Optimising cost-effectiveness of freedom from disease surveillance—Bluetongue Virus Serotype 8 as an example

Rüegg, Simon R ; Welby, Sarah ; Yassin, Hurria ; Van der Stede, Yves ; Nafzger, Rebekka ; Saatkamp, Helmut ; Schüpbach-Regula, Gertraud ; Stärk, Katharina D C

Abstract: The aim of this study was to propose a procedure for optimising the cost-effectiveness of vector borne disease surveillance using a scenario tree model and cost-effectiveness analysis. The surveillance systems for Bluetongue Virus serotype 8 (BTV-8) implemented in Switzerland and Belgium were used as examples. In twenty four different, simulated population structures, passive surveillance and five designs of active surveillance were investigated. The influence of surveillance system design and parameters such as farmer disease awareness, veterinary disease awareness, herd and within-herd design prevalence on the overall surveillance system sensitivity were assessed. Furthermore, the cost-effectiveness of mandatory and voluntary vaccination regimes in relation to disease surveillance was investigated. Under the assumption that BTV-8 manifests clinically, freedom from disease in a population can be established with almost certainty over the period of one year using clinical surveillance alone. Additional investment in active surveillance would therefore economically only be justified, if no clinical manifestation is suspected or other surveillance objectives are to be provided such as early detection. The best cost-effectiveness is obtained by sampling more herds rather than more animals within a herd. Mandatory vaccination reduces the cost of surveillance by 0.26 € per vaccine and voluntary vaccination only marginally reduces the cost of risk-based surveillance, by reducing the population at risk. Finally, in populations with predominantly dairy cattle, bulk-tank milk testing is the method of choice to actively demonstrate freedom from disease.

DOI: https://doi.org/10.1016/j.prevetmed.2018.02.009

Optimising cost-effectiveness of freedom from disease surveillance - Bluetongue Virus Serotype 8 as an example

Simon R. Rüegg[1,2]*, Sarah Welby[3], Hurria Yassin[4], Yves Van der Stede[3, 6], Rebekka Nafzger[1], Helmut Saatkamp[4], Gertraud Schuepbach-Regula[1], Katharina D.C. Stärk[6]

[1] Veterinary Public Health Institute, Vetsuisse-Faculty, University of Bern, Bern, Switzerland

[2] Section for Epidemiology, Vetsuisse-Faculty, University of Zürich, Zürich, Switzerland

[3] Veterinary and Agrochemical Research Centre, National Reference Laboratory (CODA-CERVA), Brussels, Belgium

[4] Business Economics, Wageningen University, Wageningen, The Netherlands

[5] SAFOSO Inc., Safe Food Solutions, Bern-Liebefeld, Switzerland

[6] Department of Veterinary Virology, Immunology and Parasitology. Salisburylaan 133, Ghent University, Merelbeke, Belgium

* corresponding author srueegg@vetclinics.uzh.ch

Abstract

The aim of this study was to propose a procedure for optimising the cost-effectiveness of vector borne disease surveillance using a scenario tree model and cost-effectiveness analysis. The surveillance systems for Bluetongue Virus serotype 8 (BTV-8) implemented in Switzerland and Belgium were used as examples. In twenty four different, simulated population structures, passive surveillance and five designs of active surveillance were investigated. The influence of surveillance system design and parameters such as farmer disease awareness, veterinary disease awareness, herd and within-herd design prevalence on the overall surveillance system sensitivity were assessed.

Furthermore, the cost-effectiveness of mandatory and voluntary vaccination regimes in relation to disease surveillance was investigated.

Under the assumption that BTV-8 manifests clinically, freedom from disease in a population can be established with almost certainty over the period of one year using clinical surveillance alone. Additional investment in active surveillance would therefore economically only be justified, if no clinical manifestation is suspected or other surveillance objectives are to be provided such as early detection. The best cost-effectiveness is obtained by sampling more herds rather than more animals within a herd. Mandatory vaccination reduces the cost of surveillance by 0.26 € per vaccine and voluntary vaccination only marginally reduces the cost of risk-based surveillance, by reducing the population at risk. Finally, in populations with predominantly dairy cattle, bulk-tank milk testing is the method of choice to actively demonstrate freedom from disease.

Keywords

Disease surveillance; risk-based surveillance; bluetongue virus serotype 8 ; cost-effectiveness analysis ; scenario tree modelling ; cost-effectiveness optimisation

Introduction

The emergence of Bluetongue virus serotype 8 (BTV-8) in northern Europe in 2006, lead to the European Commission regulation 1266/2007 on the surveillance of Bluetongue (European Commission, 2007; Mehlhorn et al., 2007; Toussaint et al., 2006). Based on this regulation, several countries implemented a range of surveillance strategies from 2006 onwards in order to detect circulation of BTV or alternatively prove freedom from infection with BTV after implementing mitigation and surveillance strategies. The original requirement to detect a prevalence of 0.005 in the bovine with 95% confidence was relaxed in May 2012 requesting to detect a prevalence of only 0.05.

Conventionally, surveillance approaches are divided into passive and active surveillance. Passive surveillance mainly consists of mandatory reporting of clinical suspect cases by owners and veterinarians while active surveillance is most commonly implemented as a strategy decided by the competent veterinary services, and with a certain objective on the short, mid- and long term. Active surveillance implies the whole range of activities needed to guarantee these objectives such as appropriate sample selection, collection and laboratory analysis as well as follow-up of results and interventions. In contrast, passive surveillance heavily relies on disease awareness of the involved stakeholders (Hadorn et al., 2008) and is considered to cover the entire target population. Active surveillance is designed to represent the surveyed population according to a set target (i.e. confidence level at a given design prevalence). The most generic form of active surveillance would be a random sample, however, to reduce cost, as well as increase sensitivity of detection, risk-based surveillance has been applied in many settings (Alban et al., 2008; Calvo-Artavia et al., 2012; Hadorn et al., 2009; Welby et al., 2013). The technical performance of a risk-based surveillance component applied to establish freedom from infection can be expressed by its sensitivity, i.e. the probability to detect at least one case if the disease is present at a predefined design prevalence.

Active surveillance, if designed to have a high sensitivity, incurs substantial costs for sampling and testing. The decision on how much resources are spent for surveillance of a specific disease is the result of political, technical and financial considerations. In order to guide such decisions, we propose here a combination of scenario tree modelling as first described Martin et al. (Martin et al., 2007) and cost-effectiveness analysis (CEA). CEA is a method of comparing the cost and effectiveness of two or more health care alternatives to aid decisions on resource allocation (Clasen et al., 2007; Eichler et al., 2004; Hutubessy et al., 2003; McEwan, 2012; Russel et al., 1996). It directly relates the financial and scientific implications of different interventions in a systemic way (Levin, 1995).

The aim of the present study was to propose a process for optimising surveillance performance and costs using a scenario tree model and CEA in sequence. The application of this approach is illustrated using BTV-8 as an example, because there is potential for BTV to reoccur in North-western Europe.

The BTV-8-surveillance implemented in Belgium (BE) and Switzerland (CH) in 2011 and 2012 was assessed by Nafzger (Nafzger, 2016), and the benefit of surveillance for BTV-8 has been demonstrated (Häsler et al., 2012; Pinior et al., 2015), but it was also shown that the continuation of that surveillance and intervention program might not be economically justified (Häsler et al., 2012). The question arises whether surveillance for BTV could be more cost-effective. In the present study, surveillance is optimised from two distinct perspectives: first with the objective to identify the most cost-effective system to demonstrate freedom from disease, and second under the assumption that active surveillance is mandatory in addition to clinical surveillance (as prescribed by the EC regulation, European Commission, 2007).

Material & Methods

Here we first describe the generic stochastic scenario tree model implemented in R (Core R Team, 2013, code available upon request). It is followed by a deterministic model for the cost-effectiveness analysis implemented in Excel (Microsoft Corporation, 2010, supplementary data). Finally, the example for Bluetongue serotype 8 is described with the data used for the analysis and optimisation of the surveillance approach.

Scenario tree model of disease surveillance for freedom from disease

The confidence level in a surveillance system to demonstrate freedom from disease can be measured as sensitivity to detect at least one infected animal at a given design prevalence in a given geographical unit. Martin and co-workers (Martin et al., 2007) proposed scenario tree models to compute this sensitivity. Such a tree consists of a sequence of nodes, with branches dividing the reference population into subpopulations. Nodes are categorized as infection, detection or risk nodes, where infection nodes specify the infection status of a unit, detection nodes define all events that must take place for the detection of the infection, and risk nodes represent those factors that

affect the probability of a unit being infected or detected. For the present study, risk factors were considered at herd level as represented in Fig. 1. The relative risk distributions were computed by combining expert opinions collected by Nafzger (Nafzger, 2016) and are presented in the supplementary material. The model was implemented at country level for passive surveillance, namely clinical surveillance (CLIN), while for active surveillance three different components were considered using different diagnostic methods and matrices: i) blood samples and testing with an ELISA for BTV-8-specific serum antibodies (ELISA), ii) blood samples and testing with an RT-PCR assay specific for BTV-RNA (RT-PCR), and iii) bulk milk samples and testing with an ELISA for BTV-8-specific milk antibodies (BMT). For CLIN the testing procedure was a sequence of events determined by the probability of a farmer to detect the disease and call a veterinarian (farmer's disease awareness, *fDA*), the probability of a veterinarian to take a sample and submit it for testing (veterinarian's disease awareness, *vDA*) and the sensitivity of the confirmatory RT-PCR. At herd level, the sensitivity (*SeH*) was computed according to

$$SeH = 1 - (1 - fDA \times vDA \times Se_{PCR})^{morb \times N_{inHerd} \times P*_A}, \quad (1)$$

where *morb* is the morbidity, N_{inHerd} is the number of animals in a herd, and $P*_A$ is the within-herd design prevalence. The exponent is rounded to the next larger integer. Because for clinical surveillance all animals are assumed to be looked at during clinical inspection by farmers, there is no sampling fraction included in the Equation $\left(\frac{n_{inHerd}}{N_{inHerd}} = 1\right)$. For active surveillance, the *SeH* was computed in analogy, including the sampling fraction:

$$SeH = 1 - \left(1 - Se_{Test} \times \frac{n_{inHerd}}{N_{inHerd}}\right)^{N_{inHerd} \times P*_A}. \quad (2)$$

Where Se_{Test} is the sensitivity of the diagnostic test, n_{inHerd} is the number of animals sampled in a herd, N_{inHerd} is the number of animals in a herd, and $P*_A$ is the within-herd design prevalence. The exponent is rounded to the next larger integer.

The contribution to surveillance sensitivity from the risk-based sampling of different population strata was computed and aggregated at population level as component sensitivity (*CSe*), as previously described (Martin et al., 2007; Welby et al., 2013). For combinations of two surveillance components, e.g. clinical (CSe_{clinic}) and an active component (CSe_{active}), the system sensitivity (*SSe*) was computed according to

$$SSe = 1 - [1 - CSe_{clinic}] \times [1 - CSe_{active}]. \quad (3)$$

Cost-effectiveness analysis

CEA was applied to assess the efficiency of different alternatives of disease surveillance systems. The goal of CEA is to assess if the value of an intervention justifies its cost. The method relates the financial implications and the technical performance of a surveillance design in a systemic way (Levin, 1995), and was implemented in analogy to Guo and co-workers (Guo et al., 2014). The authors describe the basic concept and consider direct costs of surveillance, in addition to the direct consequential costs and indirect costs of an outbreak. In the present study, only direct costs of surveillance were considered as total annual costs. Furthermore, the calculation was restricted to the variable costs, which included: Cost of information campaign, cost of labour, cost of material, cost of transportation, cost of diagnostic tests, cost of communication and confirmation of results, and miscellaneous costs. If not stated otherwise, costs and activities were presumed to be at an annual basis. The scenario tree model provided the data for sampling and testing activities as well as the corresponding surveillance system sensitivity (*SSe*). It was iterated 1500 times and the resulting median sampling activity was converted into total costs. Then the different surveillance designs were compared on a plot where the x-axis are median total costs and the y-axis median SSe. Due to the threshold of at least 95% for the SSe used in the surveillance optimisation (see below), only a small portion of the theoretical space for optimisation is used. The spreadsheet to perform the cost-effectiveness analysis and detailed instructions are available as supplementary data.

Surveillance optimisation for Bluetongue

Factors considered for surveillance of Bluetongue and associated costs in various countries were collected by Nafzger (Nafzger, 2016). In the present project a generic summary of these data was used: The parameters used for the scenario tree model are given in Table 1, while the surveillance specific costs and time expenditures for the cost calculation are given in Tables 2 and 3. Where deemed appropriate, parameters were modelled stochastically using a pert distribution.

Surveillance optimisation

For the present study, surveillance was optimised from two distinct perspectives: first with the objective to identify the most cost-effective system to demonstrate freedom from disease, and second under the assumption that active surveillance was mandatory in addition to clinical surveillance (as prescribed by the EC regulation, European Commission, 2007). While clinical surveillance leaves little room for optimisation, active surveillance requires some strategic decisions and depends on active implementation by the veterinary services. The aim of the following surveillance optimisation process was to inform the design of an active surveillance system for Bluetongue. Many different surveillance designs are possible. But, the study focusses on five possible designs that represent some fundamental choices that can be considered by policy makers. The designs compared were (1) a random sample, (2) risk-based surveillance targeting only high risk herds, (3) voluntary vaccination with risk-based surveillance targeting all non-vaccinated herds, (4) voluntary vaccination with risk-based surveillance targeting non-vaccinated herds at high risk, and (5) mandatory vaccination with risk-based surveillance targeting herds at high risk.

Active surveillance was only simulated on the cattle population as required by the EC 1266/2007, and reported to have been conducted in many European countries (European Commission, 2007; Nafzger, 2016). From here onwards, the term “sensitivity” as the technical performance of a surveillance system or a component thereof shall be named *SSe* or *CSe* respectively (as described above for the scenario tree model). In contrast, the description of the sensitivity of the model to its

168 input parameters (as explained below) shall be denominated “model sensitivity”. To compare the
169 surveillance designs, the *CSe* for blood serology by ELISA, blood virus detection by RT-PCR or BMT
170 was assessed.

171 The technical performance of surveillance components is strongly affected by the population
172 structure, i.e. the distribution of risk factors amongst the different subpopulations at risk. However,
173 in practice in a given territory under surveillance, this structure is given and not subject to change or
174 decisions. Hence, in order to make generic statements on how to design a surveillance system for
175 optimal cost-effectiveness, we applied active surveillance components to a set of standard
176 population structures reflecting livestock population distributions in different countries or
177 geographical units. Twenty-four combinations were evaluated using four characteristics of a standing
178 population (a) a population with a majority of cattle versus a majority of sheep, (b) primarily milk vs
179 primarily meat production, and (c) a population with primarily small herds (median= 30 animals/
180 herd) versus primarily large herds (median= 100 animals/ herd). Furthermore, either 5, 10 or 40% of
181 the population were assumed to be exposed to high infection risk, respectively. The combinations
182 considered are listed in Table 4. The focus of active surveillance exclusively on cattle was maintained
183 throughout.

184 In addition, voluntary vaccination was assumed to attain a 10% protective coverage of the
185 population, and mandatory vaccination 75%. We calculated the necessary number of herds and
186 animals to sample for attaining a *CSe*-threshold of 95% or 99%. Five hundred iterations were
187 computed with combinations of the number of animals to sample per herd between 2 and 20, and
188 the number of herds to sample between 50 and 300 (by increments of 5 herds).

189 Two combinations of the number of animals in a herd and the number of herds required to sample in
190 order to obtain 95% *CSe* were identified: (point a) sampling as few animals in a herd as possible
191 (between 0 and 20), and (point b) sampling as few herds as possible. Data for the CEA was generated
192 for points a and b performing 1500 iterations for every active surveillance component and design in

all 24 standard population structures. Thus, for each of the 24 population structures we compared technical performance and costs from three components applied in five surveillance designs (RT-PCR, ELISA, BMT applied to design 1-4; and PCR only applied to design 5) in two points (a, b).

Model sensitivity analysis

Because some parameters can be influenced by policy, their effect on the technical performance of the various surveillance components (*CSe*) was assessed, namely farmer disease awareness (*fDA*), veterinary disease awareness (*vDA*), herd design prevalence (P^*_H) and within-herd design prevalence (P^*_A). As the *CSe* also depends on the population structure, model sensitivity was assessed for primarily meat producing and primarily milk producing populations. The range of investigated values is shown in Table 5. For each parameter value the stochastic distribution of *CSe* was computed with 100 iterations. The kernel density (function kde2d{MASS} in R) , i.e. the frequency of *CSe* values was plotted in 3D as function of the changing parameter and the *CSe* value. Because production animals are routinely observed by their owners, model sensitivity of clinical surveillance was assessed first followed by clinical surveillance combined with diagnostic methods used within the active surveillance (RT-PCR, ELISA or BMT).

Results

Surveillance optimisation

The number of herds and animals within a herd to reach the thresholds of 95 or 99% *CSe* were determined for three surveillance components (RT-PCR, ELISA and BMT) in 24 standard population structures. As an example, we report in Fig. 2 the analysis of a random sampling design (design 1) for populations dominated by dairy cattle in small and large herds, with 5% of the herds at risk (A and B in Fig. 2), populations dominated by dairy cattle in small and large herds, with 40% of the herds at risk (C and D), and populations dominated by beef cattle in small and large herds, with 5 % of the

217 herds at risk (E and F). In this design, RT-PCR and ELISA required similar samples to reach 95 or 99%
218 *CSe*, despite changes in dominating species, production type, or proportion at risk. As expected, BMT
219 appeared only useful if the population was dominated by dairy type cattle (see Fig. 2 E and F). Fig. 2
220 is one example of the model output, and the corresponding plots for the remaining 18 standard
221 populations are available as supplementary data.

222 An alternative perspective is provided in Fig. 3, where BMT was compared amongst the four different
223 surveillance designs in populations with small herds and 5% of the herds at risk. For design five,
224 mandatory vaccination, neither BMT nor ELISA is suited, because both rely on antibody detection in
225 milk and in blood, respectively. Fig. 3 shows that not only the dominating production type, but also
226 the design had a significant effect on the median *CSe* reached with a given sample.

227 Cost-effectiveness analysis

228 Because clinical surveillance leaves little room for sampling optimisation, the cost-effectiveness
229 analysis was only conducted on the different active surveillance designs. The points a (sampling as
230 few animals within a herd as possible) and b (sampling as few herds as possible) were identified for
231 every active component in each surveillance design to compute the total cost of the interventions
232 and plotted in Fig. 4. Because the sampling procedure was chosen to achieve the threshold of at least
233 95% *CSe*, all components are situated close to this threshold on the y-axis. BMT did not achieve this
234 threshold in a population structure with 70% meat production, but was most cost-effective in all
235 other populations for the designs 1-4 (circles on the right side in Fig. 4). Furthermore, because the
236 bulk milk surveillance was applied at herd level, it was also quite constant in cost, i.e. the cost of BMT
237 was not very sensitive to the choice of surveillance design or population structure. Consistently, to
238 substantiate freedom from BTV-8, ELISA surveillance was more expensive than BMT, but cheaper
239 than RT-PCR surveillance, due to test costs and animal based sampling.

240 Considering random sampling (design 1, black in Fig. 4) as baseline, design 3 (green in Fig. 4)
241 generated only marginal differences in total costs for all corresponding surveillance components. The

cost of vaccination was not taken into account. The range of total costs for surveillance was smallest for a sample targeted at high risk herds (design 2, red in Fig. 4), and widest for voluntary vaccination and sampling targeted at non-vaccinated herds at high risk (design 4, light blue in Fig. 4). The cost of the latter design was also the most sensitive to population structure. Compulsory vaccination with RT-PCR surveillance (design 5, dark blue in Fig. 4) was systematically more expensive than all other designs, albeit the cost of vaccination was not considered. Design 2 systematically generated the least costs compared to the baseline random design.

In addition, it was more cost-effective to sample a minimal number of animals per herd (left side in Fig. 4) compared to sampling as few different herds as possible (right side in Fig. 4), because the information gained with an additional sample in the same herd was relatively poor, while an animal from a different herd contributed more at only slightly superior costs. This effect was minute for design two, sampling high risk herds, in meat producing populations with small herds. Conversely, design five, vaccination and sampling of non-vaccinated herds at high risk produced the largest cost divergence between the points a and b (dark blue ▲ left and right in Fig. 4, respectively). This effect was more pronounced in populations with a large proportion at risk (compare A and B with C and D in Fig. 4).

Finally, if one minute observation time per animal by farmers was accounted in the cost for clinical surveillance, the approximate annual costs in the simulated populations of 50,000 herds would arise to 500 million €. The veterinary follow-up and testing cost 0.01 million €, and the information campaign 0.02 million €.

Model sensitivity analysis

The median *CSe* for clinical surveillance was very close to one for the entire range of the investigated parameters, and for all population structures. The *CSe* was reduced only when the most likely *fDA* was set lower than 0.02, while *vDA* remained within the range defined in Table 1 (and Fig. 5). Since

SeH, and hence *CSe*, is relative to the product of *fDA* and *vDA* (Equation 1) the same applies for *vDA*, i.e. the *CSe* for clinical surveillance remains at close to one as long as the product of *fDA x vDA* is larger than 0.00015, i.e. the combined probability that farmer and veterinarian detect and pursue the case. Fig. 6 shows the probability distribution of *CSe* depending on P^*_H when P^*_A is fixed at 0.0001. The median *CSe* remains at one for values of P^*_H greater than 0.015 and reaches 0.5 for values at approximately 0.002. In reverse, *CSe* is insensitive to changes in P^*_A even with a P^*_H fixed as low as 0.01 (data not shown). Consequently, also any combination of active surveillance with clinical surveillance reached *SSe* approximating one with negligible 95% confidence intervals.

Discussion

Clinical surveillance

In this study clinical surveillance was shown to detect bluetongue infections with almost 100% certainty. This is plausible because the period of observation was one year and infections with BTV-8 cause a disease which is readily detectable by clinical observation (A.R.W. Elbers et al., 2008). The *CSe* of clinical surveillance was not sensitive to variations of disease awareness by farmers (*fDA*) or veterinarians (*vDA*) within a realistic range. The observation that *CSe* of clinical surveillance does not change upon perturbations of the design prevalence further emphasizes that this surveillance component is a high value source of information to declare freedom from disease and proves that the passive surveillance components such as clinical surveillance are of importance to exclude clinical infection. The presented results are even overestimating the effect of P^*_H on the *CSe*, as under natural conditions, infections are over-dispersed and hence P^*_A should be larger than P^*_H, in contrast to the parameters used here (Faes et al., 2011). Furthermore, the model assumes a specificity of 1, implying that every observation with symptoms suspicious for BTV-8 infection is pursued until it is confirmed with highest confidence. Concurrent diseases with similar clinical spectrum would

291 therefore raise the confirmatory activity for false positive cases (and consequently the costs). These
292 are contextual interactions, which do not affect more specific surveillance components such as ELISA
293 or RT PCR. Nevertheless, the most cost-effective system to demonstrate freedom from disease is
294 clinical surveillance. This reflects findings using other authors (Souza Monteiro et al., 2012; Welby et
295 al., 2016), it should however be noted, that due to the modelling approach employed here, this is not
296 necessarily true for alternative surveillance objectives, such as early detection or estimation of
297 prevalence.

298 The *CSe* of clinical surveillance might be overestimated due to methodological reasons; indeed, the
299 conventional approach for calculating herd-level sensitivity (*SeH*) in scenario trees might not be
300 entirely appropriate for clinical observations, because it assumes that all animals in a herd are
301 equally subject to surveillance. Although biological heterogeneity in showing clinical signs is
302 considered with a maximal sensitivity of 0.67 (A.R.W. Elbers et al., 2008), individual animals are
303 unlikely to be evenly subjected to clinical observation for practical reasons. In fact, decisions about
304 whether or not to call a veterinarian will often be taken based on information relevant at herd level
305 rather than at animal level (Even Sergeant, pers. communication), and will further depend on
306 willingness to report. Hadorn and co-workers considered these probabilities with additional factors
307 for the probability to report in the Swiss surveillance system, and calculated a median sensitivity of
308 0.924 (95% CI: 0.724-0.987) for clinical surveillance in 52,983 herds (Hadorn et al., 2009). This
309 additional fraction in Equation 1 (*morbidity* x *probability of reporting by farmer* x *probability of*
310 *reporting by veterinarian*), together with a lower pert distribution for the sensitivity of clinical signs
311 and computation of the model at herd level, account for the different estimates. If in the present
312 model the sensitivity of clinical observations would be assumed to operate at herd level, this would
313 result in a maximum *SeH* of 0.67 (A.R.W. Elbers et al., 2008), which is considerably lower than the
314 median *SeH* of >0.99% that was computed. However, considering that from a veterinary service
315 perspective, the total sensitivity of this surveillance component is aggregated for 50,000 herds, even
316 this difference of *SeH* has only marginal effects on the total *CSe*.

317 The actions induced by clinical surveillance cost 0.01 million € for case follow-up and 0.02 million €
318 for the information campaign. For case follow-up, similar costs were predicted for a medium
319 awareness level by Hadorn et al. (Hadorn et al., 2009). However, a retrospective analysis (Häsler et
320 al., 2012) suggests that we over-estimated follow-up costs and sensitisation campaign by about 50%.
321 Furthermore, we have considered one minute observation time per day and cow, which may be
322 implicit in a milking procedure, but should be performed explicitly in fattening herds and young stock
323 to reach the best possible sensitivity of clinical surveillance. Also depending on season and
324 production system the quality of the observation may vary. At a labour cost of 15 €/ h and a
325 simulated population of 1.5 million animals this time spent corresponds to an annual equivalent of
326 approximately 500 million €. Although attribution of costs is a matter of policy, it is unusual to
327 compensate the farming industry for surveillance efforts, to the extent that these costs have not
328 even been reported in previous studies (Hadorn et al., 2009; Häsler et al., 2012). Also, because
329 observation for health cannot be accounted independently of other husbandry activity, it is difficult
330 to determine its true value. However, even if it this effort was considered as a specific activity, due to
331 its syndromic focus, it would need to be divided among all notifiable diseases and ultimately
332 considered in the socio-ecological context (Rich et al., 2013).

333 Active surveillance

334 Under the assumption that active surveillance was mandatory, the components assessed for active
335 surveillance in this study were assumed to be implemented independently of clinical surveillance.
336 The European Commission regulation 1266/2007 (European Commission, 2007) allows a flexible
337 implementation of active surveillance: a risk-based design can be implemented, and in terms of
338 testing for BTV-8, bulk-tank milk testing, blood ELISA and RT-PCR are available (Hadorn et al., 2009;
339 Vandenbussche et al., 2008). Risk based surveillance was most cost-effective if a small proportion of
340 the population was at high risk. With an increasing proportion of the population at high risk the cost-
341 saving effect due to risk-based surveillance became smaller considering the same relative risk.
342 However, because the size of the population at high risk and the relative risk are usually interrelated

343 and influence each other mutually in addition to the actual cost-effect. Therefore, the result of
344 modifying the population at risk by either strengthening the criteria or combining risk factors, will
345 need to be assessed for each specific case. This should be considered when risk is defined to inform
346 the policy. Also, the model doesn't account for overlap between different surveillance components
347 and thus may overestimate the number of detected cases and consequently the surveillance system
348 sensitivity. The administration and planning of risk-based surveillance was not taken into account in
349 this model and would thus be underestimated. In order to be more cost-effective than random
350 sampling, this amount could arise to roughly 0.3 million € for 5% of the modelled population at risk,
351 but only 0.2 million € for 40% at risk (Fig. 4). This further emphasises, that with a large population at
352 high risk, risk-based surveillance is not necessarily cost-effective.

353 Although the five surveillance designs investigated in this study were just a few of many possible
354 options, the authors feel that they represent some fundamental choices that are made by policy
355 makers. Bulk-tank milk testing was most cost-effective with relatively little variance of cost between
356 designs, although its *CSe* varied depending on the choice of sampling design (Fig. 3). Moreover, it was
357 not suited to attain a required threshold of 95% sensitivity for three designs (1, 3 and 5) when a
358 proportion of 70% of the population were kept for meat rather than dairy production (Fig. 3).

359 RT-PCR and blood serology using ELISA provided similar information at similar cost in populations
360 where 5% of the herds were at high risk and risk-based surveillance was performed. However, with
361 rising proportion at high risk (with constant relative risks), the costs of risk-based surveillance
362 increased due to the larger sample size required. This amplified the four-fold higher costs for an RT-
363 PCR compared to an ELISA. These observations are primarily because the call-out fee of 65 € was
364 equal for both regimes, while the difference in test costs of 9 € (ELISA) and 40 € (RT-PCR) had
365 relatively little impact due to the comparably little added value of an additional sample in the same
366 herd. In this context it appeared that sampling a maximal number of herds (point a) was most cost-
367 effective due to the fact, that one sample from a new herd added more information than a sample
368 drawn from a herd that was already sampled. In the present model this compensated the additional

cost of 65 € for the herd visit. It must be emphasised that the distinct capacities of RT-PCR and ELISA to detect antigens and antibodies, respectively, both contribute to evidence for freedom from BTV-8. They provide distinct supplementary information for surveillance for early detection or the assessment of prevalence or vaccination coverage.

Voluntary vaccination with an assumed reduction of the susceptible herds by 10% and surveillance targeted at non-vaccinated herds only marginally reduced costs compared to random sampling. In contrast, mandatory vaccination with an assumed coverage of 75% reduced the cost of surveillance targeted at herds at high risk, particularly if this was only a small proportion of the population. These estimates considered surveillance costs only, and did not include the costs for vaccination. Therefore, the cost for vaccination justifiable with its effect on surveillance should not exceed the approximately 400'000 € saved by the surveillance design 5 compared to the baseline random design (dark blue versus black in Fig. 4). Given the population of cattle of approximately 1.5 million this would justify a cost of 0.26 € per vaccine, bearing in mind that this only covers the cost of surveillance and not the benefits of vaccination preventing the disease.

Conclusions

Under the assumption that BTV-8 manifests clinically as described by Elbers et al. (A.R.W. Elbers et al., 2008), freedom from disease in a population can be established with almost certainty over the period of one year using clinical surveillance alone. Additional investment in active surveillance would therefore economically only be justified, if no clinical manifestation is suspected or other surveillance objectives are to be provided such as early detection. In the first case, the regulatory requirement of demonstrating freedom from disease is questionable since due to the lack of clinical manifestation, the economic importance arises only from the regulation and not from the disease. In the second case, surveillance is only cost-effective if the time gain and consequently smaller impact of a disease introduction compared to clinical surveillance alone, justifies the additional costs. In this case it is important to realise that 1) this requires a high sampling frequency, 2) for emerging

diseases diagnostic tools may not be available, 3) the risk estimation to target risk-based sampling may induce high uncertainty, and 4) scenario trees cannot provide reliable information on the time gain.

With the legal requirement for active surveillance, risk-based surveillance to prove freedom from disease is only cost-effective if a small proportion of the population is at high risk. The best cost-effectiveness is obtained by sampling the maximal number of herds rather than more animals per herd. This effect is expected to grow with increasing aggregation of infections within herds. The effect of mandatory vaccination against BTV-8 on surveillance justifies a cost of < 0.26 € per vaccine and voluntary vaccination only marginally reduces the cost of surveillance. Finally, bulk-tank milk testing is the method of choice to actively demonstrate freedom from disease in populations dominated by dairy production.

Acknowledgements

The authors would like to acknowledge Jörn Gethman, Maya Gussman from the Friedrich-Loeffler-Institute Riems for discussing models and parameters used in this study, Ian Kopacka from the Austrian Agency for Health & Food Safety for cross-checking the R code of the models, and Even Sergeant from AusVet Animal Health Services for a critical discussion of scenario trees applied to clinical surveillance. The project was funded by the EMIDA ERA-NET through the Swiss Federal Food Safety and Veterinary Office.

References

Alban, L., Boes, J., Kreiner, H., Petersen, J.V., Willeberg, P., 2008. Towards a risk-based surveillance for Trichinella spp. in Danish pig production. Prev. Vet. Med. 87, 340–57.

Calvo-Artavia, F.F., Nielsen, L.R., Alban, L., 2012. Epidemiologic and economic evaluation of risk-based meat inspection for bovine cysticercosis in Danish cattle. Prev. Vet. Med. 108, 253–261. doi:10.1016/j.prevetmed.2012.11.002

Clasen, T., Haller, L., Walker, D., Bartram, J., Cairncross, S., 2007. Cost-effectiveness of water quality interventions for preventing diarrhoeal disease in developing countries. J. Water Health 5, 599–

608. doi:10.2166/wh.2007.010

Core R Team, 2013. R: A Language and Environment for Statistical Computing.

Eichler, H.G., Kong, S.X., Gerth, W.C., Mavros, P., J??nsson, B., 2004. Use of cost-effectiveness analysis in health-care resource allocation decision-making: How are cost-effectiveness thresholds expected to emerge? Value Heal. 7, 518–528. doi:10.1111/j.1524-4733.2004.75003.x

Elbers, A.R.W., Backx, A., Ekker, H.M., van der Spek, A.N., van Rijn, P.A., 2008. Performance of clinical signs to detect bluetongue virus serotype 8 outbreaks in cattle and sheep during the 2006-epidemic in The Netherlands. Vet. Microbiol. 129, 156–62. doi:10.1016/j.vetmic.2007.10.034

Elbers, A.R.W., Backx, A., Mintiens, K., Gerbier, G., Staubach, C., Hendrickx, G., van der Spek, A., 2008. Field observations during the Bluetongue serotype 8 epidemic in 2006. II. Morbidity and mortality rate, case fatality and clinical recovery in sheep and cattle in the Netherlands. Prev. Vet. Med. 87, 31–40. doi:10.1016/j.prevetmed.2008.06.003

European Commission, 2007. Ec 1266/2007. Off. J. Eur. Union 37–52.

Faes, C., Aerts, M., Litière, S., Méroc, E., Van der Stede, Y., Mintiens, K., 2011. Estimating herd prevalence on the basis of aggregate testing of animals. J. R. Stat. Soc. Ser. A (Statistics Soc. 174, 155–174. doi:10.1111/j.1467-985X.2010.00652.x

Guo, X., Claassen, G.D.H., Oude Lansink, A.G.J.M., Loeffen, W., Saatkamp, H.W., 2014. Economic Analysis of Classical Swine Fever Surveillance in the Netherlands. Transbound. Emerg. Dis. 1, 1–18. doi:10.1111/tbed.12274

Hadorn, D.C., Haracic, S.S., Stärk, K.D.C., 2008. Comparative assessment of passive surveillance in disease-free and endemic situation: example of Brucella melitensis surveillance in Switzerland and in Bosnia and Herzegovina. BMC Vet. Res. 4, 52. doi:10.1186/1746-6148-4-52

Hadorn, D.C., Racloz, V., Schwermer, H., Stärk, K.D.C., 2009. Establishing a cost-effective national surveillance system for Bluetongue using scenario tree modelling. Vet. Res. 40, 1–14. doi:10.1051/vetres/2009040

Häsler, B., Howe, K.S., Di Labio, E., Schwermer, H., Stärk, K.D.C., 2012. Economic evaluation of the surveillance and intervention programme for bluetongue virus serotype 8 in Switzerland. Prev. Vet. Med. 103, 93–111.

Hutubessy, R., Chisholm, D., Edejer, T.T., 2003. Cost Effectiveness and Resource Allocation priority-setting in the health sector. Cost Eff. Resour. Alloc. 1, 1–13. doi:10.1186/1478-7547-1-8

ID Vet, 2008. ID Screen Bluetongue Milk Indirect: Validation Data for individual and bulk milk samples (No. BT MILKver0801).

Levin, H.M., 1995. Cost-effectiveness Analysis. Int. Encycl. Econ. Educ.

Martin, P. a J., Cameron, a R., Greiner, M., 2007. Demonstrating freedom from disease using multiple complex data sources 1: a new methodology based on scenario trees. Prev. Vet. Med. 79, 71–97.

McEwan, P.J., 2012. Cost-effectiveness analysis of education and health interventions in developing countries. J. Dev. Eff. 4, 189–213. doi:10.1080/19439342.2011.649044

Mehlhorn, H., Walldorf, V., Klimpel, S., Jahn, B., Jaeger, F., Eschweiler, J., Hoffmann, B., Beer, M., 2007. First occurrence of Culicoides obsoletus-transmitted Bluetongue virus epidemic in Central Europe. Parasitol. Res. 101, 219–28. doi:10.1007/s00436-007-0519-6

Nafzger, R., 2016. Assessment of the effectiveness of bluetongue surveillance in Belgium and Switzerland. University of Bern.

Pinior, B., Lebl, K., Firth, C., Rubel, F., Fuchs, R., Stockreiter, S., Loitsch, A., K??fer, J., 2015. Cost analysis of bluetongue virus serotype 8 surveillance and vaccination programmes in Austria from 2005 to 2013. Vet. J. 206, 154–160. doi:10.1016/j.tvjl.2015.07.032

Rich, K.M., Denwood, M.J., Stott, A.W., Mellor, D.J., Reid, S.W.J., Gunn, G.J., 2013. Systems approaches to animal disease surveillance and resource allocation: methodological frameworks for behavioral analysis. PLoS One 8, e82019. doi:10.1371/journal.pone.0082019

Russel, L.B., Siegel, J.E., Daniels, N., Gold, M.R., Luce, B.R., Mandelblatt, J.S., 1996. Cost-Effectiveness Analysis as a guide to Resource Allocation in Health: Roles and Limitations. Oxford University Press, New York, New York, USA.

Souza Monteiro, D.M., Carrasco, L.R., Moffitt, L.J., Cook, A.J.C., 2012. Robust surveillance of animal diseases: An application to the detection of bluetongue disease. Prev. Vet. Med. 105, 17–24.

Toussaint, J.-F., Vandenbussche, F., Mast, J., De Meester, L., Goris, N., Van Dessel, W., Vanopdenbosche, E., Kerkhofs, P., De Clercq, K., Zientara, S., Sailleau, C., Czaplicki, G., Depoorter, G., Dochy, J.-M., 2006. Bluetongue in northern Europe. Vet. Rec. 159, 327–327. doi:10.1136/vr.159.10.327-a

Vandenbussche, F., Vanbinst, T., Verheyden, B., Van Dessel, W., Demeestere, L., Houdart, P., Bertels, G., Praet, N., Berkvens, D., Mintiens, K., Goris, N., De Clercq, K., 2008. Evaluation of antibody-ELISA and real-time RT-PCR for the diagnosis and profiling of bluetongue virus serotype 8 during the epidemic in Belgium in 2006. Vet. Microbiol. 129, 15–27. doi:10.1016/j.vetmic.2007.10.029

Welby, S., Méroc, E., Faes, C., De Clercq, K., Hooyberghs, J., Mintiens, K., Van der Stede, Y., 2013. Bluetongue surveillance system in Belgium: a stochastic evaluation of its risk-based approach effectiveness. Prev. Vet. Med. 112, 48–57. doi:10.1016/j.prevetmed.2013.07.005

Welby, S., van Schaik, G., Veldhuis, A., Brouwer-Middelesch, H., Peroz, C., Santman-Berends, I.M., Fourichon, C., Wever, P., Van der Stede, Y., 2016. Effectiveness and Cost Efficiency of Different Surveillance Components for Proving Freedom and Early Detection of Disease: Bluetongue Serotype 8 in Cattle as Case Study for Belgium, France and the Netherlands. Transbound. Emerg. Dis. 1–11. doi:10.1111/tbed.12564

Tables

Table 1. Parameters and input values used in the scenario tree model for Bluetongue surveillance in Europe. Variable or uncertain parameters were modelled stochastically as PERT distributions (with the three input values stated in the table), and otherwise fixed values were used. Where no references are given, estimates were based on combined expert opinions reported by Nafzger and co-workers (Nafzger, 2016). The time resolution of the scenario tree is one year.

Parameter description	Symbol	Minimum	Most likely	Maximum
Herd design prevalence[1]	P^*_H		0.002	
Within-herd design prevalence[1]	P^*_A		0.005	
Number of herds			50,000	
Herd size		1	30 or 100	400
Morbidity due to BTV-8 in cattle[2]	$morb_c$		0.025	
Farmer Disease Awareness in cattle[3]	fDA_c	0.002	0.150	0.670
Veterinary Disease Awareness in cattle[3]	vDA_c	0.002	0.550	0.670
Sensitivity PCR in cattle[4]	$PCR\text{-}Se_c$	0.990	0.995	0.999
Sensitivity ELISA in cattle[4]	$ELISA\text{-}Se_c$	0.853	0.887	0.923
Sensitivity BMT in cattle[5]	$BMT\text{-}Se_c$		0.540	
Morbidity due to BTV-8 in sheep[2]	$morb_s$		0.077	
Farmer Disease Awareness[3] in sheep	fDA_s	0.044	0.200	0.760
Veterinary Disease Awareness[3] in sheep	vDA_s	0.044	0.600	0.760
Sensitivity PCR in sheep[4]	$PCR\text{-}Se_s$	0.990	0.996	0.999
Sensitivity ELISA in sheep[6]	$ELISA\text{-}Se_s$	n.a.	n.a.	n.a.
Sensitivity BMT in sheep[6]	$BMT\text{-}Se_s$		n.a.	

[1]according to the current version of the EC 1266/2007 (European Commission, 2007) a prevalence of 0.05 in the bovine population of the Member State must be detected by the surveillance system with 95 % confidence. Prior to the amendment of 30th May 2012 (commission implementing regulation No 456/2012) the detection of a prevalence of 0.005 was required. Hence, these design prevalences assumed in the present study are more stringent conditions than those currently implemented in the EU.

[2]according to Elbers and co-workers (Armin R. W. Elbers et al., 2008). To compute the annual morbidity per animal, the observed mean number of sick cattle (2.1) and sheep (2.7) per herd was divided by the mean herd size (85.2 and 35.5, respectively).

[3]Minimal disease awareness (DA) was 0.2% and 4.4% for cattle and sheep, respectively, while maximal DA corresponded to the sensitivity of clinical signs estimated by Elbers and co-workers and implemented by Welby et al. (A.R.W. Elbers et al., 2008; Welby et al., 2013). Most likely values were set at roughly ¼ of the range for farmers and ¾ for veterinarians to simulate their differing professional expertise.

[4]according to Vandenbussche et al. (Vandenbussche et al., 2008).

[5]according to the diagnostic test manufacturer (ID Vet, 2008).

[6] because in the scenario, no active surveillance in sheep was considered, these values were not used.

Table 2. Costs in Euros for surveillance activity for Bluetongue surveillance. Estimates are based on the results of the questionnaire by Nafzger and co-workers (Nafzger, 2016) and the authors' opinion to represent a western European average. The same costs applied to the cattle and the sheep population, however in the present study active surveillance was only performed on the cattle population as required by the EC regulation. The worksheet provided as supplementary material allows for time dependent compensation or flat rates, e.g. clinical examination, because we calculated with time-dependent payments, the flat rate fields are set at zero.

	cost [Euros]	unit cost
Labour cost		
Farmer routine check	15	hour
Veterinarian intervention	40	hour
Abattoir worker	23	hour
Lab. Technician	23	hour
Epidemiologist/ senior scientist	60	hour
Compensations		
Call-out fee veterinarian	65	visit
Clinical examination vet.	0	sample
Lab. Technician	0	sample
Laboratory costs		
C-ELISA test	9	sample
RT-PCR	40	sample
Virus isolation	30	sample
Immunohistochemistry	20	sample
Sampling material (blood)	1	sample
Miscellaneous costs		
Transportation incl. packaging	12	visit

Communication of results	0	visit
Cost of information campaign for farmers	20,000	population and year

Table 3. Time expenditure in hours for different clinical and diagnostic activities as applied in the cost-effectiveness analysis. Estimates are based on the results of the questionnaire by Nafzger and co-workers (Nafzger, 2016) and the authors' opinion to represent a western European average. The same costs applied to the cattle and the sheep population. For laboratory analyses also covered in Table 2 flat rates are employed, hence time expenditure is stated as zero, however, the worksheet provided as supplementary material also allows for time-dependent calculations.

	hours	unit
Time for clinical visit		
Farmer routine check	0.02	animal and day
Veterinarian intervention	0.04	animal
Time for sampling		
Blood	0.08	sample
Tissue	0.17	sample
Milk	0.02	farm and day
Time for lab. work and analysis		
ELISA	0	sample
RT-PCR	0	sample
Virus isolation	0	sample
Immunohistochemistry	0	sample
Epidemiological data analysis	1.00	farm and year

Table 4. Combination of characteristics used for the 24 simulated population structures considered for the optimisation of BTV-8 surveillance. To compute a population, one option of each column are combined. The effect of population composition on surveillance component sensitivity (CSe) is reported in the results section.

Cattle:Sheep	X	Dairy:Meat	X	Herd Size	X	Proportion at high risk
70 : 30		70 : 30		S		5 %
or 30 : 70		or 30 : 70		or L		or 10 %
						or 40 %

Table 5. Parameters and their range used to analyse model sensitivity of BTV-8 surveillance scenario tree models. Dependence of surveillance component sensitivity (CSe) on the parameters is reported in the results section.

Parameter name	Symbol	Minimum	Maximum
Median farmer disease awareness	*fDA*	0.00	0.50
Median veterinary disease awareness	*vDA*	0.00	0.50
Herd design prevalence	P^*_H	0.00	0.04
Within-herd design prevalence	P^*_A	0.00	0.04

Figures

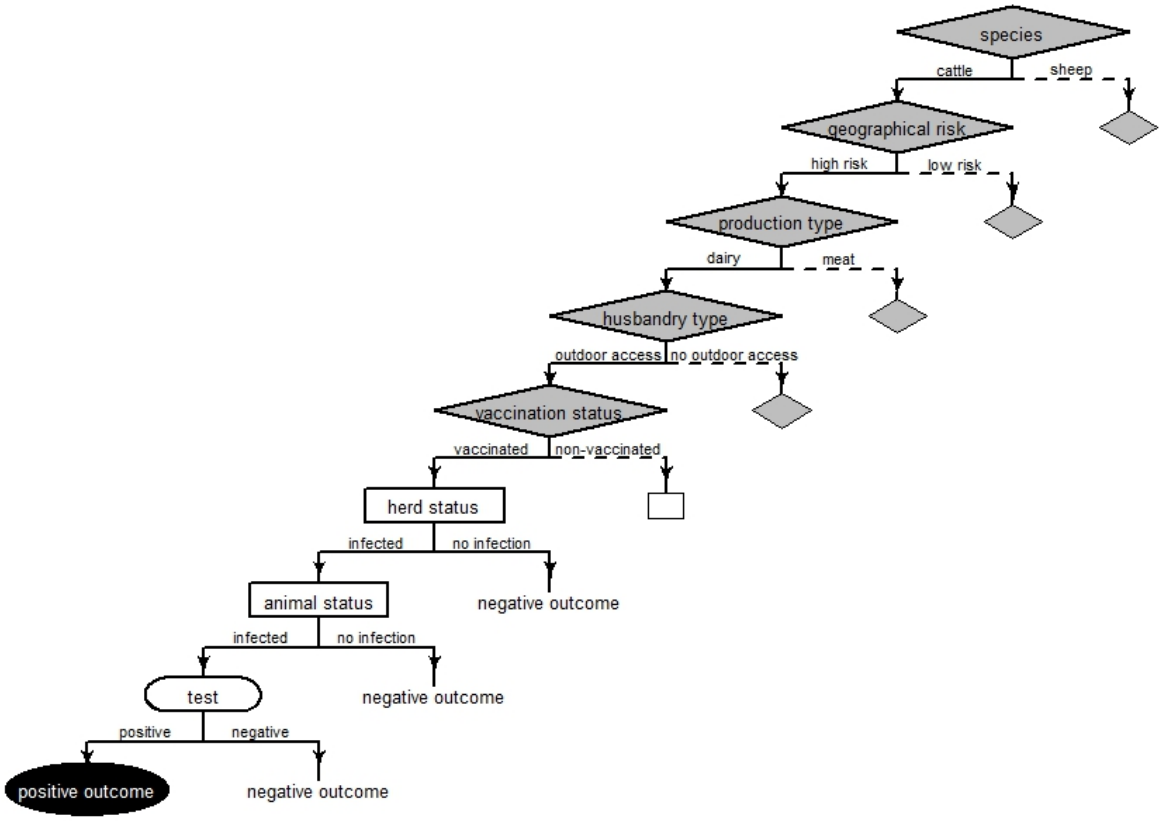


Fig. 1 Flowchart illustrating the structure of the scenario tree for an active surveillance component. Risk nodes (diamonds), infection nodes (rectangles) and detection nodes (rounded boxes) are set in sequence. Dashed lines indicate that a branch continues identically to the branch drawn in solid lines from that particular node. Perfect specificity (Sp=1) is assumed at the end of each branch and the probability of a positive outcome (black ellipse) is computed.

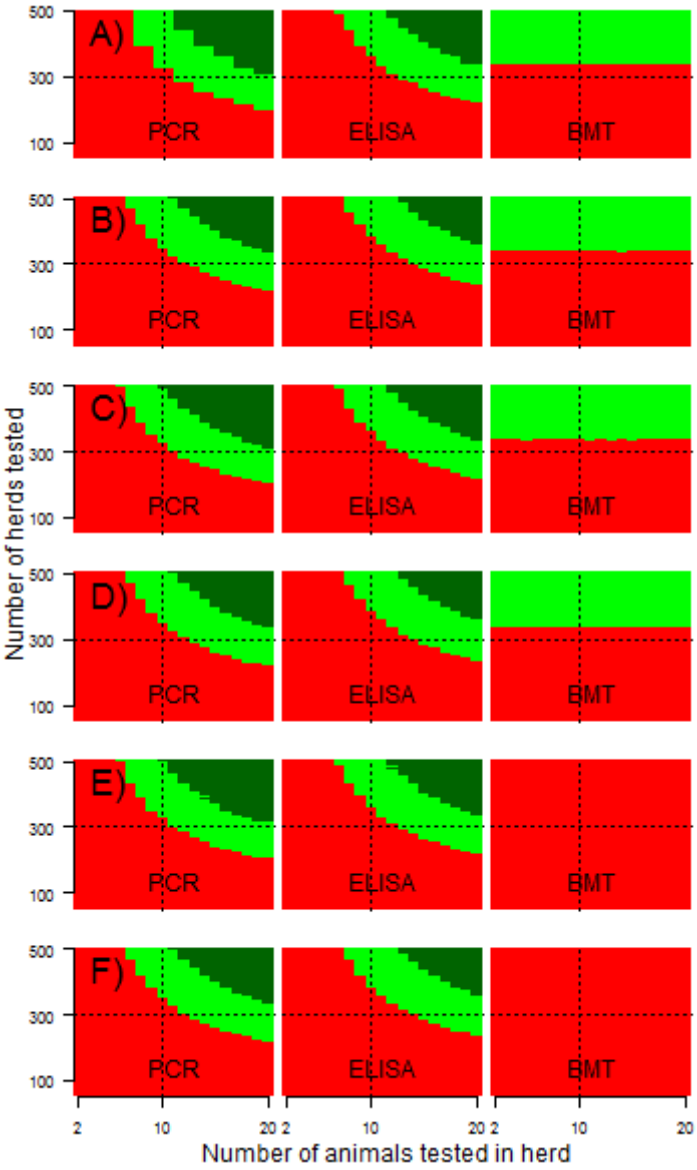
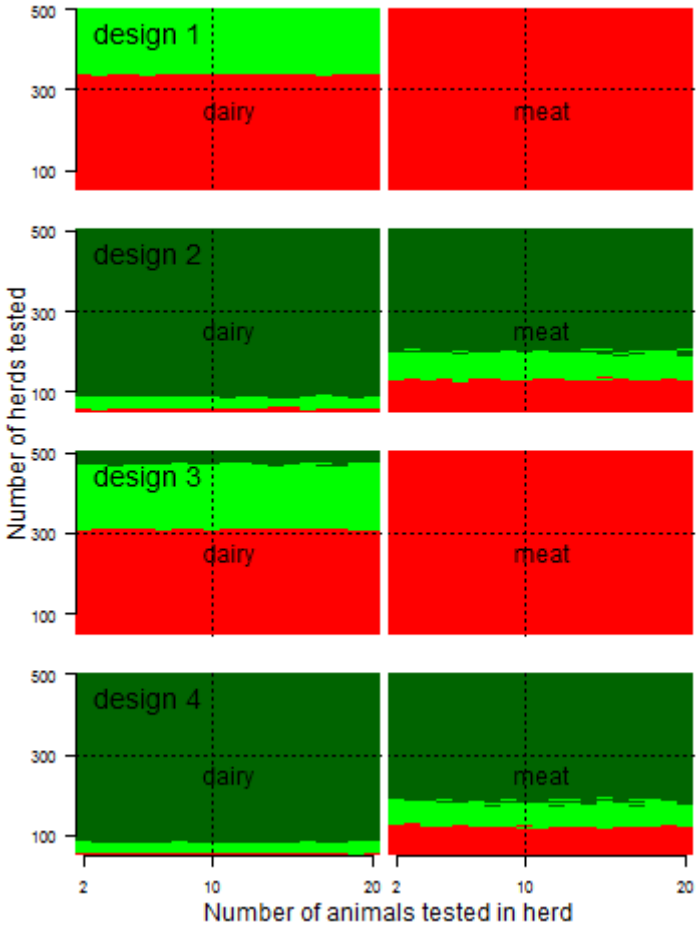


Fig. 2 Surveillance sensitivity for random sampling (design 1). The plot reports the median of 500 iterations. It shows the median number of animals sampled in a herd (x-axis) and the median number of herds sampled (y-axis) in a population of 50,000 herds to reach a surveillance sensitivity of 95% (light green) or 99% (dark green) for six population structures (the 18 others are available as supplementary data). For each population structure, three active surveillance components were assessed blood RT-PCR assay (PCR), blood ELISA (ELISA) or bulk milk testing (BMT) with ELISA. The population structures considered were: A) a population composed of small herds (median 30 cows/herd) with 70% cattle and 30% sheep, 70% dairy and 30% meat production, where 5% of the population is at high risk of infection by BTV-8; B) a population composed

562 the same as A), but with large herds (median 100 cows/herd); populations C) and D) have the same structure, but 40% are
563 at risk, while in populations E) and F) again 5% are at risk, but 70% of the animals are in meat and 30% in dairy production.

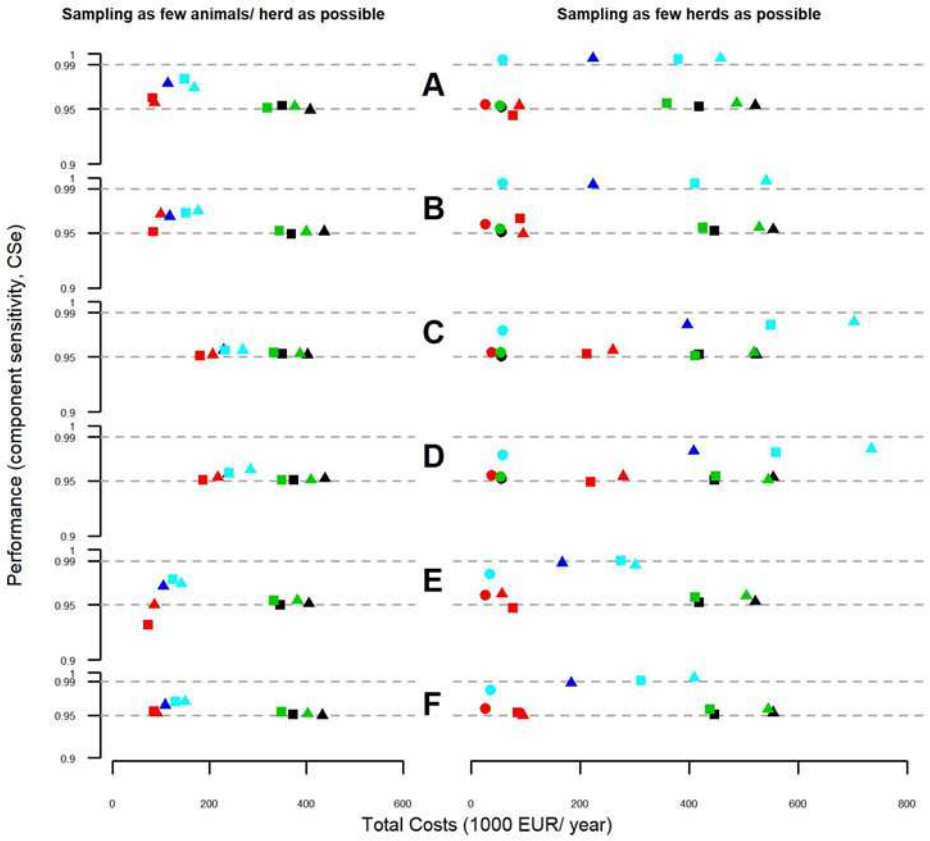
564

565



566

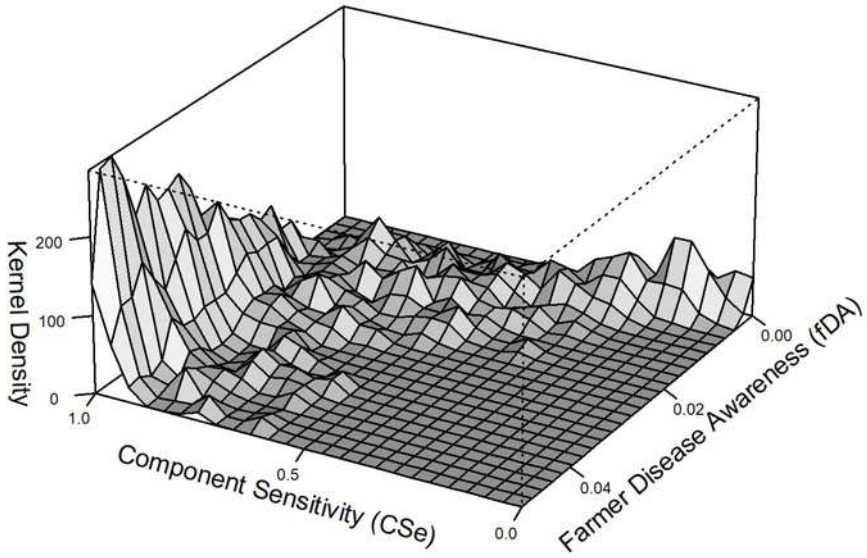
567 Fig. 3 Surveillance sensitivity for bulk milk testing (BMT) in populations composed of small herds with 5% at high risk of
568 infection with BTV-8. The plot reports the median of 500 iterations. It shows the median number of animals sampled in a
569 herd (x-axis) and the median number of herds sampled (y-axis) in a population of 50,'000 herds to reach a surveillance
570 sensitivity of 95% (light green) or 99% (dark green). The plots on the left show the sensitivity for populations dominated by
571 dairy cattle and the plots on the right populations dominated by beef production. The surveillance strategies considered
572 were: **design 1**) random sampling, **design 2**) target on high risk herds, **design 3**) voluntary vaccination and target on non-
573 vaccinated herds, **design 4**) voluntary vaccination and target on non-vaccinated herds at high risk. **Design 5**, with
574 mandatory vaccination is not suitable for BMT as the latter relies on detection of antibodies which are present in all
575 vaccinated animals.



576

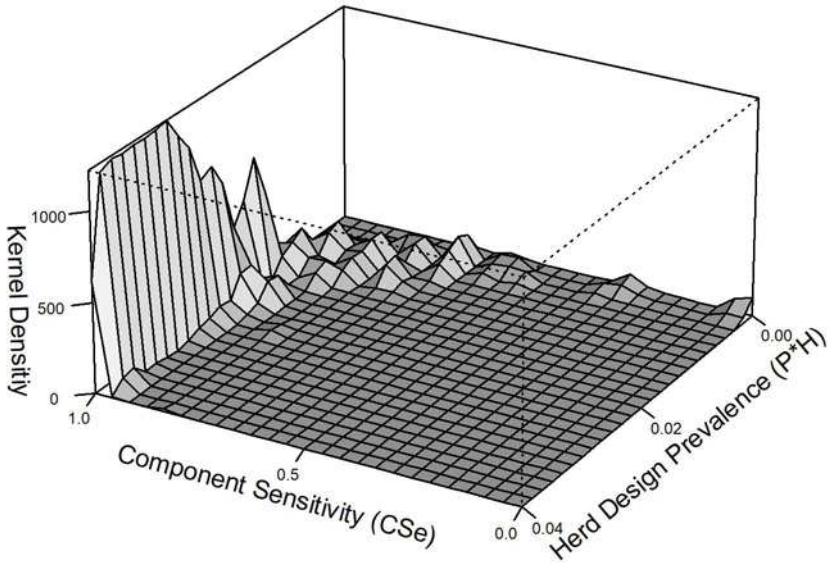
577 Fig. 4 Comparison of sampling the least number of animals per herd (also referred to as “point a”, left) and sampling the
578 least number of herds (also referred to as “point b”, right) in different population structures (letters A-F, see below). The y-
579 axis shows the median technical performance (component sensitivity, CSe) of the surveillance design and the x-axis the
580 median total annual costs of 1500 iterations for the five surveillance designs: Random sampling (design 1, **black**), high risk
581 targeting (design 2, **red**), voluntary vaccination and targeting non-vaccinated animals (design 3, **green**), voluntary
582 vaccination and targeting non-vaccinated animals in high risk herds (design 4, **light blue**), and mandatory vaccination and
583 RT-PCR in high risk herds (design 5, **dark blue**). The surveillance components are coded as shapes: RT-PCR (▲), ELISA (■)
584 and BMT (●). The component sensitivity was assessed in different population structures: **A)** a population composed of
585 small herds (median 30 cows/herd) with 70% cattle and 30% sheep, 70% dairy and 30% meat production, where 5% of the
586 population is at high risk of infection by BTV-8; **B)** a population composed the same as A), but with large herds (median 100
587 cows/herd); populations **C)** and **D)** have the same structure, but 40% are at risk, while in populations **E)** and **F)** again 5% are
588 at risk, but 70% of the animals are in meat and 30% in dairy production.

589



590

591 Fig. 5. Kernel density (z-axis), i.e. the frequency of the component sensitivity (*CSe, x-axis*) of clinical surveillance depending
592 on variation of farmer disease awareness in increments of 0.0001 (*fDA, y-axis*) in the Belgian setting as reported by Nafzger
593 and co-workers (Nafzger, 2016). The two-dimensional kernel density estimation was performed with the function
594 kde2d{MASS} in R, performing 1000 iterations for each *fDA* value. Veterinary disease awareness (*vDA*) was kept constant at
595 0.01. Due to Equation (1), for any product of *fDA*vDA* greater than 0.00015, the *CSe* was converging towards one.



596

597 Fig. 6. Kernel density (z-axis), i.e. the frequency of component sensitivity (*CSe,* x-axis) of clinical surveillance depending on
598 the variation of herd design prevalence in increments of 0.0002 (P^*_H, y-axis) in the Belgian setting as reported by Nafzger
599 and co-workers (Nafzger, 2016). The two-dimensional kernel density estimation was performed with the function
600 kde2d{MASS} in R, performing 1000 iterations for each P^*_H value. Within-herd design prevalence (P^*_A) is fixed at 0.0001.
601 Note that despite a modelled unnatural under-dispersion of infections, the mean *CSe* remains close to 1.0 from values
602 greater than 0.15. As infections are naturally over-dispersed, *CSe* should be even less sensitive to changes in P^*_H.

603

604