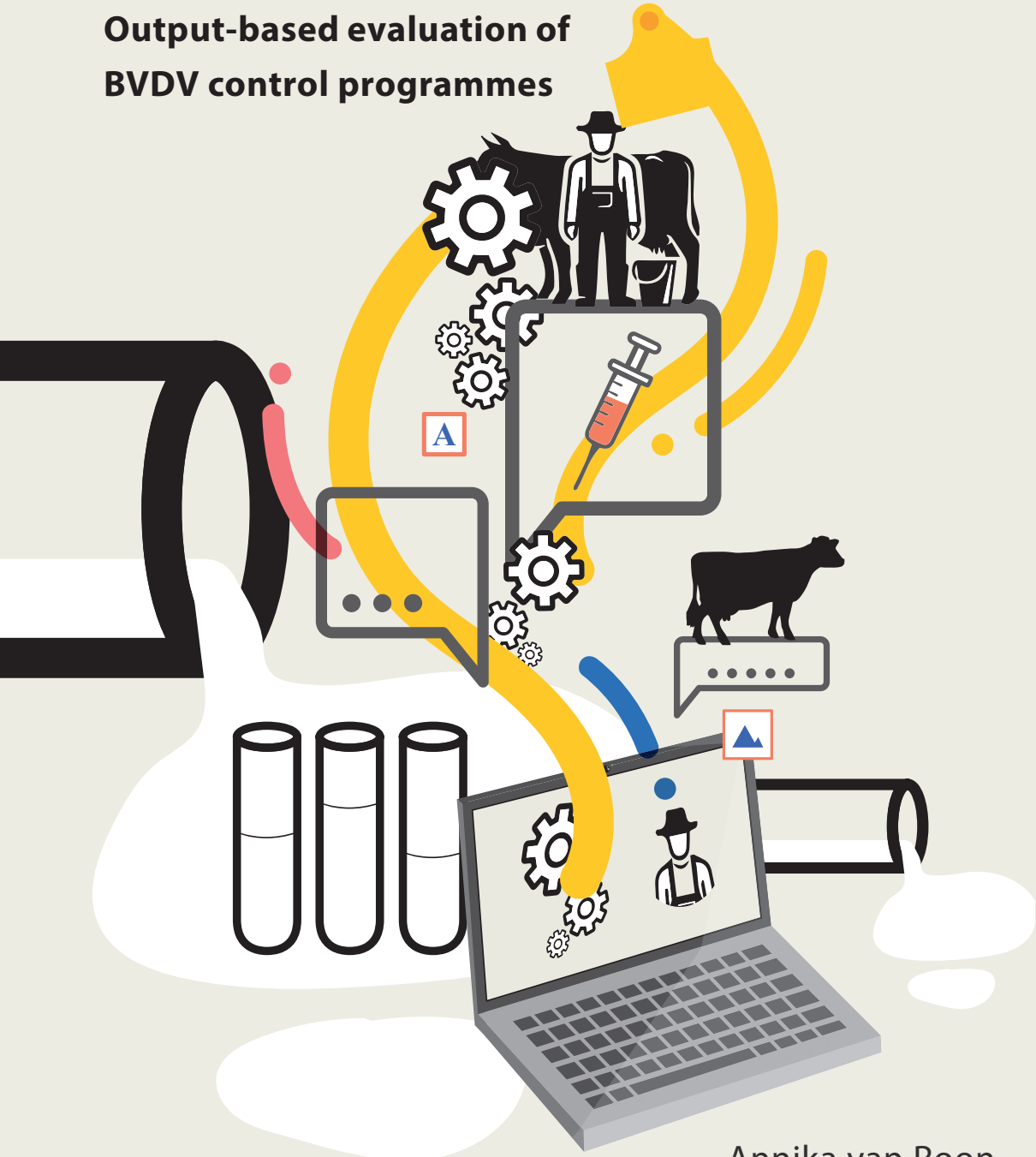
Estimating freedom from infection

Output-based evaluation of BVDV control programmes



Annika van Roon

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Colofon

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Estimating freedom from infection

Output-based evaluation of BVDV control programmes

Het schatten van vrijheid van infectie
Resultaatgerichte evaluatie van BVDV controle programma's
(met een samenvatting in het Nederlands)

Proefschrift

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Contents


A

Chapter 1

General Introduction

Output-based standards for disease control

Traditionally, input-based standards were applied to animal disease surveillance in the EU, meaning that EU legislation prescribed exactly what needed to be done in terms of control, surveillance or eradication i.e. a fixed study design, sampling scheme and type of tests that were to be performed. Alternatively, in more recent years, research has been conducted into the application of output-based standards that do not prescribe what needs to be done, but rather what must be achieved e.g. a defined surveillance sensitivity or a certain level of confidence of freedom (Cameron, 2012; More et al., 2013). This would mean that EU Member States (MS) or regions could implement different control programmes (CP) as long as they achieve the required output. On this basis, CPs implemented in different MS may vary in terms of study design, sampling scheme or type of tests performed. For example in a country with a very low prevalence of infection, risk based sampling is often considered more cost-effective, whereas countries with a higher prevalence need more intensive testing to find all cases. Additionally, CPs can be similar between countries, but still generate different levels of confidence of freedom due to differing contexts. For example, countries that import large numbers of animals have a higher risk of introducing infection compared to countries with little importation of animals although they have similar CPs. Under both of these circumstances, where programmes differ between MS, or in the case of similar CPs between countries but where the contexts differ, an objective and standardized assessment of the outputs is needed to demonstrate that the specified level of freedom from infection is achieved.

Methods for output-based assessment of confidence of freedom from infection

Currently, for the estimation of the probability of freedom resulting from CPs, the most commonly used method is scenario tree modelling (Martin et al, 2007a; Martin et al., 2007b). Scenario tree models are used to estimate the probability of freedom at a given level (design prevalence) by using a branching structure to describe surveillance components and estimate their sensitivity. Scenario tree models are well suited for estimation of the confidence of freedom of countries where the infection is considered eradicated or has never been present (Norström et al. 2014) and has been applied to many animal diseases such as Aujeszky's disease (Christensen & Vallières, 2016), classical swine fever (de Vos et al., 2004), bovine tuberculosis (de la Cruz et al., 2019), porcine reproductive and respiratory syndrome (Frössling et al., 2009) and bovine viral diarrhea (Foddai et al., 2016). At herd level, scenario tree models can be used to estimate the probability of freedom from infection for groups of herds with a specific risk profile and testing

regime (Toftaker et al., 2020; Ågren et al., 2018; Veldhuis et al., 2017; More et al, 2013). More recently, other methods for the estimation of freedom from infection have also been investigated, including latent class and Bayesian methods (Collins & Huynh, 2014; Heisey et al., 2014). Unlike scenario tree modelling, these methods do not require a design prevalence and learn from historical data and therefore rely less on modelling hypotheses. However, these methods are not yet developed to the point that they can be easily used in practice to assess the level of confidence of freedom generated by different CPs.

Biology of BVD

One cattle disease for which many countries have differently designed CPs and for which the prevalence varies greatly, is Bovine Viral Diarrhea (BVD). Bovine viral diarrhea virus (BVDV) is a pestivirus belonging to the Flaviviridae family and was first reported in 1946 in North America (Olafson and Rickard, 1947). BVDV is endemic in many parts of the world and is an economically important disease causing respiratory, enteric and reproductive issues in cattle herds (Houe, 2003). BVDV can be transmitted directly through nose-to-nose contact between cattle and indirectly by contaminated materials. When susceptible cattle are exposed to the virus they develop a transient infection (TI). Transient infection can last for two to three weeks followed by clearance of the virus and the development of lifelong antibodies that protect cattle from the effects of further exposure. TI cattle shed relatively low amounts of virus and only for a short period of time. However, when a pregnant cow undergoes a transient infection, various negative reproductive outcomes, depending on the stage of gestation of the cow, can occur (Figure 1). When a susceptible pregnant cow is infected within the first 30 days of gestation, infection of the embryo with BVDV often leads to embryonic death. Infection with BVDV after 120 days of pregnancy can either lead to abortion or an immune and healthy calf given that the fetus can be immunocompetent at this stage of pregnancy and develop an effective immune response (Brownlie et al., 1998). However, the most important scenario for BVD transmission is when the pregnant cow becomes transiently infected between approximately 30 and 120 days of gestation. At this point, the immune system of the fetus is not yet developed and therefore the BVD virus is not recognized as foreign and no immune response is produced (Brownlie et al., 1998). In these cases, the calf will be born persistently infected (PI) for life and will shed large amounts of virus in all body fluids (Brownlie et al., 1987; Lindberg & Houe, 2005). PI calves often do not grow old. Nevertheless, these calves are the main drivers of transmission of BVDV in and between herds.

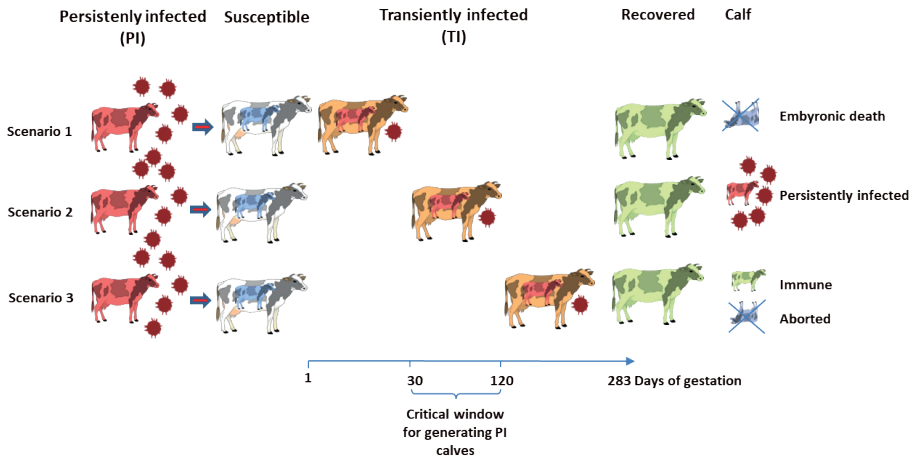

Figure 1. Simplified illustration of important aspects of BVDV infection in pregnant cattle.

EU regulation of transmissible cattle diseases and the history of BVD control

In the European Union (EU) transmissible cattle diseases are regulated within the Animal Health Law (Regulation (EU) 2016/429). This law was adopted in March 2016 and came into force on 21 April 2021. It supports human and animal health and facilitates safe trade of animals between MS by setting rules for the prevention and control of transmissible animal diseases. The degree of regulation depends on the impact of the disease on public or animal health, the economy, society and the environment. According to their impact, many transmissible animal diseases are listed and categorized into five categories i.e. from A to E (Regulation (EU) 2016/429). Diseases categorized as A or B have the highest priority for EU intervention and must be eradicated by all MS. Examples of cattle diseases categorized as A or B are foot and mouth disease and *Mycobacterium tuberculosis* complex (MTBC). For cattle diseases categorized as C, D or E, many MS conduct compulsory or voluntary CPs. For such cattle diseases there are no mandatory requirements for MS to initiate CPs. However, where these are established at national or regional level, MS may apply for formal recognition of these programmes (EU 2020/2002) provided that they are conducted in accordance with the regulations set down in EU 2020/689. Examples of diseases categorized as C, D or E include bovine viral diarrhea (BVD), Bluetongue and infectious bovine rhinotracheitis (IBR).

At the commencement of the research within this thesis, the new Animal Health law was not yet in force and BVDV control programmes did not fall under prescriptive EU regulation. Therefore many MS had introduced their own CPs to control BVDV in their country (Hodnik et al., 2021; Moennig et al., 2005). These MS were at varying stages of control. Some MS, such as the Scandinavian countries, had successfully eradicated BVDV, while some others were very close to achieving eradication or were working towards eradication of the virus (Hodnik et al., 2021). Countries that were already free of BVDV were implementing CPs that aimed to demonstrate ongoing freedom and early detection of virus should it been re-introduced, while other countries had CPs that aimed to find PIs within an eradication process. Some countries also had regional CPs in place e.g. France or several options within the CP from which farmers could choose depending on the situation of their herd or preference e.g. The Netherlands (Santman-Berends et al., 2021).

Depending on the stage of control, CPs for BVDV rely on two types of diagnostic tests i.e. detection of the virus itself (viral antigen or RNA) or antibodies. The former indicates the presence of a PI or TI and thus an on-going infection, while the latter indicates (previous) exposure to the virus or vaccination. Detection of PIs is often part of a herd or animal-level CP based on testing of (ear notch) samples of newborn calves for antigen/RNA. In these CPs, all newborn calves are tested for virus to identify PI cattle as soon as possible after birth, as well as generating indirect evidence of the status of the dam (Graham et al., 2021; Strain et al., 2021). Whether a calf that was tested virus positive is a PI or TI can only be determined by a confirmatory test after at least three weeks. When the calf still tests virus positive after three weeks, it is considered a PI calf, otherwise it is considered a TI. However, in most cases the calf is removed after the initial positive virus test and no confirmatory test is performed because timely removal of PIs greatly reduces the probability of further transmission of BVDV in the herd (Graham et al., 2015).

Detection of evidence of exposure by testing for antibodies is often performed in herds that are assumed BVDV free that wish to confirm their free status or for screening purposes to detect infected herds. This is done by repeated bulk milk testing of lactating cattle (Roch & Conrady, 2021) or by serological screening of serum samples from a representative group of youngstock within the herd, which is called “spot-testing” (Houe, 1992). These test methods are based on the assumption that when there is a PI animal in the herd, this will lead to high within herd seroprevalence due to the efficient spread of virus (Houe, 1995). Prerequisites for spot testing are that a sample should be taken from every group

of target animals that are housed separately i.e. youngstock of at least 6 months of age to avoid presence of maternal antibodies (Booth and Brownlie, 2016). When a herd tests antibody positive, follow-up testing is performed to confirm presence of a PI and to take further action.

Aim and outline of thesis

The aim of this thesis was to develop and test a generic output-based framework to determine the probability of freedom from BVD infection in cattle herds. BVDV was chosen as an example disease because of the variety of control programmes for BVDV in Europe e.g. with different tests and test-matrices and the complexity of infection e.g. transiently and persistently infected cattle and the time between infection of a herd and the birth of PI calves.

Part 1: STOC free framework

This work was part of the STOC free project (a Surveillance analysis Tool for Outcome-based Comparison of the confidence of FREEdom) which is described in Chapter 2 in Part 1.

Part 2: Context and risk factors

In Part 2, the data that are needed to assess the probability of freedom from infection are described and collected. In Chapter 3, CPs for BVDV in six European countries are qualitatively compared. The focus is on elements of these CPs that could influence the probability of freedom from BVDV. Chapter 4 provides a systematic search and meta-analysis of risk factors for the presence of BVDV in cattle herds. The goal was to obtain generic estimates that could be used as input data for the model that estimates the probability of freedom from BVDV of a herd.

Part 3: Evaluation of the STOC free framework

In part 3, a newly developed framework, the STOC free framework, for assessment of the confidence of freedom from infection is described and applied to BVDV field data. This framework consists of a data collection tool that facilitates the collection of data to feed the model that calculates a probability of freedom from infection. Chapter 5 describes the key learnings from the process of the development of an online data collection tool to uniformly collect input data to feed an output-based framework that is seeking to model freedom from infection of cattle diseases in different countries. In Chapter 6, the model was applied to data from BVDV CPs in four European countries. We describe the usefulness of this

method in the assessment of confidence of freedom from BVDV of cattle herds in different countries. Finally, in Chapter 7 an overall discussion of some important aspects related to the STOC free framework and output-based surveillance is presented.

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Part 1

STOC free framework


A

Chapter 2

STOC free: An innovative framework to compare probability of freedom from infection in heterogeneous control programmes

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Abstract

The existence, stage of eradication and design of control programmes (CPs) for diseases that are not regulated by the EU differ between Member States. When freedom from infection is reached or being pursued, safe trade is essential to protect or reach that status. The aim of STOC free, a collaborative project between six countries, is to develop and validate a framework that enables a transparent and standardized comparison of confidence of freedom for CPs across herds, regions or countries. The framework consists of a model combined with a tool to facilitate the collection of the necessary parameters. All relevant actions taken in a CP are included in a Bayesian network model, which allows prior distributions for most parameters. In addition, frequency of occurrence and risk estimates for factors that influence either the probability of introduction or temporary misclassification leading to delayed detection of the infection are included in the model. Bovine viral diarrhea virus (BVDV) is used as an example disease. Many countries have CPs in place for BVDV and although elements of the CPs are similar, biosecurity measures and testing protocols, including types of tests and testing frequency, as well as target groups, differ widely. Although the initially developed framework is based on BVDV, the aim is to make it sufficiently generic to be adaptable to CPs for other diseases and possibly other species. Thus, STOC free will result in a single general framework, adaptable to multiple disease CPs, which aims to enhance the safety of trade.

Introduction

Several European countries have implemented national or regional surveillance, control, or eradication programmes for non-regulated infections of cattle, such as bovine viral diarrhea (BVDV), paratuberculosis and salmonellosis. These programmes bring tangible benefits to participating farmers and national economies and are to be strongly supported. However, they also create difficulties for intra-community trade as free trade between European countries has the potential to allow the movement of infectious agents into regions where freedom from infection has been achieved (Gopal et al., 2006; Berends et al., 2009; Ryan et al., 2016). Control programmes (CPs) in European countries generally differ in the way that the free status is achieved and assigned, which makes it difficult to assess whether confidence of freedom from infection (the output) is equivalent. An understanding of equivalence with respect to freedom from infection is important when seeking to facilitate intra-community animal movements, whilst also managing the risk of infection. Up to now, there is a lack of agreed methodologies to assess and compare confidence of freedom from infection of cattle that are being moved between EU countries with different CPs.

There is currently minimal regulation at European level to control the spread of many important endemic diseases, including BVDV, between EU member states through the movement of animals. Therefore, there is a need for a tool that enables transparent and standardized comparison of confidence of freedom resulting from different CPs to facilitate safe trade. This tool should be able to calculate the confidence that animals moved between regions or countries are truly free from infection to prevent (re-)introduction of the infection in a free herd and/or territory. As there are many different CPs in place in different European regions and/or countries for non-regulated infections, there is an increasing need to implement output-based standards for animal health surveillance (More et al., 2009; Cameron, 2012; Norström et al., 2014; Schuppers et al., 2012; Foddai et al., 2015). With output-based standards, the emphasis is placed on comparability of the required outcome i.e., confidence of freedom from infection and its associated uncertainty, and not on the processes required to achieve this outcome, i.e., input-based standards. A growing body of scientific literature supports the development of output-based standards in animal health (More et al., 2009; Cameron, 2012; Norström et al., 2014; Schuppers et al., 2012; Foddai et al., 2015). Several methods have been developed to calculate freedom of infection, including scenario tree models and Bayesian methods where multiple surveillance components are combined, and latent class methods that take time since sampling into account

(Martin et al., 2007; Heisey et al., 2014). These methods are promising, but further research is need to allow simple and practical field-based application to enable standardized and quantitative comparison of outputs of CPs. A practical tool is needed to support the livestock industry in controlling and/or eradicating livestock infections.

STOC free

In 2017, a project was initiated by eight parties from six different countries (DE, FR, IE, NL, SE, UK) to develop and validate a Surveillance analysis Tool for Outcome-based Comparison of the confidence of FREEdom (STOC free) resulting from different control or eradication programmes. The STOC free framework fulfills the need to implement output-based standards for control of cattle infections by development of a single general output-based framework. The STOC free framework provides an objective and uniform approach to assess the probability of freedom from infection and its associated uncertainty given the heterogeneity in context and design of the CP.

The developed framework consists of a model (STOC free MODEL) combined with a tool to facilitate the collection of the necessary quantitative input information (STOC free DATA). To support the development of STOC free DATA and STOC free MODEL, a case disease was first chosen to use as example disease, i.e., BVDV. Detailed information about the different CPs for BVDV in the six partner countries was collected with the RISKSUR tool (the RISKSUR tool, http://www.fp7-risksur.eu/results/tools). Information on risk factors for introduction and delayed detection of BVDV was collected by performing a systematic review, and default values for STOC free model were generated by meta analyses. With a conceptual model, the infectious process of BVDV within the animal and transmission of BVDV within and between herds was described to fully understand the dynamics of infection and decide on the type of model that best suited the STOC free aim (see Figure 1).

Example disease: Bovine Viral Diarrhea Virus

For development and evaluation of the STOC free framework, BVD is used as an example disease. In Europe, many countries have differently designed CPs in place for BVDV and are at different stages of eradication, ranging from endemic infection to freedom. BVDV was specifically chosen as the model disease, because of the differences in infectiousness between transiently and persistently infected (TI, PI) cattle (Courcoul & Exanno, 2010; Lindberg, 2003; Houe, 1995) and the occurrence of both horizontal and vertical transmission. Horizontal transmission results in TI cattle, which are viraemic for a short period of time after which they recover and

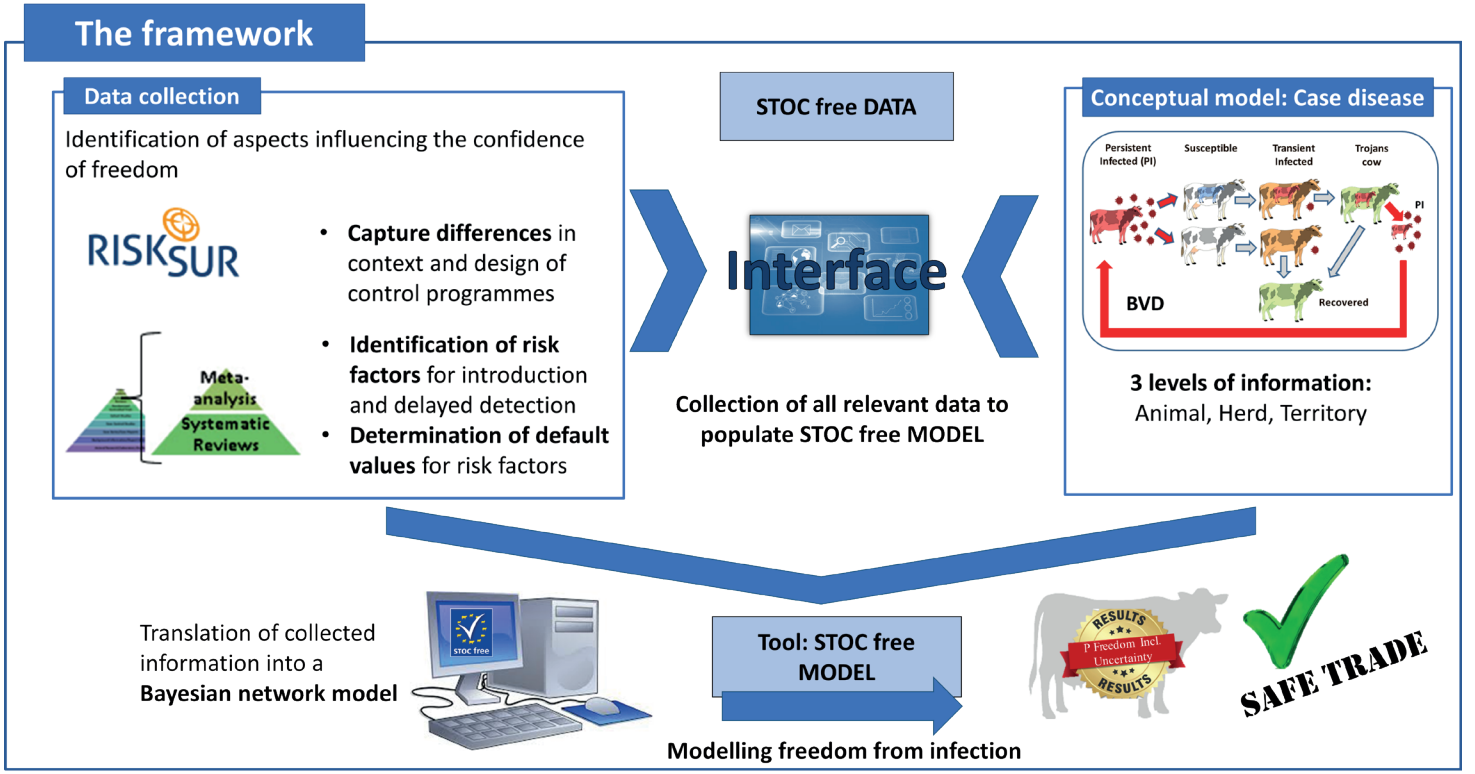

Figure 1. Graphical representation of the STOC free framework consisting of a data collection tool (STOC free DATA) and a model for calculation of freedom from infection (STOC free MODEL).

become immune for life. Vertical transmission during early gestation can result in the birth of PI calves. PI animals spread virus in large quantities throughout their lifetime and thus are the most important source for spread of the virus (Houe, 1999). BVDV is often introduced by purchase of either PI animals or cows pregnant with PI calves. The latter are commonly referred to as Trojan cows due to the hidden way in which such cows can introduce the virus into a new herd.

Development of STOC free data

The STOC free data tool (STOC free DATA) is designed to guide the user of the STOC free framework to gather the information and data needed to populate the STOC free MODEL. As a first step in the development of STOC free DATA, BVDV control programmes in place in the countries of the STOC free partners were described in a very detailed way. All aspects related to BVDV and the CPs in place in the participating partner countries were collected using an existing tool for harmonized description of surveillance programmes (the RISKSUR tool, http://www.fp7-risksur.eu/results/tools). This tool was originally developed to describe and (re-)design single surveillance components and did not meet all the criteria for application to BVDV CPs. Therefore, the RISKSUR tool was expanded to also gather information on the control actions described in the BVDV CPs and country-specific risk factors for introduction of BVDV and delayed detection. Following completion of the data collection through the RISKSUR tool by all collaborating countries, it was possible to list those variables that differed substantially between CPs and could potentially lead to variation in confidence of freedom and associated uncertainty (Table 1).

Differences and similarities between CPs were captured to identify aspects that can directly or indirectly influence the confidence of freedom from infection in a BVDV CP. The probability and associated uncertainty that an animal from a herd declared free by a given CP is truly free from infection at the moment of trade is influenced by the risk that:

- the infection was (re-)introduced into the herd after the last round of testing i.e., risk of introduction, or
- the latest round of testing resulted in a false negative result in relation to the herd's true positive status, i.e., misclassification leading to delayed detection either of newly introduced, or residual infection.

Table 1. Comparison of BVD control programmes and BVD status in six European countries in 2017.

Elements	Countries					
	Germany	**France (Brittany)**	**Ireland**	**The Netherlands**	**Sweden**	**The UK (Scotland)**
Herd level prevalence (breeding herds)	0.08%	unknown	2%	9%	0% - free	10%
Type of programme	Mandatory	Voluntary	Mandatory	Voluntary	Mandatory	Mandatory
Type of testing: Screening/ case finding	Ear notch, blood/serum	Bulk milk, ear notch, blood/serum	Ear notch	Bulk milk, ear notch, blood/serum	-	Ear notch, blood/ serum
Type of testing: Monitoring freedom of disease	Ear notch, blood/serum	Bulk milk, ear notch, blood/serum	Ear notch	Ear notch, blood/ serum	Bulk milk, blood/serum	Blood/serum
Vaccines licensed for use	Yes	Yes	Yes	Yes	No	Yes
Funding	Private and public	Private	Private and public	Private	Private and public	Private
Most important herd level risk factors for introduction						
1	Introduction of imported cattle	Boundary contact with neighboring cattle herds	Boundary contact with neighboring cattle herds	High cattle density	Introduction of imported cattle	Delayed removal of known PI animal(s)
2	Introduction of TI cattle	Introduction of cattle	Introduction of pregnant cattle	Introduction of pregnant cattle	-	Introduction of cattle with unknown status
3	Introduction of pregnant cattle	Presence of fattening unit	Indirect transmission through personnel	Indirect transmission through professional visitors	-	Boundary contact with neighboring cattle herds

The risk of introduction and delayed detection are influenced by the control measures in place in CPs but also by the existence and relative importance of country-specific risk factors. For BVDV, the most important risk factors were identified by STOC free partners as communal grazing, trade of live cattle and cattle density, i.e., number of cattle per km2, the latter being considered to be a proxy for the number of neighboring herds with which contact can potentially occur via direct or indirect transmission pathways.

Additionally, a systematic review of risk factors described in relevant scientific literature was conducted to obtain a comprehensive overview of all aspects that could influence either the probability of introduction of BVDV or could result in misclassification leading to delayed detection of the virus. Using meta analyses, we aim to determine generic risk estimates for the most influential risk factors for introduction or delayed detection that can be used as default values in the STOC free framework.

Data availability, quality and format were evaluated per country. Variables could only be included in the framework when at least some countries had quantitative data available for the respective variable. Variables for which data are lacking in some countries could still be included in the model when deemed important. Such variables would be included using default values for countries in which quantitative data was not available. The defaults can be replaced by more precise estimates once data becomes available; thereby "future-proofing" the framework.

Modeling freedom of infection

An essential step in the development of the STOC free framework was the design of a conceptual model representing the infectious process of BVDV at different levels, from animal to region. The conceptual model consisted of diagrams and explanatory text and maps the different types of information related to BVDV influencing the true status regarding infection. At the individual animal level, this included the different epidemiological states such as PI, TI, immune post infection, and susceptible, the course of infection and diagnostic results. The conceptual model at the herd level presented within herd infection dynamics, including risk factors for introduction and testing strategies employed. The conceptual model at territory level mapped the between herd infection dynamics, including contact structure both within and between territories and prevalence. Based on the information of the conceptual model and discussions among the partners, it was decided that the final STOC free MODEL should:

- Include informative priors and temporal aspects
- Allow input and output distributions to include biological variation and uncertainty
- Provide a generic probability and related uncertainty when no specific information is present, becoming more specific for individual situations by adapting the default information in STOC free DATA.
- Provide confidence in the free status of an animal at the moment of leaving the farm

Currently, the information resulting from the conceptual model is being translated into a Bayesian network model (STOC free MODEL). Bayesian networks are flexible and allow structuring heterogeneous information for the estimation of a uniform output. Within the STOC free project, the Bayesian network will be represented using directed acyclic graphs (DAG). Each node on the network represents a parameter that influences the probability or confidence of freedom from BVDV infection and is expressed by means of a statistical distribution. Each node

in the DAG is connected to one or more nodes through arrows. For example, a node herd BVD status with a Bernoulli distribution can be connected to a node bulk tank milk ELISA optical density with a Normal distribution. In this case, the value of the ELISA test result can be modeled as a function of the BVD status. Given the heterogeneity in CPs, data will be available for some of the nodes and missing for others e.g., bulk tank milk ELISA available, calf ear notch antigen test missing. Available data will be used to estimate the parameters of the statistical distributions and allow a distribution for missing data to be provided. In all cases, the distribution of the probability of freedom from infection will be the quantity of interest and will be estimated from all the available data.

Validation and wider application of the framework

The developed framework will be tested and validated using case studies to evaluate the probability of freedom from BVDV infection on animal, herd and territory level in each of the collaborating countries in which the BVDV situation varies from endemic to free. Application of the framework will result in a numerical and objective evaluation of CPs for BVDV in the EU. Transfer of this knowledge will enable countries to learn from each other, to optimize existing CPs and to improve the design of CPs for other diseases. Although BVDV will provide a rigorous test of the flexibility of the framework as initially developed, the framework should be generic enough to be adaptable to CPs for other diseases. At a later stage of the project, the possibilities for expanding the framework to other diseases and other species will be explored.

Limitations of the framework

The STOC free framework is first developed for BVDV in cattle. Currently, it is not yet applicable to other pathogens or other animal species. Within the STOC free project, the potential for expansion of the framework will be explored. There is currently no socioeconomic information incorporated in the model. At a later stage, it would be beneficial to include such information noting that CPs could generate a very high confidence of freedom, however, this may be achieved in a manner that is not cost-effective. Also social aspects should be taken into account. For example, stamping out could be very cost-effective and the fastest way to eradicate infection, but is not always easily accepted by the community. Incorporating these factors into the model are foreseen as next step in the development of a sustainable STOC free framework.

Vision

The ultimate goal is that the STOC free framework can estimate the probability of freedom from BVDV infection and the uncertainty around that probability for a traded animal from a free herd or region in a given CP and that it will be used throughout Europe to enhance safe trade. The framework can be used by organizations with access to the required data and good understanding of the disease control programmes. The process will be supported by a COST Action SOUND control (CA17110) in which a large number of participants from many European countries are involved. The COST action aims to coordinate, stimulate and assist initiatives to explore and implement a widely adaptable output-based framework. The long-term vision is that the framework will be used by European countries to objectively assess equivalence in the probability of freedom of traded animals for any infectious disease given differently designed CPs tailored to the unique demographic situation of each specific country.

Author contributions

The manuscript results from a project called STOC free which is coordinated and presented at InnovSur by GvS. AvR prepared the manuscript, which was revised primarily by GvS, IS-B, MN, DG, SM, AM, JG, AL, JF, and C-CG. Conceptual contributions were made by CF, MM, CS-L, GG, LvD, and MH.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Part 2

Context and risk factors


A

Chapter 3

A description and qualitative comparison of elements of heterogeneous bovine viral diarrhea control programs that influence confidence of freedom

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Abstract

For endemic infections in cattle that are not regulated at the European Union level, such as bovine viral diarrhea virus (BVDV), European Member States have implemented control or eradication programs (CEP) tailored to their specific situations. Different methods are used to assign infection-free status in CEP; therefore, the confidence of freedom associated with the "free" status generated by different CEP are difficult to compare, creating problems for the safe trade of cattle between territories. Safe trade would be facilitated with an output-based framework that enables a transparent and standardized comparison of confidence of freedom for CEP across herds, regions, or countries. The current paper represents the first step toward development of such a framework by seeking to describe and qualitatively compare elements of CEP that contribute to confidence of freedom. For this work, BVDV was used as a case study. We qualitatively compared heterogeneous BVDV CEP in 6 European countries: Germany, France, Ireland, the Netherlands, Sweden, and Scotland. Information about BVDV CEP that were in place in 2017 and factors influencing the risk of introduction and transmission of BVDV (the context) were collected using an existing tool, with modifications to collect information about aspects of control and context. For the 6 participating countries, we ranked all individual elements of the CEP and their contexts that could influence the probability that cattle from a herd categorized as BVDV-free are truly free from infection. Many differences in the context and design of BVDV CEP were found. As examples, CEP were either mandatory or voluntary, resulting in variation in risks from neighboring 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 disease. The observed heterogeneity in both the context and CEP design will create difficulties when comparing different CEP in terms of confidence of freedom from infection. These results highlight the need for a standardized practical methodology to objectively and quantitatively determine confidence of freedom resulting from different CEP around the world.

Introduction

Several European member states have implemented control or eradication programs (CEP) tailored to their own specific needs for controlling endemic infections in cattle that are not currently regulated at the European Union (EU) level. Each CEP can apply across an entire member state or over a territory within a member state. These CEP bring tangible benefits to participating farmers and national economies and should be strongly supported by government and other stakeholders. However, substantial differences in CEP create difficulties for intra-community trade. These arise from differences in definitions of infection-free status and the absence of an agreed framework to assess confidence in freedom from infection in cattle moved between countries and regions.

Within the EU, member states are not allowed to set trade barriers on intra-community trade for cattle diseases that are not regulated at the EU level. This is consistent with the free movement of goods within the EU, a central tenet of the common market, but does pose difficulties with respect to animal disease control. Given this context, it would greatly facilitate safe trade of cattle between member states if there were an objective means by which claims of freedom from infection for all relevant diseases could be evaluated and compared. Currently, however, the CEP can differ substantially, and CEP outputs can be very difficult to compare. In the past, freedom from infection claims were underpinned by defined input standards that provide a detailed description of the activity required, such as testing protocol(s) based on negative test result(s), and these were accepted as proof of freedom from infection (More et al., 2009; Schuppers et al., 2012). However, the probability and associated uncertainty that an animal or herd is truly free from infection is not solely dependent on test result and related test characteristics, but is also influenced by the risk that infection had been introduced into the herd before initial testing but not (yet) detected, or had been (re)introduced into the herd subsequent to testing (or between rounds of testing; Schuppers et al., 2012). This suggests that a more accurate estimation of confidence of freedom from infection can be achieved through an output-based approach, noting that differing sanitary measures have the potential to provide the same level of animal health protection (More et al., 2009). Using this approach, account should be taken of factors that influence the risks of either not detecting infection if present or of introducing infection, such as test procedures preceding export, the geographic location of herds, and animal movements (More et al., 2009; Schuppers et al., 2012; Toftaker et al., 2018).

The STOC free project (Surveillance analysis Tool for Outcome-based Comparison of the confidence of FREEdom from infection) is seeking to fill this key knowledge gap by developing an output-based framework that enables a transparent and standardized comparison of confidence of freedom for CEP across herds, regions, or countries (van Roon et al., 2019; https://www.stocfree.eu/). Ultimately, the project aims to develop simple and practical tools to inform farmers of infection risk when buying animals from certain territories and farms within territories. The project builds on earlier work to evaluate confidence in freedom in CEP, where a range of methods have been used, including scenario-tree analysis and Bayesian and latent class modelling (Martin et al., 2007; Cameron, 2012; Schuppers et al., 2012). This earlier work is promising but has not yet been translated into simple and practical field-based tools.

The current paper represents the first step in the STOC free project and focuses on detailed understanding of those elements of CEP that are relevant to the assessment of confidence in freedom. This information is critical baseline information that will inform later work toward the development of the afore-mentioned output-based framework. For this work, bovine viral diarrhea (BVD; Olafson and Rickard 1947; Houe, 2003) was used as a case study, given the complexity of its infection dynamics and the multiple differences between European member states in terms of infection prevalence, CEP design and implementation (including variation in test methods and sampling schemes), and progress toward control and eradication. Therefore, the confidence of freedom from herds considered negative will not necessarily be equivalent because of variation in context between different territories.

This study sought to describe the elements of CEP that contribute to confidence of freedom—the likelihood that a bovine from a herd categorized as bovine viral diarrhea virus (BVDV)-free is truly free from infection—and to conduct a qualitative comparison of each CEP element across 6 CEP in participating countries (Germany, France, Ireland, the Netherlands, Sweden, and Scotland). With respect to this latter objective, we did not rate CEP overall, but rather identified similarities and differences between CEP by ranking of individual elements, and highlighted challenges encountered when comparing CEP from different countries or territories.

Materials and methods

Definitions

"Context" concerns the circumstances in a territory independent of the testing protocol that can influence the confidence in freedom from infection in a given animal, herd, or territory. Three main elements are relevant: information about the background BVDV situation (herd-level prevalence), the CEP, and cattle demographics. Information on the BVDV background situation and CEP information is based on the epidemiologically relevant population. For BVDV, this includes all dairy and beef herds where calves are born. We excluded other cattle types because they are often housed and thus pose a limited risk for transmission of the virus (e.g., veal and beef fattening cattle) or because the risk of transmission is considered very low compared with that of dairy and beef breeding herds (e.g., fattening of dairy cattle before slaughter). All CEP in our study solely focus on dairy and beef breeding herds. By decreasing the number of persistently infected animals (PI) in breeding herds, the potential for PI to move into nonbreeding herds also decreases. However, we do account for the risk from other cattle types by including these herds in the information on cattle demographics (e.g., number of cattle herds and cattle density).

"Initial enrollment" describes the actions undertaken by a herd keeper from the time of enrollment of their herd into the CEP through to the time when BVDVfree status is obtained. This includes initial screening of the herd for presence of BVDV and any additional screening measures applied in the event of a positive test result or to prevent introduction of the virus.

"Surveillance" relates to those aspects of the CEP once BVDV-free herd status has been achieved and the herd is monitoring free status. This includes the definition of freedom, the test protocol for monitoring free status, the testing required to re-establish free status in the event of its being lost, and additional measures that minimize the risk of introduction of the virus through trade. This is based on the definition suggested by Hoinville et al. (2013), which was also adopted by The RISKSUR project (2015).

"Spot testing" tests for antibodies in a small representative group of young animals within the herd to indirectly indicate the presence of a PI in that management group and the animals within the herd with which they have contact.

"Bulk milk testing" tests bulk milk for antibodies to indirectly indicate the current or previous presence of a PI or for the presence of virus to directly indicate the presence of a PI.

"Ear notch testing" tests the skin of calves for virus within a few days after birth to detect PI. Sample collection is usually combined with the tagging of the calves.

BVDV control programs

The BVDV CEP are continually changing. This study is based on CEP in place in 2017, and subsequent changes (including, for example, the change to a compulsory BVDV CEP in the Netherlands at the beginning of 2018) are not included. A graphical representation of each specific CEP can be found in the Supplemental Files S1 to S6 (https://doi.org/10.3168/ jds.2019-16915). A more general description is included below.

Germany. In 1998, a voluntary BVDV CEP began, for which the individual Federal States were responsible. In 2011, a nationwide mandatory animal-level BVDV CEP based on tissue tag testing of calves was set in place (Wernike et al., 2017). The aim of this CEP is to detect and reduce the number of PI (Supplemental File S1; https://doi.org/10.3168/jds.2019-16915). In 2016, adjustments to the regulation were made to reflect experiences from the CEP to further reduce risk of transmission via trade, including a quarantine after the detection of a new case and trade restrictions for pregnant cows. Vaccination against BVDV is applied on a voluntary basis.

France (Brittany). No national standards for BVDV control in France exist, and each region can decide whether it wants to control BVDV and how to do it. In our comparison of CEP, we included Brittany, a region in the west of France where surveillance and control programs for BVDV have been implemented (Joly et al., 2005). Both programs are coordinated by Groupements de Défense Sanitaire (GDS), the regional animal health service. The surveillance program, in place since 2008, is mandatory. It is required for all cattle farmers to know their BVDV herd status by performing bulk milk testing in dairy herds or serological tests in beef herds. Since 2017, a voluntary CEP has been established for farmers who wish to eradicate BVDV from their herd as follow-up to the mandatory surveillance program. The aim of this CEP is to detect and eliminate PI in herds (Supplemental File S2; https://doi.org/10.3168/jds.2019-16915). Vaccination against BVDV is applied on a voluntary basis.

Ireland. A BVDV CEP based on tissue tag testing of newborn calves started in 2012 (Graham et al., 2014). Participation in the animal-level CEP was initially voluntary, but became compulsory on January 1, 2013. The CEP is industry-led and coordinated by Animal Health Ireland (AHI). Its target is to eradicate BVDV from Ireland before the end of 2020 (Supplemental File S3; https://doi.org/10.3168/jds.2019-16915). Vaccination against BVDV is applied on a voluntary basis.

The Netherlands. A voluntary industry-led BVDV CEP at the herd level based on bulk milk (in dairy herds) and individual blood testing for BVDV was in place between 1998 and 2018 (Mars and van Maanen, 2005; van Duijn et al., 2019). The aim of the CEP was to eliminate BVDV from herds by detecting and removing PI and monitoring the subsequent free status (Supplemental File S4; https://doi.org/10.3168/jds .2019-16915). Vaccination against BVDV is applied on a voluntary basis.

Sweden. Sweden is the only country in this study that has already achieved freedom from BVDV. In September 1993, a CEP was launched that aimed to eradicate BVD without vaccination. This is in contrast to the other territories included in this study, where vaccination is allowed. In 2001, a mandatory CEP required all cattle herds to be tested for BVDV on a regular basis (Hult and Lindberg, 2005). In 2008, few herds remained under investigation for BVDV, and risk-based surveillance was introduced. In 2011, the last case was detected, and by 2014, test results from the CEP indicated that Sweden was free from infection. This was confirmed in 2016 through a quantitative evaluation of surveillance results from 2012 to 2015 performed by SVA. The current surveillance program, based on antibody testing and surveillance at slaughter, started in 2017. This program is designed to detect the presence of infection at a herd design prevalence of 0.2%, with 99% confidence (National Veterinary Institute, 2015; Supplemental File S5; https://doi.org/10 .3168/jds.2019-16915).

Scotland. Scotland is 1 of 4 countries in the United Kingdom; each country has its own compulsory or voluntary CEP. Our study focuses on the BVDV CEP in Scotland. The industry-led BVDV CEP in Scotland is mandatory and based on spot testing. The CEP has had 4 stages to date: (1) subsidized screening of the herd for BVDV from September 2010 to April 2011; (2) mandatory screening of all breeding herds by spot testing for antibodies or antigen testing of calves, with all breeding herds to be screened by February 1, 2013, and annually thereafter; (3) control measures (e.g., movement restrictions) that came into force in January 2014; and (4) enhanced testing and further movement restrictions that were implemented on

June 1, 2015 (Scottish Government, 2016). The aim of the CEP is to eradicate BVDV from Scotland (Supplemental File S6; https:/ /doi.org/10.3168/jds.2019-16915). Vaccination against BVDV is applied on a voluntary basis.

Data collection

An existing tool, RISKSUR (The RISKSUR Project, 2015; Comin et al., 2016) was used to ensure harmonized data collection from each participating country or region (Germany, France, Ireland, the Netherlands, Sweden, and Scotland), hereafter referred to as territories, about both the target hazard BVDV and the CEP. RISKSUR is a digital tool built to support the design and evaluation of surveillance systems. The tool guides the user through all steps that should be considered when designing a surveillance system, including the surveillance objective, target population, surveillance enhancements, testing protocol, study design, sampling strategy, data generation (sample collection), data/ sample transfer, data translation (sample analyses), epidemiological analyses, dissemination of results, and surveillance review (The RISKSUR Project, 2015; Comin et al., 2016).

RISKSUR is used as a tool for detailed descriptions of surveillance programs. Because we were interested in control and all country-specific aspects that are relevant to assessing confidence in freedom, the RISKSUR tool was expanded for the current study to also collect information on aspects of control and context, such as actions taken following positive test results and risk factor occurrence. The expanded RISKSUR tool (RISKSURexp) included risk characteristics, structure of the cattle industry (i.e., size, production system, trade), CEP history and development, organizations involved, biosecurity measures, and results of the BVDV CEP. To gain a comprehensive overview of the situation in each territory, the tool was completed in early 2018 by consortium members of STOC free, supported by animal health authorities for each of the territories covered in the STOC free project (van Roon et al., 2019; https: //www.stocfree.eu/); data provided show the contexts and BVDV CEP in place in 2017.

All information was grouped under 3 main topics: (1) context (i.e., BVDV status, structure of the cattle industry, occurrence of risk factors); (2) initial enrollment (actions required to obtain a BVDV-free herd status); and (3) surveillance (measures applied to monitor herd-level BVDV-free status).

Data analysis: Comparative ranking

Separate data files were created for each CEP, containing qualitative information about all aspects of CEP, risk factor occurrence, and context. All 6 data files were

compared to identify differences and similarities. For each topic (context, initial enrollment, and surveillance), a list was created of elements that could influence the confidence of freedom from BVDV in the herd (Supplemental File S7; https://doi.org/10.3168/ jds.2019-16915). Then, beginning with context, each element was considered in turn, and, where relevant (as described below), the territories were ranked relative to each other using scales from 1 (most optimal situation) to 6 (least optimal situation) based on a trend consistent with increasing difficulty to achieve herd-level confidence of freedom. All elements were ranked separately and independently of the other elements. When the value of an element was similar between territories, the same rank was assigned to these territories and the ranking was condensed (e.g., ranked only from 1 to 3). Thus, a rank of 1 represented the territory with the most optimal situation for that particular element [e.g., the lowest risk of introduction or transmission of BVDV into the herd (context) or the highest probability of detection (outcomes of initial enrollment and surveillance)], each being important contributors to herd-level confidence of freedom. Sweden was not included in the ranking of elements relating to the third topic (surveillance), given that it is expected to be BVDV-free, and its surveillance approaches are considerably different from those of territories currently working toward freedom. Some assessed elements were excluded from the comparisons or ranking: (1) elements presenting valuable information about the context or the CEP but without direct influence on confidence of freedom, such as the program level; (2) elements with (almost) no variation between territories, such as the proportion of cattle herds that graze; and (3) elements for which few or none of the few territories possessed reliable information, such as the number of professional visitors on a farm, even though these were indicated as risk factor in several territories.

Results

All information relevant to comparison of the 6 BVDV CEP and their subsequent rankings are presented in Tables 1, 2, and 3. The context elements, including the background BVDV situation, the CEP, and cattle demographics, are presented and ranked in Table 1. The initial enrollment elements in the 6 CEP, including initial screening of the herd for presence of BVDV and any additional screening measures applied in the event of a positive test result or to prevent introduction of the virus, are presented and ranked in Table 2. Territories where all herds enrolled in the CEP in previous years (all relevant herds are already participating) were excluded from Table 2. This, for example, is the case for Sweden (which has already achieved

freedom from BVDV) and for Germany, Ireland, and Scotland (which began their compulsory CEP before 2017). The surveillance elements are presented and ranked in Table 3, including the definition of freedom, the test protocol for monitoring free status, the testing required to re-establish free status in the event of its being lost, and additional measures that minimize the risk of introduction of the virus by trade. The territory expected to be free of BVDV (Sweden) is not included in the ranking because its surveillance cannot be ranked relative to the surveillance of territories currently working toward freedom—Germany, France (Brittany), Ireland, the Netherlands, and Scotland—because their surveillance is designed for a different purpose. In Supplemental File S7 (https://doi.org/10.3168/jds.2019-16915), the rationale behind the ranking is explained for each element presented in Tables 1–3.

Context: BVD situation

Herd-Level Prevalence of BVDV in Breeding Herds. In 2017, the territories involved in this study differed greatly in their BVDV herd-level prevalence: the higher the herd-level prevalence, the greater the risk of introduction of the virus into a susceptible herd. This ranged from zero in Sweden to 10.4% in the Netherlands (Table 1). Sweden was ranked best [1] because it had the lowest risk of transmission of BVDV between herds.

Application of BVDV Vaccination. In all territories except Sweden, vaccination against BVDV is applied on a voluntary basis (Table 1). As vaccination can affect test results (e.g., on antibody testing in bulk milk), territories in which such testing schemes are applied take this into account in their CEP. In the Netherlands, it is not possible to screen bulk milk for virus by PCR until at least 23 d after live-virus vaccination, as the PCR test may detect vaccinal virus and generate a false-positive result. Additionally, unvaccinated animals must be selected for serological screening and a farm should only start vaccination after removal of all PI. Thereafter, when monitoring the BVDV-free status, screening for BVD antibodies (spot test) can be performed after vaccination of the herd, provided that the youngstock selected for the spot test have not been vaccinated. In Scotland, there are guidelines with regard to the animals that the farmer can select for testing in vaccinating herds. Ideally, unvaccinated animals should be tested but if all appropriate animals are vaccinated, then information about the date of vaccination and type of vaccine must be provided alongside the sample to facilitate interpretation of the results of the test. In Ireland and Germany, vaccination does not have consequences for the testing schemes because all newborn calves are tested for virus; in Brittany, this is also taken care of by an

alternative PI detection program. Within the context of becoming free from infection, the production of false positives (i.e., infection free but seropositive because they are vaccinated) is not directly relevant, because the focus is on false negatives. However, false-positive results could lead to a waste of resources.

Context: Program information

Program Aim(s). The CEP in the different territories were designed to achieve different program goals. For instance Sweden, now BVDV-free, has a CEP in place to detect BVDV after re-introduction. The CEP in Germany, Ireland, and Scotland aim to eradicate BVDV from the territory. The voluntary CEP in the Netherlands and Brittany aim to eradicate BVDV at the herd level (Table 1).

Program Level. Control and eradication programs that test at the animal level can be distinguished from those that test at the herd level (Table 1). Germany and Ireland test individual animals and assign free status to individual animals that test negative for BVDV. The other territories perform a testing protocol at the herd level and assign free status to the herd. However, although a CEP is designed at the animal or herd level, within a herd-level CEP, free status may also be assigned to individual animals and vice versa. For example, Ireland assigns free status to both herds and individual animals, and herd-level programs may assign free status to individual animals. Because it was impossible to conclude which of these program levels (either herd or animal) is optimal, this element was not ranked.

Mandatory or Voluntary. The Netherlands had a voluntary CEP in 2017, whereas mandatory CEP were introduced in Sweden (2001), Germany (2011), Ireland (2013), and Scotland (2013). In Brittany, cattle farms are required to know their BVDV status, but although there is a mandatory surveillance CEP, they can choose to eradicate BVDV from their farm with the voluntary eradication program. Mandatory CEP have a better ranking than voluntary CEP, because all herds in the epidemiologically relevant population are obliged to participate in the CEP and carry out control measures for BVDV (Table 1).

Herd Coverage. Control and eradication programs are developed to cover the epidemiologically relevant population. For BVDV, PI calves are the key to transmission, so the population of interest is all herds in which calves are born. All CEP include both dairy and beef breeding herds; however, the percentage of dairy and beef breeding herds included in each program varies. Mandatory CEP cover 100% of the relevant population whereas coverage in voluntary CEP is lower. In the Netherlands, 34% of breeding herds, mainly dairy herds, are covered,

whereas in Brittany, only 8% of the farms that had a positive result in the bulk milk screening started the voluntary eradication program. Herd coverage is ranked worse in the territories with lower coverage (Table 1).

***Herd Restrictions*.** All territories with a mandatory CEP have movement restrictions in place for herds or animals that do not yet have free status. All mandatory CEP prohibit movement of animals that do not have an individual negative test result when originating from a farm without free status (herd restrictions are specified in Table 1). The voluntary CEP only have movement restrictions for herds that participate in the CEP. Territories with movement restrictions are ranked better than territories without such restrictions because these restrictions lower the probability of transmission of BVDV from a possibly infected herd to a susceptible herd. Germany was ranked worse than other territories for movement restrictions because its movement restrictions for untested animals do not apply to export. However, the movement restrictions Germany has in place for farms with a positive antigen test do apply to export.

Removal of PI. Some CEP prescribe a maximum time from PI detection to removal, ranging from 7 d to 2 mo. Increasing the number of days that a PI stays on the farm increases the risk of transmission. Reducing the maximum time improves the ranking of the CEP. The actual time in days between detection and removal of a PI, which had a different ranking than the prescribed maximum time between detection and removal, was also included. The median number of days ranged from 1 to 38 (Table 1).

Context: Demographic information

Cattle Population. The total number of cattle herds ranges from approximately 12,000 in Scotland to 144,000 in Germany (Table 1). When only looking at breeding herds, it ranges from approximately 10,000 in Sweden to 83,000 in Ireland. In Germany and Brittany, no distinction could be made between breeding herds and other cattle herds. The number of cattle ranges from approximately 1.5 million in Sweden to 11.4 million in Germany. This information was not ranked but the more relevant element "cattle density" was. Territories with a low cattle density were ranked better than countries with a high cattle density because the probability of spread of BVDV by contact between cattle is lower. Sweden ranked best with a cattle density of 4 cattle per km2 of land area and the Netherlands ranked worst with a cattle density of 104 cattle per km2 (Table 1).

Risk Factors for Transmission and Introduction of BVDV. A known risk factor for introduction of BVDV is introduction of cattle into the herd. We included the percentage of herds that introduced cattle in 2017 ("purchased" if from within the territory; "imported" if from outside the territory; Table 1). Ireland ranked best with 40% of the herds purchasing cattle on an annual basis, and Scotland ranked worst with 77%. The number of cattle imported ranged from 11 in Sweden to 918,000 in the Netherlands. It should be noted that 95% of cattle imported into the Netherlands are veal calves, which are likely less relevant for transmission of BVDV, except for herds that keep veal calves and breeding cattle in the same location. Another known risk factor for transmission of BVDV between herds is direct contact between cattle from different herds. The possibility and frequency of nose-to-nose contact between cattle of different breeding herds depends on the distance between pastures, the type of boundary, type of cattle, attendance at shows, and so on. Most territories do not have quantitative data available for this element; therefore, it was estimated by expert opinion (Table 1). Sweden ranked best because contact between cattle of different farms is very rare. Ireland and Scotland were ranked worst, primarily as a consequence of farm fragmentation and possibly extended grazing and attendance at cattle shows. It should be noted, however, that farmers that visit cattle shows are often pedigree breeders who may take greater care of biosecurity, thereby mitigating the risk, at least to some extent.

Initial enrollment

Initial Screening. In Brittany and the Netherlands, the initial screening strategies are very different; for example, screening for antibodies versus virus, direct (individual) versus indirect testing (group), and different age groups and sample types tested (Table 2). The initial screening of the Dutch CEP was ranked best because all cattle are tested for virus, although a bulk milk sample is used to test lactating cows for virus in dairy herds. Brittany was ranked worst because not all cattle are directly screened.

Follow-Up. This element shows the measures taken when positive animals are detected in the initial screening (Table 2). In the Netherlands, for a herd to be allowed to continue with the CEP, PI should be removed. In Brittany, farmers have no obligation to remove PI. However, the farmer can also choose to start the voluntary eradication program, through which they also have to detect and remove all PI.

Table 1. The context elements associated with bovine viral diarrhea virus (BVDV) control programs (CEP) in six participating territories in 2017 and their ranking (ranks shown in brackets where applicable).

	Participating territory											
Context element[1]		**Germany**		**France (Brittany)**		**Ireland**		**The Netherlands**		**Sweden**		**Scotland**
BVDV situation												
Herd-level prevalence of BVDV in breeding herds[2]	[2]	0.08%	[3]	2%	[3]	2%	[5]	10.4%	[1]	0%	[4]	10%
Application of BVDV vaccination	-	Yes, on a voluntary basis	-	Yes, on a voluntary basis	-	Yes, on a voluntary basis	-	Yes, on a voluntary basis	-	No, not allowed	-	Yes, on a voluntary basis
Program information												
Aim of the program	-	Eradication of BVDV	-	Eradication of BVDV on individual herd-level	-	Eradication of BVDV	-	Eradication of BVDV on individual herd-level	-	Detect BVDV after re-introduction	-	Eradication of BVDV
Program level	-	Animal	-	Herd	-	Animal	-	Herd	-	Herd	-	Herd
Type of program	[1]	Mandatory screening + follow up	[2]	Mandatory screening, voluntary follow up[3]	[1]	Mandatory screening + follow up	[3]	Voluntary screening + follow up	[1]	Mandatory screening + follow up	[1]	Mandatory screening + follow up
Breeding herd types included in program	-	Dairy and beef breeding	-	Dairy and beef breeding	-	Dairy and beef breeding	-	Dairy and beef breeding	-	Dairy and beef breeding	-	Dairy and beef breeding
Breeding herds in program (%)[4]	[1]	100%	[3]	Screening: 90% follow up:8%[5]	[1]	100%	[2]	34%	[1]	100%	[1]	100%
Restrictions for herds or animals without BVDV-free status	[2]	Movement restrictions[6]	[3]	None	[1]	Movement restrictions[7]	[3]	None	[1]	Movement restrictions[8]	[1]	Movement restrictions[9]
Maximum time persistently infected animals (PIs) should be removed after detection	[1]	7 d, but option of confirmation test within 40 d	[2]	30 d	[3]	35 d[10]	[4]	6 wk	[5]	2 mo[11]	[6]	No maximum
Average time between detection of PI and removal (d)	[1]	median 1, mean 7.5	[4]	median 18, mean 35	[3]	median 13, mean 17	[2]	median 8, mean 11	-	N.A.[12]	[5]	median 38, mean 116
Demographic information[13]												
No. of cattle herds	-	~144,000	-	~20,000	-	~105,000	-	~35,000	-	~17,000	-	~12,000
No. of dairy and beef breeding herds	-	unknown	-	unknown	-	~83,000	-	~29,000	-	~10,000	-	~11,000
No. of cattle	-	11.4 million	-	2.5 million	-	6.5 million	-	4.3 million	-	1.5 million	-	1.8 million
Density (cattle/km^2)[14]	[3]	32[15]	[4]	74	[5]	93	[6]	104	[1]	4	[2]	23

Breeding herds that introduced cattle in 2017 (%)	[5]	~72%	[3]	~45%	[1]	~40%	[4]	~50%	[2]	~43%	[6]	~77%
No. of imported[16] cattle in 2017	[4]	~75,000	[5]	~154,000	[2]	~3,000	[6]	~918,000[17]	[1]	11	[3]	~11,000
Frequency of possible nose-to-nose contact between cattle of different breeding farms	[3]	Sometimes	[4]	Regularly, depending on herd type	[5]	Often, primarily due to farm fragmentation	[2]	Rare	[1]	Very rare	[5]	Often, due to shared boundaries and participation in shows

[1] The context elements relate to circumstances independent of the testing protocol that can influence the confidence in freedom from infection in a given animal, herd or territory, including the background BVDV situation, the CEP and cattle demographics. Where relevant and separately for each element, CEP were ranked from [1] (most optimal situation) to [6] (least optimal situation) based on a trend consistent with increasing difficulty to achieve herd-level confidence of freedom. For example, with respect to the element "herd-level BVDV prevalence in breeding herds," the CEP with the lowest and highest herd-level prevalence were ranked [1] and [5], respectively. Two CEP were ranked [3], as their herd-level prevalence is equal to each other.

[2] Percentage of virus-positive breeding herds (herds where calves are born).

[3] Mandatory screening, but when the screening gives a positive test result, the farmer can choose to start the voluntary eradication program.

[4] Dairy and beef breeding.

[5] Percentage of farms that had a positive result in the screening that chose to start the voluntary eradication program.

[6] Movement restrictions for animals that are not tested (do not apply to export) and movement restrictions for farms with a positive antigen test. In these farms, non-pregnant animals may not be moved for 40 d (also including export) and pregnant animals may not be moved until birth.

[7] All individual animals born after 1.1.13 must have a negative result to move; likewise any PI or suspect animals (e.g., dam of PI) also may not move; herds with a PI alive more than 35 d after detection are restricted—no moves in or out.

[8] The farm is not allowed to sell any livestock without individual testing.

[9] Not negative herds are not allowed to move any animal from the herd unless they test the individual animal and the animal is found virus negative. If a calf is tested and found virus negative, its dam is assumed negative and can also be moved.

[10] No maximum exists but when a herd fails to remove a PI by 35 d after the initial positive test result, this will result in restriction of all moves in and out of the herd.

[11] PI are not allowed to go out on pasture.

[12] Sweden is free of BVDV.

[13] Territory wide.

[14] The number of cattle per km2 of land area regardless of land area being unsuitable for keeping cattle.

[15] Density of all cattle, not only breeding cattle.

[16] From outside the territory, excluding cattle movements directly to slaughter.

[17] 95% of this number are veal calves.

***Trade*.** To minimize the risk of introducing BVD virus into herds, CEP in both Brittany and the Netherlands recommend or require herds to test introduced cattle (Table 2). However, their CEP differ as to whether this is recommended (Brittany) or mandatory (the Netherlands), and whether the introduced animal needs to be tested before leaving the selling herd or after arrival in the buying herd. The Dutch program ranked best because testing is mandatory. Neither program requires herds to test or quarantine their introduced animals before arrival in the herd (when herds are in the initial enrollment phase).

Surveillance: Definition of freedom

The CEP vary in the way that infection-free status is defined—at the territory, herd, or animal level (Table 3). Sweden is the only territory that has a definition of freedom at the national level because BVDV is considered absent so there is no longer a requirement for a herd-level definition of freedom. In Sweden, not all herds are necessarily tested annually, because surveillance is based on a combination of random and risk-based sampling, but all samples have to be antibody negative. In Germany and Ireland, when all animals in a herd have tested negative for BVDV and have an animal-level definition of freedom, this leads to a herd-level definition of freedom. In Brittany, a herd-level free status is assigned, and animals within a free herd can obtain a non-PI guarantee [see Table 3, Supplemental File S7 (https://doi.org/10.3168/jds.2019-16915), and Joly et al., 2005, for detailed information]. In the Netherlands, a herd-level free status is assigned, and all animals within those herds are assumed BVDV free. In Scotland, farms are classified as either negative or not negative after testing; they do not use the designation "free status." The definition of freedom was not ranked because these are overall outcomes of each CEP and the result of detailed elements that have already been ranked.

Test protocol

The test protocol in each of the territories after achieving a herd-level or animal-level free status is described in Table 3. The test protocol itself was not ranked because its success depends on many different factors. We instead ranked the probability that the test protocol would detect the virus. We also ranked the follow-up after indication of a BVDV infection and the route to re-establishment of free status.

Time From Birth to Testing. The first aspect of the test protocol that was ranked was the time between birth of a calf and the first test event (Table 3). If this calf is a PI, this time should be as short as possible, to prevent further transmission of

Table 2. Initial enrolment elements associated with bovine viral diarrhea virus (BVDV) control programs (CEP) in 6 participating territories in 2017 and their ranking (ranks shown in brackets where applicable)

	Participating territory							
Enrollment element[1]	**Germany[2]**		**France (Brittany)**	**Ireland[3]**		**The Netherlands**	**Sweden[4]**	**Scotland[5]**
Initial screening[6]	NA	[2]	Mandatory screening: Dairy: antibody (ab) bulk milk testing Beef breeding: ab screening 3–5 animals 24–35 mo and 3–5 animals 36–48 mo	NA	[1]	Milking cows: virus screening bulk milk Other cattle: virus screening individual blood AND virus detection in all cattle >30 d or virus ear notch testing of newborn calves[7]	NA	NA
Follow-up	NA			NA			NA	NA
Additional measures after a positive test result	NA	[2]	The farmer is notified and can start the voluntary eradication program[8]	NA	[1]	Retesting or removal of virus positive animal	NA	NA
Trade[9]	NA			NA			NA	NA
Testing purchase before leaving selling herd or after arrival in buying herd[10]	NA	[2]	Recommendation to test before leaving selling herd or after arrival	NA	[1]	Mandatory testing after arrival[11]	NA	NA
Testing of import before leaving selling herd or after arrival in buying herd	NA	[2]	Recommendation to test before leaving selling herd or after arrival	NA	[1]	Mandatory testing after arrival	NA	NA

[1] The initial enrolment elements describe actions undertaken by a herd keeper from the time of enrolment of their herd into the CP through to the time when BVDV-free status is obtained, including initial screening of the herd for presence of BVDV and any additional screening measures applied in the event of a positive test result or to prevent introduction of the virus. Where relevant and separately for each element, CPs were ranked (from 1 [most optimal situation] to (maximum) 6 [least optimal situation]) based on a trend consistent with increasing difficulty to achieve herd-level confidence of freedom. Territories where all herds enrolled in the CP in previous years (all relevant herds are already participating) are excluded.

[2] All breeding cattle in Germany are already included in the BVDV program, therefore there is no initial enrolment procedure

[3] All breeding cattle in Ireland are already included in the BVDV program, therefore there is no initial enrolment procedure

[4] All herds in Sweden are BVDV free therefore there is no initial enrolment procedure

[5] All breeding cattle in Scotland are already included in the BVDV program, therefore there is no initial enrolment procedure

[6] The first test a farm had to perform when starting the BVDV CP in 2017

[7] Calves that are younger than 30 days and already have an eartag at the moment of testing are blood tested after 30 days

[8] Voluntary eradication: virus screening blood of cattle <6 mo., ab screening blood sentinel cattle >6 mo., virus screening ear notch newborn calves

[9] Purchase is the introduction of animals bought from herds within the territory with the same BVDV control program in place as the buying herd and import is the introduction of animals bought from herds outside the territory.

[10] Purchase from herds without a BVDV-free status or animals with an unknown status

[11] Recommendation to buy cattle from BVDV negative farms, if not, it is recommended to test before leaving selling farm, but mandatory to test at least after arrival.

the virus. Farmers who monitor their free status by ear notch testing will normally test their calves within a few days of birth. Herds that apply bulk milk testing or spot testing will detect a new PI later, depending on the frequency of testing and the promptness of further investigations following initial serological evidence of infection. The territory in which the time from birth to testing is shortest is ranked best.

***Probability of a False-Negative Test Result*.** The second aspect of the test protocol that was ranked was the probability of a negative test result when a PI was present (Table 3). This probability depends on the sensitivity of the diagnostic test and whether it concerns direct testing (individual animals) or indirect testing (testing of a representative group of animals). Ear notch testing was ranked better than either antibody bulk milk or spot testing, because it is individual testing. Antibody bulk milk testing was ranked worse than ear notch testing and spot testing, because its sensitivity is reduced by both the dilution of positive samples and by animals that could be missing from the bulk sample.

Time to Identification of Virus in the Herd After a First Undetected PI. The third aspect of the test protocol that was ranked was the time until the virus was detected in the herd after the first PI was missed because of a false-negative test result (Table 3). Here, we ranked the spot test (performed at least twice a year) better than the ear notch test. Given that the efficiency of virus transmission by a PI is very high, the presence of a PI usually results in widespread seroconversion in herd mates. Depending on the distance between PI and susceptible herd mates (Houe et al., 2006), we assume that the virus will be detected by the next spot test. With the ear notch test, either a next PI calf needs to be born or susceptible pregnant cattle have to become infected and give birth to a PI calf, which on average could result in slightly later identification of the virus than biannual spot testing. Therefore, the Netherlands was ranked best based on the assumption that the antibody prevalence reaches 50% within a short time (<1 mo), followed by the other territories with ear notch testing (Germany and Ireland), less frequent spot testing (Scotland), or quarterly bulk milk testing combined with less frequent spot testing (Brittany).

Indication of BVDV infection

This element shows when a CEP result is considered an indication of BVDV infection in an animal or herd (Table 3). Every virus-positive test result (in Germany and Ireland) or every antibody-positive test result (in Sweden and Scotland) is assumed to be a BVDV infection. In Brittany, free status is assigned after 3 consecutive bulk milk tests in which one of the tests is allowed to be antibody

positive (details in Table 3). In the Netherlands, farmers either perform a spot test in which 5 animals are tested or they test newborn calves by blood or ear notch. In herds that choose to perform the spot test, additional actions have to be taken when at least 2 animals test seropositive (details in Table 3). Therefore, Brittany and the Netherlands are ranked worst.

Follow-Up After Indication of BVDV Infection. In all territories, PI have to be removed before BVD free status can be regained. Most territories, after removing the PI, follow their initial test protocol. The territories that have additional measures in place, such as testing the dam of the PI, are ranked better. In Brittany, farms can choose to participate in the voluntary eradication program after losing their free status following the detection of BVD antibodies in bulk milk. If the farm does not want to eradicate BVDV, it continues performing bulk milk testing (Table 3).

Re-Establishment of BVDV-Free Status: Definition of Freedom. This element shows the protocol for re-establishing herd-level free status after removing the PI and performing additional measures if included in the CEP (Table 3). The territories differ in test protocol and in the duration of the period in which no antibody- or virus-positive animals should be found to re-establish free status; this ranges from 7 mo to 2 yr. As this duration depends on previous measures and the context, this element was not ranked.

Surveillance: Trade

Trade is a known risk factor for introduction of BVDV into a farm or territory. As in the initial enrollment phase, all CEP recommend or require free herds to know or test the BVDV status of introduced cattle (Table 3). Except in Brittany, where it is only recommended, it is mandatory to test cattle purchased from non-BVDV-free herds within the territory. In Germany, Ireland, and Scotland, which are ranked best, cattle should be tested before they leave the selling herd, because animals without a negative status are not allowed to move or farmers are only allowed to buy cattle from herds with BVDV-free status. In the Netherlands, it is mandatory to test purchased cattle, although this can be conducted following their arrival on the farm. In Sweden, no requirement exists to test purchased animals on individual herds, but only cattle from free herds can be purchased. Control and eradication programs do not describe measures such as quarantine to reduce the risk of introducing a pregnant cow carrying a PI or a transiently infected cow. For imported animals, territories with mandatory testing after arrival are ranked best, because none of the CEP require imported animals to be tested before their arrival on the farm. In Sweden, it is an industry requirement that imported cattle be tested before arrival.

Table 3. The surveillance elements associated with bovine viral diarrhea virus (BVDV) control programs (CEP) in six participating territories in 2017 and their ranking (ranks shown in brackets where applicable).

	Participating territory											
Surveillance elements[1]		**Germany**		**France (Brittany)**		**Ireland**		**The Netherlands**		**Sweden**[2]		**Scotland**
Definition of freedom [3]												
Herd-level	—	All cattle are virus negative for 24 mo; no contact with non-free farms[4]	—	Dairy: At least "A" status[5] after 3 consecutive tests with results 000, 010 or 100[6] Beef breeding: 2 consecutive negative tests for all animals tested in the screening spot test (A status)	—	>3-yr participation; all animals with known negative status (direct or indirect) and no persistently infected animals (PI) present ≥1-yr	—	No virus-positive cattle during 10 mo	—	National level: Surveillance is designed to reach, annually, a 0.99 probability of freedom (design prevalence 0.2% at herd-level, 99% confidence)[7]	—	No free designation; farms are either negative or not negative after testing
Animal-level	—	Virus-negative test result or birth to virus-negative calf	—	Non-PI guarantee: Calves born in a herd with an A status for a sufficiently long time[8]. Dam of virus-negative calf.	—	Virus-negative test or birth of virus-negative calf (indirect negative)	—	Animals from a free herd	—	Follows from the national level definition[7]	—	Animals from a negative herd
Test protocol	—	Virus ear notch testing of newborn calves or before trade when status is unknown	—	Mandatory screening: dairy: quarterly antibody (ab) bulk milk testing; beef breeding: ab screening 3-5 animals 24-35 mo and 3-5 animals 36-48 mo	—	Virus ear notch testing of newborn calves	—	Virus testing all newborn calves by ear notch, virus testing all newborn calves by blood or ab spot testing 5 calves 8 to 12 mo. biannuall[9]	—	Quarterly ab bulk milk testing in dairy herds; ab testing at slaughter for beef breeding	—	Ab spot testing once or twice a year (depending on calving pattern) minimal 5-10 cattle of 9-18 mo or 6-18 mo or 18+ mo and on holding since birth
Time from birth until testing	[1]	Just after birth[10]	[3]	Quarterly or after 24-35 mo	[1]	Just after birth	[2]	Just after birth, a month after birth or after 8 to 12 mo.	—	Quarterly or at slaughter	[4]	Once or twice a year
Probability of a false-negative test result[11]	[1]	Ear notch: high sensitivity and direct testing	[3]	Bulk milk: little less sensitive and indirect testing or spot testing: high sensitivity and indirect testing	[1]	Ear notch: high sensitivity and direct testing	[2]	Ear notch/blood testing: high sensitivity and direct testing or spot testing: high sensitivity and indirect testing	—	Bulk milk: little less sensitive and indirect testing or blood testing: high sensitivity and direct testing	[2]	Spot testing: high sensitivity and indirect testing

Time to identification of the virus in the herd after a first undetected PI (undetected due to false-negative test)	[2]	Could be no detection till next PI is born from herd mate from dam of the PI, pregnant herd mates that PI infects or from the false negative PI	[2]	Possible detection next quarter or next year spot test	[2]	Could be no detection till next PI is born from herd mate from dam of the PI, pregnant herd mates that PI infects or from the false negative PI	[1]	Could be no detection till next PI is born from herd mate from dam of the PI, pregnant herd mates that the PI infects or from the false negative PI or possible detection with next spot test in 6 months[9]	—	Possible detection next quarter or next slaughtered animal	[2]	Possible detection with next spot test in 6 or 12 mo
Indication BVDV infection[12]	[1]	Virus- positive ear notch	[2]	Three consecutive tests with at least two "1" test results or one "2" test result[13]	[1]	Virus-positive ear notch	[2]	Virus-positive ear notch/ blood test or ab positive spot test in which additional actions [14] have to be taken when at least 2 calves test positive	—	Ab-positive test result	[1]	Ab-positive spot test
Follow-up after indication of BVDV infection [15]	[1]	Virus ear notch testing of newborn calves, virus testing of all cattle on the farm. No trade for 40d and no trade of pregnant cattle before giving birth.	[3]	Voluntary follow-up: Dairy: First ab testing in primiparous cows followed by (beef:) virus blood testing calves < 6 mo and ab blood testing 40% of cattle >6 mo and virus ear notch testing of newborn calves	[2]	Virus ear notch testing of newborn calves and testing dam and offspring	[2]	Virus ear notch/blood testing all newborn calves during 10 mo or in case of spot testing an extended spot test or virus blood testing of all cattle 1-16 mo[14] followed by a 10 mo period of ear notch/blood testing	—	Additional ab testing in individual animals. Infection likely: ab testing of all cattle and virus testing of ab negative animals	[2]	Virus testing of individual calves and subsequent virus testing of the dam.
Re-establishment of BVDV-free status	—	No virus positive newborn cattle during 2 yr	—	To end the voluntary eradication program: During 1 yr period no virus positive calves <6 mo and all tested cattle >6 mo ab-negative. Then: Dairy: At least "A" status after 3 consecutive bulk milk tests with results 000, 010 or 100 [5,6]. Beef breeding: negative test for all animals tested in spot test	—	No PI animal in the herd for at least 12 mo and all animals have a known neg status (direct or indirect)	—	All cattle 1-16 mo virus-negative and no virus-positive newborn cattle during 10 mo	—	No ab positive cattle in spot test youngstock >12 mo or pooled milk primiparous cows for 7 months	—	All cattle virus-negative or all newborn calves tested during a 12 mo period are virus-negative

Trade[16]												
Testing purchase before leaving selling herd or after arrival in buying herd[17]	[1]	Mandatory testing before leaving selling herd	[3]	Recommendation to test before leaving selling herd or after arrival	[1]	Mandatory testing before leaving selling herd (animals without a negative status are not allowed to move)[18]	[2]	Mandatory testing after arrival, but as soon as animals are purchased from a non-free herd, the herd loses its free status	—	No requirement on individual herds to test prior to moving animals[19], but only allowed to purchase cattle from free herds	[1]	Mandatory testing before leaving selling herd (farmers are only allowed to buy from negative herds or buy animals tested negative)
Testing of import before leaving selling herd or after arrival in buying herd	[1]	Mandatory testing after arrival	[2]	Recommendation to test before leaving selling herd or after arrival	[2]	Recommendation to test before leaving selling herd or after arrival [20]	[1]	Mandatory testing after arrival, but as soon as animals are purchased from a non-free herd the herd loses its free status	—	Industry requirement to test imported cattle before leaving selling herd	[1]	Recommendation to test before leaving selling herd or soon after arrival, but when not tested the status becomes not negative[21]

[1] The surveillance elements relate to those aspects of the CEP once BVDV-free herd status has been achieved and the herd is monitoring the free status, including the definition of freedom, the test protocol for monitoring the free status, and the testing required to re-establish free status in the event of its being lost, and additional measures that minimize the risk of introduction of the virus by trade. Where relevant and separately for each element, CEP were ranked from [1] (most optimal situation) to [4] (least optimal situation) based on a trend consistent with increasing difficulty to achieve herd-level confidence of freedom. The ranking did not include Sweden, which is expected to be BVDV-free and has different surveillance objectives.

[2] Sweden is not included in the ranking as Sweden is assumed BVDV free and cannot be ranked relative to surveillance in territories that are working towards freedom.

[3] Not ranked because this is the program outcome

[4] All cattle in the herd are free from clinical signs suggestive of BVDV infection. All cattle born in the herd have been tested for BVDV within 30 d after birth using a method described in the official set of methods with a negative result. Only BVDV-unsuspected cattle have been added to the herd. The cattle of the herd have not been in contact with cattle outside the herd that are BVDV-suspect. The cattle of the herd may be inseminated only with seeds of BVDV-unsuspected bulls or in case of natural breeding, only BVDV-unsuspected bulls have been used.

[5] Herds are classified based on 3 consecutive bulk milk tests. Status "A" means a herd had 3 results of 0 or n in the bulk milk screening. All dairy and dry cattle receive this status. After more test rounds, herds can receive "super A" status followed by "super A+" status and eventually "A+ 90 d/180 d" status. See footnote 8.

[6] The results of 3 consecutive tests. For example, 000 means 3 consecutive tests with test result 0. Test result 0: <10% of the cows are positive; test result 1: 10–30% of the cows are positive; test result 2: >30% of the cows are positive; test result n: very low percentage of cattle

[7] Definition of freedom at the national level. Because Sweden is BVD free, there is no longer requirement for an animal- and herd-level definition.

[8] These herds may receive super A status (status A + 3 times class 0 or n); super A+ status (super A + all purchased animals in past 27 mo tested negative); super A+ 90 d/180 d status (super A+ + 2 last tests had result n).

[9] Most herds perform spot testing.

[10] According to regulation within seven days after birth.

[11] The probability that a herd is considered free, while a PI is present. The lower the ranking, the lower the probability of a false-negative test result. Combination of test characteristics and whether it concerns direct testing (individual animals) or indirect testing (testing of a representative group of animals).

[12] This element shows when a CEP result is considered an indication of BVDV infection in an animal or herd.
[13] See footnote 6; all combinations that are not: 000, 010 or 100
[14] In case of 2 seropositives in spot test, then extended spot test (5 new calves and the initially 2 antibody-positive calves have to be retested). In case of more than 2 seropositives in spot test, then cohort testing: all cattle between 1 and 16 mo of age have to be tested for virus using individual blood samples.
[15] In all programs virus-positive animals are removed
[16] Purchase is the introduction of animals bought from herds within the territory with the same BVDV CEP in place as the buying herd; import is the introduction of animals bought from herds outside the territory.
[17] Purchase from herds without a BVDV-free status or animals with an unknown status
[18] Legislation requires that all animals born after January 1, 2013, must have a negative result to move. Animals born before then may move if not positive or suspect. However, at this stage only ~8,000 animals born before then are alive and have an unknown status, whereas other females have an indirect negative status by having had ≥1 negative calves.
[19] There is an annual surveillance program aimed at detecting presence of BVDV at a design prevalence of 0.2% and a probability of freedom of 99% or higher.
[20] Imported animal (born after January 2013) may not leave the herd they first enter without being tested; most animals are tested after arrival.
[21] It is not mandatory to test imported cattle, but the status of the herd will become "not negative"

Discussion

In this study, we present a detailed overview of those elements of CEP that are relevant to the assessment of confidence in freedom. In this work, we used BVDV as a case study, noting that many countries or regions in the world have implemented their own CEP. We considered BVDV CEP in 6 different territories within Europe to capture differences and similarities and to describe and compare the elements of CEP that contribute to confidence of freedom (the likelihood that a bovine from a herd categorized as BVDV-free is truly free from infection).

Many factors influence confidence of freedom. In this study, we considered all factors that differed between CEP, including context elements, because they appeared to be essential in the comparison of CEP. Many elements are interrelated; therefore, it was not possible to determine the relative contribution of each element to the overall confidence of freedom. Therefore, CEP comparisons were restricted to individual elements, and no aggregation was attempted. The CEP can be compared in different ways. They are usually compared by focusing on the current status and epidemiological or economic features of the disease (Greiser-Wilke et al., 2003; Moennig et al., 2005; Houe et al., 2006), but CEP have also been reviewed in terms of the financial and economic implications of prevention and control measures (Pinior et al., 2017). Instead of primarily focusing on comparing programs, studies of CEP outline key aspects of control activities (Houe et al., 2006; Geraghty et al., 2014). We felt that a more detailed comparison of BVDV CEP was needed, and have focused, for the first time, on differences between elements within CEP that could influence the confidence in freedom from BVDV infection in the herd.

Context

We identified substantial differences in BVDV CEP. These differences partially reflect differences in context, such that each CEP is tailored to the specific situation in a country (Sandvik, 2004; Moennig et al., 2005). Reasons for these differences can also relate to other factors, such as political realities, cost efficiency, human behavior, or cultural differences (Lindberg and Houe, 2005; Heffernan et al., 2009). This strongly suggests, in agreement with earlier studies (More et al., 2009; Schuppers et al., 2012; Toftaker et al., 2018), that context-specific key factors influence the risks of introduction and must be taken in account in any analysis meant to develop a method to compare the probability of freedom offered by different CEP.

Our approach to ranking different CEP elements should thus be interpreted with caution, because different contexts could easily change such a ranking. For example, the comparison of cattle densities in this study was based on the number of cattle per km2 of land area, regardless of land area being unsuitable for keeping cattle. In some territories, such as the Netherlands, almost all land area is suitable for keeping cattle, and cattle herds are fairly evenly distributed throughout the country. However, in other territories, such as Sweden, Scotland, and Ireland, the spatial distribution of cattle herds is heterogeneous. The ranking could therefore be different when distinguishing between low- and high density areas within the same territory.

Complexity of ranking

It could be argued that some elements should not be ranked at all in this study because they are influenced by too many factors. One example is the surveillance element "Probability of a false-negative test result (while there was a PI present)." The probability of a false negative test result can also be influenced by factors within the laboratory; for example, by human error, testing protocol applied (pooled sample or not, PCR or ELISA), or the presence of maternally derived antibodies (Fux and Wolf, 2012). In addition, the probability of a false-negative test result can be influenced by factors that operate before the point of laboratory testing. With ear notch testing, these could be factors such as interval from collection to submission of the sample, time spent in the postal system, or deliberate interference by the farmer. For spot testing, this could relate to nonrepresentative cohort sampling or neglecting to sample all separately managed groups of the target age, among others. Relevant to trade, animals from a birth cohort could be sold before spot testing is carried out, which is often the case with dairy bull calves.

Another element that was very challenging to rank was "Time until identification of the virus in a herd where the first PI was undetected due to a false negative test result." We decided to rank biannual spot testing as better than ear notch testing because the time until virus circulation is detected after the initial false-negative result may be shorter on average than that with ear notch testing. Further, spot testing is able to identify virus circulation when the PI itself is already removed from the herd (death or moved off-farm to a fattening unit). Whether a spot test is timelier than ear notch testing, however, depends on many factors, including the frequency of spot tests in the young animal group. In the case of biannual spot testing, it is assumed that spot testing will detect virus circulation faster; however, in some countries, spot testing is performed only once a year. In these

cases, ear notch testing may result in earlier detection of virus circulation in the herd. Another factor will be farm management. For example, if age groups have no direct contact, the probability of detecting antibodies with the next spot test is much lower. Additionally, in a herd with concentrated calving (e.g., spring calving), the minimum time between the primary case (birth of a PI but undetected due to a false-negative test) and secondary case(s) (birth of additional PI as a consequence of the primary case) would be approximately 12 mo. In a year-round calving herd, the minimum time from primary to secondary cases is likely to be shorter. A third factor is the design prevalence chosen to determine the number of animals to be selected for testing. The period for detection of infection using the spot test will be prolonged by the time until the design prevalence is reached. If a design prevalence of 50% is chosen, the time until detection of virus circulation in the spot test will depend on both the testing frequency and the time that it takes to reach the design prevalence of 50% in the target group (youngstock). It is well known that a PI is highly infectious and effectively transmits the virus to all other cattle in the cohort within a very short period. Nevertheless, if different age groups within a herd are housed separately, it may take time for the virus to spread between age groups. In such cases it could take more than 1 yr until the virus is transmitted throughout the cattle herd and design prevalence is reached. The time until identification of the virus in the herd is reduced with both ear notch and spot testing when multiple PI are born in the same birth cohort (quick detection of the next PI). When only a single PI is born and tests false negative with ear notch testing, the virus may be detected after 6 to 8 mo if the PI infects other susceptible pregnant cows or after at least 24 mo when the PI itself calves. This shows the difficulty of ranking this element and highlights the detailed data needed to be able to make a valid comparison.

In our study, we applied an approach in which we compared the same elements between different CEP. The ranking process led to very valuable discussions between partners in the STOC free project because each partner was provoked to think carefully about each element within their CEP relative to other CEP. The intensive and comprehensive discussions provided insight in the reasoning behind the design of different CEP in different countries and added to the scientific level of the discussion.

Challenges for comparison

The RISKSURexp tool allowed us to collect very detailed information about BVDV control and context in the 6 territories included in this study (The RISKSUR Project, 2015; Comin et al., 2016). This tool proved very valuable as a means to

precisely define the data of interest and collect information in such a way that allowed comparison between territories. Collecting information to allow direct comparison was indicated as a challenge in a review of Johne's disease control activities in 6 countries (Geraghty et al., 2014). In our study, we found that in some territories all data were readily available, whereas in others, access to the data was difficult or the required data were not collected. Especially challenging for data collection were differences in the way that territories recorded data. For example, for a seemingly easy to collect element such as "the number of dairy and beef herds," it was very difficult to obtain comparable data from different territories. Some territories categorized every farm where milk was delivered as a dairy herd, even though beef cattle were also present, whereas other territories made a clear distinction between dairy, beef, and mixed herds or even other herd categories. When methods are developed to determine the confidence in freedom from infection resulting from CEP, these differences between data will need to be addressed. The uncertainty around the confidence in freedom resulting from CEP might be affected by the ease with which data can be accessed on the herds participating in the CEP.

Another challenge for comparison was that the territories included in this study were at very different phases of control or eradication. Territories with programs that have been in place longer have gone through several stages of control with varying aims and strategies. For example, Ireland (Graham et al., 2014) and Scotland (Scottish government, 2016) each commenced with voluntary screening that subsequently evolved into mandatory CEP. As these programs progress toward eradication, additional control measures are coming into force. The suitability of a test strategy in a certain stage of control, and thus the resulting confidence of freedom, is highly dependent on the specific aim addressed at that time (Houe et al., 2006). This is also the reason for not ranking Sweden. Because Sweden is free from BVDV, a less strict CEP is sufficient because the only risk of introduction is through external introduction. However, if BVDV were to be imported into Sweden (e.g., an animal tested false negative), the consequences could be substantial. This highlights the difficulties involved in comparing CEP.

Conclusions

We identified considerable heterogeneity in the elements of CEP that influence confidence of freedom, with respect to both the context and individual control strategies, among the 6 CEP that were evaluated. In this study, both description and ranking were used, with ranking allowing us to highlight heterogeneity in a manner that is clearer than using description alone. The similarities and

differences in context, initial enrollment, and surveillance strategies in the different territories that we have identified here will need to be incorporated into a common framework aimed at quantitative comparison of confidence of freedom from infection.

Supplementary material

https://ars.els-cdn.com/content/image/1-s2.0-S0022030220301697-mmc1.pdf

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Chapter 4

Quantification of risk factors for bovine viral diarrhea virus in cattle herds: A systematic search and meta-analysis of observational studies

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Abstract

Bovine viral diarrhea virus (BVDV) is endemic in many parts of the world and multiple countries have implemented surveillance activities for disease control or eradication. In such control programs (CPs), the disease-free status can be compromised by factors that pose risks for introduction or persistence of the virus. The aim of the present study was to gain a comprehensive overview of possible risk factors for BVDV infection in cattle herds in Europe and to assess their importance. Papers that considered risk factors for BVDV infection in cattle were identified through a systematic search. Further selection of papers eligible for quantitative analysis was performed using a predefined checklist, including: (1) appropriate region i.e. studies performed in Europe, (2) representativeness of the study population, (3) quality of statistical analysis, and (4) availability of sufficient quantitative data. In total, 18 observational studies were selected. Data were analyzed by a random effects meta-analysis to obtain pooled estimates of the odds of BVDV infection. Meta-analyses were performed on six risk factors: herd type, herd size, participation in shows or markets, introduction of cattle, grazing and contact with other cattle herds on pasture. Significant higher odds were found for dairy herds (OR=1.63, 95% CI: 1.06-2.50) compared to beef herds, for larger herds (OR=1.04 for every 10 extra animals in the herd, 95% CI: 1.02-1.06), for herds that participate in shows or markets (OR=1.45, 95% CI: 1.10-1.91), for herds that introduced cattle into the herd (OR=1.41, 95% CI: 1.18-1.69) and for herds that share pasture or have direct contact with cattle of other herds at pasture (OR=1.32, 95% CI: 1.07-1.63). These pooled values must be interpreted with care, as there was a high level of heterogeneity between studies. However, they do give an indication of the importance of the most frequently studied risk factors and can therefore assist in the development, evaluation and optimization of BVD control programs.

Introduction

Bovine viral diarrhea virus (BVDV) is a pestivirus belonging to the Flaviviridae family (Olafson and Rickard, 1947). It is one of the most common viral diseases in cattle and endemic in many parts of the world (Scharnböck et al., 2018). BVDV is mainly spread by persistently infected (PI) cattle, which were infected in utero between 40 and 120 days of gestation and shed large amounts of virus into the environment after birth (McClurkin et al., 1984). BVDV can be transmitted directly through nose to nose contact between cattle or indirectly through contaminated materials (Tråvén et al., 1991; Niskanen et al., 2003). Infections with BVDV can lead to respiratory and reproductive issues causing major economic losses (Houe, 2003). Many European countries have implemented BVDV control or eradication programs (CPs) and some have already successfully eradicated the virus or reached a herd-level prevalence below 1.5% (Sweden, Norway, Finland, Denmark, Germany, Austria, Switzerland and Ireland) (Nuotio et al., 1999; Bitsch et al., 2000; Hult and Lindberg, 2005; Rikula et al., 2005; Rossmanith et al., 2010; Presi et al., 2011; Norström et al., 2014; Foddai et al., 2016; AHI, 2019). Within those CPs, animals, herds, regions or the country are ascribed a BVDV-free status which is subsequently monitored.

The probability that a herd categorized as free within a CP is truly free of infection will be influenced by risk factors for introduction of the virus, i.e. the probability that the virus is (re)introduced into the herd between test moments, and factors that cause delayed detection of the virus after (re)introduction, i.e. the probability that the virus had been introduced, but not yet detected. The effectiveness of surveillance relies on an understanding of these risk factors. Delayed detection of the virus can be associated with herd management, CP design (e.g. test population, test frequency, sample size, test validity) and test performance. Risk factors for introduction depend on the contact structure between herds, such as purchase or contact with cattle from neighboring herds. The introduction of purchased animals is a well-known risk factor. However, an overview of the magnitude of the risk, and of country-level differences, is lacking.

Risk factors for introduction and delayed detection of BVDV are not easily studied in isolation due to the difficulty of determining exactly when the virus is introduced into a herd. Risk factors for the presence of infection are more often reported (e.g. Graham et al., 2013; Byrne et al., 2017; Amelung et al., 2018) and could serve as a proxy for introduction and delayed detection. In this study, we have conducted a systematic literature search, seeking to gain a comprehensive

overview of possible risk factors for the presence of BVDV infection in cattle herds in Europe. We aimed to assess the importance of the most frequently studied risk factors and, depending on study quality and the availability of quantitative data, to perform meta analyses to obtain pooled values. This information is critical for the development, evaluation and optimization of BVDV control programs. Control program managers can list and prioritize risk factors in their country based on the pooled values, or choose the results from countries most comparable to their situation.

Materials and methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) with the PRISMA 2009 Checklist (Supplemental File S1, https://doi.org/10.3168/jds.2020-18193).

Search strategy

Three databases (PubMed, CAB Abstracts, and Scopus) were interrogated using the search terms defined below. The final complete data search in all 3 databases was performed on September 21, 2018. An additional search was performed after the full-text screening and before data analysis on July 15, 2019. This additional search was performed only in PubMed because Scopus and CAB Abstracts do not allow selection for specific publication dates, only per year. The research questions include 4 key aspects: BVDV, risk factors, introduction, and delayed detection. The BVDV search terms included the following: BVD, BVDV, bovine viral diarrh(o)ea, bovine viral diarrh(o)ea, and bovine viral diarrh(o)ea virus. Risk factor search terms included the following: risk factor, purchase, import, trade, market, grazing, nose-to-nose contact, direct contact, over the fence contact, density, contact structure, herd, herd size, seasonal calving, calving pattern, housing system, management, biosecurity, vaccination, artificial insemination, embryo transfer, PI, persistent infection, and persistently infected. Introduction search terms included the following (where * indicates a wildcard): introduction, pathway, epidemio*, incidence, prevalence, and contamin*. Finally, delayed detection search terms included the following: diagnostic test, persist*, delayed detection, test strategy, test scheme, test performance, test characteristics, sensitivity, control program*, eradication program*, surveillance, false negative, free, freedom, transmission, and spread. The full electronic search strategy is included in Supplemental File S2 (https://doi.org/10.3168/ jds.2020-18193).

Study selection

Studies published in peer-reviewed journals with full-text available were considered. They either reported risk factors for introduction of BVD virus in cattle herds or risk factors for the presence of BVD virus from which risk factors for introduction could be inferred. During the initial screening, studies were also included from which risk factors for delayed detection could be inferred e.g. studies reporting test characteristics. In a later stage it was decided to only focus on risk factors for introduction and presence of BVDV to narrow down the search. Only studies with a cross-sectional, cohort, case-control or randomized controlled trial study design were considered. Languages that were accepted were English, Dutch, French, Spanish and German. Studies published since 1980 were included to focus on modern farm management systems.

The search in Pubmed, CAB abstracts and Scopus was carried out by one researcher (AvR). The researcher imported all references into the online systematic review management tool Covidence (Covidence systematic review software, 2018). In Covidence, duplicates were deleted automatically or following a manual review. Two researchers (AvR, MM) both went independently through the following consecutive phases of the review: (1) Screening titles and abstracts based on the inclusion criteria described above, and (2) Reviewing full text articles based on the inclusion criteria described above. After these review steps, conflicting opinions on papers were discussed with the other co-authors to reach consensus on in- or exclusion.

All full-text studies that were selected based on in the inclusion criteria were further assessed for their appropriateness for meta-analyses by one researcher (AvR). This was done using the approach presented in Table 1. This checklist consists of four questions regarding internal validity (how well is the study conducted?) and external validity (generalizability). As there is no generic tool available for study appraisal of observational studies for meta-analysis (Sanderson et al., 2007), we have created our own checklist with relevant checkpoints based on our own observations and in alignment with the methods used in previous studies (National Institutes of Health (NIH), 2014; Downes et al., 2016).

Table 1. Checklist study appraisal for quantitative analysis

Item		Not appropriate for meta-analysis	Appropriate for meta-analysis
External validity			
1	Is the cattle production system comparable with the European situation?	Studies were performed outside of Europe.	Studies were performed in Europe.
2	Are the selected animals or herds representative of the target population (commercial cattle herds in Europe)?	No, with high possibility of selection bias. Animals or herds are selected purposively.	Yes, with low or medium possibility of selection bias. Animals or herds are selected randomly or in a way that represents the target population.
Internal validity			
3	Was the unit of interest appropriate for a herd-level risk factor study?	Animal-level data were used without correction for within-herd correlation.	Herd-level data were used or animal-level data that were corrected for clustering.
4	Are quantitative data available?	No, there are only descriptive studies, or some quantitative data but no odds ratios or data from which odds ratios could be derived.	Yes, there are quantitative data (odds ratios or data to derive odds ratios) of univariable or multivariable analysis.

On several occasions, multiple studies were described in a single paper (so-called split studies), for example if a risk factor study was performed on different outcome variables (e.g. antibody or virus) or different types of cattle (e.g. beef or dairy), or if more than one final risk factor model was developed. It was decided to include both split studies where beef and dairy herds were analyzed separately because these risk factor analyses were performed on different populations (for example, Gates et al., 2013, 2014). When studies concluded with more than one final model, the model indicated by the authors as best describing the data was included. If no choice was made between the different final models, we selected the model that took into account the full dataset. Risk factor analyses performed on subsets of the data were excluded.

Data collection

Data was extracted from all selected studies using an Excel form that was prepared in advance. Data was extracted by one researcher (AvR) and checked by the other researcher (MM). A pilot test of the Excel form was conducted by these two researchers working together on three selected papers to increase uniformity in extracting the data.

For each selected study, detailed data were extracted regarding study type, location, (size of the) study population, diagnostic tests used, risk factors studied in univariable and multivariable analysis, the effect size (odds ratio, relative risk), confidence intervals and the statistical analysis that was performed.

Meta-analysis

All risk factors from the studies that were selected for quantitative analysis were listed and combined into groups of similar risk factors. Per group, odds ratios reported in at least two independent studies were analyzed by a random effects meta-analysis to obtain pooled estimates of the odds of BVDV infection. In some cases, variables first had to be restructured to be able to include them in the meta-analysis. This was, for example, the case with introduction of cattle where we wanted to combine variables with "yes introduction" versus "no introduction" with categorical variables where different numbers of introduced cattle were compared to zero introduction. In this case, we first performed a within-study fixed effects meta-analysis on the different categories of this variable to obtain a summary estimate across all categories. This summary estimate could subsequently be included in the overall meta-analysis for introduction of cattle.

A random-effects approach is considered the default method in meta-analysis of observational studies (Mueller et al., 2018). This approach accounts for the fact that the study effect estimates are not drawn from a single population, which would be the case when using a fixed effects approach (Harrer et al., 2019). The random-effects models were fitted in a two-step approach. First, between study variance, represented by the distribution of the true study effects ($\tau 2$), was estimated with the DerSimonian-Laird (DL) approach. Then weights were assigned to all included studies based on the inverse of the variance as in general the population size between observational studies are not equal and pooled odds ratios were estimated (Viechtbauer, 2010). In this process, the odds ratios and their 95% confidence intervals (CI) as reported in the individual studies were log transformed, and therefore, due to rounding errors, the 95% CI in our results might slightly differ from the data reported in the individual studies. Preferably, adjusted odds ratios that resulted from multivariable analysis were used. When no multivariable results were available, crude odds ratios that resulted from univariable analysis were included. If no odds ratios were available, but frequencies were reported, odds ratios were calculated. In each forest plot, the univariable results were marked. Also, sub-analyses were performed in which univariable and multivariable results were analyzed separately.

Heterogeneity between studies was studied by the I^2 statistic. The I^2 statistic shows what proportion of the variance is due to heterogeneity in true effects rather than sampling error (Borenstein et al., 2017). To identify studies with the greatest influence on the results, an influential case analysis was performed with cut-off values proposed by Viechtbauer and Cheung (2010). The studies indicated

as outliers, were marked in each forest plot. The change in the summary estimates and I^2 statistic when retaining or removing outliers was of minor importance. Publication bias could not be properly assessed due to the low number of studies included in our meta-analyses (n<10) (Higgins et al., 2019). Funnel plots were checked for asymmetry, with some indication of publication bias, but these plots are not reported as it was not possible to determine whether this is by chance or real asymmetry due to the low number of studies. Meta-analyses were performed using R statistical software (R Core Team, 2019) and the metafor package (Viechtbauer, 2010).

Results

Literature search

The original searches revealed 12,028 papers, of which ultimately 259 papers were full-text screened and narrowed down to 51 papers (Figure 1). Based on Table 1, all 51 papers were screened for their appropriateness for quantitative analyses (Supplemental File S3, https:// doi.org/10.3168/jds.2020-18193). Eventually, 18 papers (20 studies) were selected for inclusion in the meta-analysis (Table 2).

Overview of risk factors

All risk factors that were studied in the final 18 papers were grouped into six risk factor categories: 1) herd and animal characteristics, 2) cattle movement, 3) reproduction, 4) neighborhood risk, 5) farm management and biosecurity and 6) diagnostic testing and control programs.

Description of risk factors

Herd and animal characteristics. Herd and animal characteristics that were studied included milk yield, sex, age, infection with other pathogens, mortality, region, herd type and herd size. Of all herd characteristics, variables describing herd size, herd type and region were included most frequently (Table 3).

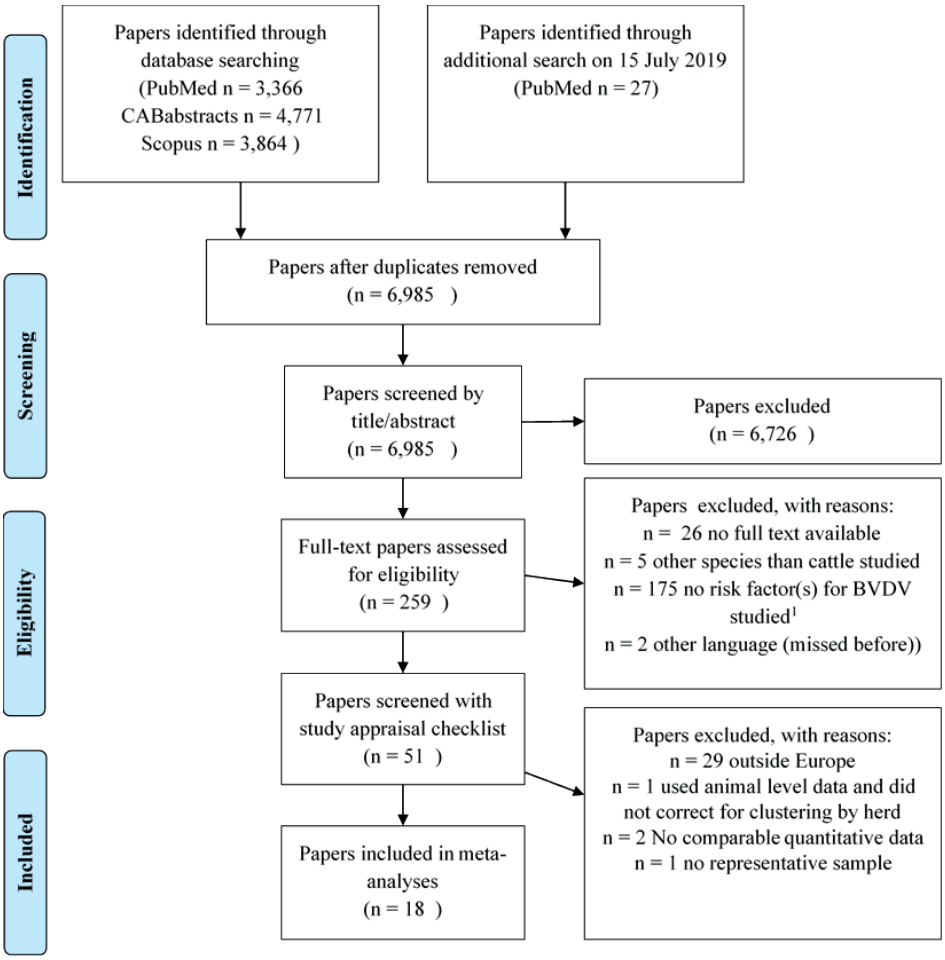

Figure 1. Flow diagram showing the total number of papers identified and excluded per stage of the selection process. At the eligibility stage, we decided to exclude papers that were initially selected for delayed detection. The 175 "no risk factor(s) for BVDV studied" papers were about BVDV test characteristics. BVDV = bovine viral diarrhea virus.

Table 2. Studies selected for the meta-analyses

Study ID[1]	Study	Country	Study design	Unit of interest in risk factor analysis	Type of cattle studied	Outcome measure	Diagnostic test[2]
2	Amelung et al. (2018)	Germany	Cross-sectional	2542 herds	Combination	Virus	ELISA on ear notch followed by PCR on ear notch
5B[3]	Barrett et al. (2018)	Ireland	Cross-sectional	139 herds	Beef	Virus	On ear notch
7	Bishop et al. (2010)	Wales	Cross-sectional	36 herds	Dairy	Antibodies	ELISA on BTM
9B[3]	Byrne et al. (2017)	Northern Ireland	Cross-sectional	2827 herds	Combination	Virus	PCR on ear notch
11	Charoenlarp et al. (2018)	Northern Ireland	Cross-sectional	17186 herds	Combination	Virus	ELISA, PCR, or both on ear notch
15	Ersboll et al. (2010)	Denmark	Cohort	7921 herds	Dairy	Virus	ELISA on BTM and blood
18A[2]	Gates et al. (2014)	Scotland	Cross-sectional	255 herds	Beef	Antibodies	ELISA on blood
18B[2]	Gates et al. (2014)	Scotland	Cross-sectional	189 herds	Dairy	Antibodies	ELISA on blood
19A[2]	Gates et al. (2013)	Scotland	Case-control	249 herds (65 cases and 184 controls)	Beef	Antibodies	ELISA on blood
19B[2]	Gates et al. (2013)	Scotland	Case-control	185 herds (119 cases and 66 controls)	Dairy	Antibodies	ELISA on blood
20A[3]	Graham et al. (2013)	Ireland	Cross-sectional	3894 herds	Combination	Virus	ELISA or PCR on ear notch
21A[3]	Graham et al. (2016)	Ireland	Cross-sectional	58479 herds	Combination	Virus	Unknown
22	Hanon et al. (2018)	Belgium	Cross-sectional	51 herds and 3017 cattle	Combination	antibodies	Different ELISA and VNT on blood and milk
24A[3]	Houe et al. (1995 A, B)	Denmark	Cross-sectional	19 herds	Dairy	Virus	Virus isolation and virus neutralization on blood
30	Mainar-Jaime et al. (2001)	Spain	Cross-sectional	529 cattle	Dairy	Antibodies	ELISA on blood
31	Martinez-Ibeas et al. (2015)	Republic of Ireland	Cross-sectional	305 herds	Dairy	Antibodies	ELISA on BTM and blood
35	Presi (2011)	Switzerland	Cross-sectional	33,188 herds	Combination	Virus	ELISA or PCR on ear notch
40A[3]	Sarrazin et al. (2013)	Belgium	Cross-sectional	664 herds	Combination	Antibodies and virus	ELISA on blood
49A[3]	Valle et al. (1999)	Norway	Case-control	314 herds (162 cases and 152 controls)	Dairy	Antibodies	BTM screening and pooled milk sample followed by ELISA on blood
50	Williams et al. (2014)	UK	Cross-sectional	1088 herds	Dairy	Antibodies	ELISA on BTM

[1] Study ID were assigned to the 51 papers that were selected in the second-last selection step (Supplemental File S3, https://doi.org/10.3168/jds.2020-18193).

[2] BTM = bulk tank milk; VNT = virus neutralization test.
[3] These rows represent one of 2 or 3 studies presented in a single paper. Each of these studies was chosen for inclusion in further analyses because they either present the best final model or were performed on the full data set. Excluded split studies can be found in Supplemental File S3.
[4] These rows represent one of 2 split studies presented in a single paper. Each of these studies had been conducted on different herds (beef or dairy) and has been analyzed separately.

Table 3. Overview of the number of risk factor studies (out of the selected 18 papers on 20 studies) that included herd and animal characteristics and the availability of quantitative data.

Factor	No. of studies	No. of variables	Study ID[1]	No. of variables with quantitative data
Milk yield	2	2	2, 30	1
Sex	1	1	22	1
Age	2	2	22, 30	2
Infection with other pathogens	3	6	5B, 9B, 30	3
Mortality	5	7	5B, 9B, 20A, 30, 35	5
Region	8	8	2, 9B, 11, 15, 20A, 21A, 30, 31	7
Herd type[2]	9	11	2, 9B, 11, 20A, 21A, 22, 30, 35, 40A	9
Herd size[2]	14	20	2, 5B, 9B, 11, 15, 20A, 21A, 22, 24A, 30, 31, 35, 40A, 50	13

[1] Study ID were assigned to the 51 papers that were selected in the second-last selection step (see Supplemental File S3, https://doi.org/10.3168/jds.2020-18193).
[2] Included in the meta-analysis

No further analysis could be performed on milk yield and sex as for both there was only one study with quantitative data. Age was included as a categorical variable in two studies (Hanon et al., 2018; Mainar-Jaime et al., 2001), both with higher odds ratios for the presence of BVD antibodies in higher age classes. However, the age categories within those two studies were not comparable and therefore unsuitable for meta-analysis. Infection with other pathogens to be associated with BVD infection was considered in three studies but could not be compared because different pathogens were studied, i.e. Neospora caninum, BoHV-1 and bTB. Mortality was considered in five studies, but as this was regarded more an outcome than a risk factor for BVDV, it was not included in the meta-analysis. Finally, region was not included in the meta-analysis even though this was one of the most studied risk factors within the herd and animal characteristics group. Because different regions were included in different studies comparison of the risk estimates between regions was impossible. Nevertheless, most studies found significant differences between regions, which makes this an important risk factor to consider. Meta-analysis was performed on herd type and herd size.

Cattle movement. Movement characteristics that were studied included introduction of cattle, cattle shows or markets and other movements (e.g. sale and exchange of calves). Of all cattle movement risk factors, variables describing introduction of cattle into a herd were included most frequently (Table 4). We considered studies on introduction of cattle into a herd and on purchase, where the latter assumes monetary transfer which is not necessarily the case with introduction. In this paper, we use "introduction" which also covers purchase.

Other types of cattle movements were studied by Valle et al. (1999) and Amelung et al. (2018). Valle et al. (1999) looked at "other animal traffic" combining mainly exchange of calves and sharing of cattle housing with other farmers during summer. They found a very high odds ratio of 28.60 (95% CI: 3.23-252.22). Amelung et al. (2018) studied sale of cattle, which was not comparable to the cattle movement studied in Valle et al. (1999). Meta-analysis was performed on cattle shows or markets and introduction of cattle.

Table 4. Overview of the number of risk factor studies (out of the selected 18 papers on 20 studies) that included cattle movement variables and the availability of quantitative data

Factor	No. of studies	No. of variables	Study ID[1]	No. of variables with quantitative data
Other movement	2	2	2, 35	2
Cattle shows or markets[2]	5	5	2, 19A, 19B, 22, 35	5
Introduction of cattle[2]	17	62	2, 5B, 7, 9B, 18A, 18B, 19A, 19B, 20A, 21A, 22, 24A, 30, 31, 35, 49A, 50	48

[1] Study ID were assigned to the 51 papers that were selected in the second-last selection step (see Supplemental File S3, https://doi.org/10.3168/jds.2020-18193).
[2] Included in the meta-analysis.

Reproduction. Reproduction variables that were studied included artificial insemination (AI) versus use of bulls and calving pattern (Table 5). The number of studies was too small or the definition of the variables varied too much between studies to enable a meta-analysis to be conducted.

Table 5. Overview of the number of risk factor studies (out of the selected 18 papers on 20 studies) that included reproduction variables and the availability of quantitative data

Factor	No. of studies	No. of variables	Study ID[1]	No. of variables with quantitative data
Calving pattern	1	1	50	1
AI/use of bulls	3	4	2, 7, 50	3

[1] Study ID were assigned to the 51 papers that were selected in the second-last selection step (see Supplemental File S3, https://doi.org/10.3168/jds.2020-18193).

Variables regarding AI or the use of bulls were only included in univariable analyses. In Amelung et al. (2018), higher but nonsignificant odds ratios were found for BVD infection in herds with AI (OR= 1.28; 95% CI = 0.96-1.71) compared to herds without AI but also in herds with a bull for insemination (OR=1.17; 95% CI=0.93-1.48) compared to herds without bull. Williams et al. (2014) compared herds with a bull present on the farm with herds with AI only and found that herds with a bull present on the farm had higher but nonsignificant odds of infection with BVD (OR=1.16; 95% CI=0.90-1.49).

Calving pattern was only found once in a univariable risk factor analysis and showed higher odds of infection (OR=1.80, 95% CI: 1.22-2.67) in herds with all year round calving compared to seasonal calving (Williams et al., 2014).

Neighborhood risk. Variables related to neighborhood risk included farm fragmentation, environment, cattle density, BVD-positive neighbor herds, contact with other animal species, and pasture. Of all neighborhood risk factors, variables describing cattle density, contact with other animal species and pasture were included most frequently (Table 6).

Table 6. Overview of the number of risk factor studies (out of the selected 18 papers on 20 studies) that included neighborhood variables and the availability of quantitative data

Factor	No. of studies	No. of variables	Study ID[1]	No. of variables with quantitative data
Farm fragmentation	1	1	20A	1
Environment	1	4	11	4
Cattle density	6	9	11, 15, 19A, 19B, 21A, 30	7
BVD[2]-positive neighbor herds	3	11	11, 15, 21A	8
Contact with other animal species	5	10	2, 19A, 19B, 20A, 49A	8
Pasture[3]	8	20	2, 11, 19A, 19B, 22, 24A, 35, 49A	14

[1] Study ID were assigned to the 51 papers that were selected in the second-last selection step (Supplemental File S3, https://doi.org/10.3168/jds.2020-18193).
2 Bovine viral diarrhea.
3 Included in the meta-analysis.

Farm fragmentation (number of individual non-contiguous parcels of land associated with the herd) and environment (i.e. natural grassland, forest) were both only studied once, therefore no meta-analysis could be performed. Cattle density and BVD-positive neighbor herds were studied more frequently, but in such different ways that meta-analysis was not possible. Both variables describe in different ways the distance to (positive) neighboring herds or the number of (positive) neighboring

herds contiguous to the farm or in a 5 or 10km radius. They are continuous or categorical. Most studies showed higher odds of BVD infection when the distance to (positive) neighbors is shorter, there are more (positive or with unknown status) neighbors close by or when BVD positive animals are retained for a longer period. One study found that seropositivity increased with a larger distance in km to the closest dairy farm (Mainar-Jaime et al., 2001). Variables regarding contact with other animal species included the presence of, contact with, close proximity of or grazing with sheep, pigs, deer or wildlife. No meta-analysis could be performed on contact with other animal species.

Farm management and biosecurity. Variables included were quarantine, vaccination, mixed beef and dairy farm, type of housing, shared equipment, people on farm and other biosecurity. None of these variables were suitable for meta-analysis because of non-comparable definitions and/or the low number of studies in which these factors were studied (Table 7).

Table 7. Overview of the number of risk factor studies (out of the selected 18 papers on 20 studies) that included farm management and biosecurity variables and the availability of quantitative data

Factor	No. of studies	No. of variables	Study ID[1]	No. of variables with quantitative data
Other biosecurity	2	2	19A, 19B	2
Hygiene	2	2	19A, 19B	2
Quarantine	3	3	7, 19A, 19B	2
Mixed beef and dairy farm	3	3	19A, 19B, 49A	2
Vaccination	3	4	22, 31, 40A	2
Housing	2	4	2, 22	4
Shared equipment	3	5	19A, 19B, 49A	4
People on farm	2	8	19A, 19B	8

[1] Study ID were assigned to the 51 papers that were selected in the second-last selection step (Supplemental File S3, https://doi.org/10.3168/jds.2020-18193).

Most farm management and biosecurity variables were studied by Gates et al. (2013). They studied the relative influence of cattle movements, local spread and biosecurity on BVDV seropositivity. The variables we included in the farm management and biosecurity group were not exactly identical to the classification of biosecurity variables in the study of Gates et al, (2013), but especially for beef herds, cattle movement had the greatest influence on BVDV seropositivity. Also, in the other studies included in Table 7, most biosecurity variables were non-significant.

Diagnostics testing and control programs. Multiple papers studied variables

related to diagnostic testing and control programs that we grouped into BVDV testing, farmer (behavior), control program and other (Table 8). However, either the number of studies was too small, or the definition of these variables varied too much between studies to enable a meta-analysis to be conducted.

BVDV testing was studied most within the diagnostic testing and control programs group. Examples of variables studied are the total number of BVDV tests undertaken, detection of PI animals in the past etc. There was one study (Amelung et al., 2018) that found that participation in a control program has slightly higher odds (OR=1.28, 95% CI: 1.01-1.64) for BVDV infection in univariable analysis than herds that do not participate. One of the studies looking at farmer behavior showed that the age of farmers was associated with the BVD status. Herds of farmers younger than 40 years were more often infected than herds of farmers between 50 and 60 years.

Table 8. Overview of the number of risk factor studies (out of the selected 18 papers on 20 studies) that included diagnostic testing and control program variables and the availability of quantitative data

Factor	No. of studies	No. of variables	Study ID[1]	No. of variables with quantitative data
Other	3	3	11, 40A, 21A	2
Farmer (behavior)	2	4	2, 49A	3
Control program	3	3	2, 11, 22	3
BVDV testing	7	8	9B, 19A, 19B, 20A, 30, 31, 40A	6

[1]Study ID were assigned to the 51 papers that were selected in the second-last selection step (Supplemental File S3, https://doi.org/10.3168/jds.2020-18193).
[2]Bovine viral diarrhea virus.

Meta-analyses

Herd and animal characteristics. Herd type was studied frequently and was always included as a categorical variable i.e. dairy, beef, mixed, beef breeding (Supplemental File S4, section 4.1.1, https://doi.org/10.3168/jds.2020-18193). A meta-analysis was conducted on the six studies that compared dairy versus beef herds (reference category; Supplemental File S4, section 4.1.2). We found a combined effect estimate of 1.63 higher odds (95% CI: 1.06-2.50) of BVDV infection in dairy herds compared with beef herds (Figure 2). The heterogeneity between studies (I^2) was 97.30% (95% CI: 91.87-99.47).

Herd size was studied frequently and was always included as an either categorical or continuous variable (Supplemental File S4, section 4.1.1). However, very few variables were comparable; therefore, meta-analysis was conducted on the 4

studies with OR per additional cow (Supplemental File S4, section 4.1.2). Other variables showing the log number of cows or different herd size categories were not included because they were not comparable.

For every extra animal in the herd, we found a combined effect estimate of 1.004 higher odds (95% CI: 1.002-1.006) of BVDV infection (Figure 2). For every 10 extra animals in the herd, this would be 1.04 higher odds of BVDV infection (95% CI: 1.02-1.06). The results of Presi et al. (2011) could not be included in the pooled estimate because weights are assigned to all factors based on the inverse of the variance and these results had a variance of zero. The heterogeneity between studies (I^2) was 55.96% (95% CI: 0.00-99.98).

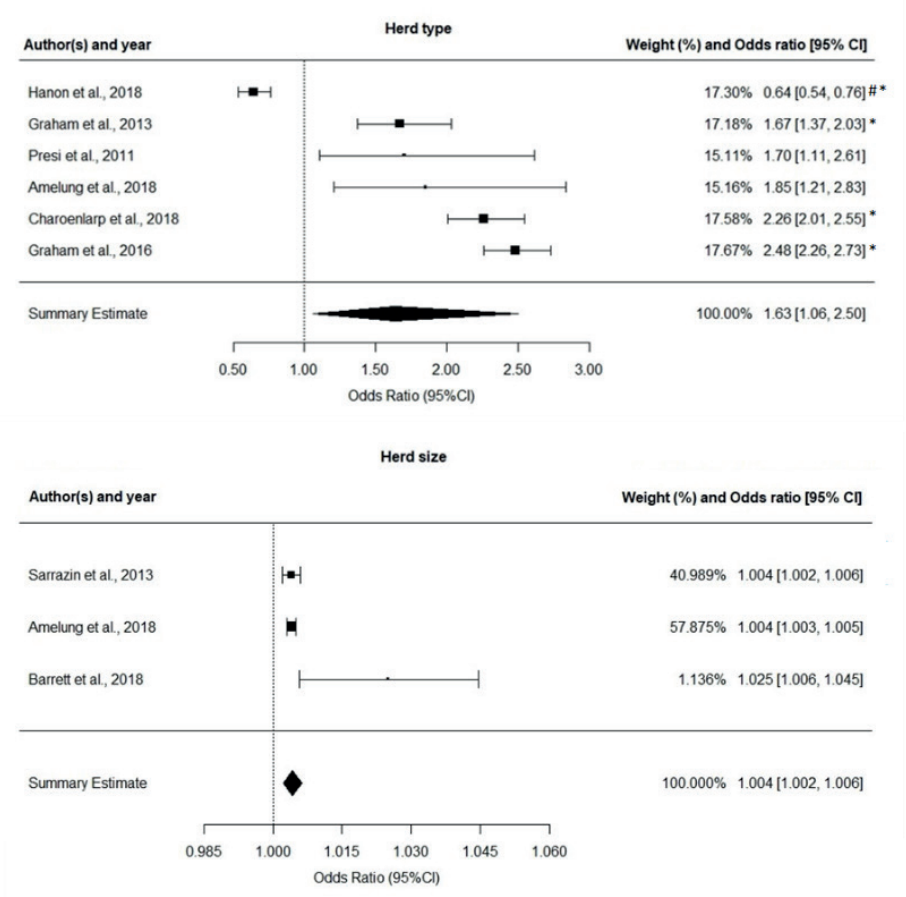

Figure 2. Forest plot of the effect of herd type with beef herds as reference category (upper plot) and herd size per additional animal in the herd (lower plot) on bovine viral diarrhea virus infection.
* Univariable result; # study indicated as outlier in the influential case analysis.

Cattle movement. In all studies, participation in cattle shows or markets was included as a yes–no variable (Supplemental File S4, section 4.2.1) and therefore they could all be included in meta-analysis (Supplemental File S4, section 4.2.2). We found a combined effect estimate of 1.45 higher odds (95% CI: 1.10–1.91) of BVDV infection in herds that participated in shows or markets compared with herds that did not (Figure 3). The heterogeneity between studies (I^2) was 61.70% (95% CI: 0.00–96.60).

Introduction of cattle was the most often studied movement variable but was not easily compared between studies because of the many different ways in which introduction of cattle was coded (i.e., introduction yes–no, source of introduced animals, continuous variables, and introduction of different types of cattle). We decided to focus further meta-analysis on introduction yes–no because these variables were most comparable (Supplemental File S4, section 4.2.2). In 2 studies (Graham et al., 2013, 2016), a sub-meta-analysis was first performed to obtain pooled estimates comparable with the estimates of the yes–no variables (Supplemental File S5, https://doi.org/10.3168/jds.2020-18193). We found a combined effect estimate of 1.41 higher odds (95% CI: 1.18–1.69) of BVDV infection in herds that introduce cattle into the herd compared with herds that do not (Figure 3). The heterogeneity between studies (I^2) was 82.98% (95% CI: 71.48–99.47).

Neighborhood risk. Pasturing of cattle was the most often studied neighborhood risk variable. Variables described whether cattle had access to pasture, the possibility of contact with cattle from other herds at pasture, and shared pasture (Supplemental File S4, section 4.3.1). First studies were compared that looked at the presence versus absence of pasture (Supplemental File S4, section 4.3.2) followed by contact between cattle on pasture (Supplemental File S4, section 4.3.2). We found a nonsignificant combined effect estimate of 1.10 higher odds (95% CI: 0.62–1.97) of BVDV infection in herds that graze their cattle compared with herds that do not (Figure 4). The heterogeneity between studies (I^2) was 73.30% (95% CI: 0.83–99.80). Studies on contact between cattle at pasture were divided into shared pasture and the possibility of contact with cattle from other herds at pasture (e.g., contact over the fence) but were also analyzed together (Figure 4).

For both shared pasture and contact at pasture, we found nonsignificant odds of BVDV infection: 1.34 (95% CI: 0.85–2.10) and 1.33 (95% CI: 0.99–1.78), respectively (Figure 4). However, we found an overall significant combined effect estimate of 1.32 higher odds (95% CI: 1.07–1.63) of BVDV infection in herds where contact between cattle at pasture is possible either because different herds share pasture or because of contact between herds in contiguous pastures (Figure 4). The heterogeneity between studies (I^2) was 53.90% (95% CI: 0.00–97.70).

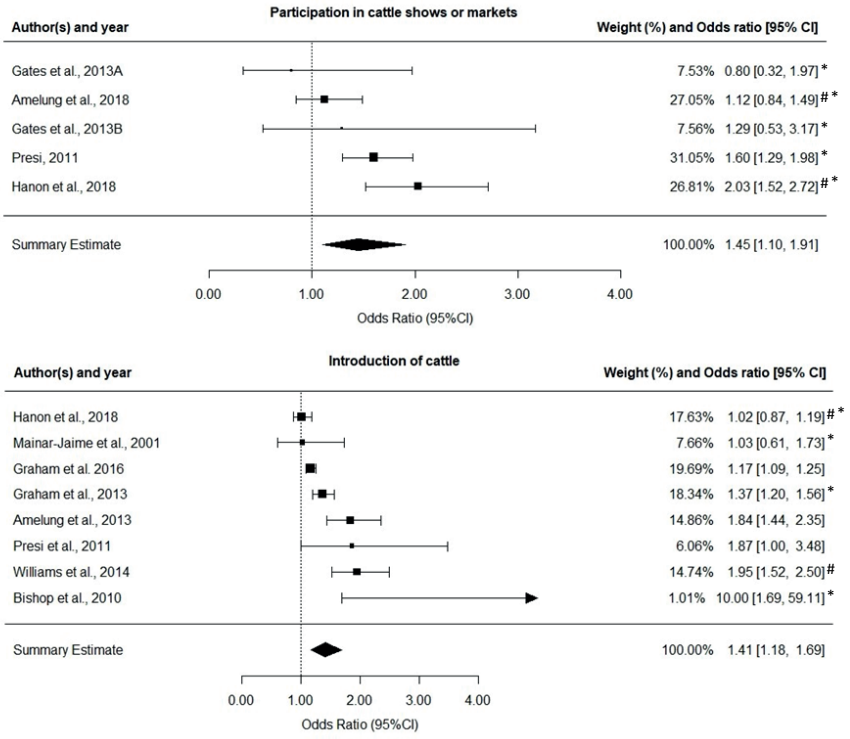

Figure 3. Forest plot of the effect of participation in shows or markets (upper plot) and introduction of cattle (lower plot) on bovine viral diarrhea virus infection. Gates et al., 2013 A and B, refers to substudies, as indicated in Table 2. * Univariable result; # study indicated as outlier in the influential case analysis

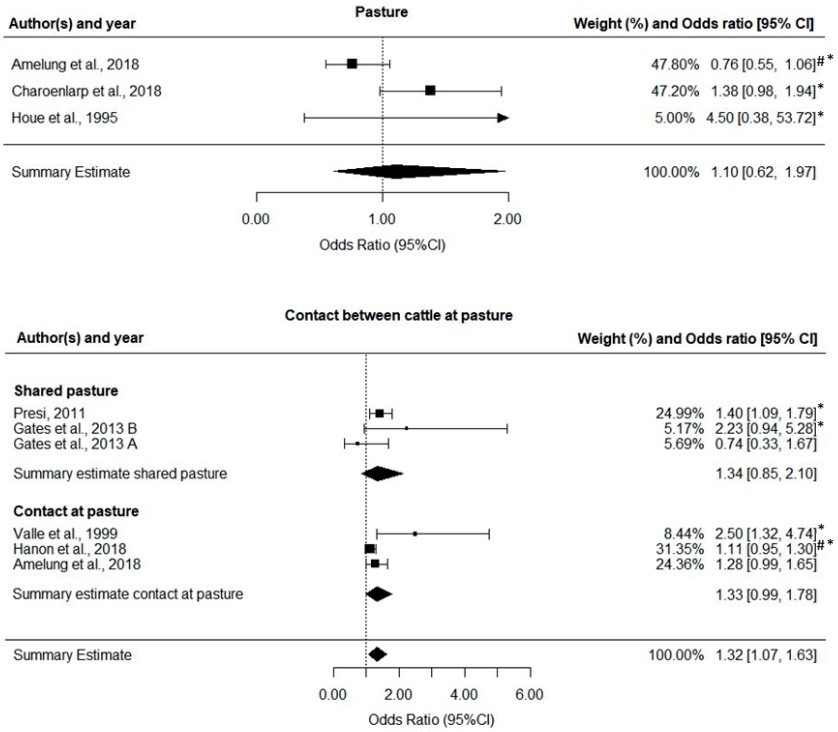

Figure 4. Forest plot of the effect of herds grazing (upper plot) and contact between cattle on pasture by either shared pasture or over the fence contact (lower plot) on BVDV infection.
* univariable result, # study indicated as outlier in the influential case analysis

Discussion

By conducting this systematic literature search we have gained a comprehensive overview of potential risk factors for the presence of BVD in cattle herds. We decided to focus on studies performed in Europe in attempt to reduce heterogeneity between results caused by different cattle production systems on different continents. However, the results could be generalized to areas outside Europe where there are similar cattle production systems, for example areas in the USA. The eighteen European publications that were included in this study showed a wide range of potential risk factors that were grouped into six categories with similar characteristics i.e. 1) herd and animal characteristics, 2) cattle movement, 3) reproduction, 4) neighborhood risk, 5) farm management and biosecurity and 6) diagnostic testing and control programs. Although there was a lot of variation

in risk factors between studies, we performed several meta-analyses and obtained pooled estimates for a number of frequently found risk factors.

Two herd characteristics that were frequently studied were herd size and herd type. Most studies found that larger herds were associated with higher odds of BVD infection. Only Hanon et al. (2018) found the highest seroprevalence in the smallest herds (<100 cattle). They did find a higher seroprevalence in farms with a higher number of stables (>3). The pooled estimate in our meta-analysis showed a significantly higher risk of infection per extra ten animals in the herd (OR=1.04 95% CI: 1.02-1.06). This could be explained by the tendency for larger herds having a decreased probability of self-clearance of infection and being more likely to contain a higher number of pregnant cattle and purchased cattle, increasing the risk of introduction of PIs into the herd (Lindberg and Houe, 2005; Sarrazin et al., 2013; Barrett et al., 2018). In our meta-analysis, dairy herds were also found to be at higher risk of infection than beef herds (OR=1.63 95% CI: 1.06-2.50). It has been suggested that this is related to the higher number of contacts between cattle and people and traffic on dairy farms compared to beef farms (Amelung et al., 2018).

Movement of cattle is considered one of the most important risk factors for BVD infection, especially purchase (Courcoul & Ezanno, 2010; Gates et al., 2013; Qi et al., 2019). Our meta-analysis showed higher odds (OR=1.41 95% CI: 1.18-1.69) for herds that introduced cattle into the herd in the previous year compared to herds that did not. However, Gates et al. (2014) illustrated that not all purchased cattle pose the same risk. They found that purchase of pregnant heifers and open cows with a calf at foot are associated with a higher risk of BVDV infection in beef herds, with odds ratios of 2.18 (95% CI: 1.17-4.08) and 2.09 (95% CI: 1.13-3.88) respectively. The number of cattle introduced was also studied several times, generally showing increasing odds with increasing numbers of introduced cattle (Gates et al., 2013; Graham et al., 2013, 2016, Byrne at al., 2017). It was, however, suggested that the number of cattle introduced is related to herd size (Graham et al., 2016; Byrne et al., 2017), indicating the importance of correcting for herd size when studying purchase. A different way to study the risk of introduction is to look at the number of source herds. Gates et al. (2013) found a significant association between BVDV infection and a larger number of source herds, in dairy (OR=4.42 in units of 10 farms, 95% CI: 1.86-10.00) and beef herds (OR=10.60 in units of 10 farms, 95% CI: 3.91-31.00). However, there was strong correlation between the number of cattle introduced and the number of source herds (Gates et al., 2013). Another risk factor related to cattle movement that was studied frequently is participation in shows

or markets. Our pooled estimate shows significant higher odds of infection for herds that visit cattle shows or markets (OR=1.45 95% CI: 1.10-1.91) compared to herds that do not. This could be explained by the possibility that cattle come in contact with BVDV-infected cattle at the show or market and infect the herd upon returning or because of infection during transport.

No meta-analysis could be performed on any of the reproduction variables because of the low number of comparable studies. However, concerns have been raised about transmission of BVDV by AI (Gard et al., 2007; Rikula et al., 2008). This may be prevented by regular testing of bulls at AI centers and testing of imported semen (Eaglesome & Garcia et al., 1997; Wentink, et al., 2000; Lindberg et al., 2006). Also, the within herd calving pattern could not be compared between studies, but Williams et al. (2014) found an increased likelihood of BVDV presence with all year-round calving compared to seasonal calving. They indicated that this could be related to the fact that with all year-round calving there are almost always pregnant cows present within the susceptible window for BVDV infection of the fetus. When developing or optimizing BVD control programs, calving pattern could be an important factor to consider. In block calving systems, tissue tag testing of new-born calves provides the opportunity to identify and remove the majority of PI calves before the breeding season commences, reducing the risk of the establishment of further PI calves to be born the following season. In year-round calving systems spot testing could be a cost-effective option to monitor new infections (Tratalos et al., 2017).

BVD can easily spread between herds when there is direct contact possible between cattle (Tråvén et al., 1991). Therefore, grazing is considered a risk factor for BVD as there may be nose-to-nose contact between cattle of different herds. Our pooled estimate did however not show significant odds (OR=1.10 95% CI: 0.62-1.97) for BVD infection for herds that graze compared to herds that do not. When results that indicated shared pasture were separated from results that indicated whether or not contact between cattle at pasture could occur (e.g. over the fence contact), our pooled estimates were non-significant, but when taken all together and thus increasing statistical power, we found a significant effect indicating that contact between cattle at pasture had a higher odds of BVD infection (OR=1.32 95% CI 1.07-1.63). Probably the risk of grazing is influenced by many factors, such as cattle density and the prevalence of BVDV in the area (Houe et al., 1995 A), regulations around communal grazing (Rossmanith et al., 2005), the number of cattle and herds sharing pasture (Presi et al., 2011) and the number of neighbors.

In the current study, no meta-analysis was performed on any of the farm management and biosecurity variables due to the low number of studies and the differing ways in which biosecurity was measured. It was unexpected that most studies did not find a significant association between biosecurity measures and BVDV infection as biosecurity is considered an important aspect of BVDV control (Moennig et al., 2005; Lindberg et al., 2006). It was suggested by Gates et al. (2013) that this could be related to the design of questionnaires. For example, questionnaires that primarily use closed yes/no questions which forces farmers to choose one of the options even if neither is completely true. Farmers could also give socially desirable answers because they fear possible consequences. Farmer behavior is another factor for which there was not enough quantitative data for meta-analysis. This lack of quantitative data does not necessarily mean that farmer behavior and biosecurity are not important factors for BVD, but they are more often studied qualitatively, which made it impossible to include them in the meta-analysis. Qualitative research into farmer behavior and biosecurity related to BVD stress the importance of addressing farmer attitudes towards BVD control (Heffernan et al., 2016; Azbel-Jackson et al., 2018). A meta-analysis on epidemiological and mitigation measures that influence production losses in cattle due to BVDV has been reported (Pinior et al., 2019). These authors found that vaccination and biosecurity had a positive influence on the annual BVDV production losses per animal. We agree that farmers attitude towards BVD control and biosecurity related measures are important and influence the impact of the risk factors we found in this paper. When, for example, a new cow is kept in quarantine and tested for BVD prior to its introduction in the herd, the risk of introduction will be lower compared to new cows that are directly introduced in the herd. Therefore we recommend to further study the quantitative association between BVD control and biosecurity and farmer behavior.

No meta-analysis could be performed on any of the diagnostic testing and control program variables because of both the small number of studies and the large variation between variables. One study found slightly higher odds for presence of BVDV when participating in control programs in univariable analysis (Amelung et al., 2018), which could probably be explained by the assumption that farms with BVDV problems are more likely to participate in a control program. Another interesting result was that herds from farmers younger than 40 years were more often infected than herds from older farmers (Valle et al., 1999). According to Valle et al. (1999) this is probably due to different attitudes and management practices of younger farmers such as not asking for health certificates when purchasing animals. This would be an interesting factor to consider in future quantitative studies about BVDV infection and farmer behavior.

In our meta-analyses, several pooled estimates were significant. The results could however be biased as most studies looked at the presence of BVDV and not introduction of the virus. With presence of infection, it is unknown when the actual infection happened, which complicates finding direct associations between infection and risk factors. However, this would probably be less influential when considering risk factors that do not change much over time, such as whether or not herds graze at pasture, herd type and herd size. When studying the introduction of BVDV, it is possible that there is a delay between introduction and detection. For example, a PI calf introduced on a farm that monitors by bulk milk testing is unlikely to be promptly detected unless individual animal testing is also conducted on newly imported animals to the farm. Situations such as this complicate efforts that seek to identify direct associations between infection and risk factors. Therefore, we think that the presence of BVDV is a reasonable proxy for introduction of the virus. In addition, the presence of risk factors does not often change as they are part of regular farm management.

Another complicating factor in comparing different studies was the way in which herds were categorized as infected or not infected, e.g. based on antibodies or virus, using different sample types, different tests and strategies to confirm the infection status. These differences could be considered by performing a formal assessment of risk of bias. However, because we already had a low number of studies per meta-analysis, we did not want to exclude any more studies and decided to include only the most important internal and external validity checkpoints (Table 1). Also, not all information was available in each publication for a proper bias risk assessment.

For several risk factors, it was not appropriate to perform a meta-analysis given that there were not enough comparable studies with sufficient quantitative data. For the risk factors with sufficient data, the meta-analyses indicated high levels of heterogeneity. This was expected as all papers included in our meta-analyses were observational studies with different objectives, study designs and context. For that reason, performing meta-analysis on observational studies and obtaining pooled estimates has been extensively debated (Egger et al., 1998; Blettner et al., 1999; Ioannidis et al., 2008). However, the number of published meta-analyses on observational data has substantially increased and the need for guidelines for performing meta-analysis on observational data is emphasized (Mueller et al., 2018; Dekkers et al., 2019). In the current study, we decided to perform meta-analyses on observational studies to provide an overview of available quantitative data, including a weighted average estimate. In this subject area, quantitative risk

factor information is only available from observational studies. A key principle underpinning this study is the potential for countries without local knowledge of risk factors for BVDV to learn from those countries where data are available. In our view, weighted average estimates have the potential to be more helpful to readers, whilst being cognizant of heterogeneity between studies, than solely a listing of all available quantitative results.

In our study, we tried to control for heterogeneity and bias as much as possible through the checklist of study appraisal for quantitative analysis (Table 1) and by very carefully choosing the factors that could be compared. The I2 statistics still showed a very high level of heterogeneity for all factors, but it is known to be not very accurate when there is only a small number of studies (N<20) available (Huedo-Medina et al., 2006). Also, the very wide 95% confidence intervals of the I2 statistic we observed show the degree of uncertainty about the heterogeneity estimations. The influential case analyses showed that the I2 estimate was often lower when removing outliers from the meta-analyses, however, confidence intervals remained wide. Given this result, and also because I2 is unreliable when few studies are available, we elected to retain the outliers, but to show the summary estimates and I^2 of each meta-analysis when excluding the outliers (Supplemental File S6, https://doi.org/10.3168/jds.2020-18193).

To maximize the amount of quantitative data we decided to include both univariable and multivariable odds ratios in our analyses. Therefore, in three of the six meta-analyses we combined univariable and multivariable results. The rationale behind this is that in different studies the multivariable odds ratios were adjusted for different factors and referred to different reference situations and are therefore not necessarily more comparable than unadjusted univariable results. On the other hand, univariable odds ratios can under- or over-estimate the strength of association. As there is not yet a uniform approach regarding the use of univariable and multivariable results in meta-analysis, often, adjusted and unadjusted ORs are combined (Liu et al., 2017). As we decided to combine adjusted and unadjusted ORs, we have performed sub-analyses in which we compared the results when only including the univariable results or the multivariable results. In most cases we only observed minor differences. In the meta-analyses on herd type and introduction of cattle, we did see a substantial decrease in heterogeneity (I^2). However, keeping in mind that the I2 statistic becomes increasingly unreliable when even fewer studies are included and because the summary estimates did not change that much, we decided to combine univariable and multivariable results. The results of the sub-analyses are reported in Supplemental File S7 (https://

doi.org/10.3168/jds.2020-18193). We also selected different observational study designs to maximize the number of studies in our meta-analyses. Therefore, in two of the six meta-analyses (participation in cattle shows and markets and contact between cattle at pasture) we combined cross-sectional studies with case-control studies. In the scientific literature, there is disagreement as to whether different study designs can be combined (Mueller et al., 2018). The influential case analysis was conducted to determine whether the case-control studies (only three out of 20 studies) were indicated as outliers, which they were not. Consequently, leaving them out would not make much difference, and therefore we decided to retain both study designs. We note that these two study designs are differing types of observational studies and use odds ratios as outcome.

All studies included in our meta-analyses used odds ratios to show the strength of association between risk factors and BVD infection. It should be kept in mind that these odds ratios are based on a certain reference population and are therefore sensitive to how the reference category is defined. For this reason, it can be questioned if odds ratios are the right means to compare studies. It would have been better to obtain probabilities of infection and risk factor occurrence. However, given that these were often not reported, and the fact that odds ratios do provide a rough risk estimate, it was decided to conduct the meta-analysis on odds ratios. This should be considered when interpreting the results of this study.

Conclusions

In this study, we found a wide range of potential risk factors and performed meta-analyses on 6 risk factors for BVDV: herd size, herd type, participation in shows or markets, introduction of cattle, pasture, and contact at pasture. We did not find any unexpected risk factors, and the pooled estimates can help guide advice to farmers and assist in the development, evaluation, and optimization of BVD control programs. The results of the meta-analyses must be interpreted with care due to a high level of study heterogeneity but can assist in the development, evaluation, and optimization of BVD control programs. They can also be used as input for BVDV modeling studies in herds that are comparable with the European cattle production systems. It was challenging to combine estimates of different studies due to heterogeneity between studies (e.g., study design, data analysis, data reporting), showing the need for more standardized methodologies in risk factor studies.

Supplementary material

https://ars.els-cdn.com/content/image/1-s2.0-S0022030220305798-mmc1.pdf

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Part 3

Evaluation of the STOC free framework


A

Chapter 5

Key learnings during the development of a generic data collection tool to support assessment of freedom of infection in cattle herds

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Abstract

Various European Member States have implemented control or eradication programmes for endemic infectious diseases in cattle. The design of these programmes varies between countries and therefore comparison of the outputs of different control programmes is complex. Although output-based methods to estimate the confidence of freedom resulting from these programmes are under development, as yet there is no practical modelling framework applicable to a variety of infectious diseases. Therefore, a data collection tool was developed to evaluate data availability and quality and to collect actual input data required for such a modelling framework. The aim of the current paper is to present the key learnings from the process of the development of this data collection tool. The data collection tool was developed by experts from two international projects: STOC free (Surveillance Tool for Outcome-based Comparison of FREEdom from infection, www.stocfree.eu) and SOUND control (Standardizing OUtput-based surveillance to control Non-regulated Diseases of cattle in the EU, www.sound-control.eu). Initially a data collection tool was developed for assessment of freedom of bovine viral diarrhea virus in six Western European countries. This tool was then further generalized to enable inclusion of data for other cattle diseases i.e. infectious bovine rhinotracheitis and Johne's disease. Subsequently, the tool was pilot-tested by a Western and Eastern European country, discussed with animal health experts from 32 different European countries and further developed for use throughout Europe.

The developed online data collection tool includes a wide range of variables that could reasonably influence confidence of freedom, including those relating to cattle demographics, risk factors for introduction and characteristics of disease control programmes. Our results highlight the fact that data requirements for different cattle diseases can be generalized and easily included in a data collection tool. However, there are large differences in data availability and comparability across European countries, presenting challenges to the development of a standardized data collection tool and modelling framework.

These key learnings are important for development of any generic data collection tool for animal disease control purposes. Further, the results can facilitate development of output-based modelling frameworks that aim to calculate confidence of freedom from disease.

Introduction

Surveillance and control of cattle diseases in Europe is essential to protect human and animal health and to facilitate safe trade between member states. This is supported by the Animal Health Law adopted in March 2016. Within the Animal Health Law (EU 2016/429), diseases are listed and categorized (A, B, C, D or E) according to their relevancy for Union intervention (EU 2018/1882). This relevancy depends on their impact on public or animal health, the economy, society or the environment. Diseases listed as category A or B must be eradicated by all Member States and therefore mandatory requirements are legislated within the European Union (EU). Examples of category A or B cattle diseases are foot and mouth disease and Bluetongue. For diseases listed as category C, D or E, there are only few or no mandatory requirements legislated within the EU (referred to as non-regulated diseases in the remainder of this paper). Examples of non-regulated diseases include bovine viral diarrhea (BVD), infectious bovine rhinotracheitis (IBR) and Johne's disease (JD). Numerous countries in Europe have implemented control programmes (CPs) for these so-called non-regulated cattle diseases. The CPs aim to eradicate, control or monitor infectious diseases in the cattle population. Although these diseases are not regulated by the EU, these CPs are beneficial for farmers, the industry and national economy as they increase animal health and welfare and reduce direct losses (e.g. production loss, morbidity and mortality) as well as indirect losses (e.g. constraints to trade) (Costa et al., 2020). Each country develops CPs to fit their specific situation, e.g. infection status and cattle demographics, and therefore these are very heterogeneous between countries, which is for example the case for BVD (van Roon et al., 2020). This variety causes difficulties for intra-community trade as the outcomes of these CPs are difficult to compare. For example, the confidence that herds deemed to be free from specified infections by a given CP are truly free from infection, and the uncertainty associated with this, may vary between CPs. There are methods, such as scenario tree analysis and Bayesian latent class modeling, that can be used to estimate the confidence of freedom resulting from CPs. However, a transparent, standardized and practical field-based tool is not yet available (Martin et al., 2007; More et al., 2009; Cameron, 2012).

Two projects were started to fill this gap: the STOC free project (Surveillance Tool for Outcome-based Comparison of FREEdom from infection, www.stocfree.eu) (van Roon et al., 2019) and the COST action SOUND control (Standardizing OUtput-based surveillance to control Non-regulated Diseases of cattle in the EU, www.sound-control.eu) (Costa et al., 2020; SOUND control, 2020). The STOC free project aims to develop an output-based framework to compare the probability of

freedom from infection for herds (or animals) assigned an infection-free status in heterogeneous CPs. In this project, partners from six European countries (Germany, France, Ireland, the Netherlands, Sweden and Scotland) have worked together to develop a framework consisting of a model to calculate the confidence of freedom for the case disease bovine viral diarrhea (BVD) and a data collection tool to collect the data needed to run the model. The aim of SOUND control is to stimulate initiatives to explore innovative methods to substantiate confidence of freedom from infection and describe requirements for an objective and standardized output-based framework for several non-regulated cattle diseases in Europe. In this COST Action, more than 100 researchers from 32 countries collaborate. Both projects have the ultimate aim to develop a set of tools, which also includes a generic data collection tool that can be used by different countries with different CPs to collect the data that are needed for the assessment of confidence of freedom. This is challenging because data are collected, stored and interpreted in different ways in different countries. As an example, national BVD eradication programmes can differ substantially in their approaches to data management and interpretation (van Roon et al., 2020). The same was earlier described for IBR (Veldhuis et al., 2017). Therefore, consensus is needed on both the data required, and the definitions of these data, to allow assessment of confidence of freedom. In existing methods aimed at demonstrating freedom from disease such as scenario tree modelling, the sensitivity of each surveillance component is assessed by including data on test sensitivity and frequency, the number of herds and animals present and tested within the cattle population, the expected prevalence and risk factors for infection (Martin et al., 2007). Further, information is needed on what data are available in different countries and the comparability of these data. The latter is, amongst others, influenced by the quality of the available data (European Centre for Disease Prevention and Control, 2014), which in turn is most commonly assessed based on its completeness, accuracy and timeliness (Chen et al., 2014).

Tools have been developed to assist in designing CPs, support decision-making and implementation of control strategies. Example include the RISKSUR (Risk-based animal health surveillance systems) project in which decision support tools were developed to assist in the design of surveillance programmes (Peyre et al., 2019) and the HOTLINE (Harmonization Of Transmissible disease Interpretation in the EU) project which sought to make disease information from different countries comparable and interpretable (Kostoulas et al., 2019). As part of this latter project, guidelines were developed for the reporting of animal health surveillance (AHSURED: Animal Health Surveillance Reporting Guidelines) (Comin et al., 2019). A list of key surveillance items, such as geographical area, susceptible population, historical

situation etc., has been published to guide the reporting of surveillance activities, such as confidence of freedom from infection or prevalence estimation (https://github.com/SVA-SE/AHSURED/wiki). Another project that has common ground with STOC free and SOUND control is the SIGMA project that aims to harmonize data models and automate the process of data submission, validation, analysis and reporting of EU member states to EFSA (European Food Safety Authority, 2018). These projects are very valuable and have aspects relating to our goal, which is comparison of the outputs of CPs. However, in our project we do not aim to harmonize the input but rather to investigate ways to compare heterogeneous input and generate homogeneous output.

Our objective was to develop a simple and practical online data collection tool that could act as part of an output-based framework that is seeking to model freedom from infection of cattle diseases in different countries. The data collection tool was initially developed for BVD, IBR and JD. These three diseases were selected because there are many different CPs within Europe (Costa et al., 2020) and they differ in terms of disease transmission dynamics, accuracy of diagnostic methods etc. The aim of this paper is to present the key learnings from the process of the development of the online data collection tool.

Materials and methods

A stepwise process was followed to obtain the current version of the online data collection tool (Figure 1). This work was performed within the STOC free and SOUND control project which are summarized in Table 1.

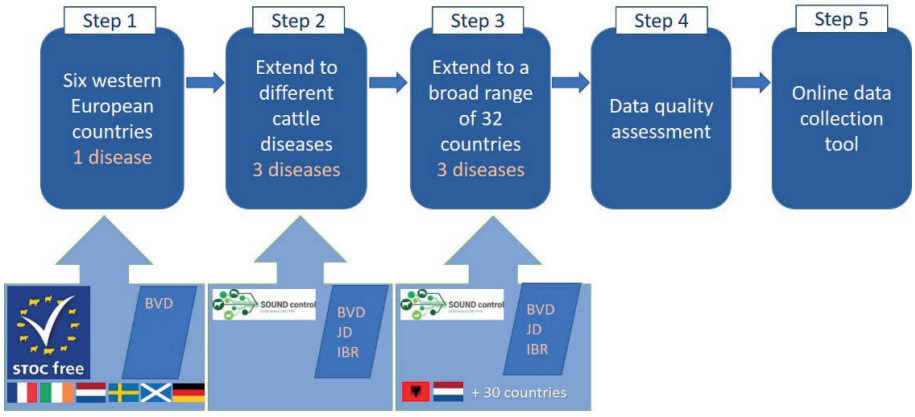

Figure 1. Stepwise process that was followed to come to the final online data collection tool.

Table 1. Overview of the STOC free and SOUND control project.

Project	STOC free	SOUND control
Start date	March 2017	29 October 2018
End date	December 2021	28 October 2022
Number of countries involved	6	32
Geographical scope	Western Europe	Europe
Aim	To develop and validate a new framework (STOC free: Surveillance Tool for Outcome-based Comparison of FREEdom from infection) that enables a transparent and standardised comparison of confidence of freedom for control programmes of both non-regulated and regulated diseases in the EU.	The aim of SOUND control is to coordinate, stimulate and assist with the initiatives to explore and implement a widely adaptable output-based framework applicable to substantiate the confidence of freedom and cost-effectiveness in current surveillance, control or eradication programmes for non-regulated cattle diseases in the EU.
More information (progress, news, output)	http://www.stocfree.eu	https://sound-control.eu/

Step 1: Data requirements and availability for comparison of freedom from BVDV infection in six western European countries

A draft data identification tool was developed using Microsoft Excel for BVD in six western European countries (Germany, Ireland, Sweden, Scotland, the Netherlands and France). In this draft tool, the required aspects that could influence the confidence of freedom from infection in a BVD CP were identified. This tool was based on an earlier study (van Roon et al., 2020) in which the differences between various BVD CPs with respect to freedom of infection for six European countries were identified using the RISKSUR tool (The RISKSUR Project, 2015) as a starting point. The RISKSUR tool was initially developed to build and/or optimize surveillance programmes but this tool has also been used to describe different CPs in a consistent manner (van Roon et al., 2020).

Further work with the tool was conducted by animal health experts from the six afore-mentioned countries, each of whom were partners in the STOC free project (https://www.stocfree.eu/partners). Specifically, information was sought to identify data considered essential for comparison of freedom from BVDV infection, the availability of these data on a quantitative basis, the quality of these data, and the most optimal format of the data. The experts were asked whether the data foreseen to be included in the data collection tool would be available in their country and to evaluate the requested format of all variables and their definitions. Within the tool, there was the possibility to add comments. The experts consulted with other animal health experts in their country when needed, for example when

the data were not available at their institute. Before the experts started with their evaluation of the tool, a plenary session was held in which the structure of the tool was explained in detail and they also received this explanation in a separate word file ("Guidelines for the identification and sources of data": www.stocfree.eu/results/deliverables). Questions that arose during evaluation of the tool could be directed to the developers by email or videocall.

The tool consisted of three sections addressing cattle demographics, the BVD CP and risk factors for introduction of BVD, respectively. All sections were displayed on one sheet within Microsoft Excel, in the format of a single large table. Each section included all variables for which quantitative data were requested, a definition of the variable, the requested format of the data, and indications of the availability and strengths and limitations of the data (Figure 2). The availability of quantitative data was separated into columns specifying whether the available data included all cattle (dairy and non-dairy) or whether more detailed data on subcategories of cattle were also available: dairy cattle, non-dairy cattle and beef breeding cattle. For BVD it was decided to only include dairy and non-dairy breeding herds (herds where calves are born), given that these populations are considered epidemiologically most relevant for BVD.

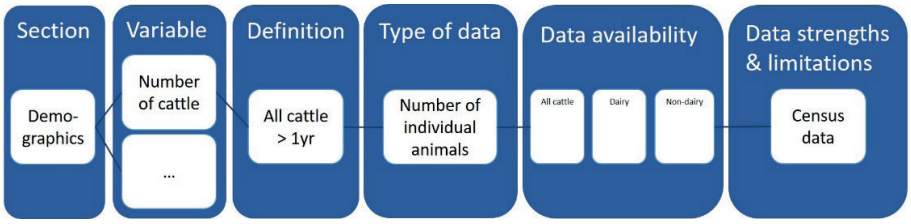

Figure 2. Column headings of the initial Microsoft Excel data collection tool developed for BVD, including an example for the variable "Number of cattle" within the section "Demographics." The first four columns (section, variable, definition, type of data) are given. Column five "data availability" should be answered with yes/no per group of cattle (all cattle, only dairy cattle, only beef cattle) by the user of the tool. Column six (data strengths and limitations) should also be answered by the user of the tool. An example could be census data.

Step 2: Data requirements when extending the tool to different cattle diseases

The tool was subsequently reviewed for possibilities to extend it to other cattle diseases. A different group of experts was involved from the SOUND control project in which more than 100 animal health experts from 32 participating European countries are involved (Costa et al., 2020; SOUND control, 2020). The data collection tool was further extended to JD and IBR in agreement with the animal health experts.

Step 3: Data comparability across a range of countries

The next step was to generalize the tool so that it could be applied to all countries throughout Europe. Therefore, the tool was pilot tested by two researchers from two countries with, respectively, developed and developing agricultural sectors i.e. the Netherlands (author ISB) and Albania (author XHK). The results of the pilot test were subsequently presented to 42 animal health experts from 32 different European countries, in a workshop organized for members of the SOUND control consortium. The participants were divided into groups of six people from different countries and were asked to provide feedback on predefined items such as data quality and data availability in their respective countries (Table 2).

Step 4: Data quality assessment

A data quality evaluation tool was discussed during the above-mentioned SOUND control workshop and developed based on four criteria common in the evaluation of health-related data i.e. accessibility, completeness, accuracy and timeliness (Chen et al., 2014; European Centre for Disease Prevention and Control, 2014). It was envisaged that this tool would enable a standardized and objective evaluation of the quality of each data entry. Within this study, such a tool was developed and incorporated in the data collection tool.

Step 5: The online data collection tool

In the final step, the feedback of the workshop was incorporated in a new version of the data collection tool which was subsequently digitalized into an online data collection tool. This was performed with the program Limesurvey (https://www.limesurvey.org/en/). All data entered into the online tool are saved into a database that at this point is only accessible by the authors of this manuscript (Rapaliute et al., 2021).

Table 2. Groups within the SOUND control workshop that discussed specific aspects of the data collection tool.

Groups	Guiding discussion points
All groups	Do you understand what data are required? Do you think the data are available in your country? Can you say something about the quality of the data? Do you think all these variables are "MUST KNOW" variables for calculating confidence of freedom? Do you have any recommendations to improve the tool?
Group 1: Functionality of the tool	Is it clear how the tool works and what data are required? Are all the variables clear? Do you feel confident about filling in this tool? What would be a good way to ask about the quality of the data? Keep in mind that it should be objective, comparable between countries and easy to analyze. Could you provide data for the dairy and beef sector separately? What would be the definitions of dairy and beef in your country?
Group 2 & 3: Demographics	Do you think that the cut-off value of cattle older than 1 year is satisfactory? Would your country have these data available? Do you think this is the most relevant age group? Would you be able to answer calving pattern with "yes, seasonal calving"/"no, year-round calving"? Another option for this variable would be to ask for the percentage of calvings in each quarter of the year. Would these data be available in your country? Can you suggest better options?
Group 4 & 5: Control programmes	How should we define a positive herd or positive animal? This can be different for different diseases and different countries.
Group 6: Test strategies	Do you think we should ask for the sensitivity and specificity of the tests used in your country? Do you think the data are available? And would you prefer sensitivity and specificity given by the manufacturer or from field studies? We could also include default values for commonly used tests or provide you with ranges of the sensitivity and specificity to choose from. Can you think of any other options?
Group 7 & 8: Risk factors	Do you think it is important to know how many (pregnant) animals are traded? How would you gather these data? In many variables we ask you for the percentage of herds, but we give you different options in a drop-down list, including "none", "0-20", "20-40" etc. Do you like this or do you prefer exact numbers?

Results

The results section describes the development of the online data collection tool and the key lessons that were learned during this process in three main sections: data requirements for different cattle diseases, data availability and comparability between countries, and data quality.

Data requirements for different cattle diseases (BVD, IBR, JD)

The first version of the tool was developed for BVD ("Guidelines for the identification and sources of data": www.stocfree.eu/results/deliverables). To facilitate inclusion of other cattle diseases, each section (cattle demographics, the BVD CP and risk factors for introduction) was evaluated to ensure that all variables were included that are essential for each of the diseases. No changes were made to the cattle demographics section, as these are similar regardless of the disease

evaluated. Small changes were made to the CP section to reflect different test strategies for the different diseases. It was decided to create a single table that can be used for the three selected diseases and, in the future, expand it to all cattle diseases (Table 3). For example, faeces and nasal swab samples were not initially included as sample types as these are not regularly used for BVD. However for JD and IBR, respectively, these samples are also relevant for diagnostic purposes and thus, they should be included in a generalized tool. Also, all variables in the tool include an open answer option which allows for inclusion of answers that were not predefined. The latter is useful when evaluating the completeness of the tool, but in a modelling framework CPs can only be compared using the predefined closed answers. Also, when generalizing the tool to JD and IBR, expansions were made to the risk factor section. Table 4 shows the list of risk factors that were evaluated for inclusion in the tool.

Table 3. Test strategy variables with answer options for BVD, JD and IBR.

Fields	Answer options
Target group	Older than 2 years, newborn calves, lactating cattle, non-lactating cattle, cattle with clinical signs, purchased cattle, at slaughter, other
Type of sample	Bulk milk, individual milk samples, blood/serum/plasma, tissue (biopsy), tissue (post-mortem), body fluid swabs, fecal smears, feces, environmental samples, slurry
Frequency of testing per year	-
Number of animals tested per test moment	All animals in the target group, representative group of animals (please specify)
Data collection point	Farm, Abattoir, Livestock assembly centers, AI center, Diagnostic laboratory, Market, Other
Collector	Farmer, Veterinarian, Abattoir personnel, other
Test method	Pathogen or antibody detection: ELISA, culture, PCR tests, other
Individual or pooled	Individually tested, Pooled, both possible
If pooled: average number of animals per pool	-

Data availability and comparability across a range of countries

To enable application of the tool in all countries throughout Europe, an understanding of data availability and comparability is crucial. When (almost) none of the countries have data available for a variable, the respective variable cannot be used to estimate freedom from infection and thus could not be included in the tool. And when (almost) none of the countries had data available in the requested format, this should be adjusted (e.g. ranges instead of exact numbers).

Data availability across six western European countries. Data availability in six western European countries (Germany, Ireland, Sweden, Scotland, The Netherlands and France) was evaluated for all variables included in the first version of the data

collection tool developed for BVD. Table 5 shows the availability of quantitative data for some of the variables in the different sections i.e. cattle demographics, CP and risk factors. The first two columns show the requested data in the tool and the remaining part of the table shows a summary of the availability of data as indicated by six countries. As it can be seen in Table 5, most variables related to cattle demographics and the BVD CP are available in (almost) all countries. Very little quantitative data are available for herd-level risk factors such as grazing practices, attendance at cattle shows, vaccination, housing features and biosecurity practices. More data are available for variables regarding purchase as registration of cattle movements is mandatory in all of the selected countries. The results indicate that for most risk factors no detailed quantitative information is available and thus cannot be included quantitatively in a model.

Table 4. Risk factors for introduction of infectious cattle diseases that were evaluated for inclusion in the data collection tool

Risk factor
Herd size
Calving pattern
Presence of small ruminants (sheep/goat)
Presence of beef cattle on dairy farms
Introduction of cattle in the herd
Introduction of calves
Introduction of pregnant cattle
Grazing
Communal grazing
Nose to nose contact with cattle from neighboring herds
Contact with wildlife
Farm fragmentation
Natural breeding
Attendance at shows
Housing calves separately from pregnant cattle
Housing calves in individual pens
Sharing transport vehicles between farms
Sharing equipment between farms
Farm clothes for visitors
Compulsory disinfection at entrance
Rodent control
Vector control
Applying manure from other farms on farmland
Feeding colostrum from own dams

In the workshop, data availability on risk factors for all three infections were discussed. The discussions confirmed that most risk factors are interesting to know but as there is often no data available, or only qualitative data, they probably cannot be included in the data collection tool. At this point, the risk factors considered most important, regardless of data availability, were chosen to be included in the current version of the tool (Supplementary material 1, https://www.frontiersin.org/articles/10.3389/fvets.2021.656336/full#supplementary-material) to further determine data availability on these risk factors in more different countries. The latter is further studied within SOUND control (Rapaliute et al., 2021) in a similar way to the initial comparison of six countries (Table 5).

Data comparability in the Netherlands and Albania. To enable comparison of confidence of freedom between countries it is essential that the collected data are comparable. Defining variables in such a way that they cannot be misinterpreted and are workable for different countries within Europe is very challenging. In the first step, the tool was optimized for use in western European countries. For some variables it was impossible to have one definition that fits all countries. As an example, 'dairy herds' were variously defined as herds that deliver milk, herds that include a certain percentage of cattle of a dairy breed, herds with newborn calves etc, and 'beef herds' could include fattening herds, veal herds and suckler herds. In this case it was decided that users of the tool should define the population that is covered by their data. For many variables, data were not available at the level of detail requested in the tool e.g. the number of purchased cattle instead of the number of purchased pregnant cattle or the number of cattle per km2 land area instead of the number of cattle per km2 farm land. For these variables, the definitions were updated into definitions that could be delivered by all countries.

In the next step, the evaluation of the tool for the Netherlands and Albania, showed that both countries are fairly similar in land area, but Albania is more sparsely populated with cattle. The average herd size differs markedly as herds in the Netherlands consist of on average 130 cattle, where the vast majority of herds in Albania consist of less than five animals. An important finding regarding herd size was that the herd size in Albania was registered as the proportion of herds per herd size category and not like in the Netherlands (and most other countries in western Europe) where for each herd the exact number of animals is known. Therefore, the data collection tool was adapted and requests the percentage of herds per herd size category as this could be delivered by both countries. This highlights that cattle demographics can be very different between countries and knowledge of the extremes is needed to decide how to define and structure

Table 5. Data availability in six European countries for variables on cattle demographics, control programmes and risk factors regarding confidence of freedom from BVDV infection.

Variable	Definition	Quantitative (Yes/No)			
		All cattle (dairy + non-dairy)	Dairy	Non Dairy	Beef breeding
Cattle demographics					
No. of cattle	Cattle > 1 year	all	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
No. of cattle herds	Total no. of cattle herds	all	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
Calving pattern	% of all calvings by month within the past 12 mo.	all	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
Average no. of births per herd	Within the past 12 mo. per herd	all	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
Cattle density	No. of cattle per km2	all	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
% of dairy cattle herds with beef cattle on same location	All dairy herds with also beef cattle		IE, SE, FR, UK		
Control program					
% of cattle herds participating in CP	% of herds that participate in the CP at the beginning of the year	all	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
% of animals tested	% of cattle tested for BVD in the territory, during the year	NL, IE, SE, DE, UK	NL, IE, SE, FR, UK	NL, IE, SE, UK	NL, IE, SE, UK
No. of herds that identified one or more PI's.	PI: animal that tested pos. in the initial test or the initial test and re-test, during the year	all	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
Age at which PI animals were culled	Age at which PI animals were culled during the year	NL, IE, SE, DE, UK	NL, IE, SE, UK	NL, IE, SE, UK	NL, IE, SE, UK
% of free cattle herds	% of cattle herds participating in the CP that have any free status according to the CP, at the beginning of the year	NL, IE, SE, DE, UK	NL, IE, SE, FR, UK	NL, IE, SE, UK	NL, IE, SE, UK
% of free cattle herds that had a breakdown	% of herds participating in CP that had a free status at start of the year but breakdown (ab or virus pos test) during that year.	all	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
Risk factors					
% of cattle herds practicing zero grazing	no grazing during the whole yr	SE	SE	SE	SE
% of cattle herds involved in communal grazing	grazing animals from different cattle herds together	IE	IE	IE	IE
No. of neighbours at pasture per herd	pasture where cattle from different herds can have nose to nose contact	NL, SE	NL, SE	NL, SE	NL, SE
% of herds that purchased cattle		All	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
% of cattle that was purchased from markets/traders	% of purchased cattle	NL, IE, FR, UK	NL, IE, FR, UK	NL, IE, FR, UK	NL, IE, FR, UK
No. of purchase moments in the territory	a purchase event on a specific day to one specific herd	All	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK	NL, IE, SE, FR, UK
% of purchased animals that were pregnant at the moment of purchase		NL, IE, FR	NL, IE, SE, FR	NL, IE, FR	NL, IE, FR
% of herds that quarantine purchased animals that have not been tested before arrival in the herd	% of herds that purchased cattle	FR	FR	FR	FR
% of herds that have animals attending shows		NL, UK	UK	UK	UK
% of herds that vaccinate cattle against BVD		SE, DE	NL, SE	SE	SE
% of cattle herds with goat and/or sheep on same location	Cattle herds with goat and sheep on same location	IE, SE, DE, UK	IE, SE	IE, SE	IE, SE
% of cattle herds that could possibly have contact with wild ruminants	Cattle herds with possible contact with wild ruminants	SE	None	None	None
% of herds that house calves separately from pregnant cattle	% of herds that breed	None	None	None	None
% of herds that share transport vehicles with other cattle herds		None	None	None	None

NL, The Netherlands; IE, Ireland; SE, Sweden; FR, France; DE, Germany; UK, United Kingdom (here Scotland). Dark green, all six countries have data available. Light green, five countries have data available. Orange, three or four countries have data available. Pink, two countries have data available. Red, at most one country has data available. Gray, not applicable.

data requests in a data collection tool. Disease control and monitoring is further developed in the Netherlands compared to Albania. In the Netherlands, there are many CPs, both compulsory and voluntary, but in Albania there are only a few voluntary CPs. Also, large volumes of high quality data are collected routinely in the Netherlands, whereas there is only limited quantitative data available in Albania. However, semi-quantitative or qualitative data was often available, which could be facilitated in a data collection tool. For example, it is not exactly known how many cattle farms purchased cattle, but experts could give an estimate. This shows the need of including a data quality assessment tool within the data collection tool and including uncertainty in an output-based framework.

Assessment of data quality

The needs of a data quality assessment tool were discussed during the workshop. All participants agreed that an objective assessment of data quality is essential to compare 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 (Table 6). For each variable, the participant is asked to score each of these criteria with a score from 1 to 3, meaning poor, fair, good. To ensure objectivity in this scoring, the meaning of each score for each criterion is described in Table 6.

The overall data quality is calculated per variable by adding up the individual scores for accessibility, completeness, timeliness and accuracy. The four criteria are equally weighted, but the individual scores per criterion are also available e.g. evaluation of accessibility of all cattle demographic data. The quality score can be used to evaluate comparability of data quality between countries.

The online data collection tool

The current version of the tool is available online through Limesurvey only for testing purposes by the COST participant countries (https://sound-control.eu/). The online tool includes some general participant information and three main sections that need to be filled: cattle demographics, risk factors and disease CPs. The cattle demographics section includes 11 variables, the risk factors section 18 variables and the disease CPs section 8 variables and a separate section about the test strategy per target group of animals tested within the CP. The CP section includes JD, IBR and BVD. All variables and the format of the requested data that are included in the tool can be found in (Supplementary material 1, https://www.frontiersin.org/articles/10.3389/fvets.2021.656336/full#supplementary-material).

The focus of the tool is on data availability, data quality and data sources (Figure 3). Each question in the tool is structured in the same way to make it easy to fill (Figure 4). Any additional explanation that was made available before in a separate word file, is now included per question in green text. Depending on the availability and accessibility of data it may take four to five hours to fill in the tool.

Table 6. Data quality evaluation tool

Quality criteria Evaluation	Accessibility	Completeness	Timeliness	Accuracy
POOR Score - 1	The variable is not routinely collected **AND** you only have access to this information via indirect sources (e.g. research studies)	The variable is not mandatory to enter in the database **AND** completeness of data is unknown **OR** lower than 80%	It is unknown when data is updated	The variable is entered manually to the dataset **AND** No data validation is performed (e.g., the data are not used for any other purpose).
FAIR Score - 2	The variable is not readily available but can be obtained by combining multiple sources **AND/OR** data is available, but access is associated with fee/ approval of data-owner	The variable is not mandatory to enter in the database**AND** completeness of data set is >80 %	The data are updated once or twice per year	The variable is entered manually **AND** data validation procedure is sometimes implemented (e.g., variable is used on a regular basis for creating reports, or combined with other data sources)
GOOD Score - 3	The variable is obtained from one data source **AND** can be extracted when needed	The variable is mandatory to enter in the database **OR** The variable is not mandatory to report, **AND** completeness of data set is close to 100 %	The data are updated real time	The variable is collected and entered by an automatic system/robot **OR** The variable is entered manually **AND** data validation procedure is always implemented (e.g., variable is used on a regular basis for creating reports, or combined with other data sources)

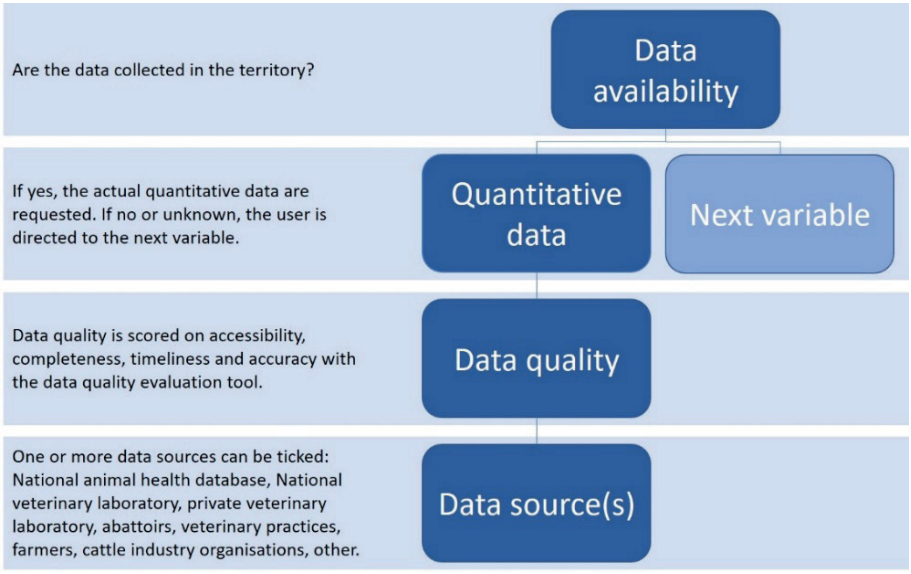

Figure 3. Schematic overview of the question structure of the online data collection tool. For each variable within the data collection tool this structure is followed from top to bottom.

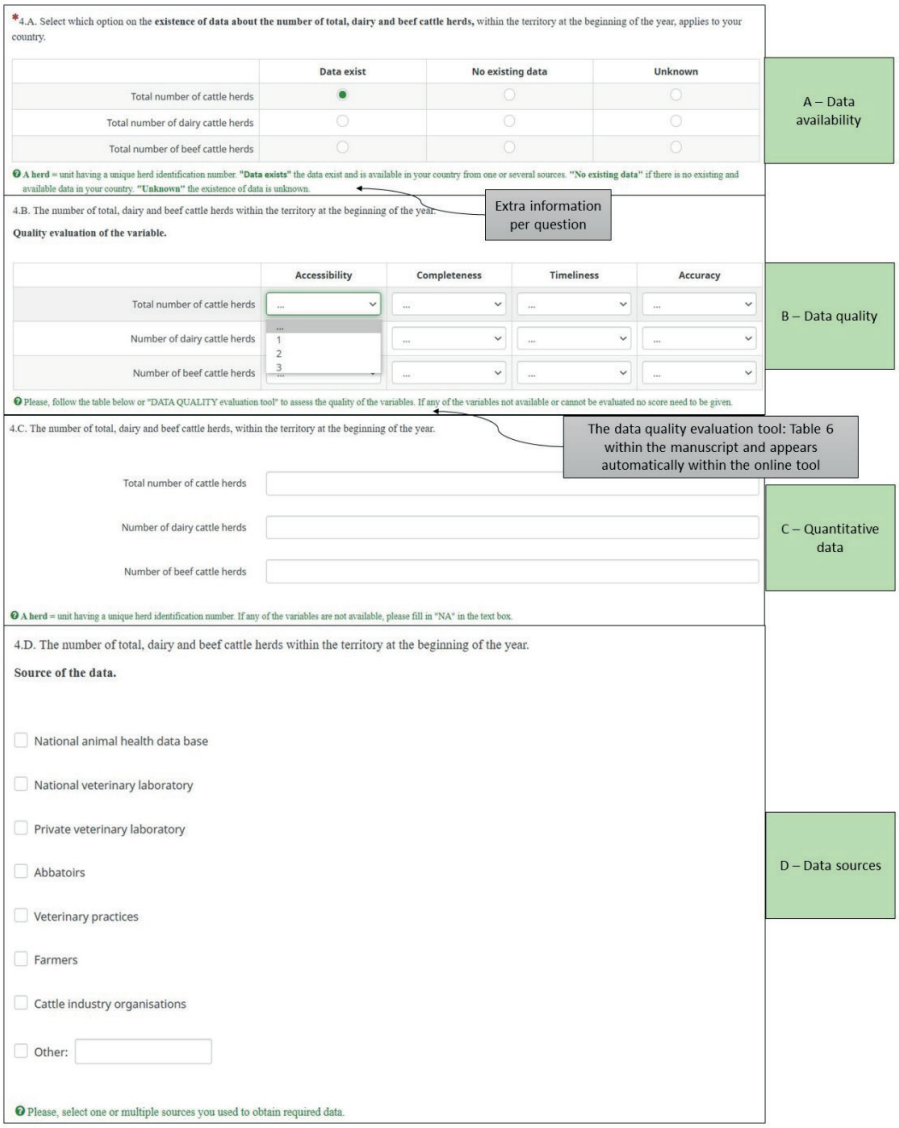

Figure 4. Format of each question within the online data collection tool.

Discussion

The data collection tool was developed to collect data required for an output-based framework for estimation of freedom of infection for a range of cattle diseases and countries within Europe. In this paper, we presented the key learnings from the development process of the data collection tool from the beginning, when it was built for a single disease and six countries, to an online tool that can be applied to multiple cattle diseases and for a large number of countries.

The tool was developed to be self-explanatory and easy to use. Depending on the number of different CPs for which the user wants to use the tool, the amount of work can be substantial. However, the demographics and risk factors section will be similar regardless of the disease within a country and therefore, only needs to be filled in once. Additionally, within a country many of the demographic parameters are already known and data is readily available. When this tool is incorporated in a modelling framework to actually calculate the confidence of freedom, data can be saved and can be easily changed or supplemented when there are changes in the cattle demographics, CPs or risk factors.

The results indicate that extending the data collection tool to different cattle diseases is achievable. At most, the cattle population of interest could differ e.g. different age groups or production types. Also, the variables regarding the CPs do not differ substantially between diseases, being mainly a matter of including a wide range of answer options in, for example, the test strategy. The risk factor part could vary, however the most important risk factors, such as cattle movements and direct and indirect contact between animals originating from different herds, are relevant for all infectious cattle diseases.

The biggest challenge was to request data in such a way that the tool could be filled in by experts from different European countries. The partners agreed with the initial version of the tool but when people actually filled the tool they encountered unforeseen difficulties, e.g. the definition was not as clear as thought, the data were not available, data were available but in a different format, data were not accessible or people felt that the entered data needed additional explanation. Therefore, it is extremely important to clearly define the variables to ensure that users understand what data should be delivered, why the specific format is requested and to have pilot test runs in which the tool actually has to be filled. To obtain a broad overview of the data availability and format in many different countries, international collaboration in projects such as STOC free

and SOUND control was crucial. In a follow up study, partners from all countries involved within SOUND control were asked to fill in the tool for their country. The results of this study can be used to further optimize the online data collection tool and to decide on how to change the online tool into a publicly available tool (Rapaliute et al., 2021). After the tool is finalized the SOUND control consortium has to discuss on the maintenance and sustainability of the tool. The tool will be made available on the SOUND control website and will be kept up to date throughout the SOUND control project. The website will remain available after the end of the project. For sustainability, the tool will be advertised to EFSA and European stakeholder organizations such as FESASS (The European Federation for Animal Health and Sanitary Security), to show the merit of keeping the tool up to date. The plan on maintenance and sustainability is still under discussion within work group 2 "Data requirements and availability" of the SOUND control project (https://sound-control.eu/about/wg/wg2/).

For some variables, such as the number of dairy and beef cattle, standardization was neither possible nor desired because an output-based framework should be flexible and each CP is set to the country-specific definitions. For these variables, each country's definition should be captured, which should in this case be the population covered by the CP. Seemingly easy to collect data on variables, such as herd size, were more difficult to query for inclusion in an output-based framework than expected. For example, in this case, some countries only count adult cattle while other countries also include calves in this number. And even with only asking for the number of adult cattle, comparison can be problematic because in some countries cattle are counted as adult at one year of age compared to two years of age or from the moment their first calf is born in other countries. Therefore, we evaluated for each variable whether standardization was desired and then whether the format of data could be delivered by all countries. In the example of the variable "cattle density", a definition of the number of cattle per km2 in the country was agreed. However, some countries can provide more detailed data at regional level in their country. Such detailed information provides the opportunity to distinguish low cattle density areas from high cattle density areas and their respective risks. Another disadvantage of the applied definition was that it did not correct for land area less suitable or not used for cattle farming e.g. mountainous or urban areas. Nevertheless, the chosen definition could be calculated for each country in a similar way which enabled comparison of the value of this variable between countries.

Another challenge was to find a balance between the amount of detail that could potentially be sought and what was actually needed. Up to this point, the inclusion of variables was mainly driven by the availability of data, while the data collection tool is intended to be linked to an output-based model. For the latter, only data should be requested that is needed to populate the model to calculate freedom from infection for different cattle diseases in different countries. At present, there is a first version of an output-based model available for BVD, the STOC free model (Madouasse et al., 2020), which is a Bayesian Hidden Markov model that incorporates test results and risk factors. The model performance was evaluated for BVD control programmes in six European countries. The current version of the data collection tool requests a lot of data to obtain a complete overview of the cattle demographics, the CPs and risk factors in a country. However, the STOC free model only incorporates a limited number of these parameters when generating an output. Consideration should be given to the added value of including an extra variable within the model. Herd-level risk factor information such as the possibility of nose-to-nose contact between herds, herds attending cattle shows, the use of quarantine facilities etc. are of epidemiological interest at herd-level but may not have major influence on the confidence of freedom at country level, and would substantially complicate the model. Even where they are deemed important, their incorporation is constrained because in most countries only an approximation can be given for these variables. Therefore, it seems challenging to include most of the risk factors. One of the questions that was raised during this study was whether qualitative data should be collected with the data collection tool when no quantitative data were available, with this being particularly relevant for many of the risk factors. Within the data collection tool, this could be facilitated together with the quality assessment tool. However, this requires further study to determine whether this is useful in the context of assessing confidence of freedom through an output-based model. The data collection tool can be further improved in an iterative process at the same time as model development. This would apply to the STOC free model, but also to any other output-based model that might subsequently be developed for estimating the confidence of freedom.

The current data collection tool requests data about cattle demographics, CP test results and risk factors. Other aspects that could influence confidence of freedom calculations include biosecurity measures and socioeconomic considerations, however, these are not currently included in the model. Currently, limited data are available to accurately quantify the concept of biosecurity. As one example, the quarantine of purchased animals could be effective means to prevent introduction of infection in the herd, but to obtain reliable data on this is very difficult. The same

challenges apply with respect to data on hygiene measures, grazing practices, housing practices etc. For socioeconomic aspects, such as farmer behavior and farm costs, more research is needed into which aspects are important and how these could be incorporated in an output-based framework. Further work on this is currently performed in the SOUND control project.

The data collection tool was developed to collect data for three relevant cattle diseases in a wide range of countries within Europe as input for output-based methods to calculate freedom of infection. In this study, we can conclude that the initial seemingly easy task of development of a data collection tool was far more complex than foreseen. Key aspects that need to be considered in such a tool are alignment and clarification of variable definitions, data availability, a clear distinction between data essential for comparison of freedom of infection versus data that are interesting to know, and an objective means for data quality assessment. These key learnings can support studies in which data on infectious diseases in livestock from different countries should be collected to compare freedom of infection.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2021.656336/full#supplementary-material

Author Contributions

AvR prepared the manuscript. Conceptual contributions were made by all authors and all authors contributed to revising the manuscript.

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Chapter 6

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

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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.

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.

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)

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 (2,032/19,243) 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 (1,305/12,012) 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.

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, Figure 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, Figure 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.

Table 1. Data description

	The Netherlands	Germany	Ireland		Scotland	
Herd type included in the model	**Dairy**	**Dairy and beef combined[1]**	**Dairy**	**Beef**	**Dairy**	**Beef**
Number of herds in the dataset (and included in the model)	1,765 (1,642)	363 (361)	16,190 (16,097)	50,760 (49,685)	580 (559)	1,922 (1,796)
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	2,475	78,884	180,604	3,724	6,413
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	1,713

[1] Herd type is not specified in Germany

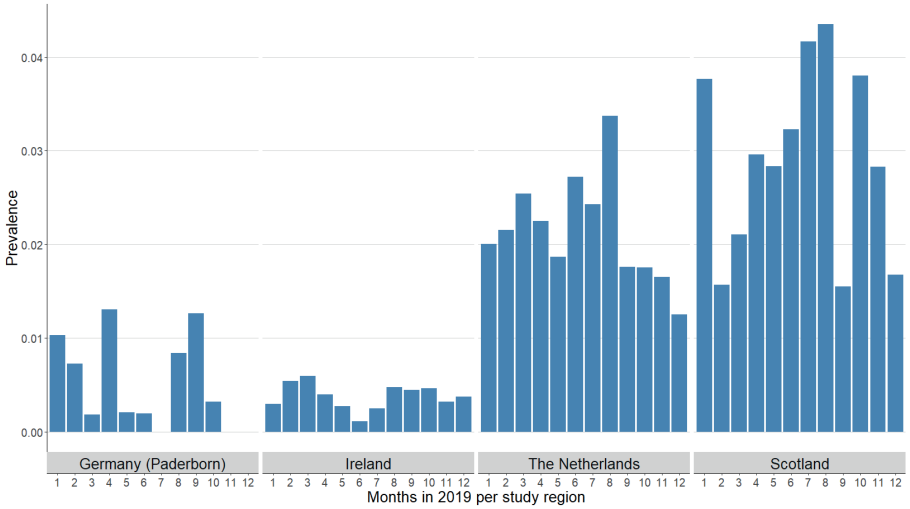

Figure 1. The BVDV between-herd prevalence per month for dairy herds in each BVDV CP (NL, DE, IE, SCO) based on ear notch testing in 2019. A herd is classified positive in a month when at least one animal tested positive.

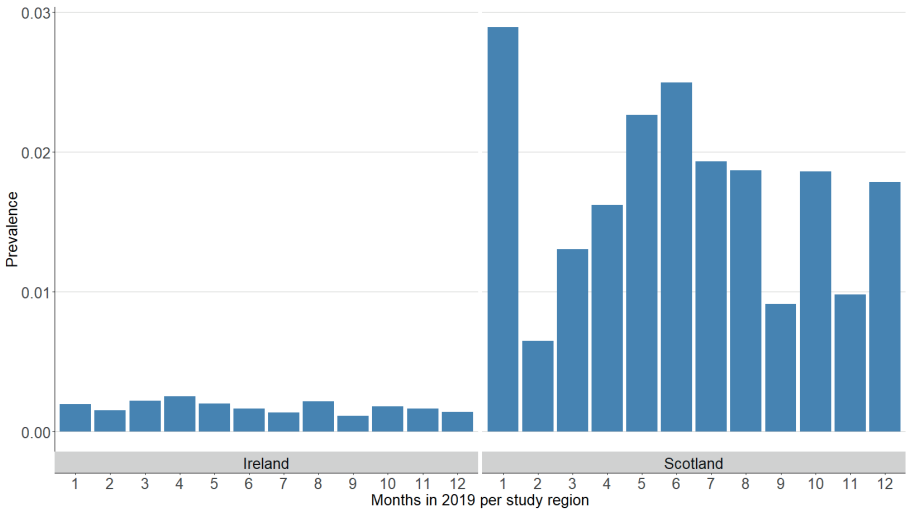

Figure 2. The BVDV between-herd prevalence per month for beef herds in each BVDV CP (IE, SCO) based on ear notch testing in 2019. In any specific month, a herd is classified positive when at least one animal tested positive.

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, Figure 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.

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

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 (Figure 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 (Figure 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 the first scenario, a uniform prior distribution was chosen (Beta(1, 1)) because the value of π1 was different between study regions (Figure 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) (Figure 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 (Figure 3), meaning that 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.

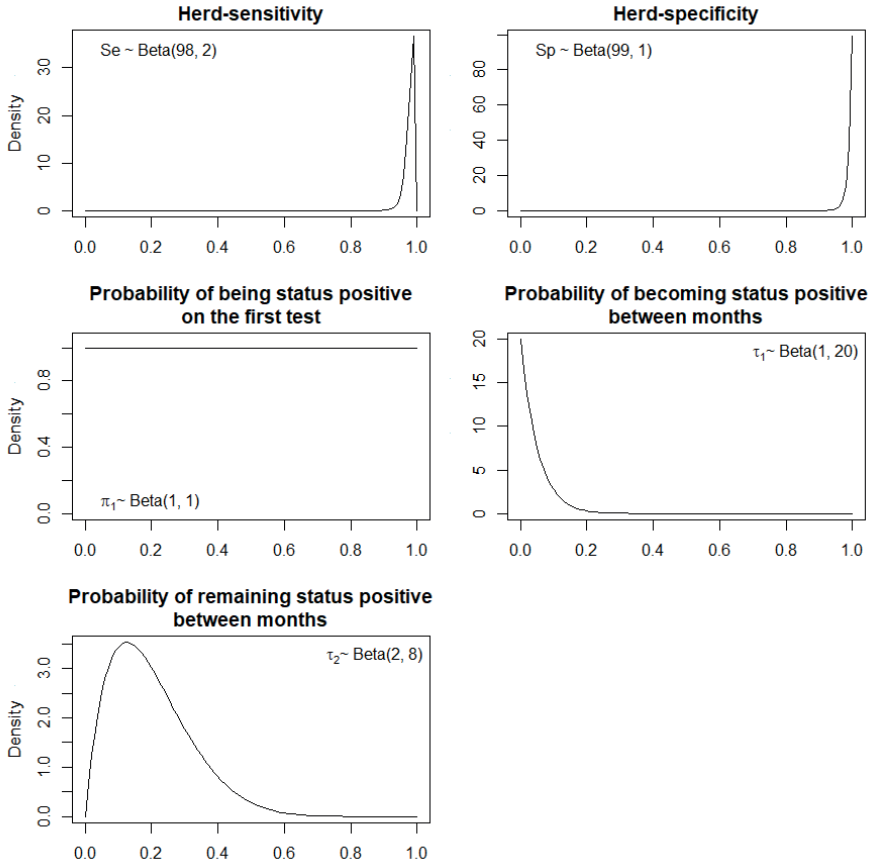

Figure 3. Prior beta distributions for all five model parameters of the STOC free model in scenario 1 in which the same default priors were used for each study region.

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, figures A1-A2.

Model parameters	Country-specific beta priors (mean (sd))					
	The Netherlands	Germany (Paderborn)	Ireland		Scotland	
	Dairy	Dairy and beef[1]	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)	"

[1] Herd type is not specified in Germany

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).

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).

Convergence

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

Parameter estimation

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.

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)

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 (Figure 4 and Appendix 3: Figure A3-A7).

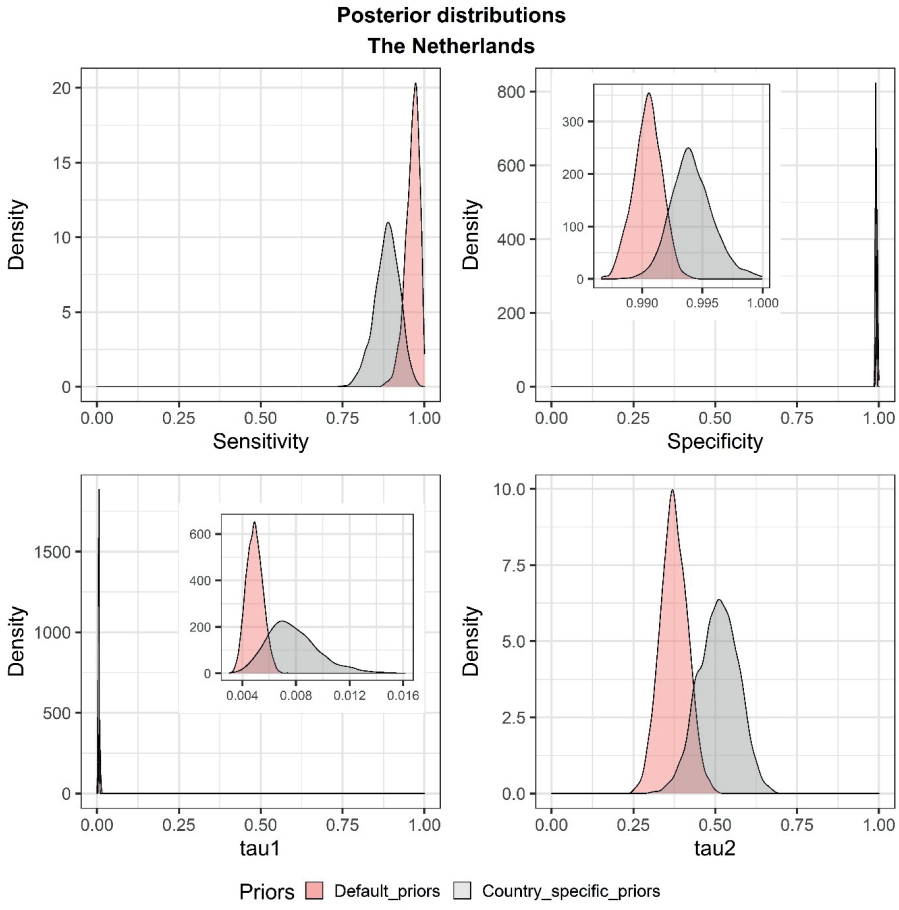

Figure 4. Posterior estimates when running the STOC free model with default priors (red) and country-specific priors (grey) for the Netherlands. Plots for the other study regions can be found in Appendix 3.

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 (Figure 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 (Figure 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

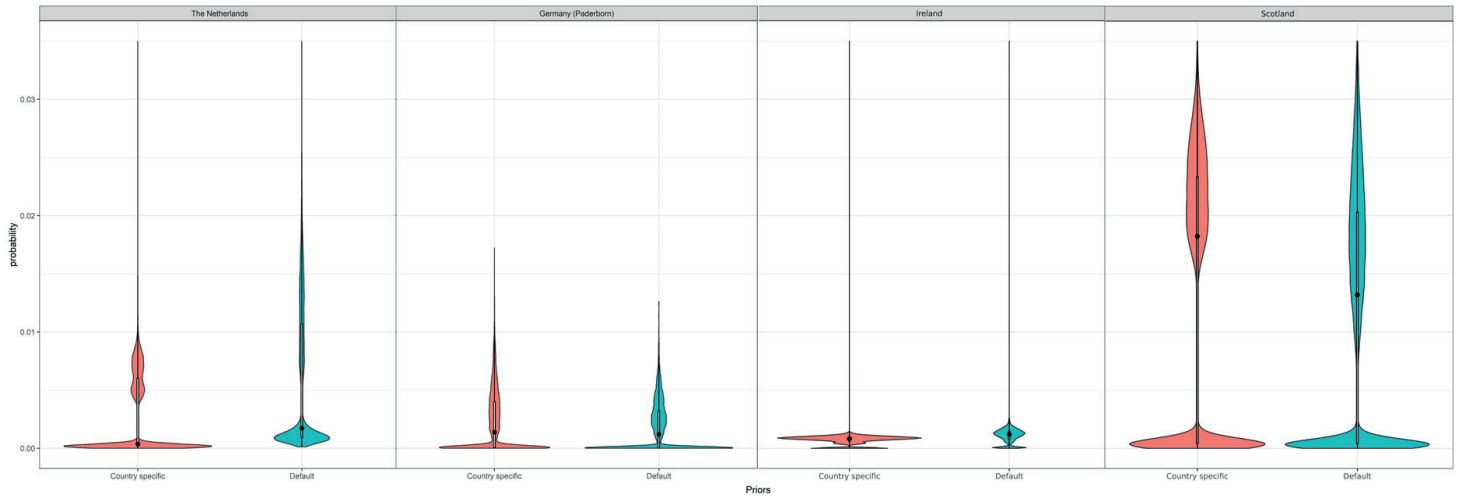

Figure 5. Predicted probability of infection (the black dot shows the median) for dairy herds with a free status on 1 December 2019 according to the BVDV CP based on ear notch testing in each study region. The plots show scenario 1 (coloured blue), in which for each study region the same default priors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

herds. For Scotland, the credibility interval was wider for dairy herds compared to beef herds.

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 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 (τ2) were mostly influenced by the priors, because the posterior herd-level sensitivity and τ2 changed when using country-specific priors instead of default priors (Figure 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 τ2 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 τ2 was higher than expected and the herd-level sensitivity lower than expected. The association between τ2 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 τ2 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 τ2 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; van Roon et al., 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

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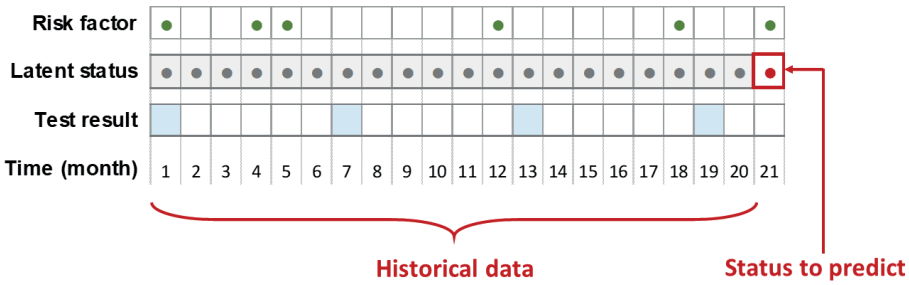
APPENDIX

Appendix 1 Description of STOC free model

The STOC free model is a Bayesian Hidden Markov Model. The model is described in detail in Madouasse et al. (2022). The Figure below, from Madouasse et al. (2022), shows an overview of the modelling framework for a herd. The model outcome is a herd-level latent status regarding infection. This latent status is not directly observed, but it determines the results of biological tests. The probability of becoming status positive can be modified by risk factors. In the model, time is discretized into month. The quantity of interest is the probability of being latent status positive on the last month of surveillance. Data available before this last month of surveillance are used as historical data for parameter estimation.



S_t, the latent status on month , follows a Bernoulli distribution with a probability of being positive:

$$S_t \sim Bernoulli(\pi_t)$$

When $t > 1$, the latent status follows a Markovian dynamics, whereby the status on a given month depends of the status on the previous month. Herds that are status negative in the previous month, have a certain probability of becoming positive called τ_1. Herds that are status positive in the previous month, have a certain probability of remaining positive called τ_2.

$$\pi_t = \begin{cases} \tau_1 & \text{if } S_{t-1} = 0 \\ \tau_2 & \text{if } S_{t-1} = 1 \end{cases}$$

The latent status S at t determines the test result T at t through test sensitivity Se and specificity Sp.

$$T_t \sim Bernoulli\big(p(T_t)\big)$$

$$\mathrm{p}(\mathrm{T_t}) = \begin{cases} 1 - Sp & \text{if } S_t = 0 \\ Se & \text{if } S_t = 1 \end{cases}$$

Beta prior distributions need to be provided for *Se* and *Sp*. For π_1, τ_1 and τ_2, priors can be provided either using Beta distributions, as was done in this paper, or using normal distributions on the logit scale.

In the Stan implementation of the model, the forward algorithm is used for parameter estimation.

The model is available as an R package on Github (https://github.com/AurMad/STOCfree).

The Github page contains a README file that guides new users through the model.

Appendix 2 Priors

Table A1. Beta prior values for scenario 2, in which all study regions calculated priors specific to their situation. The higher the values for α and β, the higher the precision of the priors.

Model parameters	Country-specific beta priors (α, β)					
	The Netherlands	Germany (Paderborn)	Ireland		Scotland	
			Dairy	Beef	Dairy	Beef
Herd-level sensitivity	98, 2	616, 7	1134, 18	1134, 18	100, 2	100, 2
Herd-level specificity	99, 1	1000, 1.1	2000, 2	2000, 2	5000, 1	5000, 1
Probability of latent status positive at first test (π1)	60, 15694	5, 466	32, 16483	34, 52731	13, 643	13, 643
Probability of a herd becoming latent status positive (τ1)	39, 9961	1.167, 459	25, 72906	25, 72906	6, 656	6, 656
Probability of a herd remaining latent status positive (τ2)	1, 59	34, 60	1, 25	1, 25	1, 20	1, 20

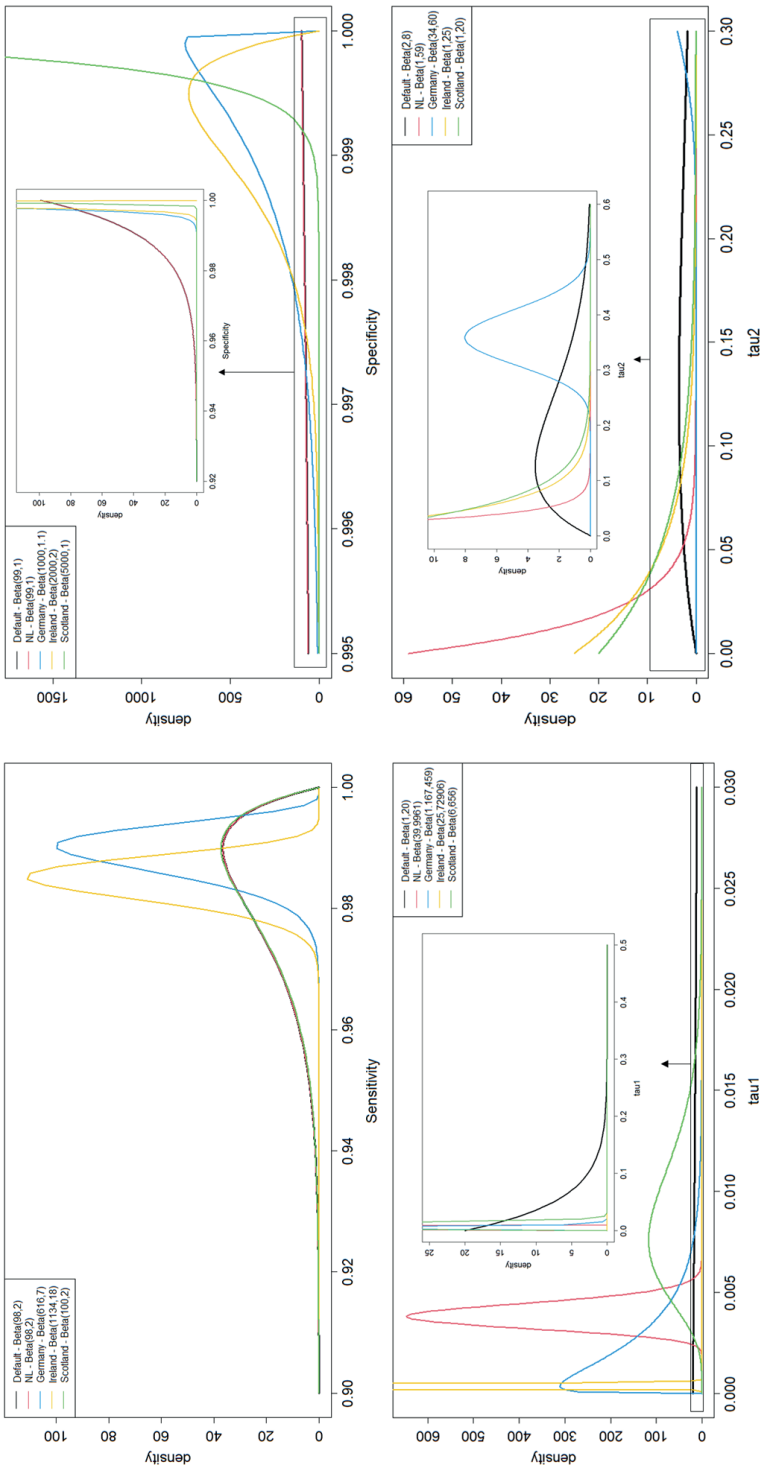


Figure A1. Prior beta distributions for the model parameters (herd-level sensitivity, herd-level specificity, the probability of becoming latent status positive (τ1), the probability of remaining latent status positive (τ2)). The plots show scenario 1, in which all study regions run the STOC free model with the same priors (default), and scenario 2, in which all study regions calculated priors specific to their situation.

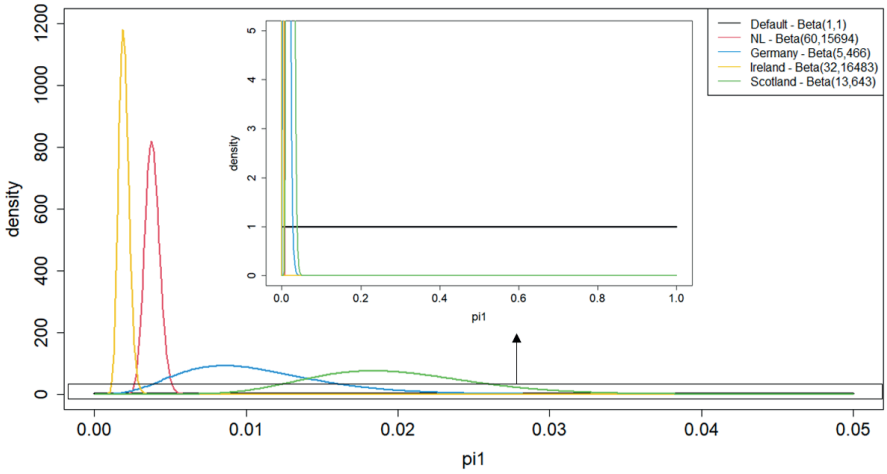


Figure A2. Prior beta distributions for the probability of being latent status positive at the first test for scenario 1, in which all study regions run the STOC free model with the same priors (default), and scenario 2, in which all study regions calculated priors specific to their situation.

Appendix 3 Parameter estimates

Table A2. Median (2.5%, 97.5%) of the posterior parameter distributions of the ear notch - dairy models for the Netherlands, Germany (Paderborn), Ireland and Scotland for scenario 1 and 2 in which all study regions used default and country-specific priors, respectively.

Model parameters (median (2.5%, 97.5%))	Type of priors	The Netherlands	Germany (Paderborn)	Ireland	Scotland
Herd-level sensitivity	1. Default priors	0.886 (0.805-0.954)	0.977 (0.926-0.996)	0.904 (0.877-0.929)	0.979 (0.967-0.988)
	2. Country-specific	0.966 (0.913-0.994)	0.989 (0.977-0.995)	0.981 (0.978-0.984)	0.983 (0.973-0.990)
Herd-level specificity	1. Default priors	0.994 (0.991-0.997)	0.998 (0.995-1.000)	0.998 (0.998-0.998)	0.994 (0.991-0.996)
	2. Country-specific	0.990 (0.988-0.993)	0.999 (0.996-1.000)	0.998 (0.998-0.998)	1.000 (1.000-1.000)
Probability of a herd becoming latent status positive (τ1)	1. Default priors	0.008 (0.005-0.12)	0.003 (0.001-0.006)	0.001 (0.000-0.001)	0.015 (0.012-0.018)
	2. Country-specific	0.005 (0.004-0.006)	0.002 (0.001-0.005)	0.000 (0.000-0.000)	0.019 (0.018-0.021)
Probability of a herd remaining latent status positive (τ2)	1. Default priors	0.511 (0.395-0.621)	0.454 (0.268-0.648)	0.624 (0.585-0.660)	0.372 (0.327-0.422)
	2. Country-specific	0.373 (0.294-0.456)	0.396 (0.308-0.491)	0.529 (0.500-0.557)	0.278 (0.249-0.307)

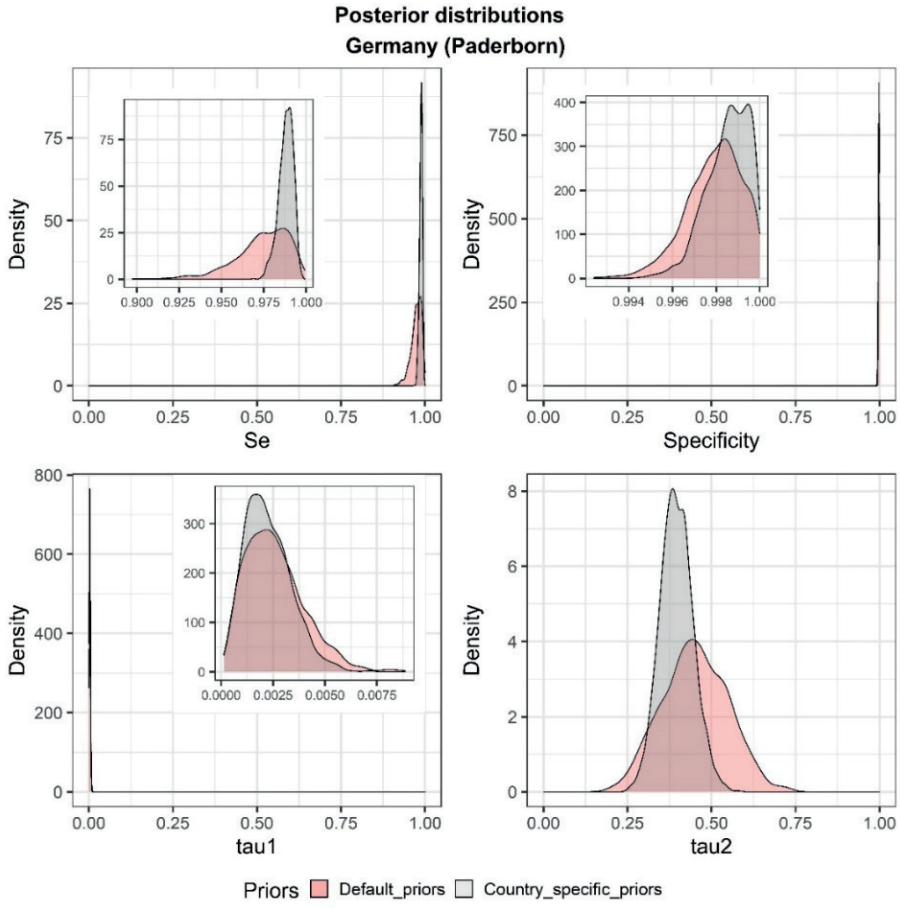


Figure A3. Posterior estimates when running the STOC free model with default priors (red) and country-specific priors (grey) for Germany (Paderborn).

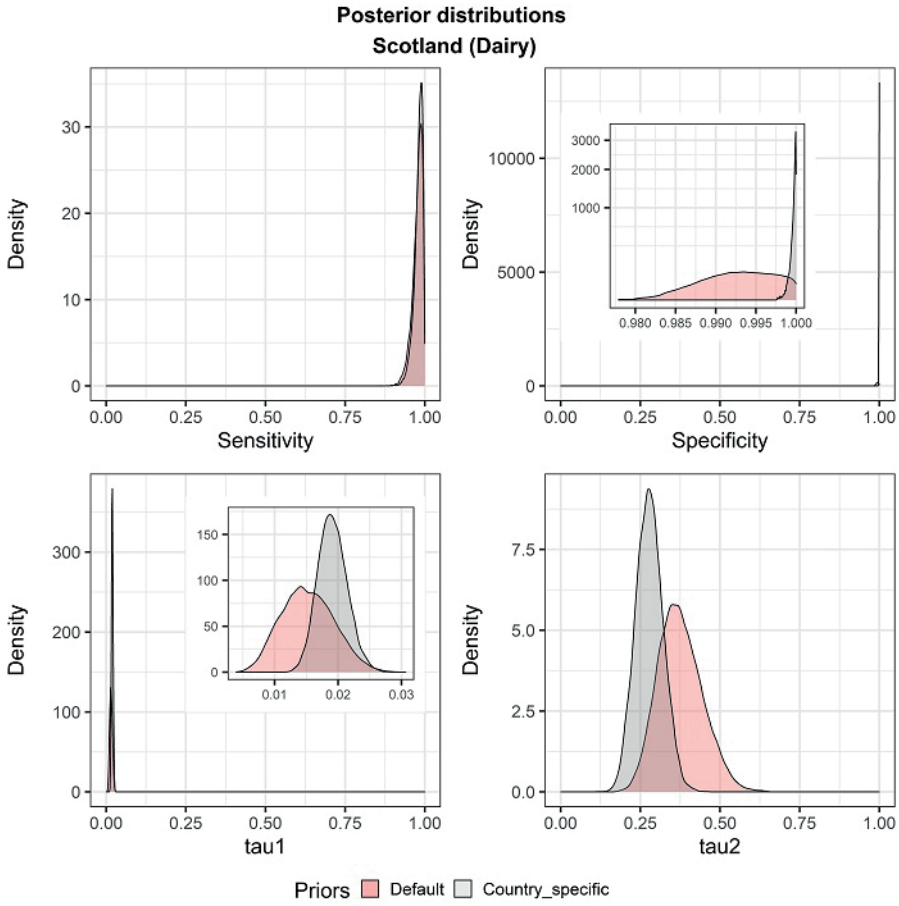


Figure A4. Posterior estimates when running the STOC free model with default priors (red) and country-specific priors (grey) for dairy herds in Scotland.

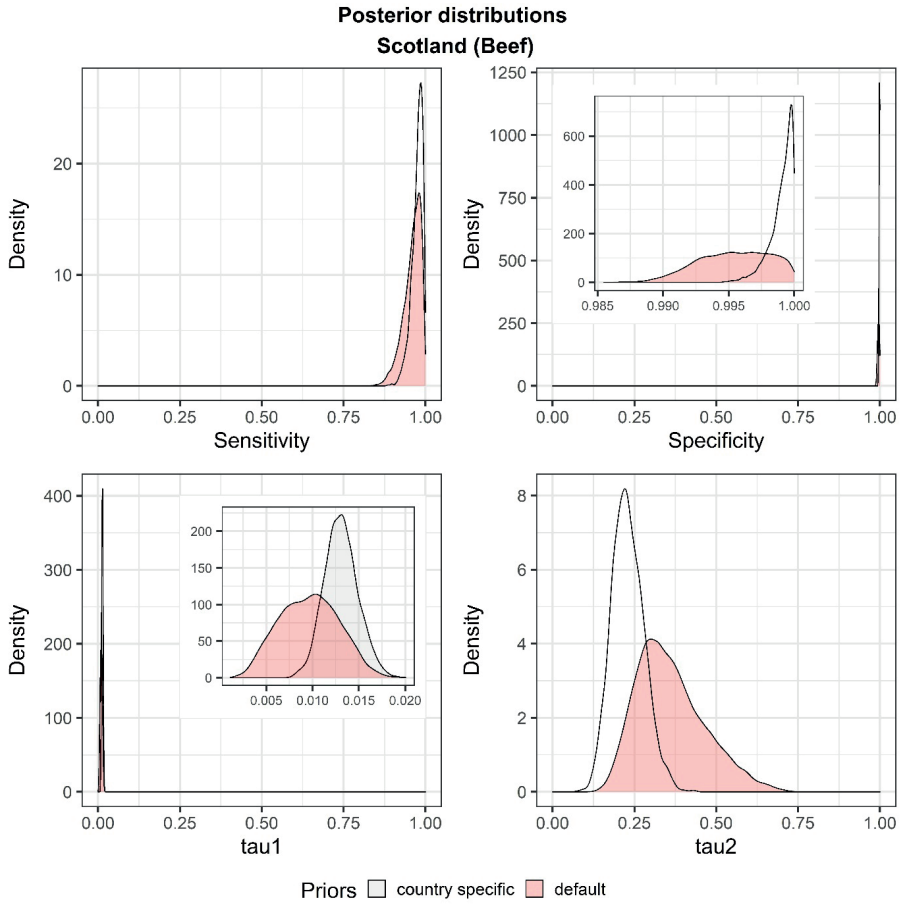


Figure A5. Posterior estimates when running the STOC free model with default priors (red) and country-specific priors (grey) for beef herds in Scotland.

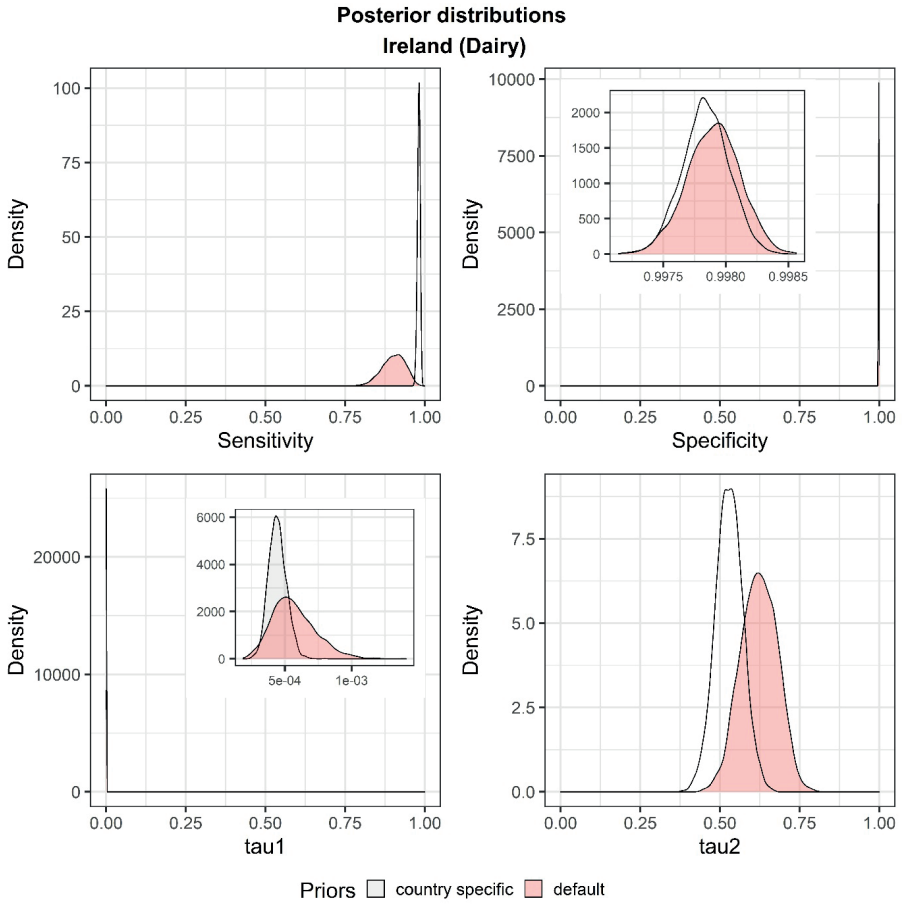


Figure A6. Posterior estimates when running the STOC free model with default priors (red) and country-specific priors (grey) for dairy herds in Ireland.

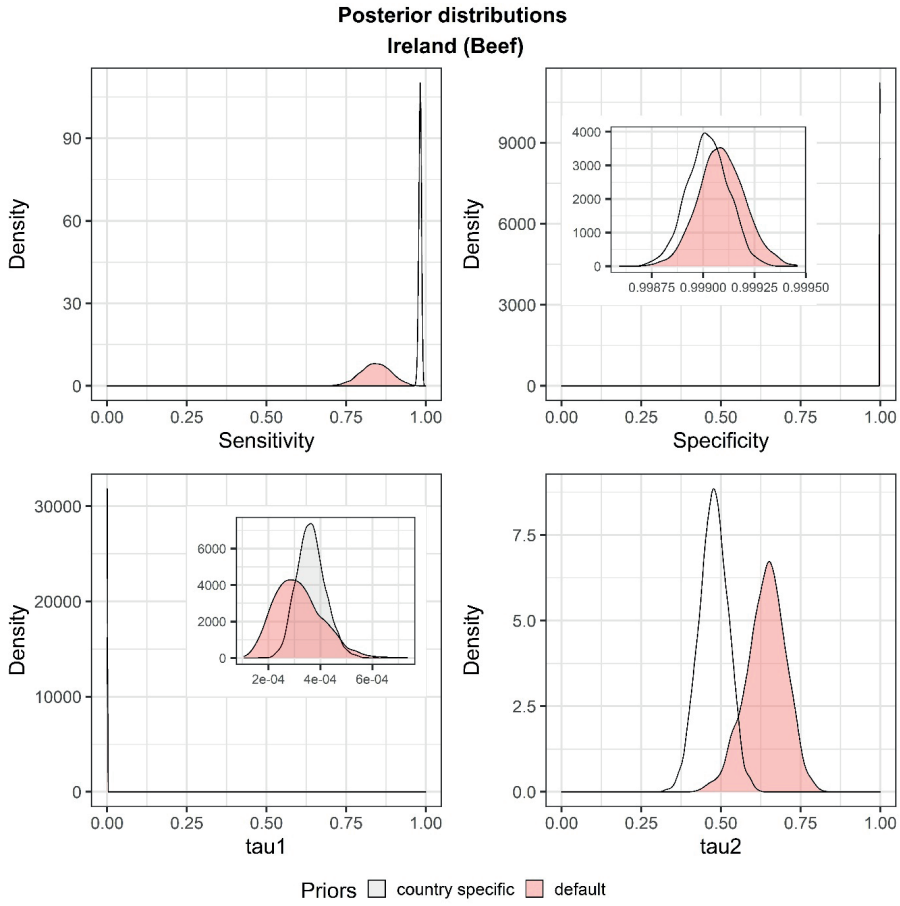


Figure A7. Posterior estimates when running the STOC free model with default priors (red) and country-specific priors (grey) for beef herds in Ireland.

Appendix 4 Predicted probability of infection

Table A3. Median (2.5%, 97.5%) predicted probability of infection for dairy herds with a free status on 1 December 2019 according to the BVDV CP based on ear notch sampling in the Netherlands, Germany (Paderborn), Ireland and Scotland for scenario 1, in which all study regions used the same default priors and scenario 2, in which all study regions used country-specific priors.

Model outcome (median (2.5%, 97.5%))	The Netherlands	Germany (Paderborn)[1]	Ireland	Scotland
Prob infection free herds – default priors	0.002 (0.000-0.019)	0.002 (0.000-0.008)	0.001 (0.000-0.002)	0.013 (0.000-0.033)
Prob infection free herds – country-specific priors	0.000 (0.000-0.009)	0.001 (0.000-0.006)	0.001 (0.000-0.001)	0.018 (0.000-0.026)

Table A4. Median (2.5%, 97.5%) predicted probability of infection resulting from the ear notch control programme for all dairy cattle in the Netherlands, Germany (Paderborn), Ireland and Scotland for scenario 1, in which all study regions used the same default priors and scenario 2, in which all study regions used country-specific priors.

Model outcome (median (2.5%, 97.5%))	The Netherlands	Germany (Paderborn)	Ireland	Scotland
Prob infection all herds – default priors	0.002 (0.000-0.021)	0.002 (0.000-0.008)	0.001 (0.001-0.002)	0.013 (0.000-0.021)
Prob infection all herds – country-specific priors	0.000 (0.000-0.009)	0.002 (0.000-0.007)	0.001 (0.000-0.001)	0.018 (0.000-0.032)

Appendix 5 Model output for beef cattle herds

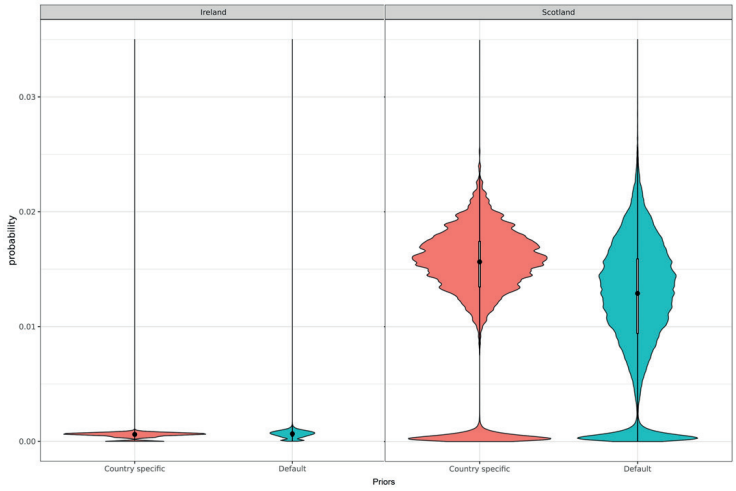


Figure A8. Predicted probability of infection (the black dots show the median) for beef herds with a free status on 1 December 2019 according to the BVDV CP based on ear notch testing in Ireland and Scotland. The plots show scenario 1 (coloured blue), in which default priors were used, and scenario 2 (coloured red), in which country-specific priors were used.

Table A5. Median (2.5%, 97.5%) of the posterior distributions of the ear notch - beef models for Ireland and Scotland for scenario 1, in which both study regions used the same default priors, and scenario 2, in which both study regions used country-specific priors.

Model parameters median (2.5%, 97.5%)	Type of priors	Ireland	Scotland
Herd-level sensitivity	1. Default priors	0.844 (0.812-0.874)	0.965 (0.944-0.980)
	2. Country-specific	0.982 (0.979-0.985)	0.979 (0.966-0.988)
Herd-level specificity	1. Default priors	0.999 (0.999-0.999)	0.996 (0.994-0.998)
	2. Country-specific	0.999 (0.999-0.999)	1.000 (1.000-1.000)
Probability of a herd becoming latent status positive (τ1)	1. Default priors	0.000 (0.000-0.000)	0.010 (0.007-0.012)
	2. Country-specific	0.000 (0.000-0.000)	0.013 (0.012-0.014)
Probability of a herd remaining latent status positive (τ2)	1. Default priors	0.646 (0.602-0.687)	0.341 (0.279-0.420)
	2. Country-specific	0.477 (0.446-0.508)	0.227 (0.195-0.263)

Table A6. Median (2.5%, 97.5%) predicted probability of infection for beef herds with a free status on 1 December 2019 according to the BVDV CP based on ear notch sampling in Ireland and Scotland for scenario 1, in which both study regions used the same default priors, and scenario 2, in which both study regions used country-specific priors.

Model outcome (median (2.5%, 97.5%))	Ireland	Scotland
Prob infection free herds – default priors	0.001 (0.000-0.001)	0.013 (0.000-0.021)
Prob infection free herds – country-specific priors	0.001 (0.000-0.001)	0.016 (0.000-0.021)

Appendix 6 Data descriptives

Table A7. The number of months in which ear notch test results from cattle herds have available.

Number of months *	Number of herds with ear notch test results					
	The Netherlands	Germany (Paderborn)	Ireland		Scotland	
	Dairy	Dairy and beef	Dairy	Beef	Dairy	Beef
1	112	9	650	7888	57	532
2	137	37	760	9528	43	366
3	132	37	2187	9969	44	288
4	124	49	4289	8759	54	215
5	122	34	3392	6401	54	201
6	135	26	1940	4008	55	121
7	118	25	1209	2222	37	81
8	136	14	754	1142	48	50
9	174	18	496	557	52	32
10	166	18	284	200	44	21
11	180	22	150	71	36	6
12	229	74	79	15	56	11
Total number of herds	1765	363	16190	50760	580	1924

* e.g. 1 means that herds have just one month of data available, which can be any month in the year. 12 means that herds have data available for every month of the year.

Table A8. The number of cattle herds that have data available in each study region for each month of the year

Month	Number of herds with ear notch test results					
	The Netherlands	Germany	Ireland		Scotland	
	Dairy	Dairy and beef	Dairy	Beef	Dairy	Beef
January	999	202	4723	12214	342	259
February	930	198	11665	12303	347	343
March	984	229	13703	18658	257	470
April	1024	230	13618	26415	280	777
May	1071	227	11723	28666	257	992
June	1029	218	6311	19331	293	923
July	1111	204	4401	16920	357	589
August	1127	193	2718	12067	318	570
September	1024	205	2246	9737	342	328
October	1141	181	2571	9384	323	450
November	1090	189	2823	8490	330	423
December	1036	199	2382	6419	264	258


A

Chapter 7

General discussion

The general aim of this thesis was to support the development of a generic output-based method and to test this method on its applicability to determine the herd-level probability of freedom from BVDV infection in cattle. In this chapter the main findings of this thesis are summarized and the application of the framework in practice is discussed. Furthermore, I provide suggestions for further generalization and potential improvement of the method such as including economic aspects of CPs to enable assessment of cost-effectiveness of CPs.

Main findings of this thesis

Elements of BVDV control programmes that influence confidence of freedom from infection

Many countries in Europe have implemented their own BVDV CPs tailored to the specific situation in their country. To support the development of an output-based framework to assess and compare the probability of freedom of herds considered free within these CPs, a detailed understanding of those CPs was critical. In Chapter 3, we therefore presented a detailed overview of similarities and differences between elements of BVDV CPs that were conducted in six European countries that could influence the confidence of freedom from BVDV infection in the herd. The considerable heterogeneity that we identified in both the context (e.g. cattle density, infection prevalence) and different diagnostic procedures/ tests and matrices showed the complexity of comparing different CPs in terms of confidence of freedom from infection. Challenges for comparison of CPs include the way that data are recorded, the different contexts and the different phases of BVDV control or eradication in the studied countries. These results highlighted the need for a standardized practical methodology to objectively and quantitatively determine confidence of freedom from infection resulting from different CPs.

Risk factors for BVDV infection in cattle herds

The BVDV disease-free status can be compromised by risk factors for introduction or persistence of the virus. Depending on risk factors being present or not, herds in the CP differ in their confidence of being free. In the STOC free model, a herd-level status regarding infection is estimated based on test results and a probability of changing between months. Therefore, in Chapter 4, we presented a systematic review of risk factors for BVDV infection in cattle herds in Europe. The importance of the most frequently reported risk factors was assessed using meta-analyses. Significantly higher odds were found for dairy herds (OR=1.63, 95% CI: 1.06-2.50) compared to beef herds, for larger herds (OR=1.04 for every 10 extra animals in the

herd, 95% CI: 1.02-1.06), for herds that participated in shows or markets (OR=1.45, 95% CI: 1.10-1.91), for herds that purchased cattle (OR=1.41, 95% CI: 1.18-1.69) and for herds that had direct contact with cattle of other herds at pasture (OR=1.32, 95% CI: 1.07-1.63). The pooled risk estimates resulting from the meta-analyses gave an indication of the importance of the most frequently studied risk factors and could be used as default priors in the STOC free framework.

Development of a generic data collection tool

To evaluate data availability and quality and to collect actual input data for an output-based framework, such as the STOC free framework, a data collection tool (STOC free DATA) was developed. Chapter 5 described the key learnings from the initial development of this data collection tool, when it was built for BVDV and was applied to six countries, to an online tool that could be applied to multiple cattle diseases and for a larger number of countries (Rapaliutė et al., 2021). The results showed that extending the data collection tool to different cattle diseases was achievable. Something to take into account is that the cattle population of interest could differ e.g. different age groups or production types. Variables, relevant to determining confidence of freedom from infection, to include regarding CPs did not differ substantially between cattle diseases. Risk factors could vary depending on the pathogen of interest, however the most important risk factors, such as cattle movements and direct and indirect contact between cattle originating from different herds, are relevant for all infectious cattle diseases. The biggest challenge was to request data in such a way that the tool could be filled in by experts from different European countries and that definitions of requested variables were clear. Often variables were interpreted differently, the data were not available, data were available but in different formats, data were not accessible or people felt that the entered data needed additional explanation. Therefore, it is important to have agreement and a common understanding of the definitions that are used. The large differences in data availability and comparability across European countries present challenges to the development of a standardized data collection tool and modelling framework.

Output-based assessment of freedom from infection

Within the STOC free project a Bayesian Hidden Markov model (STOC free MODEL) was developed to estimate the probability of infection at herd level. In Chapter 6, STOC free MODEL was applied to BVDV field data from CPs based on testing of ear notch samples of newborn calves in four countries. For cattle herds with a BVDV negative herd status according to the CP, STOC free MODEL estimated a very low probability of infection in all four countries. A very low probability of infection

implies a very high probability of freedom, suggesting that the effectiveness of CPs based on ear notch testing was comparable between countries. 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 prevalence of BVDV in 2019 was higher in The Netherlands and Scotland compared to the other regions included. A higher predicted probability of infection could also be the result of uncertainty due to missing test results i.e. months without test results because no calves were born. Test negative herds with missing test months before the month of prediction had a higher predicted probability of infection in the model 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 because negative test results are more informative than no test results and therefore the prediction of freedom from infection based on the latter was more uncertain. This study highlighted the challenges of output-based modelling of BVDV, such as the complexity of BVDV infection, the estimation of herd-level priors and analytical issues in case of a very low incidence of BVDV in study regions. The STOC free model can be used for assessment of freedom from infection but the data, priors and results need to be carefully evaluated to obtain accurate information.

Application of the STOC free framework in practice

The STOC free project was initiated in 2017 with the ambitious objective of developing a new framework that enables a transparent and standardized comparison of confidence of freedom for CPs of cattle diseases in Europe. Besides this thesis, several papers were published, describing the development of the model (Madouasse et al., 2021), model validation on simulated data (Mercat et al., 2022) and data availability and data quality on CPs for cattle diseases in Europe (Rapaliutė et al., 2021). From a scientific point of view, the project provided multiple new insights about output-based assessment of CPs, data needs and modelling possibilities and challenges. The next step is to stimulate and facilitate the use of the STOC free framework in practice to estimate the probability of freedom from infection at herd, region or CP level.

Three lessons learned in the application of STOC free MODEL with Dutch BVDV data

In an iterative process with the French partners that developed the modelling framework, I applied the model to Dutch BVDV data and the model was further refined when needed. There were three main challenges that we faced during the case studies in which we tested the model with BVDV field data.

The first challenge was the inclusion of different surveillance components of the BVDV CPs i.e. different target animals, different diagnostic tests, different sample matrices. As discussed in Chapter 6 we were able to compare one component of BVDV CPs i.e. the ear notch sampling of newborn calves. However, in some countries ear notch testing is just one of the routes towards freedom of BVDV e.g. in The Netherlands ear notch testing is used by only 11% of the herds that are in the BVDV CP. Therefore, all different diagnostic tests that are part of the BVDV free CP in the Netherlands i.e. virus or antibody testing in ear notch, bulk milk, and serum samples were initially included in STOC free MODEL for a Dutch case study. Technically it is possible to include more than one diagnostic test to STOC free MODEL. However, in practice this appeared complex because ear notch sampling is performed to detect persistently infected cattle and thus the virus infected animal itself (viral antigen or RNA), while bulk milk testing and spot testing aim at detecting antibodies which is an indirect indicator of the presence of a persistently infected animal (PI) or transiently infected animal (TI) in the herd. It was assumed that it would be possible to include all test results in one model by adapting the priors for each test to the chosen latent status i.e. the presence of one or more BVDV PIs at foot in the herd. This is however challenging because literature does not describe herd-sensitivity and herd-specificity for antibody tests to detect actual presence of virus in the herd. Also, antibody and virus tests can give contradictory information to the model, which is logical in the biology of BVDV because herds can be antibody positive, but virus negative within one time step (month). However, in the model this led to either very high sensitivities for the virus detecting tests and very low sensitivities for the antibody tests or the other way around. This issue is specific for BVDV and is irrelevant for other diseases with just one latent status. For BVDV the different routes to freedom within CPs (i.e. with different diagnostic tests and matrices) could be studied separately with STOC free MODEL. In this way a region or country will obtain a probability of freedom per CP route and per latent status.

The second and third challenge were the estimation of priors and the underlying assumptions of the disease process that need to match with the data. STOC free MODEL requires the input of prior knowledge for all its parameters. In the case studies we have learned that users of the model need clear definitions of all priors and instructions on how these can be calculated with historical data or estimated by expert opinion to avoid misunderstanding. In addition, the underlying assumption of the disease process needs to fit the test data from CPs and priors that are provided. The STOC free MODEL is a SIS model (Susceptible-Infectious-Susceptible) and thus assumes transitions from susceptible to infectious and vice versa. This is fine for BVDV at herd-level, but in the case studies we learned that the BVDV data sometimes follows a SI model. This is the case when an animal in a herd tests positive in one month and is retained, but not re-tested with ear notch or blood sampling in the next month. This cannot be identified by the model from test data because there is only a positive result in the first month and the next month the herd can be test negative by testing other newborn calves but not the PI that is retained. In this case, also the priors do not fit the data. In this example, the herd-sensitivity will drop because the prior for the probability of remaining infected between time steps informs the model that some herds remain infected and thus some negative results are considered false-negative. Therefore, users of the model need good knowledge of their CP data, which transmission pattern the model assumes and what priors mean in relation to the latent disease status, to be able to correctly interpret the results. To guide users in how to run the model and to provide insight in the definitions of the priors, we tested the model with default priors that can be used by any European country (Chapter 6). However, I would encourage to use country-specific priors as the incorporation of prior knowledge is an advantage of Bayesian modelling. It can help to improve the precision of posterior estimates and avoid inference errors especially when little data is available to update the priors. Therefore, for possible future use of STOC free MODEL for other diseases, it would be good to set guidelines on how prior knowledge can be acquired systematically (Zondervan-Zwijnenburg et al., 2017).

Implementation of the STOC free framework

In the initial stage of the STOC free project, a key consideration was the identification of the end-users of the framework. Farmers were seen as the target group that could benefit directly from the outcomes of this tool as it would give valuable information about the infection status of their herd and the herd they intent to purchase cattle from. However, the end-users need access to the required data and thus would more likely be competent authorities or the Animal Health Services (AHS) in each country or region. Within the STOC free project,

we extensively discussed how to maximize the chances that the developed framework would be implemented and used by the intended end-users. We know that general acceptance and global implementation of new tools is difficult (Matthews et al., 2007). Reasons for failure could be too much focus on technical development of models and the implementation of tools that are a black box to the intended end-user (Bennett et al., 2012; Matthews et al., 2007). Therefore, I believe it was right to first fully develop the methodology of the tool before intended end-users were invited to use the tool. Otherwise, the end-users may have been discouraged before the official implementation and could have lost faith in its validity. This would have made it extremely difficult to successfully implement a final version of the tool.

I also believe that, before tools are used in practice, uptake by the scientific community is needed first for further refinement and application. In the end, a four year project is short to develop and implement such a tool. The method that is most commonly used for output-based surveillance, scenario tree modelling, was developed in the early 2000s and first described in 2007 (Martin et al., 2007a, Martin et al., 2007b). Then, training courses were provided by the developers and other scientists started to apply the method to their own data. After many years of further refinement and implementation, the method is now widely applied and accepted by researchers for many animal diseases (e.g. Cowled et al., 2022; de la Cruz et al., 2019; Veldhuis et al., 2017). In 2018, another project, the COST action SOUND control (Costa et al., 2020) was initiated that facilitated the dissemination of the results of STOC free in the wider research community. In this project, researchers from 33 countries explore the development and implementation of output-based frameworks to assess freedom from infection. For me, this was a great opportunity to introduce the data collection tool to a large group of researchers from different fields e.g. veterinarians, epidemiologists, economists, statisticians, and social scientists from different countries (Costa et al., 2020). Valuable feedback was obtained on data needs and availability, which helped to improve and refine the data collection tool. In SOUND control the STOC free model was also presented and an hands-on workshop was provided. At this point, several researchers from different countries have shown interest and are currently in the process of applying STOC free DATA and STOC free MODEL to CPs for diseases such as Johne's disease and salmonella.

Easy to use interface

Currently, the STOC free framework runs in an R-script, which is easy to use for people that are comfortable with using R. For future implementation of the STOC

free framework, it would be helpful to build an easy to use interface around the framework which guides the user through every step of the model. First, the user should be asked to upload the required data in any of the formats that could be read by the model. Then the user should upload its priors with descriptions on how they were calculated or estimated, or upload data that can be used to automatically calculate prior values as part of the framework. Finally, the user should be guided through all output of the model i.e. confidence of freedom and parameter estimates. The STOC free framework should then deliver a uniform summary of all these steps that can be used to show that a country or region meets the minimum requirements i.e. a certain level of freedom from infection. In Chapter 6 we have shown that herds in all study regions that perform ear notch sampling have a very high probability of freedom of BVDV, ranging from 0.98 to 1.00. Acceptable levels of freedom from infection need to be defined by legislative bodies and are provided by the EU for regulated diseases (Madouasse et al., 2021, Cameron, 2012, Schuppers et al., 2012). At this point, the Animal Health law states that Member States or zones can be granted the status "free from BVDV" when vaccination has been prohibited, no cases of BVDV have been confirmed in the previous 18 months and at least 99,8% of the establishments representing at least 99,9% of the bovine population are free from BVDV ((EU) 2020/689). The free status can be maintained by annual testing that allows to detect establishments infected with BVDV at a target prevalence of 0,2% of the establishments with a 95 % level of confidence. The results of STOC free do not cover this (yet) as we have not applied the tool on country level i.e. only cattle herds applying ear notch testing were included. However, these herds from three of the four study regions had a probability of freedom from BVDV of 99,8% or higher.

Future developments in output-based assessment of disease control programmes with the STOC free framework

Importance of herd-level risk factors

In the early stages of the STOC free project, we considered the inclusion of risk factors for introduction or persistence of the BVD virus in STOC free MODEL to be very important because it was expected that these would contribute to differences in probability of freedom from infection between countries, regions or herds. However, in our case studies and in the simulation study conducted as part of the project (Mercat et al., 2022) risk factors appeared to have only limited influence on the estimated probability of freedom from infection in STOC free MODEL. This can be explained by risk factors being implicitly included in the test

results of the CPs i.e. herds that purchase from non-free herds will more often have positive tests. However, it was hypothesized that risk factors may be more important for CPs that include less frequent testing or diseases for which tests are less sensitive (Madouasse et al., 2021).

Risk factors that we identified with STOC free DATA and that could be considered for inclusion in STOC free MODEL are for example purchase and herd type. Most European countries have high quality data available for these factors (Rapaliutė et al., 2021). There were also many risk factors for BVDV that were identified but that could not be included because of limitations regarding data availability and data quality. These risk factors are for example access to pasture, communal grazing and participation in shows or markets. Factors that are also worth considering for inclusion in the framework are socio-economic aspects. The need for inclusion of socio-economic aspects in the STOC free framework when used at European level is highlighted by country-level differences in awareness and attitudes towards disease control (Gunn et al., 2005). Understanding the association between farmer behavior and BVDV control at farm level could help reduce the risk of introduction or persistent infections with BVDV. It has been found that the engagement of farmers in BVDV control is important for successful eradication or maintaining freedom at the national level (Prosser et al., 2022; Evans et al., 2018). Farmers psychosocial factors were shown to be linked to BVDV control strategies e.g. farmers that did not trust other farmers were more likely to have a closed herd, farmers with a good connection with their veterinarian were more likely to adopt BVDV control measures (Prosser et al., 2022). In the STOC free framework such factors could be included as risk factors. However, these factors are often studied qualitatively what makes including them in a modeling framework such as STOC free MODEL very complex. Therefore, further research is needed to understand influences on behavior and decision making of farmers in relation to animal disease control (Biesheuvel et al., 2021), on how these factors could be included in a modeling framework and how data could be collected by researchers.

Inclusion of economic aspects in the STOC free framework

Something that is not included in the STOC free framework that might be very useful for further development and implementation are economic aspects (Evans et al., 2018; Pinior et al., 2017). BVDV is known to cause major economic losses because of decreased growth, mortality, reduced milk production and because it is immunosuppressive (Houe, 1999; Houe, 2003). These are the main reasons that many countries implemented CPs. A recent study showed that the direct milk production losses after introduction of BVDV in herds with BVDV control

were relatively small (Yue et al., 2020), probably due to the fact that the virus is detected and eradicated in these herds participating in the CP. However, CPs also give rise to costs e.g. for research, design and implementation, testing and monitoring (Howe et al., 2013). Therefore, it would be interesting to study the balance between costs and benefits. CPs with very intensive animal-level testing probably lead to a higher probability of freedom from infection compared to CPs with less frequent or pooled testing. However, the question is how confidence of freedom should be balanced with cost-effectiveness. Economic calculations could be included in a separate tool within the STOC free framework next to STOC free DATA and STOC free MODEL. STOC free DATA could be extended to also include economic parameters such as production losses and prices with which costs and benefits of the CP can be determined. In a systematic review of financial and economic assessments of BVDV control (Pinior et al., 2017) it was demonstrated that there is a lack of accurate economic studies regarding the efficiency of BVDV CPs. Comparison between available studies was difficult due to differences in methods used, different parameters and limited access of researchers to costs and benefits of control measures (Pinior et al., 2017). Recently some studies have been performed on the production losses of herds in BVDV CPs in The Netherlands (Yue et al., 2020; Yue et al., 2021). These studies can inform about important parameters that potentially need to be taken into account. Subsequently, STOC free DATA can be used to assess which countries have data available, evaluate data quality and determine the format of the data, like we did in Chapter 5 and which was described in Rapaliutė et al. (2021), to standardize data collection on economic aspects. Then a tool should be developed that calculates the costs/benefit ratio for CPs linked to STOC free MODEL that calculates the probability of freedom for these CPs. This could help optimizing CPs in order to reach the most optimal cost/benefit ratio with a desirable level of freedom from infection.

Realizing a sustainable framework

To ensure a sustainable framework, it could be explored whether there is the possibility to have the European Food Safety Authority (EFSA) disseminate results and stimulate the use of the STOC free framework. The STOC free project was financed by EFSA and the STOC free framework facilitates some of EFSA's tasks i.e. the promotion of standardized data collection related to animal health and the development and assessment of tools for control of animal diseases. EFSA supports many activities to facilitate these tasks, such as the SIGMA project (Zancanaro et al., 2019). In this project, the data collection process by MS on animal diseases is optimized to support analysis and reporting by EFSA (Zancanaro et al., 2019). They aim to automate the collection of data that need to be submitted to EFSA

and provide MS with tools to automatically generate national reports on animal health and surveillance. This would increase the quality and comparability of data between MS and also easily keep data up to date for analysis (EFSA, 2018). I would recommend to explore possibilities to share knowledge and maybe even combine or link the SIGMA data model and STOC free framework. For example one of the tasks in SIGMA is inclusion of animal movement data. These are data that can also be included in STOC free MODEL as risk factor information. If these data are already collected by SIGMA and it could be facilitated that these data are automatically loaded into the STOC free framework in the right format, this could save users of the STOC free framework time. Further collaboration with EFSA and potentially the SIGMA project could be a great opportunity to use the STOC free framework to support continuous improvement of disease control programmes in the EU.

Concluding remarks

In this thesis, an output-based framework to determine the probability of freedom from infection was developed and evaluated. The data collection tool, STOC free DATA, is applicable to a range of cattle diseases and countries. STOC free MODEL has been applied to BVDV and is currently evaluated by multiple research groups for application to other infections such as Johne's disease and salmonella. Adapting the framework to other diseases is expected to be easier when there is only one latent disease status e.g. presence of antibodies and for diseases for which the data correspond to the modelled disease dynamics i.e. SIS model. It is recommended to apply STOC free DATA before running the model although it requests more input data than actually needed to run STOC free MODEL. Application of STOC free DATA will help to understand the infection dynamics and the structure of CPs. In this general discussion, some issues were brought forward that need consideration when these types of tools are used for other diseases and suggestions were made for further development of the framework. Currently, the STOC free framework is one of the methods that are further investigated in the SOUND control project (Costa et al., 2020).

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Summary

Traditionally, input-based standards were applied for animal disease surveillance in the EU, meaning that EU legislation prescribed exactly what needed to be done in terms of control, surveillance or eradication i.e. a fixed study design, sampling scheme and type of tests that needed to be performed. In recent years there has been a slight shift towards output-based standards, meaning that what needs to be done is not prescribed, but rather what must be achieved e.g. a defined surveillance sensitivity or a certain level of confidence of freedom from disease. This means that countries or regions could implement differently designed control programmes (CP) as long as they achieve the required output. The aim of this thesis was to develop and test a generic output-based framework to determine the probability of freedom from Bovine Viral Diarrhea virus (BVDV) infection in cattle herds.

STOC free framework

The research presented in this thesis was part of the STOC free project, which stands for the development of a Surveillance analysis Tool for Outcome-based Comparison of the confidence of FREEdom and was a collaborative project between six countries. The vision behind the STOC free project and the proposed end result were described in **Chapter 2**. The aim of STOC free was to develop and validate a framework that enables a transparent and standardized comparison of confidence of freedom in CPs across herds, regions or countries. The STOC free framework was intended to consist of a model (STOC free MODEL) combined with a tool to facilitate the collection of the necessary parameters (STOC free DATA). BVDV was chosen as an example disease because of the difference in disease status ranging from endemic to free, the variety of control programmes for BVDV in Europe and the complexity of infection with transiently (TI) and persistently infected (PI) cattle.

Context and risk factors

For the development of the STOC free framework an understanding of the CPs and transmission of BVDV in different countries was essential. Therefore, in **Chapter 3**, we described and qualitatively compared elements of CPs that contribute to confidence of freedom from infection. An existing tool, the RISKSUR tool, was used to describe heterogeneous BVDV CPs in 6 European countries: Germany, France, Ireland, the Netherlands, Sweden, and The United Kingdom (Scotland). The tool was expanded to also include aspects about disease control and the

context situation in each country i.e. prevalence and risk factor occurrence. For the six participating countries, we ranked all individual elements of the CPs and their contexts that are known to influence the probability that cattle from a herd categorized as BVDV-free are truly free from infection. Many differences in the context and design of BVDV CPs were found. As examples, CPs were either mandatory or voluntary, resulting in variation in risks from neighboring herds, and risk factors such as cattle density and the number of imported cattle varied greatly between study regions. Differences were also found in both testing protocols and definitions of freedom from infection. These results highlighted the need for a standardized practical methodology to objectively and quantitatively determine confidence of freedom from infection resulting from different CPs around the world.

To obtain generic estimates that could be used as input data for STOC free MODEL, **Chapter 4** provides a systematic search to identify papers that considered risk factors for BVDV infection in cattle followed by a meta-analysis of risk factors for the presence of BVDV in cattle herds in Europe. Selection of papers eligible for quantitative analysis was performed using a predefined checklist. Inclusion criteria were: (1) appropriate region i.e. studies performed in Europe, (2) representativeness of the study population, (3) quality of statistical analysis, and (4) availability of sufficient quantitative data. In total, 18 observational studies were selected. Data were analyzed by a random effects meta-analysis to obtain pooled estimates of the odds of BVDV infection. Significantly higher odds were found for dairy herds (OR=1.63, 95% CI: 1.06-2.50) compared to beef herds, for larger herds (OR=1.04 for every 10 extra animals in the herd, 95% CI: 1.02-1.06), for herds that participated in shows or markets (OR=1.45, 95% CI: 1.10-1.91), for herds that introduced cattle into the herd (OR=1.41, 95% CI: 1.18-1.69) and for herds that shared pasture or had direct contact with cattle of other herds at pasture (OR=1.32, 95% CI: 1.07-1.63). These pooled values must be interpreted with care, as there was a high level of heterogeneity between studies. However, they do give an indication of the importance of the most frequently studied risk factors and these values can be used as default values in STOC free MODEL when no country-specific data are available.

Evaluation of the STOC free framework

The STOC free framework, consisting of STOC free DATA and STOC free MODEL, was evaluated in **Chapter 5** and **Chapter 6**. **Chapter 5** presents the key learnings from the process of the development of the STOC free DATA tool. This tool was developed to evaluate data availability and quality and to

collect actual input data required for STOC free MODEL. Initially, the tool was developed for assessment of freedom from BVDV in six Western European countries. This tool was then further generalized to enable inclusion of data for other cattle diseases i.e. infectious bovine rhinotracheitis (IBR) and Johne's disease and for use throughout Europe. The developed online data collection tool includes a wide range of variables that could reasonably influence confidence of freedom from infection, including those relating to cattle demographics, risk factors for introduction and characteristics of disease control programmes. The results highlight the fact that the data collection tool can be generalized to different cattle diseases. However, there are large differences in data availability and comparability across European countries, presenting challenges to the interpretation of the results from the standardized data collection tool. Nevertheless, STOC free MODEL only requires longitudinal test data from CPs, thus every country with a BVDV CP can run the model on these data.

In **Chapter 6**, STOC free MODEL, a Bayesian Hidden Markov model, that was developed by the French partners in the STOC free project was applied to BVDV field data from CPs based on ear notch samples of newborn calves in four study regions. The aim of this study was to estimate the probability of herd-level freedom from BVDV. We additionally evaluated the sensitivity of the parameter estimates such as herd-level test sensitivity and specificity, probability of introduction of infection and predicted probabilities of freedom from infection to the prior distributions. First, default priors were used in the model to maximize the comparability 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 closest to reality. The complement of the probability of infection, the probability of freedom from infection, for dairy herds that were free from BVDV according to each study region's CP was predicted to be very high for all study regions ranging from 0.98 to 1.00, regardless of the use of default or country-specific priors. The parameters herd-sensitivity and the probability of remaining infected were more sensitive to the priors compared to the other output parameters, due to the low prevalence and incidence of BVDV in the study regions. For BVDV, including risk factors within STOC free MODEL did not have much influence on the probability of freedom from infection, which is probably because risk factor occurrence was implicitly included in the test results of the CPs. However, for other routes of BVDV CPs or other diseases with less frequent testing or less sensitive tests, risk factors might become more important. The advantage of STOC free model over other methods is that actual data from the

CP can be used, estimates are easily updated when new data becomes available and the probability of freedom from infection is not just a point estimate but includes a credibility interval.

Discussion

In **Chapter 7**, the main results of this thesis and some important aspects related to the STOC free framework and output-based surveillance were discussed. It describes the main challenges that we faced when applying STOC free MODEL to BVDV field data. Diseases can be modelled with STOC free MODEL when the diagnostic tests aim at detection of the same disease status, prior definitions are clearly described and the biology of the disease is represented in the data. Before the STOC free framework can be used by the intended end-users e.g. Animal Health Services, uptake by the scientific community is needed to further test and refine the tool. An easy to use interface to guide users through every step of the framework would be helpful. It could be considered to also include socio-economic risk factors. To ensure a sustainable framework, EFSA may be involved in dissemination of the results and stimulation of the use of the STOC free framework. To conclude, the data collection tool, STOC free DATA, is applicable to a range of cattle diseases and countries. The STOC free model can be used to evaluate and improve BVDV CPs and to determine whether they comply with output-based regulations of the EU. The tool is currently evaluated by multiple research groups for application to other infections such as Johne's disease and salmonella.

Nederlandse samenvatting

Surveillance van dierziekten in de EU berustte veelal op middelvoorschriften ("input-based"), wat betekent dat de EU-wetgeving precies voorschreef wat er moest gebeuren op het gebied van bestrijding of surveillance. Zo werd er voorgeschreven welke onderzoeksopzet, bemonsteringsschema's en type tests uitgevoerd dienden te worden. In de afgelopen jaren is er meer nadruk gekomen op surveillance met resultaatvoorschriften ("output-based"). Dit houdt in dat niet langer wordt voorgeschreven wat er moet gebeuren, maar wat er moet worden bereikt. Dit is bijvoorbeeld een vastgestelde gevoeligheid van het surveillancesysteem of een bepaalde zekerheid over het vrij zijn van een infectie in het land. Dit betekent dat landen hun eigen ontworpen controleprogramma's (CP's) zouden kunnen implementeren, zolang ze de vereiste resultaten bereiken. Het doel van dit proefschrift was om een generieke methode te ontwikkelen en testen waarmee de kans op het vrij zijn van Bovine Virale Diarree virus (BVDV) infectie op rundveebedrijven kon worden bepaald.

De STOC free tool

Het onderzoek dat is beschreven in dit proefschrift maakt deel uit van het STOC free project. STOC free staat in het Engels voor "Surveillance analysis tool for Outcome-based Comparison of the confidence of FREEdom" en betekent dat de focus van het onderzoek lag op de ontwikkeling van methodieken die kunnen evalueren of controle programma's voldoen aan resultaatvoorschriften. Dit onderzoek was een samenwerkingsverband tussen zes landen. De visie achter het STOC free project en het verwachtte eindresultaat zijn beschreven in **Hoofdstuk 2**. Het doel van STOC free was om een methode te ontwikkelen en valideren die op transparante en gestandaardiseerde wijze kan bepalen hoe vrij van ziekte bedrijven, regio's of landen zijn met verschillende CP's. Het was voorzien dat deze methode zou gaan bestaan uit een model (STOC free MODEL) gecombineerd met een hulpmiddel voor data verzameling (STOC free DATA). BVDV werd gekozen als voorbeeldziekte door de verschillen in ziektestatus tussen landen, variërend van endemisch tot vrij, de variëteit aan CP's voor BVDV in Europa en de complexiteit van de infectie met transiënte (tijdelijke) en persistente infecties in runderen.

Context en risicofactoren

Voor de ontwikkeling van de STOC free methode was het essentieel om inzicht te krijgen in de CP's, de risicofactoren voor insleep en incidentie en prevalentie van BVDV in verschillende landen. Om deze reden hebben we in **Hoofdstuk 3**

de elementen van CP's die bijdragen aan de betrouwbaarheid van de vrij status van infectie beschreven en kwalitatief vergeleken. Dit werd gedaan voor zes Europese landen (Duitsland, Frankrijk, Ierland, Nederland, Zweden en Groot-Brittannië (Schotland)) met behulp van een bestaande methode, de RISKSUR tool. Deze tool werd uitgebreid zodat ook aspecten van dierziektebestrijding en de context situatie, namelijk prevalentie en risicofactoren, in elk land meegenomen konden worden. Alle individuele elementen van CP's en hun context, waarvan bekend is dat ze de kans dat een BVDV-vrij gecertificeerd bedrijf werkelijk vrij van infectie is kunnen beïnvloeden, hebben we gerangschikt. Er werden veel verschillen gevonden in de context en het ontwerp van BVDV CP's. Controle programma's waren bijvoorbeeld verplicht of vrijwillig, wat resulteerde in variatie in risico's van direct diercontact, en ook risicofactoren zoals veedichtheid en het aantal geïmporteerde runderen varieerden sterk tussen de landen. Er werden ook verschillen gevonden in zowel testprotocollen als definities voor vrijheid van infectie. Deze resultaten benadrukten de behoefte aan een gestandaardiseerde, praktische tool om objectief en kwantitatief de betrouwbaarheid van een vrij status van infectie als gevolg van verschillende CP's te bepalen.

Om standaardwaarden te verkrijgen als invoerparameters voor STOC free MODEL, beschrijft **Hoofdstuk 4** een systematische review van wetenschappelijk onderzoek naar risicofactoren voor BVDV infectie op rundveebedrijven, gevolgd door een meta-analyse. Studies werden geselecteerd voor kwantitatieve analyse met behulp van een vooraf gedefinieerde checklist. Criteria om een studie mee te nemen in ons onderzoek waren: (1) studies beschrijven de situatie in Europa, (2) representativiteit van de onderzoekspopulatie, (3) kwaliteit van statistische analyse en (4) beschikbaarheid van voldoende kwantitatieve gegevens. In totaal werden 18 observationele studies geselecteerd. De data werden geanalyseerd door middel van een random-effect meta-analyse om gepoolde schattingen van de kans op BVDV infectie te verkrijgen. Significant hogere odds ratio's werden gevonden voor melkveebedrijven (OR=1,63, 95% BI: 1,06-2,50) in vergelijking met vleesveebedrijven, voor grotere bedrijven (OR=1,04 voor elke 10 extra dieren, 95% BI: 1,02-1,06), voor bedrijven die deelnamen aan keuringen of markten (OR=1,45, 95% BI: 1,10-1,91), voor bedrijven die runderen aankochten (OR=1,41, 95% BI: 1,18-1,69) en voor bedrijven waar runderen op de weide direct contact konden hebben met runderen van andere bedrijven (OR=1,32, 95% BI: 1,07-1,63). Deze gepoolde waarden moeten met zorg worden geïnterpreteerd, aangezien er een hoge mate van heterogeniteit was tussen de studies, wat betekent dat de

achtergrond van de studie in een grote mate verschillend was. Ze geven echter wel een indicatie van het belang van de meest bestudeerde risicofactoren en kunnen worden gebruikt als standaardwaarden in STOC free MODEL wanneer er geen land-specifieke gegevens beschikbaar zijn.

Evaluatie van de STOC free tool

De STOC free methode, bestaande uit STOC free DATA en STOC free MODEL, werd getest in **Hoofdstuk 5** en **Hoofdstuk 6**. **Hoofdstuk 5** presenteert de belangrijkste lessen die we geleerd hebben uit het ontwikkelingsproces van STOC free DATA. Deze methode is ontwikkeld om de beschikbaarheid en kwaliteit van data te evalueren en om input data te verzamelen voor STOC free MODEL. In eerste instantie was de tool ontwikkeld voor het beoordelen van vrijheid van BVDV in zes West-Europese landen. Deze tool werd vervolgens verder gegeneraliseerd voor gebruik in andere landen in Europa en andere rundveeziekten, d.w.z. infectieuze boviene rhinotracheïtis (IBR) en paratuberculose. De online data collectie tool omvat een breed scala aan variabelen die redelijkerwijs van invloed kunnen zijn op vrijheid van infectie, zoals variabelen met betrekking tot de demografie van runderen, risicofactoren voor introductie van infectie en kenmerken van CP's. De resultaten lieten zien dat de data collectie tool kan worden gegeneraliseerd naar verschillende rundveeziekten. Er zijn echter grote verschillen in de beschikbaarheid en daarmee de vergelijkbaarheid van data tussen Europese landen, wat een uitdaging vormt voor de interpretatie van de resultaten van de data collectie tool. Desalniettemin vereist STOC free MODEL alleen longitudinale testresultaten uit CP's en kan dus elk land met een BVDV CP het model op deze data toepassen.

In **Hoofdstuk 6**, werd STOC free MODEL, een Bayesiaans Hidden Markov model, dat is ontwikkeld door de Franse partners, toegepast op BVDV velddata van CP's gebaseerd op het testen van oorbiopten van pasgeboren kalveren op BVDV in vier landen. Het doel van deze studie was om op bedrijfsniveau de kans op vrijheid van BVDV te schatten. Daarnaast hebben we de gevoeligheid van de parameterschattingen, zoals de testsensitiviteit en testspecificiteit op bedrijfsniveau, de kans op introductie van infectie en de kans op vrijheid van infectie, voor de a-priori-verdelingen ("priors") geëvalueerd. Eerst werden standaardwaarden voor de priors in het model gebruikt om de vergelijkbaarheid van de resultaten uit het model tussen landen te vergroten. Daarna werden land-specifieke priors gebruikt die zijn vastgesteld op basis van advies van deskundigen of historische data, om de invloed van de

priors op de resultaten te bestuderen en om land-specifieke schattingen te verkrijgen die de werkelijkheid het dichtst benaderen. Het tegenovergestelde van de kans op infectie, de kans op vrijheid, werd zeer hoog geschat voor melkveebedrijven die volgens de verschillende CP's vrij waren van BVDV. De kans op vrijheid van infectie varieerde in de verschillende landen van 0,98 tot 1,00, ongeacht het gebruik van standaard of land-specifieke priors. De parameters testsensitiviteit op bedrijfsniveau en de kans voor bedrijven om besmet te blijven tussen twee maanden waren gevoeliger voor de verandering in priors dan de andere uitkomst parameters. Dit komt waarschijnlijk door de lage infectieprevalentie en incidentie van BVDV in de data van de vier landen. Voor BVDV had het includeren van risicofactoren in STOC free MODEL niet veel invloed op de kans op vrijheid van infectie, wat waarschijnlijk komt doordat de risicofactoren impliciet opgenomen zijn in de testresultaten van de CP's. Voor andere routes van BVDV CP's of andere infectieziekten met een minder frequent testschema of minder gevoelige tests, kunnen risicofactoren wel van invloed zijn. Het voordeel van het STOC free model ten opzichte van andere methoden is dat data van het CP kunnen worden gebruikt. Daarmee kunnen schattingen gemakkelijk kunnen worden bijgewerkt wanneer nieuwe data beschikbaar komt. Een ander voordeel is dat de kans op vrijheid van infectie op basis van het STOC free Model niet slechts een puntschatting is, maar een betrouwbaarheidsinterval omvat.

Discussie

In **Hoofdstuk 7**, werden de belangrijkste resultaten van dit proefschrift en een aantal belangrijke aspecten van de STOC free methode en op resultaat gerichte surveillance besproken. Het beschrijft de belangrijkste uitdagingen waarmee we werden geconfronteerd bij de ontwikkeling van het model en het daaropvolgend toepassen van STOC free MODEL op BVDV velddata. Infectieziekten kunnen worden gemodelleerd met STOC free MODEL wanneer de diagnostische tests gericht zijn op het detecteren van dezelfde ziekte status, wanneer definities van priors duidelijk zijn beschreven en de biologie van de ziekte op een juiste en volledige manier in de data wordt weergegeven. Voordat de STOC free methode gebruikt kan worden door de beoogde eindgebruikers, zoals gezondheidsdiensten of andere uitvoerende instanties van CP's, is opname door de wetenschappelijke gemeenschap nodig om de tool verder te testen en te verfijnen. Een eenvoudig te gebruiken interface om gebruikers door elke stap van de methode te leiden zou nuttig zijn. Voor een verdere ontwikkeling zou kunnen worden overwogen om ook sociaaleconomische factoren op te nemen. Om een duurzame tool te

garanderen, kan EFSA betrokken worden bij het verspreiden van de resultaten van de STOC free methode en het stimuleren van gebruik van de methode. In conclusie, de STOC free methode kan gebruikt worden om BVDV CP's te evalueren en te verbeteren en om te bepalen of ze voldoen aan de op resultaat gerichte regelgeving van de EU. De tool wordt momenteel geëvalueerd door meerdere onderzoeksgroepen voor toepassing op andere infecties zoals paratuberculose en salmonella.

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Curriculum Vitae

Annika van Roon was born on 30 March 1988 in Amsterdam, the Netherlands. After attending high school at Damstede in Amsterdam, she moved to 's-Hertogenbosch to study Animal Husbandry at the HAS University of Applied Sciences. In her third year she did two research internships abroad. One at Monarto Zoo in Australia where she studied social behavior between chimpanzees and mating behavior of Tasmanian devils, and one at Marineland in New Zealand where she studied regurgitation and reingestion behavior of California sea lions. This is where her enthusiasm for research began. She graduated in 2011 and started the Master Animal Sciences at Wageningen University. She did her minor thesis for the department of Communication Strategies at Wageningen University where she studied the identity and responsibility work by stakeholders of the Q-fever outbreak. She finished her Master study with a major thesis at the Institute for Public Health and the Environment (RIVM) at which she studied risk factors for the spread of *Echinococcus multilocularis* in red foxes, dogs and rodents in the Netherlands. After some detours, Annika started to work as a junior researcher at the Centre for Zoonoses and Environmental Microbiology at the RIVM in 2015. Here she performed research on zoonoses with a focus on wild animal populations and livestock. In 2017, Annika started her PhD at the Department of Farm Animal Health of the Faculty of Veterinary Medicine of Utrecht University in collaboration with the epidemiology group of Royal GD in Deventer. The results of this work are described in this thesis. Currently, Annika is employed as a researcher on COVID-19 at the Centre for Infectious Diseases, Epidemiology and Surveillance at the RIVM.

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