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

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A framework for assessing 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 the outputs of different control programmes (CPs) 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 these CPs comply with the European Union's pre-defined output-based standards. 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 the 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, although 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 it needs the presence of some infection to estimate 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 – Cattle – Control programmes – Output-based surveillance – Probability of freedom from infection.

Introduction

Several European member states have implemented control programmes (CP) for endemic infections of cattle. These programmes are tailored to each country's specific situation, and their design can vary extensively. As a consequence, outcomes can be difficult to compare, highlighting the need for methods to objectively and quantitatively compare programme outputs such as 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 European Union regulations.

Bovine viral diarrhoea virus (BVDV) was chosen as the case disease for this project because of the complexity of the disease, which results in a large variation in both programme design and prevalence among European member states. 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 in which 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 seeks 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. Control programmes usually require repeated testing of all enrolled herds. In some cases, risk factors for infection are also available to incorporate into 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.

This paper describes the framework that 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

The study had two main aspects 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 STOC free data, all six participating countries completed the risk-based animal health surveillance (RISKSUR) tool (https://www.fp7-risksur.eu) to identify differences among various BVDV CPs with respect to freedom from infection. For this use, the RISKSUR tool was adapted to facilitate collection of data 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. This questionnaire queried all aspects that can influence, either directly or indirectly, the confidence of freedom from infection in a BVDV CP. 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. The resulting data collection table was first optimised for use for BVDV and later extended to other cattle diseases, namely Johne's disease (JD) and infectious bovine rhinotracheitis (IBR).

In a collaboration with the European Cooperation in Science and Technology (COST) SOUND control project (https://sound-control.eu), the data collection table was generalised so that it could be applied to all countries throughout Europe. Elements 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 were 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 that described the infection process at three levels: 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 was identified as meeting all these constraints. Preliminary work on Q fever had previously been conducted with this type of model [5]. Hidden Markov models 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 depending only 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. Figure 1 provides 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 (shown as 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 one minus the probability of infection.

Results

The STOC free data prototype was completed by each of the partner countries, and the different BVDV CPs were quantitatively described [6]. In summary, all individual elements of the CP that could influence the probability that cattle from a herd categorised as BVDV-free are infected were ranked, including those related to the contextual situation, e.g. prevalence and risk factor occurrence. 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 [7].

The data collection tool was adapted and generalised for two other cattle diseases, IBR and JD, and applied throughout Europe. Twenty-four countries completed the online data collection [3]. In most countries, data on cattle demographics and data from CPs for IBR and BVDV 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 BVDV 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 that could be applied in countries where this information is not available [4].

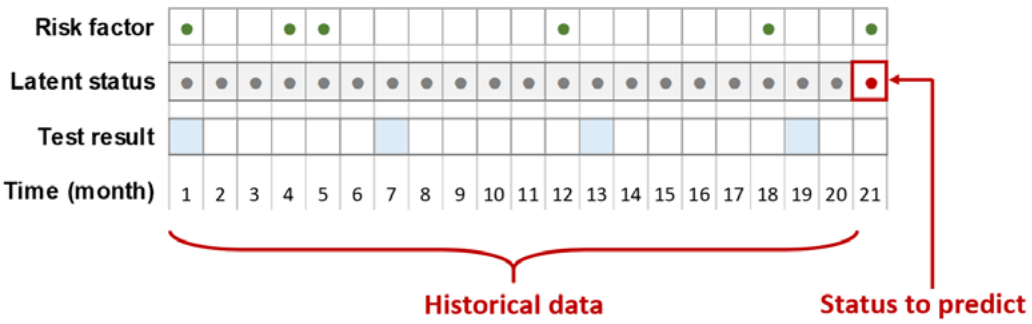


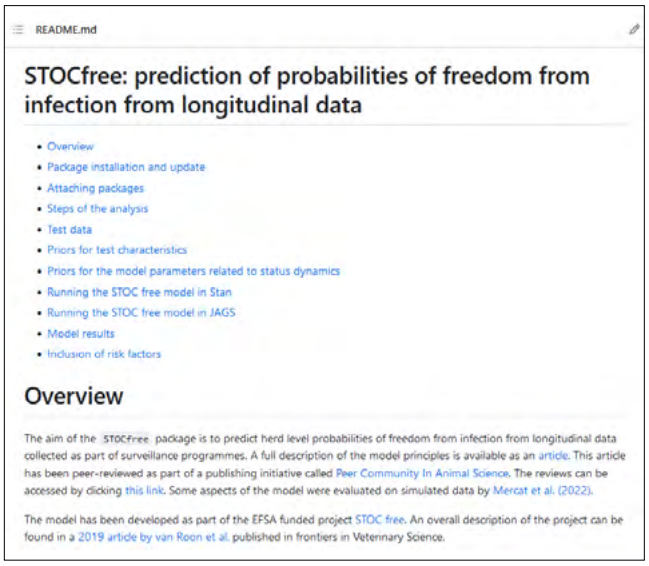
Figure 1

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

Green dots represent occurrence of risk factors, grey dots the true but unknown (latent) disease status and blue shaded squares the diagnostic test results

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 at 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 Table I.

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].


README.md

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

- Overview
- Package installation and update
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- Priors for test characteristics
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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. This article has been peer-reviewed as part of a publishing initiative called Peer Community In Animal Science. The reviews can be accessed by clicking this link. Some aspects of the model were evaluated on simulated data by Mercat et al. (2022).

The model 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)

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]. 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 to 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 a susceptible-infectious-susceptible (SIS) model, specified as a hidden Markov model to account for test uncertainty. Hence, the model assumes 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 poorly suited for establishing freedom from infection at population level when transition probabilities are close to zero – in other

Table I

A sample data set for the STOC free model with longitudinal monthly test results aggregated at herd level

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

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 CP and thus absence of further testing, or placing the herd in a non-free category with transport restrictions. If the data do not fit an SIS model, the STOC free model is not a suitable method to determine freedom from infection.

The definition of being infected must be clear. This definition can either be provided by (European) legislation or defined in private CPs but must be consistent 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 focused on detecting antibodies as an indicator that one or more PI animals were present while other CPs focused 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 both antibody and antigen tests can 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 subsequent 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 animal. In the CP, following the detection of a PI animal, the herd will be considered infected until all potential PI calves are born and tested (typically a period of 12 to 18 months). In the STOC free model, such herds may be considered free because a PI animal 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 that parameters are 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 data set and default prior distributions for BVDV are provided to familiarise the user with the method. Users 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 the COST action SOUND control, the framework was applied to other infectious cattle diseases, such as IBR, JD and salmonellosis. Given the flexible nature of the methodology, this process should be relatively straightforward.

Another factor to consider in the STOC free framework is the socio-economic aspect. The data collection tools allow for collection of some economic parameters, such as the costs of diagnostic tests, but these parameters are currently not included in the model. The impact of cultural differences such as the risk perception of farmers or likelihood of compliance with the CP are more challenging to establish, let alone explicitly include in the model. However, the data required for the STOC free model are crude, consisting of 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 model can be used to evaluate disease CPs and to determine whether they comply with output-based European Union regulations. 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 socio-economic aspects.

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Un dispositif d'évaluation du niveau de confiance dans l'absence d'infection dans le cadre de programmes de contrôle des maladies animales

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Résumé

Dans le cadre du projet européen STOC free (*Surveillance Tool for Outcome-based Comparison of FREEdom from infection*, outil de surveillance permettant de comparer les probabilités d'absence d'infection sur la base des résultats, https://www.stocfree.eu), un outil de recueil des données a été construit pour faciliter une collecte normalisée des données d'entrée ; un modèle a également été élaboré pour permettre une comparaison normalisée et harmonisée des données sur les résultats des différents programmes de contrôle des maladies des bovins. Le modèle STOC free peut être utilisé pour évaluer la probabilité d'absence d'infection au sein des troupeaux dans le cadre des programmes de contrôle et déterminer si ces programmes sont conformes aux normes définies par l'Union européenne en termes de résultats attendus. L'infection par le virus de la diarrhée virale bovine a été choisie comme maladie d'étude pour ce projet en raison de la diversité des programmes de contrôle dans les six pays participants. Les informations relatives aux programmes de contrôle et aux facteurs de risque d'infection ont été recueillies à l'aide de l'outil de collecte des données. Les aspects clés et valeurs par défaut ont été quantifiés en vue d'être inclus dans le modèle STOC free. Un modèle de Markov caché dont les paramètres sont estimés par inférence bayésienne a été considéré comme le plus adapté et développé pour une application aux données issues des programmes de contrôle de la diarrhée virale bovine. Ce modèle a été testé et validé en utilisant des données réelles des programmes de contrôle du virus de la diarrhée virale bovine des pays participants ; le code informatique correspondant a été rendu public. Le modèle STOC free utilise des données au niveau des troupeaux, même si des données au niveau des animaux individuels peuvent être incluses une fois agrégées au niveau du troupeau. Le modèle STOC free s'applique aux maladies endémiques, puisqu'un certain niveau de présence de l'infection est nécessaire pour estimer les paramètres et permettre la convergence. Dans les pays ayant obtenu le statut indemne d'infection, un modèle du type arbre de scénario pourrait être un outil plus adapté. Des travaux supplémentaires sont recommandés pour généraliser le modèle STOC free à d'autres maladies.

Mots-clés

Bovins – Probabilité d'absence d'infection – Programmes de contrôle – Surveillance basée sur les résultats – Virus de la diarrhée virale bovine.

Sistema para determinar el nivel de confianza respecto a la ausencia de infecciones en programas de control de enfermedades animales

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Resumen

Como parte del proyecto europeo STOC free (*Surveillance Tool for Outcome-based Comparison of FREEdom from infection*, herramienta de vigilancia para comparaciones por resultados respecto a la ausencia de infecciones, https://www.stocfree.eu), se confeccionó una herramienta de obtención de datos para facilitar la recogida normalizada de datos entrantes y se elaboró un modelo que posibilitara una comparación normalizada y armonizada de los resultados (datos salientes) de distintos programas de control de enfermedades bovinas. El modelo STOC free puede servir para calcular la probabilidad de ausencia de infección en los rebaños como parte de los programas de control y para determinar si estos programas se ajustan a las normas predefinidas de resultados de la Unión Europea. Como ejemplo de estudio para el proyecto se eligió el virus de la diarrea viral bovina (virus DVB) por la diversidad que presentaban los correspondientes programas de control de los seis países participantes. Empleando la herramienta de obtención de datos, se reunió información pormenorizada de los programas de control del virus DVB y los factores de riesgo. Para incluir los datos en el modelo STOC free, se cifraron unos aspectos clave y valores predeterminados Juzgando conveniente el empleo de un modelo oculto de Markov cuyos parámetros se estiman por inferencia bayesiana, se elaboró un modelo de esta índole aplicable a los programas de control del virus DVB. Para ensayar y validar el modelo se utilizaron datos reales de los programas de control del virus DVB de los países participantes, tras lo cual se hizo público el correspondiente código informático. El modelo STOC free trabaja con los datos por rebaño, aunque tras la agregación por rebaños pueden incluirse también datos por individuo. Para que este modelo sea aplicable a una enfermedad es preciso que esta sea endémica, pues el modelo requiere la presencia de cierto nivel de infección para calcular los parámetros y determinar convergencias. En aquellos países donde ya esté reconocida la ausencia de infección, sería más apropiado utilizar como herramienta un modelo de árbol de hipótesis. Los autores recomiendan ahondar en esta línea de trabajo para poder extender a otras enfermedades el uso del modelo STOC free.

Palabras clave

Ganado bovino – Probabilidad de ausencia de infección – Programas de control – Vigilancia por resultados – Virus de la diarrea viral bovina.

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