Output-based assessment of herd-level freedom from infection in endemic situations: Application of a Bayesian Hidden Markov model

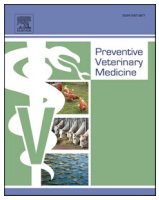
Annika M. van Roon, Aurélien Madouasse, Nils Toft, Inge M. G. A. Santman-Berends, Jörn Gethmann, Jude Eze, Roger W. Humphry, David Graham, Maria Guelbenzu-Gonzalo, Mirjam Nielen, et al.

Preventive Veterinary Medicine 204 (2022) 105662

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

journal homepage: www.elsevier.com/locate/prevetmed



Output-based assessment of herd-level freedom from infection in endemic situations: Application of a Bayesian Hidden Markov model

A.M. van Roon [a,*], A. Madouasse [b], N. Toft [c], I.M.G.A. Santman-Berends [d], J. Gethmann [e], J. Eze [f,k], R.W. Humphry [f], D. Graham [g], M. Guelbenzu-Gonzalo [g], M. Nielen [a], S.J. More [h], M. Mercat [b], C. Fourichon [b], C. Sauter-Louis [e], J. Frössling [i,j], E. Ågren [i], G.J. Gunn [f], M.K. Henry [f], G. van Schaik [a,d]

[a] Department of Population Health Sciences, Unit Farm Animal Health, Faculty of Veterinary Medicine, Utrecht University, The Netherlands
[b] INRAE, Oniris, BIOEPAR, 44300 Nantes, France
[c] IQinAbox ApS, Værløse, Denmark
[d] Royal GD, Deventer, The Netherlands
[e] Institute of Epidemiology, Friedrich-Loeffler-Institute, Südufer 10, 17493 Greifswald, Germany
[f] Scotland's Rural College, Kings Buildings, West Mains Road, Edinburgh EH9 3JG, United Kingdom
[g] Animal Health Ireland, Carrick on Shannon, Co. Leitrim, Ireland
[h] Centre for Veterinary Epidemiology and Risk Analysis, UCD School of Veterinary Medicine, University College Dublin, Dublin, Ireland
[i] Department of Disease Control and Epidemiology, National Veterinary Institute (SVA), 751 89 Uppsala, Sweden
[j] Department of Animal Environment and Health, Swedish University of Agricultural Sciences, 532 23 Skara, Sweden
[k] Biomathematics and Statistics Scotland (BioSS), Kings Buildings, Peter Guthrie Tait Road, Edinburgh EH9 3FD, United Kingdom

ARTICLE INFO

Keywords:
Freedom from infection
Output-based surveillance
Control program
Bovine viral diarrhoea virus

ABSTRACT

Countries have implemented control programmes (CPs) for cattle diseases such as bovine viral diarrhoea virus (BVDV) that are tailored to each country-specific situation. Practical methods are needed to assess the output of these CPs in terms of the confidence of freedom from infection that is achieved. As part of the STOC free project, a Bayesian Hidden Markov model was developed, called STOC free model, to estimate the probability of infection at herd-level. In the current study, the STOC free model was applied to BVDV field data in four study regions, from CPs based on ear notch samples. The aim of this study was to estimate the probability of herd-level freedom from BVDV in regions that are not (yet) free. We additionally evaluated the sensitivity of the parameter estimates and predicted probabilities of freedom to the prior distributions for the different model parameters. First, default priors were used in the model to enable comparison of model outputs between study regions. Thereafter, country-specific priors based on expert opinion or historical data were used in the model, to study the influence of the priors on the results and to obtain country-specific estimates.

The STOC free model calculates a posterior value for the model parameters (e.g. herd-level test sensitivity and specificity, probability of introduction of infection) and a predicted probability of infection. The probability of freedom from infection was computed as one minus the probability of infection. For dairy herds that were considered free from infection within their own CP, the predicted probabilities of freedom were very high for all study regions ranging from 0.98 to 1.00, regardless of the use of default or country-specific priors. The priors did have more influence on two of the model parameters, herd-level sensitivity and the probability of remaining infected, due to the low prevalence and incidence of BVDV in the study regions. The advantage of STOC free model compared to scenario tree modelling, the reference method, is that actual data from the CP can be used and estimates are easily updated when new data becomes available.

* Corresponding author.
E-mail address: a.m.vanroon@uu.nl (A.M. van Roon).

https://doi.org/10.1016/j.prevetmed.2022.105662
Received 31 January 2022; Received in revised form 16 April 2022; Accepted 25 April 2022
Available online 30 April 2022

1. Introduction

In the European Union (EU), bovine viral diarrhoea virus (BVDV) is a formerly unlisted cattle disease that is now listed as category C in the new Animal Health Law ((EU) 2016/249). Across Europe, there is a wide variety of control programmes (CPs), tailored to each country-specific situation. This means that disease surveillance and control measures are based on factors such as between-herd prevalence, cattle density, farm management practices and other risk factors resulting in variation between CPs. Currently, few validated methods exist to assess the output of these CPs in terms of the confidence of freedom from infection that is achieved (Cameron, 2012). From these heterogeneous surveillance data collected in different epidemiological contexts, practical methods are needed to quantify the probability that infection is absent, commonly referred to as confidence of freedom from infection.

Scenario tree modelling (STM) is the most frequently used method to assess the confidence of freedom from infection (Martin et al., 2007), often to confirm a free status at country or region level (Norström et al., 2014). With this method, the probability of freedom is calculated for a given design prevalence, a hypothetical prevalence of infection at herd-level against which surveillance sensitivity is measured, and the probability of introduction of the modelled pathogen while assuming that the specificity of the surveillance system is 100% (Martin et al., 2007; Cameron, 2012). More recently, the STM approach has been adapted to situations in which the probability of freedom can be estimated for groups of herds in countries that are not free from infection (Toftaker et al., 2020; Ågren et al., 2018; Veldhuis et al., 2017). The disadvantage of STM is the prerequisite to include a design prevalence and a probability of introduction of infection, which can be challenging when a design prevalence is not provided by legislation or when infection has been absent for many years. Therefore, new, more data-driven methods are being investigated to estimate the confidence of freedom for (individual) herds.

Modelling freedom from infection was recently investigated using Bayesian latent class methods (Flay et al., 2021; Yang et al., 2019; Heisey et al., 2014). As part of the STOC free project (van Roon et al., 2019), a Bayesian Hidden Markov model (HMM) to estimate the probability of infection at herd-level was developed, called the STOC free model (Madouasse et al., 2022; Mercat et al., 2022). The aim of this model is to use heterogeneous inputs to generate objective and standardised outputs to assess the validity and performance of CPs. The main advantage of a Bayesian HMM over other Bayesian latent class methods is that, in addition to test imperfection, a HMM accounts for temporal correlation in longitudinal surveillance data. The STOC free model uses longitudinal test results from CPs to model the latent status regarding infection at the herd-month level. This latent status is the true (but unknown) herd status that is predicted using test results with a certain sensitivity and specificity. The herd status in each month depends on the herd status in the previous month, is influenced by prior information on infection dynamics, and is re-estimated considering new test results. Moreover, it can be influenced by information on presence of risk factors e.g. trade or local infection prevalence, that are modelled using logistic regression.

To test the usefulness of the STOC free model in the assessment of probability of freedom from infection, this method was applied to BVDV field data from CPs based on ear notch samples in four study regions i.e. the Netherlands, the Paderborn district in Germany, the Republic of Ireland (called Ireland in the remainder of this paper) and Scotland. BVD was selected as a case disease because these study regions have similar CPs based on ear notch testing, but have different contexts i.e. different prevalence, disease transmission dynamics and risk factors. The objectives of this study were two-fold. First, to estimate the herd-level probability of freedom from BVDV achieved in different study regions with CPs based on ear notch sampling. Second, to evaluate the sensitivity of the parameter estimates and predicted probabilities of freedom from infection to the prior distributions used for the different model parameters.

2. Materials and methods

The STOC free model is described in detail by Madouasse et al. (2022) and Mercat et al. (2022). Features of the model that are important for the current study are described in more detail in Appendix 1. Briefly, the model outcome is a herd-level status regarding infection that is imperfectly measured by one or several tests and that has a certain probability of changing between consecutive months. The status of each herd is predicted on the last month for which test results are available in the CP. Data from previous months are used for parameter estimation. Test imperfection is accounted for using herd-level sensitivity and specificity. The infection dynamics are modelled with two parameters: (1) one parameter describing the probability of new infection per time-step and (2) another parameter describing the probability of remaining infected between consecutive time-steps. The discrete outcome that is imperfectly observed and that undergoes a Markovian dynamic makes this model a Hidden Markov Model. The estimation of model parameters and the prediction of the probabilities of infection are performed in a Bayesian framework which allows the incorporation of available knowledge on test characteristics and infection dynamics.

In the current study, the latent status of interest is defined as the presence of one or more BVDV-infected, persistently infected animal(s) (PIs) at foot in the herd. An animal is defined as positive when at least one virus test result is positive, even if the result has not been confirmed with a second virus test. All BVDV CPs within this study are based on ear notch testing of newborn calves (details see section 2.1).

The model requires longitudinal test data per herd (see section 2.2) and prior information on the model parameters (e.g. herd-level test sensitivity and specificity, probability of becoming status positive, see section 2.3).

2.1. BVDV CPs in four different study regions

In the Netherlands, a voluntary CP was in place between 1998 and 2017 (van Duijn et al., 2019). Following slight adaptation, an industry-led CP became mandatory for dairy herds in 2018. The aim of the CP was to eliminate BVDV from herds by detecting and removing PIs and monitoring the subsequent BVDV free status. Within the BVDV CP, farmers can choose different routes to obtain a BVDV free status, i.e. testing for virus or antibodies in different matrices such as blood, ear notch or milk. For this study, data were limited to those herds in which ear notch testing of newborn calves had been undertaken. The ear notch testing route was followed by 11% of herds (2032/19,243) in the BVDV CP in the fourth quarter of 2019. Cattle herds obtained a free status when there were no virus positive animals for a period of ten months.

In Germany, a nationwide mandatory BVDV CP was implemented on 1 January 2011 (Wernike et al., 2017). The main objective of this CP is fast and efficient reduction in the prevalence of PI animals, and the establishment of herds with a status, meaning that the herd consists of "BVDV-unsuspicious" (i.e. virus free) cattle only. The CP includes mandatory testing for virus of all newborn calves by ear notch sampling. In addition to ear notch samples, blood samples are investigated for BVDV, primarily for confirmatory testing. All cattle within the country must have a negative BVDV status before being allowed to move to other farms within the country. A farm with a positive test will be under quarantine for 40 days and pregnant cows are not allowed to leave the farm until after they have given birth to a negative tested calf. In Germany, there is no official recognition of a free herd status within the BVDV CPs. Therefore, in this study, the requirements of EU 2020/689 for a herd to be recognised as established free from BVDV were applied, with herds in Germany that did not have a PI animal in the 18 months before 1 December 2019 being considered free.

The BVDV CP in Ireland is implemented nationally and testing is performed at animal-level (Graham et al., 2014). All cattle within the

country born after the start of the CP (1st January 2013) must have a negative BVDV status before moving off farm. The CP includes testing of ear notch samples of newborn calves and serum testing of imported cattle for BVDV. After a positive ear notch test, confirmatory virus tests may be conducted, supplemented by serum sampling of the dam and offspring of a PI. In 2019, herds received a negative herd status after participating for more than three years in the CP, when all animals in the herd have a negative status and there have been no PIs for at least one year.

In Scotland, a mandatory industry-led CP is in place, which has had five stages to date and is aiming to eradicate BVDV from Scotland (Scottish government, 2016). Breeding herds are required to update their herd status annually using one of the three routes currently available – check-test, calf screening and whole herd screening. Check tests are serum antibody tests of young cattle that indicate whether the herd was recently exposed to BVDV. Calf screening entails individual testing of all calves born in the herd for BVDV by blood or ear notch samples. During whole herd screening, all animals in the herd are individually tested for BVDV by serum or ear notch samples. Strict movement restrictions are imposed on BVDV positive herds. For this study, only data resulting from testing ear notch samples of newborn calves were used. Ear notch sampling was used by 11% of the herds (1305/12,012) in the BVDV CP in the fourth quarter of 2019. In Scotland, herds are classified as BVD negative when there is no evidence of BVD infection in the herd, and BVD not negative when a PI is removed or BVD positive when a PI is found. However, because these statuses are very variable, for this study it was decided to adopt the requirements of EU 2020/689, like Germany.

2.2. Data

All four study regions ran the STOC free model with field data from all dairy herds that submitted ear notch samples as part of the BVDV CP in their country in 2019 (Table 1, Fig. 1). In two study regions, Ireland and Scotland, the BVDV CPs are also mandatory for beef herds and therefore the model was extended to include data from beef herds that submitted ear notch samples as part of the CP in these two study regions in 2019 (Table 1, Fig. 2). In Germany, the BVDV CP is also mandatory for beef herds, but it is not compulsory for cattle herds to define their herd type. Therefore, dairy and beef herds cannot always be distinguished, and were not assessed separately. The selection of herds includes dairy cattle, suckler cows or a combination, but no fattening cattle herds as, according to the regulations, all fattening animals are tested as calves, thus there are no additional tests performed in fattening herds. For Germany, all herds are called dairy herds subsequently. Three study regions used national level data (the Netherlands, Ireland and Scotland). In Germany, only one district could be analysed (Paderborn) because of the low number of affected farms in the rest of the country. Also, the number of cattle herds is decreasing over time in Paderborn because farms ceased operating. Therefore, only herds that had at least 10 animals at the beginning and end of 2019 were selected. In all study regions, only those herds in which at least one calf was born and tested in 2019 were included in the model (Table 1). The required input data for the STOC free model are herd IDs, test dates and test results as a binary variable at herd-level, virus negative (0) or positive (1). In this study, individual animal test results were aggregated to provide a maximum of one herd-level test result per month, with a herd being considered positive in a month when there were one or more positive ear notch test (s) results.

2.3. Priors

The model requires prior distributions for the herd-level sensitivity (Se) and specificity (Sp) of the diagnostic tests with respect to the latent status of interest, i.e. a PI being present in the herd. Prior distributions are also required for the herd-level probability of being status positive at the first time-step (π1), for the probability of becoming status positive between consecutive months (τ1), and for the probability of remaining status positive between consecutive months (τ2) (Table 2). These priors are specified using *beta* distributions. To allow comparison of model results between study regions, default beta priors were defined (Scenario 1, Table 2, (Fig. 3) based on literature (https://www.stocfree.eu/sites/default/files/documents/Deliverables/1.2_final.pdf, page 22 and 23) and expert opinion within the STOC free consortium. From literature, animal-level estimates were specified, which were discussed within the STOC free consortium to obtain herd-level estimates by means of expert opinion. Subsequently, to obtain estimates that reflect the situation in the field and would be used in practice, all study regions also used priors specific to the situation in their region (Scenario 2, Table 3). These country-specific priors were estimated with historical data (2018 or before) or by expert opinion.

The herd-level sensitivity in the model is defined as the probability that the test will correctly identify infection in an infected herd. The prior distribution needs to include the sensitivity of the entire diagnostic series, i.e. not only the laboratory values for sensitivity and specificity, but also corrected for mistakes that can occur during the sampling process that may result in false-negative outcomes. In addition, when animal-level sampling is performed, which is the case with ear notch testing, the sensitivity of each test in the model should be translated to a herd-level sensitivity. The probability of false negative results at herd-level is very small, given that every animal in the herd is individually tested for virus with a very sensitive test. In the first scenario, this prior is set as (α) 98, (β) 2 (Fig. 3), meaning that out of every 100 herds with at least one PI, two herds test negative while they are infected (i.e. false negative results). A herd-level sensitivity below 100% is mostly due to sampling errors, e.g. a calf is missed or there is insufficient tissue in the sample, or errors in the laboratory, e.g. mistakes by the lab technician or limitations of the test.

The herd-level specificity is the probability that the test correctly identifies the absence of infection in an uninfected herd. In the first scenario, this prior is set as a *beta* distribution with parameters (α) 99 and (β) 1 (Fig. 3), meaning that out of every 100 uninfected herds, one herd tests positive while it is not infected (i.e. false positive results). Imperfect specificity in ear notch sampling is mainly due to transient infection(s) in a herd.

Herd prevalence of infection at the first month of testing (π1) is defined as the probability of a herd being status positive on the month of its first test. This is a monthly prevalence of infection at sector level. For

Table 1
Data description.

	The Netherlands	Germany	Ireland		Scotland	
Herd type included in the model	Dairy	Dairy and beef combined[a]	Dairy	Beef	Dairy	Beef
Number of herds in the dataset (and included in the model)	1765 (1642)	363 (361)	16,190 (16,097)	50,760 (49,685)	580 (559)	1922 (1796)
Herds with 1 or more positive test result(s) in 2019	161	11	231	267	64	77
Number of observations (herd test months) in dataset	12,566	2475	78,884	180,604	3724	6413
Number of positive test months	270	25	316	340	111	117
Number of herds free according to CP on 1 December 2019	486	319	14,743	45,989	332	1713

[a] Herd type is not specified in Germany

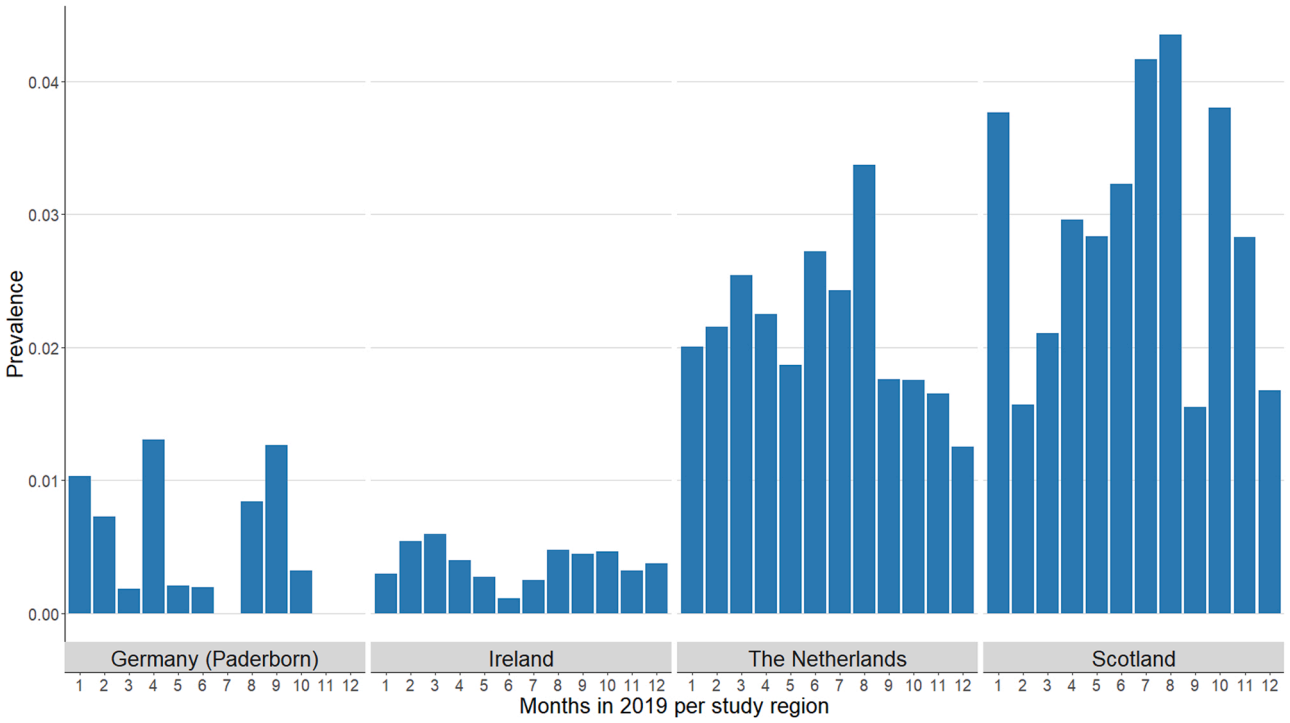


Fig. 1. The BVDV between-herd prevalence per month for dairy herds in each BVDV CP (NL, DE, IE, SCO) based on ear notch testing in 2019. A herd is classified positive in a month when at least one animal tested positive.

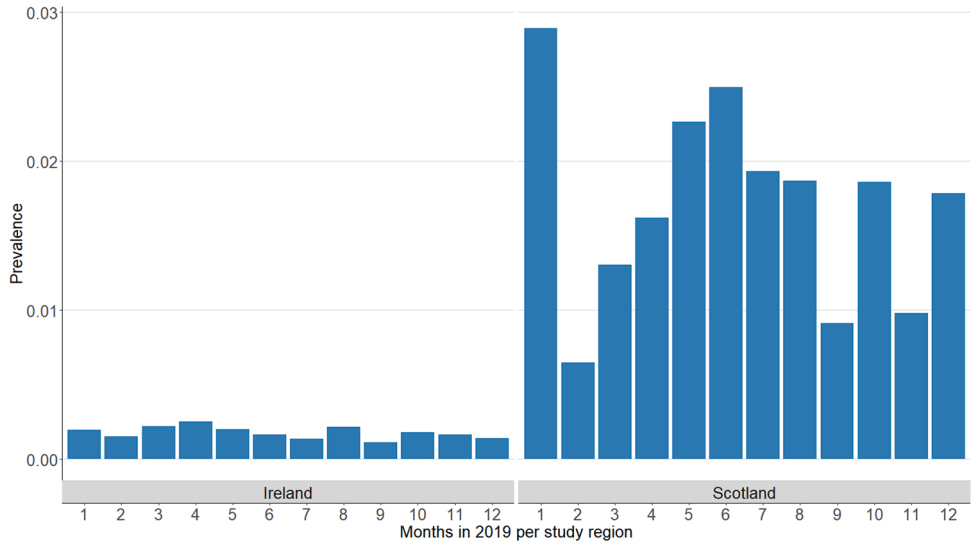


Fig. 2. The BVDV between-herd prevalence per month for beef herds in each BVDV CP (IE, SCO) based on ear notch testing in 2019. In any specific month, a herd is classified positive when at least one animal tested positive.

the first scenario, a uniform prior distribution was chosen (Beta(1, 1)) because the value of π1 was different between study regions (Fig. 3). For the second scenario, for each study region the number of infected herds (one or more positive ear notch results) in December 2018 was used as the α parameter and the number of herds in the ear notch CP in December 2018 as β (Table 3). If data were only available on a yearly basis, an average was calculated for the whole of 2018, i.e. the number of infected herds per year divided by 12 as α, and the number of herds in the ear notch CP in 2018 as the β parameter.

The probability of becoming status positive between two months (τ1) is the monthly probability of uninfected herds becoming infected in the next month. In the first default scenario, the prior distribution was *beta* (1, 20) (Fig. 3), meaning that out of every 21 uninfected herds, one herd becomes infected. The experts expect the probability to be low, but variable between study regions. In the second scenario, for each study region the number of uninfected herds that became infected in 2018 (divided by 12 to obtain a monthly figure) was used for α, and the number of uninfected herds in the ear notch CP in 2018 for the β parameter.

The probability of a herd remaining status positive between two months (τ2) is the monthly probability that infected herds remain infected in the next month. Herds would remain infected because another PI animal is born. In the first default scenario, this prior is set as a *beta* distribution with parameters (α) 2 and (β) 8 (Fig. 3), meaning that

Table 2
Model parameters for which prior information is needed, and the default beta prior values that were used by all study regions to run the STOC free model in scenario 1.

Model parameters	Definition	Prior		
		Mean	Standard deviation	Beta prior (α, β)
Herd-level sensitivity (Se)	The probability of ≥ 1 positive test result(s) in a herd with at least one PI in a specific month	0.98	0.014	98, 2
Herd-level specificity (Sp)	The probability of 0 positive test results in a herd with no PI in a specific month	0.99	0.010	99, 1
π1	Probability of a herd being latent status positive at the first test	0.50	0.289	1, 1
τ1	Probability of a herd becoming latent status positive between two months	0.05	0.045	1, 20
τ2	Probability of a herd remaining latent status positive between two months	0.20	0.121	2, 8

of every 10 infected herds, two would remain infected in the next month. In the second scenario, this was done for each study region by using the number of infected herds that detect another PI in the next month as α, and all infected herds (with PI) as β parameter.

2.4. Model output

STOC free model draws samples from the posterior distributions of the model parameters (Se, Sp, τ1, τ2) and of the predicted probabilities of infection. The STOC free model calculates a distribution of the probability of infection. The distribution for the probability of freedom from infection was computed as one minus the parameters for the distribution for probability of infection (i.e. median, upper and lower level of credibility interval). The models were run with 500–1000 iterations and three chains. A warm-up of 2000 iterations was used. Trace plots of model parameters were checked to assess convergence. STOC free model is available on Github as R package (https://github.com/AurMad/STOCfree). 3.

3. Results

The posterior distributions were obtained by running the model for each study region. Data were included from all herds that submitted ear notch samples as part of the BVDV CP in their region in 2019. The outcome of the model, i.e. the predicted probability of infection, was extracted for the herds of interest, i.e. those herds that were free according to each region's CP on 1 December 2019 (Table 1).

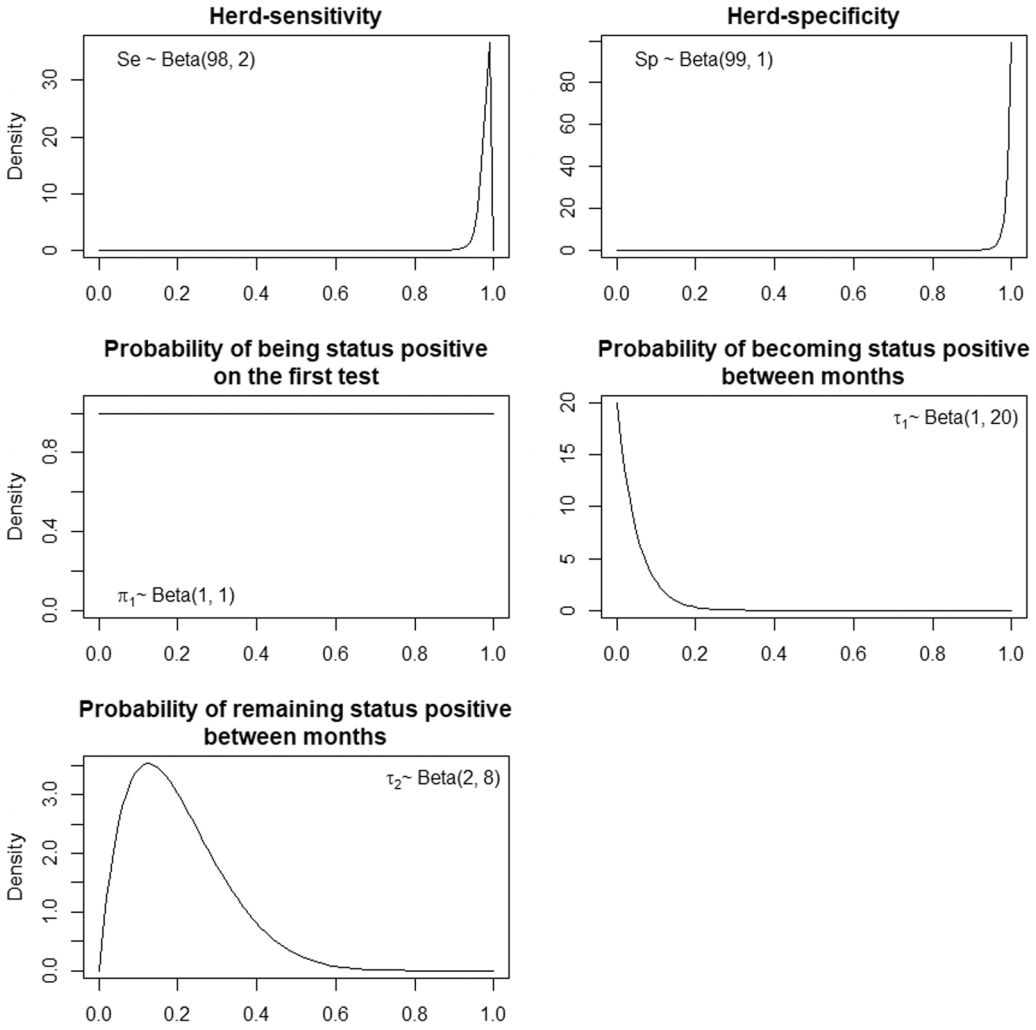


Fig. 3. Prior beta distributions for all five model parameters of the STOC free model in scenario 1 in which the same default priors were used for each study region.

Table 3
Median and standard deviation of the country-specific prior beta distributions (scenario 2). The parameters of the beta distribution (α, β) are presented in Appendix 2: Table A1, Figs. A1-A2.

Model parameters	Country-specific beta priors (mean (sd))					
	The Netherlands	Germany (Paderborn)	Ireland		Scotland	
	Dairy	Dairy and beef[a]	Dairy	Beef	Dairy	Beef
Herd-level sensitivity	0.980 (0.0139)	0.989 (0.0042)	0.984 (0.0037)	"	0.980 (0.0137)	"
Herd-level specificity	0.990 (0.0099)	0.999 (0.0010)	0.999 (0.0007)	"	0.9998 (0.0002)	"
Probability of latent status positive at first test (π1)	0.004 (0.0005)	0.011 (0.0047)	0.002 (0.0003)	0.001 (0.0001)	0.020 (0.0054)	"
Probability of a herd becoming latent status positive (τ1)	0.004 (0.0006)	0.003 (0.0023)	0.0003 (0.0001)	"	0.009 (0.0037)	"
Probability of a herd remaining latent status positive (τ2)	0.017 (0.0164)	0.362 (0.0493)	0.038 (0.0370)	"	0.048 (0.045)	"

[a] Herd type is not specified in Germany.

3.1. Convergence

The trace plots showed good mixing for all parameters, indicating convergence of the models.

3.2. Parameter estimation

3.2.1. Scenario 1: default priors

First, the model was run for each study region with default priors. The posterior distributions (Table 4) showed varying median test sensitivities between study regions ranging from 89% to 98%. The median specificity was high (>99%) for all study regions. The probability of herds becoming latent status positive between 2 months was very low for all study regions, ranging from 0.001 to 0.015. The probability of positive herds remaining latent status positive between 2 months was around 50% (range 0.372–0.624) for most study regions.

3.2.2. Scenario 2: country-specific priors

In the second scenario, the model was run with country-specific priors (Table 3). The posterior estimates (Appendix 3: Table A2) show that the change in priors, i.e. more specific and narrow priors, resulted in different posterior distributions. For some study regions and parameters, there were minor differences when more specific priors were used, such as the herd-level specificity and the probability of a herd becoming latent status positive (τ1) in all study regions. For other study regions and parameters (i.e. herd-level sensitivity and the probability of a herd remaining latent status positive τ2), a larger difference was observed (Fig. 4 and Appendix 3: Figs. A3–A7).

3.3. Predicted probability of infection in cattle herds

The probability of infection for dairy herds that were free according to each region's CP was predicted to be very low for all study regions (Fig. 5, Appendix 4: Table A3). The median probability of freedom (1-median probability of infection) ranged from 0.98 (98%) to 1.00 (100%). When extracting the predicted probabilities of infection for all herds (Appendix 4: Table A4), including herds that do not yet achieved a free status, the results did not change markedly (Fig. 5, appendix 4: Table A3). In both situations, the predicted probability of infection was very low, however in all cases the model with default priors that were less informative (wider beta distribution) gave a slightly wider credibility interval. In two study regions, Ireland and Scotland, the model was also run on data from beef herds (Appendix 5). For both of these study regions, the predicted probability of infection was similar for both dairy and beef herds. For Scotland, the credibility interval was wider for dairy herds compared to beef herds.

4. Discussion

A Bayesian Hidden Markov model for output-based assessment of the probability of infection, the STOC free model, was applied to BVDV field data from CPs based on testing of ear notch samples of newborn calves in four study regions. In this study, we present estimates of the probability of freedom from BVDV resulting from these CPs based on testing of ear notch samples of newborn calves. We also evaluated how sensitive the model output was to default or country-specific prior distributions. The results show a very low probability of infection, and thus a very high probability of freedom, for cattle herds with a BVDV negative herd status in all four study regions, suggesting that the effectiveness of CPs based on ear notch testing is comparable between study regions. However, some differences were observed between the study regions, with higher predicted probabilities of infections for Scotland and wider credibility intervals for Scotland and the Netherlands compared to the other study regions. This was as expected, because the data included in this study (year 2019) for the Netherlands and Scotland had a higher proportion of herds with at least one positive test result, respectively 9% and 11%, compared to Germany (Paderborn) and Ireland, respectively 3% and 1%. However, a higher predicted probability of infection can also be the result of uncertainty due to missing test results. Test negative herds with missing test months before the month of prediction had a higher predicted probability of infection compared to herds that had a positive test result in some months followed by negative test results in the last month (s) before prediction. This was, for example, seen in some herds with scarce data from Germany (Paderborn) where the incidence was extremely low compared to herds in the Netherlands with a higher incidence. This can be explained because the predicted probability of

Table 4
Median (2.5%, 97.5%) of the posterior distributions of the ear notch - dairy models for the Netherlands, Germany (Paderborn), Ireland, Scotland for scenario 1, in which all study regions used the same default priors.

Posterior distributions (median (2.5%, 97.5%))	The Netherlands	Germany (Paderborn)	Ireland	Scotland
Herd-level sensitivity	0.886 (0.805–0.954)	0.977 (0.926–0.996)	0.904 (0.877–0.929)	0.979 (0.967–0.988)
Herd-level specificity	0.994 (0.991–0.997)	0.998 (0.995–1.000)	0.998 (0.998–0.998)	0.994 (0.991–0.996)
Probability of a herd becoming latent status positive (τ1)	0.008 (0.005–0.12)	0.003 (0.001–0.006)	0.001 (0.000–0.001)	0.015 (0.012–0.018)
Probability of a herd remaining latent status positive (τ2)	0.511 (0.395–0.621)	0.454 (0.268–0.648)	0.622 (0.585–0.663)	0.372 (0.327–0.422)

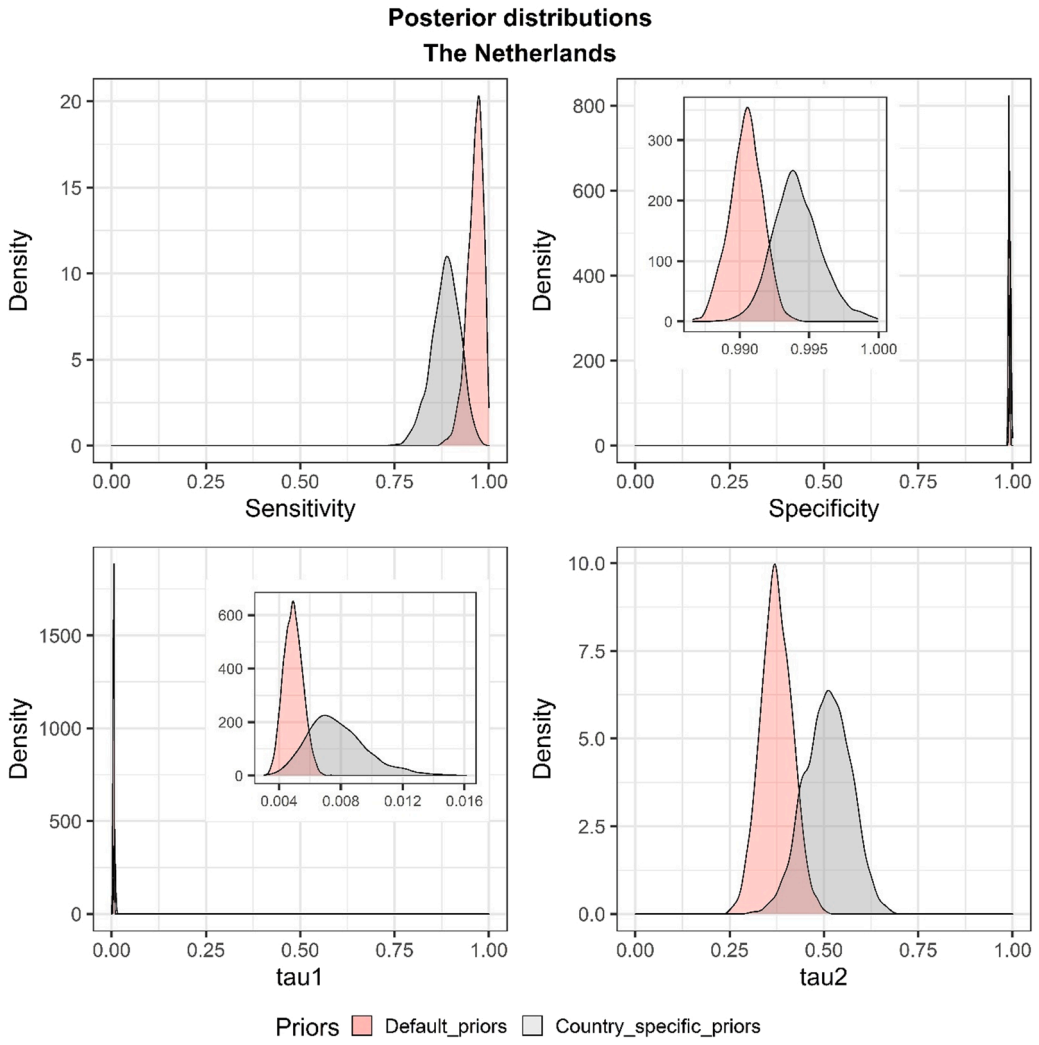


Fig. 4. Posterior estimates when running the STOC free model with default priors (red) and country-specific priors (grey) for the Netherlands. Plots for the other study regions can be found in Appendix 3.

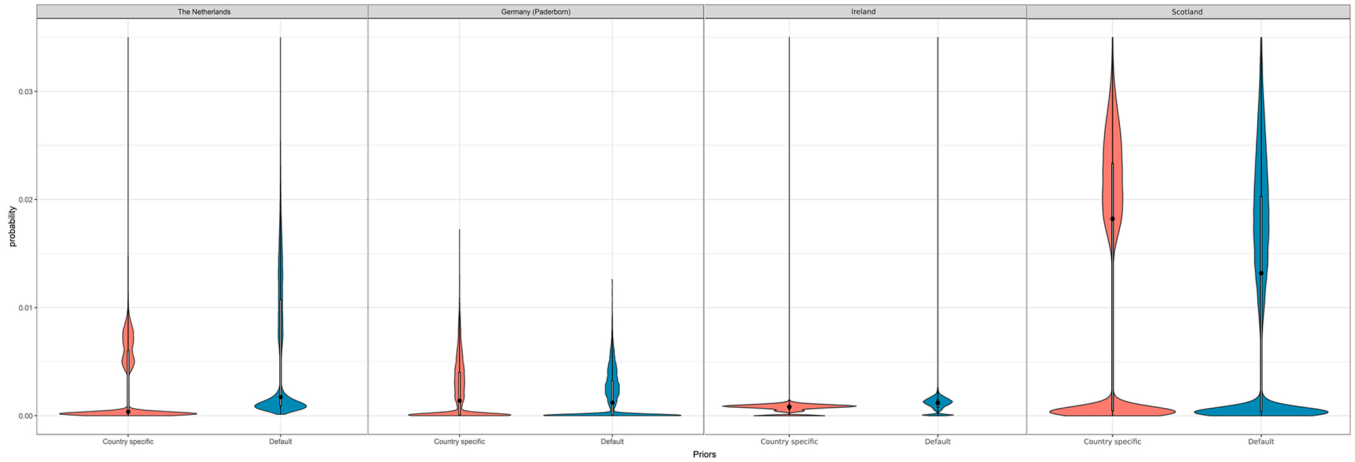


Fig. 5. Predicted probability of infection (the black dot shows the median) for dairy herds with a free status on 1 December 2019 according to the BVDV CP based on ear notch testing in each study region. The plots show scenario 1 (coloured blue), in which for each study region the same default priors were used, and scenario 2 (coloured red) in which country-specific priors were used.

infection increases with the estimated values of $\tau 1$, in case of a negative test result in the previous month, and $\tau 2$, in the case of a positive result in the previous month. For a given herd, as the interval since the last test increases, the predicted probability of infection evolves as a function of $\tau 1$ and $\tau 2$ and the uncertainty in the predicted status increases. This is not surprising because without test results, the uncertainty about the

free status increases, as virus could have been introduced or could be still present (trojan cow, which is a cow carrying a PI, or retained PI).

The STOC free model was run with default priors to enable comparison of the model output between study regions without the influence of different prior values. Thereafter, the model was run with country-specific priors based on expert opinion or historical data, to study the influence of the priors on the model results and to obtain more realistic country-specific estimates. For the latter, most study regions estimated priors with narrower beta distributions compared to the default priors. The results showed that the herd-level sensitivity and the probability of remaining infected ($\tau 2$) were mostly influenced by the priors, because the posterior herd-level sensitivity and $\tau 2$ changed when using country-specific priors instead of default priors (Fig. 4, Table A2). The change in posterior herd-level sensitivity was small for Germany and Scotland (+0.01), but higher for the Netherlands and Ireland (+0.08). The change in $\tau 2$ was a little greater, ranging from 0.06 for Germany to 0.14 for the Netherlands, when using country-specific priors. Small changes were probably caused by the fact that there was not much information in the data for the model to estimate these parameters due to the low incidence of infection in the cattle populations. However, the different priors did not affect the predicted probability of infection much. In all cases, the credibility interval was a little wider for the models with default priors and, only in the case of Scotland, the median predicted probability of infection was slightly higher (+0.005) in the model with country-specific priors.

In most models, the posterior estimate for $\tau 2$ was higher than expected and the herd-level sensitivity lower than expected. The association between $\tau 2$ and herd-level sensitivity can be explained because i) the posterior estimates for herd-level specificities were close to 1, implying that almost all positive test results were considered true positives by the model, ii) higher $\tau 2$ values were associated with positive test results in a given month having an increased probability of being followed by a positive status in the following months, iii) negative test results within months following a positive test result were therefore more likely to be considered false negatives, thus reducing the estimated sensitivity at herd-level. Using lower values on the prior for $\tau 2$ reduces the conditional dependence between consecutive test results, and as a consequence mitigates the impact of positive test results on the probability of false negatives in subsequent months.

The models were run for dairy and beef herds in two study regions that could distinguish the two herd types, Ireland and Scotland. Only minor differences were found in the predicted probabilities of infection for both herd types, even though the prevalence i.e. the percentage of test positive herds, was lower for beef compared to dairy in Ireland (0.5% and 1% respectively) and Scotland (4% and 11% respectively). We did see a wider credibility interval of the predicted probability of infection for dairy herds compared to beef herds. The lack of difference in the predicted probability of infection between dairy and beef herds for Ireland was probably because the BVDV prevalence was very low in both herd types. For Scotland, a greater difference was expected, however, the more seasonal testing in beef herds increased the uncertainty about the probability of infection in the months without test results. The model does not include animal-level information, so the uncertainty around the predicted probability of infection does not decrease when more cattle are tested.

The model output was extracted for herds declared free within each CP as well as for all herds present within the CP dataset (Appendix 4: Table A4). The results did not change markedly, which is again probably associated with the fact that the BVDV prevalence was already very low in the study regions in 2019.

Output-based modelling of BVDV is challenging due to complexity of the infection, e.g. time between infection and birth of PI(s) and the high level of heterogeneity between CPs (van Roon et al., 2021, 2020). For this reason, we did not model BVDV CPs with different test strategies, but focused on one testing method, i.e. testing ear notch samples of newborn calves for presence of virus. Nonetheless, the model can be used for other (combinations of) testing methods, but informative priors are required.

A challenge in modelling BVDV CPs based on ear notch sampling with STOC free model was to estimate herd-level priors, noting that data from CPs were available at the level of the animal, especially with regards to test characteristics. Considering that most tests rarely return false positive results, herd-level specificity is usually not a problem. The situation is different for herd-level test sensitivity, which results from sensitivity at the level of the individual animal as well as the sampling scheme, which may exclude infected animals. Examples of events that influence herd-level sensitivity are calves that were not tested because they were stillborn, mistakes in the whole process of sampling etc.

STOC free model is best suited for free herds in regions or countries where infections are still endemic. Most model parameters can only be estimated when the infection is present (herd-level sensitivity and the probability of becoming infected) and when transitions from uninfected herds to infected herds occur ($\tau 1$). When countries are free from infection, there is no information in the data for the model to estimate herd-level sensitivity, the probability to become infected ($\tau 1$), or the probability to remain infected ($\tau 2$). Therefore, the model can be used in countries that are completely free from infection, but this would be equivalent to performing stochastic simulations from prior distributions, in which case methods such as the scenario tree methods are better suited. The study regions in this study are close to eradication, especially Germany and Ireland, resulting in very little information for the model to estimate its parameters. In addition, only a single year of data was included in the model due to recent changes in some of the CPs and for practical reasons, e.g. execution time. In these cases, the prior distributions have much greater influence on posterior inference than in situations with a higher prevalence and incidence. For this reason, it is essential to use correct and informative priors. Also, in the case of very small herds in which no or only few calves are born in a year or in herds with seasonal calving, testing data was often sparse. In most datasets, there were many herds with only a few datapoints and only a small proportion of the herds had 12 months of data (Appendix 6: Table A7). In dairy herds in Ireland and beef herds in Scotland, the calving pattern is seasonal, with most calvings and thus test results generated between February and May and April and June, respectively (Appendix 6: Table A8). When we want to predict the probability of infection in December, there are fewer recent test results available. This means the probability of infection will be more uncertain because of the estimated risk of introduction and thus more uncertainty about the true infection status. On the other hand, it could also be argued that herds in which no calves were born and no animals were purchased since the last test result, have a lower probability of introduction in these months and therefore the last test results could still be valid. In the model, heterogeneity on the risk of introduction can be included with risk factors (Madouasse et al., 2022).

Compared to other methods, the main advantages of STOC free model are its simple structure (it is basically an SIS model) and its ability to estimate relevant epidemiological parameters (Se, Sp, $\tau 1$, $\tau 2$) from surveillance data. STOC free model estimates these four parameters and a monthly probability of infection and predicts the probability of infection for the last month. Unlike simulation methods such as the scenario tree method, the estimation of these parameters allows inconsistencies in the modelling hypotheses to be identified. In our method, the data will modify the priors, resulting in posterior estimates for the model parameters. When posteriors differ substantial from the priors, either the input data needs to be checked for inconsistencies or the prior knowledge needs to be reconsidered. Furthermore, parameter estimates obtained when running the model with data from a given CP can be used as priors when running the model with data from other CPs.

The biology of the disease, i.e. the length of time between infection of the herd and the birth of a PI, and the use of animal-level data, created some challenges for the model, especially in the definition of prior distributions for the different model parameters. Therefore, when used in

practice, guidelines are needed for the estimation of priors, especially when there is only limited information in the data and thus informative priors are needed.

Regardless of the validity of the model inputs, the scenario tree model will return a result. In this regard, STOC free model is safer to use because it runs on real CP data. The STOC free model does not include all details and additional measures that are included in CPs. In the Netherlands, for example, herds (temporarily) lose their free status after purchasing an animal from non-free herds. STOC free model does not include this information, but is reflected in the data because when this animal tests positive, and thus leads to introduction of BVDV in the herd, this is included with the test result. Another advantage of using real longitudinal CP data is that when new predictions are desired, extra months of data are easily added. Formal validation of the model has been done before with simulated data, but with an initial version of the STOC free model running with JAGS (Mercat et al., 2022). The STOC free model performed much better with STAN (Madouasse et al., 2022). Therefore, a new validation study with simulated data would be desirable, given that we expect that the model will converge better with STAN.

In conclusion, we were able to estimate the probability of freedom from BVDV of individual cattle herds in different study regions with STOC free model. The results show a very low predicted probability of infection for cattle herds in all four study regions. When this model is used to check whether these results comply with legislation, the minimum required level of freedom should be decided on to define free herds. The model output was evaluated by using default and country-specific priors: the former mainly for comparison of the results without the influence of priors, and the latter as a much more realistic scenario as this would be the way the model would be used in practice. This study has highlighted the challenges of output-based modelling of BVDV. STOC free model can be used for this purpose, but the data, priors and results need to be carefully evaluated. It is expected that STOC free model can be adapted to other cattle diseases and even to CPs in other animal species.

Acknowledgements

This work was carried out with the financial support of the Dutch Ministry of Agriculture, Nature and Food Quality (13000224506) and is part of the STOC free project that was awarded a grant by the European Food Safety Authority (EFSA, Parma, Italy, grant GA/EFSA/AFSCO/2016/01-03) and was co-financed by public organizations in the countries participating in the study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prevetmed.2022.105662.

References

Ågren, E.C.C., Lewerin, S.S., Frössling, J., 2018. Evaluation of herd-level sampling strategies for control of Salmonella in Swedish cattle. J. Dairy Sci. 101 (11), 10177–10190. https://doi.org/10.3168/jds.2018-14786.

Cameron, A.R., 2012. The consequences of risk-based surveillance: developing output-based standards for surveillance to demonstrate freedom from disease. Prev. Vet. Med. 105, 280–286. https://doi.org/10.1016/j.prevetmed.2012.01.009.

Flay, K.J., Yang, D.A., Wilson, M.T., Lee, S.H., Bhardwaj, V., Hill, F.I., Pfeiffer, D.U., 2021. Absence of serological or molecular evidence of Leptospira infection in farmed swine in the Hong Kong Special Administrative Region. One Health 13, 100321. https://doi.org/10.1016/j.onehlt.2021.100321.

Graham, D.A., Lynch, M., Coughlan, S., Doherty, M.L., O'neill, R., Sammin, D., O'flaherty, J., 2014. Development and review of the voluntary phase of a national BVD eradication programme in Ireland. Vet. Rec. 174, 67. https://doi.org/10.1136/vr.101814.

Heisey, D.M., Jennelle, C.S., Russell, R.E., Walsh, D.P., 2014. Using auxiliary information to improve wildlife disease surveillance when infected animals are not detected: a bayesian approach. PLoS One 9, e89843. https://doi.org/10.1371/journal.pone.0089843.

Madouasse, A., Mercat, M., van Roon, A., Graham, D., Guelbenzu, M., Santman Berends, I., van Schaik, G., Nielen, M., Frössling, J., Ågren, E., Humphry, R., Eze, J., Gunn, G., Henry, M.K., Gethmann, J., More, S.J., Toft, N., Fourichon, C., 2022. A modelling framework for the prediction of the herd-level probability of infection from longitudinal data. Peer Community J. 2. https://doi.org/10.24072/PCJOURNAL.80.

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. https://doi.org/10.1016/j.prevetmed.2006.09.008.

Mercat, M., van Roon, A.M., Santman-Berends, I., van Schaik, G., Nielen, M., Graham, D., More, S.J., Guelbenzu-Gonzalo, M., Fourichon, C., Madouasse, A., 2022. Capacity of a Bayesian model to detect infected herds using disease dynamics and risk factor information from surveillance programmes: a simulation study. Prev. Vet. Med. 200, 105582 https://doi.org/10.1016/J.PREVETMED.2022.105582.

Norström, M., Jonsson, M.E., Åkerstedt, J., Whist, A.C., Kristoffersen, A.B., Sviland, S., Hopp, P., Wahlström, H., 2014. Estimation of the probability of freedom from bovine virus diarrhoea virus in Norway using scenario tree modelling. Prev. Vet. Med. 116, 37–46. https://doi.org/10.1016/j.prevetmed.2014.06.012.

Scottish government, 2016. The Scottish BVD Eradication Scheme. ⟨https://www2.gov.scot/Topics/farmingrural/Agriculture/animal-welfare/Diseases/disease/bvd/eradication⟩ (accessed 22 November 2021).

Toftaker, I., Ågren, E., Stokstad, M., Nødtvedt, A., Frössling, J., 2020. Herd level estimation of probability of disease freedom applied on the Norwegian control program for bovine respiratory syncytial virus and bovine coronavirus. Prev. Vet. Med. 181, 104494 https://doi.org/10.1016/j.prevetmed.2018.07.002.

van Duijn, L., Veldhuis, A.M.B., Mars, M.H., de Roo, B., Lam, T.J.G.M., 2019. Efficacy of a voluntary BVDV control programme: experiences from the Netherlands. Vet. J. 245, 55–60. https://doi.org/10.1016/j.tvjl.2018.12.016.

van Roon, A.M., Santman-Berends, I.M.G.A., Graham, D., More, S.J., Nielen, M., Madouasse, A., Mercat, M., Fourichon, C., Gethmann, J., Frössling, J., Lindberg, A., Correia-Gomes, C., Gunn, G.J., Sauter-Louis, C., Henry, M.K., van Duijn, L., van Schaik, G., 2019. STOC free: an innovative framework to compare probability of freedom from infection in heterogeneous control programmes. Front. Vet. Sci. 6, 133. https://doi.org/10.3389/fvets.2019.00133.

van Roon, A.M., Santman-Berends, I.M.G.A., Graham, D., More, S.J., Nielen, M., van Duijn, L., Mercat, M., Fourichon, C., Madouasse, A., Gethmann, J., Sauter-Louis, C., Frössling, J., Lindberg, A., Correia-Gomes, C., Gunn, G.J., Henry, M.K., van Schaik, G., 2020. A description and qualitative comparison of the elements of heterogeneous bovine viral diarrhea control programs that influence confidence of freedom. J. Dairy Sci. 103, 4654–4671. https://doi.org/10.3168/jds.2019-16915.

van Roon, A.M., Santman-Berends, I., Nielen, M., Graham, D., More, S., Guelbenzu-Gonzalo, M., Mercat, M., Fourichon, C., Madouasse, A., Gethmann, J., Sauter-Louis, C., Frössling, J., Ågren, E., Eze, J., van Schaik, G., 2021. Confidence of freedom from infection with BVDV in the EU: application of a bayesian hidden markov model on field data in G. van Schaik & M. Brennan (Eds.), Society for Veterinary Epidemiology and Preventive Medicine - Proceedings. SVEPM.

Veldhuis, A., Santman-Berends, I., Schauer, B., Mars, J., Waldeck, F., Staubach, C., Van Schaik, G., 2017. Epidemiological performance and subsequent costs of different surveillance strategies to control bovine herpesvirus type 1 in dairy farms. Prev. Vet. Med 139, 105–114. https://doi.org/10.1016/j.prevetmed.2016.12.003.

Wernike, K., Gethmann, J., Schirrmeier, H., Schröder, R., Conraths, F.J., Beer, M., 2017. Six years (2011–2016) of mandatory nationwide bovine viral diarrhea control in germany - a success story. Pathogens 6, 50. https://doi.org/10.3390/pathogens6040050.

Yang, D.A., Johnson, W.O., Müller, K.R., Gates, M.C., Laven, R.A., 2019. Estimating the herd and cow level prevalence of bovine digital dermatitis on New Zealand dairy farms: a Bayesian superpopulation approach. Prev. Vet. Med. 165, 76–84. https://doi.org/10.1016/j.prevetmed.2019.02.014.