the screening test and a gold standard test.

This value is expressed as a PERT distribution with possible values within a range between 0 and 1.

$$se_t = \text{PERT}(\min_t, \text{mode}_t, \max_t, \lambda = 4) \quad (1)$$

The Se_{Sampl1} is calculated using a modified hypergeometric distribution based on the approach proposed by Cameron and Baldock (1998) [10]. The Se_{Samp1} is expressed as:

$$Se_{Samp1} = 1 - \left(1 - \frac{n_1}{N - \frac{(N \times P^* \times se_t)^{1/2}}{2}}\right)^{N \times P^* \times se_t} \quad (2)$$

3. If all the samples of the Samp1 test negative, the model estimates the probability of the farm being free ($PrFree_{Samp1}$) using a bayesian inference approach that considers the $Pr_{InitInf}$ and the Se_{Samp1}

$$PrFree_{Samp1} = \frac{1 - \mathrm{PrInitInf}}{\left(1 - Se_{Samp1}\right) \mathrm{x\ PrInitInf}}$$

(3)

4. Once the $\mathrm{PrFreeSamp1}$ is computed the model estimates the probability of being infected ($\mathrm{PrInfAf_{Samp1}}$).

$$\mathrm{PrInfAf_{Samp1}} = 1 - PrFree_{Samp1}$$

(4)

5. However during the production cycle there is still risk of incursion; and this risk affects the probability of being free of disease. To model this parameter, it is included the probability of disease incursion between consecutive samplings ($\mathrm{PrInfBwSamp}$) as input.

This risk depends on trade movements, biosecurity measures, proximity to other infected farms and environmental viability. Here, the exact value of $\mathrm{PrInfBw_{Samp}}$ is variable and uncertain too and is incorporated as a PERT probability distribution with possible values within a range between 0 and 1. These values may be defined based on risk assessment analysis, models of spread among farms or historical data of outbreaks occurred in the herd.

$$\mathrm{PrInfBw_{Samp}} = \mathrm{PERT}\left(\mathrm{min_{BS}}, \mathrm{mode_{BS}}, \mathrm{max_{BS}}, \lambda = 4\right)$$

(5)

6. Using the $\mathrm{PrInfBw_{Samp}}$ and the $\mathrm{PrInfAf_{Samp1}}$ the model computes the probability that the herd is infected before the second sampling ($\mathrm{PrInfBf_{Samp2}}$).

$$\mathrm{PrInfBf_{Samp2}} = \mathrm{PrInfBw_{Samp}} + \mathrm{PrInfAf_{Samp1}} - (\mathrm{PrInfBw_{Samp}} X \mathrm{PrInfAf_{Samp1}})$$

(6)

7. For each sampling conducted over the production cycle (SampT) the model develops an analogous process to the previous calculations (steps 2-6). The process computes recursively the values of probability of being infected before conducting the next sampling T ($\mathrm{PrInfBf_{SampT}}$

106), the sensitivity at herd level (Se_{SampT}) and the probability of being free given all the
107 samples result negative ($PrFreeAf_{SampT}$). To calculate these values we use: the $SeSampT\text{-}1$,
108 the $PrFreeAf_{SampT\text{-}1}$ and the $PrInfBf_{SampT}$. Overall, the probability of being infected before
109 the next consecutive sampling T ($PrInfBf_{SampT}$) is the result of being infected after the
110 previous sampling ($PrInfAf_{SampT\text{-}1}$) or becoming infected between consecutive samplings
111 ($PrInfBw_{Samp}$) and is expressed as:

$$PrInfBf_{SampT} = PrInfBw_{Samp} + PrInfAf_{SampT-1} - (PrInfBw_{Samp} X PrInfAf_{SampT-1}) \quad (7)$$

112

113

114 In the same way, the probability of detecting at least one infected animal in a sampling T
115 (Se_{Samp}) is calculated as:

$$Se_{SampT} = 1 - \left(1 - \frac{n_T}{N - \frac{(N \times P^* \times se_t)^{1/2}}{2}}\right)^{N \times P^* \times se_t} \quad (8)$$

116

117 And the probability of being free after a sampling T ($PrFreeAf_{SampT}$) given that all the
118 samples at T-1 tested negative is computed as:

$$Pr Free_{SampT} = \frac{1 - PrInfBf_{SampT}}{(1 - Se_{SampT}) \times PrInfBf_{SampT}} \quad (9)$$

119

120 8. These calculations are applicable if the consecutive samplings are conducted on the same
121 group selected randomly. However due to structure and management of the farm, the
122 samplings sometimes are performed in different groups of animals. To assess the influence of
123 the sampling selection for these cases, the model includes a parameter to describe the degree
124 of relatedness between sampled groups. This parameter is equivalent to the statistics named

intraclass correlation (ICC_{BS}).'Optisample' provides two different outputs based on the selection process conducted across samplings.

In the first output, by default, the model estimates the $PrFree$ assuming that in the event of infection this will be homogeneously distributed across the whole farm. This assumption is valid when all animals of the farm share the same environment and management, or when the sampling is conducted over time in unique and representative group of animals. For these cases the information extracted from a specific sampling can be inferred to the rest of the herd and the ICC_{BG} is equal to 1.

In the second output the model takes into account that the spread within the farm may differ among different groups of animals, depending on the herd structure and management and biosecurity measures for each group. In this case the estimates can be only partially inferred to the other groups according to the value of ICC_{BG}.

The value ICC_{BG} is defined as a continuous PERT distribution that can take values between 0 and 1 based on the structure and management of the herd that determines how contiguous the groups are. In these cases the $PrInfAf_{SampT}$ will depend on the degree of relatedness between sampled groups or ICC_{BG}.

$$PrInfAf_{SampT} = 1 - (PrFree_{SampT}) \text{ X } ICC_{BG} \quad (10)$$

9. The previous steps estimate the $PrFree_{SampT}$. To get the overall probability of being free of disease over all the period and easily compare different scenarios we compute the Area under the Curve (AUC). This integrated measurement is used as a cumulative measurement of confidence of disease freedom.

$$AUC = \int_0^T PFree_{SampT}\, d(PFree_{SampT}) \quad (11)$$

This value ranges between 0 and 1. An AUC of 1 indicates that the PrFree over the entire period is 100% and a 0 is the opposite. Depending on the degree of relatedness or ICC_{BG} among the sampled groups it is abbreviated as AUCs (same sampled group) or AUCd (group sampled varies over time).

10. Finally, the model computes the cost of testing ($Cost_t$). The model sums all the samples tested over time and multiplies this value by the price of each individual test ($Price_t$).

Here the user should introduce the $Price_t$.

$$Cost_t = Price_t \sum_{1}^{T} n_T \qquad (12)$$

Visualization procedure

'Optisample' is accessible from www.umn.XXXXXX.

The layout of this web application is displayed in three parts.

The first part includes a basic explanation of the operation modeling, the inputs and the outputs obtained. The second part consists in a panel of inputs where the user introduces the values of each parameter. These inputs are related to the herd structure, the epidemiological context and the strategy of sampling. Finally the third part shows the outcomes represented in two plots indicating the AUCs or AUCd, the $PrFree_{SampT}$ and the $Cost_t$ of testing.

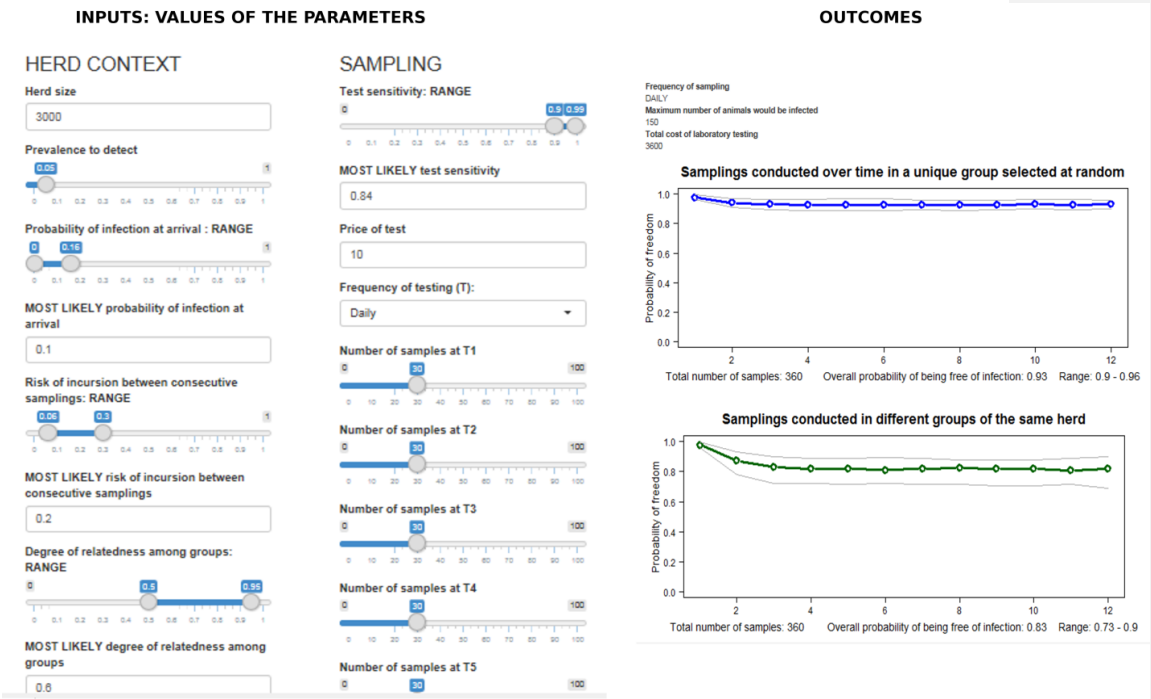


Figure 1. Layout of 'Optisample for the input values and outcomes.

Development environment

'OptiSample' was developed using the 'base' package of the statistical R software [11] with 'FFD' [12],'lattice' [13], 'xtable' [14], 'LearnBayes' [15], 'reshape' [16], 'mc2d' [17], 'zoo' [18], 'shiny' [19] and Rstudio [20] as integrated environment of R.

Simulation of scenarios

To show the functionality of 'Optisample' we assess the probability of being free of PRRSv and the costs of testing in three swine farms with disparate epidemiological contexts and using three different sampling schemes. In these three farms we aim at detecting a hypothetical design prevalence of 5%.

178 Farm A: a multiplier herd with 3000 sows in a context of very low incidence of PRRSv (i.e.
179 between 1 and 2 outbreaks every 10 years) with negative infection status (IV) according to
180 ASAV [5]. This farm recently has not introduced any pigs, the level of bioecurity is high and
181 the number of pig movements to other farms is relatively small. The last serological tests gave
182 negative results and the owner is interested in improving the cost-efficacy of the active
183 surveillance. The samples are tested using commercial PRRSv antibody ELISA kit. The
184 sensitivity of this test is 98% (97%-99%) based on available scientific publications [21-22].
185 Farm B: a multiplier herd with 3000 sows located in an area with a medium incidence of
186 PRRSv (i.e. between 1 and 2 outbreaks every 3 years) with negative infection status (IV). This
187 farm has introduced pigs and there are numerous movements of pigs to other farms. The owner
188 is interested in detecting PRRSv as earlier as possible. The samples are tested using the same
189 commercial PRRSv antibody ELISA kit than farm A.
190 Farm C: a commercial herd with 3000 pigs in a context of medium incidence (i.e. between 1
191 or 2 outbreaks every 3 years) classified as positive stable undergoing elimination (II-B). The
192 samples are tested using a PRRSv PCR. The sensitivity of this test is 98% (97%-99%) based
193 on scientific references [23].
194 We assume a hypothetical price of 5 dollars per each serological test and 10 dollars per each
195 PCR test.
196 Table 2 summarizes the inputs considered for each farm and the respective sampling schemes
197 applied.
198
199 Table 2. Inputs values of the scenarios proposed
200

INPUTS	Farm A	Farm B	Farm C
Demographical and epidemiological context			
N	3000	3000	3000
$Pr_{InitInf}$	0 - .05- .1	.5 - .7 - .8	.8 - .9 - 1
$Pr_{InfBwSamp}$	0 - .02 - .07	.03 - .06 - .1	.03 - .06 - .1
Sampling strategy			
p_*	.05	.05	.05
SCHEME I	30 monthly	30 monthly	30 monthly
SCHEME II	50 monthly	50 monthly	60 at T1 + 30 monthly
SCHEME III	30 bimonthly	30 bimonthly	60 at T1 + 30 bimonthly
se_t	.97 - .98 - .99	.97 - .98 - .99	.97 - .98 - .99
ICC_{BS}	.5 - .7 - .9	.5 - .7 - .9	.5 - .7 - .9
$Price_t$	5	5	10

201

202 **Results of simulated scenarios**

203 The probabilities of being free of PRRSv for the farm A, B and C after conducting each
204 sampling and over all productive cycle with the costs of testing are shown in table 3 and
205 plotted in figures 2-4.Table 3 summarizes the inputs introduced by each farm and the outputs
206 of the model.

207 Table 3. Inputs and outputs for the scenarios proposed

INPUTS									
Scenario	Farm A			Farm B			Farm C		
Scheme	I	II	III	I	II	III	I	II	III
Total n_T	360	600	180	360	600	180	360	390	240
N	3000			3000			3000		
p_*	.05			.05			.05		
se_t	Pert(.97, .98, .99)			Pert(.97, .98, .99)			Pert(.97, .98, .99)		
$Pr_{InitInf}$	Pert(0, .05, .1)			Pert(.5, .7, .8)			Pert(.8, .9, 1)		
Pr_{InfBS}	Pert(0, .02, .07)			Pert(.03, .06, .1)			Pert(.03, .06, .1)		
ICC_{BS}	Pert(.5, .7, .9)			Pert(.5, .7, .9)			Pert(.5, .7, .9)		
$Price_t$	5			5			10		
OUTPUTS									
AUC_S	.97-.98-.99	.99-.99-1	.92-.94-.95	.94-.96-.97	.98-.99-.99	.84-.87-.9	.86-.9-.94	.92-.96-.97	.85-.9-.93
AUC_d	.77-.81-.87	.95-.96-.98	.45-.51-.62	.79-.86 -.91	.93-.95-.97	.42-.54-.63	.69-.78-.87	.76-.85-.91	.47-.59-.69
$Cost_t$	1800	3000	900	1800	3000	900	3600	3900	2400

208

209 The AUC_S for the scheme I indicate that the confidence of being free of PRRSv over all the
210 period diminishes when the risk of being infected at arrival or between samples increases (i.e.

.98 (.97 - .99) for the farm A, .96 (.94 - .97) for the farm B and .90 (.86 -.94) for the farm C).

The results of AUC_d for the farm A, B and C indicate a marked decrease of confidence if the group selected varies over time and the ICC_{BS} follows a Pert(.5, .7, .9). In these cases, to substantiate freedom of PRRSv, it would be necessary to almost double the number of samples over time (e.g. see scheme II in the farm A and B).

The results of the farm C show that to demonstrate the freedom of infection when the risk of being initially infected is high is necessary to increase substantially the sample size during the first samplings. In this case, due to the price of the PCR, the costs of testing would increase even though the AUC is lower.

The plots shown in figure 2 and 4 allow comparing the results over time for the different scenarios. From these outcomes we observe the high influence of the risk of being initially infected on the probability of being free after each sampling. This impact is very marked on the farm C. Finally the zigzag patterns of the plots of the scheme III demonstrate the probability of substantiating disease over time based on previous sampling and the impact of the risk of incursion between samplings.

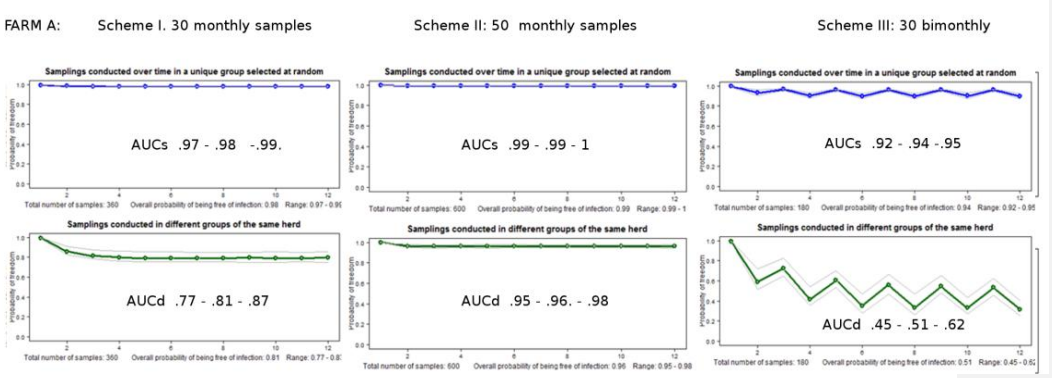
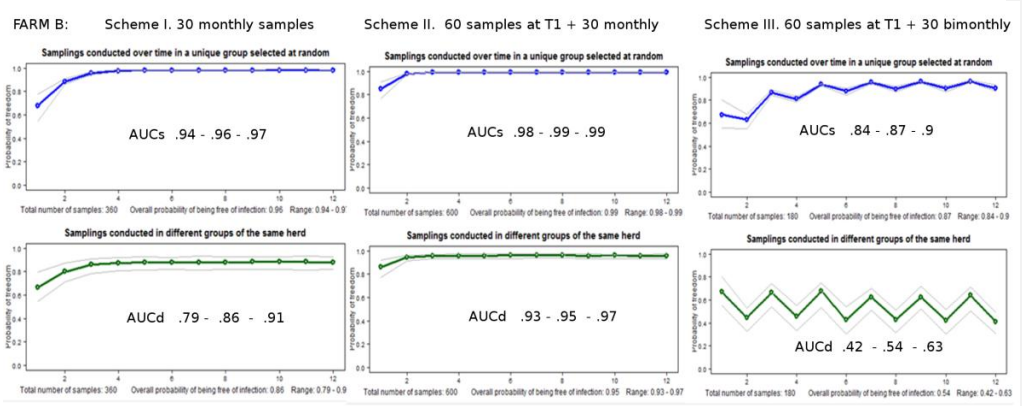
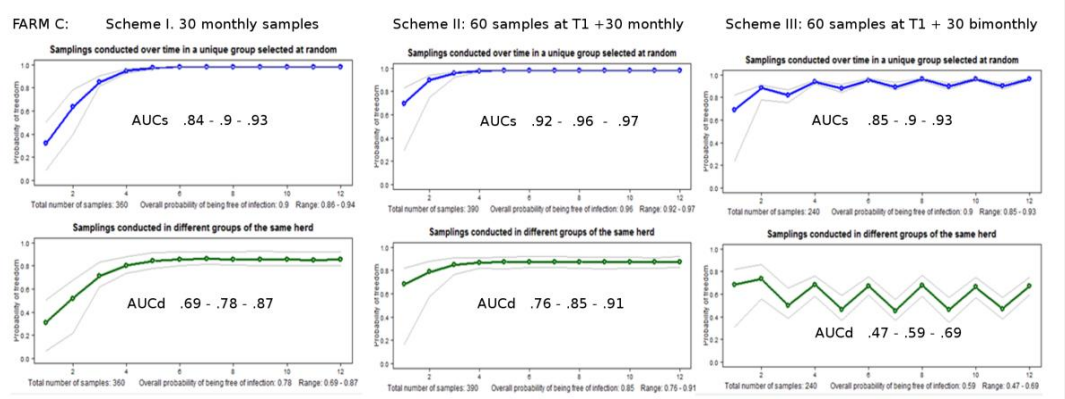


Figure 2. Farm A: A multiplier herd with low risk of infection at Figure 3. Farm Figure 3.



230 Figure 3. Farm B: A multiplier herd with unknown risk of infection at the arrival and medium
231 risk between consecutive samplings.



232

233 Figure 4. Farm C: A commercial positive stable herd undergoing elimination with a
234 medium risk between consecutive samplings

235

Discussion

The prevention, control and elimination of infectious animal diseases require continuous information of the infection status of the herd. Most of this information often is obtained from routine samplings conducted in different farms under the same fixed schemes. For example, in the event of PRRSv a common practice in a sow herd to claim for a free PRRSv infection status is to test monthly 30 sera from weaned pigs, and finding none PCR positive in four consecutive samplings, we conclude that we are .95 confident that the prevalence of PRRSv is less than 10% in this herd and is considered free of PRRSv infection. The outcomes of our model puts in evidence how this strategy, depending on the farm context, might not be the most optimum to detect the infection or substantiate freedom from this infection.

In our model, although in most of the cases the exact value of the inputs is variable or even unknown, we can assess independently or jointly the influence of different determinants on the probability of freedom of infection for each farm.

The model shows the importance of checking the sanitary status of the animals at the arrival in order to get the maximum guarantee that the new animals introduced are not infected. If the probability of being free at origin is very high or uncertain, our approach shows that, to demonstrate the freedom from PRRSv, we need to take more samples during the initial samplings (e.g.: the farm C versus the farm A or B). Also, depending on the herd infection status, the risks of incursion and the impact of the disease, the standards to achieve might be different. For example, in the farm A, which does not introduce pigs or has a small number of movements to other herds, the risk of incursion at the arrival or between consecutive samples is very unlikely; a value of P* of 5% might be acceptable and the laboratorial diagnosis may be based on the antibodies detection. Whereas in the farm B interested in detecting the infection as soon as possible in the new animals, we might be interested in detecting lower prevalence and viraemic animals. In this case a PCR to detect the infection

at earlier stages and a lower P* would be more appropriate. 'Optisample' allows to assess the probability of being free adjusting the hypothetical prevalence and test sensitivity.

Obviously, if the P* or the sensitivity of the tests are lower, we will require a larger sample size to increase the confidence. From the outcomes of our model we can observe that the probability of being free over time also depends on the risk of incursion between consecutive samplings. This risk varies according to the biosecurity measures put in place, the frequency of direct or indirect contacts with other infected farms and the viability of PRRSv in the environment. If there is available information to state that the risk of incursion between consecutive samplings is low, the previous negative outcomes also provide cumulative information to substantiate that the herd is free from PRRSv infection; as result, the lag between samplings can be longer (eg: see scheme III for the farm A). In contrast, when the probability of incursion between samplings is high, the probability of being free over time decreases and the frequency of samples cannot diminish (e.g.: see scheme III for the farm B).'Optisample' also includes a parameter to illustrate the importance of the samples selection. As far as we know, all the previous available software's [24], [25] used to calculate the sample size to detect infection assume that, in the event of infection, this will be homogeneously distributed across the whole farm. However, from our outcomes we observe that, if the groups sampled are heterogeneous and we sample different groups over time, the confidence of being free decrease dramatically. The value of CorBS can be very difficult to estimate, since this parameter depends on the management and structure of each farm. And thus, to get plausible values for each case, we would require a more accurate model to assess the spread within each specific farm. Despite these limitations, we believe that the inclusion of this parameter put in evidence the importance of assessing the process of samples selection to substantiate the freedom of disease.

Despite the innovations previously described, Optisample represents a simplification of a dynamic and complex process in which the hosts, the pathogens, the environment and the

human intervention are continuously interrelated. To facilitate the programming, the computation and a better understanding of all the process, we opted for an initial conservatory approach where the user introduces unique values for the prevalence, the herd size, the risk of incursion between consecutive samplings for all period. However, since in the reality these values vary over time, to get a better accuracy of the outcomes, an improvement for future versions would be to add some extensions that allow including different values according to the available information of each context over time.

This work demonstrates how 'Optisample' may enhance the design of active surveillance for PRRSv at farm level. But this model may not be only limited to PRRSv. Its principles and methods can be easily extended to other contexts of surveillance for other species or animal diseases. Moreover, the fact of being built as an interactive model, accessible to veterinarians, stakeholders or other users, contribute to explain the main factors that affect the probability of being free of infection in each farm and help the decision making process at this level.

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