Simulation modelling to support national policy making in the control of bovine herpesvirus 1

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Simulation modelling to support national policy making in the control of bovine herpesvirus 1.
Ontwikkeling en toepassing van simulatiemodellen ter ondersteuning van nationaal beleid inzake de bestrijding van bovine herpesvirus 1.

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Abstract
Bovine herpesvirus 1 (BHV1) is the causative agent of infectious bovine rhinotracheitis (IBR), a respiratory disease in cattle. Increased international legislation, together with a high prevalence of BHV1 infected cattle in The Netherlands, put pressure on Dutch livestock industry to eradicate BHV1. The main objective of this thesis was the development and application of simulation models to support policy makers in various phases of the decision-making process with respect to a national BHV1 eradication programme in The Netherlands. To meet this objective, three simulation models were developed. First, a state-transition model was developed to evaluate the epidemiological and economic consequences of various control strategies for endemic BHV1 in The Netherlands. Based on international developments and results of this model, a compulsory vaccination programme for BHV1 was implemented in The Netherlands in May 1998. According to model outcome, this programme was expected to reduce the prevalence of infected dairy cattle to 5% in about 5 years, with expected direct costs approximately EUR 100 million, a pay-back period of about 8 years and less than 1% outbreaks per year on certified BHV1-free herds. A second model, classified as spatial, dynamic and stochastic, was developed to evaluate control strategies for outbreaks in a BHV1 free country. Results showed that farm type with first introduction of BHV1 had a considerable impact on the number of secondarily infected farms and total costs. To support policy makers during the eradication programme, the epidemic model was adapted for an endemic situation, resulting in the third model called 'InterIBR-endemic'. This model closely interacted with a BHV1 monitoring programme. As part of internal validation, various experiments with this model were performed to improve understanding of model behaviour. To support sensitivity analysis, the techniques of experimental design and metamodelling were applied to help set priorities for further epidemiological research. The uncertainty of the yearly reactivation rate of latently infected animals affected the costs by EUR 43 million, which is about 40% of the expected total costs. Also, survival analysis was applied to quantify the association between farm characteristics and the risk of certificate loss during simulation. Early 1999, compulsory vaccination in The Netherlands was postponed due to contamination of live marker vaccine with bovine virus diarrhoea virus.

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Voorwoord

In 1995 klopte ik bij Aalt Dijkhuizen aan met de vraag of er mogelijkheden waren voor een zesmaands afstudeervak. “Iets met IBR-bestrijding bijvoorbeeld”, dat was actueel. Destijds kon ik niet vermoeden dat het IBR-virus mij nog jarenlang zou bezighouden, wat zeven jaar later zelfs zou resulteren in de afronding van dit promotieonderzoek. Na het uitvoeren van een vervolgproject op het afstudeervak leek het vanzelfsprekend dat ik na mijn afstuderen in 1998 het IBR-onderzoek in de vorm van een promotieonderzoek bij Agrarische Bedrijfseconomie voortzette. Toch is het werk beschreven in dit ‘boekje’ beslist niet vanzelfsprekend tot stand gekomen. De goede samenwerking met en enthousiasme van vele personen zijn daarbij van groot belang geweest. Al deze mensen wil ik dan ook van harte bedanken, een aantal in het bijzonder.

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Antonie Vonk Noordegraaf
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Contents

Chapter 1

General introduction

1.1 Introduction

Bovine herpesvirus 1 (BHV1) is the causative agent of infectious bovine rhinotracheitis (IBR), a respiratory disease in cattle which is characterised by acute inflammation of the upper respiratory tract (Engels and Ackermann, 1996). Acute infection with BHV1 can result in severe production losses, abortion and mortality (Wiseman et al., 1978; Wiseman et al., 1979). The original cases of IBR were first observed in cattle housed under feedlot conditions in Colorado in 1950 and within a few decades outbreaks of IBR were observed world wide (Straub, 1990). Differences in livestock production systems and measures to control BHV1 between countries have resulted in a diversity of BHV1 prevalence (Ackermann et al., 1990a). Countries free of BHV1 can impose restrictions on import of cattle and cattle products, since introduction of the virus into these countries can lead to major outbreaks and severe economic losses. These restrictions are in agreement with international rules of trade, as defined in the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) of the World Trade Organisation (WTO) in 1994 (Marabelli et al., 1999; Zepeda et al., 2001).

Within the European Union (EU) directives have also been set up to allow member states to stipulate requirements to be met for the import of cattle, semen and embryos (EU directives 64/432, 88/407 and 93/60). Furthermore, since 1999 only BHV1-free bulls have been allowed at artificial insemination centres in EU countries. Within the EU, Denmark, Finland, Sweden, Austria and the province of Bolzano in Italy are recognised as free from BHV1 under EU legislation (Commission Decision 93/42/EEC). Other EU countries have also started to control BHV1, but there is great diversity of control programmes between countries and even within countries (pers. comm. Gevaert, D., 2001; pers. comm. Bielsa, J.M., 2001).

In The Netherlands, clinical signs of IBR were observed early 1973 for the first time (Van Nieuwstadt and Verhoeff, 1983). High intensity of animal trade and contacts between farms, together with wide use of traditional vaccines to prevent clinical symptoms, have been favourable conditions for the virus to become endemic. Early 90's about 85% of the dairy herds had one or more infected animals (Van Wuijkhuise et al., 1998). As the infection became endemic, the severity of clinical signs in The Netherlands decreased (De Wit et al., 1998; Hage et al., 1998; Van Schaik et al., 1999a). Since Dutch livestock production strongly depends on international trade of cattle and cattle products (Tazelaar and Gerats, 1995), international developments described above have put pressure on the Dutch livestock industry to eradicate BHV1 in The Netherlands.

1.2 Characteristics of BHV1

An important characteristic of BHV1 is the ability to establish latent infection in the neuronal cells of the sensory ganglia (Ackermann et al., 1990a). Latent virus can be reactivated and shed into the environment (Hage et al., 1996). Therefore, once infected with BHV1, an animal must be regarded as a lifelong risk to BHV1-free herd mates (Pastoret et al., 1984). Reactivation and re-excretion of latent BHV1 can be triggered by several stimuli related to physical and social stress, such as transport (Thiry et al., 1987), infections with *Dictyocaulus viviparus* (Msolla et al., 1983), parturition (Thiry et al., 1985) and treatment with high doses of corticosteroid (Kaashoek et al., 1996)

Cattle excreting BHV1 can infect herd mates by direct nose-to-nose contact and by coughing or sneezing aerolized droplets over relatively short distances (Wentink et al., 1993; Mars et al., 1999; Mars et al., 2000a). Introduction of BHV1 into a BHV1-free herd often results in most cattle being infected within a few weeks (Wentink et al., 1993; Hage et al., 1996). Transmission of BHV1 between herds is believed to be mainly due to introduction of cattle in the acute phase of infection and to introduction of latently infected cattle (Straub, 1990). Also indirect contacts, such as contaminated semen, humans, contaminated materials and airborne transmission can play a role (Wentink et al., 1993).

1.3 Tools for BHV1 eradication

Detection methods with high sensitivity and specificity are available to detect BHV1 antibodies, both in serum and milk (Kramps et al., 1994). In some countries with a low prevalence of BHV1, such as Denmark and Switzerland, the virus has been eradicated by identifying and removing infected cattle from the population, followed by surveillance of the free status (Ackerman et al., 1990b; Nylin et al., 1998). In countries with a high prevalence of BHV1 infected cattle, a 'test-and-cull' strategy is economically not feasible nor ethically acceptable. It will, therefore, be more feasible to start eradication of BHV1 with control measures that lower the incidence of outbreaks and thereby the prevalence of infection.

Control measures to reduce the incidence of outbreaks should focus on preventive actions that reduce both the number and the risk of contacts between infected and non-infected farms. The number and risk of contacts between herds can be reduced by application of more closed farming systems in combination with bio-security measures (Van Schaik et al., 1999b). Another important tool that can be used in an eradication programme is vaccination. To eradicate a pathogen, vaccination must be able to increase herd immunity (Stegeman, 1995). Herd immunity can be achieved by reducing the susceptibility of an individual against

infection and by reducing the infectivity after the occurrence of an infection (De Jong and Bouma, 2001).

When massive vaccination is applied in an eradication programme, it is essential to be able to differentiate cattle infected by the wild-type virus from cattle that have been vaccinated (Strube et al., 1996). Whereas traditional BHV1 vaccines did not have this property, marker vaccines and companion diagnostic tests have been developed that enable this differentiation (Kaashoek et al., 1995; Van Oirschot et al., 1996; Wellenberg et al., 1998). The first marker vaccines developed and applied on a large scale were those against pseudorabies virus (PRV) and those vaccines have shown to be a very effective tool in eradication (Stegeman, 1995; Van Nes et al., 1996). For BHV1, both live (attenuated) and killed (inactivated) marker vaccines have been tested for their safety and efficacy in vaccination challenge experiments, transmission experiments and under field conditions (Kaashoek and Van Oirschot, 1996; Bosch et al., 1997; Bosch et al., 1998; Van Oirschot, 1999; Mars et al., 2000b; Mars et al., 2001). Field trials with killed and live marker vaccine showed that both vaccines significantly reduced the transmission ratio R_0 (De Jong and Kimman, 1994) in vaccinated herds, but not sufficiently enough to prevent the occurrence of major outbreaks within herds (Bosch et al., 1998; Mars et al., 2001). Whether the observed reduction of within herd transmission will be enough to achieve eradication at a national level will, therefore, also depend on the rate of contacts between herds.

1.4 Simulation as a decision support tool for BHV1 control

Because of the high prevalence of BHV1 in The Netherlands and international regulations as described in section 1.1, the availability of BHV1 marker vaccines in the 90's induced a new discussion on opportunities to eradicate BHV1 (Miedema, 1995; Franken, 1999). Proposed strategies in this discussion ranged from continuation of voluntary vaccination on the one side to compulsory vaccination for all herds on the other, with in between a variety of alternatives to these strategies, such as vaccination exemption for certified BVH1-free herds. The most important question raised at that time was which strategy would be able to eradicate BHV1 most cost-effectively, while meeting the criteria of farmers' support and operational feasibility.

To determine the most appropriate, technically feasible and economically sound control strategy, quantification of each strategy - in both economic and epidemiological terms - is required (Perry et al., 2001). When dealing with disease control strategies that cannot easily be implemented and evaluated for their effectiveness in the field, a useful tool to support the decision-making process is the development of a model that combines both epidemiological and economic (lack of) knowledge to explore 'what-if' scenarios (Dijkhuizen and Morris,

1997). Simulation modelling has frequently been applied to support decision-making regarding disease control, both at the individual farm level (e.g. Sørensen et al., 1995; Van der Fels-Klerx et al., 2000) and at a regional or national level (Berentsen et al., 1992; Saatkamp et al., 1996; Buijtels et al., 1997; Jalvingh et al., 1999; Mangen et al., 2001). Simulation can be defined as the imitation of a real world system and usually involves the generation and analysis of an artificial history of the system, to draw inferences concerning the real system that is represented (Banks, 1998). Dijkhuizen and Morris (1997) distinguish three important functions of modelling: 1) to provide an objective basis for assessing and assimilating available information about the system, 2) to detect where essential knowledge of the system is inadequate and 3) to assist in the management control of the system. When using models to support decision-making, special attention must be paid to validation, which must determine whether the simulation model is an accurate representation of the real world that is simulated (Kleijnen, 1995).

1.5 Implementation of BHV1 eradication programme in The Netherlands

Based on EU developments concerning discussion on BHV1 eradication and on results of models described in this thesis, a compulsory eradication programme for BHV1 was implemented in The Netherlands in May 1998. The main reasons to start this programme were, in order of priority (Landbouwschap, 1996):

1- EU regulation for embryos and semen
2- Regulation for international trade of cattle
3- Voluntary programme not likely to result in eradication of BHV1
4- Preventive measures with regard to animal contacts and bio-security will also affect other infectious diseases
5- Outbreaks of BHV1 result in direct economic losses for individual farms

The Dutch eradication programme was primarily based on compulsory half-yearly vaccination with marker vaccine of all cattle older than three months, with exemption of cattle on beef and veal farms and BHV1-free certified herds. A herd could obtain the BHV1-free status if individual blood tests showed that the herd was free of BHV1, or after removal of a few infected cattle. Certified BHV1-free herds were only allowed to purchase cattle from other certified BHV1-free herds, the free status was monitored by monthly bulk-milk tests on dairy herds and half-yearly serological sampling on non-dairy herds. Beef and veal farms, defined as farms with no female cattle older than one year, were only exempted from vaccination if cattle left to the slaughterhouse. During the eradication programme, progress was evaluated by a BHV1 monitoring programme, which aimed to get insight into the incidence of outbreaks on various farm types and the prevalence of infection over time

(Assink et al., 2001). At the start of the eradication programme in 1998, about 25% of Dutch dairy herds was certified BHV1-free and the average within herd prevalence of infected dairy cattle on non-certified herds was estimated to be 30% (Assink et al., 2001).

At the end of February 1999, vaccination against BHV1 was postponed after severe disease problems on 11 dairy farms shortly after vaccination were observed. One batch of the live BHV1 marker vaccine appeared to be contaminated with bovine virus diarrhoea virus (BVDV) type 2 (Falcone et al., 2000; Barkema et al., 2001). From a few other batches of the live BHV1 marker vaccine used in the eradication programme, BVDV type 1 could be isolated (Bruschke et al., 2001). Since then, vaccination only continued on a voluntary basis. Alternative strategies were evaluated by the models described in this thesis and proposed at more than 40 special meetings with farmers in the winter of 2000, but farmers' support was not considered sufficient to continue a compulsory programme.

1.6 Objectives of the thesis

The main objective of this thesis was the "development and application of simulation models to support policy making in various phases of the decision-making process with respect to a national BHV1 eradication programme in The Netherlands". More specifically, the main objectives of this study were to provide insight into:

1. Epidemiological and economic consequences of various control strategies for endemic BHV1 in The Netherlands;
2. Cost-effectiveness of various strategies to control BHV1 following reintroduction into The Netherlands once free of BHV1;
3. Gaps in knowledge on BHV1 spread that would have most impact on the progress and costs of the BHV1 eradication programme;
4. Model behaviour with respect to associations between farm characteristics and the loss of the BHV1-free certificate during the simulated eradication programme.

1.7 Outline of the thesis

Chapters 2 and 3 describe two simulation models that were developed and applied in an early phase of the decision-making process on BHV1 eradication in The Netherlands, before a final decision on implementation of control measures in the field was made.

Chapter 2 describes a model that was developed to evaluate various control strategies for BHV1 in The Netherlands and was used to support policy making regarding the question which strategy would be able to eradicate BHV1 most cost-effectively. The framework of this

model was based on a state-transition approach, as earlier developed to evaluate control strategies for eradication of pseudorabies virus (Buijtels et al., 1997). Results of this model were taken into account in the development and implementation phase of the Dutch BHV1 eradication programme.

Because a BHV1 eradication programme would be a large investment for the Dutch cattle sector, insight was also required into the expected consequences of reintroduction of the virus once The Netherlands would be free of BHV1 and the cost-effectiveness of various control strategies. In Chapter 3, the simulation model InterIBR-epidemic is described and applied to outbreaks in a free country. This model was based on the framework of InterSpread, a spatial, dynamic, stochastic and discrete simulation model originally developed for outbreaks of foot-and-mouth disease (Sanson et al., 1993; Jalvingh et al, 1995).

To support policy makers during the course of the eradication programme, two complementary decision support tools were developed: (1) a BHV1 monitoring programme to evaluate the observed progress of the eradication in the field (Assink et al., 2001) and (2) a BHV1 simulation model to predict and evaluate the expected progress in the field. Chapter 4 describes the simulation model InterIBR-endemic, of which the development was based on experience obtained from the earlier two models. Detailed information on the population of cattle farms and animal movements between these farms in The Netherlands was analysed and implemented in the model. Furthermore, information available from the BHV1 monitoring programme was included and model output was compared with observations from the monitoring programme.

In Chapters 4, 5 and 6 various experiments with the simulation model InterIBR-endemic were performed to get more insight into the behaviour of the model, thereby also meeting objectives 3 and 4 of this study. Since the model contained many uncertain epidemiological parameters, an important step was to identify parameters that were expected to be most relevant for the progress and costs of the eradication programme. This information could then be used to set priorities for further empirical research. Chapter 5 describes how the techniques of experimental design and regression metamodelling were applied to meet this objective, as opposed to a simple sensitivity analysis which often is applied. Results and implications are presented in Chapters 4 and 5. An important aspect of the eradication programme was the loss of the BHV1-free certificate due to detection of outbreaks on certified BHV1-free herds. The rate of certificate loss can be observed both in real life and in the model. In Chapter 6, an experiment was performed to quantify associations between farm characteristics, such as density of farms in a region, and the risk of certificate loss during simulation, using the technique of survival analysis (Kleinbaum, 1996).

Chapter 7 is a general discussion on some critical steps of development and application of the simulation models presented in this thesis and the role of these models as decision

support tools in the BHV1 eradication programme. The chapter ends with recommendations for further research. A summary of the study is provided at the end of the thesis along with the main conclusions.

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Chapter 2

An epidemiological and economic simulation model to evaluate the spread and control of infectious bovine rhinotracheitus in The Netherlands

Paper by Vonk Noordegraaf, A., Buijtels, J.A.A.M, Dijkhuizen, A.A., Franken, P., Stegeman, J.A., Verhoeff, J., 1998. *Preventive Veterinary Medicine* 36, 219-238. Reproduced with permission of Elsevier Science.

Abstract

Bovine herpesvirus type I (BHV1), causing infectious bovine rhinotracheitis (IBR), was first recognised in The Netherlands in 1972. In 1993, about 42% of the dairy cows had antibodies against BHV1. In the future, stricter requirements are anticipated regarding the health status of exported breeding cows and material. To support policymakers in their decisions on IBR-eradication, a simulation model was developed in which the epidemiological and economic consequences of various control strategies were evaluated. This paper describes the model and provides an overview of some important outcomes.

In the model, dairy herds were classified into different disease states based on (1) the reproduction ratio of the disease (R, defined as the number of secondary cases caused by one infectious animal) (2) the within-herd prevalence, within each value of R and (3) the expected number of infectious animals in an infectious herd within each prevalence range. The dynamic transition probability of a herd going from one state to another per week depends on direct contacts between animals, and other contacts such as transmission through fomites, indirect transmission through other species, airborne transmission and minor disease-specific routes such as venereal or iatrogenic transmission.

Five control strategies, including a voluntary vaccination programme and a compulsory vaccination programme for all dairy herds were evaluated. A voluntary vaccination programme with 50% participation was not expected to lead to eradication of IBR. It appeared that compulsory vaccination would be necessary to reach an IBR-free status.

2.1 Introduction

Bovine herpesvirus type I (BHV1), causing infectious bovine rhinotracheitis (IBR), was first recognised in The Netherlands in 1972. Within a few years, the infection had spread over the whole country – in most cases causing severe clinical signs such as abortion, reduction in milk production and mortality (Van Nieuwstadt and Verhoeff, 1983). Gradually, the character of the disease changed from a clinical epidemic to a situation of endemicity, in which most of the infections reported were subclinical. In 1993, about 42% of the dairy cows had antibodies against BHV1 and about 85% of the herds had one or more infected animals (Van Wuijkhuise et al., 1993). As with all Alphaherpesvirinae, BHV1 has the property to induce latent infection. Therefore, an animal, once infected with BHV1, must be regarded as a potential source of the virus and is consequently a risk to BHV1-free herd mates (Pastoret et al., 1984).

In the near future, stricter requirements are expected in the European Union (EU) (and some other countries outside the EU) regarding the health status of exported breeding cows

and material. For example, from the beginning of 1999, EU legislation will require exported semen to be free of IBR. Therefore, there is a need for eradication of IBR in exporting countries such as The Netherlands. While eradication can be accomplished by culling all animals with antibodies against BHV1, this so-called 'stamping-out' method is economically infeasible, and might not be socially accepted, in countries with a high prevalence of BHV1 (Kaashoek, 1995).

Gene-deleted marker vaccines (gE-delete) and companion diagnostic tests for the disease have been described recently (Kaashoek, 1995) and allow animals infected with BHV1 to be detected in populations that have been so vaccinated. Therefore infected animals are in this study referred to as gE-positive. Bosch (1997) observed that vaccination significantly reduced transmission of BHV1. Therefore, vaccination might be a valuable tool for the eradication of the virus in BHV1-endemic countries.

The aim of this study was to develop a simulation model to evaluate different scenarios with respect to the epidemiological and economic effects of infections and control strategies to be applied at a national level – thereby assisting policymakers in their decisions on IBR-eradication. This simulation model also provides insight into the impact of uncertain epidemiological and economic input factors on the outcome of the strategies through sensitivity analysis.

2.2 Model structure and contents

2.2.1 Introduction

The structure of the model was based on a model developed for Aujeszky's disease (Buijtels, 1997). The input values used for the IBR model were based on results of experiments where possible, and on estimates of experts when experimental data were not available. To simulate the spread of animal disease and control of infections over time, the state-transition approach, based on the Markov-chain analysis, is often used (Dijkhuizen, 1989; Van der Kamp et al., 1990; Berentsen et al., 1992; Houben et al., 1993; Pasman et al., 1994; Buijtels, 1997). The key factor in this technique is the transition between disease states in which the experimental unit can exist. In this study, the unit to be modelled is a dairy herd (because the focus is on the spread of BHV1 between herds). The time unit is one week.

The population of dairy herds was divided into a number of mutually exclusive disease states, which characterise the ability of the virus to spread within a herd and the initial prevalence of infected and infectious cows. The population of herds in the different states are elements of the state vector, and the probabilities of the herds moving to a different state in the next time period are elements in a standard transition matrix (Buijtels, 1997). By

multiplying the current state vector by the transition matrix, the development of the infection over time can be simulated (Jalvingh, 1993).

2.2.2 Characterisation of herds in states

To characterise the spread of an infection, the reproduction ratio of the disease (R) is used. If R is less than 1, only a minor outbreak will occur. When R is greater than 1, however, the virus may be transmitted to most of the susceptible animals in the population: that is, a major outbreak (De Jong and Diekmann, 1992). However, shortly after introduction of the virus (when only a few animals are infected) probability processes may cut off the chain of infections even when R is above 1.

There is a distinction between the 'R within herds' (R_{ind}) and the 'R between herds' (R_{herd}). R_{ind} is the average number of infected animals caused by 1 infectious animal within a herd. R_{herd} is the average number of infected herds, caused by 1 infectious herd. In this study, R_{ind} is used as an input value to characterise the way virus will spread following introduction. The value of R_{ind} depends on the vaccination strategy applied to the herd. A field experiment indicated that R_{ind}=5.6 in a non-vaccinated dairy herd and R_{ind}=2.6 when using an inactivated vaccine (Bosch, 1997). Experimental results also suggest live vaccines give better protection against infection than inactivated vaccines (Kaashoek, 1995). Under laboratory conditions, Bosch (1997) found R_{ind} of 0.9 for the live vaccine. In this model, however, a value of R_{ind}=1.5 is used for herds vaccinated with a live vaccine, because in the field animals may become infected before they are effectively immunised. Risk factors might also be present (such as concomitant infections, stress) that could interfere with the effectiveness of vaccination or the transmission of BHV1. The choice of this value of R_{ind} for live vaccine is somewhat arbitrary, but was used to prevent overestimation of vaccine efficacy when used in the field. Currently, the live vaccine is being tested under field conditions. On the other hand inactivated marker vaccines are more efficient in reducing field BHV1 excretion after reactivation of a latent BHV1 infection than a live marker vaccine (Bosch, 1997). The two types of vaccines also differ in the number of days that infectious animals will spread virus. This, and other important input variables are listed in Appendix 2.1.

Furthermore, the spread of the infection in a herd depends on the initial prevalence of gE-positive cows within the herd. Infection induces immunity; therefore herd immunity increases as the number of gE-positive cows increases (De Jong et al., 1994). To reflect this dynamic, within each value of R_{ind}, five different gE-prevalence classes were distinguished. When virus is introduced into a herd, the number of infectious cows will depend on the prevalence of gE-positive cows and the vaccination strategy applied by the farmer. The calculation of the expected number of infectious cows per infectious herd is based on a deterministic

susceptible infectious removed-model (SIR-model, Becker, 1989). Infection of young-stock on dairy farms is not included in the model.

Table 2.1 Definition of the different disease states of dairy herds, for the strategy 'not vaccinating', 'inactivated vaccine' and 'live vaccine', in the model for infectious bovine rhinotracheitis in The Netherlands

	Not vaccinating			Inactivated vaccine			Live vaccine		
State	*R*	*% P*	*I**	*R*	*% P*	*I**	*R*	*% P*	*I**
1	5.6	0	0	2.6	0	0	1.5	0	0
2	5.6	0	2	2.6	0	2	1.5	0	1
3	5.6	0	15	2.6	0	12	1.5	0	4
4	5.6	≥0 -<20	0	2.6	≥0 -<20	0	1.5	≥0 -<20	0
5	5.6	≥0 -<20	2	2.6	≥0 -<20	1	1.5	≥0 -<20	1
6	5.6	≥0 -<20	13	2.6	≥0 -<20	8	1.5	≥0 -<20	3
7	5.6	≥20-<50	0	2.6	≥20-<50	0	1.5	≥20-<50	0
8	5.6	≥20-<50	2	2.6	≥20-<50	1	1.5	≥20-<50	1
9	5.6	≥20-<50	9	2.6	≥20-<50	3			
10	5.6	≥20-<50	0	2.6	≥50-<80	0	1.5	≥50-<80	0
11	5.6	≥50-<80	1	2.6	≥50-<80	1	1.5	≥50-<80	1
12	5.6	≥50-<80	3						
13	5.6	≥80	0	2.6	≥80	0	1.5	≥80	0
14	5.6	≥80	1	2.6	≥80	1	1.5	≥80	1

R Reproduction ratio
% P Prevalence of gE-positive cows within a herd
*I** Number of infectious animals within a herd

In short, the different states that herds can be in depend on (1) the value of R_{ind}, (2) the prevalence of gE-positive cows within a herd, within each value of R_{ind} and (3) the expected number of infectious animals in a herd within each prevalence range (Table 2.1).

2.2.3 Transition matrix

Now that the different states were defined, the transition probabilities between the different states were estimated. These probabilities are shown in a transition matrix M, which is subdivided into 4 sub-matrices (Buijtels, 1997):

$$M = \begin{vmatrix} nn & in \\ ni & ii \end{vmatrix} \qquad (2.1)$$

where

nn	herds going from non-infectious to non-infectious disease states
ni	herds going from non-infectious to infectious disease states
in	herds going from infectious to non-infectious disease states
ii	herds going from infectious to infectious disease states

In Appendix 2.2, the transition matrix is shown when no vaccination strategy is applied. The transition probabilities in sub-matrix nn, of herds going to a lower prevalence class if no infection occurs, depend on the probability of disposal of gE-positive cows. In the model this is calculated as the probability of voluntary and involuntary disposal of cows in each lactation number (Jalvingh, 1993). Sub-matrix ni shows which disease state a herd enters, the first week after introduction of the virus. The transition probabilities in the in and ii sub-matrices were based on the outcomes of the SIR-model.

The probability of herds becoming infected depends on several factors – requiring that a dynamic element be included in the calculation of the transition probabilities. The probability of non-infectious herds with disease state s to become infected in week t ($pi_s(t)$) is calculated as (Buijtels, 1997):

$$pi_s(t) = 1 - e^{-\sum_{s=1}^{14} (\gamma_s + \beta_s + \alpha_s) \times f_s(t-1)} \qquad (2.2)$$

where

$f_s(t-1)$	fraction of herds in disease state s at week (t-1)
γ	rate of virus introduction by purchase of infectious cows
β	rate of virus introduction by purchase of gE-positive cows which reactivate during transport
α	rate of virus introduction from other contacts

The sub-matrices nn and ni were multiplied by (1- $pi_s(t)$) and $pi_s(t)$, respectively, because the subclass probabilities add up to 1.

2.2.4 Introduction by purchasing infectious cows (γ)

Rate γ is a function of the number of cows purchased per week and the probability that one of these animals is infectious.

$$\gamma_s = n \times \lambda_s \qquad (2.3)$$

where

n	average number of cows purchased per week on a dairy farm
λ_s	probability of purchase of an infectious cow from a herd in disease state s

The disease states distinguished provide the expected number of infectious cows for each infectious herd. The probability of purchasing an infectious cow from a herd in state s can be calculated as:

$$\lambda_s = \frac{I^*_s}{N_s} \tag{2.4}$$

where

I^*_s expected number of infectious cows in a herd that is in disease state s

N_s number of cows in a herd that is in disease state s

2.2.5 Introduction by purchasing gE-positive cows which reactivate during transport (β)

Especially during stressful periods such as transport, the virus can reactivate and in this way be introduced on the receiving farm. Rate β_s is calculated as:

$$\beta_s = n \times \phi_s \times r \tag{2.5}$$

where

n average number of cows purchased per week on a dairy farm

ϕ_s probability of purchase of a gE-positive cow, from a herd in state s (this probability is equal to the prevalence in that herd).

r probability of a gE-positive cow reactivating during transport, followed by transmission of the virus on the receiving farm

2.2.6 Introduction by other contacts (α)

Virus can also be spread from an infectious to a non-infectious herd by other contacts, such as transmission through fomites, indirect transmission through other species, airborne transmission and disease-specific routes such as venereal or iatrogenic transmission.

$$\alpha_s = \frac{I^*_s}{N_s} \times o \tag{2.6}$$

where

o the number of herds to which virus is delivered per week through other contacts by a herd with 100% infectious animals.

2.2.7 Addition of reactivation in the farm's own herd

Besides reactivation of the virus in gE-positive cows during transport, it can also take place in the farm's own herd during calving, illness and other stress-prone activities. Depending on

the contact rate between animals and the amount of virus shed, gE-negative cows in the herd can be infected. By assuming a linear relationship between the within-herd prevalence of gE-positive cows and the probability of reactivation in a herd that is in disease state s in week t ($React_s(t)$), the following formula was derived:

$$\text{React}_s(t) = P_s(t) \times \frac{1}{(R_{100\%} \times 52)} \tag{2.7}$$

where

$P_s(t)$ prevalence of gE-positive cows in a herd that is in state s in week t

$R_{100\%}$ expected number of years before reactivation occurs on a farm with 100% gE-positive cows

52 number of weeks in a year

2.2.8 Subdivision into herd-types

An important risk factor for the health status of a herd is the purchase of cows, because these cows can excrete or be latent carriers and infect other cows. There is a wide variation among herds in the number of cows purchased each year. To take this variation into account, herds were divided into three types, depending on the average number of cows purchased per year (open ≥ 2, open <2 and closed, see Appendix 2.1). By including these different herd-types and adding the reactivation in the farm's own herd, the basic formula can be expanded as follows:

$$pi_{js}(t) = 1 - e^{-\left(\sum_{s=1}^{14} \left\{\frac{(\gamma_s + \beta_s)}{N_j} + \frac{\alpha_s}{N}\right\} \times x_s(t-1)\right)} + \text{React}_s(t) \tag{2.8}$$

where

$x_s(t-1)$ number of herds with state s in week t-1

N_j total number of herds with which herd-type j has animal contacts

N total number of herds in the population

Note that in theory, pi_{js} can exceed 1 because of $React_s(t)$. In this case pi_{js} is set equal to 1. Now the transition probabilities in the sub-matrices nn and ni can be calculated for each week. The values for the parameters r, o and $R_{100\%}$ were based on estimates of experts and knowledge of the prevalence of gE-positive cows in different herd-types in The Netherlands (Appendix 2.1).

2.2.9 Costs of a programme

Programme costs are associated with vaccination, diagnosis, monitoring and early disposal of gE-positive cows (see Appendix 2.1). The parameters used to calculate the total vaccination costs were: vaccination costs per animal (vaccine costs and labour), number of milking cows and youngstock that have to be vaccinated, frequency of vaccination, and the veterinary costs of visits. Value Added Tax is also included in the total costs of vaccination, depending on whether the costs are charged by the veterinarian (17.5% VAT) or the animal health service (6% VAT). With the input values for Dutch circumstances (Appendix 2.1), this results in total vaccination costs of Dfl[1] 1709 per year on an average farm with 50 cows and 40 youngstock, with a vaccination frequency of twice a year.

For detection of BHV1, there are 2 possibilities: identification of BHV1-antibodies in either serum or milk. Total costs depend on the number of animals to be checked and the costs of ELISA-screening, labour and administration. In this model, monthly monitoring of the IBR-free state of a herd is needed for herds which are exempted from vaccination. Furthermore, we assumed that during a vaccination programme, each year 5 cows of a vaccinated herd have to be screened for infection, to monitor the progress of the programme. To all herds an average profile of cow culling is applied. When a vaccination strategy involves disposal of cows before their economically optimal replacement time, the costs of early disposal were based on calculations of Houben et al. (1994).

2.2.10 Benefits of a programme

The benefits of a vaccination programme were derived as the reduced economic losses due to IBR. Losses caused by IBR include a lower milk production of gE-positive cows, clinical and subclinical losses from infectious cows, outbreaks at artificial insemination (AI) stations and potential losses due to export bans.

The losses on a farm due to a lower milk production of gE-positive cows were based on the prevalence of gE-positive cows in the herd, the reduction in milk production per gE-positive cow and the economic value of an extra kg of milk. A recent investigation indicated the average decrease in milk production of gE-positive cows to be about 150 kg per year, which is about 2%. (Smid, 1996). To calculate the losses of clinically and subclinically infectious cows, the following parameters were used: the percentage of infectious cows that either have clinical or subclinical signs, the reduction in milk production of cows with either clinical or subclinical signs, the probability of abortion and average losses due to abortion.

[1] 1 Dfl = EUR 0.45

An outbreak at an AI station within the EU has serious economic consequences, because infected semen and young bulls cannot be used for breeding (Brandsma, 1995). A reduction in the number of outbreaks on dairy farms will reduce the probability of an outbreak of IBR at AI stations. In this model the losses at AI stations were therefore calculated as:

$$AIL_t = AL \times \frac{I_t}{IE} \tag{2.9}$$

where

AIL_t losses at AI stations in week t, due to an outbreak of IBR

AL actual losses per week due to outbreaks at AI stations

I_t number of infectious cows in week t

IE number of infectious cows in the equilibrium situation, when no vaccination occurs

In the base model, potential economic losses due to export bans were not included. The effect of different sizes of export bans was calculated in a sensitivity analysis. The key factor in this calculation is the percentage of decline in export when no vaccination is applied. In a sensitivity analysis the effects of various percentages (basis, 50% and 100%) of decline in export were estimated. Applying a vaccination programme that achieves eradication will reduce the prevalence, and will therefore have benefits due to export. This relationship is calculated as:

$$EB_t = \frac{EP - P_t}{EP} \times DE \times GE \tag{2.10}$$

where

EB_t weekly benefits from export due to a vaccination programme

EP prevalence in the equilibrium situation with no vaccination

P_t prevalence in week t

DE percentage decline in export, if the prevalence remains as EP

GE weekly profits from export in current situation

The weekly profits from export in the current situation were calculated by multiplying the number of cows exported per week and the extra profits per exported cow (see Appendix 2.1).

The weekly calculated costs and benefits were both discounted by an annual interest rate of 4% (i.e. market interest rate minus inflation). The economic parameter we chose to use to further compare vaccination strategies is the ‘pay-back period’, – in this study defined as the number of weeks after the beginning of the strategy until the cumulative discounted benefits are equal to the cumulative discounted costs of a programme.

2.2.11 Vaccination strategies

Each strategy has a threshold value of 5% cow-level prevalence in the national population, below which the remaining gE-positive cows will be slaughtered. It is assumed that no reintroduction of virus occurs thereafter.

Strategy I assumes a voluntary participation in the vaccination programme of a certain percentage of the dairy herds, divided at random among the different herd-types and disease states. We looked at the effects of two arbitrarily chosen participation rates, 30% and 50% respectively. Strategy II is based on a compulsory programme for all herds. For this strategy, the epidemiological consequences of using either live or inactivated vaccines were analysed. The preferred vaccine was used in the other strategies. Strategy III encourages the farmers to cull their last gE-positive cows, because herds that are IBR-free can be certified, and exempted from compulsory vaccination. It is required that these certified herds purchase cows only from other certified herds – in this way reducing the probability of introduction of the virus into a certified herd. It is assumed that a farmer, after diagnosis, culls the last 10% of gE-positive cows. Furthermore, the effect of a reduction of the probability of introduction of virus by other contacts on certified herds was calculated. Strategy IV gives partial exemptions to some closed herds without certification and is subdivided into IVa and IVb: the first exempts all youngstock in closed herds from vaccination and the second exempts all gE-negative stock in closed herds with prevalences less than 50% from vaccination. Strategy V is a combination of two years of application of Strategy I, with 30% participation, followed by Strategy III. Using a simulation model with varying but uniquely defined probabilities, one set of input variables produced one set of outputs for each strategy described above. There was no statistical testing applied to the results, comparisons were only done 'by inspecting'.

2.3 Results

2.3.1 No vaccination

The equilibrium situation (defined as the situation where the prevalences do not change importantly) when there is no vaccination applied was taken as a base point for the comparison of the various vaccination strategies. Table 2.2 shows this equilibrium situation, with the distribution of the herd-types over the different prevalence classes. In the equilibrium situation, about a quarter of the herds were free of IBR, with a great difference between herd types. Almost half of the closed herds were IBR-free – but only 14% of open herds with lots of cow movements.

Table 2.2 The percentage of each herd-type that is in each prevalence class in the equilibrium situation without vaccination against infectious bovine rhinotracheitis in The Netherlands (R=5.6)

Prevalence class	Open ≥ 2 (%)	Open <2 (%)	Closed (%)
0%	14.4	40.3	46.0
>0-<20%	14.1	15.6	14.8
≥20-<50%	22.3	17.4	15.7
≥50-<80%	28.4	16.4	14.6
≥80%	20.8	10.3	8.9

Table 2.3 shows the proportions, in the equilibrium situation, of the virus introductions that were caused by reactivation of gE-positive cows, other contacts, reactivation of purchased gE-positive cows or purchase of infectious cows.

Table 2.3 Percentage of outbreaks of infectious bovine rhinotracheitis (in the equilibrium situation in The Netherlands of no vaccination), caused by either reactivation of gE-positive cows, other contacts, reactivation of purchased cows or purchase of infectious cows

	Open ≥ 2 (%)	Open <2 (%)	Closed (%)
Reactivation of gE-positive cows	3.5	5.1	5.3
Other contacts	31.8	79.3	94.7
Reactivation of purchased cows	53.1	12.8	0.0
Purchase of infectious cows	11.6	2.8	0.0

2.3.2 Vaccination strategies

Figure 2.1 illustrates the changes in prevalence with voluntary participation in the vaccination programme of either 30% or 50% (Strategy I), using a live vaccine that gives no protection against transmission of virus after reactivation of a gE-positive animal. Participation of only 30% of the dairy herds leads to an equilibrium situation with a national prevalence of 23% gE-positive cows. Average prevalence in equilibrium is about 12% for vaccinated herds and 28% in non-vaccinated herds. Furthermore, there is a great variability in within-herd prevalence between the different herd-types. When 50% of the herds participate in the programme, a national prevalence of about 13% will be reached. Even in such cases IBR will not be eradicated without further measures.

In contrast, a compulsory vaccination programme for all herds (Strategy II) can eradicate IBR – depending on the type of vaccine used. Figure 2.2 shows the change through time in the national prevalence of gE-positive cows when using an inactivated vaccine, for different levels of protection against transmission of virus after reactivation of a gE-positive animal. Only a nearly absolute protection against transmission of virus after reactivation of a latent

infected animal will eventually lead to the eradication of IBR. In contrast to the inactivated vaccine, there will be very little influence of this uncertain element for the live vaccine.

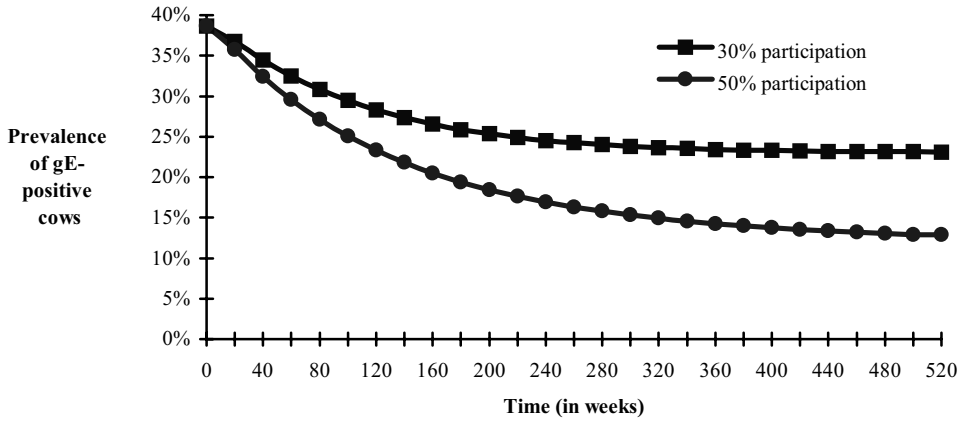

Figure 2.1 Changes in the national prevalence of gE-positive cows in The Netherlands with 30% or 50% of the herds participating in a vaccination programme for infectious bovine rhinotracheitis, using live vaccine which gives no protection against transmission of virus after reactivation of a gE-positive animal

The eradication of IBR will be attained even though there is no protection against transmission of virus after reactivation of a latent infection. This vaccine has therefore been used in the calculation of the changes in the prevalence, when applying the other strategies.

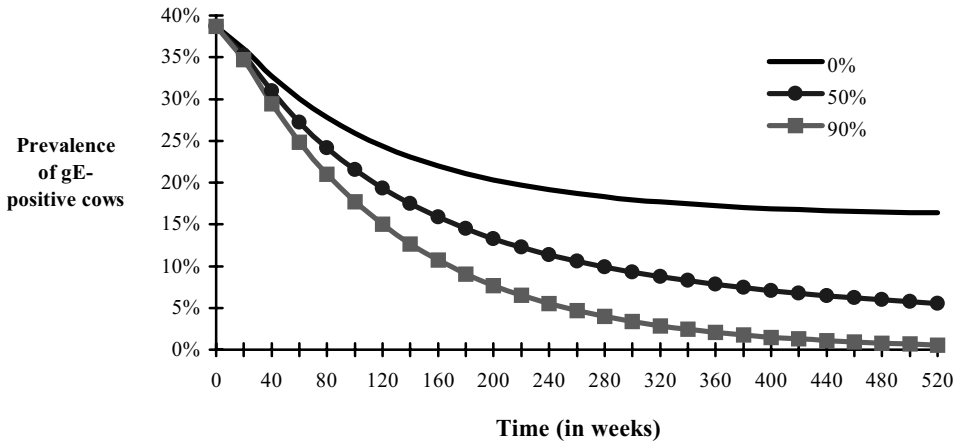

Figure 2.2 Changes in the national prevalence of gE-positive cows in The Netherlands during a compulsory vaccination programme for infectious bovine rhinotracheitis with inactivated vaccine, with different values of protection against transmission of virus after reactivation of a BHV1 positive animal

The threshold value of 5% prevalence can also be reached if certified herds are exempted from compulsory vaccination. However, if the certified herds take no measures to reduce the probability of introduction of virus by other contacts, the prevalence will increase again (Figure 2.3). This increase of prevalence at the end of the campaign can be explained by the increasing number of certified herds that lose their certification (Figure 2.4).

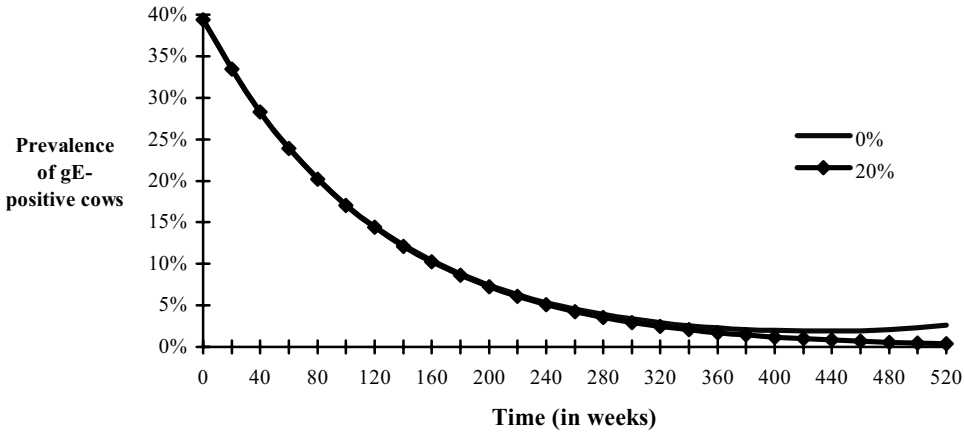

Figure 2.3 Changes in the national prevalence of gE-positive cows when certified herds are exempted from compulsory vaccination for infectious bovine rhinotracheitis in The Netherlands, with 0% and 20% decrease in the probability of introduction of the virus by other contacts into certified herds

Figure 2.4 indicates that when no measures are taken to reduce the probability of virus introduction by other contacts into certified herds, the number of herds losing their certification increases exponentially at the end of the campaign. As illustrated in Figure 2.4 this can be prevented by reducing the probability of transmission by other contacts with 20%. This percentage does not represent a threshold value; it was arbitrarily chosen.

Table 2.4 shows the epidemiological and economic results of the different vaccination strategies. The first column displays the number of weeks before the national prevalence of gE-positive cows reaches the culling threshold value of 5%. Compulsory vaccination (Strategy II) leads to a prevalence of 5% after 288 weeks. Strategies III, IVa and IVb, which assume exceptions from compulsory vaccination, result in a prevalence of 5% after about 240 weeks of the vaccination programme. Preceding Strategy III with two years of voluntary participation in the vaccination programme (Strategy V), will prolong the period to 5% prevalence by 71 weeks.

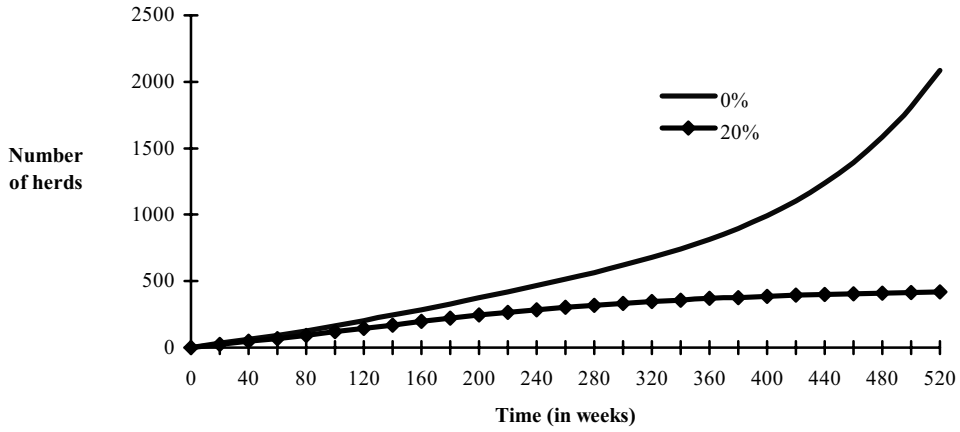

Figure 2.4 Development of the cumulative number of herds losing the BHV1-free certification because of an outbreak of for infectious bovine rhinotracheitis, with 0% and 20% decrease in the probability of introduction of the virus by other contacts into certified herds

Total costs of the vaccination programme, incurred in the period presented in the first column, are shown in the second column. It appears that a compulsory vaccination programme for all herds (Strategy II) incurs by far the highest costs – whereas Strategy V (with two years of voluntary participation) incurs the lowest.

Table 2.4 Epidemiological and economic outcomes of different vaccination strategies for infectious bovine rhinotracheitis in The Netherlands

	Weeks until national prevalence of gE-positive cows is 5%	Costs to 5% (Million Dfl)	Costs for programme-required culling (Million Dfl)		Pay-back period (weeks)
			Testing	Cow losses	
Strategy I	Does not lead to eradication of IBR				
Strategy II	288	320	25.9	56	598
Strategy III	241	225	6.0	55	405
Strategy IVa	241	219	6.0	55	397
Strategy IVb	242	217	5.9	56	394
Strategy V	312	197	5.5	51	400

Strategy I	Voluntary programme, 30% or 50% participation
Strategy II	Compulsory vaccination for all farms
Strategy III	As II, exemptions for certified herds
Strategy IVa	As III, exemptions for youngstock on closed herds
Strategy IVb	As III, exemptions for gE-negative animals on closed herds
Strategy V	2 years voluntary with 30% participation, followed by III

When a national prevalence of 5% gE-positive cows is reached, the model assumes that the last positive cows in the population have to be detected, so that they can be culled. The

costs of testing and culling were not included in the second column of table 4. Detecting is done by testing serum of all cows in the non-certified herds – resulting in the costs presented in the third column of Table 2.4. Because Strategy II does not include certification, all cows in the population have to be checked, incurring large costs of Dfl 25.9 million. The costs of culling of the last 5% gE-positive cows in the population are presented in the fourth column. At the time a national prevalence of 5% gE-positive cows is reached, the percentage of herds with a within-herd prevalence between 1-50% varies from 16-21% and the percentage of herds with a within-herd prevalence higher than 50% varies from 1-2%.

The pay-back period, earlier defined as the number of weeks after the beginning of the strategy until the cumulative discounted benefits are equal to the cumulative discounted costs of a programme, is presented in the fifth column of Table 2.4. Preference is given to a vaccination strategy with a short pay-back period. Strategy II has by far the longest pay-back period, and is therefore economically not attractive.

Table 2.5 shows which part of the costs as presented in the second column of Table 2.4, is due to vaccination, diagnosis, monitoring and early disposal of gE-positive cows. The costs of vaccination explain about 60% of the total costs for Strategies III-V, to about 98% for Strategy II. As shown in the last column of Table 2.5, almost 20% of the total costs of the strategies encouraging early culling of gE-positive cows (Strategies III-V) can be attributed to that early culling. Vaccination costs of Strategies III-V are less than half the vaccination costs of Strategy II, whereas expanding the vaccination programme by allowing exemptions increases the costs of diagnosis, monitoring and early disposal.

Table 2.5 Distribution of the total costs for each strategy till a national prevalence of 5% gE-positive cows is reached, over vaccination, diagnosis, monitoring and early culling, in millions of Dfl and as a percentage of total cumulative costs

	Vaccination		Diagnosis		Monitoring		Culling	
	Million Dfl	%	Million Dfl	%	Million Dfl	%	Million Dfl	%
Strategy II	315	98.4	-	-	5	1.6	-	-
Strategy III	143	63.5	22	9.8	17	7.6	43	19.1
Strategy IVa	137	62.5	23	10.5	17	7.8	42	19.2
Strategy IVb	131	60.3	24	11.1	19	8.8	43	19.8
Strategy V	126	63.9	21	10.7	15	7.6	35	17.8

Strategy II	Compulsory vaccination for all farms
Strategy III	As II, exemptions for certified herds
Strategy IVa	As III, exemptions for youngstock on closed herds
Strategy IVb	As III, exemptions for gE-negative animals on closed herds
Strategy V	2 years voluntary with 30% participation, followed by III

In the calculations so far, it has been assumed that the export of Dutch breeding cows is not influenced by the presence of IBR. Table 2.6 shows the pay-back periods at different

assumed percentages of decline in export (decline that would occur when no measures against IBR were taken). When exports decline due to the presence of IBR, there will be increased benefits from IBR eradication – resulting in shorter pay-back periods for vaccination strategies. Because application of Strategy V results in such a long period before the 5% prevalence is reached, the pay-back period of this strategy is hardly influenced by the decline in export.

Table 2.6 Results of sensitivity analyses of the effects of different assumptions on the pay-back period for infectious bovine rhinotracheitis control strategies in The Netherlands

	Payback period under baseline assumptions (weeks)	Decline in export 50% (weeks)	Decline in export 100% (weeks)	Vaccination once per year (default = twice) (weeks)	Decline in milk production of 75 kg (default = 150 kg) (weeks)
Strategy II	598	513	453	370	869
Strategy III	405	354	318	315	566
Strategy IVa	397	347	312	313	553
Strategy IVb	394	345	311	313	548
Strategy V	400	397	394	331	523

Strategy II	Compulsory vaccination for all farms
Strategy III	As II, exemptions for certified herds
Strategy IVa	As III, exemptions for youngstock on closed herds
Strategy IVb	As III, exemptions for gE-negative animals on closed herds
Strategy V	2 years voluntary with 30% participation, followed by III

This table also shows the effect on the pay-back period of vaccinating each cow once a year (rather than twice) with live vaccine, assuming an equal level of protection. Since the costs of vaccination were a major part of the cumulative costs (Table 2.5), this reduction in frequency of vaccination will importantly shorten the pay-back period. A large part of the benefits of a vaccination strategy is due to reducing the decline in milk production of gE-positive cows. If the effect of IBR on milk production is 75 kg per year, rather than 150 kg, pay-back periods will increase tremendously (Table 2.6). In this case, a strategy with low costs results in the shortest pay-back period (Strategy V).

As was shown in Table 2.2, there is a large difference in average prevalence among herd-types when there is no vaccination. During a vaccination programme the prevalence changes through time will also differ among the herd-types – resulting in a clear relationship between herd-type and economic consequences of a vaccination programme. In Table 2.7 this is shown for one of the vaccination strategies, Strategy IVa. The costs of an outbreak of IBR at AI stations were divided proportionally over the herd-types, for example, by an increase in semen prices.

Cumulative costs on open farms are about twice as high as on closed farms, which are especially caused by the higher costs of vaccination on open farms. The pay-back period on open herds ≥ 2 and open herds < 2 is about 3 and 2 years longer, respectively, than on closed herds.

Table 2.7 Economic outcomes when applying Strategy IVa for infectious bovine rhinotracheitis in The Netherlands, calculated per herd-type

	Pay-back period	Total and break-down of costs on a herd during pay-back period (Dfl)			
	(weeks)	Total	Vaccination	Test and cull	Monitoring
Open ≥ 2	434	10524	4918	4350	1256
Open < 2	378	7025	3168	2918	939
Closed	282	4890	1640	2632	618

2.4 Discussion and conclusions

The major sources for outbreaks in the simulation model were 'other contacts' and reactivation of purchased gE-positive cows. The probability of reactivation of a gE-positive cow and the impact of the 'other contacts' used in these simulations, however, could not be based on experimental results. Therefore, it is important that more attention is paid to these aspects in future research. The prevalence of gE-positive cows in the equilibrium situation without vaccination is about 4% lower than the actual prevalence of 42% in The Netherlands. This difference can be explained by the fact that non-marker vaccines were used The Netherlands. Because it is not possible to discriminate between the antibody response following vaccination and the antibody response following infection, vaccination has in fact only increased the prevalence of gE-positive cattle (Ackermann et al., 1990).

A voluntary vaccination programme with 30% or even 50% participation of the Dutch dairy farmers will not lead to eradication of IBR in The Netherlands. Because the current participation rate of farmers vaccinating against IBR is only about 20%, it seems that a compulsory programme is necessary to achieve an IBR-free status in The Netherlands. A 2-year period of voluntary participation in the vaccination programme, followed by compulsory vaccination, will lead to an undesirable slower decrease of prevalence, compared to directly making vaccination compulsory.

The type of vaccine used has great influence on the rate of prevalence decrease, especially with regard to the decrease in transmission rate of virus after reactivation of a gE-positive animal. The value R_{ind} of the live vaccine is still unknown under field conditions, but under experimental conditions it is lower than that of inactivated vaccine. Based on current

knowledge of live and inactivated vaccines, the outcomes of our study suggest that preference should be given to live vaccine.

From the scenarios studied, it appeared that when IBR-free herds are exempted from compulsory vaccination and when it is required that these certified herds purchase cows from other certified herds only, eradication of IBR is attained more quickly. To prevent a large number of herds from losing their IBR-free status, it will be necessary to reduce the probability of introduction of the virus by 'other contacts'. This can likely be accomplished through standard biosecurity measures such as disinfection of visitors' shoes and making agreements with neighbours as to pasture use. The quantitative effect of these measures under field conditions is, however, still unknown.

Further research is necessary on factors not included in our model. These factors include variation in farm size, infection of young cattle and beef cattle, distinction of different regions in one country and reintroduction of virus after eradication of IBR. Also the modelling of animal contacts between farms is of great importance. This model assumes random contacts between herds and does not include seasonal effects on culling and replacement of cattle. Purchased animals enter the herd evenly throughout the year, which is believed to be a fairly good approach of the situation in The Netherlands. However, if cattle is purchased in groups and purchase occurs mainly in a few, discrete, time periods, the risk of virus introduction on a farm is periodic. This might alter the outcomes of the model, but it is believed that the ranking of vaccination strategies will not be influenced.

The type of model presented in this paper includes varying but uniquely defined probabilities, meaning that a given set of input values produces one single outcome. Sensitivity analyses provides insight into the impact of uncertain elements. To get more insight into the variation of outcome, future modelling for infectious bovine rhinotracheitis in The Netherlands will focus on spatial and stochastic simulation techniques, as described by Jalvingh et al. (1995).

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Appendix 2.1

Major input variables of the epidemiological and economic simulation model[1]

Variable	Literature	Default value
Number of dairy herds in The Netherlands		34,000
Number of dairy cows per herd		50
Number of youngstock older than 3 months in the dairy herd		40
Percentage of herds in each herd-type depending on number of purchased animals		
Open herds ≥ 2 (buying on average more than 2 cows per year)	Bosch, 1997	61.6
Open herds < 2 (buying on average less than 2 cows per year)	Bosch, 1997	22.4
Closed herds	Bosch, 1997	16
Average number of cows purchased per year in		
Open herds ≥ 2		12.4
Open herds < 2		1.2
Number of days that infectious animals excrete virus, in case of		
no vaccine	Hage, 1997	10
inactivated vaccine	Kaashoek, 1995	7
live vaccine	Kaashoek, 1995	3
Parameter r (%) (formula 5)		7
Parameter o (formula 6)		0.65
Parameter $R_{100\%}$ (years) (formula 7)		20
Vaccination costs per animal (Dfl)		8.50
Frequency of vaccination with live and inactivated vaccine (year 1 /later years)		3 / 2
Costs of veterinary visits (Dfl)		39.25
Costs of ELISA-screening (Dfl)		4.25
Costs of administration (Dfl)		12.50
Labour costs per sample of: (Dfl)		
Milk diagnosis		0.50
Serum diagnosis		4.75
Monitoring costs of bulk milk screening per year (Dfl)		212
Average milk production per cow per year (kg)		7500
Price of 1 kg of milk (Dfl)		0.75
Economic value of 1 kg of extra milk under the quota system (Dfl)		0.30
Milk reduction of clinically infected cows (kg)		263
Milk reduction of subclinically infected cows (kg)	Hage, 1997	15
Percentage of infectious cows with clinical signs		5
Percentage of infectious cows with an abortion		0.25
Costs of abortion caused by IBR (Dfl)		565
Actual losses at AI stations caused by IBR per year (Dfl)	Brandsma, 1995	2.1×10^7
Number of cows exported per year		50,000
Extra value of an exported cow (Dfl)		340

[1]Unless indicated the input is based on common records in The Netherlands or expert opinion.

Appendix 2.2

Transition matrix when no vaccination strategy against infectious bovine rhinotracheitis is applied in the Dutch dairy herds, with submatrices nn, ni, in,ii

To	From *%P*	0%	>0-<20 %	20-<50%	50-<80 %	≥80%	0%		>0-<20 %		20-<50%		50-<80 %		≥80%
%P	*I**	0	0	0	0	0	2	15	2	13	2	9	1	3	1
0%	0	1.00	0.01	-	-	-	-	-	-	-	-	-	-	-	-
>0 -<20%	0	-	0.99	0.01	-	**nn**	0.06	-	0.07	-	-	-	-	**in**	-
≥20- <50 %	0	-	-	0.99	0.02	-	-	-	-	-	0.09	-	-	-	-
≥50- <80 %	0	-	-	-	0.98	0.03	-	-	-	-	-	-	0.17	-	-
≥80%	0	-	-	-	-	0.97	-	0.20	-	0.20	-	0.20	-	0.14	0.50
0%	2	1.00	-	-	-	-	0.53	-	-	-	-	-	-	-	-
	15	-	-	-		**ni**	0.41	0.80	-	-	-	-	-	**ii**	-
>0-<20 %	2	-	1.00	-	-	-	-	-	0.53	-	-	-	-	-	-
	13	-	-	-	-	-	-	-	0.40	0.80	-	-	-	-	-
≥20-<50 %	2	-	-	1.00	-	-	-	-	-	-	0.54	-	-	-	-
	9	-	-	-	-	-	-	-	-	-	0.37	0.80	-	-	-
≥50-<80 %	1	-	-	-	1.00	-	-	-	-	-	-	-	0.58	-	-
	3	-	-	-	-	-	-	-	-	-	-	-	0.25	0.86	-
≥80%	1	-	-	-	-	1.00	-	-	-	-	-	-	-	-	0.50

%P Prevalence of gE-positive cows within a herd

I* Number of infectious animals within a herd

Chapter 3

Evaluating control strategies for outbreaks in BHV1-free areas using stochastic and spatial simulation

Paper by Vonk Noordegraaf, A., Jalvingh, A.W., De Jong, M.C.M., Franken, P., Dijkhuizen, A.A., 2000. *Preventive Veterinary Medicine* 44, 21-42. Reproduced with permission of Elsevier Science.

Abstract

Several countries within the EU have successfully eradicated bovine herpesvirus type I (BHV1), while others are still making efforts to eradicate the virus. Reintroduction of the virus into BHV1-free areas can lead to major outbreaks – thereby causing severe economic losses. To give decision-makers more insight into the risk and economic consequences of BHV1 reintroduction and into the effectiveness of various control strategies, the simulation model InterIBR was developed.

InterIBR is a dynamic model that takes into account risk and uncertainty and the geographic location of individual farms. Simulation of a BHV1-outbreak in The Netherlands starts with introduction of the virus on a predefined farm type, after which both within-farm and between-farm transmission are simulated. Monitoring and control measures are implemented to simulate detection of the infection and subsequent control. Economic consequences included in this study are related to losses due to infection and costs of control. In the simulated basic control strategy, dairy farms are monitored by monthly bulk-milk tests and miscellaneous farms are monitored by half-yearly serological tests. After detection, movement-control measures apply, animal contacts are traced and neighbour farms are put on surveillance.

Given current assumptions on transmission dynamics, it is concluded that a strategy with either rapid removal or vaccination of infected cattle does not reduce the number of infected farms compared to the basic strategy – but will cost more to control. Farm type with first introduction of BHV1 has a considerable impact on the expected number of secondarily infected farms and total costs. To limit the number of infected farms and total costs due to outbreaks, we suggest intensifying the monitoring programme on farms with a high frequency of cattle trade, and monthly bulk-milk testing on dairy farms.

3.1 Introduction

Further integration of markets within the European Union (EU) facilitates trade between member states. The diversity in animal-health status, however, still restricts trade of cattle. Part of these constraints for cattle is due to bovine herpesvirus type I (BHV1) – the cause of infectious bovine rhinotracheitis (IBR).

BHV1 is a member of the family of Herpesviridae and the subfamily of Alphaherpesvirinae, and can establish lifelong latency in the neurons of sensory ganglia (Pastoret et al., 1984; Engels and Ackermann, 1996; Kaashoek et al., 1996; Bosch et al., 1997). Import of latently infected animals into a BHV1-free country is a risk for reintroduction because stress factors (like transport) can lead to reactivation and reexcretion

of virus (Thiry et al., 1987; Hage et al., 1996). Other sources of BHV1 reintroduction are semen, wildlife and wind-borne (Ackermann et al., 1990; Wentink et al., 1993). BHV1 can lead to severe clinical symptoms (Wiseman et al., 1978) or can be inapparent (Engels and Ackermann, 1996; Hage et al., 1998).

Several countries within the EU have successfully eradicated BHV1 (Denmark, Finland and Sweden) or have an EU-approved national compulsory eradication programme (Austria). Reintroduction of the virus into these susceptible populations can lead to major outbreaks and severe economic losses (Straub, 1990; Nylin, 1993). Hence, EU-directives (64/432, 88/407 and 93/60) allow member states to stipulate requirements to be met for the import of cattle, semen and embryos.

To avoid losses due to export restrictions and to diminish the on-farm costs of reduced milk production and of abortion, plans were developed to eradicate BHV1 in The Netherlands. This eradication programme primarily consists of compulsory half-yearly vaccination with marker vaccine for all herds (with exemption of beef and veal farms and BHV1-free certified herds) starting in May 1998. This programme has a large economic impact on the Dutch cattle sector (Vonk Noordegraaf et al., 1998). The objective of this study is, therefore, to give more insight into the expected between-farm spread of infection should BHV1 be reintroduced into The Netherlands after being free from the virus and into the possibilities of controlling such outbreaks at reasonable costs.

Documentation of outbreaks in BHV1-free countries is scarce (Nylin et al., 1998). To help maximise the efficacy of existing or future strategies, and to evaluate in advance the consequences of possible alternatives, computer simulation is a valuable decision-support tool (Dijkhuizen and Morris, 1997). Sanson (1993) developed the concepts of InterSpread (a simulation model for FMD), that takes into account risk and uncertainty for spread and control mechanisms and the geographic location of individual farms. This was further adapted to Dutch and EU conditions (Jalvingh et al., 1995). We made additions and modifications to the general framework of InterSpread to produce InterIBR. These additions and modifications mainly concern transmission dynamics of infection (modelled both within and between herds), and the detailed use of Dutch farm data. Furthermore, a framework was built to calculate the economic consequences of reintroduction and various control strategies. This paper describes the main characteristics of InterIBR and the economic model. Results focus on the variation in the expected number of secondarily infected farms after reintroduction, the economic consequences of infection and control, and the impact of various control strategies.

3.2 Model structure and contents

3.2.1 General framework

InterIBR is programmed in Borland C++, and output is imported into a spreadsheet to generate an overview of epidemiological and economic parameters. A brief schematic representation of the general framework of InterIBR is shown in Figure 3.1. Each module is addressed in more detail below.

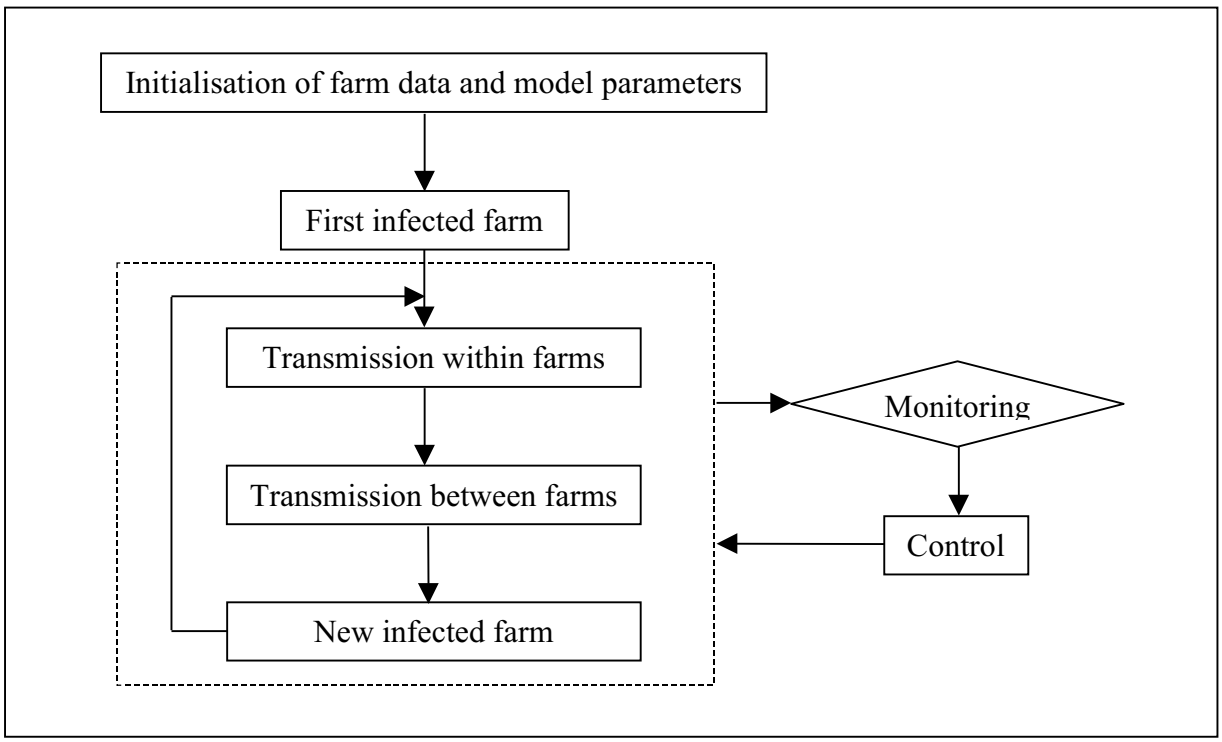

Figure 3.1 Schematic representation of the general framework of InterIBR

In the initial phase, a dataset of farms is loaded and values are assigned to parameters for spread and control. Simulation of a BHV1 outbreak starts with introduction of virus on a predefined farm type. Transmission within and between farms is simulated, and continues until no more infected farms are present. Animals are either susceptible, infectious or latently infected. Each week, between-farm contacts of infected farms that might carry virus are simulated; probabilities of transmitting BHV1 by each of these contacts are a function of the spread within the infected farm. Three routes of transmission between farms are simulated: animal contacts, professional contacts and local contacts. Next to this infection-spread module, monitoring and control measures are implemented to simulate detection of the infection and subsequent control activities.

To take into account risk and uncertainty, Monte Carlo simulation (Law and Kelton, 1991; Vose, 1996) is implemented in spread and control mechanisms. Each replication of the

simulation represents a simulated outbreak of BHV1 after reintroduction. To measure the minimum number of replications required, the approximate expression containing the relative error of the estimated mean is applied (Law and Kelton, 1991). The relative error is calculated as the half length of the 95% confidence interval divided by the estimated mean, and is required to be less than 0.15 for both the number of infected farms and total costs. The number of replications is set once, and used for all simulation experiments in this study: 200 replications for first introduction on a dairy or miscellaneous farm type; 500 replications for first introduction on a beef or veal farm type and 100 replications for first introduction on a miscellaneous 100+ farm type (a miscellaneous type of farm that sells >100 animals for life per year).

3.2.2 Farm data

The simulation model contains a dataset of 25,000 fictional, uniquely identified individual farms – each farm with its own characteristics. The herd characteristics are (1) farm type, (2) herd size, (3) open versus closed, (4) yearly number of animals sold for life (i.e. for uses other than immediate slaughter) and (5) geographic location. To generate a realistic dataset, information on cattle farms is obtained from the Dutch Identification and Recording (I&R) system. The four farm types are: dairy, beef, veal and miscellaneous (such as suckler herds) (Table 3.1).

Most farms (about 30%) are dairy farms with 30-70 animals older than 2 years. Data of number of animals sold per farm-type-herd-size combination is based on a sample of 30% of Dutch farms from the I&R system. For dairy farms, distinction is made between animals sold for life at <2 and at ≥2 years of age. We assume that beef and veal farms only sell cattle to slaughterhouses; animal-movement contacts off these farms are therefore considered not to be a source of transmission. Each farm in the dataset is assigned a fictitious location (x- and y-coordinate) at random, representing a heterogeneous density of cattle farms with an average farm density of 1.5 farms per km^2.

Simulation starts with virus introduction on a predefined farm type. The first infected farm is taken at random from this type and can vary between replications. To get more insight into the potential risk of farms that trade frequently, a special group of miscellaneous farms is defined “miscellaneous 100+,” that sells >100 animals for life per year.

3.2.3 Transmission within farms

Animals excreting BHV1 can infect herd-mates by direct nose-to-nose contact and by coughing or sneezing aerolized droplets over relatively short distances. Indirect

Table 3.1 Summary information on Dutch cattle farms (October 1996), used to generate the dataset of individual farms

Farm type (FT)	Herd size (HS)	% of total	% herds closed [b]	% of herds per FT-HS combination per number of cattle (all ages) sold for life (per year)							
		herds	per FT-HS	0	1-2	3-6	7-10	11-15	16-25	26-50	>50
Dairy	<30[a]	11.3	34.0	2.4 (2.4)[c]	4.8 (65.9)	13.8 (25.1)	19.7 (6.0)	27.6 (0)	25.1 (0.6)	6.0 (0)	0.6 (0)
Dairy	30-70[a]	30.3	38.0	1.0 (1.0)	0.8 (41.4)	2.1 (52.7)	2.8 (4.9)	6.6 (0)	29.1 (0)	52.7 (0)	4.9 (0)
Dairy	71-100[a]	8.8	34.3	0.5 (1.0)	0.5 (9.0)	0.7 (60.4)	0.8 (29.5)	1.7 (0)	6.6 (0)	59.7 (0)	29.5 (0)
Dairy	>100[a]	4.0	23.2	1.2 (1.2)	0.7 (4.0)	0.9 (28.8)	1.3 (66.0)	1.1 (0)	3.5 (0)	25.3 (0)	66.0 (0)
Beef	<100	8.9	29.1	100	0	0	0	0	0	0	0
Beef	100-200	0.4	4.4	100	0	0	0	0	0	0	0
Beef	>200	0.2	2.0	100	0	0	0	0	0	0	0
Veal	<100	0.7	1.6	100	0	0	0	0	0	0	0
Veal	100-200	0.3	0	100	0	0	0	0	0	0	0
Veal	>200	1.1	0	100	0	0	0	0	0	0	0
Miscellaneous	<30	26.8	32.2	37.1	24.2	21.4	8.1	4.3	2.8	1.4	0.7
Miscellaneous	30-70	4.9	16.4	11.8	8.7	14.7	14.3	16.3	18.1	11.8	4.3
Miscellaneous	71-100	0.9	13.3	13.0	7.9	6.8	7.1	10.2	15.0	24.1	15.9
Miscellaneous	>100	1.4	5.8	13.8	10.3	8.6	5.1	4.0	9.3	19.8	29.1

[a] based on number of cows > 2 years

[b] no purchase of animals

[c] between brackets the percentage of herds for sales of dairy cattle >2 years

transmission may occur via humans and contaminated food and water (Wentink et al., 1993; Engels and Ackermann, 1996). Introduction of BHV1 within a BHV1-free herd often results in all animals being infected within a few weeks (Wentink et al., 1993; Hage et al., 1996).

To simulate the within-farm spread of BHV1, a deterministic SIR-model (using the concept of basic reproduction ratio; R_0) is applied (Becker, 1989; Anderson and May, 1991; De Jong, 1995). With this model, dynamic transitions of animals between the states susceptible (S), infectious (I) and latently infected (R) are simulated daily, using the true mass-action formula given by De Jong (1995). Infection is assumed to start with a single infectious animal, and no animals are assumed to enter the herd during the infectious period. The R_0 and the mean number of days of virus shedding for BHV1-free herds are based on Bosch et al. (1996) and Bosch (1997) (Appendix 3.1). When $R_0 > 1$, infection can result in many infected individuals (major outbreak), or an infection can by chance fade out in an early stage of the infection with probability $1/R_0$ (minor outbreak) (Van Nes et al., 1998). In case of a minor outbreak, 5% of the herd is assumed to become latently infected, while a major outbreak is simulated by the deterministic SIR-model.

Farms can be either infectious (I>0), latently infected (I=0 and R>0), or BHV1-free (I=0 and R=0). Movement of farms between these states is determined by stochastic processes and related to (1) BHV1 introduction, (2) reactivation of latently infected animals and (3) natural replacement. These processes can be influenced by control measures (such as vaccination or removal of infected cattle). For veal calves, a half-year fattening period is assumed, with all calves leaving the herd at the same time. Values of various parameters for modelling spread of BHV1 are given in Appendix 3.1. Whereas for other farm types the total herd is considered one homogeneous group, transmission within dairy farms is simulated using the SIR-model for dairy cattle (≥2 years) only. On dairy farms, the probability of transmission from dairy cattle to youngstock within the farm is assumed to be 10%, which is taken into account when simulating transmission between herds.

3.2.4 Transmission between farms

Various risk factors for BHV1 transmission between farms and for presence of BHV1 antibodies have been described (Wentink et al., 1993; Hage, 1997; Van Schaik et al., 1998; Van Wuijckhuise et al., 1998); transmission of BHV1 between farms is mainly due to introduction of cattle in the acute phase of infection and to latently infected cattle. Other risk factors described are transmission from neighbouring farms, transmission by humans, infected semen and aerogenic transmission; these routes, however, are considered of minor importance.

InterIBR simulates three routes of transmission between farms: (1) animal contacts, (2) local contacts and (3) professional contacts. For each infected farm, the number of infectious

and latently infected cattle condition the risk of transmission to other farms by each of these routes.

3.2.4.1 Animal contacts

On infectious and latently infected farms, each animal sold for uses other than immediate slaughter is simulated as animal contact. On these farms, the weekly number of animal contacts is derived stochastically by a Poisson distribution (Vose, 1996). The parameter for this distribution (λ, the average number of animal contacts per week), is calculated by dividing the individual-herd characteristic 'yearly number of animals sold for life' by 52.

For each animal contact, the state of the animal is taken randomly from the SIR-distribution within the herd. A destination farm is selected based on the animal-contact structure between farm types and the probability distribution for distance classes (Appendix 3.2). (When the selected farm has the herd characteristic 'closed,' a new farm is selected.) If the animal contact is either infectious or latently infected and reactivates during transport, the process of transmission within the receiving farm starts.

3.2.4.2 Local contacts

All neighbourhood contacts that can lead to transmission of BHV1 are encompassed into the spread mechanism 'local contacts,' which is affected by herd density. For each farm j within a certain radius (default 1 km) of infectious farm i, the weekly probability of becoming infected by local contacts is calculated as:

$$p_{l(t,i \rightarrow j)} = c_l \times \{1 - e^{-(I_{i,t} \times d_i \times (w_c \times R0_{,within}))}\} \qquad (3.1)$$

where $p_{l(t,i \rightarrow j)}$ is the probability of infecting at least 1 animal on farm j by local contact with infectious farm i in week t, c_l the probability of adequate local contact, $I_{i,t}$ the average number of infectious animals on farm i in week t, d_i the herd density within a certain radius of infectious farm i (number of farms / km^2), w_c the scaling factor for $R_{0,\ within}$ and $R_{0,\ within}$ is the reproduction ratio within a herd.

The exponent $I_{i,t} \times d_i \times (w_c \times R_{0,within})$ is equal to the expected number of animals that are infected through local contacts in week t on farm j, by infectious animals on farm i. The number of infectious animals on farm i in week t ($I_{i,t}$) is therefore weighted by farm density (d_i, related to average distance between farms) and by a scaled reproduction ratio (w_c x $R_{0,\ within}$). The scaling factor w_c is used to calibrate the average impact of local contacts. Beef and veal farms are assumed to practise stricter hygiene, and to have no outdoor grazing. Therefore, these farm types have a lower probability of transmitting virus when infected

(reduced w_c), and a lower probability of receiving virus by local contacts (reduced c_l) (Appendix 3.1).

3.2.4.3 Professional contacts

The third simulated route of transmission between farms is 'professional contacts,' such as veterinarians, animal traders and AI-technicians. Data from Nielen et al. (1996) and Van Schaik et al. (1998) are used to estimate the weekly number of professional contacts for each farm-type-herd-size combination, and the distance over which these contacts take place (Appendix 3.2). As with animal contacts, a Poisson distribution is used stochastically to derive the number of professional contacts in a certain week. For each professional contact, a destination farm is selected and the probability of becoming infected by professional contacts is calculated as:

$$p_{p(t,i \rightarrow j)} = c_p \times \{1 - e^{-(I_{i,t} \times w_p)}\} \qquad (3.2)$$

where $p_{p(t,i \rightarrow j)}$ is the probability of infecting at least 1 animal on farm j by professional contact with infectious farm i in week t, c_p the probability of adequate professional contact, $I_{i,t}$ the average number of infectious animals on farm i in week t and w_p the scaling factor for professional contacts.

As with local contacts, the exponent is equal to the expected number of animals that are infected through professional contacts in week t on farm j, by infectious animals on farm i. The values for the scaling factors w_c (local contacts) and w_p (professional contacts) are calibrated such that when no control is applied after reintroduction, on average 90% of the transmission between farms is due to animal contacts and 10% is equally divided over local and professional contacts. Because the true risk of both local and professional contacts is unknown, in the sensitivity analysis we calculated the effect of doubling the scaling factors for local and professional contacts.

3.2.5 Monitoring and control

In the basic situation, dairy farms are monitored monthly by bulk-milk tests and miscellaneous farms by half-yearly serological tests. No monitoring is implemented on beef and veal farms. Using bulk-milk tests, a small fraction of seropositive animals will most-likely go undetected (Frankena et al., 1997) – only major outbreaks are detected by bulk-milk tests. A probability distribution for the interval from infection to detection is used (Appendix 3.2), and when a farm becomes infected, a random number is drawn from this distribution and the date of detection is set.

After detection of an infected farm, infection-control mechanisms are activated which can affect the infected farm, neighbouring farms and contact farms. Three control strategies are explored: a so-called basic strategy (basic), a strategy with fast removal of infected cattle (removal), and a strategy with vaccination of infected farms (vaccination).

In the basic strategy, after detection of an infected farm, all animals are tested serologically, no animal contacts on and off farm are allowed, and additional hygiene measures are taken to prevent transmission. This is accounted for in the model by parameters reflecting movement control for each transmission route (Appendix 3.1). In case of a minor outbreak on the detected farm, latently infected cattle are removed immediately. In case of a major outbreak, direct stamping out is not an option. When no new outbreak occurs on the farm, the prevalence will reduce by natural replacement and the remaining latently infected cattle are culled within five years after infection at the latest. During this period, no animal movements off the infected farm are allowed, except for youngstock going to veal farms and cattle going directly to slaughter. Furthermore, animal contacts on and off the infected farm are traced. Traced herds and herds within a 1-km radius are put on surveillance for 4 weeks. Animals on these farms are tested twice, no animal movements are allowed, and additional hygiene measures are taken to reduce the risk of introduction and transmission by local and professional contacts (Appendix 3.1).

The removal strategy differs from the basic strategy such that all infected animals on detected farms are removed within 4 weeks after the within-farm spread of BHV1 has ended. The vaccination strategy implements, in addition to the basic strategy, half-yearly vaccination of all animals on detected farms. Vaccination reduces the effective reproduction ratio, the infectious period of an infected animal and the probability that a latently infected animal transmits virus after reactivation (Appendix 3.1).

Sensitivity analysis is carried out to study the effect of changes to some elements of the basic strategy: omission of the 1-km surveillance zone; increasing frequency of serological testing on miscellaneous farms from twice to four times a year; decreasing frequency of bulk-milk testing from monthly to 3-month intervals. Omission of a surveillance zone is expected to affect costs of control. More-frequent serological monitoring will increase yearly standard monitoring costs with 5.4 million Dfl[2] and less-frequent bulk-milk testing will decrease yearly costs of monitoring by 6.6 million Dfl. Decision makers, therefore, want insight into the effect of these changes on the expected number of infected farms and total costs to control outbreaks. Two other scenarios included in the sensitivity analysis are 10% 'illegal' transport (not complying with the movement ban) and 10% increase in the number of animal movements.

[2] 1 Dfl = EUR 0.45

To test if alternative strategies differ significantly from the basic strategy, a two-tailed, two sample Student t-test with unequal variance is performed on mean outcomes of each scenario. Comparisons are done for mean total number of infected farms and mean total losses and costs.

3.2.6 Costs of infection and control

For each replication, InterIBR generates output to calculate national economic consequences of reintroduction of BHV1. The economic consequences included in this study are related to 1) losses due to infection and 2) costs of control. A list of input values used for these calculations is given in Appendix 3.3.

Losses due to infection include reduced production (milk or growth), extra feeding costs, abortion and mortality (taking into account both clinical and subclinical infection). Data on reduced production due to clinical and subclinical infection are based on Wiseman et al. (1979) and Hage et al. (1998). To quantify the economic impact of lower production and mortality, Dutch data on average investments, costs and returns on the various farm types are used. We assume that a decreased growth rate due to infection is compensated for by an increased fattening period. To calculate the costs of an increased fattening period, costs items related to the length of the fattening period are used to determine the income margin per day. Furthermore, change in feed-conversion efficiency due to infection is included, to calculate the extra feeding costs. Assuming that, on average, mortality occurs halfway through the lactation or fattening period, losses due to mortality include costs before death and return to labour and housing foregone after death (Dijkhuizen and Morris, 1997). The cost items for miscellaneous farms are based on the average of the other farm types. Some important cost items related to infection and control are given in Table 3.2.

Table 3.2 Average losses per infectious animal used for simulation calculations of bovine herpes virus 1 infection in The Netherlands

Category of losses	Dairy	Beef	Veal	Miscellaneous
Clinical (Dfl./animal)	111	57	69	79
Subclinical (Dfl./animal)	3	4	7	5
Early culling (Dfl./animal)	878	617	308	601
Open place (Dfl./animal/week)	88	6	5	33

To calculate costs of control, InterIBR generates for each farm type the number of farms and animals on surveillance, removed and vaccinated. For farms on surveillance, only costs of serological testing are included. Additional costs of animal-movement restrictions and policing the movement ban are not included. Calculations of costs for testing and vaccination are similar to Vonk Noordegraaf et al. (1998). For removed animals, average costs of being

culled before the economically optimal life span, and average costs of missed income and idle production factors due to temporary open places are included. We assumed that culled animals still have a slaughter value.

3.3 Results

3.3.1 Basic strategy

Table 3.3 shows the probability that first introduction onto each farm type is followed by transmission of infection to at least one other farm, for both the situation without monitoring and control, and when applying the basic strategy.

Table 3.3 Probability (%) of transmission of infection to at least one other Dutch cattle farm when simulating first introduction of BHV1 onto each farm type

	First introduction on				
Simulated	Dairy farm	Beef farm	Veal farm	Miscellaneous farm type	
strategy				100+	All
No control	76	2	7	99	46
Basic strategy	42	2	7	96	34

For both situations, farm type with first introduction has a great impact on the probability of further spread. Especially for beef and veal farms, there is a high probability that virus is not transmitted to other farms (98% and 93%, respectively). Application of the basic strategy reduces the probability of transmission from 76% to 42%, when first introduction is on a dairy farm. Reintroduced virus on a miscellaneous 100+ farm will nearly always be transmitted to other farms.

Due to stochastic processes and the heterogeneity of farm characteristics, wide variation in the expected number of secondarily infected farms can be seen when applying the basic strategy, as shown by the quantile summary[3] (Table 3.4). After first introduction of BHV1 on a dairy, beef or veal farm, virus will be transmitted on average to less than one other farm. Reintroduction on a miscellaneous 100+ farm will have much more impact, with an average of 21.6 secondarily infected farms.

Applying the basic strategy, first introduction on a dairy farm has a 99% probability of causing 6 secondarily infected farms at most. In case of first introduction on a miscellaneous 100+ farm, the 0.99-quantile is 56 infected farms.

[3] For $0 < q < 1$, the q-quantile of $F(x)$ is that number x_q such that $F(x_q) = q$. The q-quantile is equivalent to the 100qth percentile (Law and Kelton, 1991; Kleijnen and Van Groenendaal, 1992)

Table 3.4 Cumulative frequency distribution of secondarily infected cattle farms when simulating application of the basic monitoring-and-control strategy for BHV1 in The Netherlands

	First introduction on				
	Dairy farm	Beef farm	Veal farm	Miscellaneous farm type	
				100+	All
Mean	0.9	0.1	0.2	21.6	1.4
Quantiles					
$x_{0.25}$	0	0	0	11	0
$x_{0.50}$	0	0	0	21	0
$x_{0.75}$	1	0	0	30	1
$x_{0.90}$	2	0	0	38	5
$x_{0.95}$	3	0	1	43	7
$x_{0.99}$	6	1	3	56	14

Not all secondarily infected farms counted in Table 3.4, however, suffer a major outbreak. On average, 55% of the infected farms is infected by purchase of a latently infected animal, without reactivation and transmission of virus to other animals on the farm. Farms infected by other transmission routes suffer a minor (10%) or major outbreak (35%).

Table 3.5 gives information on the probability and timing of detection – which are both functions of the spread within and between farms and the monitoring strategy applied. Detection can occur on either the primary or a secondarily infected farm. With first introduction on beef and veal farms, the probability of detection is very low (1% for beef and 5% for veal farms). After first introduction on other farm types, there is a high probability of detection. On an average, infection is detected earliest after first introduction on dairy and miscellaneous 100+ farms; however, there is a wide range in the time until detection.

Table 3.5 Probability (%) of detecting BHV1 reintroduction into The Netherlands and the interval between reintroduction and first detection (weeks) when simulating the basic monitoring strategy

Simulation outcome	First introduction on				
	Dairy farm	Beef farm	Veal farm	Miscellaneous farm type	
				100+	All
Probability of detection (%)	81	1	5	93	79
Time until first detection (weeks)					
Mean	7	19	17	9	22
Quantiles					
$x_{0.025}$	3	9	6	3	3
$x_{0.975}$	12	31	39	27	38

Mean national losses due to infection and costs of control vary from about Dfl. 1,000 after first introduction on a beef farm, to Dfl. 300,000 when reintroduction occurs on a miscellaneous 100+ farm (Table 3.6). As shown by the 0.95 and 0.99-quantiles, worst-case scenarios have a big impact on the economic consequences of reintroduction.

Table 3.6 Cumulative frequency distribution of total national economic consequences (x1000 Dfl.) when simulating application of the basic monitoring-and-control strategy for BHV1 in The Netherlands

	First introduction on				
	Dairy farm	Beef farm	Veal farm	Miscellaneous farm type	
				100+	All
Mean	44	1	5	300	22
Quantiles					
$x_{0.25}$	16	0	0	159	3
$x_{0.50}$	36	0	2	297	8
$x_{0.75}$	61	0	5	438	22
$x_{0.90}$	86	0	5	538	68
$x_{0.95}$	110	1	9	611	108
$x_{0.99}$	186	20	81	765	154

3.3.2 Rapid-removal and vaccination strategies

Rapid removal of infected animals and half-yearly vaccination of infected farms have no significant impact on the number of secondarily infected farms, compared to the basic control strategy. Both strategies, however, show a similar reduction of the probability that, on at least one latently infected farm, reactivation results in renewed on-farm spread of BHV1 (Table 3.7).

Table 3.7 Probability (%) that reactivation occurs on at least one latently infected cattle farm, when simulating application of the basic, removal and vaccination strategy for BHV1 in The Netherlands

	First introduction on				
Simulated	Dairy farm	Beef farm	Veal farm	Miscellaneous farm type	
strategy				100+	All
Basic	5.5	2.2	0.6	37.0	5.5
Removal	0.5	2.0	0.2	6.0	2.5
Vaccination	0.5	2.0	0.2	6.0	2.5

Although there is no significant effect on the total number of secondarily infected farms, the three strategies differ in their national economic consequences, as can be seen from the cumulative probability distribution for first introduction on a miscellaneous 100+ farm (Fig. 3.2).

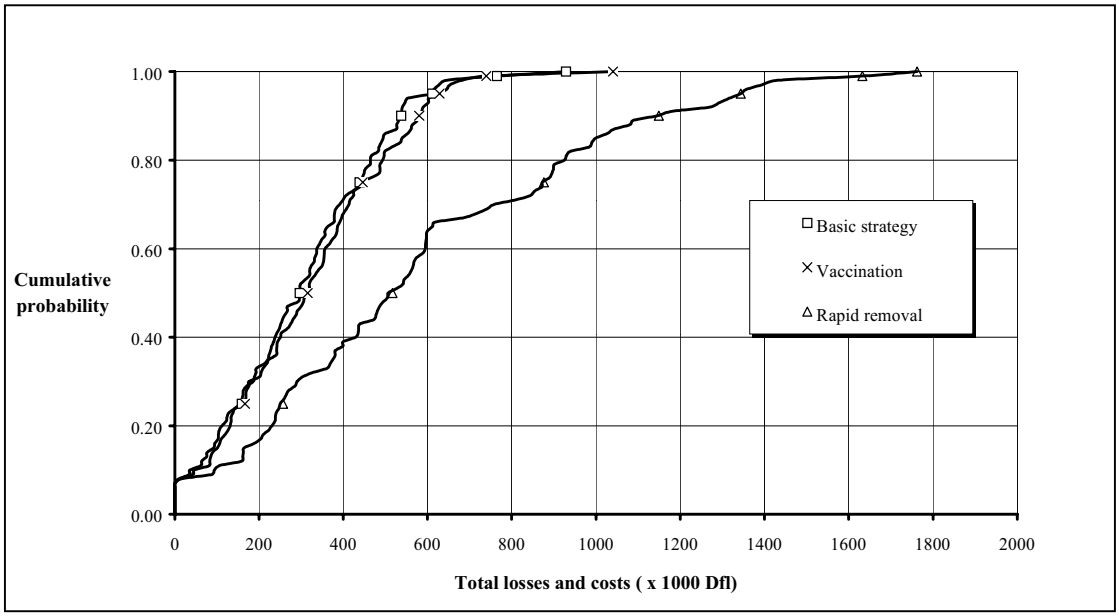

Figure 3.2 Cumulative probability distribution of total national losses due to infection and cost of control (x1000 Dfl.) when simulating application of the basic, removal and vaccination strategies for BHV1 with first introduction on a miscellaneous farm type selling >100 cattle per year in The Netherlands

Carrying out half-yearly vaccination of infected farms increases average national costs by 10%, but the difference is not significant. A strategy with rapid removal of infected cattle doubles average costs, which is significantly different from the basic strategy. Breaking down total economic consequences into the various cost items, provides more insight into the reason of changes in costs when applying alternative control strategies (Table 3.8). Costs for the standard monitoring programme are not included in Table 3.8, because these costs are not affected by an outbreak.

Much of the total costs of the basic strategy are for serological testing of cattle on infected farms and farms on surveillance. Rapid removal of all infected animals results in a decrease of losses due to infection. This is, however, outweighed many times by the increase in costs due to early removal of infected cattle. Compared to the basic strategy, the lower risk of reactivation with half-yearly vaccination results in a slight decline of costs due to infection, removal and open places (fewer infected animals) – which partly compensates for the vaccination costs.

Table 3.8 Mean and 0.95-quantile ($x_{0.95}$) of total economic consequences of BHV1-introduction and of each related cost item (x1000 Dfl.), when simulating application of the basic, removal and vaccination strategies for BHV1 in The Netherlands[a]

Start on	Simulated strategy		Total	Losses	Costs of control			
				Infection	Testing	Removal	Open place	Vaccination
Dairy farm	Basic	Mean	44	7	21	12	5	0
		$x_{0.95}$	110	19	58	32	13	0
	Removal	Mean	86*	1	21	45	19	0
		$x_{0.95}$	208	3	58	113	45	0
	Vaccination	Mean	48	7	21	11	4	6
		$x_{0.95}$	120	18	58	28	12	14
Miscellaneous farm type selling >100 cattle per year	Basic	Mean	300	19	196	55	29	0
		$x_{0.95}$.	611	51	399	152	81	0
	Removal	Mean	581*	7	196	230	148	0
		$x_{0.95}$	1344	17	399	571	410	0
	Vaccination	Mean	319	19	195	46	24	35
		$x_{0.95}$	629	49	399	100	49	77

[a] Mean total economic consequences are compared for significant difference (t-test) with the basic scenario at $p<0.05$

* Significantly ($p<0.05$) different from the basic scenario

3.3.3 Sensitivity analysis

Results of the sensitivity analysis are shown in Table 3.9. When doubling the scaling factors for transmission by local and professional contacts, the number of infected farms and total costs only increase slightly (and not significantly). In the basic scenario, all farms within a 1-km radius of a detected farm are put on surveillance for four weeks. Leaving out the surveillance zone only has a minor effect on the number of secondarily infected farms, but a significant impact on total economic consequences. Total national costs due to reintroduction of BHV1 decrease about 30%.

Table 3.9 Mean, 0.95 ($x_{0.95}$) and 0.99 ($x_{0.95}$) quantiles of the number of secondarily infected farms and economic consequences (x1000 Dfl.) for the basic strategy and some alternative scenarios, when simulating reintroduction of BHV1 into The Netherlands[a]

	First introduction on					
	Dairy farm			Miscellaneous farm type selling >100 cattle per year		
	Mean	$x_{0.95}$	$x_{0.99}$	Mean	$x_{0.95}$	$x_{0.99}$
Basic scenario						
Number of infected farms	0.9	3	6	21.6	43	56
Total losses and costs	44	110	186	300	611	765
Double risk local contacts						
Number of infected farms	1.0	3	7	22.1	46	57
Total losses and costs	46	114	186	307	616	788
Double risk professional contacts						
Number of infected farms	1.0	4	7	22.6	44	56
Total losses and costs	46	118	186	307	627	766
No surveillance zone						
Number of infected farms	0.9	3	6	22.1	45	56
Total losses and costs	36[*]	98	154	197[*]	439	530
Serological tests 4 times a year						
Number of infected farms	0.7	2	3	15.1[*]	33	36
Total losses and costs	41[b]	98[b]	126[b]	203[b,*]	385[b]	462[b]
Bulk-milk tests at three-month intervals						
Number of infected farms	1.5[*]	5	13	28.1[*]	58	78
Total losses and costs	60[c,*]	144[c]	257[c]	372[c,*]	738[c]	930[c]
10% 'illegal' animal transports						
Number of infected farms	3.8[*]	14	50	67.7[*]	152	217
Total losses and costs	49	131	247	354	750	843
10% more selling of animals						
Number of infected farms	1.0	3	7	23.3	57	74
Total losses and costs	45	114	192	321	675	852

[a] Mean outcomes are compared for significant difference (t-test) with the basic scenario at $p<0.05$.

[b] Excluding the increase in yearly standard serological monitoring costs from 5.42 to 10.85 million Dfl.

[c] Excluding the decrease in yearly standard bulk-milk monitoring costs from 9.97 to 3.32 million Dfl.

[*] Significantly ($p<0.05$) different from the basic scenario.

Doubling the frequency of monitoring on miscellaneous farms to four times per year has a significant impact when first introduction is on a miscellaneous 100+ farm. After first introduction on miscellaneous 100+, the 0.99-quantile of number of secondarily infected farms reduces from 56 to 36. As a consequence, total costs of an outbreak reduce; yearly costs for standard monitoring, however, will increase by Dfl.5.42 million. Less-frequent bulk-milk testing results in a significant increase in number of infected farms and total losses and costs, both after introduction on dairy and miscellaneous 100+ farm.

Of the other scenarios in Table 3.9, a significant effect on the size of an outbreak can be seen from a 10% non-compliance with the movement-ban off infected farms and farms on surveillance (illegal animal transports). The mean number of secondarily infected farms increases three-fold, although the economic impact is much smaller. This is explained by the increased purchase of latently infected cattle.

3.4 Discussion and conclusions

The most-important addition made to the general framework of Interspread (Jalvingh et al., 1995) for InterIBR is the inclusion of virus transmission between animals within a farm, and relating this to the probabilities of virus transmission between farms by various routes. Furthermore, data of the Dutch Identification and Recording system are used to generate a representative dataset of individual farms, each with its own characteristics.

To model transmission within herds, the principle of mass action is applied. This assumes random mixing of animals within the herd (Van Nes et al., 1998). For transmission between farms, non-random contacts are taken into account. Allocating each farm a geographic location makes it possible to define spatial zones, in which the various routes of transmission take place – thereby taking into account some of the spatial heterogeneity. Because farms are allocated at random in space with a pre-set density, the resulting spatial distribution is two-dimensional Poisson. When heterogeneity in spatial clustering matters, it becomes important to take real spatial aggregation of the population of farms into account. This will make it possible to target high-risk areas in The Netherlands. Also, different rates of animal contacts between farms are believed to be a source of heterogeneity in transmission (some farms being more likely to infect other farms, due to existing contacts between farms). In our study, a crude animal-contact structure between farm types is applied to deal with this issue. More data are necessary, however, to get better insight into variation of contact-structures between farms.

The output of the model shows that farm type with first introduction has a big impact on the probability and timing of detection, and the expected number of secondarily infected

farms, and consequently, on the total costs of the infection and its control. We conclude that when farmers comply with a movement ban in the case of an outbreak, a strategy with rapid removal of infected animals is not necessary to control outbreaks, and will incur much-higher costs than the so-called basic strategy described in this paper. Costs of animal-movement restrictions and policing the movement ban are, however, not included in the present calculations. Vaccination of infected farms will increase total costs – but could be advised to reduce the risk of BHV1-reactivation on infected farms. Furthermore, establishment of a 1-km surveillance zone around infected farms will engender a lot of organisational efforts and implementation costs – but (under current assumptions) has no significant impact on the number of secondarily infected farms. To limit the number of secondarily infected farms, more frequent monitoring on farms with frequent trade of cattle is an especially important instrument. Furthermore, monthly bulk-milk testing on dairy farms plays an important role in early detection of BHV1 reintroduction (also when first introduction is on another farm type).

Whereas this model only shows the consequences of a single reintroduction of BHV1, an important issue that policy makers have to take into account (and also essential for a sound cost-benefit analysis of various monitoring and control strategies) is the expected frequency of BHV1 reintroduction into a free area. This will be influenced mainly by the intensity of contacts with other areas, the prevalence of infection in these areas and the application of hygiene measures to prevent 'import' of virus. Yearly profits from a BHV1-free Netherlands are estimated to be Dfl. 53 million. Subtracting from this the yearly monitoring costs of the basic scenario (Dfl. 15 million), we conclude that in the case of first introduction on a farm that trades frequently, the estimated costs of a single reintroduction are with 95% confidence less than 2% of the estimated yearly gain from being free of BHV1 in The Netherlands. No data are available yet, however, to give insight into the expected frequency of reintroduction, and future research will have to focus also on this issue, similar to Horst et al. (1998).

The output of the simulation model depends on the quality of the assumptions and parameters used. Although we attempt to use real data as much as possible, some parameters or distributions have to be based on best-guesses of experts. Also, no data of real outbreaks are available to validate the model. The simulation model, however, provides a flexible tool to quantify the impact of modified parameters on the complex system of transmission dynamics and economics.

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Appendix 3.1

Input values of epidemiological parameters to model the spread and control of BHV1 within and between herds (unless indicated, input is based on common records in The Netherlands or expert opinion)

Variable	Value
Annual replacement rate (%)	
Dairy farm	30
Beef farm	73
Miscellaneous farm	34
Fattening period for veal calves, all-in all-out (weeks)	26
Reproduction ratio within herds ($R_{0, within}$)	
Non-vaccinated population (Bosch, 1997)	5.6
Week 1-3 after vaccination	3.5
Week 4-26 after vaccination	1.5
Infectious period (days) (Bosch et al., 1996)	
Non-vaccinated population	10
Week 1-3 after vaccination	7
Week 4-26 after vaccination	5
Fraction of herd infected after minor outbreak (%)	5
Probability of reactivation per latently infected cow (% / year)	0.13
Probability of reactivation per latently infected cow during transport (%)	7
Reduction by vaccination of probability to transmit virus after of reactivation (%)	
Week 1-3	45
Week 4-26	90
Probability of BHV1 transmission from dairy cattle to youngstock within the farm (%)	10
Local contacts (Eq. (1))	
Radius of local spread (km)	1
Probability of adequate local contact on dairy and miscellaneous farms (c_l)	1.00
Probability of adequate local contact on beef and veal farms (c_l)	0.25
Scaling factor for $R_{0, within}$ (w_c) on dairy and miscellaneous infected farms	2×10^{-5}
Scaling factor for $R_{0, within}$ (w_c) on beef and veal infected farms	0.5×10^{-5}
Professional contacts (Eq. (2))	
Probability of adequate professional contact on dairy and miscellaneous farms (c_p)	1.00
Probability of adequate professional contact on beef and veal farms (c_p)	0.25
Scaling factor for professional contacts (w_p) off dairy and miscellaneous infected farms	1×10^{-4}
Scaling factor for professional contacts (w_p) off beef and veal infected farms	0.25×10^{-4}
Percentage animal contacts on and off farm traced after detection of infected farm	
Week 1	95
Week 2	5
% contacts on and off detected farms and farms on surveillance, that carry on after detection	
Animal contacts	0
Local contacts	10
Professional contacts	10
Period of surveillance (weeks)	4

Appendix 3.2

Animal-contact structure between farm types, showing the distribution (%) of the destination of animal contacts off dairy farms (<2 years and ≥2 years) and off miscellaneous farms

	From		
	Dairy		Miscellaneous farm type
To	<2 years	≥2 years	
Dairy	6	47	26
Beef	5	9	17
Veal	61	0	18
Miscellaneous	28	44	39

Number of off-farm professional contacts per week per farm-type-herd-size combination

Farm type	Herd size	Number of professional contacts
Dairy	<30	23
Dairy	31-70	34
Dairy	71-100	34
Dairy	>100	48
Beef	1-100	2
Beef	101-200	3
Beef	>200	4
Veal	1-100	2
Veal	101-200	3
Veal	>200	4
Miscellaneous	<30	8
Miscellaneous	31-70	12
Miscellaneous	71-100	12
Miscellaneous	>100	17

Probability distribution for the distances across which animal contacts and professional contacts occur

	Distance class (km)				
Type of contact	0-5	>5-10	>10-20	>20-30	>30
Animal (%)	30	28	19	5	18
Professional (%)	48	24	14	6	8

Probability distribution for the interval from infection to detection on dairy farms with monthly bulk-milk tests

Weeks	3	4	5	6	7	8	9	10	11	12	13	14
Probability	0.05	0.10	0.15	0.20	0.20	0.14	0.08	0.04	0.01	0.01	0.01	0.01

Appendix 3.3

Input values to calculate costs of infection and control (unless indicated, input is based on common records in The Netherlands or expert opinion)

Variable	Value
Percentage of infectious animals with clinical symptoms	5
Mortality rate among clinically infected animals	2
Infectious period (days)	10
Dairy farm	
Average 305-day milk production per cow (kg)	7500
Price of 1 kg of milk (Dfl.)	0.75
Economic value of 1 kg of extra milk applying the quota system (Dfl.)	0.30
Monitoring costs of bulk-milk screening per year (Dfl.)	212
Clinical infection	
Number of weeks of reduced milk production	3
Percentage reduction in milk production	50
Percentage of infectious cows with an abortion	0.25
Costs of abortion (Dfl.)	650
Mortality costs (Dfl./animal)	2900
Subclinical infection	
Milk reduction per cow (kg) (Hage et al., 1998)	9.5
Beef and veal farms	
Fattening period (days)	
Beef	500
Veal	190
Slaughterweight (kg)	
Beef	366
Veal	155
Slaughter value (Dfl/kg)	
Beef	7.59
Veal	9.83
Clinical infection	
Number of weeks of reduced growth	3
Percentage reduction in growth	100
Percentage reduction in feed intake per week of reduced growth	50
Mortality costs (Dfl./animal) (beef / veal)	2006 / 1069
Subclinical infection	
Number of weeks of reduced growth	0.5
Percentage reduction in growth	50
Percentage reduction in feed intake per week reduced growth	50
Control measures	
Average period open place after culling (weeks)	4
Vaccination costs per animal (Dfl.)	8.50
Costs of veterinary visits (Dfl.)	43.50
Labour costs per sample of serum (Dfl.)	4.75
Costs of ELISA-screening (Dfl.)	6.00
Costs of administration (Dfl.)	13.00
Frequency of screening farms on surveillance	2
Value Added Tax (%)	6.0

Chapter 4

Simulation modelling of BHV1 control programme at national level, with special attention to sensitivity analysis

Paper by Vonk Noordegraaf, A., Nielen, M., Franken, P., Dijkhuizen, A.A., 2002. *Livestock Production Science*. In Press. Reproduced with permission of Elsevier Science.

Abstract

In this paper, the framework and basic results of the simulation model InterIBR-endemic are presented. This model was developed to support policy makers during the compulsory eradication programme for bovine herpesvirus type 1 (BHV1), that was implemented in The Netherlands in May 1998. The model closely interacted with a BHV1 monitoring programme, also related to the eradication campaign. The main objective of this study was to identify gaps in knowledge on BHV1 relevant for the eradication programme. For this, a detailed sensitivity analysis was performed for 31 model parameters.

Simulation of the Dutch BHV1 eradication programme resulted in a median period of 334 weeks to reach a cow-level prevalence of 5% in the dairy cattle population, with median costs of EUR 106 million. Uncertainty of parameters for local spread and reactivation of BHV1 had most impact on both the period and costs of the simulated eradication programme. The uncertainty of the yearly reactivation rate of latently infected animals affected the costs by EUR 43 million. These factors should, therefore, have priority in further research.

4.1 Introduction

A compulsory eradication programme for bovine herpesvirus type I (BHV1) (Engels and Ackermann, 1996) was implemented in The Netherlands in May 1998. The main reason to start this programme was the increased legislation with respect to BHV1 for international trade of cattle, bovine semen and embryos (EU-directives 64/432, 88/407 and 89/556). The eradication programme involved half-yearly vaccination with marker vaccine (Van Oirschot, 1999) for all non-certified cattle herds (except beef and veal herds), surveillance of certified BHV1-free herds and restrictions on cattle trade between herds. Spring 1999, the compulsory eradication programme was postponed due to BVD contamination of the vaccine, but most likely the programme will be continued in the near future.

To support policy makers during the eradication programme, two decision support tools were developed: (1) a BHV1 monitoring programme and (2) a BHV1 simulation model. The monitoring programme aimed to get insight into the incidence of outbreaks on various farm types, and the prevalence of infection over time (Assink et al., 2001). Main goal of the simulation model was to provide insight into the expected epidemiological and economic consequences of the eradication programme, and to identify gaps in the knowledge on BHV1 relevant for the eradication programme. Both the monitoring and simulation tool were based on the same farm data, available from several national farm databases. Furthermore, prevalence data from the monitoring programme were used to assign the starting conditions of simulation. In this way, both tools closely interacted and a ‘realistic’ simulation of the

BHV1 eradication programme was expected. However, many parameters in the model could not be based on data. Therefore, special attention was given to sensitivity analysis of these parameters.

The goal of this paper is to describe the framework of the model developed for simulation of the BHV1 eradication programme and to show some basic results. More specifically, we discuss how this model was used to identify relevant gaps in knowledge on BHV1 in order to support decision makers in setting priorities for further research.

4.2 Material and methods

4.2.1 Introduction

To model the Dutch eradication programme, the model InterIBR, developed to simulate control of epidemics in BHV1-free areas (Vonk Noordegraaf et al., 2000), was adapted to account for the simulation of control of an endemic situation. This resulted in the model InterIBR-endemic. Whereas the epidemic model started with virus introduction on a single herd, in the endemic situation a high fraction of the herds was infected at the starting point of simulation. Furthermore, the control strategy applied to an endemic situation differed significantly from control of epidemics, and involved regular vaccination and certification of BHV1-free herds.

The spatial simulation model InterIBR-endemic is classified as dynamic, stochastic and discrete (Law and Kelton, 1991). The model is dynamic, in that it simulates a system over time (as opposed to static models), stochastic in that it contains random components (as opposed to deterministic models) and discrete in that state variables change at separate points in time (as opposed to continuous) (Law and Kelton, 1991). The entities in this model are individual herds and attributes of each entity are the herd characteristics, such as farm type, herd size and BHV1 prevalence. We simulated events (e.g. vaccination) and interactions between entities (e.g. animal contacts), and studied the dynamic behaviour of the entities with respect to BHV1 infection.

4.2.2 Contents of simulation model InterIBR-endemic

4.2.2.1 General framework

A diagram of the general framework of InterIBR-endemic is shown in Figure 4.1. In the initialisation phase, farm data and values of model parameters were read from input files. Since the model included random components, multiple replications were run, where each replication simulated a possible pattern of the BHV1 control programme. A replication

started with assignment of characteristics to each herd, available from empirical distributions functions, such as the vaccine type used (live or killed marker vaccine) and within-herd prevalence of infected cattle.

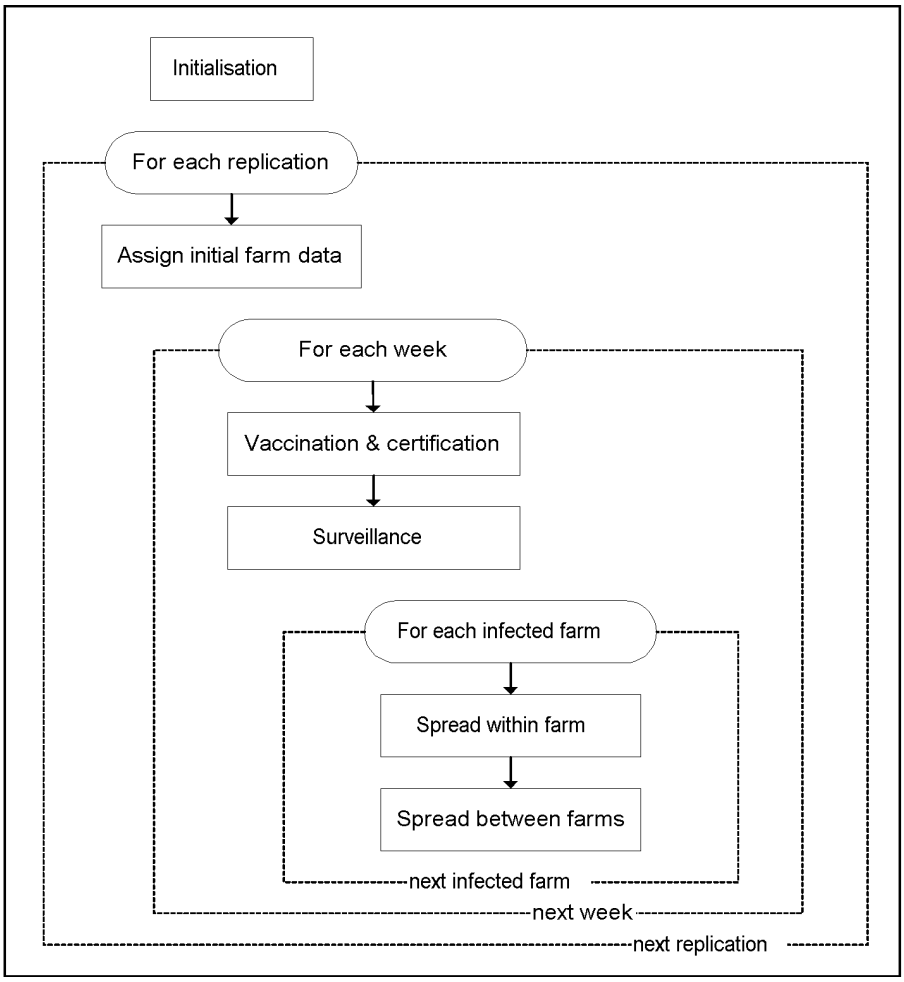

Figure 4.1 Diagram of the general framework of the model InterIBR-endemic, developed to simulate spread and control of endemic BHV1 within and between herds

The starting point of simulation (t=0) represented January 1999, when all Dutch cattle herds had started the compulsory vaccination. Time step of simulation was a week, and each week events related to spread and control of BHV1 were simulated. Adaptation of the epidemic model to an endemic situation mainly involved changes to the procedures of vaccination, certification and surveillance (see sections 4.2.2.3 and 4.2.2.4 for details). Simulation of transmission dynamics, within and between herds, was almost similar to the epidemic model (Vonk Noordegraaf et al., 2000), with small changes to infection of youngstock on dairy herds and simulation of between-herd animal contacts (section 4.2.2.5). In the current study, simulation ended when a simulated cow-level prevalence of 5% was reached in the population of dairy cattle, or when the number of simulated weeks was 1000.

Output of the simulation model was analysed (SPSS, 1999) to provide insight into the costs of the eradication programme and various epidemiological characteristics such as prevalence and incidence of infection on various farm types over time and routes of BHV1 transmission between herds. We observed only small variation of model output across replications, as opposed to the epidemic model (Vonk Noordegraaf et al., 2000). Computing time, however, was increased to about five hours for each replication, versus about ten minutes for the simulation of BHV1 epidemics. Simulation results in this study were based on ten replications and the sensitivity analysis on the mean of two replications only.

4.2.2.2 Farm data

Because of access to several national farm databases, the fictional farms of the epidemic model could be replaced by the actual data of farms present in The Netherlands. Furthermore, records of all animal movements in 1999 were obtained from the Dutch Identification and Registration system, and analysed to quantify model parameters related to between-herd animal contacts. All cattle herds with a status for BHV1 during the whole year of 1999, and with a herd size of at least one, were included in the model. This resulted in a total of 57,283 cattle herds. Summary information on cattle herds as included in the model with respect to farm type, herd size, BHV1 state, purchases and sales are given in Appendices 4.1 and 4.2. Each herd in the model was characterised by (1) farm type, (2) herd size, (3) geographic location, (4) BHV1 state at start of simulation, (5) yearly number of cattle purchased, (6) yearly number of cattle sold for life and (7) yearly number of youngstock (<2 years) sold for life on farm type dairy. Of these herd characteristics, only the BHV1 state could change during simulation.

Whereas the national farm database contained many combinations of farm types, in the model this was reduced to four farm types. The model farm types were dairy (if original type included dairy), beef (if original type was beef only), veal (if original type was veal only) or miscellaneous (for all combinations of original farm types without dairy). Most herds had farm type dairy or miscellaneous (52% and 44% respectively), while farm type beef and veal was only a small group. The average herd size of the period August-December 1999 was considered the herd size in the model. Geographic location was represented by the x-y co-ordinates of the farms. Ten herd states for BHV1 were distinguished in the model, similar to the BHV1 control programme, of which the states ‘vaccinated’, ‘vaccination exemption for beef and veal’ and ‘certified’ were most relevant. Overall, 69% of the cattle herds had BHV1 state ‘vaccinated’ at t=0, and 21% of the herds was certified BHV1-free (Appendix 4.1). In general, the fraction of certified herds was lower on farms with a bigger herd size.

Other individual herd characteristics included in the model were the type of marker vaccine used, a decision date on continuation of vaccination for each vaccinating herd, a

surveillance date for each certified BHV1-free herd and the number of infectious and latently infected cattle within each infected herd. These characteristics were assigned at the start of a replication to each herd from empirical distributions (Appendix 4.3). For example, the initial prevalence of infected cattle on each farm type was based on distributions available from the BHV1 monitoring programme (Assink et al., 2001). As with the BHV1 state, simulation of spread and control of BHV1 evoked changes of these herd characteristics over time.

4.2.2.3 Vaccination and certification

The Dutch BHV1 eradication programme involved half-yearly compulsory vaccination, which was simulated by a half-yearly decision moment for each vaccinating herd. Each week, the model checked for herds with BHV1 state 'vaccinated' if the decision date was reached. When reached, the simulation procedure of vaccination and certification, as shown in Figure 4.2, was initialised.

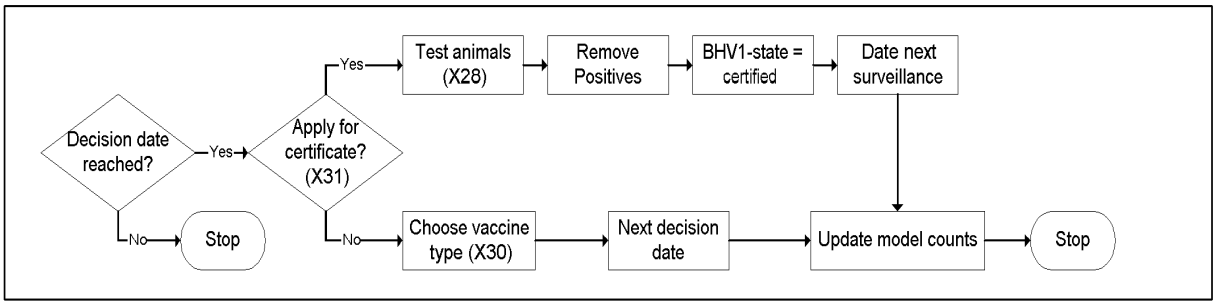

Figure 4.2 Diagram of the simulation procedure for vaccination and certification on vaccinating herds in the model InterIBR-endemic (parameters X given in Appendix 4.3)

The simulation procedure started with the decision whether to re-vaccinate the herd or to apply for a BHV1-free certificate. This decision process was simplified in the model by a probability to apply for a certificate, given the within-herd prevalence of infected cattle (Appendix 4.3, factor *X*31). At default, a herd that had less than 10% of its cattle infected, had a 50% probability to apply for a certificate in the model. If the herd applied for a certificate, cattle was tested and positives found were removed. The BHV1 state of the herd then became 'certified BHV1-free' and a surveillance date was assigned, based on the surveillance scheme for that farm type. The number of latently infected cattle that tested positive was simulated with a binomial process bin(t,p) (Law and Kelton, 1991) in which t was the number of truly infected cattle and p the test sensitivity (Appendix 4.3, factor *X*28). If a herd did not apply for a certificate, vaccine type live or killed (Appendix 4.3, factor *X*30) and a next decision date were assigned to the herd. The procedure ended with an update of model counts, such as the number of cattle vaccinated.

4.2.2.4 Surveillance

In the epidemic model for BHV1 (Vonk Noordegraaf et al., 2000), and also in related models for CSF and FMD (Jalvingh et al., 1999), the event of detection of an outbreak was based on a pre-defined probability distribution for the interval between infection and detection. In InterIBR-endemic, factors related to this interval were modelled: frequency of surveillance, fraction of infected animals in the herd, sensitivity and specificity of the tests and number of animals included in the sample (Graat et al., 2001). Surveillance in the Dutch programme was based on monthly bulk-milk tests for certified dairy herds and half-yearly serological sampling on certified non-dairy herds. As described above, each certified herd was assigned a surveillance date in the model. Each week, the model checked for herds with BHV1 state 'certified' if this date was reached. When reached, the simulation procedure for surveillance, as shown in Figure 4.3, was initialised.

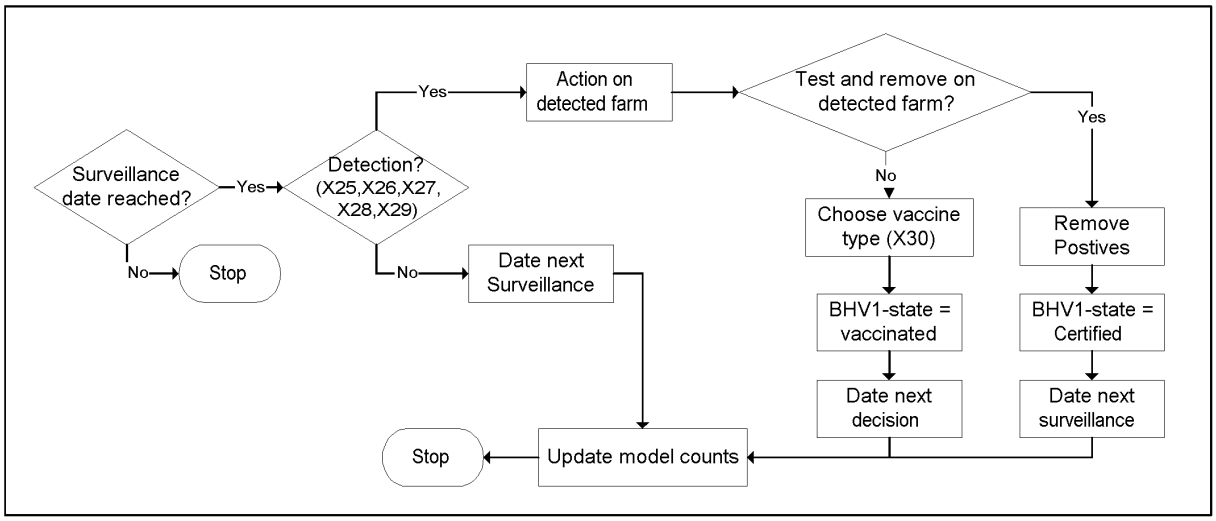

Figure 4.3 Diagram of the simulation procedure for surveillance of certified herds in the model InterIBR-endemic (parameters X given in Appendix 4.3)

Simulation of the stochastic event of detection was based on calculation of the herd-level sensitivity (HSE) and the herd-level specificity (HSP) (Martin et al., 1992; Noordhuizen et al., 1997). For bulk-milk tests on dairy herds, it was assumed that outbreaks could only be detected if the prevalence of infected animals was above a certain fraction of infected animals in the herd (Appendix 4.3, factor *X*27). On non-dairy farms it was assumed that a herd was declared positive when at least one of the animals in the sample was tested positive. The number of herds with false positive test-results was counted in the model, but no further actions were simulated on these herds. It was assumed that at detection of an outbreak, infected animals were only removed if less than 10% of the herd was infected. Otherwise, the BHV1 state became 'vaccinated' and a next decision date was assigned (see section 4.2.2.3).

4.2.2.5 Spread within and between farms

Simulation of BHV1 spread within infected herds was based on a mathematical SIR-modelling approach (De Jong, 1995), taking into account the occurrence of minor and major outbreaks at virus introduction (Graat et al., 2001). Reactivation of latently infected cattle in a herd was accounted for with weekly rate 1- $(1 - r / 52)^{P}$ (with P the number of latently infected cattle and r the reactivation rate of latently infected cattle; Appendix 4.3, factor *X*5). For more details on the simulation of within-herd spread we refer to Vonk Noordegraaf et al. (2000). Changes were made to model infection of youngstock on farm type dairy. Whereas in the epidemic model there was a constant probability of transmission from dairy cattle to youngstock, in the current model only major outbreaks in the dairy herd could cause infection of youngstock (Appendix 4.3, factor *X*15 and *X*16). Furthermore, spread of infection from youngstock to other herds was only assumed possible by animal contacts during the short period of virus circulation. Infection of youngstock also affected the natural replacement rate of infected dairy cattle. It was assumed that during the period that youngstock was infected, the prevalence of infected dairy cattle did not decrease because of natural replacement.

Spread of BHV1 between farms was simulated by animal contacts, local spread and professional contacts. For each route, transmission depended on the number of contacts and the risk of each contact, as described in detail by Vonk Noordegraaf et al. (2000). The expected number of animal contacts (Appendix 4.2), the animal-contact matrix between farm types (Appendix 4.4), and the distribution function for distance of animal contacts (Appendix 4.4) were based on analysis of the recorded animal movements in The Netherlands of the year 1999. According to regulations of the BHV1 programme in The Netherlands, the BHV1 state of herds determines whether an animal contact is allowed. For example, herds with BHV1 state 'certified' are not allowed to purchase an animal from a non-certified herd. This was included in the simulation of animal contacts. For each simulated animal contact, selection of a destination farm in the model included criteria related to (a) distance of contact, (b) farm type, (c) BHV1 state and (d) expected yearly number of animals purchased on farms that meet criteria (a), (b) and (c).

4.2.3 Sensitivity analysis using a metamodel approach

4.2.3.1 Background of metamodels

An objective of the current study was to use the model InterIBR-endemic to identify gaps in the knowledge on BHV1 that were relevant for the eradication programme. For this we applied a statistical approach to sensitivity analysis, based on the techniques of Design of Experiments (DOE) and metamodels. Whereas sensitivity analysis is often limited to

changing only one input at a time, this approach is considered more effective and efficient to estimate the relationship between model input and output (Kleijnen and Sargent, 2000). In DOE terminology, model input parameters are called *factors (X)*, and output measures are called *responses (Y)* (Law and Kelton, 1991). A metamodel approximates the input-output transformation of a simulation model by statistical analysis (e.g. least squares regression) of a simulation experiment. In such an experiment, of which the design should be guided by the statistical theory of DOE, values of one or more factors change and each set of factor combinations is a scenario in the experiment. For more details we refer to Kleijnen (1998).

4.2.3.2 Application of metamodel approach

The metamodel approach was applied to 31 parameters of the simulation model InterIBR-endemic (Appendix 4.3). These factors were related to the spread of BHV1 within and between herds. Each factor was assigned two levels in the experiment, which reflected the range within which the true value was expected to be. These levels were based on experimental data and discussion with experts, and were standardised at 0 (low) or 1 (high) in the metamodel. The design consisted of 64 scenarios, and for each simulation response of interest a regression metamodel was estimated. For a more detailed description of the application we refer to Vonk Noordegraaf et al., (2002).

Three simulation responses, considered most relevant by policy makers, were used as dependent variables in the sensitivity analysis: ($Y1$) number of weeks to reach a cow-level prevalence of 5% in the population of dairy cattle, ($Y2$) total discounted programme costs in period $Y1$ (EUR x 10^6) and ($Y3$) number of virus circulations per year on certified BHV1-free dairy herds. Since response $Y1$ was highly correlated to response $Y2$, and discussed elsewhere in relation to methodological peculiarities (Vonk Noordegraaf et al., 2001), in this paper only metamodel results of responses $Y2$ and $Y3$ are discussed. Analysis was based on a second order polynomial estimated by OLS regression. For response $Y2$, costs were discounted at an annual rate of 4%. These costs included the costs of the BHV1 eradication programme due to vaccination, tests for certification, surveillance by bulk-milk and serological screening and early removal of infected animals (Appendix 4.5).

4.3 Results

4.3.1 Simulation output

Results of descriptive analysis of three simulation outcomes considered most relevant by policy makers are given in Table 4.1. Simulation of continuation of the compulsory Dutch

eradication programme for BHV1 resulted in a median period of 334 weeks to reach a cow-level prevalence of 5% in the dairy cattle population. Median costs in this period were EUR 106 million and the median number of outbreaks per year on certified BHV1-free dairy farms was 102.

Table 4.1 Descriptive analysis of three model outcomes considered most relevant by policy makers, with simulation of a compulsory eradication programme for BHV1 as implemented in The Netherlands. Outcomes are based on ten replications of the model InterIBR-endemic

Simulation Outcome	Median	Min	Max	Mean	St. dev.
*Y*1	334	316	360	335	11.8
*Y*2	106	103	111	106	2.6
*Y*3	102	84	140	106	16.8

*Y*1 = number of weeks to reach a cow-level prevalence of 5% in the population of dairy cattle
*Y*2 = total discounted costs in period *Y*1 (EUR x 10^6)
*Y*3 = average number of outbreaks per year on certified-free dairy farms in period *Y*1

The min and max column of Table 4.1 show the range of each model outcome based on ten replications. Comparing these ranges to the mean, *Y*3 showed the widest range, whereas other ranges were relatively narrow. It is important to note that the presented variation of model outcome does not include the impact of parameter uncertainty (see section 4.3.2 on metamodel results). Of the total costs (*Y*2), on average 55% was due to vaccination, 19% to surveillance tests, 17% to early removal of infected cattle on farms applying for a certificate and 9% due to serological tests required for certification. These costs did not include the costs that were made before 1999, or costs required for final eradication of the virus following the cow-level prevalence of 5% in the dairy cattle population.

The simulated temporal pattern of animal-level BHV1 prevalence on the various farm types is shown in Figure 4.4. In the cattle population on farm type dairy (Figure 4.4a) the simulated prevalence of infected cows > 2 years decreased from 22% at t=0, to about 5% after 6.5 years of control, showing very small variation between replications. In the cattle population on farm type beef (Figure 4.4b) the simulated prevalence decreased with more variation, and the prevalence was around 15% after 6 years of control. Simulated prevalence in the cattle population on farm type veal (Figure 4.4c) was low and quite stable within a range of 1-5%. On farm type miscellaneous (Figure 4.4d), the simulated prevalence of infected cattle initially increased, followed by a stabilisation at 20% of infected cattle.

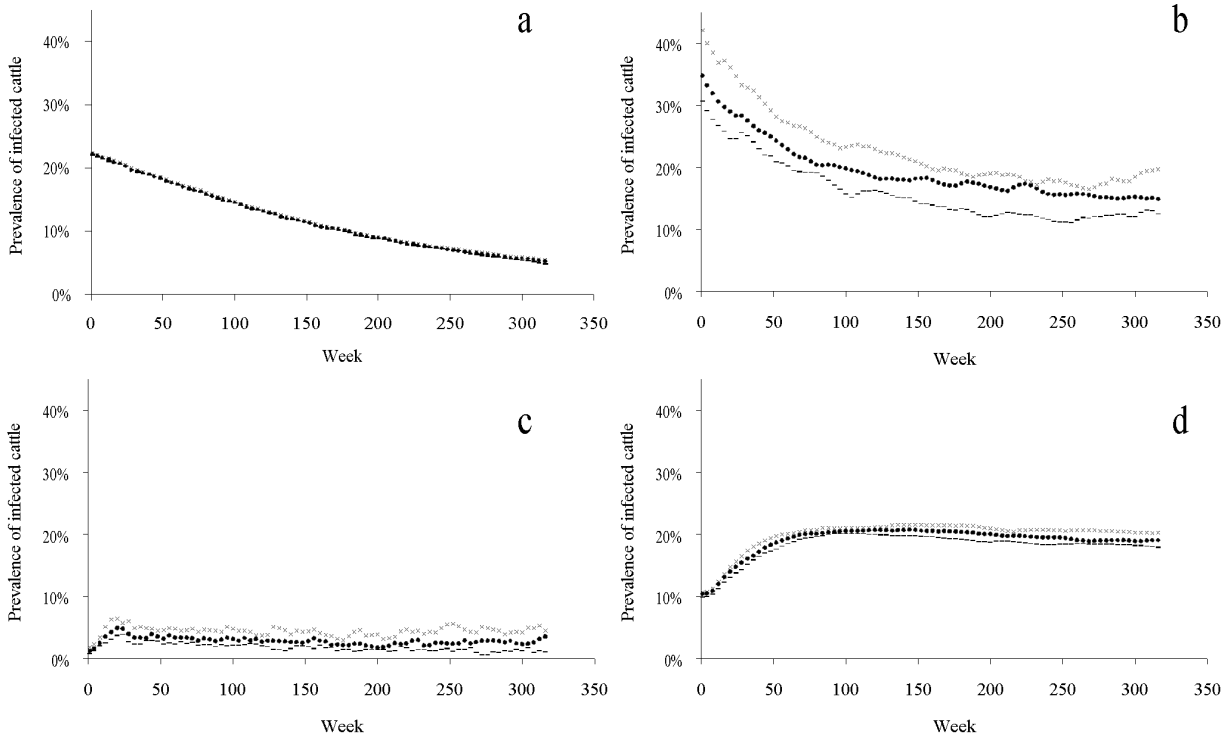

Figure 4.4 Simulated prevalence of BHV1 infection in the cattle population on farm type dairy (a) (n=1,716 x 10^3 cows > 2 years), (b) farm type beef (n=34 x 10^3 animals), (c) farm type veal (n=507 x 10^3 animals) and (d) farm type miscellaneous (n=618 x 10^3 animals) for a compulsory BHV1 eradication programme as implemented in The Netherlands. Data points show, with a time step of four weeks, the median (•), minimum (-) and maximum (x) prevalence of infected cattle based on ten replications of the model InterIBR-endemic

Simulation outcomes of the number of certified BHV1-free herds and the incidence of virus circulation on certified herds, for farm type dairy and miscellaneous, are presented in Table 4.2. On both farm types the simulated number of certified BHV1-free herds increased to about 75-80% of total herds when the cow-level prevalence of 5% was reached in the population of dairy cattle. In the first simulated year, a large increase in the number of certified herds was observed. The incidence of virus circulation on certified herds, causing both small and large outbreaks, showed much variation between replications. This was especially true for farm type miscellaneous, which also had a higher number of virus circulations than on farm type dairy. For both farm types, a drop in the number of virus circulations was observed in the fourth year of the programme, after which the number increased again. Table 4.2 also shows the number of virus circulations that were detected each year by the surveillance programme, which was about 80% of the simulated circulations.

Table 4.2 Simulated number of certified BHV1-free herds at the end of each year and the number of certified herds with virus circulation and detected outbreaks per year on farm type dairy (A) and farm type miscellaneous (B), for a compulsory BHV1 eradication programme as implemented in The Netherlands. For each year the median, minimum and maximum number is shown, based on ten replications of the model InterIBR-endemic

Year	No. certified herds (x 10^3)	No. certified herds with virus circulation per year			No. detected outbreaks on certified herds per year		
	Median	Median	Min	Max	Median	Min	Max
(A) Farm type dairy (n=29.9 x 10^3 farms; farms certified at start = 7.3 x 10^3)							
1	12.5	82	70	98	71	56	86
2	15.3	104	74	130	85	60	105
3	17.3	112	51	138	86	42	108
4	19.1	67	45	105	58	36	83
5	20.7	108	63	209	81	48	149
6	22.3	118	65	196	91	52	140
(B) Farm type miscellaneous (n=25.0 x 10^3 farms; farms certified at start = 4.7 x 10^3)							
1	14.5	160	129	192	96	86	131
2	17.3	201	144	233	192	146	216
3	18.4	204	99	257	170	111	207
4	19.1	126	71	252	129	75	205
5	19.6	199	62	342	160	70	288
6	19.9	222	77	389	189	80	283

Based on the incidence of virus circulations and the number of herds at risk in the model (Table 4.2), a virus circulation rate was calculated for both certified and non-certified herds for each year of the simulated programme (Table 4.3). The circulation rate on non-certified herds was about 35 times higher than on certified herds. Due to vaccination and natural immunity, circulation on non-certified herds, however, mostly resulted in a small outbreak. Whereas 67% of the simulated circulations on certified herds resulted in a large outbreak, this was only 6% on non-certified herds. The rate of large outbreaks, therefore, was three times higher in non-certified herds. The virus circulation rate on farm type miscellaneous appeared to be almost twice as high as compared to farm type dairy, for both certified and non-certified herds.

The relative importance of each transmission route on virus circulation, on both certified and non-certified herds of all farm types, is shown in Table 4.4. Local spread accounted for more than half of the simulated virus circulations on certified herds, about 29% was due to purchase of animals. On non-certified herds, almost two-third of the circulations was due to BHV1-reactivation of latently infected cattle in the herd and 26% was due to transport related reactivation of a purchased animal. A time trend was observed for the relative importance of

Table 4.3 Simulated rate of virus circulation on certified and non-certified herds, defined as the incidence of virus circulation per 1000 farms at risk per year, on farm type dairy (A) and farm type miscellaneous (B) for a compulsory BHV1 eradication programme as implemented in The Netherlands. For each year the median, minimum and maximum rate is shown, based on ten replications of the model InterIBR-endemic

Year	Circulation rate certified herds			Circulation rate non-certified herds		
	Median	Min	Max	Median	Min	Max
(A) Farm type dairy (n=29.9 x 10^3 farms)						
1	8.2	7.0	9.8	275	267	281
2	7.4	5.3	9.3	268	256	278
3	6.9	3.1	8.5	246	237	254
4	3.7	2.5	5.8	213	204	228
5	5.4	3.2	10.5	200	190	213
6	5.5	3.0	9.1	189	170	204
(B) Farm type miscellaneous (n=25.0 x 10^3 farms)						
1	16.0	13.0	19.2	364	353	371
2	12.6	9.1	14.7	472	448	490
3	11.4	5.5	14.5	468	452	482
4	6.8	3.8	13.5	406	380	430
5	10.3	3.2	17.8	357	340	387
6	11.3	3.9	19.7	305	278	326

each transmission route on certified BHV1-free herds. The relative impact of local spread decreased from 72% in the first year to 49% in year 6. The relative impact of animal purchase increased from 8% in the first year to 34% in year 6.

Table 4.4 Fraction of virus circulations on certified and non-certified herds caused by each route of transmission, simulated for a compulsory BHV1 eradication programme as implemented in The Netherlands. For the total eradication period of 6.5 years, the median, minimum and maximum fraction is shown, based on ten replications of the model InterIBR-endemic

Transmission route	Certified herds			Non-certified herds		
	Median	Min	Max	Median	Min	Max
Local	0.53	0.47	0.63	0.05	0.04	0.05
Professional	0.10	0.09	0.13	0.01	0.01	0.01
Purchase animal						
- infectious animal	0.21	0.13	0.24	0.04	0.03	0.07
- reactivated at transport	0.08	0.06	0.12	0.26	0.26	0.27
Reactivation within herd	0.08	0.07	0.11	0.64	0.61	0.65

4.3.2 Metamodel results

Dependent variable *Y*1 was highly correlated to *Y*2 (ρ=0.98), the correlation coefficient between dependent variable *Y*2 and *Y*3 was 0.72, and between *Y*1 and *Y*3 it was 0.70. The final metamodel for *Y*2 (Table 4.5) contained the same factors as the metamodel for *Y*1 (Vonk Noordegraaf et al., 2001).

Table 4.5 Significant factor estimates (P<0.05) from a multivariable OLS regression model for dependent variable *Y*2; the mean total discounted costs (EUR x 10^6) in the period to reach a cow-level prevalence of 5% in the total dairy cattle population (R^2_{adj} = 0.83)

Factor	Description	β	S.E.	P
*X*0	Intercept	62.9	10.4	0.000
*X*1	Local spread	34.2	10.0	0.001
*X*4	Reactivation rate transport	31.1	5.7	0.000
*X*5	Yearly reactivation rate	42.9	5.7	0.000
*X*6	Professional contact	17.1	5.7	0.004
*X*8	R_0 non-vaccinated	14.1	8.1	0.090
*X*10	R_0 killed vaccine	20.4	8.1	0.015
*X*24	Hygiene certified herd	-6.1	8.1	0.457
*X*28	Sero sensitivity	-16.4	5.7	0.006
*X*30	Vaccine type used	15.5	8.1	0.062
*X*1 x *X*8	Local spread x R_0 non-vacc.	45.7	11.5	0.000
*X*1 x *X*24	Local spread x Hygiene cert. herd	-32.3	11.5	0.007
*X*10 x *X*30	R_0 killed vaccine x Vaccine type	37.8	11.5	0.002

Factor estimates in Table 4.5 show the expected effect on calculated costs, when a factor is changed from its low to its high level. For example, changing the yearly reactivation rate (*X*5) from low to high increased calculated costs based on the simulation experiments by almost EUR 43 million. If local spread (*X*1) was high, a high level of hygiene on certified herds (*X*24) significantly decreased costs by EUR 32 million, as shown by the negative interaction effect (*X*1 x *X*24).

The metamodel for *Y*3 contained five main effects and two two-factor interactions (Table 4.6). The number of outbreaks per year on certified BHV1-free dairy herds was affected most by a change of the local spread parameter (*X*1): 220 outbreaks per year. Local spread also strongly interacted with the R_0-value in non-vaccinating herds (*X*8) and with the level of hygiene on certified herds (*X*24).

Table 4.6 Significant factor estimates (P<0.05) from a multivariable OLS regression model for dependent variable *Y*3; the mean number of outbreaks per year on certified BHV1-free dairy herds (R^2_{adj} = 0.78)

Factor	Description	β	S.E.	P
*X*0	Intercept	-59.1	32.8	0.078
*X*1	Local spread	219.5	40.2	0.000
*X*4	Reactivation rate transport	95.7	23.2	0.000
*X*6	Professional contact	125.4	23.2	0.000
*X*8	R_0 non-vaccinated	28.7	32.8	0.386
*X*24	Hygiene certified herd	-20.0	32.8	0.545
*X*1 x *X*8	Local spread x R_0 non-vacc.	191.2	46.5	0.000
*X*1 x *X*24	Local spread x Hygiene cert. herd	-151.4	46.5	0.002

4.4 Discussion and conclusions

4.4.1 Model development and validation

The simulation model InterIBR-endemic, described in this paper, was developed as a decision support tool for the BHV1 eradication programme in The Netherlands. The model is a simplified representation of the complex system of BHV1 spread and control within a country, and model output must of course be treated as such. An important issue in model development is validation, which is concerned with determining whether the simulation model is an adequate representation of the system under study, given the goal of the model (Law and Kelton, 1991). True validation requires a statistical comparison between model output and data from the real system, based on observed variation of both real life and model outcome. In this study some data on the real system were available from the BHV1 monitoring programme to compare with simulation outcomes. These data, however, are based on measurements of one large-scale 'experiment' only, and therefore can not be used for statistical comparison. Another issue is that compulsory vaccination was postponed after the first year of the eradication programme, which was not accounted for in this study. Strong validation claims are, therefore, impossible, but experimentation with the model gave insight into the model's input-output behaviour. This behaviour should agree with prior knowledge of the real system (Kleijnen, 1999). The metamodel approach to sensitivity analysis, discussed in section 4.4.2, was therefore considered a very important tool in the validation process of the simulation model InterIBR-endemic.

Comparison of model output and real data from the first year of the programme (1999) was considered important for the face validity of the model. In 1999, the real number of certified dairy herds was almost constant at 7450 herds and 63 outbreaks were detected by surveillance. This implied an outbreak rate of 8.4 per 1000 farms at risk in 1999. Based on

simulation results (Table 4.2), the number of certified dairy herds was expected to increase in 1999. This difference can mainly be explained by the postponed compulsory vaccination. Correcting the number of simulated outbreaks (median of 82) for the average number of herds at risk, the median outbreak rate on certified dairy farms was 8.2, with a range from 7.0 to 9.8 per 1000 farms at risk in 1999 (Table 4.3). The actually observed rate, therefore, was within the range of the simulated outbreak rate. Although this does not prove that the model is valid for its parameters and mechanisms, face value is considered important for the confidence decision makers can have in the model.

4.4.2 Metamodel approach to sensitivity analysis

When a system is modelled stochastically, total variation of the outcome can be based on two components: variability and uncertainty. Whereas variability is a function of the system, uncertainty is due to imperfect knowledge about the parameters that characterise the system that is being modelled (Vose, 2000). Decision making should account for both variability and uncertainty (Hardaker et al., 1997). Variability and uncertainty can both be modelled with a Monte Carlo approach, which requires probability distributions to reflect the uncertainty of parameters and to reflect the inherently variable stochastic nature of the system. Model output will then show a probability distribution for each model outcome, based on both variability and uncertainty.

The model presented in this paper contained many parameters and a Monte Carlo approach to each parameter would, therefore, need a high number of probability distributions to be estimated and as a consequence a high number of replications. As one replication already required about 5 hours computing time, time would then become a serious limitation. Furthermore, a Monte Carlo approach in itself would not give insight into which of the parameters had most impact on the model outcome, which actually was one of the main objectives of this study. The current model was, therefore, structured around the variability of the system and parameter values remained constant. Variation of simulation outcomes presented in section 4.3.1 was based on this system variability, without accounting for parameter uncertainty. The latter was quantified by the metamodel approach in section 4.3.2, in which parameter values were set at different levels. Compared to one-factor-at-a-time sensitivity analysis, this approach more effectively described the input-output transformation implied by the simulation model, and gave insights into interactions between factors. Furthermore, the techniques of experimental design and metamodeling gave insight into which parameters had most impact on model outcome, without the need to estimate a full uncertainty probability distribution for all parameters (Van Groenendaal and Kleijnen, 1997).

An important issue in sensitivity analysis is how to choose the factor levels, since obviously the importance of the factors is related to the experimental frame chosen. Whereas

in some studies dealing with sensitivity analysis, all parameter values are changed by a fixed percentage (e.g. 25%), we tried to take into account the uncertainty related to each individual parameter by discussions with experts, re-analysis of existing data and screening of literature. The low and high values assigned to each parameter in the experiment more or less reflected the borders of the interval within which the true value was expected to be.

4.4.3 Practical implications of results

Development of the simulation model for BHV1 provided a basis for collection and assimilation of various data with regard to the population of cattle farms in The Netherlands. By itself, this already was considered a very important function of the simulation process. Furthermore, we suggest that this study can help to set priorities for further empirical research, and hypotheses based on simulation results can be used in the discussion on the design of a BHV1 monitoring and eradication programme.

4.4.3.1 Implications for empirical research

Assuming that the chosen levels in the experimental design reflected true uncertainty of the model parameters, factors found significant for model outcome should have priority in further empirical research. To reduce total uncertainty, more information should be collected on these factors. A next step could then be to replace the most important deterministic parameters by probability distributions obtained from the new information. Application of a quantitative risk analysis approach could then account for overall variability as well as for uncertainty of the most important factors.

The two factors that affected both the period and costs of the simulated eradication programme most were local spread and reactivation. Local spread strongly interacted with the factors 'hygiene' and 'R_0 of non-vaccinated animals'. The uncertainty of the yearly reactivation rate of latently infected animals affected the eradication costs by almost EUR 43 million. The outbreak rate on certified dairy herds was affected most by the parameters for local spread and professional contacts. This outbreak rate was deemed critical by the decision makers, because it would greatly influence the motivation of farmers to certify the herd BHV1-free.

4.4.3.2 Implications for BHV1 monitoring programme

An initial increase of the prevalence on farm type miscellaneous was observed in the simulation. One explanation could be that one or more parameters or mechanisms in the model overestimated the risk of outbreaks on this farm type. Another explanation could be

that the observed prevalence in the monitoring programme underestimated the true prevalence, since prevalence data were mainly based on small herds. Whereas 80% of the miscellaneous herds have a herd size of less than 30 animals (Appendix 4.1), almost 70% of the animal population on this farm type is housed on the other 20% of miscellaneous herds. Simulation results (not shown) suggested that outbreaks were more likely to occur on farms with a bigger herd size, and the high population prevalence observed in the model was mainly due to these herds. To test this hypothesis, the BHV1 monitoring programme should stratify by herd size, when sampling herds for estimation of population prevalence.

Since the BHV1 monitoring programme mainly focused on the incidence of outbreaks on certified herds, no data are yet available to estimate the incidence of outbreaks on non-certified herds. Simulation results suggested that the incidence of outbreaks is very high on non-certified herds, and that reactivation of latently infected animals is the main reason of these outbreaks. Outbreaks in this non-certified population of herds will greatly influence the progress of the eradication programme in the field. Estimation of the incidence of outbreaks on non-certified herds in the field is, therefore, considered very important.

4.4.3.3 Implications for BHV1 eradication programme

In this study, the model was not used to explore the efficiency of alternative control strategies. Based on results shown, however, some implications for the BHV1 eradication programme can be discussed. Towards the end of the simulated eradication programme, an increase of the virus circulation rate on certified herds was observed. This coincided with an increased relative impact of animal purchase as a route of virus introduction. This shows the importance of a more closed farming system and quarantine measures for animals purchased. Farmers should, therefore, be made aware of the risks concerning introduction of BHV1, and how their management can reduce these risks. Also, measures at national level could be taken, such as a compulsory test for BHV1 of all animals purchased, or more frequent surveillance of certified herds, to reduce the risk from animal purchase. The simulation model can be used to explore the efficiency of these strategies in more detail.

Results of the metamodels showed the impact of bio-security measures on certified herds on the expected costs of the eradication programme and the outbreak rate on certified herds. In the model, increased hygiene decreased the risk of BHV1 introduction by local spread. The effect of bio-security measures strongly interacted with the level of local spread. If local spread was at its high level, increased hygiene reduced total expected costs of the programme by EUR 32 million. Furthermore, metamodel results showed that, based on knowledge about how BHV1-vaccines influence disease transmission, preference should be given to live vaccine. Use of killed vaccine prolonged the eradication period, and increased total costs with

a range between 15.5 to 53.3 million Euro, depending on the R_0 of animals vaccinated with killed vaccine.

4.4.4 Final remarks

We conclude that, although much research has been done on BHV1, there still are many uncertainties that can greatly influence the epidemiological and economic consequences of a national BHV1 eradication programme. Development of a simulation model, together with a metamodel approach for sensitivity analysis, is a useful tool to detect where essential knowledge is inadequate. Furthermore, the model can be used to generate hypotheses, and thereby help in the design of an eradication programme combined with a monitoring programme. Future research will focus on exploration of alternative control strategies.

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Appendix 4.1

Summary information on cattle herds (*n*=57,283) with respect to farm type, herd size and BHV1-state at January 1999, used as input for the simulation model InterIBR-endemic

Farm type (FT)	Herd size class (HS)	No. herds	Average herd size	% of herds per FT-HS combination in each BHV1-state			
				Vaccinate	Exemption	Certified	Other [b]
Dairy	<30[a]	5,499	19[a]	66.3	0.0	29.7	3.9
Dairy	30-70[a]	16,368	50[a]	69.1	0.0	18.6	4.1
Dairy	71-100[a]	5,511	82[a]	76.3	0.0	18.6	5.1
Dairy	>100[a]	2,490	132[a]	83.3	0.0	10.9	5.9
Dairy total	All	29,868	58[a]	71.1	0.0	24.5	4.4
Beef	<100	623	32	30.5	68.4	0.6	0.5
Beef	100-200	57	130	15.8	82.5	0.0	1.8
Beef	>200	23	291	30.4	69.6	0.0	0.0
Beef total	All	703	48	29.3	69.6	0.6	0.6
Veal	<100	459	52	30.3	69.1	0.2	0.4
Veal	100-200	370	158	13.8	86.2	0.0	0.0
Veal	>200	920	466	12.2	87.8	0.0	0.0
Veal total	All	1,749	290	17.3	82.6	0.1	0.1
Miscellaneous	<30	20,022	9	73.4	2.1	19.8	4.7
Miscellaneous	30-70	3,259	45	71.2	6.5	18.1	4.2
Miscellaneous	71-100	681	83	70.9	14.7	10.6	3.8
Miscellaneous	>100	1,001	232	53.5	40.1	4.8	1.6
Miscellaneous total	All	24,963	25	72.3	4.6	18.7	4.5

[a] Based on number of cows > 2 years

[b] BHV1-state 'other' included the states 'exemption youngstock vaccination', 'refuse to vaccinate', 'conscientious objector' 'research1', 'research 2', 'observation' and 'unknown'

Appendix 4.2

Summary information on cattle herds (*n*=57,283) with respect to farm type, herd size, purchases and sales of animals for life, used as input for the simulation model InterIBR-endemic, based on analysis of data from the Dutch Identification and Registration system of the whole year 1999

Farm type	Herd size class	No. herds	% of herds closed [b]	% of herds with number of cattle sold for life in 1999 [c] (rows add up to 100%)							
(FT)	(HS)		per FT-HS	0	1-2	3-6	7-10	11-15	16-25	26-50	>50
Dairy	<30[a]	5,499	42.2	9.6 / 34.8	18.2 / 27.6	31.8 / 20.3	19.7 / 6.3	12.4 / 3.4	5.7 / 3.8	2.0 / 3.0	0.5 / 0.7
Dairy	30-70[a]	16,368	44.8	2.4 / 29.1	7.1 / 26.8	20.8 / 27.5	19.7 / 9.8	19.6 / 3.7	21.1 / 1.6	8.7 / 1.1	0.6 / 0.3
Dairy	71-100[a]	5,511	41.1	1.2 / 24.4	4.6 / 23.3	13.4 / 26.2	15.4 / 13.8	17.7 / 7.2	25.1 / 3.7	20.2 / 0.9	2.4 / 0.5
Dairy	>100[a]	2,490	31.6	0.7 / 24.1	2.4 / 19.7	9.0 / 24.2	10.9 / 13.1	12.7 / 8.6	25.2 / 6.3	26.5 / 2.5	12.5 / 1.5
Dairy total	All	29,868	42.5	3.3 / 28.9	8.3 / 25.7	20.5 / 25.6	18.2 / 10.2	17.3 / 4.7	19.4 / 2.8	11.1 / 1.5	1.9 / 0.5
Beef	<100	623	17.3	65.3	12.4	7.1	2.9	3.0	3.4	4.3	1.6
Beef	100-200	57	3.5	59.6	17.5	5.3	3.5	1.8	0.0	8.8	3.5
Beef	>200	23	13.0	43.5	21.7	4.3	0.0	4.3	8.7	4.3	13.0
Beef total	All	703	16.1	64.2	13.1	6.8	2.8	3.0	3.3	4.7	2.1
Veal	<100	459	17.0	69.9	12.6	3.1	0.9	0.0	1.3	2.8	9.4
Veal	100-200	370	8.1	76.2	11.4	2.4	0.5	0.3	0.3	0.5	8.4
Veal	>200	920	4.1	67.4	19.2	3.2	1.0	0.7	0.8	1.4	6.4
Veal total	All	1,749	8.3	69.9	15.8	3.0	0.9	0.4	0.8	1.6	7.6
Miscellaneous	<30	20,022	41.5	36.7	25.2	20.7	8.1	4.0	2.9	1.6	0.8
Miscellaneous	30-70	3,259	24.1	14.9	9.7	16.2	13.7	14.9	15.0	9.8	5.8
Miscellaneous	71-100	681	19.7	16.6	9.5	7.8	7.5	11.3	16.0	18.8	12.5
Miscellaneous	>100	1,001	8.0	34.1	10.4	6.7	4.4	4.8	6.3	12.3	21.1
Miscellaneous total	All	24,963	37.3	33.2	22.2	19.2	8.7	5.6	5.0	3.5	2.6

[a] Based on number of cows > 2 years

[b] No purchase of animals in 1999

[c] For dairy farms, the first fraction shown is for cattle sold < 2 years and the second fraction for cattle >2 years

Appendix 4.3

Factors in the experimental design, with default, low (-) and high (+) value. Values of parameters were discussed with members of the IBR study group, and based on literature or expert opinion

Factor and description		Default	0 (low)	1 (high)	References
X1	Local spread per farm type				
	Dairy	0.00002	0	0.00006	Vonk Noordegraaf et al., 2000;
	Beef	0.000005	0	0.000015	Jalvingh et al., 1999
	Veal	0.000005	0	0.000015	
	Others	0.00002	0	0.00006	
X2	Introduction factor local spread				Vonk Noordegraaf et al., 2000
	Farm type dairy and others	1.0	1.0	1.0	
	Farm type beef and veal	0.25	0.25	1.0	
X3	Infected animals small outbreak	2	1	4	
X4	Reactivation rate at transport	0.07	0	0.20	Vonk Noordegraaf et al., 2000; Thiry et al., 1987
X5	Yearly reactivation rate per latently infected animal	0.012	0.00125	0.023	Vonk Noordegraaf et al., 1998; De Koeijer et al., 2001
X6	Professional contact				Vonk Noordegraaf et al., 2000;
	Farm type dairy and others	0.0001	0	0.0005	Jalvingh et al., 1999
	Farm type beef and veal	0.000025	0	0.00013	
X7	Movement distance animal contact	table 1 (Appendix 4.4)	table 2[a]	table 1 (Appendix 4.4)	Vonk Noordegraaf et al., 2000
X8	R_0 non-vaccinated animals	3.2	3.0	7.8	Bosch et al., 1998; Hage et al., 1996
X9	R_0 animals vaccinated with live vaccine	1.2	0.5	1.5	Mars et al., 2001
X10	R_0 animals vaccinated with killed vaccine	2.4	1.8	3.0	Bosch et al., 1998
X11	Infectious period non-vaccinated animal (days)	10	9	11	Kaashoek et al., 1995
X12	Infectious period animals vaccinated with live vaccine (days)	6	2	9	Mars, 2000
X13	Infectious period animals vaccinated with killed vaccine (days)	6	4	8	Bosch et al., 1996
X14	Reduction of reactivation rate by killed vaccine	27%	0%	27%	Bosch et al., 1997; De Koeijer, 2000 (pers. comm.)

Appendix 4.3 continued

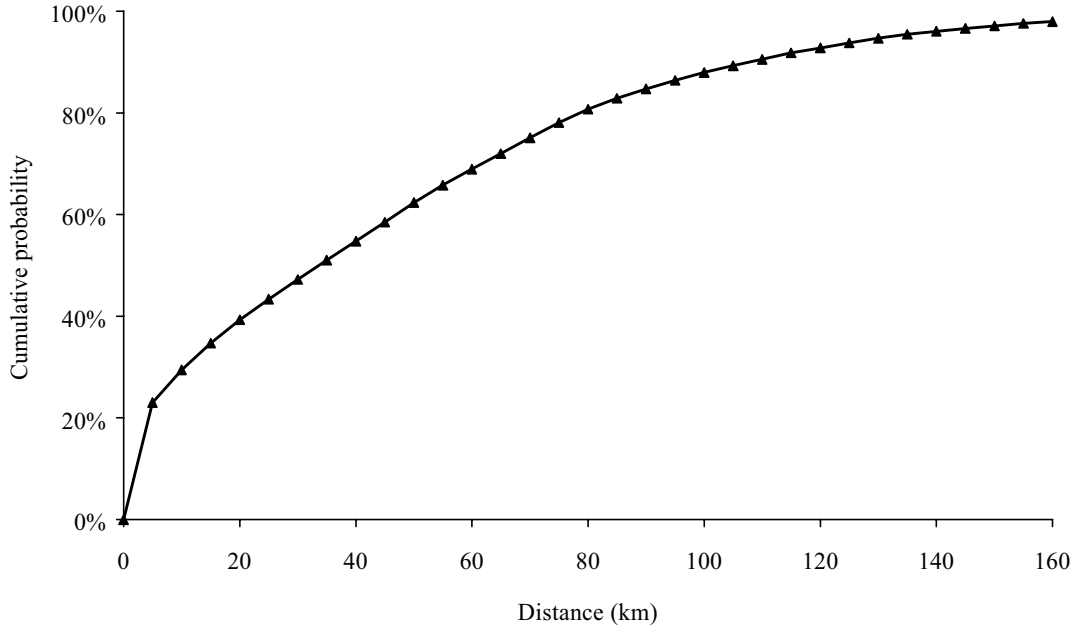
Factor and description		Default	0 (low)	1 (high)	References
X15	Transmission rate from major outbreak in dairy herd to youngstock				
	Youngstock vaccinated	0.10	0	0.10	Mars et al., 2001
	Youngstock not vaccinated	0.41	0	0.41	
X16	Weeks youngstock infected	104	52	104	
X17	Initial infection distribution dairy farms	Table 3[a]	Table 3[a]	table 4[a]	Assink et al., 2000
X18	Initial infection distribution beef farms	table 5[a]	table 5[a]	table 6[a]	Assink et al., 2000
X19	Initial infection distribution veal farms	table 7[a]	table 7[a]	table 8[a]	
X20	Initial infection distribution others farms	table 9[a]	table 9[a]	table 10[a]	Assink et al., 2000
X21	Initial fraction infectious farms per farm type				
	Dairy (certified / non-certified)	0.0015 / 0.0018	0 / 0	0.0015 / 0.0018	Vonk Noordegraaf et al., 1998
	Beef (certified / non-certified)	0.0 / 0.0	0 / 0	0.0 / 0.0	
	Veal (certified / non-certified)	0.0 / 0.0	0 / 0	0.0 / 0.0	
	Others (certified / non-certified)	0.0015 / 0.0018	0 / 0	0.0015 / 0.0018	
X22	Initial fraction dairy farms with infected youngstock	25%	10%	25%	Mars et al., 2001
X23	Increase animals sold (dairy cows per year)	0	1	0	
X24	Hygiene factor certified farms	0	0	0.5	
X25	Bulkmilk test sensitivity	99.9%	95%	100%	Wellenberg et al., 1998
X26	Bulkmilk test specificity	99.9%	95%	100%	Wellenberg et al., 1998
X27	Bulkmilk prevalence threshold	15%	10%	30%	Frankena et al., 1997
X28	Serological test sensitivity	84%	80%	100%	De Wit et al., 1997
X29	Serological test specificity	99.9%	95%	100%	De Wit et al., 1997
X30	Vaccine type used (live / killed)	90% / 10%	90% / 10%	0% / 100%	
X31	Certification probability at decision date when on-farm prevalence is less than 10%	50%	25%	50%	

[a] Data available from first author

Appendix 4.4

Animal-contact matrix between farm types, showing the distribution (%) of the destination of animal contacts sold by each farm type. Numbers are based on analysis of all animal movements recorded by the Identification and Registration system in The Netherlands in 1999.

	From				
	Dairy		Beef	Veal	Miscellaneous
To	<2 years	≥2 years			
Dairy	6.0	41.3	11.4	2.5	15.4
Beef	1.9	0.5	13.7	4.0	4.3
Veal	55.6	0.1	10.1	51.4	31.9
Miscellaneous	36.6	58.2	64.9	42.2	48.3



Cumulative distribution function for distance of animal contacts between farms used as model input, based on analysis of all animal movements recorded by the Identification and Registration system in 1999 in The Netherlands

Appendix 4.5

Input values to calculate costs of eradication programme

Variable	Value
Costs of vaccination, certification and surveillance (incl. 6% VAT)	
Vaccination costs per animal (EUR)	3.60
Costs of veterinary visits (EUR)	17.07
Labour costs per sample of serum (EUR)	2.28
Costs of ELISA test per sample (EUR)	3.90
Costs of administration per farm (EUR)	6.73
Surveillance costs of bulk-milk test per year (EUR)	128.00
Costs of early removal per infected animals (Vonk Noordegraaf et al., 2000)	
Dairy (EUR)	398
Beef (EUR)	280
Veal (EUR)	140
Miscellaneous (EUR)	273
Discount rate per year (%)	4.00

Chapter 5

Sensitivity analysis by experimental design and metamodelling:

case study on simulation in national animal disease control

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Abstract

Simulation is a frequently applied tool in the discipline of animal health economics. Application of sensitivity analysis, however, is often limited to changing only one factor at a time (OAT designs). In this study, the statistical techniques of Design of Experiments (DOE) and regression metamodelling were applied to a simulation model developed to support decision making in national animal disease control. Since the simulation response of interest was censored, we applied – besides ordinary least squares (OLS) regression - tobit and logistic regression. Furthermore, a comparison was made with analysis based on an OAT design.

The metamodel estimated by OLS regression showed reasonable fit, but was not considered a valid approximation of the simulation model. We concluded that logistic regression can be applied if output data are binary, whereas tobit regression is most appropriate when dealing with censored data. Furthermore, we concluded that the DOE and metamodelling approach, compared with a simple OAT design, is more effective in describing the relationships between model input and output in this case study.

5.1 Introduction

The discipline of animal health economics supports the decision-making process in animal health management, by providing a framework of concepts, procedures and data (Dijkhuizen et al., 1995). Support of decision making is mainly at the individual farm level (e.g. Sorensen et al., 1995) and the (inter)national level; examples are control strategies for highly contagious diseases (Berentsen et al., 1992). An important tool in operational research is simulation, which is also frequently applied in animal health economics. It enables experimenting with various disease control strategies for which real-life experimentation would be very costly or even impossible. True validation of a model requires that data on the real system are available (Law and Kelton, 2000). In practice, however, real-life data are often absent or limited. Some studies, therefore, strongly rely on expert opinion (e.g. Horst et al., 1998). Applications of simulation to support management decisions regarding animal health are widespread and, especially when dealing with national policy, often involve risky and costly projects, as the foot-and-mouth disease crisis in Europe demonstrated (Morris et al., 2001).

An important step in simulation analysis of a system is sensitivity analysis (Dent and Blackie, 1979). Sensitivity analysis can be defined as the assessment of the consequences of changes in model inputs, not accounting explicitly for the probability of these changes; the latter is risk analysis (Van Groenendaal and Kleijnen, 1997). Especially when real-life data

are missing, sensitivity analysis is considered important in the validation of a simulation model (Kleijnen, 2000). When a model is used for prediction under uncertainty, sensitivity analysis further helps to identify those uncertain parameters that are most important and can jeopardise the project. In this way, sensitivity analysis can help to set priorities for further (empirical) research. This interaction between normative and positive modelling approaches is considered fundamental to the study of disease and disease control (Dijkhuizen et al., 1995) and provides decision makers with valuable information.

Application of sensitivity analysis in animal health economics is often limited to changing only one input parameter or variable at a time (OAT designs), sometimes in combination with a few strategies for disease control. In principle, this approach assumes that inputs do no interact, which may be too crude a simplification of the underlying model. The techniques of Design of Experiments (DOE) and regression metamodelling support a structural approach to sensitivity analysis. Furthermore, this approach is considered more effective and efficient in estimating the relationship between model output and controllable inputs in the experiment (Kleijnen and Sargent, 2000). Although these techniques have been used in real-life experimentation in livestock sciences for many decades, they are not common in the analysis of simulation models used in this area.

The main goal of this study was to get more insight into the behaviour of a simulation model, developed to support animal disease control at the national level, by screening for environmental factors that had greatest impact on the simulation response. Therefore, the techniques of experimental design and metamodelling were applied, following Kleijnen and Sargent (2000). Traditionally, DOE uses ordinary least squares (OLS) regression for simulation analysis. Since the simulation response of interest in this case-study was censored, which means that output had a limited range, also tobit and logistic regression were applied. The latter types of regression techniques have, to the best of our knowledge, not been used before in simulation analysis. Furthermore, a comparison was made with analysis based on an OAT design. In this case-study, computer time was a limiting factor. Building an efficient design for a simulation experiment was, therefore, essential.

5.2 The case study

In the current study, DOE was applied to the simulation model called InterIBR-endemic. This spatial, dynamic and stochastic simulation model was developed to support decision makers in the national eradication programme for endemic infectious bovine rhinotracheitis (IBR) in The Netherlands (Vonk Noordegraaf et al., 2000; Vonk Noordegraaf et al., 2002). Several countries within the EU have successfully eradicated the virus causing IBR (Denmark, Finland and Sweden), while others are still making efforts. This diversity in animal-health

status restricts the cattle trade between member states of the EU. At the start of the compulsory eradication programme in 1998, about 25 per cent of all 60,000 Dutch cattle farms was certified-free; that is, free of the virus causing IBR (Assink et al., 2001). Based on an earlier simulation model, including dairy farms only, expected direct costs of this programme were EUR 127 million, taking about six years to eradicate the virus (Vonk Noordegraaf et al., 1998).

The model simulates - on a weekly base - the spread and control of the virus within and between cattle farms, using individual farm data from a geographical database. Control measures originally applied in The Netherlands involved half-yearly vaccination of all farms not certified-free, restrictions on cattle trade between farms and surveillance of certified-free farms. The simulation model generates the direct financial costs of the simulated programme and various epidemiological parameters such as the incidence of outbreaks on certified-free farms.

Inputs of the simulation model InterIBR-endemic can be classified as being either decision or environmental factors, depending on whether or not they represent action options to managers of the eradication programme (Kleijnen et al., 1979). Values of environmental input parameters, mainly related to the risk of virus spread by various mechanisms, were estimated using experimental data or expert opinion. As the eradication programme implies a large investment for the Dutch cattle sector, insight was required into which of these uncertain environmental parameters would be most important for the progress of the programme. Decision makers could use this information when monitoring the eradication programme and when designing adjustments when progress is not as expected.

5.3 Background of DOE and metamodelling

A metamodel is defined as an approximation of the input-output transformation, implied by experimenting with the simulation model (Kleijnen and Sargent, 2000). In DOE terminology, input parameters, variables and structural assumptions composing a model are called *factors* and output measures are called *responses* (Law and Kelton, 2000). Selection of factors depends on the goal of the experiment. During an experiment values of one or more factors change; therefore, each factor requires at least two levels (Kleijnen, 1998). In a simulation context, DOE is defined as selecting - out of the great number of possible combinations of factor levels - the set that actually needs to be simulated in an experiment with the simulation model, in order to quantify factor effects (Hunter and Naylor, 1970). The simulation model is run for this set of factor combinations (scenarios) and the resulting input-output data are analysed to estimate the metamodel (Kleijnen, 1998). Treating the simulation model as a

black box, the metamodel can then be used to gain insight into the effects of changes in factor levels on simulation response.

With k factors, each at two levels, a full factorial design would require 2^k scenarios. Since such a design usually leads to an excessive amount of computer time, fractional factorial designs can be used. Fractional designs must be carefully arranged, so that estimates of effects thought to be important are only confounded with effects not thought to be important (Hunter and Naylor, 1970). Classic designs are R-3 (resolution III), R-4, R-5 and Central Composite (CC) designs (Kleijnen, 1998). R-3 designs give unbiased estimators of the k parameters of a first-order polynomial regression model, using only $n = k + 4 - (k \text{ modulo } 4)$ scenarios (Kleijnen and Sargent, 2000). Estimation of certain linear combinations of two-factor interactions requires a higher resolution (R-4). This can be obtained by adding the mirror image to the original R-3 design; each run is the opposite of an earlier run (Hunter and Naylor, 1970; Kleijnen, 1998). It has been proven that the accuracy of estimators is maximised when the design matrix is orthogonal, provided the assumption of 'white noise' holds: the additive noise is normally and independently distributed (n.i.d.) with zero expectation and constant variance ; see the term e in equation 5.1 below (Kleijnen, 1987).

Often, a metamodel is specified as a regression model where the independent regression variables are simulation input parameters and the dependent variable is the simulation response of interest (Law and Kelton, 2000). Assuming white noise, OLS gives best linear unbiased estimates (BLUE), where best means minimum variance (Kleijnen, 1998).

An important step in the metamodelling process is to test the validity of the fitted metamodel with respect to the simulation model. This can be done by running new scenarios and comparing simulation output with metamodel prediction. An alternative procedure is cross-validation, which requires no new simulation runs (Kleijnen, 1995; Van Groenendaal and Kleijnen, 1997). Applying cross-validation, scenarios are eliminated one by one and the regression model is re-estimated. The resulting metamodel is then used to predict the simulation realisation of the deleted scenario. These predictions can then be compared with the corresponding simulation responses, using the Pearson linear correlation coefficient (Van Groenendaal and Kleijnen, 1997).

Figure 5.1 shows the relationships among problem entity, simulation model and metamodel. In our case study, the problem entity is the real system of virus transmission and control in The Netherlands. The simulation model InterIBR-endemic is intended to describe relationships among inputs and outputs of this system and the metamodel approximates the behaviour of the simulation model with regard to its parameters. As we move from problem entity to simulation model and then to metamodel, the assumed functional relationship between input and output becomes simpler.

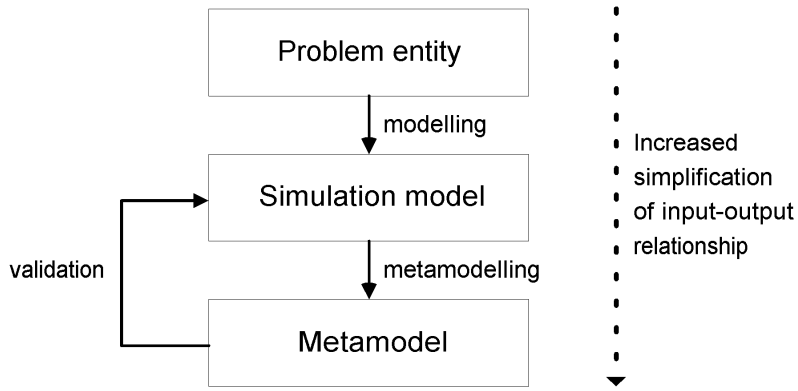

Figure 5.1 Metamodel, simulation model and problem entity

5.4 Statistical methods

5.4.1 Metamodel variables

A total of 31 environmental parameters of the simulation model were selected as factors for the simulation experiment (see Chapter 4, Appendix 4.3). These factors had in common that they were related to the risk of virus spread within and among farms and estimates of factor values were uncertain. Although the simulation model was stochastic in nature, 26 of these factors were entered with single values. Using these single values, randomness in the simulation was triggered by a pseudo-random number generator, to assess whether events related to these parameters did occur (e.g. did an animal excrete the virus, did a farm become infected, was an outbreak detected?). Five parameters were entered as probability distributions, representing variability, not uncertainty. From these distributions, values were generated during simulation by Monte Carlo sampling. Simulation input related to decision variables was fixed during the experiment, in accordance with the control strategy originally applied in The Netherlands.

For each factor a low and high level were assigned (see Chapter 4, Appendix 4.3), reflecting uncertainty of these factors in real life. These low and high levels were based on experimental data or expert opinion. These levels determined the experimental frame for which the metamodel was considered valid. The probability distributions were considered as quantitative variables. To enable comparison of factor effects by relative importance, factor levels were standardised to 0 (low value) and 1 (high value) (Bettonvil and Kleijnen, 1996). Only in the OAT design, each factor was also assigned a default value that for some factors was an intermediate value and for other factors coincided with the high or low value (see Chapter 4, Appendix 4.3).

Whereas the simulation model provided multiple outputs, in this study we looked only at a single simulation response, namely 'number of weeks to reach a prevalence level of 5% in the national dairy cattle population'. For each scenario, the average output of two replications was taken as the response variable. Simulation either ended when the simulated prevalence level in the national dairy cattle population was below 5%, or when the simulated period reached 1,000 weeks. Output, therefore, was *censored* at 1,000 weeks. Scenarios with censored responses were not excluded from the analysis, but included with an output value of 1,000.

5.4.2 Metamodel specification and estimation techniques

Initially, the metamodel was specified as the following simple first-order polynomial or additive metamodel with k factors:

$$y_i = \beta_0 + \sum_{h=1}^{k} \beta_h x_{i,h} + e_i \qquad (5.1)$$

where y_i denotes the average simulation response of scenario i, β_0 the intercept, β_h the main effect of factor h, $x_{i,h}$ the value of the standardised factor h in scenario i, and e_i the approximation error plus intrinsic noise in scenario i. To estimate the metamodel parameters, metamodel (5.1) was fitted to data from the simulation experiment. Quadratic effects, which would require more than two levels for each factor (for example a Central Composite design), were not considered. Using OLS, a stepwise selection procedure (with $p \leq 0.05$) was performed (SPSS, 1999) to fit the first-order polynomial. Non-significant factors were thereby excluded from the model. Next, biologically plausible interactions were tested for significance, assuming that only two-factor interactions between factors with significant main effects could occur. Significant interactions were added to the metamodel. The fit of the metamodel was evaluated by the adjusted R^2 and the linear correlation coefficient (ρ) between metamodel prediction and simulation realisation.

In general, censored output data cause OLS regression to produce inconsistent estimates (Long, 1997). Therefore, in addition to OLS, logistic and tobit regression were applied (Hosmer and Lemeshow, 1989; Greene, 1997; Long, 1997). For the logistic regression model, the dependent variable was made dichotomous by transforming the simulation output to 1 if censored (y=1,000) and to 0 if not censored (y<1,000). Logistic regression uses a log-linear model in which the probability of the censored simulation outcome is modelled as (Hosmer and Lemeshow, 1989):

$$E(y_i \mid \mathbf{x}_i) = \frac{e^{\beta_0 + \beta_1 x_{i,1} + ... + \beta_k x_{i,k}}}{1 + e^{\beta_0 + \beta_1 x_{i,1} + ... + \beta_k x_{i,k}}} \tag{5.2}$$

which satisfies the constraint that the conditional mean of the regression be between zero and one. Estimation of the factor effects in (5.2) uses a maximum likelihood procedure. Calculations were performed using the binary logistic regression procedure (SPSS, 1999). We applied the following model building strategy, suggested by Hosmer and Lemeshow (1989). Starting with univariable analysis of each independent variable, only variables with $p<0.25$ were selected for a multivariable logistic model, based on Wald's statistic with a chi-square distribution. Next, backward elimination of main effects was performed, followed by testing of possible interactions. Significance testing with $p \leq 0.05$ was based on the change in the -2log-likelihood, which has a chi-square distribution. The fit of the logistic metamodel was evaluated using Nagelkerke's R^2 statistic and the fraction of correctly classified scenarios (SPSS, 1999).

Tobit regression (also called censored regression) has been applied in econometrics for several decades and is also used in other disciplines such as biometrics and engineering (Amemiya, 1984). The form of the tobit metamodel defined in our study was similar to metamodel (5.1), except that now dependent variable y was a latent variable y^* (Long, 1997):

$$y^*_i = \beta_0 + \Sigma_{h=1}^{k} \beta_h x_{i,h} + e_i \tag{5.3}$$

where the latent variable y^* is observed for all values smaller than τ and is censored for values greater than or equal to τ, with τ = 1,000 weeks. To estimate the factor effects in (5.3), tobit regression uses a maximum likelihood estimation procedure. The log-likelihood of the censored regression model consists of two parts: one corresponding to the classic linear regression for the non-censored observations and one corresponding to the probabilities for the censored observations. Calculations were performed using the tobit regression procedure in Limdep 7.0 (Greene, 1997). The model building strategy applied for tobit regression was similar to the one for OLS regression, using stepwise selection of main effects and subsequent testing for interactions.

5.4.3 Experimental Design

A R-3 design was constructed for the 31 factors, containing only 32 scenarios. This design was specified by writing down all 2^5 scenarios for the factors $X1$ through $X5$ in the first five columns and specifying the levels for the factors $X6$ through $X31$ by all possible pairwise

multiplications (called generators) of the elements in the columns 1 through 5. For example, $X6 = 1.2$ means that element i - with $i = 1, \ldots, 32$ - of the column for factor 6 equals the product of the element i in the columns of the factors 1 and 2 (see Appendix 5.1 where – means low value and + means high value).

Because we were also interested in testing certain linear combinations of two-factor interactions, the final experimental design was a R-4 design with 64 scenarios. To reduce the risk of confounding, factors which were expected a priori to interact, were not entered as $X1$ through $X5$: suppose there was in fact interaction between the factors $X1$ and $X2$ and factor $X6$ was generated as $X1$x$X2$, then the main effect of factor $X6$ would be confounded with this interaction effect. If this interaction was negligible, however, confounding would be acceptable (Hunter and Naylor, 1970).

Since the simulation model was stochastic, another tactical issue involved the number of replications for each scenario. From earlier trials with the model, only very small variation between replications was observed for the output of interest in this study. Although underlying mechanisms were stochastic in nature (e.g. the dynamics of virus spread among farms differs for each replication), the overall observed outcome resulting from a very large number of these random events appeared to be almost deterministic. Since computer time was a limiting factor with this model, only two replications for each scenario were run. Although more replications would have resulted in smaller confidence intervals for mean response values for each scenario, it is believed that a low number of replications already provided valuable information on model sensitivity. The simulation experiment with 64 scenarios was run on five computers (Pentium 533 MHz processors with 128 MB RAM). Total calculation time was about two weeks.

5.4.4 Validation of OLS metamodel

Cross-validation was applied to the metamodel estimated by OLS, using the DfFit diagnostic (SPSS, 1999). This diagnostic calculates the change in the predicted value that results from the exclusion of a particular scenario. To indicate the quality of the predictions obtained through cross-validation, a scatter plot of metamodel predictions and simulation realisations for each scenario was made. Performance was quantified by the Pearson linear correlation coefficient.

5.4.5 One-at-a-time sensitivity analysis

Before starting the sensitivity analysis using the R-4 design and metamodelling approach described in the sections 5.4.2 and 5.4.3, a simple OAT design for all 31 factors was applied. This design required two scenarios for each factor, adding up to 62 scenarios in total. Each

factor was at its low level in one scenario, at its high level in a second scenario, and at its default level in all other scenarios. Again, for each scenario two replications were run. Factors were treated as categorical variables, with three levels.

Analysis of this OAT design was done by OLS regression and backward elimination, with a first-order polynomial. No interactions effects could be tested in the OAT design. Since we were interested in the effect on the simulation response of changing a factor from its low to its high level, these estimates were tested for significance ($p<0.05$).

5.5 Results

5.5.1 OAT design

Table 5.1 shows those factors that have estimates significantly different from zero at $p<0.05$ in the OAT design. The adjusted R^2 of this model was 0.98. The estimates in Table 5.1 reflect the expected effect on the response variable when changing a factor from its low to its high level. For example, changing factor *X*5 from its low to high value increased the output with 158 weeks. So, 10 out of 31 factors were significant, with the factors *X*4, *X*8, and *X*30 having the largest impact (namely 696, 678 and 526 weeks respectively).

Table 5.1 Significant factor effects ($p<0.05$) based on OLS regression of OAT design; dependent variable is the number of weeks needed to reach a prevalence level of 5% in the national dairy cattle population

Factor	Estimate	Standard Error	*p*-value
*X*0	155	44	0.001
*X*1	112	18	0.000
*X*3	66	18	0.000
*X*4	696	18	0.000
*X*5	158	18	0.000
*X*6	72	18	0.000
*X*8	678	18	0.000
*X*9	96	18	0.000
*X*25	36	18	0.049
*X*28	-54	18	0.004
*X*30	526	18	0.000

5.5.2 R-4 design: linear regression metamodel

Of the 64 scenarios simulated with the R-4 design, 23 scenarios gave outputs censored at 1,000 weeks. The stepwise selection procedure resulted in eleven significant main effects and

three significant two-factor interactions (Table 5.2). The adjusted R^2 increased from 0.72 to 0.82 after addition of significant interactions to the first-order polynomial.

Table 5.2 Significant factor effects (p<0.05) based on OLS regression of R-4 design; dependent variable same as in Table 5.1

Factor	Estimate	Standard Error	p-value
$X0$	218	68	0.002
$X1$	176	61	0.005
$X4$	159	35	0.000
$X5$	226	35	0.000
$X6$	92	35	0.011
$X8$	91	49	0.070
$X10$	126	49	0.014
$X16$	-90	35	0.013
$X24$	-52	49	0.294
$X27$	-99	35	0.007
$X28$	-119	35	0.001
$X30$	104	49	0.041
$X1$ x $X8$	281	70	0.000
$X1$ x $X24$	-201	70	0.006
$X10$ x $X30$	188	70	0.010

The signs of factors $X16$ and $X27$ were opposite to prior expectation. Therefore, the programming code involving these parameters was verified, but no errors were detected. Whereas most factors showed a positive effect on the length of the eradication programme, $X24$ and $X28$ had negative effects (-52 and -119). These signs agreed with prior expectation, since these factors represented preventive measures in the eradication programme. Whereas the main effects of $X8$ and $X24$ were not significant in the metamodel, they both were involved in significant two-factor interactions with $X1$.

5.5.3 Cross validation of linear regression metamodel for R-4 design

Figure 5.2 shows a scatter plot of metamodel predictions and simulation realisations for all 64 scenarios, based on cross-validation of the metamodel estimated in Table 5.2. The resulting correlation coefficient was 0.97. The scatter plot shows that the upper limit for the simulation response was 1,000 weeks, whereas the OLS metamodel prediction did not remain under this limit.

Additionally, a scenario with all factors at their default values was simulated. This resulted in an average simulation output of 350 weeks, whereas the metamodel prediction was 394 weeks. So the absolute relative error was 12.6% for this interpolated additional scenario.

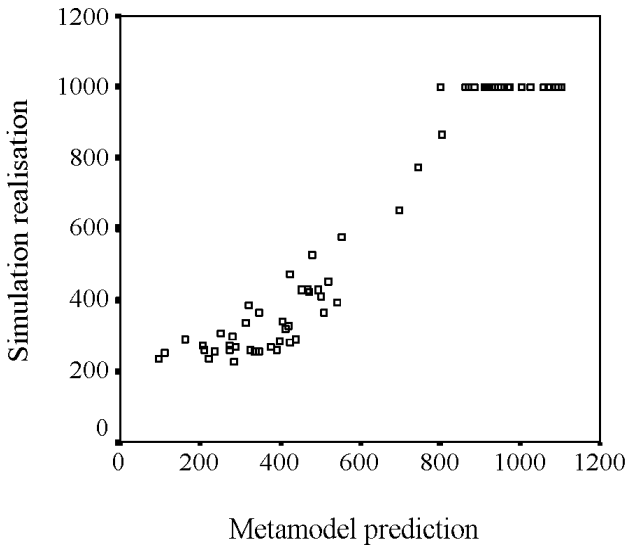

Figure 5.2 Scatter plot of metamodel prediction and simulation realisation, based on cross-validation

5.5.4 Logistic regression analysis

In the logistic metamodel, the event of interest was a simulation output censored at 1,000 weeks. Of the 31 factors, 8 were univariable significant at $p<0.25$ in this model and selected for the multivariable logistic model. Backwards elimination resulted in removal of two factors ($X4$ and $X6$); no two-factor interactions were found significant (Table 5.3). For this model Nagelkerke's R^2 was 0.81.

Table 5.3 Significant factor effects of R-4 design analysed through a logistic metamodel with the simulation output censored at 1,000 weeks

Factor	Estimate	Standard Error	*p*-value
$X0$	-10.6	3.2	0.001
$X1$	4.2	1.5	0.005
$X5$	3.4	1.4	0.013
$X8$	4.1	1.4	0.004
$X10$	4.1	1.2	0.004
$X24$	-2.9	1.4	0.013
$X30$	4.1	3.2	0.004

All the factors significant in this logistic metamodel also appeared in the OLS metamodel (Table 5.2). From this logistic metamodel, the probability of a censored response was calculated for each scenario and compared with the simulation response. Using a cut-value of 0.5, the overall fraction of scenarios correctly classified by the metamodel was 92.2%. Of the censored scenarios, 21 out of 23 were classified correctly by the metamodel. Of the uncensored scenarios, 38 out of 41 were classified correctly.

5.5.5 Tobit regression analysis

Table 5.4 shows the significant effects based on tobit regression. These main and interaction effects were also significant in the OLS metamodel (Table 5.2). Now, however, the factors *X*16 and *X*27, which had unexpected signs in the OLS metamodel, did not show up. A scatter plot with simulation response versus tobit response gave a correlation coefficient of 0.91.

Table 5.4 Significant factor effects of R-4 design analysed through a tobit metamodel; dependent variable same as in Table 5.1

Factor	Estimate	Standard Error	*p*-value
*X*0	-18	90	0.840
*X*1	252	87	0.004
*X*4	221	50	0.000
*X*5	297	51	0.000
*X*6	140	50	0.005
*X*8	110	65	0.093
*X*10	200	69	0.004
*X*24	-64	65	0.325
*X*28	-117	50	0.020
*X*30	173	68	0.011
*X*1 x *X*8	445	107	0.000
*X*1 x *X*24	-297	104	0.004
*X*10 x *X*30	213	105	0.042

As in logistic regression, the output of tobit analysis shows the probability of each scenario being censored. Again using a cut-value of 0.5, the overall fraction of scenarios correctly classified by tobit regression was 89.1%. Of the censored scenarios, 16 out of 23 were classified correctly. Of the uncensored scenarios, all 41 scenarios were classified correctly by the tobit metamodel.

5.6 Discussion and conclusions

The model InterIBR-endemic is a typical example of simulation models in the discipline of animal health economics; its goal is to support decision makers in disease control at national level, accounting for uncertainty. We emphasised the importance of sensitivity analysis as part of verification and validation of the simulation model, before actually using the model as a decision support tool. Whereas sensitivity analysis in animal health economics is often limited to a simple OAT design, we also applied the statistical techniques of experimental design and metamodelling. OAT designs implicitly assume that all interactions are zero, implying a first-order polynomial. Comparison of results based on the OAT design with the

R-4 design analysed by OLS metamodelling (Table 5.5) shows that both approaches agreed on the importance of most factors, but disagreed on some other factors. Furthermore, three significant two-factor interactions were missed by the OAT design.

The OLS regression estimates for the R-4 design gave a reasonable fit to the simulation input-output data (R^2_{adj}=0.82). Furthermore, cross validation showed that this metamodel predicted simulation realisations quite well (ρ=0.97). However, two significant factors had estimates with signs opposite to prior expectation. Therefore, this metamodel was not considered valid with respect to the simulation model.

Table 5.5 Significant factor effects for the dependent variable 'number of weeks to reach a prevalence level of 5% in the national dairy cattle population', estimated from an OAT design and an R-4 design analyzed by OLS, logistic and tobit regression respectively, denoted by X

Factor	OAT design	R-4 design		
		OLS	Logistic	Tobit
*X*1	X	X	X	X
*X*3	X			
*X*4	X	X		X
*X*5	X	X	X	X
*X*6	X	X		X
*X*8	X	X	X	X
*X*9	X			
*X*10		X	X	X
*X*16		X		
*X*24		X	X	X
*X*25	X			
*X*27		X		
*X*28	X	X		X
*X*30	X	X	X	X
*X*1 x *X*8		X		X
*X*1 x *X*24		X		X
*X*10 x *X*30		X		X

Since output data were censored in 23 out of the 64 scenarios, regression techniques more suitable for censored data were applied: logistic and tobit regression. Logistic regression gave information on factors that were significantly related to the probability of a scenario being censored. The overall fit of the logistic model was reasonable and the fraction of correctly classified scenarios was high (92.2%). The tobit metamodel gave a fraction of correctly classified scenarios similarly high (89.1%). This tobit model, however, gave more information, since it also provided factor estimates related to the non-censored area of the response variable. Comparing results from OLS and tobit regression (Table 5.5), the tobit

metamodel did not contain the two factors with unexpected signs. Together with the fact that tobit regression is, from a theoretical point of view, more appropriate for censored data, we considered the tobit model valid with respect to the simulation model.

Actually, the simulation model gave other non-censored responses, such as the costs of the eradication programme and the number of outbreaks per year on certified-free dairy farms. We analysed these additional responses through OLS; results have been presented in a companion paper (Vonk Noordegraaf et al., 2002).

Neither OAT designs nor DOE provides rules for choosing factor levels for sensitivity analysis. This is a weakness of sensitivity analysis in general. In some studies dealing with sensitivity analysis, factor levels are varied arbitrarily over a range of ±25%, regardless of the degree of uncertainty of factors involved. When we chose factor levels, we tried to take into account uncertainty of these factors in real-life, but this was also a subjective approach. It is, therefore, essential to realise that the importance of factors is partly based on the experimental frame chosen: if a very narrow range is imposed on one important factor, and a very wide range on another factor that is less important, results could suggest that the latter was more important than the former (see Bettonvil and Kleijnen, 1996). Extreme care is required when extracting conclusions from the metamodel to the real system. Only if the model is a good representation of the real system, and factor levels chosen reflect true uncertainty, a sensitive region established in the model applies to the real system.

Based on the results of this case study, it was concluded that the DOE and metamodelling approach is more effective in describing the relationships between the simulation model's input and output than a simple OAT design. With the same number of simulated scenarios, analysis of the R-4 design gave insight into important interactions between factors, which could not be detected with an OAT design. It was also concluded that, when dealing with censored data, OLS regression did not result in a valid metamodel. Both logistic and tobit regression metamodels were considered more valid for the analysis of the censored data in this study. If output data are truly binary - or interest is in a binary outcome only (e.g. is simulation response censored) - then logistic regression can be applied to get insight into factors related to this binary event. Tobit regression is most appropriate if a continuous response variable is censored.

We advocate that the approach of DOE and metamodelling for sensitivity analysis of simulation models, should be applied to all future simulation studies. In the discipline of animal health economics, important implementation areas are simulation studies on food-safety risks for humans (for example Salmonella; see Van der Gaag et al., submitted) and highly contagious animal diseases with large economic impact on society (such as Classical Swine Fever; see Mangen et al., 2001). Furthermore, the regression techniques applied in this study deserve further exploration in future research; examples are the application of logistic

simulation analysis in rare event simulations with fixed-time horizons, and the application of tobit analysis in queuing simulations with non-negative waiting times. Other issues for further research are possible violations of the assumptions of normality of output (Amemiya, 1984), homogeneity of variances (Greene, 1997), and use of common random numbers (Kleijnen, 1998).

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Appendix 5.1

Resolution-3 design for 31 factors, used in the experimental design for the simulation model InterIBR-endemic

Factor	X1	X2	X3	X4	X5	X6	X7	X25	X26	X27	X28	X29	X31	X14	X15	X16	X17	X18	X19	X20	X21	X22	X23	X24	X11	X12	X13	X8	X9	X10	X30
				Generator		12	13	14	15	23	24	25	34	35	45	123	124	125	134	135	145	234	235	245	345	1234	1235	1245	1345	2345	12345
Scenario 1	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	-
2	+	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	+	+
3	-	+	-	-	-	-	+	+	+	-	-	-	+	+	+	+	+	+	-	-	-	+	+	+	-	-	-	-	+	-	+
4	+	+	-	-	-	+	-	-	-	-	-	-	+	+	+	-	-	-	+	+	+	+	+	+	-	+	+	+	-	-	-
5	-	-	+	-	-	+	-	+	+	-	+	+	-	-	+	+	-	-	+	+	-	+	+	-	+	-	-	+	-	-	+
6	+	-	+	-	-	-	+	-	-	-	+	+	-	-	+	-	+	+	-	-	+	+	+	-	+	+	+	-	+	-	-
7	-	+	+	-	-	-	-	+	+	+	-	-	-	-	+	-	+	+	+	+	-	-	-	+	+	+	+	-	-	+	-
8	+	+	+	-	-	+	+	-	-	+	-	-	-	-	+	+	-	-	-	-	+	-	-	+	+	-	-	+	+	+	+
9	-	-	-	+	-	+	+	-	+	+	-	+	-	+	-	-	+	-	+	-	+	+	-	+	+	-	+	-	-	-	+
10	+	-	-	+	-	-	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	+	+	-	+	+	-	-
11	-	+	-	+	-	-	+	-	+	-	+	-	-	+	-	+	-	+	+	-	+	-	+	-	+	+	-	+	-	+	-
12	+	+	-	+	-	+	-	+	-	-	+	-	-	+	-	-	+	-	-	+	-	-	+	-	+	-	+	-	+	+	+
13	-	-	+	+	-	+	-	-	+	-	-	+	+	-	-	+	+	-	-	+	+	-	+	+	-	+	-	-	+	+	-
14	+	-	+	+	-	-	+	+	-	-	-	+	+	-	-	-	-	+	+	-	-	-	+	+	-	-	+	+	-	+	+
15	-	+	+	+	-	-	-	-	+	+	+	-	+	-	-	-	-	+	-	+	+	+	-	-	-	-	+	+	+	-	+
16	+	+	+	+	-	+	+	+	-	+	+	-	+	-	-	+	+	-	+	-	-	+	-	-	-	+	-	-	-	-	-
17	-	-	-	-	+	+	+	+	-	+	+	-	+	-	-	-	-	+	-	+	+	-	+	+	+	+	-	-	-	-	+
18	+	-	-	-	+	-	-	-	+	+	+	-	+	-	-	+	+	-	+	-	-	-	+	+	+	-	+	+	+	-	-
19	-	+	-	-	+	-	+	+	-	-	-	+	+	-	-	+	+	-	-	+	+	+	-	-	+	-	+	+	-	+	-
20	+	+	-	-	+	+	-	-	+	-	-	+	+	-	-	-	-	+	+	-	-	+	-	-	+	+	-	-	+	+	+
21	-	-	+	-	+	+	-	+	-	-	+	-	-	+	-	+	-	+	+	-	+	+	-	+	-	-	+	-	+	+	-
22	+	-	+	-	+	-	+	-	+	-	+	-	-	+	-	-	+	-	-	+	-	+	-	+	-	+	-	+	-	+	+
23	-	+	+	-	+	-	-	+	-	+	-	+	-	+	-	-	+	-	+	-	+	-	+	-	-	+	-	+	+	-	+
24	+	+	+	-	+	+	+	-	+	+	-	+	-	+	-	+	-	+	-	+	-	-	+	-	-	-	+	-	-	-	-
25	-	-	-	+	+	+	+	-	-	+	-	-	-	-	+	-	+	+	+	+	-	+	+	-	-	-	-	+	+	+	-
26	+	-	-	+	+	-	-	+	+	+	-	-	-	-	+	+	-	-	-	-	+	+	+	-	-	+	+	-	-	+	+
27	-	+	-	+	+	-	+	-	-	-	+	+	-	-	+	+	-	-	+	+	-	-	-	+	-	+	+	-	+	-	+
28	+	+	-	+	+	+	-	+	+	-	+	+	-	-	+	-	+	+	-	-	+	-	-	+	-	-	-	+	-	-	-
29	-	-	+	+	+	+	-	-	-	-	-	-	+	+	+	+	+	+	-	-	-	-	-	-	+	+	+	+	-	-	+
30	+	-	+	+	+	-	+	+	+	-	-	-	+	+	+	-	-	-	+	+	+	-	-	-	+	-	-	-	+	-	-
31	-	+	+	+	+	-	-	-	-	+	+	+	+	+	+	-	-	-	-	-	-	+	+	+	+	-	-	-	-	+	-
32	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Chapter 6

Assessment of BHV1 simulation model behaviour using survival analysis

Paper by Vonk Noordegraaf, A., Labrovic, A., Frankena, K., Pfeiffer, D.U., Nielen, M.
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Abstract

A compulsory eradication programme for bovine herpesvirus 1 (BHV1) was implemented in The Netherlands in 1998. At the start of the programme, about 25% of the dairy herds was certified BHV1-free. Simulation models have played an important role in the decision-making process associated with BHV1 eradication. The objective of this study was to improve understanding of model behaviour, as part of internal validation, with respect to loss of the BHV1-free certificate. Using a Cox proportional hazards regression model, the association between farm characteristics and the risk of certificate loss during simulation was quantified. The overall fraction of herds experiencing certificate loss amongst initially certified BHV1-free herds during simulation was 3.0%. Significant risk factors in the final multivariable Cox model were the farm characteristics 'yearly number of cattle purchased', 'farm density within a 1-km radius' and 'cattle density within a 1-km radius'. Qualitative behaviour of risk factors found in this study agreed with observations in field studies. For external validation of the simulation model, a next step is quantification of risk factors for certificate loss in the field.

7.1 Introduction

Bovine herpesvirus 1 (BHV1) is the causative agent of infectious bovine rhinotracheitis (IBR), a respiratory disease in cattle characterised by acute inflammation of the upper respiratory tract (Engels and Ackermann, 1996). A compulsory eradication programme for BHV1 was implemented in The Netherlands in May 1998. This eradication programme was primarily based on half-yearly vaccination with marker vaccine (Van Oirschot et al., 1996) of all cattle older than three months, with the exemption of cattle on beef and veal farms and certified BHV1-free herds. At the start of the eradication programme, about 25% (7,400) of the dairy herds and 18% (5,400) of non-dairy herds were certified BHV1-free in The Netherlands (Assink et al., 2001). Since outbreaks of BHV1 on these certified herds would not only affect the costs and progress of the national eradication programme, but also were expected to influence the motivation of farmers to apply for a certificate, control measures were aimed to keep the number of outbreaks low. Certified BHV1-free herds were, therefore, only allowed to purchase cattle from other certified herds. Furthermore, the certified BHV1-free status was monitored through monthly bulk-milk tests of dairy herds and half-yearly serological sampling of non-dairy herds.

Simulation models have had an important role in the decision-making process associated with the BHV1 eradication programme in The Netherlands (Vonk Noordegraaf et al., 1998; Vonk Noordegraaf et al., 2000; Vonk Noordegraaf et al., 2002). They have been used to

provide insight into the expected epidemiological and economic consequences of various strategies to eradicate BHV1 at national level and to identify gaps in knowledge about BHV1 relevant for the eradication programme. The dynamic, stochastic and spatial simulation model InterIBR-endemic simulated BHV1 spread and control within a population of cattle herds based on real farms and their characteristics present in The Netherlands in 1999 (Vonk Noordegraaf et al., 2002). Comparison of model expectations with data from the first year of the programme (Assink et al., 2001) showed that the observed rate of detected outbreaks on dairy herds (8.4 per 1000 farms at risk in 1999) was within the range of the simulated outbreak rate (5.7-8.7). This agreement, however, does not prove that the simulated processes and parameters for transmission between farms correctly reflect true transmission dynamics.

Since opportunities for external validation of the simulation model were only limited, the objective of this study was to improve understanding of model behaviour particularly with respect to certificate loss. More specifically, it was investigated how farms that lost the certificate during simulation differed from farms without this event. It was expected, for example, that farm density and purchase frequency were important risk factors for certificate loss in the model. A simulation experiment was performed to collect data from which the association between farm characteristics and the risk of certificate loss during simulation could be quantified, using the technique of survival analysis (Kleinbaum, 1996). This information was then used to assess whether the model performed as intended and whether this behaviour agreed with current knowledge, which was only partly based on Dutch field data.

7.2 Material and methods

7.2.1 Simulation model

The general framework of the simulation model InterIBR-endemic is similar to models used for epidemics of classical swine fever (Mangen et al., 2000) and foot-and-mouth-disease (Morris et al., 2001). These models are all based on a population of individual farms in which virus spread and control measures are simulated over time, taking into account variability and spatial aspects related to spread and control. Vonk Noordegraaf et al. (2002) describes details of InterIBR-endemic. Of special interest for this study were the farm characteristics included in the model and the simulated BHV1 transmission routes between farms.

The farm population used in the model was based on real data from individual cattle herds in The Netherlands, obtained from national farm databases. This resulted in a total of 57,283 cattle herds included in the model. The starting point of simulation (t=0) represented January 1999, the time step of simulation was a week and simulation stopped at a cow-level

prevalence of 5% in the population of dairy cattle. The simulated period was on average about 6.5 years.

Simulation of virus transmission between farms was based on the weekly number of contacts and the risk of each contact of an infected herd to other herds. Transmission routes simulated include cattle trades between farms, local spread within a 1-km radius and professional contacts, as described in detail by Vonk Noordegraaf et al. (2002). Furthermore, reactivation of latently infected cattle could also result in circulation of virus on a farm. A surveillance programme simulated detection of outbreaks on certified BHV1-free herds, which resulted in certificate loss. The frequency of surveillance on each farm type and the probability to detect antibodies to the virus (herd-sensitivity) was taken into account for simulation of surveillance.

7.2.2 Data collection

7.2.2.1 Study population

The population of interest in this study contained certified BHV1-free herds at the start of simulation, which represented about 22% of all herds. These herds had been officially certified in January 1999. A case was defined as an initially certified BHV1-free herd which experienced an outbreak during the simulation, resulting in loss of the BVH1-free certificate. A herd that maintained the certified-free status during the simulated period was considered censored. Since the simulation model included stochastic components, multiple replications were run, where each replication simulated a possible pattern of the national BHV1 control programme. As discussed by Vonk Noordegraaf et al., (2002), model output was about stable with ten model replications. A single replication contained many stochastic events relating to disease spread and control.

Outcome data for each herd and replication was joined into a database table, resulting in a total of 123,373 records of which 3,629 (2.9%) had experienced certificate loss during simulation. The NCSS 2000/PASS 2000 software (Number Cruncher Statistical Systems, Kaysville, Utah, USA; available at www.ncss.com) was used to determine the sample size required to compare survival curves statistically. A total of 10,036 farms were randomly selected from the 123,373 records, about equally distributed over the ten replications. This sample size was sufficient to provide 90% power at a 5% significance level to detect a 1% difference given a baseline survival probability of 0.97 using a two-sided log rank test.

7.2.2.2 Farm characteristics

The goal of this study was to assess the association between farm characteristics related to BHV1 introduction in the simulation model and the risk of certificate loss during simulation. Risk factors evaluated in this study were: farm type, yearly number of cattle purchased, farm density within a 1-km radius and cattle density within a 1-km radius.

Two farm types were distinguished: dairy and non-dairy farms (excluding beef and veal farms). The study population contained 6,040 dairy herds and 3,996 non-dairy herds. An overview of the other variables is given in Table 7.1. For each farm, the number of cattle purchased was based on analysis of the cattle movements recorded by the Dutch Identification and Registration system in 1999. The farm characteristic 'number of purchased cattle per year' was used to select a destination farm for each simulated cattle contact off an infected farm.

Table 7.1 Descriptive analysis of farm characteristics in the sampled study population, used as explanatory variables in the analysis of the rate of certificate loss during simulation of a BHV1 eradication programme in The Netherlands with the model InterIBR-endemic ($X_{0.z}$ is the z% percentile)

Variable	Mean	St. Dev.	Median	$X_{0.05}$	$X_{0.95}$
Purchase (cattle/year)	2.8	14.7	0	0	11
Farm density (farms/km^2)	3.5	3.1	2.9	0.6	7.3
Cattle density (100 cattle/km^2)	5.0	5.7	3.8	0.6	12.9

On average, farms in the model purchased 2.8 cattle per year, although there was a difference between the two farm types: for dairy farms the average was 1.8 ($X_{0.95}$ = 8.0), whereas it was 4.1 ($X_{0.95}$ = 14.0) for non-dairy farms. More than half of the farms did not purchase any animals, implying that these farms could not be infected by animal contact during simulation. Farm density and animal density within a 1-km radius around each farm were calculated using the geographical point location information (X,Y) for each individual farm in the model. On average, the density measures were 3.5 cattle farms and 500 cattle per square km within a 1-km radius around each farm.

7.2.3 Data analysis

Relationships between farm characteristics and the rate of certificate loss were assessed using Cox proportional hazards regression model (Kleinbaum, 1996; Therneau and Grambsch, 2001). It models the time to the event of interest (certificate loss) for each case or alternatively the time at risk for all farms never experiencing this event as censored observations. Cox regression has been used to analyse the association between herd factors

and the rate of infection outbreaks in herds in a number of epidemiological investigations (e.g. Van Schaik et al., 1999; Benard et al., 1999; Norström et al., 2000).

The hazard function describes a probability distribution that quantifies the risk of an event occurring at time t (Allore et al., 2001). Cox regression models the hazard function h(t,X) as the product of the baseline hazard (h_0) and an exponential expression involving the predictor variables X (Kleinbaum, 1996):

$$h(t,X) = h_0(t) \times e^{\sum_{i=1}^{p} \beta_i X_i} \qquad (7.1)$$

The outcome of Cox regression gives estimates of the coefficients for the i^{th} predictor variable, from which the hazard ratio (*HR*) can be calculated as $HR = e^{\beta_i X_i}$.

Collinearity between predictor variables was assessed using a bivariate two-tailed correlation coefficient matrix. To provide initial insight into the data, the continuous variables were categorised into a small number of groups and for each group the fraction of herds with the event 'loss of certified-free status' was calculated.

The regression analysis was carried out using the STCOX procedure in Stata 6.0 (Stata Corporation, College Station, Texas). The proportionality assumption underlying the Cox model was evaluated for both continuously and categorically scaled variables with a statistical test of Schoenfeld residuals (Stata, 1999; Therneau and Grambsch, 2001). Since preference was given to inclusion of continuous variables in order to provide more accurate effect estimates in the multivariable Cox model, a check for linearity of effect for each continuous variable was performed through visual inspection of martingale residual plots (Stata, 1999). If these plots showed deviation from linearity and no other functional form of the variable was adequate, a categorised version of the variable was included in the Cox model, provided that the assumption of proportionality was valid. If the assumption of proportionality did not hold for a variable, the Cox model was stratified for that variable (Stata, 1999). The most important variables to be included in the multivariable Cox regression model were selected using backward elimination based on exclusion of variables non-significant at $p>0.05$ on the basis of a likelihood-ratio test used to compare hierarchical models.

Since data used in the survival analysis were sampled from ten replications of the simulation model, replication number was included as random effect in a frailty model (provided with S-plus 2000, Therneau and Grambsch, 2001) and tested for significance.

7.3 Results

An overview of the fraction of herds with certificate loss in various categories of each explanatory variable is given in Table 7.2. Whereas the overall fraction of herds experiencing certificate loss amongst initially certified BHV1-free herds during simulation was 3.0%, this fraction was about 1.7 times (4.0/2.4) greater on non-dairy farms compared with dairy farms. With regard to the farm characteristic 'purchase', the fraction of certificate loss increased with increasing number of cattle yearly purchased. On closed farms (purchase=0) certificate loss was 2.4%, whereas in the highest category (purchase >10) 8.2% lost the BHV1 certified-free status. Figure 7.1 shows Kaplan-Meier failure curves for each category of purchase, representing the cumulative proportion of cattle herds with certificate loss during the period of simulation.

Table 7.2 Descriptive analysis of total number of farms in various strata of explanatory variables and number of farms with certificate loss in each stratum, during simulation of a BHV1 eradication programme in The Netherlands with the model InterIBR-endemic

Variable	Level	Total	Number events	Fraction events (%)
Farm type	dairy	6,040	142	2.4
	non-dairy	3,996	160	4.0
Purchase (cattle/year)	0	6,460	154	2.4
	1-10	3,042	104	3.4
	>10	534	44	8.2
Farm density (farms/km^2)	0-2	3,026	38	1.3
	>2-4	4,085	75	1.8
	>4	2,925	189	6.5
Cattle density (100 cattle/km^2)	0-4	5,336	68	1.3
	>4-8	3,476	65	1.9
	>8	1,224	169	13.8
Overall		10,036	302	3.0

The univariate analysis suggested that both farm and cattle densities were positively associated with the fraction of certificate loss. A test of Schoenfeld residuals showed that none of the categorical variables in Table 7.1 met the assumption of proportionality. On a continuous scale, however, proportionality was true for all variables. Since the martingale plots also suggested that the continuous variables had linear effects, it was decided to include them at a continuous scale in a multivariable Cox model. Since farm type did not meet the proportionality assumption, the model was stratified by farm type. The Pearson correlation

coefficient between farm density and cattle density within a 1-km radius was 0.65, suggesting a limited degree of collinearity.

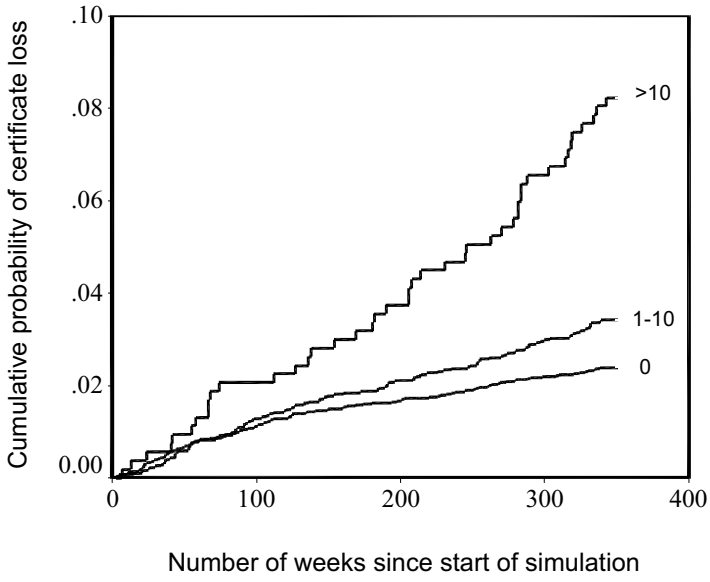

Figure 7.1 Kaplan-Meier failure curves of the cumulative probability of simulated certificate loss amongst certified BHV1-free cattle herds during simulation of a BHV1 eradication programme in The Netherlands with the model InterIBR-endemic, stratified by purchase category (0, 1-10 and >10 animals per year)

Multivariable models of the association between farm characteristics and hazard of certificate loss are shown in Table 7.3. Since correlation between farm density and cattle density was moderate, separate models were developed for each variable (model A and B) as well as a model that included both variables (model C).

The random effect of replication number was not significant in a frailty model for model A, B and C. The final Cox model included all other variables since the likelihood ratio tests did not meet the exclusion criterion. The HR for purchase was about 1.009 in the various models, indicating the change in hazard resulting from the purchase of one extra cow per year. Both farm density and cattle density within a 1-km radius were significant factors in models A and B, respectively. Farm density was positively associated with the hazard of certificate loss (HR=1.142 in model A) and animal density was also positively associated with the hazard of certificate loss (HR=1.065 in model B). Including both variables resulted in an improvement of model fit (model C). The HR's of farm density and animal density remained significant, but were lower than in models A and B (1.102 and 1.048 respectively).

Table 7.3 Three multivariable Cox proportional-hazard regression models (stratified by farm type) of farm characteristics related to certificate loss during simulation of a BHV1 eradication programme in The Netherlands with the model InterIBR-endemic (N=10,036 with 302 events; –2LogL of model without covariates = 5,116.6)

Variable	Beta	SE	P	HR	95% CI
Model A: -2logL = 4,840.7					
Purchase (cattle/year) [a]	0.009	0.001	<0.001	1.009	1.007-1.012
Farm density (farms/km^2) [b]	0.133	0.006	<0.001	1.142	1.129-1.156
Model B: -2logL = 4,833.5					
Purchase (cattle/year)	0.008	0.001	<0.001	1.008	1.006-1.011
Cattle density (100 cattle/km^2) [c]	0.063	0.003	<0.001	1.065	1.060-1.071
Model C: -2logL =4,736.0					
Purchase (cattle/year)	0.009	0.001	<0.001	1.009	1.006-1.011
Farm density (farms/km^2)	0.097	0.008	<0.001	1.102	1.086-1.119
Cattle density (100 cattle/km^2)	0.047	0.004	<0.001	1.048	1.040-1.055

[a] range $X_{0.05} - X_{0.95}$: 0 - 11
[b] range $X_{0.05} - X_{0.95}$: 0.6-7.3
[c] range $X_{0.05} - X_{0.95}$: 0.6-12.9

7.4 Discussion and conclusions

Simulation models have played an important role in the decision-making process on BHV1 eradication in The Netherlands. Opportunities for external validation of the simulation models, however, have been very limited. The objective of the current study, therefore, was to improve understanding of model behaviour. This is regarded an important aspect of internal validation of simulation models. More specifically, this study focused on the simulation event of certificate loss amongst certified BHV1-free herds in order to quantify relationships between farm characteristics and the occurrence of certificate loss. Since the model dealt with a population of individual farms, the approach to this problem was similar to what could be done in real-life: collect information on a sample of farms with and without the event of interest and identify differences between these farms. Furthermore, since the simulation model was dynamic, Cox regression analysis could be used to analyse the effect of risk factors on the time to loss of BHV1 certified-free status in the simulation model.

An important characteristic of the BHV1 simulation model used for this study is that for simulation of virus transmission between herds, primary focus is on farms with virus circulation. The risk of transmitting virus to other farms by various transmission routes is based on characteristics of the infected farm. For example, for the transmission route ‘animal contact’, the fraction of infected animals on the farm in a certain week and the yearly number of cattle sold determine the risk of selling an infected animal to another farm. Subsequently,

if a contact results in infection, the model selects a destination farm. It is in this simulation step that characteristics of other farms, such as the yearly number of cattle purchased, are taken into account. Associations between farm characteristics and loss of certified-free status after detection of an outbreak can, therefore, not directly be derived from model input parameters, but require collection of data from a simulation experiment.

With default parameter values, Vonk Noordegraaf et al. (2002) concluded that local spread and animal purchase accounted for most of the simulated virus circulations on certified BHV1-free herds, 53% by local spread and 29% by animal purchase, respectively. In the field, however, the actual routes of virus introduction are often unknown. The results of this study showed that in the BHV1 simulation model, density of both the number of farms and animals within a 1-km radius were significant risk factors for loosing BHV1-free certificate status due to detection of outbreaks. This model behaviour agrees with the conclusion of Assink et al. (2001) that during the first two years of the Dutch eradication programme the fraction of certificate loss was higher in more densely populated provinces. Furthermore, Van Wuijckhuise et al. (1997) concluded that dairy herds in a high herd-density area (>3 farms/km^2) had an approximately 1.5 higher odds to have a positive BHV1 bulk-milk status than herds in a low density area (<1 farm/km^2). However, Van Wuijckhuise et al. (1997) found no significant effect of animal density.

Van Schaik et al. (1999) found a HR of 1.10 for purchase of cattle in relation to time since latest BHV1 outbreak, which is much higher than the HR of 1.009 per animal purchased per year in the BHV1 simulation model. An important difference between both studies, however, is that the study population of Van Schaik et al. (1999) contained both BHV1-free and non-free farms, whereas this study focused on certified BHV1-free herds only. Since certified BHV1-free herds are only allowed to purchase cattle from other certified herds, the risk of cattle purchase on certified herds is expected to be less than on non-certified herds. Furthermore, purchase data of Van Schaik et al. (1999) were based on data of 1995. At that time, the prevalence of BHV1 infected cattle in The Netherlands was at a higher level and no national control programme was implemented.

In conclusion, the main importance of this study has been an improvement of the understanding of the BHV1 simulation model behaviour. With respect to certificate loss, qualitative behaviour of risk factors found in this study seemed to agree with observations in field studies. Quantification of risk factors was based on a simulation experiment with default input parameters, the HR's of the variables will, therefore, be sensitive to changes in the input parameters. For external validation of the simulation model, an important next step is quantification of risk factors for certificate loss in the field during the eradication programme. Such a comparison will also give more insight into the most likely range of parameter values related to virus spread mechanisms.

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Chapter 7

General discussion

7.1 Introduction

The main objective of this thesis was to develop and apply simulation models that could support policy making in various phases of the decision-making process with respect to a national BHV1 eradication programme in The Netherlands. This objective was divided into four parts, which were dealt with in the various chapters of this thesis: control strategies for endemic BHV1 (Chapters 2 and 4); control strategies for BHV1 epidemics (Chapter 3); identification of economically most important gaps in current epidemiological knowledge (Chapters 4 and 5); and model behaviour related to loss of BHV1-free certificate (Chapter 6). In general, a decision-making process includes five stages (Boehlje and Eidman, 1984):

1. Recognise the problem
2. Develop alternative solutions
3. Make a choice among these alternatives
4. Implement the decision
5. Evaluate the results (and go back to an earlier stage if necessary)

The decision-making process regarding BHV1 control fits well into these stages and the research described in this thesis coincided with these stages. In the 90's, Dutch livestock industry was facing increased international regulations with regard to trade of cattle, semen and embryos, in combination with a high prevalence of BHV1 infected cattle in The Netherlands (stage 1). With the development of a BHV1 marker vaccine, a tool was available to control BHV1 and various options were considered to apply this tool in a national eradication programme (stage 2). The simulation model described in Chapter 2 was used to support the decision on which control strategy would be able to eradicate BHV1 most cost-effectively (stage 3). Before the final decision was made to start an eradication programme, insight was required into possibilities to control possible future outbreaks of BHV1in a free country (Chapter 3). Together with implementation of a national BHV1 eradication programme in The Netherlands in May 1998 (stage 4), a monitoring programme was set up to evaluate the progress of the eradication programme in the field (stage 5). Information available from the monitoring programme and available insights into relevant processes and parameters were used to develop the simulation model described in Chapter 4. An important goal of this model was to support decision-making if, based on results of the monitoring programme, it would be necessary to reconsider some aspects of the eradication strategy. This model was also used to set priorities for empirical research during the eradication programme (Chapters 4 and 5) and to assess model behaviour for loss of the BHV1-free certificate (Chapter 6).

As described above, three simulation models that combine epidemiological and economic aspects of BHV1 spread and control were developed in this thesis. Starting with a relatively simple state-transition model, the complexity of the following models increased due to

advances in knowledge on modelling of biological processes, improvement of quality and availability of data and technical improvements of simulation frameworks. In this general discussion, some critical aspects of the use of simulation models in decision support are discussed. First, consequences of simulating the population of farms as the system of interest and alternative ways to study this system are discussed. Next, attention is given to model validation, one of the most critical steps in system simulation. The chapter ends with suggestions for research priorities during the period of postponed vaccination.

7.2 Definition of the system

A first essential step in a simulation study is to choose the system of interest, which primarily depends on the objectives of the research. In general, a system can be defined as a collection of entities that act and interact together (Law and Kelton, 1991). When the objective of research is to assess how farmers' management can influence the process of infection between animals or groups of animals within a herd, simulation studies often place the boundary of a system at the herd level (e.g. Sørensen et al., 1995; Van der Fels-Klerx et al., 2000). In this research, the aim was to identify how control strategies at national level can reduce the prevalence of BHV1 infected farms and infected cattle in The Netherlands. Since especially spread of infection between farms is important for control of contagious diseases, the system of interest was the population of cattle farms involved in the spread and control of BHV1.

An important consequence of this system choice is that conclusions about control strategies at national level cannot always be interpolated to individual farms. For example, in Chapter 2 a national control strategy with live marker vaccine showed to be more cost-effective than a strategy with killed marker vaccine. At the individual farm level, however, the optimal choice between these vaccine types will depend on many specific aspects, such as the number of BHV1-infected cattle and risk of virus introduction. Also, costs and benefits calculated at national level will be unequally distributed between farms. This implies that, although it could be economically sound to eradicate BHV1 for the population of cattle farms as a whole, this might not be true for each individual farm.

Models that focus on a single farm as the system of interest often take into account many details on individual farm management and specific farm characteristics (Jalvingh, 1992). Van Schaik et al. (2001) developed an economic model to support on-farm decisions of management strategies to reduce the risk of introduction of infectious diseases. This model can be adapted to a specific farm, to calculate costs and benefits of management scenarios to prevent e.g. BHV1 introduction on a certified BHV1-free farm.

Another important question for individual farmers in the BHV1 eradication programme is whether to repeat vaccination of the herd or to remove the last few infected cattle and apply for a BHV1-free certificate. In the simulation models developed in this research, this decision was simplified by a probability to apply for a certificate given the within-herd prevalence of infected cattle. In real life, this decision for individual farmers involves much more factors, such as age and production level of the infected cattle and risk attitude of the farmer. A farm level model, therefore, must be developed to support this decision. This farm level model should not only include costs and benefits of removal of infected cattle versus costs of continued vaccination, but also account for the impact of this decision on the risk and consequences of BHV1 re-introduction, which partly depends on the BHV1 status of neighbourhood farms.

In conclusion, since interaction between farms is a very important issue in national control strategies for contagious diseases, decision support models developed in this research focused on the population of cattle farms as the system of interest. Farm specific models, however, can be important additional tools to support individual farmers in their decisions on how to control the infection most cost-effectively, within the framework set by national regulations.

7.3 Ways to study a system

Discussion about eradication of BHV1 in The Netherlands increased the need to gain more insight into the consequences of various control strategies on the behaviour of the system of cattle farms and BHV1 spread: how would it perform under new conditions? The research described in this thesis focused on development and application of simulation models to support decision-making. In the last decades, simulation has shown to be an attractive tool to deal with complex problems and has increasingly been used for decision support (Oriade and Dillon, 1997). There are, however, various other important ways to increase insight into a system, as shown in Figure 7.1. These will be discussed below, illustrated with examples related to BHV1.

Sometimes it is possible to experiment with the real-world system, by repeatedly changing some aspects and then observing and analysing the operation of the system under the new conditions. This often is the most desirable way to increase knowledge and make a choice between alternative strategies. If the system of interest is at farm level, real-life experiments can be very useful to optimise decision-making. However, dealing with evaluation of national disease control strategies not earlier applied, such experiments often are much too costly, time-consuming, disruptive and unethical if other tools are available.

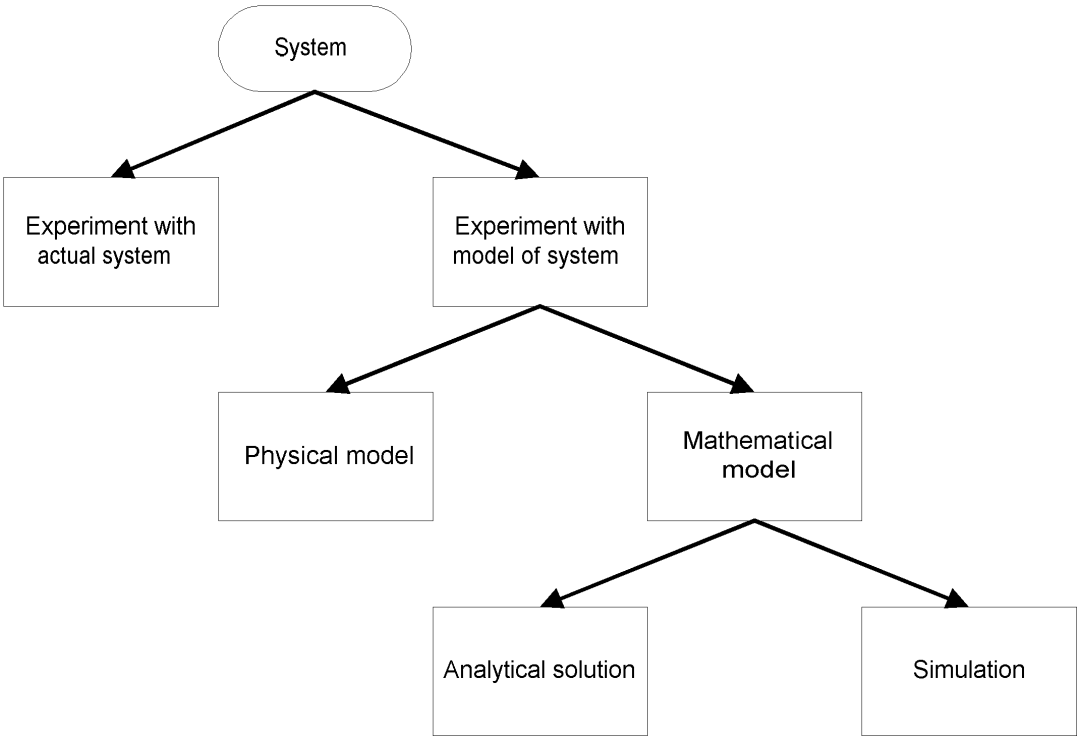

Figure 7.1 Ways to study a system (Law and Kelton, 1991)

When experiments with the whole system are not possible, experiments with a subset of the actual system can be useful to increase understanding of system behaviour. For BHV1, various experiments with a subset of the actual system of interest were carried out to increase insight into the epidemiology of BHV1 and effectiveness of vaccination with marker vaccine within a herd. This subset either was a group of farms selected from the total population (McDermott et al., 1997; Bosch et al., 1998; Van Schaik et al., 1999; Mars et al. 2001), a single farm (Hage et al., 1996) or a group of animals in transmission experiments (Kaashoek et al., 1996; Bosch et al., 1997; Mars et al. 2000). These experiments provided extremely valuable information about the effectiveness of control measures on the risk of introduction and spread of BHV1 within a herd. However, more information was required to support decisions on the cost-effectiveness of national control strategies for BHV1.

Another way to increase insight into system behaviour is to develop and experiment with a model of the system. A model can be defined as a simplified representation of a real system, used to approximate or mimic real-world systems (Martin et al., 1987). As shown in Figure 7.1, a model can be a physical representation (e.g. models of farm buildings to test the effect of building design on local air movement) or a mathematical representation. A mathematical model represents a system in terms of logical and quantitative relationships that are manipulated and changed to see how the model reacts and thus how the system would react – if the model is valid (Law and Kelton, 1991).

Mathematical models can be examined either by analytical solution or by simulation. Simulation means numerically exercising a model for the inputs, to see how they affect the output measures of performance. Law and Kelton (2000) state that, if an analytical solution to a mathematical model is available, it is usually desirable to study the model in this way rather than via simulation. However, when mathematical models are highly complex, simulation often is the only way to analyse model behaviour.

In the discipline of veterinary epidemiology and economics, distinction is made between mathematical models and simulation models, although this is not totally in agreement with Figure 7.1. Mathematical models often represent a system with differential equations that are solved by analytical techniques. Simulation models frequently are individual-based-models, where the properties of the model are defined for individual units within a population and the simulation is run to see what happens at the population level. The models developed in this research are characterised as simulation models, although some internal relationships include techniques from mathematical modelling (e.g. the within-herd spread of virus is simulated with a SIR model (De Jong, 1995)). Both mathematical and simulation models have frequently been applied to model the impact of control measures at national level for infections such as classical swine fever (CSF) (Klinkenberg et al., 2001; Mangen et al., 2001), pseudorabies virus (PRV) (Van Nes et al., 1998; Buijtels et al., 1997) and foot-and-mouth disease (FMD) (Keeling et al., 2001; Morris et al., 2001).

For BHV1, two mathematical models have been developed to evaluate the effect of surveillance programmes on the spread of BHV1 between cattle herds in a BHV1-free country (Graat et al., 2001a; Graat et al., 2001b). Whereas Graat et al. (2001a) modelled between herd spread for one farm type only, assuming random contacts with constant rate, Graat et al. (2001b) accounted for differences in the number and structure of contacts between various farm types. This improvement of modelling animal contacts between herds has also been a main issue in the development of the simulation models described in this thesis. Moreover, the mathematical model of Graat et al. (2001b) and the simulation model InterIBR-endemic (Chapter 4) have used the same database on animal contacts to estimate model parameters. Both models have actually been used to support policy makers regarding BHV1-control in The Netherlands. An advantage of the BHV1 simulation model InterIBR in decision support, compared with the mathematical models for BHV1, has been the ability to calculate costs of control. Some other differences in framework and model design, related to BHV1 spread and control, between Graat et al. (2001b) and the simulation model InterIBR (Chapters 3 and 4) are discussed below. These differences are partly related to the objectives of each study and the time spent on model development.

First, the mathematical model for BHV1 deals with surveillance programmes to detect outbreaks in a BHV1-free country, without accounting for the effectiveness of strategies to

control such outbreaks. In contrast, the simulation model InterIBR has been used for both an epidemic (Chapter 3) and endemic situation (Chapter 4), in which detection of outbreaks is followed by simulation of various control measures such as vaccination, removal of infected cattle or movement control zones.

Second, the mathematical model for BHV1 is static and deterministic. The simulation models, in contrast, are dynamic and stochastic and thereby provide insight into BHV1 spread and control over time and variability of expected outcome. Especially when control measures on average are feasible, but have a small probability of adverse results, it is important to be aware of this variability in decision-making.

Finally, InterIBR accounts in more detail for the demography of the population of cattle farms (e.g. variation of herd size), heterogeneities that influence transmission between herds (e.g. variation in contact rate) and the impact of spatial processes in transmission and control (e.g. local spread and control zones). Morris et al. (2001) state that, when dealing with complex interactions involved in spread and control of infections at national level, the ability of a model to account for dynamic, stochastic and spatial components is important for support of policy making.

In conclusion, there are several ways to increase insight into the behaviour of a system and some of them have contributed to the decision-making process of BHV1 control. Experiments with a subset of the system were extremely valuable to increase knowledge of the impact of control measures at farm and animal level. The added value of system models, both mathematical and simulation, was to use these experimental data to draw inferences about surveillance and control strategies at population level. Also, both types of models have been useful to set priorities for further empirical research. Comparison of mathematical and simulation models should mainly be based on quality of input data, validity of assumptions and usefulness of results. In general, simulation models often are more complex in design and require more parameters than mathematical models. This is both a strength and weakness of simulation as opposed to mathematical modelling. It is, therefore, strongly advised to start simulation with a model that is only moderately detailed (Banks, 1998). The combination of both mathematical and simulation modelling to support policy makers has shown to be very useful to increase understanding of aspects related to BHV1 spread and control.

7.4 Validity of BHV1 simulation models

7.4.1 Introduction

One of the most critical aspects in development and application of models concerns validation. Model validation can be defined as substantiating that, within its domain of

applicability, the model behaves with satisfactory accuracy consistent with the study objectives (Balci, 1998). Validation, therefore, deals with all steps in a simulation study, from problem definition to actual decision support. Because by definition all models are simplified representations of reality, the art of model building is to determine what aspects of the complex real-world should be included in a model. It must be kept in mind, however, that no matter how much effort is put in developing a model, it will always be an approximation of the real system and, therefore, never be absolutely valid (Kleijnen, 1995). Dillon et al. (1991) state that the objective of validation should be to ascertain the usefulness, rather than the truthfulness of the model.

Distinction is made between internal and external validation. Internal validation mainly refers to design of the model, quality and availability of data and behaviour of the model under various conditions (e.g. assessed by sensitivity analysis). External validation refers to comparison of model performance against the performance of the real system. Another important issue in the development and application of a model concerns credibility. Credibility refers to the acceptance and use of a model and its results in the decision-making process (Law and Kelton, 1991). Model validity is a necessary, but not sufficient condition for the credibility of simulation results (Balci, 1998).

Discussion points related to model design, data quality and data availability were addressed for the developed models in the previous chapters. An important note is that good quality of input data for models requires careful design of how to collect and analyse these data. Close interaction between model development and design and analysis of real-life experiments is, therefore, essential in building valid models. When no data from experiments are available, quantification of expert knowledge can be a useful alternative (Horst et al., 1998). In the following section, results from the BHV1 monitoring programme are compared with model output (external validation). Next, techniques used in this research to study model behaviour (internal validation) are discussed.

7.4.2 External validation

The models described in Chapters 2 and 3 were developed and used to support decision-making prior to implementation of the BHV1 eradication programme in The Netherlands. For that reason, comparison of model performance with performance of the real system was not possible at that time. To evaluate the progress of the implemented BHV1 eradication programme in the field, a monitoring programme was set up (Assink et al., 2001). The aim was to assess whether observed progress was sufficiently similar to expectations of decision makers, which were based on simulation results. The monitoring programme mainly focused on the incidence of BHV1 outbreaks on certified BHV1-free herds and the prevalence of infection over time on various farm types. Because available data were from one large scale

'experiment' only, statistical comparison between model performance and real-life observation was not possible. Furthermore, the simulation models did not account for the postponement of compulsory vaccination starting February 1999 (see Chapter 1), thereby effectively precluding proper external validation.

Table 7.1 shows the number of certified BHV1-free dairy herds, the number and rate of detected outbreaks on these herds and the prevalence of BHV1 infected dairy cattle in year 1999 and 2000 based on results of the monitoring programme (Assink et al., 2001). The same variables are shown for year 1 and 2 of the BHV1 state-transition model (Chapter 2) and the stochastic model InterIBR-endemic (Chapter 4). Although it is not possible to draw any hard conclusions, Table 7.1 illustrates some interesting differences and agreements between observations in real-life and model expectations.

Table 7.1 Observed and simulated number of certified BHV1-free dairy herds, number and rate of detected outbreaks per year on these herds and prevalence of BHV1 infected dairy cattle at the start of the programme (Jan 1999) and in year 1999 and 2000. Simulation results are shown for both the state-transition model (Chapter 2) and the stochastic model InterIBR-endemic (Chapter 4)

Year	Variable	Monitoring [a]	State-transition model	InterIBR-endemic
Jan 99	Certified herds (x 10^3)	7.5	8.3	7.3
	Prevalence infected dairy cattle (%)	25	39	22
1999	Certified herds (x 10^3) [b]	7.5	11.7	12.5
	Detected outbreaks / year	63	60	71 (56-86) [d]
	Detection rate [c]	8.4	6.0	7.2 (5.7-8.7) [d]
2000	Certified herds (x 10^3)	7.5	15.8	15.3
	Detected outbreaks / year	52	64	85 (60-105) [d]
	Detection rate [b]	7.0	4.7	6.1 (4.3-7.6) [d]
	Prevalence infected dairy cattle (%)	15	17	14

[a] based on Assink et al., 2001

[b] number of certified BHV1-free dairy herds at the end of the year

[c] detected outbreaks per 1000 farms on average at risk per year

[d] minimum and maximum value based on ten replications

The number of certified BHV1-free dairy herds was about constant in the first two years of the eradication programme, whereas from both models it was expected to double in this period. Most likely, the reason for this difference is the postponed compulsory vaccination. The conclusion of Assink et al. (2001) that 43% of the non-certified dairy herds had an on-

farm prevalence of less than 10% in the winter of 2000, shows that much more farms could easily apply for a BHV1-free certificate.

Based on the prevalence of infected dairy cattle and the detection rate of outbreaks on certified BHV1-free dairy herds, the stochastic simulation model InterIBR-endemic resembled monitoring data more closely than the state-transition model. The detection rate observed in the monitoring programme was within the simulated range of the stochastic model. Also, the observed change in prevalence of infected dairy cattle was about similar to the stochastic model. However, whereas simulation results were based on a compulsory half yearly vaccination programme, in real-life compulsory vaccination was already postponed early 1999. Postponement of compulsory vaccination was, therefore, expected to result in an increase of the incidence of major outbreaks on infected herds due to declining herd immunity. Indirectly, this was expected to result in more outbreaks on certified BHV1-free herds. Several reasons for not observing these expectations are possible, although more research is required to test them. First, one or more model parameters involved in virus spread could be overestimated, such as the reactivation rate of latently infected cattle. Since vaccination both reduces the rate of reactivation and the probability of a major outbreak within a herd following reactivation, the impact of postponed vaccination will be less at lower reactivation rate. Second, although compulsory vaccination was postponed, about one-third of the farmers continued vaccination. A third reason can be that in the last few years farmers have become more aware of risk factors for virus introduction into a herd and measures to prevent introduction. Whereas, simulation of animal contacts was based on animal movement data of 1999, this increased awareness may have resulted in less animal movements between farms. A final reason can be that vaccine coverage is longer than half a year, which will have important economic implications for possible future continuation of the programme (see section 7.5).

In conclusion, although no statistical comparison between real-world data and simulation output was possible, simulation results appeared to be in reasonable agreement with observations from the monitoring programme. More research is required, however, to explain why no clear effect of postponement of compulsory vaccination has yet been observed in the field. It will be interesting to study whether the prevalence of BHV1 infected cattle will continue to decrease or if after some time a new equilibrium level will be reached.

7.4.3 Model behaviour

As described above, external validation of the simulation models was limited to subjective judgement. Therefore, much emphasis was put on insight into the behaviour of the models. For all three models, quantitative insight was gained into the dynamic behaviour of underlying processes such as certification, surveillance and transmission routes between

herds (Chapters 2, 3 and 4). Furthermore, additional techniques were applied to quantify some aspects of model behaviour in more detail, which will be discussed below.

Sensitivity analysis is a powerful technique in simulation analysis to study how simulation outcome reacts to changes of the input. Especially for models that contain many parameters, sensitivity analysis is important to identify which parameters have most impact on model results. In Chapters 2 and 3 of this thesis, sensitivity analysis was performed by selecting a few parameters expected to be important and changing these parameters one at a time (also called an OAT-design). Although this relatively simple approach to sensitivity analysis is applied in many simulation studies and often provides useful results, the basic underlying assumption of parameter independence may not always be valid. In Chapters 4 and 5, the techniques of experimental design and metamodelling (Kleijnen and Sargent, 2000) were applied to support sensitivity analysis. This statistical approach to sensitivity analysis showed to be more efficient (required less simulation runs) and more effective (accounted for interactions) than changing parameters one by one. Efficiency was of great importance in this research, since one replication of the model InterIBR-endemic already required about five hours computing time and the model contained many parameters. Accounting for interactions showed to be effective to assess the relative importance of parameters. For example, bio-security measures on certified herds only had a small impact on costs and length of a BHV1 eradication programme according to an OAT analysis, whereas in the metamodel a strong interaction was found between this factor and the probability of virus introduction by local spread.

It is advocated that future simulation studies in veterinary epidemiology and economics use the experimental design and metamodel approach to sensitivity analysis, instead of changing parameters one by one. Whereas in this study the control strategy was fixed and only epidemiological parameters were changed in the experiment, this approach can also be very useful to study the impact of parameter uncertainty on the cost-effectiveness of various control strategies.

The sensitivity analysis described above studied model behaviour with respect to overall model input and output. In Chapter 6, model behaviour relative to one sub-process only was described: the event of certificate loss due to detection of outbreaks on certified BHV1-free herds. Whereas the models provided expectations for the number of outbreaks and routes of transmission, no insight was obtained into why some farms did have this event in the model and others did not. In this study, survival analysis (Kleinbaum, 1996) was used to analyse simulation data, but for other sub-processes of interest other techniques might be more appropriate. Actually, the survival model can also be regarded as a metamodel, since quantification of relationships required collection and analysis of data from a simulation experiment.

From experience in this research, it is concluded that insight into model behaviour is very important to help in the process of validation and decision support in two ways, especially when data are lacking for external validation. First, it provides a useful ground for discussion on model validity and credibility with experts of the real system and policy makers. In general, if model behaviour does not agree with prior knowledge of the real system, the validity and credibility of a model will be of doubtful value. Second, insight into model behaviour is very useful in the discussion about what aspects of the real system need to be studied in more detail.

7.5 Research priorities during period of postponed vaccination

After the problems with contaminated live marker vaccine (Barkema et al., 2001), farmers' support was not considered sufficient to continue a compulsory BHV1 eradication programme (see Chapter 1). Based on experience from this research, four items should have priority in research to help in discussions on possible future continuation of the programme. The simulation models developed in this study can be helpful tools for these issues.

First of all, more insight is required into the economic benefits of BHV1 eradication under current and future conditions of international trade of cattle, embryos and semen. In an early stage of the decision-making process on BHV1 eradication (Chapter 2), calculation of these benefits included major assumptions that had a great impact on the expected benefits of BHV1 eradication for the Dutch cattle sector. Increased international legislation with respect to trade of cattle, embryos and semen were important arguments to start the eradication programme. However, once the decision was made to eradicate BHV1, no priority was given to more detailed economic analysis of these benefits. To convince farmers to support a future eradication programme, this item is of major importance.

Another aspect that needs further research is the frequency of vaccination. As discussed in section 7.4.2, it was expected that the postponed compulsory vaccination would result in an increase of the incidence of major outbreaks on infected herds due to declining herd immunity. Indirectly, this was also expected to result in more outbreaks on certified BHV1-free herds. However, monitoring data showed no increase of detection rate. Furthermore, the decrease of prevalence of infected dairy cattle from 1999 to 2000 was similar to model expectations based on compulsory vaccination (Table 7.1). Although several explanations have been suggested for this phenomenon, an important hypothesis is that vaccine coverage is much longer than half a year. As no data on incidence of outbreaks on non-certified herds were available from the monitoring programme, more research is required to test this hypothesis. Total vaccination costs were expected to be about EUR 60 million based on half

yearly vaccination and switching to less frequent vaccination would be very cost-effective, if the hypothesis is true.

Third, more research is required on the feasibility of BHV1 control strategies that rely less on the tool of vaccination and fit into a more integrated approach to control of infectious diseases. An example of such a strategy is the exemption of vaccination for farms that apply a closed-farming system with respect to purchase of cattle, which was discussed by decision makers after the problems with the contaminated live marker vaccine occurred. Model calculations showed that the feasibility of this strategy mainly depended on the estimated reactivation rate of latently infected cattle. Better estimation of this rate is, therefore, very important to be able to compare the feasibility of alternative BHV1 control strategies.

Finally, in this research focus was mainly on the first phase of a BHV1 eradication programme, until a cow-level prevalence of 5% in the dairy cattle population was reached, and on outbreaks in a BHV1-free country. Not much attention was given to the final phase of BHV1 eradication, at a low prevalence level. An important issue in the final phase will be whether and when it will be cost-effective to take additional measures to minimise the risk of the last BHV1 infected cattle in the population. The simulation model InterIBR-endemic (Chapter 4) can be a very useful tool to explore control strategies in this final phase, although it is recommended to first update model input based on experience obtained from the first phase of BHV1 eradication.

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Summary

Introduction

Bovine herpesvirus 1 (BHV1) is the causative agent of infectious bovine rhinotracheitis (IBR), a respiratory disease in cattle. Acute infection with BHV1 can result in severe production losses, abortion and mortality, but most infections nowadays occur sub-clinical. An important characteristic of BHV1 is the ability to establish latent infection. Latent virus can be reactivated and shed into the environment. Therefore, once infected with BHV1, an animal must be regarded as a lifelong risk to BHV1-free herd mates.

Countries free of BHV1 can impose restrictions on import of cattle and cattle products. Within the European Union (EU) directives have also been set up to allow member states to stipulate requirements for the import of cattle, semen and embryos. Furthermore, since 1999 only BHV1-free bulls have been allowed at artificial insemination centres in EU countries. In The Netherlands, high intensity of cattle trade and contacts between farms, together with widespread use of traditional vaccines have been favourable conditions for the virus to become endemic. Early 90's about 85% of the dairy herds had one or more infected cattle. International developments described above have put pressure on the Dutch livestock industry to eradicate BHV1. In countries with a high prevalence of BHV1 infected cattle, a 'test-and-cull strategy' is economically not feasible nor ethically acceptable. It will, therefore, be more feasible to start eradication of BHV1 with control measures that lower the incidence of outbreaks and thereby the prevalence of infection.

The development of marker vaccines, which enable differentiation between cattle infected by the wild-type virus from cattle that have been vaccinated, induced a discussion on opportunities to eradicate BHV1 in The Netherlands. The most important question raised was which strategy would be able to eradicate BHV1 most cost-effectively, while meeting the criteria of farmers' support and operational feasibility. When dealing with disease control strategies that cannot easily be implemented and evaluated for their effectiveness in the field, a useful tool to support the decision-making is the development of a model that combines both epidemiological and economic knowledge to explore control strategies. The main objective of this thesis was the "development and application of simulation models to support policy making in various phases of the decision-making process with respect to a national BHV1 eradication programme in The Netherlands". More specifically, the main objectives of this study were to provide insight into:

1. Epidemiological and economic consequences of various control strategies for endemic BHV1 in The Netherlands;

2. Cost-effectiveness of various strategies to control BHV1 following reintroduction into The Netherlands once free of BHV1;
3. Gaps in knowledge on BHV1 spread that would have most impact on the progress and costs of the BHV1 eradication programme;
4. Model behaviour with respect to associations between farm characteristics and the loss of the BHV1-free certificate during the simulated eradication programme.

Development of simulation models

In an early phase of the decision-making process on BHV1 eradication in The Netherlands, before a final decision was made on implementation of control measures in the field, two simulation models were developed and applied (Chapters 2 and 3).

The simulation model described in Chapter 2 was developed to evaluate various control strategies for endemic BHV1 in The Netherlands and thereby support policy making regarding the question which strategy would be able to eradicate BHV1 most cost-effectively. The framework of this model was based on a deterministic state-transition approach, as earlier developed to evaluate control strategies for eradication of pseudorabies virus.

Calculated programme costs were associated with vaccination, diagnosis, monitoring, and early removal of latently infected cattle. The benefits of a vaccination programme were derived as the reduced economic losses due to BHV1, based on clinical and sub-clinical infections, outbreaks at artificial insemination centres and potential losses due to export bans. Five control strategies, including a voluntary and a compulsory vaccination programme for all dairy herds were evaluated with the model. Comparison of strategies was based on the number of weeks to reach a cow-level prevalence of 5% infected dairy cattle, costs of each strategy and the pay-back period of the investments.

Model outcome showed that a voluntary vaccination programme with 50% participation was not expected to result in eradication of BHV1. Compulsory vaccination would, therefore, be necessary to reach a BHV1-free status. Furthermore, a national control strategy with live marker vaccine was expected to be more effective than a strategy with killed marker vaccine. Also, a national programme with certification of BHV1-free herds and vaccination of non-certified herds showed to be more cost-effective to eradicate BHV1 than a compulsory vaccination programme for all herds.

Based on EU developments towards BHV1 eradication and based on results of the model described above, a compulsory eradication programme for BHV1 was implemented in The Netherlands in May 1998. This programme involved half-yearly vaccination with marker vaccine for all non-certified cattle herds, surveillance of certified BHV1-free herds and restrictions on cattle trade between herds. This strategy was expected to reduce the

prevalence of infected dairy cattle to 5% in about 5 years, with expected direct costs approximately EUR 100 million, a pay-back period of about 8 years and less than 1% outbreaks per year on certified BHV1-free herds.

Because a BHV1 eradication programme would be a big investment for the Dutch cattle sector, insight was also required into the expected consequences of reintroduction of the virus once The Netherlands would be free of BHV1 and the cost-effectiveness of various control strategies. In Chapter 3, the simulation model InterIBR-epidemic was described and applied to outbreaks in a free country. This model was based on the framework of InterSpread, a spatial, dynamic and stochastic model originally developed to simulate outbreaks of foot-and-mouth disease. Farm data were based on a sample obtained from the Dutch Identification and Recording system. These data provided insight into the demography of the cattle farm population with respect to farm type, herd size and animal contacts between farms. Farm types included were dairy, beef, veal and miscellaneous.

Simulation of a BHV1-outbreak started with introduction of the virus on a predefined farm type, after which both within-farm and between-farm transmission were simulated. Between-farm transmission included animal contacts, local contacts and professional contacts. Surveillance and control measures were implemented to simulate detection of the infection and subsequent control. Economic consequences included in this study were related to losses due to infection and costs of control. In the basic simulated control strategy, movement-control measures were applied, animal contacts were traced and neighbour farms were put on surveillance.

Simulation results showed that farm type with first introduction of BHV1 had a considerable impact on the expected number of secondarily infected farms and total costs. Furthermore, it was concluded that a strategy with either rapid removal or vaccination of infected cattle did not reduce the number of infected farms compared to the basic strategy, but would cost more to control. Also, a one-km surveillance zone was not cost-effective. Frequent surveillance on farms with a high frequency of cattle trade was suggested, together with monthly bulk-milk tests on dairy farms.

To support policy makers during the eradication programme, two decision support tools were developed: (1) a BHV1 monitoring programme and (2) another BHV1 simulation model. The monitoring programme was set up to evaluate the progress of the eradication programme in the field. Information available from the monitoring programme and available insights into relevant processes and parameters were used to develop the simulation model InterIBR-endemic (Chapter 4). The framework of this model was based on the epidemic model described in Chapter 3, thereby accounting for spatial and stochastic events. Model adaptations mainly involved changes to the procedures of vaccination, certification and surveillance. An important goal of this model was to support decision-making if, based on

results of the monitoring programme, it would be necessary to reconsider some aspects of the eradication strategy. Furthermore, the model was used to identify gaps in knowledge on BHV1 relevant for the eradication programme and to assess model behaviour for loss of the BHV1-free certificate (see section 'test of model behaviour'). Farm data of InterIBR-endemic were based on actual data of farms present in The Netherlands in 1999, to handle more realistically the extended information from field research. Furthermore, records of all animal movements in 1999 were analysed to quantify model parameters related to between-herd animal contacts. The model contained about 57,000 cattle herds, of which 21% was certified BHV1-free in January 1999.

Based on ten model replications, simulation of the Dutch BHV1 eradication programme resulted in a median period of 334 weeks to reach a cow-level prevalence of 5% in the dairy cattle population (range: 316-360), with median costs of EUR 106 million (range: 103-111). The median number of outbreaks per year on certified BHV1-free dairy farms was 102 (range: 84-140). These ranges did not include the impact of parameter uncertainty (see section 'test of model behaviour'). The rate of large outbreaks observed in the model on non-certified herds was about three times higher than on certified BHV1-free herds. Local spread accounted for most of the simulated virus circulations on certified herds, whereas on non-certified herds reactivation of latently infected cattle was the major source of virus circulation. With regard to the monitoring programme, simulation results suggested to stratify by herd size when sampling herds for estimation of population prevalence. Furthermore, it was concluded that the incidence of outbreaks on non-certified herds had a major impact on the progress of the eradication programme and should, therefore, be measured in the field.

Internal validation

A critical aspect in development and application of models concerns validation. Since opportunities for external validation were limited in this research, internal validation was emphasised with various studies on model behaviour. In Chapters 4, 5 and 6 various experiments with the simulation model InterIBR-endemic were performed to improve understanding of model behaviour, thereby also meeting objectives 3 and 4 of this study.

Sensitivity analysis is an important technique to study how simulation outcome reacts to changes of model input. Since the model InterIBR-endemic contained many epidemiological parameters, sensitivity analysis was used to identify which parameters had most impact on model outcome and could, therefore, be expected to be most relevant for the progress and costs of the eradication programme. This information could then be used to set priorities for further empirical research. Application of sensitivity analysis is often limited to changing

only one input parameter at a time. In Chapters 4 and 5, the techniques of experimental design and metamodelling were applied to support sensitivity analysis. This statistical approach to sensitivity analysis showed to be more efficient (required less simulation runs) and more effective (accounted for interactions) than changing parameters one by one.

The metamodel approach was applied to 31 parameters of the simulation model InterIBR-endemic. Three simulation responses, considered most relevant by policy makers, were used as dependent variables in the sensitivity analysis. To estimate the metamodels, analysis of simulation data was based on ordinary least squares (OLS) regression. Since the simulation response of interest in Chapter 5 was censored, tobit and logistic regression were also applied. It was concluded that tobit regression resulted in more valid outcomes than OLS regression when dealing with censored data. Uncertainty of parameter values for local spread and reactivation of BHV1 had most impact on both the period and costs of the simulated eradication programme. These factors should, therefore, have priority in further epidemiological research. The uncertainty of the yearly reactivation rate of latently infected animals affected the costs by EUR 43 million, which is about 40% of the expected total costs.

An important aspect of the eradication programme was the loss of the BHV1-free certificate due to detection of outbreaks on certified BHV1-free herds. The objective of Chapter 6 was to improve understanding of model behaviour with respect to loss of the BHV1-free certificate. Using a Cox regression model, the association between farm characteristics and the risk of certificate loss during simulation was quantified. Amongst the initially certified BHV1-free herds, the overall fraction of herds with BHV1-free certificate loss during simulation was 3.0%. Significant risk factors for loss of the BHV1-free certificate in the simulation model were the farm characteristics ‘yearly number of cattle purchased’, ‘farm density within a one-km radius’ and ‘cattle density within a one-km radius’. Qualitative behaviour of risk factors found in this study agreed with observations in field studies.

Discussion

Chapter 7 is a general discussion on some critical steps in development and application of the simulation models presented in this thesis and the role of these models as decision support tools in the BHV1 eradication programme. Consequences of between-farm simulation, as opposed to a farm-level model, were discussed. It was concluded that farm specific models could be important additional tools to support individual farmers on policy and decision-making within a national eradication programme for BHV1. Furthermore, alternative ways to study a system were discussed: experiment with (a subset of) the actual system versus experiment with a model of the system. A comparison was made between a mathematical modelling approach for BHV1 and the simulation models developed in this research. It was

concluded that the added value of both mathematical and simulation models in the Dutch BHV1 eradication programme had been the use of experimental data to draw inferences about surveillance and control strategies at population level. Also, observations from the BHV1 monitoring programme were compared with model output. It was concluded that, based on the prevalence of infected dairy cattle and the detection rate of outbreaks on certified BHV1-free dairy herds, the simulation model InterIBR-endemic resembled monitoring data rather closely. However, whereas simulation results were based on a compulsory half yearly vaccination programme, in reality compulsory vaccination in The Netherlands was already postponed early 1999 due to contamination of live marker vaccine with bovine virus diarrhoea virus. The chapter ends with recommendations for research priorities during the period of postponed vaccination. It was concluded that more research is required on (1) the economic benefits of BHV1 eradication, (2) the frequency of vaccination, (3) the feasibility of control strategies that rely less on vaccination and (4) the final phase of BHV1 eradication at a prevalence level below 5% of BHV1 infected cattle.

Main conclusions

Based on *model results* in this research, the following conclusions can be drawn:

- Since a voluntary vaccination programme is not expected to result in eradication of BHV1 in The Netherlands, compulsory vaccination is an important tool to eradicate BHV1.
- A national control strategy with live marker vaccine is expected to be more cost-effective than a strategy with inactivated vaccine, provided that both vaccine types meet the safety criteria. Only if inactivated vaccines reduce the reactivation rate of latently infected cattle with more than 70%, will such vaccines be as cost-effective as the live marker vaccine.
- In The Netherlands, a national eradication programme with certification and surveillance of BHV1-free herds and vaccination of non-certified herds is more cost-effective to eradicate BHV1 than a compulsory vaccination programme for all herds.
- Quantitative uncertainty of parameters for local spread and reactivation of latent BHV1 has a large impact on both the estimated period and costs of a BHV1 eradication programme in The Netherlands. These factors should, therefore, have priority in further epidemiological research.
- On average, less than 1% of the certified BHV1-free herds is expected to have an outbreak of BHV1 per year in the compulsory Dutch eradication programme. Moreover, the fraction of large outbreaks of BHV1 on vaccinating herds is expected to be three times higher than on non-vaccinating certified BHV-free herds.

- In the simulation model, the risk of herds losing the BHV1-free certificate is positively associated with the farm characteristics 'yearly number of cattle purchased', 'farm density within a one-km radius' and 'cattle density within a one-km radius'.
- To limit the number of infected farms and control costs of BVH1-oubreaks in a BHV1-free country, frequent surveillance on farms with a high frequency of cattle trade and monthly bulk-milk tests on dairy farms are efficient surveillance tools.

Based on *applied methodologies* in this research, the following conclusions can be drawn:

- Simulation modelling has been a very important and useful tool in the support of policy makers in various phases of the decision-making process for a national BHV1 eradication programme in The Netherlands.
- Whereas sensitivity analysis of models in the discipline of Animal Health Economics (and elsewhere) has often been based on changing parameters one by one, the techniques of experimental design and metamodelling are more efficient and effective in sensitivity analysis.
- High involvement of policy makers in the process of model development and application, together with close interaction between empirical and model research, have been critical aspects for the acceptance and use of model results in the decision-making process on BHV1 eradication in The Netherlands.

Samenvatting

Inleiding

Bovine herpesvirus 1 (BHV1) is de verwekker van infectieuze bovine rhinotracheitis (IBR), een luchtwegaandoening bij rundvee. Acute infectie met BHV1 kan leiden tot aanzienlijke productieverliezen, verwerpen en sterfte. Tegenwoordig hebben de meeste infecties echter een sub-klinisch verloop. BHV1 kenmerkt zich door het ontstaan van latente infectie, waardoor reactivatie op een later moment kan leiden tot heruitscheiding van het virus. Een BHV1 besmet dier vormt daarom een blijvend risico voor BHV1-vrije koppelgenoten.

BHV1-vrije landen kunnen beperkingen opleggen aan de import van rundvee en rundvee producten. In de Europese Unie (EU) zijn regels opgesteld op basis waarvan lidstaten eisen kunnen stellen aan de import van rundvee, sperma en embryo's. Verder zijn sinds 1999 alleen BHV1-vrije stieren toegestaan op KI-stations in EU-landen. Het frequent optreden van (dier)contacten tussen bedrijven, tezamen met wijdverbreid gebruik van traditioneel vaccin, zijn voor het virus gunstige omstandigheden geweest om endemisch te worden in Nederland. Begin jaren negentig was ongeveer 85% van de melkveebedrijven in Nederland besmet. Bovengenoemde internationale ontwikkelingen hebben de rundveesector in Nederland onder druk gezet om BHV1 te bestrijden. In landen met een hoge besmettingsgraad van BHV1 is een zogenaamde 'test-en-ruim strategie' economisch niet haalbaar en bovendien ethisch niet acceptabel. Eradicatie van BHV1 zal daarom moeten starten met bestrijdingsmaatregelen die de incidentie van uitbraken verlagen en zodoende de besmettingsgraad reduceren.

De ontwikkeling van marker vaccins, waarmee gevaccineerde dieren onderscheiden kunnen worden van dieren besmet met het veldvirus, bracht discussie teweeg omtrent mogelijkheden om BHV1 in Nederland uit te roeien. Belangrijkste vraag daarbij was welke strategie economisch het meest rendabel zou zijn, rekening houdend met uitvoerbaarheid en het draagvlak onder veehouders. Het combineren van economische en epidemiologische kennis in een model is een nuttig hulpmiddel om besluitvorming omtrent dierziektenbestrijding te ondersteunen. Dit geldt met name als het gaat om bestrijdingsmaatregelen die niet eenvoudig in het veld kunnen worden geïmplementeerd en geëvalueerd. De belangrijkste doelstelling van dit proefschrift was de "ontwikkeling en toepassing van simulatiemodellen ter ondersteuning van nationaal beleid in verschillende fasen van het besluitvormingsproces inzake de bestrijding van BHV1 in Nederland". Subdoelstellingen waren het verkrijgen van inzicht in:

1. Epidemiologische en economische gevolgen van een aantal strategieën ter bestrijding van endemisch BHV1 in Nederland;

2. Kosteneffectiviteit van een aantal strategieën ter bestrijding van BHV1 uitbraken in een BHV1-vrij Nederland;
3. Onzekerheden in kennis omtrent BHV1 verspreiding, die de meeste invloed hebben op de voortgang en kosten van een BHV1 bestrijdingsprogramma;
4. Model gedrag met betrekking tot associaties tussen bedrijfskenmerken en verlies van het BHV1-vrij certificaat tijdens simulatie van BHV1 bestrijding.

Ontwikkeling van simulatiemodellen

Voordat een definitief besluit over maatregelen ter bestrijding van BHV1 in Nederland werd genomen, zijn twee simulatiemodellen ontwikkeld en toegepast (hoofdstuk 2 en 3).

Het simulatiemodel beschreven in hoofdstuk 2 werd ontwikkeld om een aantal bestrijdingsstrategieën voor BHV1 in Nederland te evalueren. De uitkomsten van dit model zijn gebruikt om besluitvorming te ondersteunen omtrent de vraag welke strategie om BHV1 uit te roeien economisch het meest haalbaar zou zijn. Het raamwerk van dit model was gebaseerd op een deterministische modelbenadering, eerder gebruikt om bestrijdingsmaatregelen voor eradicatie van de ziekte van Aujeszky te evalueren.

Berekende kosten hadden betrekking op vaccinatie, laboratoriumonderzoek, monitoring en vervroegde afvoer van latent besmet rundvee. Berekening van de baten van een vaccinatieprogramma was gebaseerd op reductie van economische verliezen als gevolg van BHV1. Hierbij werd rekening gehouden met schade van klinische en sub-klinische infectie, uitbraken op KI-stations en potentiële exportverliezen. Met het model werden vijf bestrijdingsstrategieën doorgerekend, waaronder een vrijwillig en een verplicht vaccinatieprogramma voor melkveebedrijven. Deze strategieën werden met name vergeleken op basis van de verwachte periode die nodig zou zijn om een besmettingsgraad van 5% in de melkveepopulatie te bereiken, de hiermee gepaard gaande kosten en de terugverdientijd van deze kosten.

Uitkomsten van het model toonden aan dat een vrijwillig vaccinatieprogramma met 50% deelname hoogstwaarschijnlijk niet zou leiden tot eradicatie van BHV1.Verplichte vaccinatie zou daarom nodig zijn om tot een BHV1-vrije status te komen. Landelijke bestrijding met levend marker vaccin bleek effectiever te zijn dan toepassing van dood marker vaccin. Bovendien liet het model zien dat een nationaal bestrijdingsprogramma met certificering van BHV1-vrije bedrijven en vaccinatie van niet-gecertificeerde bedrijven, economisch efficiënter zou zijn om BHV1 uit te roeien dan verplichte vaccinatie van alle bedrijven.

Op basis van EU ontwikkelingen aangaande BHV1 bestrijding en rekening houdend met de uitkomsten van bovenbeschreven model, werd in mei 1998 gestart met een verplicht

BHV1 eradicatie programma in Nederland. Dit programma was gebaseerd op halfjaarlijkse enting met marker vaccin van alle niet-gecertificeerde rundveebedrijven, monitoring van BHV1-vrij gecertificeerde bedrijven en beperkende maatregelen voor diercontacten tussen bedrijven. Op basis van modelberekeningen werd verwacht dat dit programma de besmettingsgraad onder melkvee in ongeveer vijf jaar zou reduceren tot 5%, tegen directe kosten van ongeveer 100 miljoen Euro en een terugverdientijd van circa acht jaar. Verder werd verwacht dat per jaar op minder dan 1% van de BHV1-vrij gecertificeerde bedrijven een uitbraak zou plaatsvinden.

Vanwege de enorme kosten die gepaard zouden gaan met een BHV1 eradicatie programma in Nederland, was eveneens inzicht nodig in de gevolgen van uitbraken in een toekomstig BHV1-vrij Nederland, zoals de kosteneffectiviteit van een aantal bestrijdingsmaatregelen. In hoofdstuk 3 is het simulatiemodel 'InterIBR-epidemic' beschreven en toegepast voor uitbraken in een BHV1-vrij land. Het raamwerk van dit model was gebaseerd op 'InterSpread'. Dit ruimtelijke, dynamische en stochastische model was oorspronkelijk ontwikkeld om uitbraken van mond- en klauwzeer (MKZ) te simuleren. Bedrijfsgegevens in InterIBR-epidemic waren gebaseerd op een steekproef uit het Identificatie en Registratie (I&R) systeem in Nederland. Hiermee werd inzicht verkregen in de demografie van de populatie rundveebedrijven met betrekking tot bedrijfstype, bedrijfgrootte en diercontacten tussen bedrijven. Voor bedrijfstypen werd onderscheid gemaakt in melkvee-, vleesstier-, vleeskalver-, en zogenaamde 'overige' bedrijven.

Simulatie van een BHV1 uitbraak startte met introductie van het virus op een vooraf vastgesteld bedrijfstype. Vervolgens werd verspreiding van het virus, zowel binnen als tussen bedrijven, gesimuleerd. Verspreiding tussen bedrijven vond plaats via diercontacten, lokale contacten en professionele contacten. Daarnaast waren een monitoringsprogramma en bestrijdingsmaatregelen ingebouwd om een uitbraak te detecteren en daaropvolgende bestrijding uit te voeren. Economische gevolgen meegenomen in dit model hadden betrekking op schade als gevolg van infectie en kosten van bestrijding. Het basis-scenario bestond uit vervoersverboden, traceren van diercontacten en screenen van buurtbedrijven.

Model uitkomsten lieten zien dat het bedrijfstype waarop een uitbraak van BHV1 begint, van grote invloed was op het aantal secundair besmette bedrijven en de totale kosten van een uitbraak. Verder werd geconcludeerd dat een bestrijdingsstrategie met versneld ruimen of vaccinatie van besmet vee, vergeleken met het basis-scenario, het aantal besmette bedrijven niet verminderde. Deze strategieën brachten echter meer kosten met zich mee. Ook een toezichtgebied van één kilometer bleek niet kosteneffectief. Wat betreft het monitoringsprogramma, werd frequent onderzoek op bedrijven met intensieve handelscontacten aanbevolen, tezamen met maandelijks tankmelkonderzoek op melkveebedrijven.

Om beleidsmakers te ondersteunen gedurende de bestrijdingscampagne, gestart in 1998, werd een tweetal hulpmiddelen ontwikkeld: (1) een BHV1 monitoringsprogramma en (2) een aanvullend BHV1 simulatiemodel. Doel van het monitoringsprogramma was de voortgang van de bestrijding in het veld te evalueren. Informatie die hieruit voortkwam, tezamen met voortschrijdend inzicht wat betreft relevante processen en parameters, werden gebruikt om het simulatiemodel 'InterIBR-endemic' te ontwikkelen (hoofdstuk 4). Het raamwerk van dit model was gebaseerd op het epidemisch model beschreven in hoofdstuk 3. Zodoende werd in het endemisch model eveneens rekening gehouden met ruimtelijke en stochastische processen. Model aanpassingen hadden voornamelijk betrekking op de processen van vaccinatie, certificering en monitoring van BHV1-vrije bedrijven. Een belangrijk doel van dit model was het ondersteunen van het besluitvormingsproces, wanneer resultaten van het BHV1 monitoringsprogramma aanleiding zouden geven tot heroverweging van enkele aspecten van de bestrijding. Tevens werd het model gebruikt om onzekerheden omtrent BHV1 vast te stellen die relevant zouden zijn voor de voortgang en kosten van het bestrijdingsprogramma. Ook werd het modelgedrag met betrekking tot verlies van het BHV1-vrij certificaat onderzocht (zie paragraaf 'interne validatie'). Bedrijfgegevens in InterIBR-endemic waren gebaseerd op Nederlandse data van 1999. Verder waren gegevens van alle dierbewegingen in 1999 geanalyseerd, om modelparameters met betrekking tot diercontacten tussen bedrijven te kwantificeren. Het model bevatte ongeveer 57.000 rundveebedrijven, waarvan 21% in januari 1999 gecertificeerd BHV1-vrij was.

Om het Nederlandse BHV1 bestrijdingsprogramma te simuleren, zijn 10 replicaties van het model InterIBR-endemic uitgevoerd. Dit resulteerde in een mediaan van 334 weken om een besmettingsgraad van 5% in de melkveepopulatie te bereiken (min-max: 316-360), met bijbehorende kosten van 106 miljoen Euro (min-max: 103-111). Het aantal uitbraken per jaar op BHV1-vrij gecertificeerde melkveebedrijven had een mediaan van 102 (min-max: 84-140). De weergegeven minima en maxima hielden echter geen rekening met de invloed van parameter onzekerheden (zie paragraaf 'interne validatie'). Het aantal grote uitbraken per jaar op niet-gecertificeerde bedrijven lag in het model ongeveer drie maal zo hoog als op BHV1-vrij gecertificeerde bedrijven. Lokale spreiding was in het model verantwoordelijk voor het merendeel van de uitbraken op gecertificeerde bedrijven, terwijl op de niet- gecertificeerde bedrijven reactivatie van latent besmette dieren de voornaamste bron van uitbraken was. Met betrekking tot het BHV1 monitoringsprogramma gaf het model aan dat, om de prevalentie besmette dieren in de populatie 'overige' bedrijven te schatten, stratificatie op bedrijfsgrootte nodig was bij het selecteren van een steekproef. Verder werd geconcludeerd dat de incidentie van uitbraken op niet-gecertificeerde bedrijven een grote invloed had op de voortgang van het bestrijdingsprogramma. Hiermee werd het belang aangegeven om deze incidentie in het veld te meten.

Interne validatie

Validatie is een belangrijke stap in de ontwikkeling en toepassing van modellen. De mogelijkheden voor externe validatie waren in dit onderzoek beperkt. Daarom werd, als onderdeel van interne validatie, de nadruk gelegd op het verkrijgen van inzicht in model gedrag. Voor het verkrijgen van dit inzicht werden in de hoofdstukken 4, 5 en 6 een aantal experimenten uitgevoerd met het simulatiemodel InterIBR-endemic. Hiermee werd voldaan aan de subdoelstellingen 3 en 4 van dit onderzoek.

Gevoeligheidsanalyse is een belangrijke techniek om te onderzoeken hoe model uitkomsten reageren op verandering van model invoer. Omdat het model InterIBR-endemic veel onzekere epidemiologische parameters bevatte, werd gevoeligheidsanalyse toegepast om vast te stellen welke parameters de meeste invloed hadden op model uitkomsten. Kennis omtrent deze parameters is waarschijnlijk het meest relevant voor de voortgang en kosten van het BHV1 bestrijdingsprogramma en zou daarom prioriteit moeten hebben in empirisch onderzoek. Gevoeligheidsanalyse wordt veelal beperkt tot het veranderen van slechts één parameter tegelijk. Een andere benadering van gevoeligheidsanalyse gebruikt de technieken van experimentele proefopzet en metamodellen (hoofdstuk 4 en 5). Deze statistische benadering van gevoeligheidsanalyse bleek efficiënter (minder simulaties vereist) en effectiever (schatting van interacties mogelijk) te zijn dan parameters één voor één te veranderen.

De metamodel benadering werd toegepast op 31 parameters van InterIBR-endemic. Drie simulatie uitkomsten, door beleidsmakers aangeduid als meest relevant, werden als afhankelijke variabelen gebruikt in de gevoeligheidsanalyse. Simulatiegegevens werden geanalyseerd met behulp van regressie volgens de ‘kleinste-kwadraten-methode’. Omdat één van de simulatie uitkomsten een bovengrens had, werden in hoofdstuk 5 eveneens tobit en logistische regressie toegepast. Geconcludeerd werd dat de resultaten van tobit regressie meer valide waren dan van regressie volgens de ‘kleinste-kwadraten-methode’. Zowel de duur als de kosten van het gesimuleerde bestrijdingsprogramma waren het meest gevoelig voor de onzekerheid omtrent parameterwaarden voor lokale spreiding en reactivatie van BHV1. Deze factoren zouden daarom prioriteit moeten hebben in toekomstig epidemiologisch onderzoek. De onzekerheid van de jaarlijkse kans op reactivatie van latent besmette dieren beïnvloedde de kosten met 43 miljoen Euro, ongeveer 40% van de totale verwachte kosten.

Een belangrijk onderdeel van het BHV1 bestrijdingsprogramma was verlies van het BHV1-vrij certificaat als gevolg van BHV1 uitbraken op gecertificeerde bedrijven. Het doel van hoofdstuk 6 was meer inzicht verkrijgen in model gedrag ten aanzien van certificaat verlies. Met behulp van Cox regressie analyse werd het kwantitatieve verband onderzocht tussen bedrijfskenmerken en het risico van certificaat verlies tijdens simulatie. Van de

aanvankelijk BHV1-vrij gecertificeerde bedrijven verloor 3% het certificaat. Significante risicofactoren voor verlies van het BHV1-vrij certificaat in het simulatiemodel waren de bedrijfskenmerken 'jaarlijks aantal aangekochte dieren', 'dichtheid van bedrijven in een straal van één km' en 'dierdichtheid in een straal van één km'. Het kwalitatieve gedrag van deze risicofactoren kwam overeen met waarnemingen uit veldonderzoek.

Discussie

Hoofdstuk 7 bevat een algemene discussie over een aantal kritische stappen in de ontwikkeling en toepassing van simulatiemodellen in dit onderzoek. Verder is stilgestaan bij de rol van deze modellen bij beleidsondersteuning. Aan de hand van een discussie over simulatie van ziekteverspreiding tussen bedrijven versus een bedrijfsspecifiek model, werd geconcludeerd dat bedrijfsspecifieke modellen belangrijke hulpmiddelen zijn bij het ondersteunen van beslissingen van individuele veehouders, binnen het raamwerk van een nationaal bestrijdingsprogramma voor BHV1. Vervolgens werden alternatieve methoden bediscussieerd om een systeem te onderzoeken: experimenteren met (een deel van) het werkelijke systeem versus experimenteren met een model van het systeem. Ook werd een vergelijking gemaakt tussen een mathematische modelbenadering voor BHV1 en de simulatiemodellen ontwikkeld in dit onderzoek. Geconcludeerd werd dat beide typen modellen toegevoegde waarde hebben gehad voor het BHV1 bestrijdingsprogramma in Nederland. Deze waarde zat met name in het gebruik van experimentele data als model invoer, waarmee uiteindelijk op populatieniveau conclusies werden getrokken over monitorings- en bestrijdingsstrategieën. Verder werden waarnemingen uit het BHV1 monitoringsprogramma vergeleken met model uitkomsten. Op basis van de besmettingsgraad onder melkvee en de fractie gedetecteerde uitbraken op BHV1-vrij gecertificeerde melkveebedrijven, werd geconcludeerd dat model resultaten van InterIBR-endemic vrij goed overeenkwamen met waarnemingen uit de BHV1 monitoring. Het model ging echter uit van verplichte halfjaarlijkse enting, terwijl in werkelijkheid de entverplichting al begin 1999 was opgeschort als gevolg van vervuiling van het marker vaccin met BVD virus. Het hoofdstuk eindigt met aanbevelingen voor onderzoeksprioriteiten gedurende de periode van opgeschorte vaccinatie. Geconcludeerd is dat meer onderzoek nodig zou zijn betreffende (1) de economische baten van BHV1 eradicatie, (2) de frequentie van vaccinatie, (3) de haalbaarheid van bestrijdingsstrategieën die minder afhankelijk zijn van vaccinatie en (4) BHV1 eradicatie nadat de grens van 5% BHV1-besmet melkvee bereikt is.

Belangrijkste conclusies

Op basis van model resultaten uit dit onderzoek, kunnen de volgende conclusies worden getrokken:

- Omdat een vrijwillig vaccinatieprogramma hoogstwaarschijnlijk niet zal leiden tot eradicatie van BHV1 in Nederland, is verplichte vaccinatie een belangrijk middel om BHV1 uit te roeien.
- Een landelijke bestrijdingsstrategie met levend marker vaccin is naar verwachting kosteneffectiever dan een strategie met dood marker vaccin, mits beide typen vaccins voldoen aan de eisen van veiligheid. Slechts wanneer dood vaccin in staat is om de reactivatie kans van latent besmette dieren met meer dan 70% te onderdrukken, zal dit vaccin net zo effectief zijn als levend marker vaccin.
- Een landelijk eradicatie programma in Nederland, met certificering en monitoring van BHV1-vrije bedrijven en vaccinatie van niet-gecertificeerde bedrijven, is economisch efficiënter om BHV1 uit te roeien dan een verplicht vaccinatieprogramma voor alle bedrijven.
- Kwantitatieve onzekerheid over parameters voor lokale spreiding en reactivatie van latent BHV1 heeft een grote invloed op zowel de verwachte duur als de kosten van een BHV1 eradicatie programma in Nederland. Deze factoren moeten daarom prioriteit hebben in toekomstig epidemiologisch onderzoek.
- Binnen het verplichte Nederlandse eradicatie programma zal naar verwachting per jaar gemiddeld minder dan 1% van de BHV1-vrij gecertificeerde bedrijven een uitbraak van BHV1 hebben. Verder zal de fractie grote BHV1 uitbraken op vaccinerende bedrijven naar verwachting drie maal zo hoog zijn als op niet-vaccinerende BHV1-vrij gecertificeerde bedrijven.
- In het simulatiemodel stijgt het risico van verlies van het BHV1-vrij certificaat met een toename van de bedrijfskenmerken ‘jaarlijks aantal aangekochte dieren’, ‘dichtheid van bedrijven in een straal van één km’ en ‘dierdichtheid in een straal van één km’.
- Frequent onderzoek op rundveebedrijven met intensieve handelscontacten en maandelijks tankmelkonderzoek op alle melkveebedrijven, zijn efficiënte middelen om het aantal besmette bedrijven en de kosten van bestrijding van BHV1 uitbraken in een BHV1-vrij land te beperken.

Op basis van de toegepaste methodiek in dit onderzoek, kunnen de volgende conclusies worden getrokken:

- Simulatiemodellen hebben een erg belangrijke en nuttige rol gespeeld bij de ondersteuning van beleid in verschillende fasen van het besluitvormingsproces aangaande een landelijk eradicatie programma voor BHV1 in Nederland.
- Gevoeligheidsanalyses van modellen in het vakgebied 'Economie van Dierziekten' (en elders) zijn veelal gebaseerd op het één voor één veranderen van parameters. De technieken van experimentele proefopzet en metamodellen zijn echter efficiënter en effectiever voor gevoeligheidsanalyse.
- Een grote mate van betrokkenheid van beleidsmakers in het proces van modelontwikkeling en -toepassing, tezamen met nauwe interactie tussen empirisch en model onderzoek, zijn belangrijke aspecten geweest voor acceptatie en gebruik van model resultaten in het besluitvormingsproces aangaande BHV1 eradicatie in Nederland.

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Curriculum vitae

Antonie Vonk Noordegraaf werd 9 november 1974 geboren op een melkveebedrijf te Rotterdam. Vanwege stadsuitbreiding verhuisde hij op 2-jarige leeftijd mee naar Plumpton Green, East-Sussex in Engeland. In 1981 keerde hij terug weer naar Nederland en groeide hij op in het Land van Heusden en Altena, op de nieuw betrokken boerderij van zijn ouders in Wijk en Aalburg. In 1992 behaalde hij het VWO diploma aan het Willem van Oranje College te Waalwijk. Na uitgeloot te zijn voor de studie Diergeneeskunde, begon hij in datzelfde jaar met de opleiding Zoötechniek aan de toenmalige Landbouwuniversiteit Wageningen. In de periode 1995-1996 vervulde hij het voorzittersschap van studievereniging 'De Veetelers', de vereniging van Wageningse Zoötechniek studenten. In 1997 bracht hij een stage door bij het departement Population Medicine van het Ontario Veterinary College in Guelph, Canada. Met de specialisaties Veehouderij en Agrarische Bedrijfseconomie studeerde hij in maart 1998 met lof af. Voor zijn afstudeerscriptie bij Agrarische Bedrijfseconomie betreffende een 'oriënterende modelstudie naar verspreiding en bestrijding van IBR in Nederland' ontving hij de C.T. de Wit prijs. Als toegevoegd onderzoeker bij de leerstoelgroep Agrarische Bedrijfseconomie van Wageningen Universiteit, vervolgde hij het IBR-onderzoek vanaf april 1998. Dit leidde tot het voor u liggende proefschrift, dat in februari 2002 werd afgerond. Tijdens zijn promotieonderzoek presenteerde hij zijn werk op een groot aantal internationale congressen. In 2001 nam hij deel aan de organisatie van het SVEPM congres, gehouden te Noordwijkerhout. Sinds maart 2002 is hij als keten-onderzoeker werkzaam bij Nutreco R&D in Boxmeer.

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