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Comparison of the confidence in freedom from infection based on different control programmes between EU member states: STOC free

G. van Schaik[1,2], A. Madouasse[3], A. van Roon[1], J. Frössling[4], J. Gethmann[5], C. Fourichon[3], M. Mercat[3], S. More[6], E. Ågren[4], C. Sauter-Louis[5], G. Gunn[7], J. Eze[7], R. Humphry[7], M. Henry[7], D. Graham[8], M. Guelbenzu[8], M. Nielen[1], I. Santman-Berends[1,2]

[1]Department of Population Health Sciences, Unit Farm Animal Health, Faculty of Veterinary Medicine, Utrecht University, the Netherlands
[2]Royal GD, Deventer, The Netherlands
[3]INRAE, Oniris, BIOEPAR, 44300, Nantes, France
[4]Department of Disease Control and Epidemiology, National Veterinary Institute (SVA), 751 89 Uppsala, Sweden
[5] Institute of Epidemiology, Friedrich-Loeffler-Institute, Südufer 10, 17493 Greifswald, Germany
[6]Centre for Veterinary Epidemiology and Risk Analysis, UCD School of Veterinary Medicine, University College Dublin, Dublin, Ireland
[7]Scotland's Rural College, Kings Buildings, West Mains Road, Edinburgh, EH9 3JG, United Kingdom
[8]Animal Health Ireland, Carrick on Shannon, Co. Leitrim, Ireland

Abstract

The STOC free project constructed a generic framework that allows a standardised and harmonised description of different control programmes (CP) for cattle diseases. The STOC free model can be used to determine the confidence of freedom from infection that has been achieved in disease CPs, in support of an ongoing assessment of progress towards output-based standards as outlined in the EU Animal Health Law. With this information, and as required, further CP actions can be taken to mitigate the risks of persistence and (re-)introduction on the probability of freedom from infection. Bovine viral diarrhoea virus (BVDV) was chosen as the case disease because of the diversity in CPs in the six participating countries. A Bayesian hidden Markov model was considered the best modelling method. Detailed BVDV CP information was collected in the participating countries and the key aspects for inclusion in the STOC free model were identified. A first version of STOC free model was developed and tested on simulated data. The risk factors for BVDV infection that needed to be included in the model were defined and default values for these risk factors were quantified. A data collection tool was finalised with which the data for the STOC free model was collected. Subsequently, the developed model was tested and validated using real BVDV CP data from partner countries. Based on the feedback, the model was finalised and the report and corresponding computer code were made publicly available. There were roughly three different BVDV situations that occurred in the partner countries: 1. Endemic situation with a CP operating at herd level, 2. Endemic situation with a CP operating at animal level and 3. BVD free situation. The STOC free model is able to include herd level data only and animal level data has to be aggregated to herd level before the model can be applied. The STOC free model is not applicable for a country that is completely BVDV free given that it needs some infections to estimate its parameters and converge. In the latter situation, a scenario tree model could be a better suited tool, and this was evaluated in the Swedish case study. Further work is needed for generalisation of the method to other diseases and expansion of the method to include socioeconomic aspects of CPs.

Key words: output-based surveillance, control programmes, probability of freedom from infection, BVDV, cattle

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Correspondence: BIOHAW@efsa.europa.eu

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

This grant was awarded by EFSA to: the STOC free consortium

Beneficiaries: Utrecht University (UU, NL), Nantes Atlantic National College (ONIRIS, FR), University College Dublin (UCD, IE), Swedish National Veterinary Institute (SVA, SE), Friedrich Loeffler Institut (FLI, DE).

Subcontractors: Animal Health Ireland (AHI, IE), Royal GD (GD, NL), Scotland's Rural College (SRUC, UK)

Grant title: STOC free - A Surveillance analysis tool for outcome-based comparison of the confidence of FREEdom generated by control or eradication programmes

Contract/Grant number: GA/EFSA/AFSCO/2016/01-03

Several European Member States (MS) have implemented control programmes (CP) for endemic infections with no or limited regulation by the EU. Therefore, the design of these programmes is tailored to each country's specific situation and vary extensively. This large variation results in difficulties when comparing these programmes, highlighting the need for methods to objectively and quantitatively compare programme outputs e.g. confidence of freedom from infection.

In the STOC free project, six countries are collaborating to construct the generic framework to allow for standardised and harmonised comparison of the output of different CPs for cattle diseases that are not regulated by the EU. The framework allows the integration of heterogeneous data and results in standardised and comparable outputs (Van Roon et al., 2019).

During this project, BVD was chosen as a case disease because of the large variation in both programme design and prevalence that exists between MS. The framework was designed and optimised using pilot-scenarios describing the CPs in each of the consortium partner countries. Thereafter, information about BVDV CPs, combined with test specifications and demographic context information, formed the basis of further case studies in which the developed methods were applied and optimised in the consortium Member States. Finally, advantages and disadvantages and possible generalisation to other cattle diseases of the developed methodology were discussed.

2. Data and Methodologies

2.1. Data collection

The data that are needed to feed the model include data on disease dynamics, test results from the CP in place and information on the context situation i.e. prevalence of relevant risk factors in the country of interest (Van Roon et al., 2020A).

As a first step in the development of the data collection tool, all six participating countries filled in the RISKSUR tool (The RISKSUR Project, 2015) to identify differences between various BVD CPs with respect to freedom from infection. The RISKSUR tool was intended for building and optimizing surveillance programmes and therefore was modified within the STOC free project to also collect information about the context and aspects of CPs.

The differences between CPs that were identified by filling in the adapted RISKSUR tool were used as input for a first draft questionnaire on aspects of freedom. In this questionnaire all aspects that can influence, either directly or indirectly, the confidence of freedom from infection in a BVDV CP were queried.

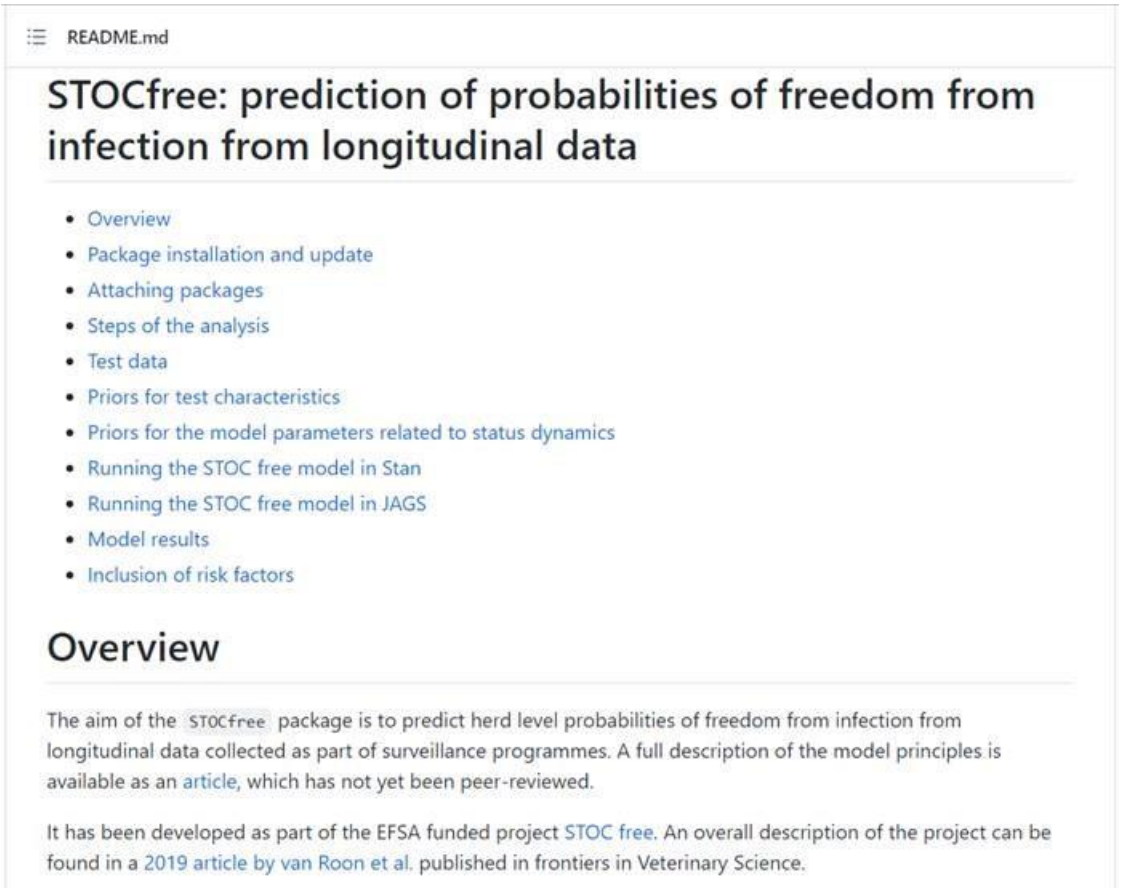
The next step was to list all variables for which quantitative data is needed to calculate the confidence of freedom with the STOC free model. All variables were included in a large data collection table in which all participating countries were asked about the availability of quantitative data, the format of the

data, the source(s) of the data and strengths and limitations of the data. This data collection table was first optimized for use for BVDV and later extended to other cattle diseases i.e. JD and IBR.

In a collaboration with the SOUND control project (www.sound-control.eu), the data collection table was generalized so that it could be applied to all countries throughout Europe. Over 30 countries were asked to fill in the table and valuable lessons were learned about data availability and the format in which data were available. All users of the table agreed that a data quality tool is essential in the comparison of the confidence in the probability of freedom. Aspects that were considered important were data sources and accessibility, completeness of data, timeliness of data and data accuracy. These aspects were incorporated in a data quality evaluation tool.

The data collection tool with the data quality evaluation tool were made available online through Limesurvey (Van Roon et al., 2021; Rapaliute et al., 2021).

The longitudinal data[1] required for the STOC free model are described in a document on https://github.com/AurMad/STOCfree (Figure 1). R functions to read the data and use it in the STOC free model are freely available as part of an R package that can be installed from this same site. An example of such data is provided in Figure 2.


README.md

STOCfree: prediction of probabilities of freedom from infection from longitudinal data

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- Attaching packages
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- Test data
- Priors for test characteristics
- Priors for the model parameters related to status dynamics
- Running the STOC free model in Stan
- Running the STOC free model in JAGS
- Model results
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Overview

The aim of the `STOCfree` package is to predict herd level probabilities of freedom from infection from longitudinal data collected as part of surveillance programmes. A full description of the model principles is available as an article, which has not yet been peer-reviewed.

It has been developed as part of the EFSA funded project STOC free. An overall description of the project can be found in a 2019 article by van Roon et al. published in frontiers in Veterinary Science.

Figure 1. The documentation for the STOC free framework on GitHub.

[1] Longitudinal data, sometimes referred to as panel data, track the same sample at different points in time. The sample can consist of individuals, herds, establishments, and so on. In contrast, repeated cross-sectional data, which also provides long-term data, gives the same survey to different samples over time.

Herd_id	Month	Test_date	Test_type	Test_result	Herd_status_CP
1	1	2019-01-01	virus_earnotch	0	Free
1	3	2019-03-01	virus_earnotch	0	Free
1	4	2019-04-01	virus_earnotch	0	Free
1	5	2019-05-01	virus_earnotch	1	Not free
1	7	2019-07-01	virus_earnotch	0	Free
2	3	2019-03-01	virus_earnotch	0	Free
2	7	2019-07-01	virus_earnotch	0	Free
2	8	2019-08-01	virus_earnotch	0	Free
3	5	2019-05-01	virus_earnotch	0	Not free
3	6	2019-06-01	virus_earnotch	1	Not free
3	7	2019-07-01	virus_earnotch	0	Not free
3	8	2019-08-01	virus_earnotch	0	Not free

Figure 2. An example dataset for the STOC free model with longitudinal monthly test results on herd-level.

2.2. The STOC free model

At the start of the project, the only method used for substantiating freedom from infection was the scenario tree methodology. This method is well suited to quantifying a probability of freedom from infection at the country when this infection has never been present or is considered to have been eradicated. On herd-level, scenario tree models have been adapted to situations where there is an ongoing CP for an infection that is still present. In such cases, the probability of introduction of infection has to be included in the (stochastic) model. Scenario tree models provide estimates for surveillance system sensitivity and probability of freedom from infection across all herds with a specific risk profile and a specific testing regime.

The objective to model freedom from infection on herd-level, is to distinguish infected from uninfected herds, to eliminate infection from herds found to be infected and consequently to identify herds that are highly likely to be free from infection and can safely trade cattle. CPs usually have a requirement for ongoing testing of all enrolled herds. In some cases, risk factors for infection are also available for surveillance. However, not every herd always adheres to the sampling scheme and risk of disease introduction may vary between herds and over time. Additionally, the probability of freedom will be higher immediately after testing compared to a later period when there is more time between testing and determination of the probability of freedom. Thus, within a single CP, the probability of freedom from infection may vary both between herds and within a single herd over time. The STOC free model can be used to determine the confidence of freedom from infection that has been achieved in disease CPs, in support of an ongoing assessment of progress towards output-based standards as outlined in the EU Animal Health Law. With this information, and as required, further CP actions can be taken to mitigate the risks of persistence and (re-)introduction on the probability of freedom from infection.

The STOC free model had to be able to accommodate all of the following defining features of CPs against infectious diseases that are still present:

i) longitudinal test data from all herds in the CP with possibly variable time intervals between consecutive tests

ii) imperfect test sensitivity and specificity and

iii) the possibility to include risk factors of infection.

A Bayesian Hidden Markov Model (HMM) was identified as meeting all these constraints. Preliminary work on Q-fever was conducted with this type of model (Nusinovici et al., 2015). Briefly, HMMs are a class of model whose outcome is a latent variable with a Markovian dynamic that is imperfectly measured. The Markovian dynamic implies discrete time steps with the state at a given step only depending on the state at the previous step. In the STOC free model, the latent state of interest is the herd level true state regarding infection. For BVDV this was the presence of a persistently infected (PI) animal in the herd. This state is imperfectly observed by tests characterised by a certain sensitivity and specificity. Time is discretised to monthly intervals, with model parameters for the probability of acquiring or eliminating the infection between consecutive months. Lastly, the probability of new infection is modelled as a function of data on risk factors using logistic regression. The model predicts a probability of current infection based on the last month of surveillance for each herd in the CP given all of the historical data on test results and risk factors. See Figure 3 for a conceptual representation of the STOC free model. The estimation in a Bayesian framework permits the incorporation of available knowledge, notably about test characteristics, in the form of prior distributions. One major difference from the scenario tree method is that the STOC free model, by learning from historical data, does not rely as much on modelling hypotheses.

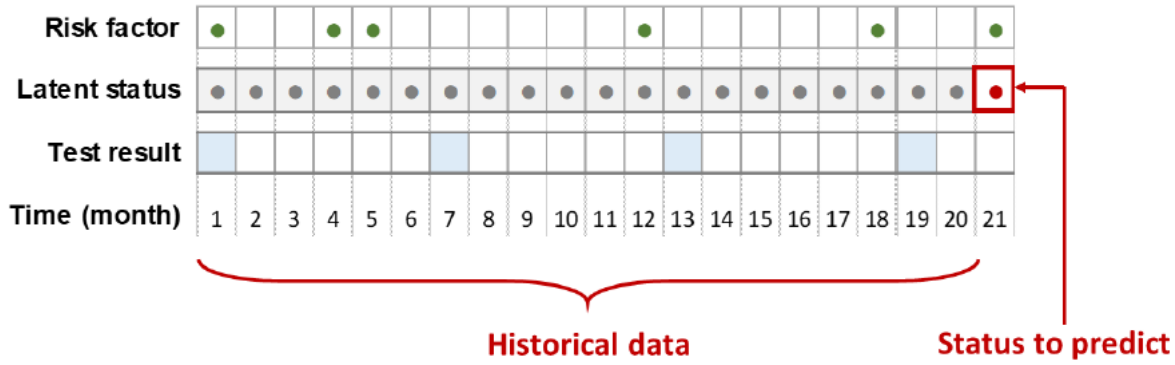

Figure 3. Conceptual representation of the implementation of a control programme within a herd. The focus of the model is the latent status regarding infection, which is modelled at the herd-month-level. This status partly depends on risk factors (green dots) and test results (blue shaded squares). The model predicts a probability of infection for the most recent month in the control programme using all the data collected for the estimation of model parameters.

3. Results

In the STOC free project, the conceptual model of BVDV was developed which described the infection process at 3 levels i.e. animal, herd and territory. The model connected the biological processes of BVDV infection with information about control programmes and demographic context information. The aim of the conceptual model was to support the selection of the most appropriate statistical models that will integrate different pieces of information (data) for the estimation of probabilities of being in each single state of interest (outcome) at different levels. The conceptual model was deliverable number 1.1. In addition, an approach to uniformly describe heterogeneous control programmes for cattle diseases that are implemented in EU member states was developed by tailoring a previously developed tool (RISKSUR) to the needs of STOC free. The information required by the tool was filled in by all partner countries and resulted in a first and second version of a questionnaire (deliverable 2.1 and 2.2), which ultimately evolved into the data format needed for the STOC free model (STOC free data).

Guidelines for the identification and sources of data were developed. The aim of these guidelines was to indicate the availability and the quality of data for parameters that could potentially be used as input parameters in the STOC free model. In addition, the guidelines provided definitions of the required parameters and information on the type and format of the data for the model. The assessment criteria included availability of quantitative or qualitative data, the sources of the data and the strengths and

limitations of the data (deliverable number 1.2). Each of the partner countries filled this table for their specific situation and the different BVDV CPs were described in Van Roon et al., 2020A. Additionally, a literature review and meta-analysis was initiated to obtain default values for risk factors for BVDV infection for inclusion in the statistical model (Van Roon et al., 2020B). In collaboration with a COST action, SOUND control, the data collection tool was extended to two other cattle diseases i.e. infectious bovine rhinotracheitis (IBR) and Johne's disease and was adapted to make it applicable throughout Europe. Subsequently, the tool was pilot tested by a Western (Netherlands) and Eastern (Albania) European country and a data quality evaluation module was included. Aspects that were considered important were data sources and accessibility, completeness of data, timeliness of data, and data accuracy. This version of the tool was improved based on the pilot results and feedback that was provided by the SOUND control consortium. In the subsequent step the tool was made available online through LimeSurvey, although at this point only for testing purposes by the STOC free and SOUND control consortia (Rapaliute et al., 2021). A scientific paper was written about the key learnings during the development of a generic data collection tool to support assessment of freedom from infection in cattle herds (Van Roon et al., 2021).

The STOC free model was developed using simulated data (Mercat et al., 2022). It was then tested and validated using French data with bulk milk BVDV test results and risk factors related to the number of cattle introduced. The specifics of the model development and the results of the French case were published (Madouasse et al., 2021). The final code of the model is freely available as an R package on https://github.com/AurMad/STOCfree .

The STOC free model provided some challenges in combination with the case disease BVD. The STOC free model is an SIS-model (Susceptible-Infectious-Susceptible), specified as a Hidden Markov Model to account for test uncertainty. Hence, the model is assuming that transitions occur both ways, i.e., from susceptible to infectious and from infectious to susceptible, which is biologically logical for a herd level model. As both the infectious and susceptible stages essentially are modelled as a probability, a non-zero value is implied. Consequently, the STOC free model is not well suited for establishing freedom from infection at population level when transition probabilities are close to zero, in other words when hardly any infection is present. Furthermore, if a specific test result e.g. test positive, changes the sampling scheme then this will either affect the interpretation of the probability to remain infected or essentially make the data follow an SI, rather than SIS model. Examples of changes in the sampling scheme include detection and removal of infected animals, removal of the herd from the control program, or placing the herd in a non-free category with transport restrictions. Therefore, if the data does not fit an SIS-model, the STOC free model is not a suitable method to determine freedom from infection. This might be a particular concern whenever a control program moves towards successfully eradicating the infection in question. In those cases, a scenario tree model would be the preferred methodology to determine surveillance system sensitivity and probability of freedom from infection. This was also successfully evaluated in the case study for BVDV surveillance in Sweden. The information gained from each of these methods (STOC free model, scenario tree modelling) contributes to an ongoing assessment of progress towards output-based standards as outlined in the EU Animal Health Law.

Eventually, BVDV CPs from four countries based on antigen tests on tissue samples from newborn calves were modelled and the freedom from infection was determined for herds officially free in the CP (Van Roon et al., in prep.). We learnt from this and the previous case studies what the properties and challenges are when applying the STOC free model.

The output of the project is extensively disseminated in scientific publications, at conferences and by organising webinars and workshops for either potential users or policymakers. These dissemination activities will also continue within a COST action SOUND control, which will run until the end of 2022. The STOC free framework is also explained in videos available at https://www.stocfree.eu/results/videos or on the STOC free YouTube channel https://www.youtube.com/watch?v=MlfWEbGCPd0

4. Discussion

The STOC free framework can be used to describe disease CPs and estimate the probability of freedom from infection for herds in a CP. In principle, the STOC free model can predict posterior probabilities of infection and thus probabilities of freedom from infection using data from any control program. Still, there are some points to consider:

1. Ongoing spread of infection in the population – The underlying SIS-model in the STOC free framework implicitly assumes that there is ongoing transmission of infection in the population under the CP i.e. the infection is still endemic in the country of interest and herds can either be free or infected. In a disease-free population or when only sporadic infections occur, the suggested model is a scenario tree.
2. Comparable latent class in the model - The definition of being infected has to be clear. Further, these definitions must be similar when evaluation is being undertaken of CPs in multiple countries. The herd-level test sensitivity and specificity must be specified in relation to this common definition. In the case of BVDV this was a complicating factor given that some CPs focussed on detecting antibodies as an indicator that one or more persistently infected animals were present while other CPs focussed on detection of the persistently infected (PI), and thus virus-positive, animals themselves.
3. Test schemes must reflect the true status of the herd – As an example, testing new-born calves for BVDV with an ear-notch test will detect PI calves shortly after birth, but if the animal is not removed, then the continued presence of a PI animal in the herd will not be recorded in the next month(s). In the STOC free model such herds may be considered free again in the next month(s) if no additional PI calves are born during this period, while in the CP it is not considered free. In addition, the biology of BVD is such that an unborn foetus can also be PI. Therefore in the CP, when a PI is detected the herd will be considered infected until all potential PI calves are born and tested (a period of 12-18 months in most CPs). In the STOC free model such herds may be considered free because a PI will not be detected until it is born. The latent class of the STOC free model is the presence of a PI animal "on the ground" (i.e. excluding those in utero).
4. Length of the time series versus changing parameters - Sufficiently long series of test results for individual herds are needed to estimate the parameters concerning disease dynamics from data. In other words, when only a few records are available for each herd, the disease dynamics will mostly be determined by the priors, hence the posterior estimates of probability of infection at herd level will be heavily influenced by these priors. Additionally, there is an underlying assumption about parameters being constant for the period covered by the data. Thus, whenever the CP is adjusted/modified, consideration is needed as to whether the changes can be expected to affect the probability of disease transmission. And if so, then the data should be analysed separately for the period before and after the change. Alternatively, a risk factor that incorporates the risk difference between the two periods could be added to the model. For BVDV CPs, the key output from the STOC free model (probability of freedom from infection) could be estimated with about two test results per herd. Hence, the probability of freedom may be low while the uncertainty will be high with only two test results.
5. Missing test results - In the absence of a test result, the model takes the last known result as measuring the true status (provided high sensitivity and specificity), and simulates all possible dynamics from this on. In such case, the higher the incidence of infection is, the higher the probability of infection following an initial negative result or missing test results.

In addition to knowledge on the disease CP and basic knowledge on disease modelling, the use of the STOC free framework also requires some knowledge about the use of the R-package. The provided information in the R-package guides the user through the data interface and the model. A default dataset and default prior distributions for BVDV are provided. The user can also include longitudinal monthly herd-level data from their own BVDV CP and include prior distributions for test validity,

incidence and prevalence. The data collection tools that were developed in the STOC free project were also used for IBR and Johne's disease (Rapaliute et al, 2021) and can be used for other cattle disease CPs. The data collection tools could be used for CPs in other animal species as well. However, this was not tested in the project. The generalisability of the STOC free model to CPs for other infectious cattle diseases and/or other animal species would be a next step in the development of the framework. Given the flexible nature of the methodology, this should be relatively straightforward.

Another factor to consider in the STOC free framework is the socioeconomic aspect. The data collection tools allow for collection of some economic parameters, such as the costs of diagnostics tests. The behaviour of farmers is already incorporated in the tool. The data required for the STOC free model is crude, being longitudinal test data from all herds in the CP, and thus a reflection of what is actually happening in those herds. For example, when a sample is taken later than scheduled, or not at all, this results in a missing test outcome in the data. Consequently, the model will estimate more uncertainty about the true infection status of such a herd.

The advantage of the STOC free framework is that it is a data-driven approach that only requires prior distributions on parameters that are usually well known when a CP is in place e.g. herd-level test sensitivity and specificity, the incidence and prevalence of the infection and the probability of clearing infection from one test event to the next. In contrast to scenario tree models, the STOC free model provides estimates not only for the probability of freedom from infection but for all model parameters.

5. Conclusions and recommendations

The STOC free framework allows a uniform and harmonized description of disease CPs. The STOC free model can be used to determine the confidence of freedom from infection and corresponding uncertainty that has been achieved in disease CPs, in support of an ongoing assessment of progress towards output-based standards as outlined in the EU Animal Health Law. With this information, and as required, further CP actions can be taken to mitigate the risks of persistence and (re-)introduction on the probability of freedom from infection. The framework is freely accessible with default values for BVDV. Further work is needed to test the model for other infectious cattle diseases, to extend it to other animal species and to include socioeconomic aspects.

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Glossary and Abbreviations

Glossary:

Longitudinal data	Longitudinal data, sometimes referred to as panel data, track the same sample at different points in time. The sample can consist of individuals, herds, establishments, and so on. In contrast, repeated cross-sectional data, which also provides long-term data, gives the same survey to different samples over time.

Abbreviation:

BVDV	Bovine Viral Diarrhoea Virus
CP	Control programme
IBR	Infectious Bovine Rhinotracheitis