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A framework for assessing the confidence in freedom from infection in animal disease control programmes

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Summary

In the Surveillance Tool for Outcome-based Comparison of FREEdom from infection (STOC free) project (https://www.stocfree.eu), a data collection tool was constructed to facilitate standardised collection of input data, and a model was developed to allow a standardised and harmonised comparison of different control programmes' (CP) output for cattle diseases. The STOC free model can be used to evaluate the probability of freedom from infection for herds in CPs and to determine whether they comply with pre-defined output-based standards of the European Union. Bovine viral diarrhoea virus (BVDV) was chosen as the case disease for this project because of the diversity in CPs in the six participating countries. Detailed BVDV CP and risk factor information was collected using a data collection tool. For inclusion of the data in the STOC free model, key aspects and default values were quantified. A Bayesian hidden Markov model was deemed appropriate, and a model was developed for BVDV CPs. The model was tested and validated using real BVDV CP data from partner countries and corresponding computer code was made publicly available. The STOC free model focuses on herd level data, noting that animal level data can be included after aggregation to herd level. The STOC free model is applicable to diseases that are endemic, given that the model needs the presence of some infection to estimate its parameters and enable convergence. In countries where infection free status has been achieved, a scenario tree model could be a better suited tool. Further work is recommended to generalise the STOC free model to other diseases.

Keywords

Bovine viral diarrhoea virus – BVDV – Cattle – Control programmes – Output-based surveillance – Probability of freedom from infection.

Introduction

Several European Member States (MS) have implemented control programmes (CP) for endemic infections of cattle. The design of these programmes is tailored to each country's specific situation and can vary

extensively. As a consequence, the outcomes can be difficult to compare, highlighting the need for methods to objectively and quantitatively compare programme outputs e.g. confidence of freedom from infection.

In the Surveillance Tool for Outcome-based Comparison of FREEdom from infection (STOC free) project, six countries collaborated to construct a generic framework to allow for standardised and harmonised comparison of the output of different CPs for cattle diseases. The framework allows the integration of heterogeneous data, however, model outputs are standardised and comparable [1]. The framework should be able to evaluate disease CPs and to determine whether they comply with output-based regulations of the European Union (EU).

Bovine viral diarrhoea virus (BVDV) was chosen as the case disease for this project because of the complexity of the disease, which causes a large variation in both programme design and prevalence that exists between MS. 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 for quantifying probability of freedom from infection at country level in those situations when infection has never been present or is considered eradicated [2]. With this method, however, it is not possible to account for the dynamics of ongoing infections between herds in a country.

In an endemic situation, herd-level modelling towards freedom from infection is seeking 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 that can safely trade cattle. CPs usually require repeated testing of all enrolled herds. In some cases, risk factors for infection are also available to incorporate in the design of a surveillance strategy. However, not every herd always adheres to the sampling scheme and risk of introduction of infection may vary between herds and in time. Thus, probability of freedom from infection in a herd may differ among herds within the same CP.

Our paper describes the framework which was designed and optimised using pilot-scenarios that describe 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 for further case studies in which the developed methods were applied and optimised. Finally, advantages and disadvantages of the developed methodology and possibilities for generalisation to other cattle diseases are discussed.

Materials and methods

There were two aspects to the study that together form the framework. A model (the 'STOC free model') was developed to determine the probability of freedom from infection, and a data collection tool ('STOC free data') was constructed to collect input data for the model in a standardised manner.

Data collection using STOC free data

As a first step in the development of the data collection tool, all six participating countries completed the risk-based animal health surveillance systems (RISKSUR) tool (https://www.fp7-risksur.eu) to identify differences between various bovine viral diarrhoea (BVD) CPs with respect to freedom from infection. For this use, the RISKSUR tool was adapted to facilitate data collection about the context and aspects of CPs as well as broader infection surveillance.

Observed differences between CPs, as identified using the adapted RISKSUR tool, were used as input for a first draft of the questionnaire. In this questionnaire, all aspects that can influence, either directly or indirectly, the confidence of freedom from infection in a BVDV CP were queried. Guidelines for the identification and sources of data were developed. The aim of these guidelines was to indicate the availability and 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.

The next step was to list all variables for which quantitative data were needed to calculate the confidence of freedom with the STOC free model. 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 optimised for use for BVDV and later extended to other cattle diseases i.e. Johne's disease (JD) and infectious bovine rhinotracheitis (IBR).

In a collaboration with the Sound control project (https://sound-control.eu), the data collection table was generalised so that it could be applied to all countries throughout Europe. Aspects for consideration included data sources and accessibility, completeness of data, timeliness of data, and data accuracy. Over 30 countries were asked to fill in the table [3].

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 [4].

The STOC free model

In the STOC free project, a conceptual model was developed for BVDV which described the infection process at three levels i.e. animal, herd and territory. The model connected the biological processes of BVDV infection with information about CPs and demographic context information. The STOC free model had to accommodate each of the three defining features of CPs against infectious diseases that are still present:

a) longitudinal test data from all herds in the CP with possible variation in the time intervals between consecutive tests;

b) imperfect test sensitivity and specificity;

c) 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 had previously been conducted with this type of model [5]. 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 a new infection is modelled as a function of data on risk factors using logistic regression. The model predicts a probability of 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 1 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, is less reliant on modelling hypotheses and is able to include data about infection dynamics.

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 CP using all the data collected for the estimation of model parameters. The probability of freedom from infection is then one minus the probability of infection.

Results

The prototype of the data collection tool was completed by each of the partner countries and the different BVDV CPs were quantitatively described [7]. In summary, all individual elements of the CP were

ranked including the context situation e.g. prevalence and risk factor occurrence, that could influence the probability that cattle from a herd categorised as BVDV-free are infected. Many differences in the context and design of BVDV CPs were found between countries. For example, CPs were either mandatory or voluntary, resulting in variation in risks from neighbouring herds, and risk factors such as cattle density and the number of imported cattle varied greatly between territories. Differences were also found in both testing protocols and definitions of freedom from infection [6].

The data collection tool was adapted and generalised for two other cattle diseases i.e. IBR and JD and applied throughout Europe. The online data collection was completed by 24 countries [3]. In most countries, data on cattle demographics and data from CPs for IBR and BVD were available. However, information on JD CPs and risk factors for introduction of infection were not available for the majority of the countries. The overall quality of data varied, being defined as good for the sections on demographics and CPs for IBR and BVD and fair for other aspects [3]. The key learnings during the development phase were described [8]. Data quality was mostly influenced by accessibility and accuracy of the data. Based on these results, it was decided to focus on the inclusion of those data that are available in most countries, and to develop default values for risk factors which could be applied in those countries where this information is not available [4].

R functions to read the data and use it in the STOC free model are freely available as part of an R package (https://github.com/AurMad/STOCfree). The package as well as the required longitudinal data and model parameters are described in a document on https://github.com/AurMad/STOCfree and depicted in Figure 2. The inputs required are actual CP test results, risk factor data when available, and information relating to CP context for the definition of prior distributions for test characteristics and infection dynamics. An example of such data is provided in Figure 3.

The STOC free model was developed using simulated data [9]. It was further tested and validated using French data with bulk milk BVDV

test results and risk factors related to the number of cattle introduced [6].

Modelling was undertaken of BVDV CPs from four countries that utilise antigen tests on tissue samples from newborn calves, and freedom from infection was determined for herds recognised as free in the CP [10]. The probability of infection in dairy herds that are free based on tissue testing of newborn calves is predicted to be very low. The median probability of freedom ranged from 0.98 (98%) to 1.00 (100%). Uncertainty (i.e. wider credibility intervals), slightly increased when less informative default priors (i.e. wider distributions) were used relative to more informative country-specific priors [10]. 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.

Discussion

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

The STOC free model provided some challenges, in particular when applied to BVDV, the initial case disease. The STOC free model is an susceptible-infectious-susceptible (SIS)-model, specified as a HMM 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 [9, 10]. This might be a particular concern as a region approaches successful eradication of the disease in question. In those cases, a scenario tree

model would be the preferred methodology to determine surveillance system sensitivity and the probability of freedom from infection. Furthermore, if a specific test result, e.g. test positive, leads to a change in the sampling scheme then this will affect the interpretation of the probability of remaining infected. Examples of changes in the sampling scheme include detection and removal of infected animals (whole herd testing) after an initial positive test result, removal of the herd from the control programme and thus no more tests carried out, or placing the herd in a non-free category with transport restrictions. If the data does not fit an SIS-model, the STOC free model is not a suitable method to determine freedom from infection.

The definition of being infected has to be clear. This definition can either be provided by (European) legislation or defined in private CPs, but must be similar when evaluation of CPs is being undertaken across 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 PI animals were present while other CPs focussed on detection of the PI, and thus virus-positive, animals themselves. For an infectious cattle disease such as IBR, this difficulty will be avoided as antibody and antigen tests can both indicate an infectious animal.

Another important prerequisite is that test schemes in CPs must reflect the true status of the herd. As an example, testing newborn calves for BVDV with a tissue test will detect PI calves shortly after birth. However, if these animals are not removed, then the continued presence of these PI animals 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. In contrast, within the CP these herds are not considered free. In addition, the biology of BVDV is such that an unborn foetus can also be a PI. In the CP following the detection of a PI, the herd will be considered infected until all potential PI calves are born and tested (typically a period of 12–18 months). In the STOC free model, such

herds may be considered free because a PI will not be detected until it is born.

Finally, sufficiently long series of test results for individual herds are needed to estimate the parameters from data relating to the dynamics of infection. In other words, when only a few records are available for each herd, the posterior estimates for infection dynamics will mostly be determined by the priors. Additionally, there is an underlying assumption about parameters being constant for the period covered by the data. Thus, whenever the CP is adjusted or modified, consideration is needed as to whether the changes can be expected to affect the probability of transmission. 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 probability of freedom from infection could be estimated with at least two test results per herd. However, in this case the estimated probability of freedom may be low and the uncertainty will be high.

The use of the STOC free framework requires some knowledge about the use of R. The information provided 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, to familiarise the user with the method. The user can subsequently 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 [3] are also applicable for other cattle disease CPs, and could probably be used for CPs in other animal species. The generalisability of the STOC free model to CPs for other infectious cattle diseases or other animal species would be a next step in the development of the framework. Within a COST (European Cooperation in Science and Technology) action called Sound control (https://sound-control.eu) the framework was applied to other infectious cattle diseases, such as IBR, JD and Salmonella. 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 diagnostic tests but this is currently not included in the model. The impact of cultural differences such as the risk perception of farmers or likelihood to comply with the CP are more challenging to establish, let alone explicitly include in the model. However, 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 for 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 between test events. 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.

Conclusions

The STOC free framework allows a uniform and harmonised description of disease CPs. In addition, the STOC free model provides estimates for the probability of freedom from infection with corresponding uncertainty. The STOC free model can be used to evaluate disease CPs and to determine whether they comply with output-based regulations of the EU. Based on the required standards, CPs can be improved and the impact of improved biosecurity to mitigate risks of (re-)introduction of infection on the probability of freedom from infection can be determined. 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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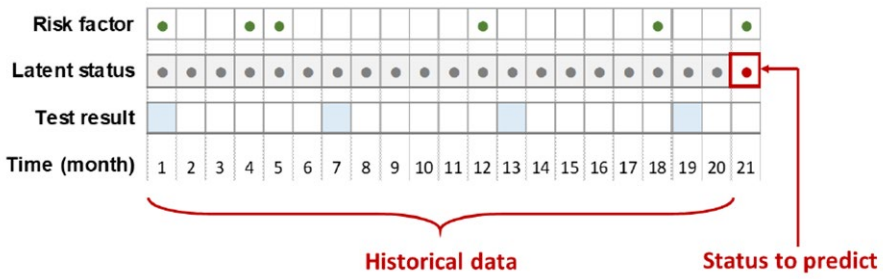
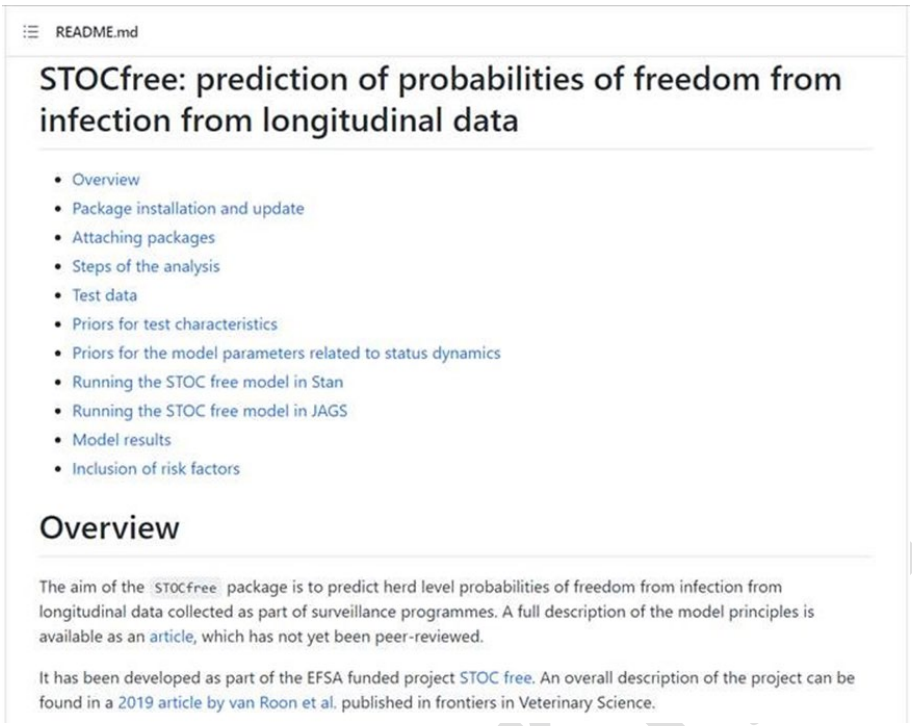


Figure 1
Conceptual representation of the implementation of a control programme within a herd (from Madouasse *et al.* [6])


README.md

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

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- Package installation and update
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- Running the STOC free model in JAGS
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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 2

The documentation for the STOC free framework on Github (https://github.com/AurMad/STOCfree)

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	Not 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

CP: control programme
ID: identity

Figure 3

An example dataset for the STOC free model with longitudinal monthly test results aggregated at herd-level