THE COMPARISON OF EXISTING AND ALTERNATIVE SURVEILLANCE STRATEGIES TO PROVE FREEDOM OF BHV1 IN DAIRY FARMS: A CASE STUDY WITHIN THE RISKSUR PROJECT

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SUMMARY

This study aimed at the application of the RISKSUR surveillance design framework to describe and redesign the surveillance program of bovine herpesvirus type 1 (BHV1) as laid down by EU-legislation. Scenario-tree analyses were carried out to determine surveillance system sensitivities (and components thereof) and the monthly herd-level confidence of freedom with two different surveillance designs. At a within-herd design prevalence of 10%, the conventional (EU) design led to a varying probability of freedom between 99.6-100% in an endemic situation, compared to a constant probability of freedom of >99.8% in the alternative design. In a disease-free situation, both designs performed equally well. The RISKSUR surveillance design framework provided easy-to-use guidance to describe and redesign the BHV1 surveillance program, potentially contributing to a standardisation of surveillance documentation. The assessment of various surveillance designs could be highly useful to support decision-making towards a more risk-based approach of animal health surveillance.

INTRODUCTION

This study was conducted within the context of the RISKSUR project, which was an international research project aiming at developing an integrated surveillance system design and evaluation framework. The project was conducted between 2012 and 2015 and funded by the Seventh Framework Programme of the European Union (http://www.fp7-risksur.eu). Within the RISKSUR project, a surveillance design framework (SDF) was developed to guide scientists and policymakers in the development of disease surveillance systems by structuring the process of designing, documenting and redesigning the system. We used bovine herpesvirus type 1 (BHV1) in dairy farms as a case study for the use of the SDF. BHV1 is a member of the alphaherpesvirinae and causes infectious bovine rhinotracheitis (IBR) and infectious pustular vulvovaginitis/ balanoposthitis (IPV/IPB). EU Member States have the possibility to obtain an official BHV1-free status as laid down in EU Directive 64/432/EC. This directive allows Member States with a BHV1-free status to impose restrictions on the importation of cattle from countries or regions that are not free from BHV1. The current study aimed at (i) the application of the SDF to describe and redesign the surveillance program of bovine herpesvirus type 1

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(BHV1) in dairy farms as laid down in EU legislation, and (ii) to compare the epidemiological performance of the conventional and alternative design using scenario tree modelling in both an endemic and disease-free situation.

MATERIALS AND METHODS

Surveillance design

By using the SDF, the user is presented with the surveillance decisions that need to be made when designing a surveillance system, such as defining the target hazard and surveillance objective, target population, surveillance enhancements, testing protocol, study design, sampling strategy, sample collection, data/sample transfer, sample analyses, epidemiological analyses, dissemination of results and surveillance review. The framework is available in Excel and can be downloaded in the educational Wikispace created for the framework at: https://surveillance-design-framework.wikispaces.com. In the current study, the SDF was used to describe the BHV1 program as prescribed by EU Decision 2004/558/EC and 2007/584/EC.

Conventional design: The BHV1 surveillance regime as required according to EU legislation is described as follows:

- Obtaining the BHV1-free status (OBTconv): All cattle >9 months of age should be tested serological negative twice with a maximal interval of five to seven months.

- Monitoring the free status (MONconv): All cattle >24 months of age should have negative test results following serological investigation at intervals of not more than 12 months[1].

According to the EU legislation, certified holdings are not allowed to have animals in the herd that originate from non-free herds. Therefore, purchase testing is not part of the conventional surveillance design (i.e. it was assumed that animals from non-free herds will not be introduced into the free herd).

Alternative design: An alternative surveillance approach based on monthly bulk milk testing was designed. A risk-based component based on additional testing of cattle purchased from non-free herds was added. This design is based on the voluntary BHV1 control program for dairy herds that is currently operational in the Netherlands[2]. The alternative surveillance design consists of three components and can be described as follows:

- Obtaining the free status (OBTalt): All cattle older than 12 months should be subjected to a serological test (gE-ELISA) after which animals with positive test results should be removed from the holding. After removal of seropositive animals (if any), the free status of the herd is validated within 4-8 weeks by a bulk milk test.

[1] In addition, EU Decisions 2004/558/EC and 2007/584/EC describe alternative control regimes to attain and maintain a BHV1 free status, which were not considered in this study.
[2] In addition to the components included in the alternative design, the BHV1 control program in the Netherlands consists of a passive clinical surveillance component including testing of aborting cows.

- Monitoring of free status (MONalt): Seronegative bulk milk test (gE-ELISA) results need to be obtained from the holding, at least nine times per year[3], with intervals of at least one month. The gE-ELISA test in bulk milk is 98% sensitive given a prevalence of at least 10% in the group of lactating cows (Wellenberg et al., 1998). A positive test result should be followed by a new bulk milk test within seven days. The free status of the holding is maintained if the second test result is negative. If the second sample also tests positive then the free status of the holding is suspended.

- Purchase testing (PURalt): Cattle purchased from non-free herds[4] need to be tested for serology within eight weeks after being introduced in the herd. Cattle with positive test results must be removed from the holding. After removal of seropositive animals (if any), the free status of the herd is validated within 4-8 weeks by either a bulk milk test or a random sample of three blood samples (depending on the age of the purchased animal).

Scenario-tree model

A scenario tree analysis method was applied to the conventional and alternative surveillance designs to estimate (i) the sensitivity of the surveillance system's components to detect an infected herd and (ii) the monthly probability of disease freedom during one year monitoring of a herd's free status. In this study, sensitivity is defined as the probability of detecting an infected herd given that BHV1 is prevalent in the herd at the level of the design prevalence (PstarA). A stochastic scenario-tree model was developed for each surveillance component, as described by Martin et al. (2007a,b). Briefly, in these models, the probability that a single unit (eg. animal) will yield either a positive or a negative outcome when subjected to the testing protocol laid down in the component is calculated.

In each scenario tree, we used a within-herd PstarA of 10%, which has been used previously by EFSA (EFSA, 2006). Within the component MON_{alt}, PstarA was transformed to a group level probability of infection, as the testing protocol (bulk milk testing and its test sensitivity) applies to the pool of lactating cattle. To do so, we assumed that with an animal-level prevalence of 10%, the prevalence within the group of lactating cattle will be 10% as well (i.e. the disease is distributed homogenously throughout the herd), thus classifying the group of lactating cattle as infected.

The monthly probability of introduction of the virus into a herd (PIntro) was assumed to be influenced by purchase of cattle originating from non-free herds. In addition, in an endemic environment (country or region), BHV1 could be introduced in a herd via over-the-fence contacts, aerosols, neighborhood contacts, persons or material. In this study, we used different values of PIntro depending on the disease status at country level (free or endemic) and whether or not cattle from non-free herds were purchased by the farmer (in an endemic environment). In an endemic situation, a baseline PIntro was estimated to be 0.04% per month, based on a breakdown rate of 0.5% per year in certified herds in the Netherlands in 2014 (GD Animal Health, unpublished data) (Table 1). PIntro was increased by a hazard rate of 1.1 per purchase. In a disease-free situation, PIntro was assumed to be constant at 0.01% per month.

[3] Preferably 12 times a year. In 2014, 12 bulk milk samples per herd were tested in 81% of the certified dairy herds.
[4] Or cattle that have been in contact with cattle from non-free herds (on a fair of exhibition)

The model was developed using @RISK 5.7.1 (Palisade Corporation) in Excel (Microsoft) and outputs were based on 5,000 iterations, which appeared sufficient to obtain stable output values (mean and variance). Spread sheets were created in Microsoft Excel 2010 to represent each surveillance component (OBT_{conv}, MON_{conv}, OBT_{alt}, MON_{alt} and PUR_{alt},). The corresponding scenario trees are illustrated in Figures 1-4.

Table 1. Input parameters used in the scenario tree model to proof freedom of BHV1 in dairy herds in the Netherlands

Description of input parameter	Value	Source
Within-herd design prevalence (PstarA)	0.10	EFSA, 2006
Baseline monthly probability of introduction of BHV1 into a certified holding (PIntro)		Data from the BHV1 control program in the Netherlands (GD Animal Health) and expert opinion
in an endemic country	0.004	
in a disease-free country	0.001	
Proportion of risk factors and their relative risk (RR)		
Relative risk of seropositivity in animals ≥ 24 months of age vs. animals < 24 months of age	3	Van Wuyckhuise et al., 1993; Mars et al., 2001
Hazard rate per purchased animal for introduction of BHV1 into dairy farms	1.1	Van Schaik et al., 1999
Test sensitivities for serology and virus detection		
BHV1 gE-specific ELISA		Perrin et al., 1996; Van Oirschot et al, 1997; Wellenberg et al., 1998
on serum samples	0.87[b,c]	
on bulk milk samples	0.98[d]	
BHV1-specific real-time duplex PCR	0.99	Internal validation at GD Animal Health

[a] Specificity is assumed to be 100%

[b] Average of estimates from Perrin et al., (1996), Van Oirschot et al., (1997) and Wellenberg et al., (1998).

[c] When used on a sample of three animals, a herd sensitivity of 23,9% is reached given a design prevalence of 10% in an infinite population.

[d] When used on bulk milk samples, the gE-ELISA test is 98% sensitive to detect an infected herd provided that the animal level prevalence in the group of lactating cows is 10% or more (Wellenberg et al., 1998)

Component sensitivities: The probability that a single unit (animal) yields a positive outcome when subjected to the testing protocol laid down in the component, was calculated (component sensitivity at unit level, CSeU for component *i*). The $CSeU_i$ is calculated by summing up the limb probabilities for all limbs with positive outcomes in the scenario tree. $CSeU_i$ was transformed to an overall estimate of the component sensitivity (CSe_i), representing the probability of a positive outcome at herd level when all units (*n*) within component *i* are subjected to the testing protocol:

$$CSe_i = 1 - (1 - CSeU_i)^{n_i} \quad (1)$$

with i being components OBTconv, MONconv, OBTalt, MONalt or PURalt. Appropriate distributions were chosen for ni, based on movement and herd population data derived from the Dutch Identification and Registration database in 2014.

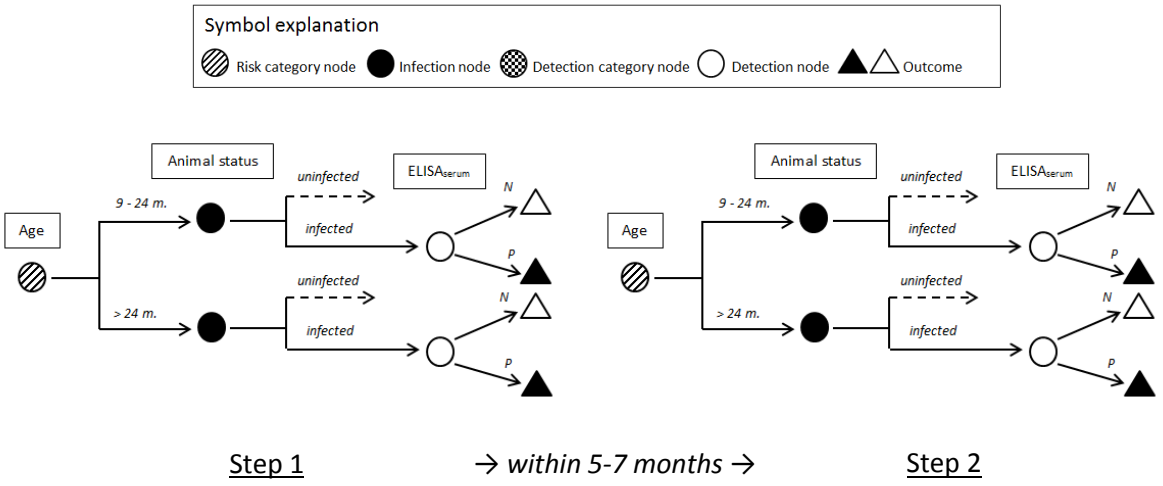

Fig. 1 Scenario tree illustrating the surveillance system component for obtaining the BHV1-free status in the conventional BHV1 surveillance design (OBT_{conv})

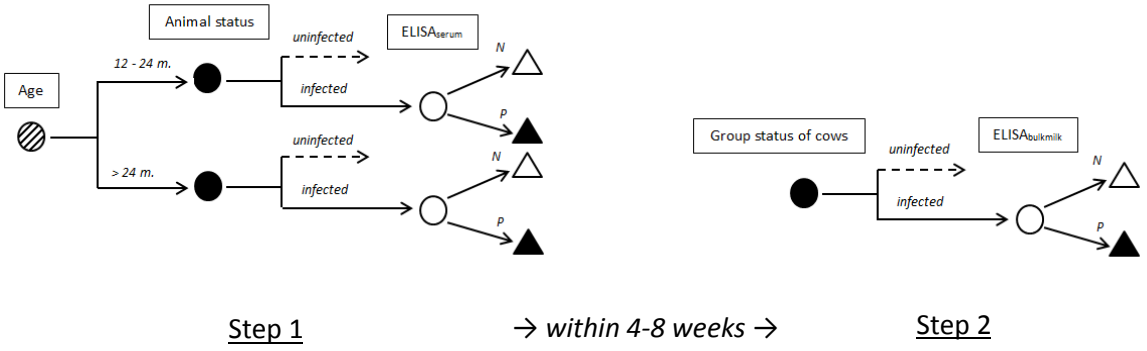

Fig. 2 Scenario tree illustrating the surveillance system component for obtaining the BHV1-free status in the alternative BHV1 surveillance design (OBT_{alt})

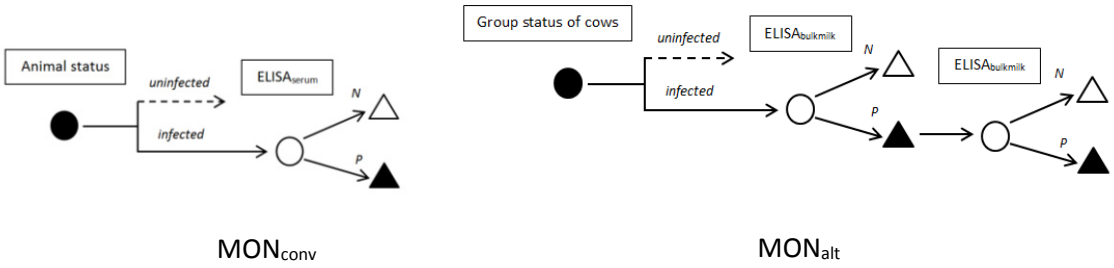

Fig. 3 Scenario trees illustrating the surveillance system component for monitoring the BHV1-free status in the conventional (left) and alternative BHV1 surveillance design (right)

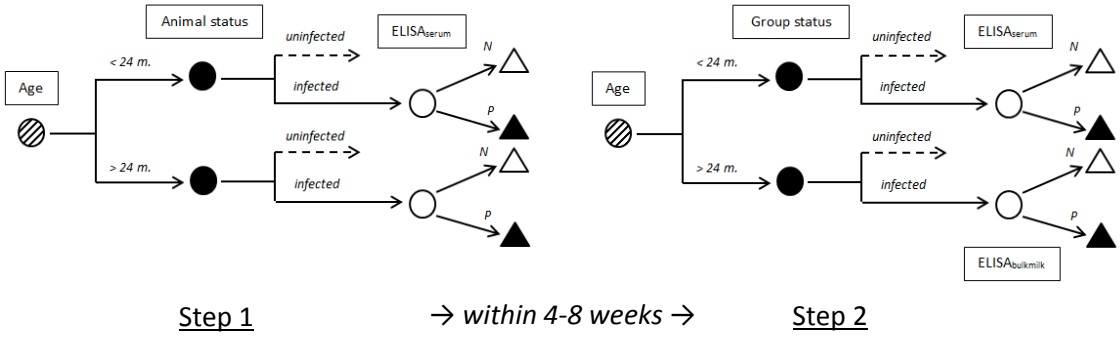

Fig. 4 Scenario tree illustrating the surveillance system component for testing of animals that are purchased from non-free farms in the alternative BHV1 surveillance design (PUR_{alt})

The sensitivity of the total surveillance program (SSe) is a combination of the CSe's of the different components in place. SSe is equal to OBTconv or OBTalt when a herd has entered the program to obtain a free status. During the phase in which the free status is monitored, the component MONconv or MONalt represents the SSe. If in addition purchase testing is carried out, the component PURalt is in place as well. If multiple surveillance components are in place, the sensitivity of the total surveillance program is calculated as:

$$SSe_t = 1 - (1 - CSe_1)(1 - CSe_2) \quad (2)$$

with CSe_1 and CSe_2 being the component sensitivities of the surveillance components in place in month *t*.

Probability of freedom: The probability of freedom from BHV1 per month t (PostPFreet) was calculated for the phase in which a herd's free status is monitored, with t=1 being the first month after the free status was obtained. PostPFreet was calculated based on the probability of infection at the beginning of the month (PriorPInft) and the sensitivity of the total surveillance system in that month. PostPFreet was estimated in time steps with a 1-month interval, by the following formula:

$$PostPFree_t = \frac{1 - PriorPInf_t}{1 - PriorPInf_t + (PriorPInf_t \text{ X } (1 - SSe_t))} \quad (3)$$

This formula corresponds to the standard calculation of a negative predictive value when assuming that the specificity of the surveillance system is equal to 1. $PriorPInf_t$, the prior probability that the herd is infected at the beginning of month *t*, is calculated as:

$$PriorPInf_t = PostPInf_{t-1} + PIntro - (PostPInf_{t-1} \text{ x } PIntro) \quad (4)$$

where $PostPInf_{t-1}$ is the estimated posterior probability of infection in the preceding month, adjusted for the introduction of BHV1 in between (PIntro) and is described by:

$$PostPInf = 1 - PostPFree \quad (5)$$

At t=1, the posterior probability of infection after obtaining the free status was used as PriorPInf.

Scenarios: The monthly probability of freedom from BHV1 was calculated for three different scenarios, depending on the probability of introduction of BHV1 in the herd:

A. BHV1-free herd without purchase of animals from non-free herds, assuming BHV1 is endemic at country level
B. BHV1-free herd without purchase of animals that originate from non-free herds‡, in a situation in which the country is free from BHV1
C. BHV1-free herd that purchases animals that originate from non-free herds, assuming BHV1 is endemic at country level

Sensitivity analyses: To determine whether the model outcome was sensitive to the probability of introduction assumed in this study, the model was re-run with a probability of introduction that was double the default value (0.08% per month).

To assess the effect of (passive) clinical surveillance on the probability of freedom, a clinical surveillance component (CLIN) was added to both surveillance designs. Observation of typical BHV1-related clinical signs (high fever, drop in milk production, nasal discharge, etc.) in cattle must be notified to the competent authority as soon as possible, followed by immediate sampling (nasal swab) of the affected cattle and subsequent virus detection by PCR. The free status of the holding is terminated in case of at least one positive test result. Affected cattle with negative test results must be subjected to serology within 4-8 weeks after the suspicion to validate the holding's free status.

It was deemed unrealistic to assume that all cattle within a herd are continuously subject of clinical surveillance. Therefore it was decided to include lactating animals only. Additional input parameters were defined, describing the probability of clinical disease after BHV1 infection (assumed to vary between 0 and 0.4 with a most likely value of 0.1) and disease awareness of the farmer (assumed to vary between 0.2 and 0.9 with a most likely value of 0.75). The clinical surveillance component is illustrated in Figure 5.

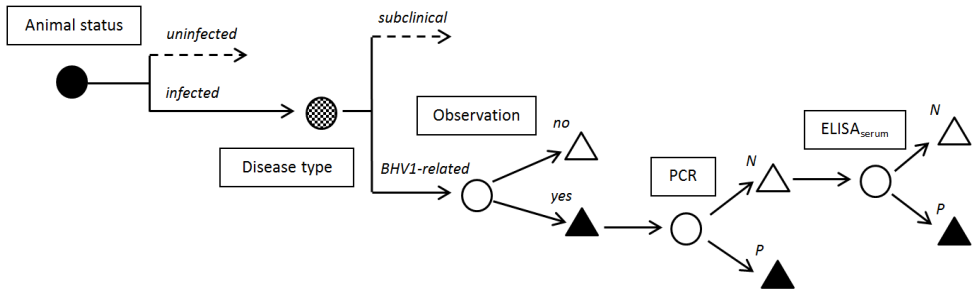

Fig. 5 Scenario tree illustrating the surveillance system component for clinical surveillance of BHV1 (CLIN)

RESULTS

Surveillance re-design feedback

The performance attributes of interest for redesign were sensitivity, timeliness and the negative predictive value of the system. Regarding these attributes, the SDF provided several

‡ In the Netherlands, the free status of a BHV1-free dairy herd is temporarily suspended between the day of purchase and the test result. For this study it was assumed that this interval is minimal (i.e. several days).

pieces of advice regarding testing protocol and sampling strategy that were applicable to the conventional surveillance design, the alternative design, or both (Table 2).

Table 2. Advice of the surveillance design framework (SDF) which was applicable to mprove timeliness, sensitivity and the negative predictive value of conventional and alternative surveillance system designs to detect and proof freedom of BHV1. For each advice it was indicated whether the conventional and alternative design lacked (✗) or comprised (✓) the advice

Advice provided by SDF	Inclusion in design		Comment
	Conv.	*Alt.*	
Timeliness			
Increased sampling frequency will reduce the time to detection.	✗	✓	Yearly sampling (conventional) vs. ≥ 9 times per year (alternative)
Choosing a sampling point that allows frequent and easy access of the target population may improve timeliness.	✓	✓	Sampling at the herd in both designs, which allows frequent and easy access to the target population
Sensitivity			
Risk-based targeting can increase sensitivity	✗	✓	No risk-based sampling (conventional) vs. sampling of purchased cattle originating from non-free herds (alternative)
Negative predictive value (NPV)			
NPV can be increased by taking differences in the risk of introduction into account.	✗	✓	No difference in risk of introduction (conventional) vs. Increased risk of introduction through purchase is accounted for (alternative)
Pooling will increase the NPV when inference is made at animal level, but it will reduce it in case the inference is made at herd level.	✓	✗	Individual sampling of cows (conventional) vs. testing of a (pooled) bulk milk sample (alternative).

Surveillance sensitivities

Both designs reached 100% sensitivity with the intake procedure to obtain a free status (OBT) (Table 3). The sensitivity of the component to monitor a herd's free status (MON), i.e. to classify a herd as positive when infected at an within-herd design prevalence of 10%, was 99% for the conventional design and 96% for the alternative design. In the alternative design, the purchase testing component (PURalt) led to a component sensitivity of 55%. The total surveillance system sensitivity of a herd increased from 96% to 98% when additional testing of purchased animals was done besides monitoring the free status in the alternative design. When additional passive clinical surveillance was in place, both designs led to a total system sensitivity of 100% when monitoring the free status of a holding.

Table 3. Mean sensitivity values (with 5th percentile and 95th percentile values) of conventional and alternative surveillance system components to detect a BHV1 infection at herd level based on a within-herd design prevalence of 10% and total system sensitivity when monitoring the free status of a herd

	Conventional design	Alternative design
Component sensitivity		
OBT	1.00 (1.00-1.00)	1.00 (1.00-1.00)
MON	0.99 (0.93-1.00)	0.96[a]
PUR	n.a.	0.55 (0.23-0.93)
Total system sensitivity		
Monitoring free status	0.98 (0.91-1.00)	0.96[a]
Monitoring free status + purchase	n.a.	0.98 (0.97-1.00)
Monitoring free status + clinical surv.	1.00 (1.00-1.00)	1.00 (1.00-1.00)

[a] Single output value as all input parameters were fixed.

Probability of freedom

Conventional design: In an endemic situation (Scenario A), the conventional design led to a mean probability of freedom of 99.6 - 100%, depending on the time since the serological investigation of all lactating cattle (Fig. 6). When the probability of introduction (PIntro) was doubled to 0.08% in de endemic situation (not shown), the resulting mean probability of freedom varied from 99.8% in the first month after obtaining the free status to 99.2% in the month before serology on all lactating animals[§]. In a situation where the country is free from BHV1 (Scenario B), the conventional design led to a mean probability of freedom of 99.9% or more throughout the year (Fig. 6).

Alternative design: In an endemic situation (Scenario A), the alternative design led to a probability of disease freedom of >99.9%, even in the months without bulk milk testing (Fig. 7). The increased risk of introduction when purchasing animals from non-free herds (Scenario C) resulted in a slight reduction of the monthly probability of freedom but did not result in a mean monthly probability of freedom of <99.9%. In a situation where the country is free from BHV1 (Scenario B), the alternative design led to a constant 99.99% probability of freedom per month (Fig. 7). When the probability of introduction (PIntro) was doubled to 0.08% in the endemic situation, the resulting mean probability of freedom decreased to 99.8% in months without bulk milk testing, 99.9% in months with bulk milk testing and 99.9% in months with bulk milk testing and purchase (not shown).

DISCUSSION

During the last decade, scenario tree methods have been widely used to evaluate surveillance systems (Martin et al. (2007a,b); Frössling et al. (2009); Blickenstorfer et al. (2011); Calvo-Artavia et al. (2013)). The models we used in this study focussed on sensitivity of detection on herd level given a new introduction in a BHV1-free herd and proofing freedom from disease, and could easily be adapted to country level.

[§] Arbitrarily chosen to be carried out in month 10.

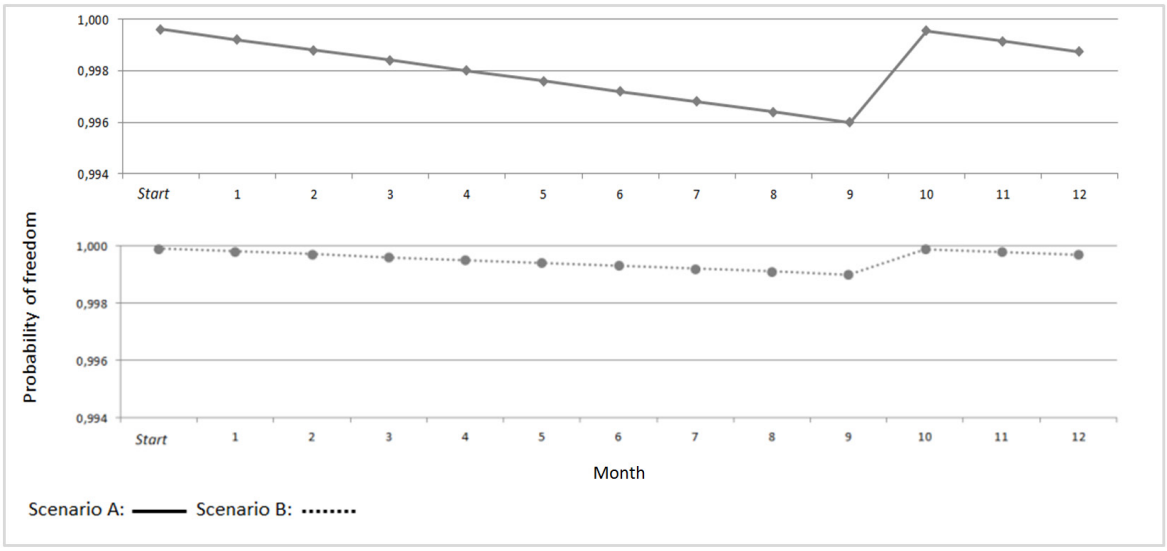

Fig. 6 Mean monthly probability of freedom of certified dairy herds as estimated based on a scenario-tree model of the conventional surveillance system for BHV1 infections, i.e. yearly serology on all lactating animals (in month 10 here). Estimations were made for the situation in which BHV1 is endemic at country level (Scenario A; top) and for the situation in which the country is disease-free (Scenario B; bottom)

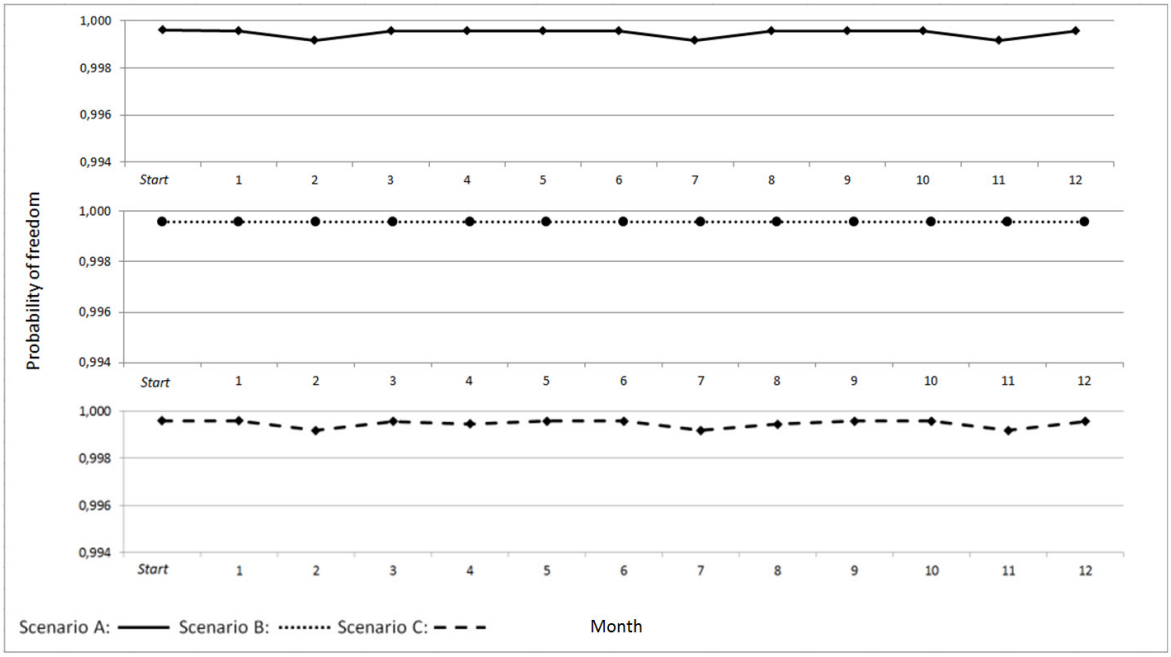

Fig. 7 Mean monthly probability of freedom of certified dairy herds as estimated based on a scenario-tree model of the alternative surveillance system for BHV1 infections, i.e. bulk milk testing is carried out 9 times a year (months 2, 7 and 11 are omitted). Estimations were made for the situation in which BHV1 is endemic at country level (Scenario A; top), for a disease free situation (Scenario B; middle) and for the situation in which BHV1 is endemic at country level + animals from non-free herds are purchased in months 4 and 8 (Scenario C; bottom)

The alternative surveillance design described in this study was based on the voluntary BHV1 control program in the Netherlands. In a disease free situation, the conventional and alternative designs performed equally well in terms of substantiating disease freedom at a within-herd design prevalence of 10%. It would therefore be interesting to assess differences in costs related to these two designs, which was no included in the current study. In an endemic situation, assuming a monthly probability of introduction of BHV1 of 0.04% at herd level, the alternative design led to a constant probability of freedom of minimum 99.8%. This is sufficient according to the recommendations of the Terrestrial Animal Health Code of the OIE and was superior to the conventional design as described by EU legislation. However, if the design prevalence were to be lower, eg. 5%, the performance of the alternative design might be inferior to the conventional design, as the bulk milk test is not sensitive to detect small outbreaks (Wellenberg et al., 1998). Minor outbreaks (without clinical signs) may therefore remain undetected until they reach a within-herd prevalence of 10% or more. Nevertheless, given BHV1's high reproduction ratio (Bosch, 1997), within-herd prevalences will rapidly reach levels of 10% or more. The alternative surveillance design based on monthly bulk milk testing has been reported before as being adequate to detect BHV1 infection timely, thus reducing spread of infection after introduction (Graat et al., 2001).

The efficacy of any animal health program relies on timely case detection. Timeliness of detection was not assessed in the current study but is related to the length of the period between sampling moments. The low frequency of testing in the BHV1 control regime as described by EU-legislation could be considered as a drawback of the system in terms of timeliness of detection. In addition, this study showed that in an endemic situation, the monthly confidence of freedom in the EU-design decreased to the minimum of 99.8% (as laid down by the Terrestrial Animal Health Code of the OIE) within 5 months after the serological investigation of all cattle >24 months of age. Nevertheless, once the serological investigation is carried out, it is likely that each infected individual will be detected by the testing protocol, given its high level of sensitivity.

Risk-based veterinary surveillance can be defined as a form of surveillance in which exposure and risk assessment methods have been applied together with traditional approaches to assure appropriate and cost-effective data collection (Stärk et al., 2006). In this study, the conventional and alternative surveillance systems to substantiate disease freedom in certified dairy herds were both targeted at adult (lactating) cattle, as seropositive animals are most often observed in this age cohort. In addition, we extended the alternative design with a testing scheme for cattle that are purchased from non-free herds, as they have an increased risk of infection. This risk-based surveillance component resulted in an increase in total surveillance sensitivity. However, due to an increase in probability of introduction, the probability of freedom decreased slightly in months in which animals were purchased.

The RISKSUR surveillance design framework provided easy-to-use guidance to describe and redesign BHV1 surveillance programs, potentially contributing to a standardisation of surveillance documentation. The results of this study provided a description of two surveillance designs that could be used to control BHV1 infection in dairy herds, including a comparison of the sensitivity and negative predictive value of these systems. Such an assessment of various surveillance designs could be highly useful to support decision-making towards a more risk-based approach of animal health surveillance.

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