Infectious diseases among animals: combining models and data

Aline A. de Koeijer

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Verspreiding van besmettelijke dierziekten : koppeling van modellen en data

(met een samenvatting in het Nederlands)

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Introduction

New Advances in Veterinary Epidemiology

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Abstract

The introduction gives an overview of recent advances in veterinary epidemiology. Especially the influence of dynamical modelling is discussed, as that is the main topic of this thesis, but it also explains a bit about the political, practical and general scientific influences that induce new developments and new lines of research. Veterinary epidemiology is a science that aims at results being applied soon and is easily influenced by new trends and developments.

The introduction also gives a short overview of the scientific contents of this thesis, describing the general type of methods and results obtained. The binding factor in this thesis is that it uses theoretical modelling and analysis aiming at results that can be applied in the field, or at least in further research. Therefore, the use of data to quantify or validate models is essential.

1.1 New Advances in Veterinary Epidemiology

Throughout history, control of infectious diseases involved hygiene and avoiding contacts. The development of sterilisation and pasteurisation methods have helped a lot in improving the hygiene, but up to today, avoiding contacts still remains a good method to prevent transmission. Vaccination has become a major method to prevent severe disease symptoms, and together with eradication of infections diseases, these are considered to be major achievements. Especially when world wide eradication is realised, as that solves the problem forever. At least in theory, because the discussions on storage of eradicated infectious agents in labs to guarantee fast production of vaccines in case things go wrong also poses a risk in relation to (bio-)terrorism. When eradication cannot be achieved, we need to remain on the alert for recurring epidemics and persistent infections.

Apart from these basic tools, recent epidemiology has shown that especially in animal diseases, control can often be based on small scale eradication, i.e. create an infection free herd or region possibly based on rigorous measures, and then follow it up by strict control of all contacts to that herd or region. However, such local eradication can only reliably persist, when supported by good surveillance. Development and evaluation of surveillance programs has therefore become yet another major tool in veterinary epidemiology. Trade restrictions for husbandry animals and their products are heavily leaning on epidemiological and statistical arguments derived from a surveillance program and thus, veterinary epidemiology has a major impact on world wide trade in animals and their products.

Epizootiology has recently been renamed into Veterinary Epidemiology. Although the word epidemiology includes the greek word demos, meaning the human population, it has still become a practical renaming of the profession, because methodology and aims of epidemiology and epizootiology are mostly the same. As epizootiology is a much smaller scientific field than its human counterpart, collaboration and adoption of their methods and terminology can only be profitable. Therefore, the word veterinary epidemiology has gradually taken over the term epizootiology over the last few decades.

Recent advances in microbiology, virology, immunology, molecular biology have led to major developments in veterinary epidemiology, especially by making more tests for the prevalence of infection, but also through the creation of new vaccines that can be used to control infections. However, the scientific field was probably influenced even more by the advances in computer science and computational techniques, which have allowed for major progress in data analysis, statistical methods and simulation.

Problems that used to be too complicated or would have taken too much time, may now be solved in a minute and data sets that used to be too large to extract the relevant information have offered surprising new insights. The work of Donnely and Ferguson [31], for example, shows the possibilities of analysing large data sets in combination with major computational work. The book of Diekmann and Heesterbeek [24] offers a good basic overview on recent advances in the analysis of epidemics with modelling tools. Such new developments lead to new research lines in veterinary epidemiology. For instance, to analyse the effect of various risk factors for development of disease into far more detail than before, when logic and intuition tended to be the main tools to work with in disease prevention and control. Furthermore, the computational developments also extended in new tools to analyse the geographical spread of infections, which is one of the topics that can become of major importance in the future, when more geographical information becomes available. The open exchange of information is essential to allow for progress there, but several EU research studies have worked hard on opening up data sources, and the advances are promising.

As for the biological advances mentioned before, new developments in the use and choice of vaccines and tests have affected international trade, but also vice versa. Existing trade restrictions due to risks of transporting infectious diseases have given a major push to developing new methods in veterinary epidemiology. The international community (in the form of the OIE, Office International des Epizooty) has agreed on the use of international standards concerning tests, surveillance and analysis, to prove freedom of disease status. Due to several agreements, for most infections a non vaccination strategy in a region free from an infection is the most profitable situation, considering economical aspects. However, it also carries a high risk, in case the infection reoccurs, because the population will be totally unprotected. When such reoccurrences can be prevented sufficiently well, this strategy will lead to enormous economic benefits and export options for those countries that are able to maintain the status. Therefore, the prevention and control of epidemics has become even more important than in previous years. The economic impact of losing the disease free status has increased, but due to the large increase in animal husbandry, the situation for controlling epidemics also changed. The intensified husbandry systems nowadays can work at much higher hygienic levels than before, but the enormously increased number of animals which has occurred simultaneously, has led locally to such high densities of animals, that, once an infection is introduced, eradication has become extremely difficult.

Furthermore, increased trade within the EU allows for faster spread to other EU countries, as was shown in the Foot and Mouth disease outbreak in the UK in 2001.

The increased movement of animals between and through countries is economically speaking very beneficially for all concerned, but it leads to increasing risk of epidemics. On the other hand, scientific methods to detect infections early on have also improved, and more professional organisation of the animal husbandry has decreased the risk of disease transmission between farms. Given the large economic impacts of any choice concerning animal disease control, an increased interest developed to determine a cost benefit balance for different disease prevention and control methods and models became important in analysing the various scenario's influencing the cost benefit balance. Recent developments in the Netherlands have brought the ethical aspects of disease control in the discussion. These aspects can somehow also be quantified, everything has its value in politics, and it can be expected that especially more disease control scenario's which exclude major culling of animals will be included in the analyses. However, political agreement within the EU will be essential to enable application of for instance large scale vaccination for list A diseases.

In most of these new advances, analytical modelling of the transmission of infections has become a useful tool for the veterinary epidemiology. In human medicine analytical models have been used for many years already. Especially for infections where control and eradication with hygiene and vaccination have been rather unsuccessful. Malaria and Aids are often found in papers where mathematical models are applied to determine general conclusions concerning the infection. In veterinary epidemiology models were also used before, but until recently, their impact on policy remained rather limited. The impact of new infections like BSE and new interest for eradication of endemic diseases (non list A) has led to new developments in the field. Because the questions addressed are generally very much to the point, a very applied version of models can be used, and in general, a lot of data is available, to either quantify, or validate the models. The link between data and models is a challenge that is one of the binding factors of this thesis. Furthermore, in this thesis, we restrict ourselves to the so-called "simple" models, which does not mean they are simple to use and analyse, but means that a minimum of parameters is used to describe the system. Thus, the sometimes hopeless task of quantifying hundreds of parameters, which has to be confronted in simulation modelling work, is avoided here. The other major advantage is that solutions can be easily generalized, and the sensitive points of the analysis can easily be detected.

This thesis gathers several papers in which analytical models are applied to specific questions in veterinary epidemiology and always links the model results to some available data. Depending on the availability of the data, this can be either just to support the results (see Chapter 2) or it can be used to fully quantify the model and

calculate the result, as is for example shown in Chapter 4. A wide range of topics is addressed in this thesis, and at first sight there is no reason to gather all those papers within one volume. However, the methodology applied to solve the questions addressed, is the same in all those papers. A problem is analysed, a simple model is built, data are gathered and patterns in the data are sought for. From these initial steps, the result will then be deduced, and depending on the topic, this last step can still be a very complicated long road, but sometimes a fast method can be found. The results can again vary widely, from attempts at predicting the pattern of present or future epidemics (Chapter 2), Quantification of possibilities for eradication versus spontaneous extinction (Chapter 3) to quantifying the efficacy of control measures (Chapter 4) and risk assessment (Chapter 5). Chapters 6 and 7 are not as technical, but give an overview of the possibilities to apply mathematical modelling in targeting surveillance (Chapter 6) and a basic method to use the results of a surveillance program to minimize risks of importing or exporting infection via trade (Chapter 7).

1.2   Overview of the Thesis

Chapter 2 describes a modelling exercise that compares two different transmission models. Theoretical arguments suggest that herd-like behaviour should often be modeled with a constant density of hosts, in contrast to the often applied concept of host density decreasing with population size. For the case of Phocine Distemper Virus (PDV), there are sufficient data available to support the choice for the first model with constant density, independent of the population size. The implications of this for a deadly infection like PDV (about 50% mortality rate) is a higher proportion of infected animals in the population than would be the case if reducing numbers would lead to lower transmission risk. Therefore, very deadly diseases can lead to full extinction of a population under this model, where a model with transmission risk decreasing with population size would always have a small proportion of the population that escapes infection. For infections without mortality, there is no relevant difference, because the population size would not be influenced by the epidemic. The general conclusion is that for herds modelling of density dependence needs attention, and this point is kept up throughout this thesis. All of the topics that are addressed in this thesis are concerned with infections in herds. However, mostly the mortality of the infection is not as high, or in the case of BSE, not as fast, which means that further analysis may be necessary to derive new results and conclusions.

Chapter 3 addresses an extinction problem for Bovine Herpes Virus (BHV), which

has the typical reactivating capacities of herpes viruses. Due to this, the infection is not extinct when an epidemic has ended, extinction is not complete before all seropositive animals are removed from the population. Thus, population demography needs to be combined with epidemiology. To analyse the probability of new outbreaks, and the time it takes before this happens, was an interesting challenge, that asked for some creative solutions. Finally we find that it is possible to quantify this time to extinction from the model ingredients, but we also found that the variation over the expected time to extinction is huge. Therefore, in practical terms it is not worthwhile waiting for spontaneous extinction of BHV in the Netherlands. However, it is also clear, that a careful eradication program can benefit enormously from the rather good chances of extinction in a fraction of the herds, which saves major expenses in active culling to eradicate the infection. A good vaccine (in terms of reducing transmission) can give a major support to this, by decreasing the probability of new epidemics. In general we see that herpes viruses have a successful evolutionary survival strategy that requires long living hosts, which can shed infection all through their lives due to reactivation. Thus the disadvantages of fast spread and fast exhaust of hosts is solved by waiting for the new born susceptibles.

Chapter 4 shows a calculation to quantify the basic reproduction ratio of BSE from the ingredients, as a method for BSE risk assessment. Careful assessment of the many steps that partake in a BSE infection and transmission, especially focussing on the effect of various control measures, allows for a comparison of the efficacy of control measures, and were the infection not so scary, it would have allowed for optimization of these controls in a cost benefit manner. As a result of this work, many other studies in BSE risk assessment followed, and examples thereof are found in Chapters 5 and 6. This chapter does not offer general conclusions useful for future epidemiological research in general, but is really focussed on the issue of BSE, and is only useful for very slow developing infections. An early version [10] of the work in Chapter 4 has been influencing the development of the EU's Geographical BSE Risk assessment [34]. Due to the, at that time limited, development of this work, and the limited availability of data, this has so far been mainly restricted to a qualitative risk assessment, which has still proven its success by pointing out several EU countries into a risk class with BSE present, where the first BSE prevalence in the countries was only detected after the assessment.

Chapter 5 shows how to apply the quantitative result of Chapter 4 in a model that can be used to estimate the future or past prevalence of BSE infection. An age structured model is needed for proper analysis of BSE, due to the slow development of the infection. Therefore, a derived result of this model is a good prediction of the

age distribution of BSE under specific conditions. This is worked out graphically into a more popular version in Chapter 6, whereas Chapter 5 restricts itself to showing the mathematical patterns that can be expected. Next, the model is transformed into a discrete time version, because in practice, that is applied much more easily. Two versions of a BSE transmission model are given. A simple version, which is very suitable for a good quantitative regional BSE risk assessment. An extended model is available for exploring data sets and analysing the impact of simplifying assumptions. Both discrete time models have been applied successfully, and publications on these are in progress. We find that to make models easily applicable for policy advisers, it is useful to make them discrete. That simplifies the formulation of the model for those who fear mathematical equations. Spreadsheet, as generally available on most PCs can be a very helpful tool in applying the methodology, because they tend to be very suitable for discrete time models.

Chapter 6, as explained above, shows graphically, and explains in logical terms, the effects of population and infection processes on the age distribution of BSE in a cattle population. The increasing age of BSE cases in the UK in the decreasing phase of the epidemic can ve fully explained as a result of the longer delay that is necessary for long incubation periods. Thus, more complicated assumptions are not necessary to explain this phenomenon. In general we can say that in an increasing phase of an epidemic, cases with shorter incubation periods are expected to be overrepresented, whereas in a decreasing phase of an epidemic, underrepresentation of the short incubation period can be expected in the case data. The basic methodology can be applied to determine which age groups to focus on for active BSE surveillance, when trying to establish the presence of the infection as efficiently as possible. Furthermore, it can be applied the other way around: by looking at the results of the Dutch active BSE surveillance in 2001, we can analyse the estimated growth rate of the epidemic in the last decade. And thus, we also have an objective estimate of the efficacy of the BSE control measures.

Chapter 7 finally gathers a lot of ideas on assessing surveillance, but especially, on rating surveillance systems, while keeping in mind that an infectious disease is constantly spreading, once introduced. For trade reasons, there is always a lot of discussion on the quality of surveillance systems. Every country adopts its own system, depending on its leading scientists and the local conditions. Once we can agree on an objective method to determine the quality of such surveillance systems, the endless discussions on whatever others are not doing well, may end. When such assessments were adopted by the international trading community, a full inclusive method that would prevent major transmission between countries would even become one of the

future possibilities. But first agreement on methodology will be essential. This Chapter gives just another suggestion on how to solve the relevant problems in this area, without suggesting to be complete. Actually, the work as it is, suggests that a lot more needs to be done before full application of any system can be satisfactorily.

1.3   Future

Overall, this thesis builds up from a simple modelling exercise in Chapter 2, to an attempt to improve the world in Chapter 7. Obviously, the latter is still restricted to an attempt, but I am keen on continueing this topic and hope to be able to work this out in far more detail, so as to finally arrive at a system that can be used easily by all countries that trade animals and their products (i.e. all countries). At present the control of epidemics is still the topic that attracts the most attention, due to several major epidemics that have recently struck the Netherlands, and besides that, risk assessment and spatial spread are still the key words needed to get large research proposals accepted. However, personally I believe that the future of applied mathematical modelling in veterinary epidemiology is to be found especially in topics concerning surveillance and trade restrictions. When the effort in constructing good surveillance programs will lead to lower risk of epidemics, the focus will soon shift from control of epidemics, back to prevention of epidemics, which is traditionally the topic where the biggest gain is to be made. When the dynamics of transmission can be wrll described in a model, the analysis of surveillance results can become far more sophisticated than presently applied and accepted internationally. Obviously, to obtain such international acceptance, lots of work needs to be done to prove the efficacy of modelling in answering these questions. And once this work is done, publication of the results and presentation at major international meetings may finally lead to such acceptance.

At present however, we can still improve a lot on the methodologies that are applied in assessing and comparing surveillance programs. Next, comparison of the theoretical work to field data will be very valuable for the validation of the new methods. Extension of the very simplistic basic model that is described in Chapter 7 will be needed to properly analyse the international transmission risk of many relevant list A diseases. Only for BSE, this work has been done at a pretty high level (Chapters 4 and 5), but for other infections, more specific models need to be developed and analysed, and to quantify these properly, some very specific data needs to be gathered. In most cases, we expect that a good choice would be a two step model, where first the transmission within a herd is analysed, including the effect of surveillance within that

herd. And this is than followed by an analysis of the transmission in the national or regional population of herds, using the results of the within-herd model. In assessing this typical two step pattern, we may profit from work in meta-population modelling, which has so far, not been applied much in veterinary epidemiology.

Chapter 2

Modelling the Spread of Phocine Distemper Virus among Harbour Seals

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Abstract

Data presented in earlier publications on the 1988 epizootic among seals in N.W. Europe show a pattern, that is somewhat inconsistent with the predictions of the standard mathematical model of epidemics. We argue that for animals living in herds or colonies, like seals, the mutual contact behaviour is such that models for the transmission of infectious diseases should be applied with special care for the distinction between numbers and densities. This is demonstrated by using a mechanistic description of the contacts among seals, which leads to a slightly different formulation of the model. Results of the analysis of this formulation are more in line with the PDV data.

The model introduced here can be applied to epidemics among all kinds of animals living in herds and in fact to any species with constant local density, independent of the total population size (so occupying a variable area). Application of the traditional formulation, using different parameters for herds of different size, will give equally good results for non-lethal diseases. However, especially for diseases with a low reproduction ratio and with a high death rate, like the PDV-disease, the two formulations give quite different results.

Further analysis of the model is performed to determine the most important factors influencing such an epidemic. The survival of infected animals turns out to have a disproportionately great influence on the intensity of the epidemic. Therefore in the case of the PDV epizootic we conclude that marine pollution may not only have contributed to the high death rates, but, if so, it has intensified the epizootic as well.

2.1 Introduction

On a short timescale (weeks) one can think of seals inhabiting the coastal waters of Northern Europe as constituting a meta-population, a collection of many local subpopulations (colonies) loosely coupled by incidental migrations. Within a colony, contacts are probably at random. In the spring and summer of 1988 this meta-population was struck by an infectious disease that caused the death of a substantial fraction of all individuals (estimates vary from 40 to 60%). The morbilli virus causing the disease was identified by Osterhaus and Vedder [70] and baptized Phocine Distemper Virus (PDV).

The following characteristics appear from data acquired and analysed by Heide-Jørgensen and Härkönen [47]:

- Almost all colonies in the studied area suffered from an outbreak.

- The fraction that caught the disease was more or less the same for all colonies, and in particular independent of the size of the colony; (in Eastern Scotland this fraction was a bit lower). A more elaborate presentation of these data can be found in tables 1-3.

While analyzing the Kermack and McKendrick [56] epidemic model in its traditional form, one arrives at the following conclusions:

- The basic reproduction ratio R_0, i.e. the expected number of secondary cases per primary case in the initial phase of an outbreak, is proportional to the colony size. Hence, since R_0 has a threshold value 1, there exists a critical colony size below which the virus can only cause minor outbreaks affecting a negligible fraction.

- The final size, i.e. the fraction ultimately infected, increases (nonlinearly) with R_0, hence with colony size (the overshoot is stronger when the peak is higher, which is the case in larger colonies).

Clearly these general conclusions are at variance with the data (see the above and [47]). Harwood and Hall [44] suggested that the traditional epidemic model might not be very suitable for this epizootic, because the periodical aggregation of seals would keep the contact rate rather high, although 'density' might become low. Nevertheless, the traditional model was applied both by Grenfell et al. [40] and Heide-Jørgensen

et al., [47]. The latter authors achieved a correction of the results by adapting the key contact parameter to the colony size. They motivate such an adaptation by noting that "seal density within a herd is relatively high regardless of population size". A larger colony will simply occupy a larger area during haul-out, while the effective, local density remains constant. (See also Harada *et al.*, [43])

When disease always leads to immunity and never to death, an adaptation of the contact parameter to colony size is indeed all that is needed to take into account that numbers may vary wildly while density stays constant and, more importantly in the present context, contact intensity remains constant. But when, as in the case of PDV among seals, a substantial fraction of all cases ends with death, a slightly more complicated correction is required. In a sense the adaptation of the contact parameter has to be updated as the colony becomes smaller due to the virus making victims. One can also put it this way: as immunes receive part of the contacts of infectives, they serve to protect susceptibles; when infected individuals die, rather than becoming immune, they don't contribute to this protection and a larger outbreak is to be expected. This argument suggests that the final size should not only depend on R_0, but also on the probability to survive an infection.

The aim of this paper is to present the final size equation for a situation of constant local density as described above and to analyse the data on the PDV epidemic with this equation as the main tool.

2.2   Materials and methods

Usually the common seal (*Phoca vitulina*) is solitary in the water, where they have their own private fishing routes. Social life, if at all, takes place on haul-out sites; in the Wadden Sea these are the tidal sand banks. When the tide is out and the banks appear, seals aggregate (and more or less form a row) on the shore. The virus is thought to spread during this resting period on the banks, so to formulate a model we will only consider this period.

On the sand banks of the Dutch Wadden Sea the seals typically lie down along the waterline, thus forming a sort of row. Morbilli viruses are usually transferred by aerosols secreted while coughing and snarling. In such a system the viruses are thought not to be able to 'fly' very far; only near neighbours of the infectious animals can be reached. As long as space is not a limiting factor, the typical nearest neighbour distance is constant, that is, independent of colony size. When the colony is not too small boundary effects don't matter very much. Hence the per capita contact intensity

does not depend on the number of seals hauling out at the sand bank and in particular it will remain constant when the colony size decreases during an epidemic. As a consequence, the force of infection (the probability per susceptible per unit of time of becoming infected) is proportional to the **fraction** of seals that is infectious and **not** to their absolute number. This is the keypoint underlying the model.

2.2.1   The model

Morbilli viruses usually cause lifelong immunity, so we will assume that when a seal recovers from the disease, it will have become immune. Choose S to represent the number of susceptible seals in the colony. Let I denote the number of infectious and R the number of resistant (immune) animals. N denotes the total number of seals in the colony, therefore $N = S + I + R$. Note that we describe numbers now, not densities.

Let α denote the average number of contacts of one infectious animal per unit of time, multiplied by the probability of spreading the infection indeed during such a contact. β denotes the probability of removal from the infectious class in one tide period, and f is the (average) survival probability for animals that reach the end of the infectious period. Then an epidemic in the seal population can be described by the following set of differential equations:

$$\frac{dS}{dt} = -\alpha S \frac{I}{N} \tag{2.1}$$

$$\frac{dI}{dt} = \alpha S \frac{I}{N} - \beta I \tag{2.2}$$

$$\frac{dR}{dt} = f\beta I \qquad f \in [0..1] \tag{2.3}$$

$$\frac{dN}{dt} = -(1 - f)\beta I \tag{2.4}$$

The third equation could actually be left out, as it gives the same information as the fourth one. Note that for $f \neq 1$ N is a dynamic variable. For $f = 1$ we recover the traditional ODE form of the Kermack-McKendrick model.

We derived and analysed this system [11] simultaneously with Lefèvre and Picard [58] and [71], who give a detailed analysis of the model. A more elaborate mathematical study of a general version of the model can be found in Diekmann et al. [20]. They describe the model in the spirit of the general Kermack-McKendrick model of 1927, which is (it cannot be stated often enough) much more general than the special

case described by the ODE system.

2.3 Results

2.3.1 Analysis

Important information on the initial phase of an epidemic is given by R_0 (by definition, the average number of new infections caused by an infectious seal living in a completely susceptible population). In this model the expected infection time is $\frac{1}{\beta}$ during which the infectious individual makes new victims at rate α, therefore R_0 is equal to α/β (and independent of population size). If R_0 is smaller than or equal to one, the infection will soon disappear from the population. If R_0 is larger than one an epidemic outbreak may occur.

The situation at the end of the epidemic can be derived from eq. (1) and (4) by integration. We assume that at the start of the epidemic all seals are susceptible to the disease. Then a relation between the fraction of the population that survives the epidemic (x), and the fraction of the initial population that does not get infected at all (y), can be calculated for any combination of the parameters f and R_0 from eq. (2.5) and (2.6):

$$\frac{(1-f)}{R_0} \ln y = \ln x \qquad (2.5)$$

$$(1-x) = (1-y)(1-f) \qquad (2.6)$$

We can see that the final situation is independent of the population size N, but only depends on the parameters f and R_0. Note that eq. (2.6) has a clear interpretation: The fraction of seals dying as a result of the infection must be equal to the total fraction that got infected during the epidemic multiplied with the probability to die due to the infection.

When, conversely, x and y can be estimated from data of a certain epidemic, then the disease specific parameters f and R_0 can be calculated from:

$$f = \frac{x-y}{1-y} \qquad (2.7)$$

$$R_0 = \frac{(1-f)\ln y}{\ln x} \qquad (2.8)$$

In the case of the PDV-seal epizootic, these results are valid for one subpopulation, i.e. one herd. However, during this epizootic all the different herds in the area of the

Wadden Sea, Kattegat and Skagerrak were affected. In all these herds the epizootic will give equal final fractions, because the size of the (sub)-population does not make any difference, hence the same fractions apply to the metapopulation.

Graphical representations of the final fractions under varying parameter values (Figs 1 and 2) show the influence of the parameters f and R_0 on the outcome of the epidemic. As to be expected, f is the parameter that influences the final fractions x and y the most. For an R_0 smaller than 2 we can see that there is quite a substantial influence of the precise value of R_0, but for higher values only the value of f really makes a difference.

The main difference between the predictions of the current model and those of the more traditional variant lies in the influence of the survival probability. If all animals survive the disease, ($f = 1$), then N will be constant and the traditional formulation is obtained. For diseases inducing high mortalities, the difference can be quite substantial. This is shown in Fig. 3, which pictures the (different) final fractions in one plot: The total fraction of the population that died due to the disease, $1 - x$, as it depends on the value of f. For very small R_0 and low f the difference is very large, so obviously in such cases it is really important to make the right assumptions. For R_0 higher than 3, the difference in the total number of deaths is very small. However for very high death rates, it depends on what is considered more important: the fraction that died or the fraction that survived? Under certain conditions survival may be estimated at 1% under the current model and 2% for the traditional model, a substantial difference (100%), while the total fraction of deaths in these cases, 98% or 99% are almost equal. The survival seems to be more important from a conservation biology point of view, while farmers might consider the fraction of deaths more important.

2.3.2 Parameter estimates

To see what new information this model can supply in the case of the PDV epidemic, we analysed available data from literature, which leads to the parameter estimates as displayed in tables 1-3. Unfortunately there was a limited amount of data available, coming from many sources and collected with different aims and methods, so large variation in our results can be expected. The data, used to determine x in the different regions, come from estimated numbers before and after the epidemic. The number of carcasses found in different areas was a second, though equally unreliable indicator for x. Estimates for y come from other sources [47] offer information on pup survival rates, which supplies an estimate for the fraction of seals that escape infection, assuming that if a mother gets infected, its pup will surely die. This, of course, has

to be related to 'normal' pup survival rates. Their detailed data on several different colonies are embodied in Table 1 (See: [47],[48], and [26]). In Table 2, x estimates from our own data ([72]) are combined with an over-all estimate for y, an average of all the relevant data we could find. Table 3 shows data and parameter estimates for Great Britain only. Antibody tests on blood samples collected in 1989 supply good information to estimate y in that area, [44]. Here y can be calculated from the data as $y = \hat{y}x$, where $\hat{y}$ denotes the fraction of seals with antibodies in the (sampled) group of survivors.

Using the more traditional formulation, one would determine f equally as we did in (6) and (7). In that situation R_0 would be as follows:

$$R_0 = \frac{1 - x\ln(y)}{1 - y\ln(x)} \tag{2.9}$$

Then, when comparing the data of the outbreak in Waddensee and Kattegat area with the Scottisch data, under these model assumptions, survival rate f is also estimated half as high in the Waddensee but R_0 is estimated about 50% higher (3.6 vs. 2.2) in the Waddensee area. The difference with the parameter estimates from the model formulation as described in this article lies in the R_0 estimate only. These R_0 estimates are all about equal for the different regions.

2.3.3   Sensitivity analysis

For the data gathered on the seal epizootic (tables 1-3), we can not really give a proper confidence interval, because the unreliability of these estimates is mostly in the methods used to determine them. However, a sensitivity analysis of the parameter estimates for R_0 and f will reveal their dependence on x and y, and hence their sensitivity to variation in these variables. The matrix A of partial derivatives of f and R_0 with respect to x and y is given by (10).

$$A = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial y} \\ \frac{\partial R_0}{\partial x} & \frac{\partial R_0}{\partial y} \end{pmatrix} = \begin{pmatrix} \frac{1}{1-y} & \frac{x-1}{(1-y)^2} \\ \frac{(x-1-x\ln x)\ln y}{(1-y)x\ln^2 x} & \frac{(1-x)(1-y+y\ln y)}{(1-y)^2 y\ln x} \end{pmatrix} \tag{2.10}$$

For the Waddensea area, with $x = 0.4$ and $y = 0.03$ (and local estimates $f = 0.38$ and $R_0 = 2.4$), we find:

$$A = \begin{pmatrix} 1.0309 & -0.63769 \\ 2.5133 & -20.062 \end{pmatrix} \tag{2.11}$$

We see that for the magnitude of x and y we are talking about here, the error in f is more or less equal to the error in x and less than the error in y,(but reversed, increase of y gives decrease of f). The error in R_0 depends strongly on y, but R_0 is also an order 100 larger, so the influence remains relatively small.

This can better be seen from a matrix with relative sensitivies:

$$\begin{pmatrix} \frac{x}{f}\frac{\partial f}{\partial x} & \frac{y}{f}\frac{\partial f}{\partial y} \\ \frac{x}{R_0}\frac{\partial R_0}{\partial x} & \frac{y}{R_0}\frac{\partial R_0}{\partial y} \end{pmatrix} = \begin{pmatrix} 1.1 & -0.050 \\ 0.42 & -0.25 \end{pmatrix} \qquad (2.12)$$

This shows that the relative error in x is slightly amplified (1.1 times) in the estimate of f and is reduced in the estimate of R_0. The error in y reduces strongly for both estimates, f and R_0. Thus we see that the estimates of the parameters f and R_0 are not very sensitive to errors in the collected data.

2.4   Discussion and Conclusions

The model we describe here is, we admit, very crude and superficial. It certainly does not describe exactly what happens in 'real life', but it offers a convenient frame to organise one's thoughts about the key issues of a certain epidemic. Therefore we think that this model will be a good tool in the study of infectious diseases in species with gregarious behaviour.

From Figs 1 and 2 we can see that the most important parameter in the development of the epizootic is f, the survival probability of infected seals. If survival f is small, obviously more seals will die as a consequence of the infection. However, as can be seen in Fig. 3 the total number of deaths will be disproportionately larger, because the total fraction $(1 - y)$ of seals that become infected during the epizootic is higher, due to a positive feedback in the system: If the survival rate f is low, then the *fraction* of susceptible seals will remain high during the epidemic and therefore the force of infection will also remain at a higher level. With higher survival rates, a susceptible will have more contacts with immunised (recovered) animals, thus reducing the number of contacts with infectious individuals and lowering the force of infection. This feature of such an epidemic is supported by data of the PDV-epizootic from Scotland, where, compared to the Wadden Sea, higher survival x was found in combination with lower prevalence of PDV antibodies, i.e. lower y ([44]).

The importance of carefull modelling of contact behaviour is shown by the different results that are obtained by modelling these contacts only slightly different. We repeat that, in populations with gregarious behaviour, local density should be used,

because it may divert enormously from the overall density of the species.

The previously described contradictions between model and data ([47]) are explained by applying this new model to the data. The parameter estimates show little variation over the different colonies, although the difficulty of estimating y results in a rather low precision of R_0. A minimal group *size* needed to allow for an epidemic does not exist, but all seals seem to live at local densities well above the minimal *density* needed to sustain an epidemic. An epidemic according to this model will follow the same pattern in all colonies and (sub-)populations, independent of their size. In an equal time interval, an equal fraction of the population will become infected. Obviously, stochastic differences will cause small differences between those colonies, but these will be reduced by averaging over several colonies in a region. As none of the colonies in the affected area managed to escape from a large outbreak, we conclude that the contact rate between colonies must have been high. More distant colonies in Norway and the Baltic Sea remained free from infection; very low local density or low migration to and from the affected area may explain their lucky escape.

Although colonies in the Wadden Sea, Kattegat and Skagerrak seem to be affected equally, data from Great Britain display different results (Table 3). Only about 15% of the Scottish population died during the epidemic, but even there the intensity of the epidemic was still quite high ([80]). Previously suggested explanations for this include the timing of the infection in relation to seasonal behaviour and presence of secondary infections ([54]). Thompson *et al.* [80] conclude that it must have been due to either a mutation of the virus or higher resistance of the Scottish seals against the infection.

Comparison of our parameter estimates in the different areas shows that survival f is much higher in Scotland, while R_0 estimates are almost equal in all areas. The differences in survival could be explained by the different levels of pollution. Hall *et al.* [42] postulate that high organochlorine levels were associated with higher mortality from PDV, although a direct link could not be established. Reduction of immune functions of seals feeding from the heavily polluted Baltic sea has been shown by de Swart *et al.* [16], Ross *et al.* [73] and de Swart, [17]. These reduced immune functions may explain higher case mortality $(1 - f)$ in more polluted areas as the Wadden Sea, Irish Sea, Kattegat and Skagerrak. Parameter estimates show that survival f in Scotland is much higher. As, under our model assumptions, R_0 turns out to be quite constant in all areas, mutation of the virus during the epizootic seems unlikely.

Although other suggested influences, as mentioned above, should not be neglected altogether, we conclude that the model presented here, explains the striking features of the PDV-seal epizootic very well.

Tables

Values for f and R_0 in tables 1-3 are calculated from x and y estimates. These estimates are taken from literature.

1. Denmark

Location	x	y	f	R_0
Koster	0.38	0.05	0.33	2.1
Varberg	0.38	-	-	-
Hesselø	0.40	0.01	0.39	3.0
Anholt	0.33	0.03	0.31	2.4
Måkläppen	0.41	<0.03	0.4	>2.3

2. Kattegat and Waddensea area

Location	x	y	f	R_0
Netherlands	0.44	0.03	0.42	2.5
Niedersachsen	0.50	0.03	0.48	2.6
Schlesw.H	0.39	0.03	0.37	2.3
Denmark	0.49	0.03	0.47	2.6

3. Great Britain

Location	x	y	f	R_0
East Anglia	0.52	0.03	0.51	2.6
Irish sea	0.60	0.03	0.59	2.8
Scotland	0.90	0.16	0.88	2.1

Chapter 3

Calculating the time to extinction of a reactivating virus, in particular Bovine Herpes Virus

Aline de Koeijer
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Abstract

The expected time to extinction of a herpes virus can be calculated from a rather simple population-dynamical model that incorporates transmission, reactivation and fade-out of the infectious agent. We also derive the second and higher moments of the distribution of the time to extinction. These quantities help to assess the possibilities to eradicate a reactivating infection. The key assumption underlying our calculations is that epidemic outbreaks are fast relative to the time scale of demographic turnover.

Four parameters influence the expected time to extinction: the reproduction ratio, the reactivation rate, the population size, and the demographic turn-over in the host population.

We find that the expected time till extinction is very long when the reactivation rate is high (reactivation is expected more than once in a life time). Furthermore, the infectious agent will go extinct much more quickly in small populations.

This method is applied to Bovine Herpes Virus (BHV) in a cattle herd. The results indicate that without vaccination, BHV will persist in large herds. The use of a good vaccine can induce eradication of the infection from a herd within a few decades. Additional measures are needed to eradicate the virus from a whole region within a similar timespan.

3.1   Introduction

A typical question in epidemiology concerns the feasibiliy to eradicate a specific infectious agent. Extinction is a stochastic process and consequently it is hard to study this in the context of a deterministic model. Therefore, stochastic modelling is essential. The main questions are: under which conditions will an infectious agent go extinct and, given these conditions, what is the probability of extinction within a given time period.

The problem has been studied for well mixed populations and we know that the probability of extinction depends in particular on incubation time and infectious period relative to the hosts life expectancy, the basic reproduction ratio of the infectious agent, and the average host population size. Recent developments concerning this topic can be found in Nåsell [65] and an overview is given in [33].

Up to now, questions about extinction were mainly analysed for viral infections with a rather short infectious period leading to immunity or death of the infected host. Consequently, a previously infected animal cannot be infected again, and nolonger contributes to the spread of the infection.

Herpes viruses have a special mechanism to persist in the host. After recovery of the host, the virus is usually still present in the neural tissues where it remains dormant. Either spontaneously, or due to certain events (stress), the virus may reactivate, is then transported along the axons and excreted onto the same mucosa where it has entered the host. Subsequently, another infectious period starts with normal replication of the virus. Thus, a host that has recovered from infection may become infectious later on, without the need for transmission from an infectious individual. This may influence the long term dynamical behaviour of the virus-host system enormously, as we show in the following. The probability of, and time to, extinction need a specific analysis, because in this case absence of infectious individuals does not imply absence of the infectious agent. The main goal of this paper is to determine the probability distribution of the time to extinction for a reactivating viral infection.

In this paper a fast developing infection process is superimposed on relatively slow dynamics of a host population. We consider a rather large host population and want to use, as much as possible, a determininstic description. Stochasticity however, does play a role in both virus reactivation, which is a rare event, as well as in the starting phase of an outbreak, when there are just a few infectives. Accordingly we shall treat the population state at which reactivation occurs as a stochastic variable and we shall incorporate the possibility that even when the susceptible subpopulation exceeds the critical level, reactivation may lead to a minor outbreak only.

The substitution of previously infected animals by susceptible newborns is described deterministically. In other words, we develop a hybrid model, that incorporates some stochastic sub-modelling into an otherwise deterministic model. The stochastic part handles the strong stochastic effects during certain phases of the dynamics, whereas in all other aspects deterministic modelling is applied.

As an example of the practical use of our results, we will answer a question concerning eradication of bovine herpes virus (BHV). Important issues are: how fast will eradication be achieved in different herds; where can problems be expected, and can BHV persist in feral cattle herds, if these herds remain untreated.

3.2   The model

3.2.1   Overview

To determine the time to extinction, we model the presence of a herpes infection in the host population. Several assumptions underlie the model:

- Reactivation of the virus in a host occurs with a fixed probability per unit of time, among all the animals that have previously been infected.

- The time scale of an epidemic outbreak is much shorter than the time scale of demographic turn-over. Accordingly, the time that an outbreak lasts can be neglected at the demographic time scale.

- Stochasticity in the birth-death process is neglected, using a constant birth rate (b) in deterministic demography. The size of a herd (N) is assumed constant, which requires that the population birth and death rate are equal.

After an epidemic outbreak, the herd is not at risk for a new major outbreak for a certain period of time, until the fraction of susceptibles has passed a critical value. In such an epidemiologically closed system (no introduction of the virus from outside the population) there is a certain probability that the virus will go extinct, i.e. all previously infected animals are removed from the system before a new outbreak occurs and only susceptible hosts remain.

A simple deterministic model serves as the basis from which we will determine the major features and impacts of an epidemic outbreak. The reproduction ratio of the infection is one of the features we use. This was chosen firstly because the reproduction ratio can generally be estimated rather easily from various kinds of data and

secondly because the impact of an outbreak can immediately be calculated from this reproduction ratio (in the context of a certain transmission model).

It is important to note that the basic reproduction ratio, R_0, is defined as the expected number of new infections, caused by a typical infectious individual, during its full infectious period, in a fully susceptible population [24].

For reactivating viruses, we need to be aware that for each infected individual there may be several infectious periods, where the later periods are not induced by a new introduction of the virus. Therefore we define the primary reproduction ratio, R_1, as the expected number of new infections, caused by a typical infectious individual, during **one** full infectious period, in a fully susceptible environment; and in accordance with the general definition, R_0 as the expected number of new infections, caused by a typical infectious individual, during its entire life (which may consist of several infectious periods), in a fully susceptible environment.

3.2.2 Dynamics of a single outbreak

Let us call S the number of susceptibles, I the number of infectious animals and N the total herd size. γ denotes the recovery rate of infectious animals and β is the transmission parameter of the infection, where the rate of transmission is given by $\beta \frac{SI}{N}$.

Then, ignoring the relatively small birth, death and reactivation rates for the duration of an outbreak, we observe the infection process. If the agent is introduced in a naive host population and we focus on the initial phase of an outbreak, we may replace the rate of transmission by βI . The reproduction ratio, R_1, for such a model is wel known (See for example Diekmann and Heesterbeek [24]):

$$R_1 = \int\limits_0^\infty A(\tau)d\tau = \int\limits_0^\infty \beta\, e^{-\gamma\tau} d\tau = \frac{\beta}{\gamma}$$

N.B. Now we may realise that the basic reproduction ratio for a reactivating infection, R_0, is equal to the primary reproduction ratio, R_1 (that applies to one infectious period only) plus the probability of reactivation for that individual (reactivation rate α divided by the overall removal rate from the recovered state, $\alpha + b$) multiplied by R_0 (since if there is reactivation of the virus, we are back at the start of an infectious period, where the whole process repeats itself; a renewal event). Thus we are led to the equation

$$R_0 = R_1 + \frac{\alpha}{\alpha + b} R_0$$

which has the solution

$$R_0 = \frac{\alpha + b}{b} R_1 \qquad (3.1)$$

We see that it is possible that $R_1 < 1$, while, with a high reactivation rate α, $R_0 > 1$, so that virus may still spread (and persist) in the population.

The final size as calculated from a deterministic model yields a coarse approximate description of the behaviour of the full stochastic system. Suppose the infectious agent is introduced and there are sufficiently many susceptibles in the population so that a large outbreak may strike. Such a situation does not necessarily lead to a large outbreak. By chance, the infection may die out after only a few animals are infected, before a true outbreak has started. Moreover, the calculated final size is the expected size of a large outbreak in the corresponding stochastic model. Depending on the size of the population and the realisation of the contacts and transmissions, the actual final size for large outbreaks will show some variance around the deterministic value. Thus, the density of the final size after introduction of the virus is a bimodal function with one peak close to zero and a second peak around the deterministic solution. This phenomenon has been analysed before for similar models [74].

Based on all this we determine the final size of an outbreak from the deterministic value for a large outbreak, while a minor outbreak is approximated by assuming that no new infections occur at all. In other words, the full bimodal distribution of the final size from the stochastic infection model is approximated by a combination of two Dirac measures, one concentrated at zero and the other at the deterministic final size value. The probability of a minor outbreak (i.e. the probability that a supercritical branching process started with one individual goes extinct) is, in case of a single exponentially distributed infectious period equal to $1/R_1$ (see e.g. [24], section 1.2.2).

This simplification in the description of the final size distriution obviously has a major impact on the analysis in this paper, as a major source of variance is fully neglected. Simulations of the full stochastic model have been performed recently, showing that for large population sizes, the impact of this source of variance is very small. However, for smaller population sizes (less than 25) neglecting the variance in the final size of a major outbreak leads to an underestimation of the total variance in the order of 10%. For low values of R_1 (less than 1.2) the simplification has an even stronger effect, it leads to underestimation of the expected time to extinction and the

variance. This is logical because minor outbreaks do induce new infections leading to delayed extinction. The effect of the variance in the final size of a major outbreak is rather small, because it is reduced by the effect of fast replacement of previously infected animals right after an outbreak as explained in section 3 and following.

The effect of a virus being introduced in a fully susceptible population is described as follows. (See [74] but also [58], [12] and Exercise 1.12 of [24]):

event	probability	effect on fraction susceptibles: $\frac{S(t)}{N}$
minor outbreak	$\frac{1}{R_1}$	1
major outbreak	$1 - \frac{1}{R_1}$	$\ln \frac{S(\infty)}{N} = R_1 \left(\frac{S(\infty)}{N} - 1 \right)$

For a partially susceptible population we find that the final size of a major outbreak should be calculated as follows. Let x denote the fraction of susceptible animals in the herd. Then the fraction $1 - x$ must have been infected, so in these animals reactivation of the virus may occur. Let $f(x)$ describe the deterministic effect of an outbreak on x, by giving the fraction of remaining susceptibles immediately after an epidemic, that started with a fraction x of susceptibles. Then $x = \frac{S(0)}{N}$, where time is set equal to zero at virus reactivation, i.e. at the beginning of the outbreak, and $f(x) = \frac{S(\infty)}{N}$. The infection has disappeared when time goes to infinity on the relatively fast epidemic time scale, which is immediately after the epidemic on the relatively slow demographic time scale. For general $x \neq 0$ the quantity $f(x)$ is calculated from

$$\ln(f(x)) - f(x)R_1 = \ln(x) - xR_1 \qquad (3.2)$$

The function $f(x)$ cannot be described explicitly, but is implicitly completely characterised by (3.2).

The shape of the graph of $f(x)$ can be seen in Figure 1 ($R_1 = 3$). For values of x below a critical value, $\frac{1}{3}$ (see (3.5)) we have $f(x) = x$, i.e. a minor and hence negligible outbreak. The second part of the graph describes the remaining fraction of susceptibles after a major outbreak.
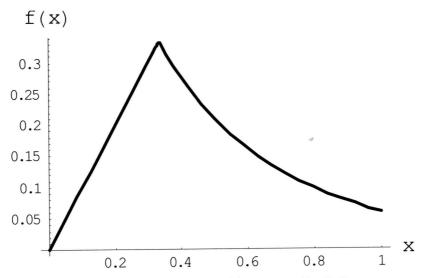
Figure 1. The graph of the function $f(x)$, as defined by (3.2).

3.2.3   Demography and reactivation

Apart from the epidemic outbreaks, there is a much slower continuous process of constant entry of susceptible animals (birth) and random removal (death). When the host life expectancy is chosen to be equal to the unit of time to simplify calculations, then the change in state x is, as long as no outbreak occurs, described by:

$$\frac{dx}{dt} = 1 - x \Rightarrow x(t) = 1 - (1 - x(0))e^{-t} \tag{3.3}$$

Let α denote the probability per unit of time that the virus will reactivate in a previously infected animal, and let $a = \alpha N$, so that $a(1 - x)$ is the probability per unit of time of reactivation in the herd. Then, given the above definition of major and minor outbreaks, the probability per unit of time, $g(x)$, that an outbreak will occur in a herd of size N can be described as

$$g(x) = \begin{cases} a(1 - x)h(x) & \text{provided} & xR_1 > 1 \\ 0 & \text{if} & xR_1 \leq 1 \end{cases} \tag{3.4}$$

where $h(x)$ is the probability of a major outbreak, i.e.

$$h(x) = \begin{cases} 1 - \frac{1}{xR_1} & \text{for } xR_1 \geq 1 \\ 0 & \text{for } xR_1 < 1 \end{cases}$$

Let us define

$$x_0 = 1/R_1 \qquad (3.5)$$

and call x_0 the *critical point*, where a herd switches from a 'safe' state into a 'super-critical' or 'vulnerable' state.

When xR_1 is far above 1, $h(x)$ is close to one. x is continuously increasing by demographic turn-over as described by (3.3). Thus, for infections with large R_1, the probability that virus reactivation does not lead to a major outbreak is only relevant during a relatively short time period after passing the critical point x_0 and that short period can usually be neglected. When, on the other hand, R_1 is rather close to one, $h(x)$, the probability of a major outbreak, is, for most values of x, not even approximately equal to one.

When an epidemic has recently occurred in a certain herd, the fraction of susceptible animals in that herd, x, is always less than $1/R_1$. The susceptible fraction will gradually increase according to (3.3). Until $x = x_0$ no new epidemic can occur. At some point in time, x reaches x_0. We will choose this moment as a calibration or renewal point, where for the sake of the calculation time is reset to zero.

When the reactivation rate is rather high, it will be rather unlikely that the virus will go extinct. We expect several more outbreaks, initiated by reactivation of the virus in one of the recovered animals. So we are led to consider the embedded discrete time population process of passage through the critical point x_0. In between two such passages there is a continuous increase of x according to (3.3) and next a possible jump to a value below x_0. The value of x before the jump is a stochastic variable determined by (3.4) and the value after the jump is determined from the value of x before the jump, by f as defined in (3.2).

3.3 The time to extinction

3.3.1 Calculating the expected time to extinction

Interesting questions now are: how many outbreaks do we expect, and how much time will pass between two outbreaks? The second question depends on the fraction of susceptibles in the population, x, when a new outbreak strikes, because the size of the outbreak depends on the population state x just before the outbreak. Therefore,

to make an estimate of the time until extinction, we calculate the time that will have passed between two consecutive times that the population state passes the critical state x_0.

First we calculate the length t of the time interval it takes a herd to go from population state $x(0)$ at time 0 to state $x(t)$ at time t, on the condition that there is no major outbreak in the mean time:

$$t = \int_{x(0)}^{x(t)} \frac{dt}{dx} dx = \int_{x(0)}^{x(t)} \frac{1}{(1-x)} dx = \ln(1 - x(0)) - \ln(1 - x(t)) \qquad (3.6)$$

The stochastic part of the model is incorporated in the moment that a new epidemic strikes. So, let X be the stochastic variable describing the susceptible fraction of the population at the moment an epidemic strikes. Next, let Y be the stochastic variable describing the time $s(X)$ of a single round, i.e. the total time interval it takes, to go from the critical point x_0 via state X, when an outbreak will occur, and then back to the critical point from the state $f(X)$ immediately after the epidemic outbreak. (Recall the assumption that an epidemic develops so fast compared to the turnover rate in the herd that we can neglect the time that the outbreak itself lasts.) Then, using (3.6) we find that the total time period Y is given by:

$$Y = s(X) = \ln \frac{(1 - f(X))}{(1 - X)}$$

Let $G(x)$ denote the survival function describing the probability for the herd to go from x_0 to state x without a new epidemic phase. Then, starting at $t = 0$ in x_0, with $G(x_0) = 1$ and using (3.4), $\dot{G}$ can be determined as

$$\frac{dG(x(t))}{dt} = -a(1 - x(t))h(x(t))G(x(t)) \qquad (3.7)$$

and with (3.3)

$$\frac{dG(x(t))}{dt} = -a\frac{dx}{dt}h(x(t))G(x(t))$$

So

$$\frac{dG(x)}{dx} = -ah(x)G(x) \qquad (3.8)$$

Defining H by $\frac{dH(x)}{dx} = h(x)$ and $H(x_0) = 0$ for $x \leq x_0$ we find

$$G(x) = G(x_0)e^{-aH(x)} = e^{-aH(x)} \tag{3.9}$$

and

$$H(x) = x - \frac{1 + \ln(xR_1)}{R_1}$$

From formula (3.9) we can now deduce the probability μ to become completely virus free ($x = 1$) without any further outbreaks:

$$\mu = G(1) = e^{-aH(1)}$$

Using formula (3.8) we can now calculate the expected single cycle time $E(Y)$, i.e. the time between two consecutive times of passing x_0, while conditioning on an outbreak taking place (i.e. no extinction):

$$E(Y) = \int\limits_{x_0}^{1} \frac{s(x)ah(x)G(x)}{1 - \mu}dx$$

This expected time between two outbreaks, $E(Y)$, is graphically represented in Figure 2 as a function of the parameters. Time is scaled by life expectancy and is not given in years. The figure shows that for very low values of R_1 the time between two outbreaks exceeds the generation time of the host population.
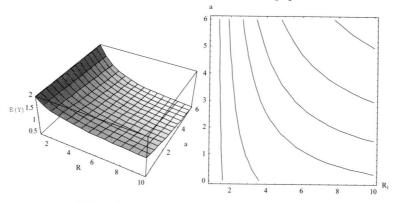

Figure 2a   Figure 2b

Figure 2. Expected time between two outbreaks in 3-D (2a) and contourplot (2b) with level lines at 0.6, 0.8, 1, 1.2, 1.5 and 1.8.

The duration of each full cycle between two outbreaks is totally independent of the previous, because we use state x_0 as a reference point, and the population will pass through that state in between any two outbreaks. For the calculation of the expected time to extinction we will assume that time will start when the population is in the critical state x_0. We neglect the time between the last passage of the critical state and real extinction (i.e. all previously infected animals are removed), firstly because due to the choice of constant removal rates that time would be infinite in this model, and secondly because if there will be no new outbreak, from a more practical point of view eradication is already achieved.

Let T be the stochastic variable describing the time until reaching x_0 after the last outbreak ever. (This approximates the total time to extinction of the virus in that herd, as explained above.) As the probability to reach a fully virus free state without new outbreaks is μ, the expected number of times a herd passes the critical point before reaching this virus free state will be $\frac{1}{\mu}$. We here include the starting passage of the critical state, so the average number of intervals between two outbreaks will be $\frac{1}{\mu} - 1$. Hence, we can calculate the expected value of T:

$$
\begin{aligned}
E(T) &= (\frac{1}{\mu} - 1)E(Y) = \int_{x_0}^{1} \frac{s(x)ah(x)G(x)}{1-\mu}dx(\frac{1}{\mu} - 1) = \int_{x_0}^{1} \frac{s(x)ah(x)G(x)}{\mu}dx \\
&= e^{aH(1)} \int_{x_0}^{1} \ln(\frac{1-f(x)}{1-x})ah(x)e^{-aH(x)}dx \qquad (3.10) \\
&= a \int_{x_0}^{1} \ln(\frac{1-f(x)}{1-x})(1 - \frac{1}{xR_1})e^{a(1-x+\frac{\ln x}{R_1})}dx
\end{aligned}
$$

The outcome of the numerical evaluation of this integral is graphically represented in Figure 3 (and 4).

Note: $E(T)$ only depends on R_1 of the infection and on a, which is the reactivation rate of the virus, α, times the herd size, N. The expected life time is also important for the total time to extinction. That cannot be seen from formula (3.10), because, as a first step in the modelling, time is scaled such that the expected life time of the animals is 1 time unit. Thus we are able to calculate the time to extinction without specifying the host and the pathogen more specifically.
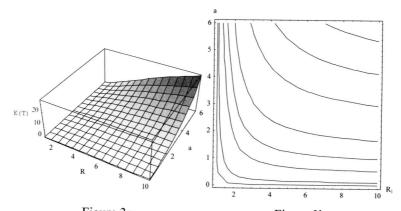
Figure 3a   Figure 3b

Figure 3. Expected time to extinction, $E(T)$ in 3-D plot and contourplot for $E(T) = 0.01, 0.1, 0.5, 1, 2, 5, 10$ and 20.

3.3.2 Probability density function of the time to extinction, T.

We have calculated the expected time between two outbreaks in a herd, $E(Y)$ (from population state x_0 via an outbreak back to state x_0) and the expected time to extinction, $E(T)$ (from state x_0 via several outbreaks, until the last time the population goes through state x_0). To gain more insight into the probability distribution of these stochastic time periods the first two moments of these distributions are calculated. No doubt, experienced probabilitists will find that we provide too many details here (Section 3.2 and 3.3).

The probability distribution of Y is absolutely continuous (since the probability distribution of X is absolutely continuous, see (3.8)), and will be described by its density $\Lambda(y)$. With $x = \phi(y)$ we describe the state x where an epidemic will have started, when it is given that the herd has returned to state x_0 at time y; so ϕ is the inverse function of $s(\tilde{x})$ and $G(\phi(y))$ is the corresponding survival function, i.e. it describes the probability that it will take longer than y to return to x_0. Then $-\Lambda(y)$ is the properly normalized derivative of $G(\phi(y))$ and hence can be calculated as follows

$$\Lambda(y) = -\frac{1}{(1-\mu)}\frac{d}{dy}G(\phi(y)) = -\frac{G'(\phi(y))\,\phi'(y)}{1-\mu}$$

Next we can also calculate the probability distribution of T, the total time until a herd is virus free. This distribution has an atom of size μ at $t = 0$ (no further outbreak

at all); and it is otherwise absolutely continuous, with a density denoted by $\Gamma(t)$. As we explain below,

$$
\begin{aligned}
\Gamma(t) \;=\; & \mu(1-\mu)\Lambda(t) \\
+ \;& \mu(1-\mu)^2 \Lambda^{2*}(t) \\
+ \;& \mu(1-\mu)^3 \Lambda^{3*}(t) \\
+ \;& \ldots
\end{aligned}
$$

i.e.

$$
\Gamma(t) = \mu \sum_{n=1}^{\infty} (1-\mu)^n \Lambda^{n*}(t) \tag{3.11}
$$

where by definition

$$
\begin{aligned}
\Lambda^{n*}(t) \;=\; & \int_0^t \Lambda^{(n-1)*}(t-\sigma)\Lambda(\sigma)d\sigma \tag{3.12} \\
\Lambda^{1*}(t) \;=\; & \Lambda(t)
\end{aligned}
$$

This can be seen as follows: if there is only one further outbreak, which has probability $\mu(1-\mu)$, then the distribution of t is described by $\Lambda(t)$. Exactly two outbreaks has probability $\mu(1-\mu)^2$ and the distribution of the time t it then takes to return to the critical point is described by a convolution integral of Λ with itself, so by:

$$
\Lambda^{2*}(t) = \int_0^t \Lambda(t-\sigma)\Lambda(\sigma)d\sigma
$$

where σ is the time taken by the first outbreak free interval. For higher numbers of outbreaks an analogous reasoning is applied.

3.3.3   The variance of the time to extinction.

Define λ_i as the i-th moment of Y, i.e.

$$
\lambda_i = \int_0^{\infty} s^i \Lambda(s)ds \tag{3.13}
$$

We find $\lambda_0 = 1$ and $\lambda_1 = E(Y)$ and

$$\text{Var}(Y) = \int_0^\infty s^2 \Lambda(s) ds - E(Y)^2 = \lambda_2 - \lambda_1^2 \tag{3.14}$$

As to be expected, from (11) we can determine the moments of the stochastic time to extinction, T, in terms of μ and λ_i.

Proposition 1

$$E(T) = \frac{1 - \mu}{\mu} \lambda_1 \tag{3.15}$$

To prove this, first we will calculate the first moment of higher order convolutions of Λ in the following lemma:

Lemma 2

$$\int_0^\infty t \Lambda^{n*}(t) dt = n\lambda_1 \tag{3.16}$$

Proof Lemma 2. From formula (3.12) it follows that

$$\int_0^\infty t \Lambda^{n*}(t) dt = \int_0^\infty t \int_0^t \Lambda^{(n-1)*}(t - \sigma) \Lambda(\sigma) d\sigma dt$$

$$= \int_0^\infty \int_\sigma^\infty t \Lambda^{(n-1)*}(t - \sigma) \Lambda(\sigma) dt d\sigma$$

which, by putting $t = s + \sigma$ is seen to be equal to

$$\int_0^\infty \int_0^\infty (s + \sigma) \Lambda^{(n-1)*}(s) \Lambda(\sigma) ds d\sigma$$

$$= \int_0^\infty \int_0^\infty (s + \sigma) \Lambda(\sigma) d\sigma \Lambda^{(n-1)*}(s) ds$$

which by definition (3.13) is equal to

$$\int_0^\infty (\lambda_1 + s)\Lambda^{(n-1)*}(s)ds$$

So we see that

$$\int_0^\infty t\Lambda^{n*}(t)dt = \lambda_1 + \int_0^\infty s\Lambda^{(n-1)*}(s)ds$$

For $n = 2$ this means that

$$\int_0^\infty t\Lambda^{2*}(t)dt = 2\lambda_1$$

By induction, Lemma 2 is now readily proven. ∎

Proof Proposition 1. Since

$$E(T) = \int_0^\infty t\Gamma(t)dt$$

we deduce from formulas (3.11) and (3.16)

$$
\begin{aligned}
E(T) &= \sum_{n=1}^\infty \mu(1-\mu)^n \int_0^\infty t\Lambda^{n*}(t)dt \\
&= \sum_{n=1}^\infty \mu(1-\mu)^n n\lambda_1 \\
&= \frac{1-\mu}{\mu}\lambda_1
\end{aligned}
$$

∎

Note that the assertion of Proposition 1 is in fact equal to the first identity in formula (3.10), as $\lambda_1 = E(S)$. Thus two different methodologies were used to deduce an expression for the expected time to extinction, reassuringly leading to the same result.

A bit more complicated is the derivation of the variance of T:

Proposition 3

$$Var(T) = \frac{1-\mu}{\mu}\lambda_2 + \left(\frac{1-\mu}{\mu}\lambda_1\right)^2 \tag{3.17}$$

To prove Proposition 3, we calculate the second moment of higher convolutions of Λ:

Lemma 4

$$\int_0^\infty t^2 \Lambda^{n*}(t)dt = n\lambda_2 + n(n-1)\lambda_1^2$$

Proof Lemma 4.

$$
\begin{aligned}
\int_0^\infty t^2 \Lambda^{n*}(t)dt &= \int_0^\infty t^2 \int_0^t \Lambda^{(n-1)*}(t-\sigma)\Lambda(\sigma)d\sigma dt \\
&= \int_0^\infty \int_\sigma^\infty t^2 \Lambda^{(n-1)*}(t-\sigma)\Lambda(\sigma)dt d\sigma \\
&= \int_0^\infty \int_0^\infty (s+\sigma)^2 \Lambda^{(n-1)*}(s)\Lambda(\sigma)ds d\sigma \\
&= \int_0^\infty \int_0^\infty (s+\sigma)^2 \Lambda(\sigma)d\sigma \Lambda^{(n-1)*}(s)ds
\end{aligned}
$$

Expanding and using the defining formula 3.13, while remembering that $\int_0^\infty \Lambda^{n*}(\sigma)d\sigma = 1$, we continue with

$$
\begin{aligned}
\int_0^\infty t^2 \Lambda^{n*}(t)dt &= \int_0^\infty (\lambda_2 + 2\lambda_1 s + s^2)\Lambda^{(n-1)*}(s)ds \\
&= \lambda_2 + 2\lambda_1 \int_0^\infty s\Lambda^{(n-1)*}(s)ds + \int_0^\infty s^2 \Lambda^{(n-1)*}(s)ds
\end{aligned}
$$

and with Lemma 2 we finally derive that

$$\int\limits_0^\infty t^2 \Lambda^{n*}(t)dt = \lambda_2 + 2(n-1)\lambda_1^2 + \int\limits_0^\infty s^2 \Lambda^{(n-1)*}(s)ds$$

And by induction Lemma 4 can be derived from this. ■

With the results from Lemma's 2 and 4 at hand, we can now prove Proposition 3:

Proof Proposition 3.

$$\text{Var}(T) = \int\limits_0^\infty t^2 \Gamma(t)dt - E(T)^2$$

which by formula (3.11) is equal to

$$(\sum_{i=1}^\infty \mu(1-\mu)^i \int\limits_0^\infty t^2 \Lambda^{i*}(t)dt) - \left(\frac{1-\mu}{\mu}\lambda_1\right)^2$$

which, according to Lemma 4, equals

$$(\sum_{i=1}^\infty \mu(1-\mu)^i (i\lambda_2 + i(i-1)\lambda_1^2)) - \left(\frac{1-\mu}{\mu}\lambda_1\right)^2$$

Evaluation of the sum yields

$$\frac{1-\mu}{\mu}\lambda_2 + \left(\frac{1-\mu}{\mu}\lambda_1\right)^2$$

thus proving Proposition 3 ■

3.3.4   Numerical elaboration of the results

We find that when the maximal reactivation rate per herd, a (equal to the individual reactivation rate α times the population size N) is very low, (a smaller than the average life span of a host), then reactivating viruses tend to go extinct within a few host generations (see Figure 3). The expected number of new outbreaks is also low (< 10) for a low reactivation rate. However, the extinction time may exceed the host's life span with several orders of magnitude when the reactivation rate of the population (a) is large (a much bigger than the average hosts life span), because the expected time

to extinction grows extremely fast with increasing reactivation rate and herd size (see Figure 3).

When the primary reproduction ratio, R_1, is small, we find that the expected time to extinction is very sensitive to the precise value of R_1, the higher R_1, the longer the time to extinction will be. However, at high values of R_1 variation in R_1 has relatively little impact on the expected time to extinction. On the other hand, the expected time to extinction is very sensitive to a high reactivation rate in the herd. The sensitivity of the extinction time to a behaves just opposite from the sensitivity to R_1, here we find that the extinction time is hardly influenced by some perturbation at small values of a, ($a < 1$). All calculations of time are expressed in expected life time of the host, which is therefore also an important factor, when a specific infection is studied.

In Figures 4 (a-d) the expected time to extinction, $E(T)$, is combined in one graph with its standard deviation, $sd(T)$. We see that generally the standard deviation of T has the same order of magnitude as $E(T)$. We can analyse this further by observing the coefficient of variation for T, which is the standard deviation divided by the expectation of T. Using (3.15) and (3.17)

$$
\begin{aligned}
\frac{\sqrt{Var(T)}}{E(T)} &= \sqrt{\frac{1-\mu}{\mu}\lambda_2 + \left(\frac{1-\mu}{\mu}\right)^2 \lambda_1^2} \left(\frac{\mu}{(1-\mu)\lambda_1}\right) \\
&= \sqrt{\frac{\mu}{(1-\mu)}\frac{\lambda_2}{\lambda_1^2} + 1}
\end{aligned}
$$

we see that for $\{\lambda_1, \lambda_2\} \neq 0$ the coefficient of variation goes to infinity for $\mu \uparrow 1$ (i.e. small a or R_1) and for $\mu \downarrow 0$ (i.e. large a and R_1) the coefficient of variation becomes asymptotically equal to 1.

The calculation method for the time to extinction neglects the variance in the final size of a major outbreak. This variance is indeed mostly negligible, as can be seen from the following analysis. A major outbreak must (by definition) have an outcome between 0 and x_0. The time it takes to go from 0 to x_0, $(-\ln(1-x_0))$, must therefore be higher than the variance in the single cycle time Y, that is induced by the variance in the final size. In Figure 5 the time to close a single cycle (thick line) is compared to the time to go from 0 to x_0 (decreasing function $-\ln(1-x_0)$). We notice that $-\ln(1-x_0)$ is much less than $E(Y)$, when R_1 is sufficiently large and a sufficiently small. Thus we conclude that under those conditions, the impact of the neglected variance from the final size is rather small.
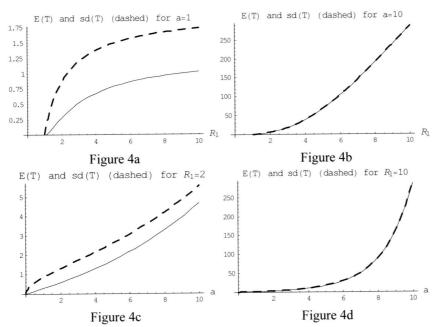
E(T) and sd(T) (dashed) for a=1

Figure 4a

E(T) and sd(T) (dashed) for a=10

Figure 4b

E(T) and sd(T) (dashed) for $R_1=2$

Figure 4c

E(T) and sd(T) (dashed) for $R_1=10$

Figure 4d

Figure 4. $E(T)$ and standard deviation (dashed) for various parameter values.

Figure 5a shows $E(Y)$ and $-\ln(1 - x_0)$ for $a = 10$, and Figure 5b shows $E(Y)$ and $-\ln(1 - x_0)$ for $R_1 = 10$. The neglected variance has a major impact for very small values of a and R_1, where this method can lead to a major underestimation of the variance. A comparison of $E(Y)$ and $-\ln(1 - x_0)$) can be used to decide on the necessity of further analysis.
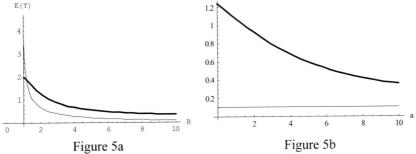

E(Y)

Figure 5a

Figure 5b

Figure 5. Comparison of $E(Y)$ and $-\ln(1 - x_0)$ for $a = 10$ in 5a and $E(Y)$ for $R_1 = 10$ in 5b.

3.4 Application to Bovine Herpes Virus

The results derived above are now applied to quantify the expected time to extinction of Bovine Herpes Virus (BHV) in the Netherlands. The influence of control measures on the extinction time will also be assessed.

In 1997, a control program was started, aiming at eradication of Bovine Herpes Virus in the Netherlands. To achieve this, a marker vaccine was selected which reduces, but does not stop, the transmission. From field studies, the reproduction ratio is estimated to be slightly higher than 1, $R_1 \approx 1.5$ [38],[59] and [4]. Although this reproduction ratio is above 1, and immediate extinction of the virus is therefore not to be expected, local extinction of the virus may still induce eradication. To obtain an estimate of the time it would take to eradicate BHV in the Netherlands, we assessed the expected time to extinction of BHV in a typical Dutch cattle herd.

The Netherlands also has a few feral cattle herds living in extensively managed natural area's. For obvious reasons, in these herds only oral vaccination is allowed, but there is not yet a useful and good oral vaccine against Bovine Herpes Virus (BHV) available. Therefore BHV-vaccination is not applied in these herds. We assessed whether the virus may persist long in such feral herds, thus posing a threat to the eradication process.

The previous analysis can very well be used to assess the expected extinction time, for both vaccinated and non-vaccinated herds. The only parameters needed to tackle the problem described in this paper, are the reactivation rate of BHV in individual cattle and the basic reproduction ratio of BHV in herds. As we have only access to data collected in husbandry herds, we are forced to assume that the parameters are similar for feral cattle. In dairy cattle, the primary reproduction ratio of BHV has been estimated at $R_1 = 3.2$ [3] for non-vaccinated herds.

To estimate the reactivation rate for BHV, we used original data collected in a vaccination-control experiment by Bosch et al [3], where transmission of BHV was quantified. The controls in this experiment were treated with a placebo vaccine and the vaccine used was a dead marker vaccine, not the same one as used for the Dutch eradication process. The control group consisted of 45 farms and the vaccine group consisted of 42 farms. At all these farms there was BHV positive cattle present at the beginning of the screening period. During the whole screening period of 13 months, the farmers were asked to minimize trade in and out of the farm. Dairy cattle were always kept separate from the calves and heifers, so each farm has two separate herds. The cattle were all regularly screened for antibodies against BHV. Thus outbreaks of the infection could be detected in several of these herds. It was not possible to

distinguish between outbreaks induced by reactivation of the virus in one of the BHV carrying animals and outbreaks due to renewed introduction of the virus from the outside.

We estimate the reactivation rate of the virus by assuming that no introduction of the virus from elsewhere did occur. Thus, we may overestimate the reactivation rate if the virus was actually reintroduced at the farms regularly. The vaccinated groups were assessed separately, and from these data we estimated the reactivation rate for vaccinated animals.

The data on the dairy herds were used because there was always at least one seropositive animal in the herd. The data on the young stock were neglected. For each herd i, the number of positive animals Z_i was registered at the beginning of the experiment. Furthermore during and at the end of the experiment it was noted whether animals in the herd showed seroconversion indicating an outbreak ($i+$) or not ($i-$). A very simple model was used for a first assessment

Call the probability of reactivation per seropositive animal in those 13 months p, then the probability of no reactivation in this period in herd i is $(1-p)^{Z_i}$ and the probability of reactivation is $1-(1-p)^{Z_i}$. Thus we are led to a maximum likelihood estimator for p by maximising the quantity

$$\prod_{i-}(1-p)^{Z_i} \prod_{i+} 1-(1-p)^{Z_i} \tag{3.18}$$

This method implicitly assumes that reactivation always leads to at least one new infection.

We soon concluded that the model underlying this first maximum likelihood estimator was too simplistic. It can easily be improved, by taking account of the probability of seroconversion relative to the probability of transmission. Furthermore we assume that seropositive animals are not susceptible. Thus the susceptible fraction of the population, ($\frac{S}{N}$), is the relevant variable for the probability of transmission, given reactivation of the virus. Assuming a constant density within the herd (true mass action) as sub-model for transmission, we propose the following maximum likelihood function to estimate the reactivation rate:

$$\prod_{i-} \sum_{k=0}^{Z_i} \binom{Z_i}{k} p^k (1-p)^{Z_i-k} \left(1 - \frac{R_1}{N_i}\right)^{k\,S_i} \tag{3.19}$$

$$\prod_{i+} \sum_{k=1}^{Z_i} \binom{Z_i}{k} p^k (1-p)^{Z_i-k} \left(1 - \left(1 - \frac{R_1}{N_i}\right)^{k\,S_i}\right)$$

where $\binom{Z_i}{k} p^k (1-p)^{Z_i-k}$ gives the probability of k reactivations among the Z_i seropositive cattle within the given time-span. $\frac{R_1}{N_i}$ gives the probability for each susceptible in the population to become infected if one animal reactivates and therefore $(1 - \frac{R_1}{N_i})^{k\,S_i}$ describes the probability of no seroconversions among the S_i susceptibles, while the virus reactivates in k animals in group Z_i, during the period surveyed.

Applying the first maximum likelihood method (3.18) to the data of Bosch, we find $p = 0.028$ per 13 months or 0.026 per year. The second, improved method (3.19) is based on a stochastic mass-action transmission model and leads to a much higher estimate of the reactivation rate: $p = 0.10$ per 13 months or 0.09 per year. The second method includes the probability of transmitting the infection to a susceptible animal, which is neglected in the first method. These differences lead to a major difference in the outcome. Therefore we conclude that in the present case the formula (3.18) is too simplistic and more elaborate modelling, as underlying (3.19), is needed for a good assessment of the reactivation rate. Still, both methods overestimate the reactivation rate by neglecting possible reintroduction of the virus from outside the herd.

Now we estimate the expected time to extinction for vaccinated production herds. The inactivated virus vaccine, which was used in the experiments of Bosch et al., is expected to lead to a somewhat lower reactivation rate than the live vaccine which was used for the eradication process. Data from Jet Mars [59] support this. However, the different estimates for the reactivation rate for untreated cattle are not significantly different from the reactivation rate in cattle vaccinated with either vaccine. Thus, we apply the same estimate for the reactivation rate. Using the above method (3.19) on the original data from the vaccinated herds [3], the reactivation rate is estimated at 0.09 per year. With all the above, we derive that the expected extinction time ranges from about 15 years for rather small vaccinated herds of 40 animals up to about 90 years for vaccinated herds of 100 animals (see Figure 6).
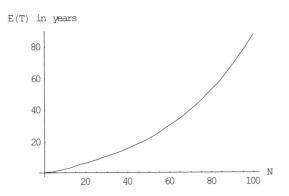
Fig 6. Expected time to extinction for BHV in vaccinated herds of size N

We find that despite vaccination, the expected time to extinction is still rather long for large herds. In practice many farms enhance the extinction process by increased removal of seropositive animals from the herd, once their prevelance has become rather low. Various scenario's of culling in BHV eradication are analysed in more detail applying a stochastic simulation model by VonkNoordegraaf. [82]. For full analysis of this extinction problem on a national scale, a meta-population study would be helpful, but intuition suggests that the outliers, i.e. the herds with an extremely long time to extinction, may cause problems for the full metapopulation by reintroducing the virus into virus free herds, depending on the level of coupling. Removal of the last seropositive herds in the country will probably be applied, once their number has become small enough, thus reducing the total time to eradicate the virus substantially at minimal cost.

The same analysis was performed for unvaccinated herds, domestic and feral. The average life-span of feral cattle is estimated to be similar to that of domestic cattle, about 5 years. Feral cattle herds, just like domestic herds, range from very few animals up to several hundreds of animals. Using (3.10) we calculate the expected time to extinction of BHV in a population of size 250 (largest feral herd) to be of the order of a hundred million (10^8) years, but in small herds (20 animals) the expected time to extinction would be much less, 40 years only (Figure 7). Without vaccination or other control measure, BHV will go extinct with high probability in the small herds, but is expected to persist forever in larger ones. Reintroduction of the virus will be prevented by import restrictions and testing, according to the EU regulations on exotic infections.
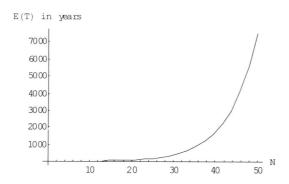
E(T) in years

Figure 7. Expected time to extinction $E(T)$ for BHV in herds of size N.

3.5 Discussion and Conclusions

When the reactivation rate of herpes virus is very low, this infective agent behaves very similar to other viruses, as can be expected. However, with higher reactivation rates, herpes viruses are much more persistent, even in rather small populations. Extinction becomes highly unlikely, when both the primary reproduction ratio and the reactivation rate in the herd are large. With an increasing reactivation rate, the time to extinction soon becomes essentially infinitely long.

The expected time to extinction turns out to be very sensitive to the primary reproduction ratio and therefore (partial) vaccination may have an enormous impact on the persistence of a herpes infection in a population. Thus, for eradication of reactivating viruses it may be sufficient to only bring the reproduction ratio (R_1) close to one, and not necessarily below one, while still obtaining rather fast extinction of the infection.

In small vaccinated herds (<50 animals), BHV will probably go extinct within one or two decades. In unvaccinated herds the virus will be very persistent, (centuries). This is confirmed by the frequent occurence of this virus in untreated herds. In large herds (>100), vaccinated or not, the virus will persist for many, many centuries. Therefore, once introduced, we expect BHV to persist in most of the Dutch feral herds.

When R_1 is smaller than 1, large outbreaks can not occur. Such infections might still persist in a closed population if the reactivation rate per individual, α is sufficiently large to bring R_0 above 1. *Herpes simplex* in the human population may be an example of a virus with such a strategy. However, in the model as described in this paper, the advantages of such a strategy cannot be shown, because this model neglects

the effect of minor outbreaks completely. For very low value's of R_1 the impact of minor outbreaks can be rather large and become the basis for prolonged persistence of the infection. (Unpublished results of an extended fully stochastic version of the model [63]).

However, a basic rule applies for all types of infections: when the basic reproduction ratio, R_0 is below 1, any introduced infection will go extinct. This also applies to reactivating infections, like those caused by herpes viruses, except that in those cases extinction may take a bit longer, i.e. a few host generations.

Constant removal rates are often used in mathematical modeling to describe all kinds of state transition processes, because it makes the analysis of the models a lot easier, although the implied exponential distribution of the residence time may show little similarity with the actual distribution. Experience learns that in general, such a simplification of reality still leads to a good model of the system. However, in a few situations one must be careful with the use of a constant removal rate and the concomitant exponential distribution of residence time. For instance, with a constant removal rate extinction is only reached in the limit of time going to infinity. The method described in this paper elegantly avoids this artefact, by declaring the agent extinct at the moment that criticality is reached and yet there will not be another outbreak.

The deterministic model leads to a long tail in the distribution of the hosts life span, which does not fit "real life". However, a numerical check, while setting the tail of the distribution to zero above 12 years, showed that this has little impact on the time to extinction if R_1 is sufficiently large. For $R_1 = 2$, this method overestimates the time to extinction with about 5%. However, for *very* small R_1, the error may become substantial: for $R_1 = 1.1$, the total time to extinction is overestimated by about 60%. Overall, in most cases the very low probability of reactivation in the long tail of the survival distribution leads to a minor impact on the expected time to extinction. The elegance of modelling with constant removal rates is thus conserved while avoiding the disadvantages.

Chapter 4

Quantifying BSE control by calculating the basic reproduction ratio R_0 for the infection among cattle.

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Abstract

The safety of using meat and bone meal (MBM) in mammal feed was stud-ied in view of BSE, by quantifying the risk of BSE transmission through different infection routes. This risk is embodied in the basic reproduc-tion ratio R_0 of the infection, i.e. the average number of new infections induced by one initial infection. Only when R_0 is below 1, will the dis-ease die out with certainty and the population will become free from BSE. Unfortunately this is a slow process due to the slow progression of the disease.

We calculate R_0 explicitly from basic ingredients taking several different transmission routes into account. Several of the basic ingredients are functions of age or of infection-age. We also calculate the exponential growth rate r in terms of the same basic ingredients.

Next we quantify the ingredients from available data and compute the effects on R_0 of various scenario's for controlling BSE, with examples for the UK and the Netherlands.

4.1   Introduction

Major public attention recently focused on bovine spongiform encephalopathy (BSE) and related diseases. BSE may pose a threat for human health, as consumption of BSE infected beef may induce a new variant of Creutzfeldt-Jakob disease (vCJD) [6]. The risk for humans to contract vCJD seems to be very small, when assuming an average incubation period of less than ten years, but because the incubation period may be much longer, we may not yet have reached the peak of the vCJD-epidemic and infection risks may be underestimated so far. Presently, the BSE epidemic in the UK is far below its peak of 1992 and many food-safety measures make sure that the risk of contracting new infections in the human population has decreased enormously.

The BSE epidemic in the United Kingdom was probably due to BSE infected meat and bone meal (MBM) in cattle feed [85]. In the 1980s a major part of MBM in the UK was produced at low temperatures (about 100^oC). Later it was shown that such conditions are insufficient for the inactivation of the BSE agent [79].

To answer questions about the efficacy of control measures and to quantify regional risk of BSE outbreaks, we calculate the basic reproduction ratio R_0, incorporating the postulated mechanisms of BSE transmission in an age-structured population of cattle. The basic reproduction ratio R_0 of an infection is the expected (average) number of new infections, caused by a typical infected individual. (See [24].) We will derive an explicit expression for R_0 of BSE in terms of basic ingredients that describe cattle demography and transmission routes of the BSE agent. In section 2 we describe the ingredients, the calculation of R_0 and of the real-time exponential growth rate r of the early part of an epidemic. In section 3 we quantify all ingredients from data. In section 4 we compute values for R_0 under various realistic combinations of control measures, and provide confidence intervals for R_0-estimates. Finally we briefly discuss implications for EU-guidelines in section 5.

4.2   The ingredients

4.2.1   Infection routes

A model of infection-host interaction intended for risk assessment by quantifying R_0 should include all characteristics of the infection and the host that may have a major impact on R_0. The characteristics that we consider important in BSE epidemiology are, firstly, the incubation time of BSE, which is extremely long, close to the average life time of cattle. Secondly, new born calves are more susceptible than adult cattle,

as a result of which the average age at infection is rather low, therefore age needs to be taken into account. Thirdly, different infection routes exist.

We consider the following five infection routes. (1) Recycling of proteins in MBM that is used in cattle feed (horizontal infection). (2) Maternal infection, i.e. from mother to calf (vertical infection) probably at birth, (3) Birth related infection may also affect other cattle at close proximity during birth (diagonal infection). The afterbirth is supposed to be a risk factor. (4) Direct animal to animal transmission (horizontal). (5) Infectious material in the environment (use of MBM as fertilizer and remaining infection from feed, left in manure).

Infection routes (4) and (5) seem of minor importance, but are included in the model to allow an assessment of their impact. Given the difficulties in inactivating the BSE agent, infectious material may persist in the environment for a long time. Scrapie material is known to remain infectious for several years in the environment [5] and for BSE similar survival may be expected. Therefore, although infection route (5) may cause only a small risk at any moment in time, it is possible that new cases will arise by this route over a very long period to come. This delay effect of the environment is not incorporated into the model.

As infection routes (3), (4) and (5) can not be estimated separately from the data presently available, we clustered them into one parameter ω. During the initial stage of the epidemic in the UK, these routes were probably negligibly small compared to the feed infection route. However, when infection via the feed infection route has become small due to BSE control measures, ω may become of influence.

4.2.2 Fundamental assumptions.

Two fundamental assumptions underlie the model of the BSE-cattle interaction. One assumption is very common in epidemiological models: infection is transmitted during random contacts between animals, so spatial structure is not incorporated. This implies that all infectious contacts are randomly distributed in space over the whole cattle population and the model neglects clustering of the infection in space. Generally, such a model is well suited for describing contact infections within a herd, and can be applied to a regional or national population when there is contact (direct or indirect) between all herds.

The second main assumption underlying the model is that the infectious agent of BSE behaves according to the 'single hit theory' [45]. This means that there are numerous infectious particles (in case of BSE prions) in an animal with clinical BSE and each of these particles has a very small probability of inducing infection. Present

knowledge of BSE (and Transmittable Spongiform Encephalopathy's, TSEs in general) suggests that the infection does not trigger any immune reaction in the host, so multiple doses of ingested infectious material are not supposed to lead to increasing resistance.

4.2.3 The parameters

We list the parameters of our description of cattle demography and BSE-cattle interactions. Some of these are functions of age (a) and infection-age (τ, i.e. time elapsed since the animal got infected). The latter variability is introduced since susceptibility of cattle depends on age and infectiousness depends on infection-age. The population dynamics of cattle is described by age-dependent culling and age-dependent birth rate. The infectious load in an infected animal grows with the time τ since the animal was infected. All newborn animals arrive in the susceptible class, except those that already get infected maternally. For infected animals, culling can be either due to age, or due to recognition of BSE-symptoms.

The model contains parameters that can be influenced by control measures against BSE or local conditions, and parameters that cannot. The parameters that remain fixed in this study are:

- age-dependent susceptibility of cattle, $\beta(a)$

- infection-age dependent infectious load of an infected animal, $\gamma(\tau)$

- maternal transmission rate (per unit of infectious load of the mother), m

- contact infection rate via the environment, ω

The following parameters can be affected by control measures or local conditions:

- per capita culling rate for cattle (not infected), μ

- per capita birth rate, b

- the reduction of infectious load by the rendering process, k_1

- the fraction of MBM that is fed to cattle (not to other animal species), k_2

- the fraction of infectious load from a non-BSE suspect carcass that enters the rendering process, c_1

- the fraction of infectious load from a BSE suspect carcass that enters the rendering process, c_2

- the per capita culling rate of infected cattle by recognizing BSE symptoms at time τ after infection, $\nu(\tau)$.

4.2.4   Characterization of R_0

After naming the basic ingredients of the BSE cattle interactions, the basic reproduction ratio R_0 can be characterized. It applies to a set of models, which may include features like heterogeneity and stochasticity, which need not be specified at this point. Such model details are not essential for the methodology, but they may influence parameter estimations. A general description of the method to calculate R_0 can be found in [24]. During an epidemic, the fraction of susceptible animals decreases and due to that, the expected number of infections initiated by an infected animal also decreases. Although the basic reproduction ratio is a measure for the initial phase of an outbreak, it also supplies information about the expected number of animals that will get infected during the whole outbreak, (see also [24]).

To characterize the basic reproduction ratio R_0, we need to define the 'typical' infected individual. Reviewing the five different infection routes, it appears that there are two typical distributions for age at infection. Maternal infection takes place at birth, and thus for maternally infected animals infection age is equal to their real age. Animals infected by the other infection routes all have a distribution of age at infection, depending on the age-dependent susceptibility and age-dependent survival. For animals infected via MBM, the age distribution will also depend on the amount of MBM ingested at different ages. As data are very hard to obtain, we assume this to be a constant for all ages, thus leading to only two different groups of infected animals: a group of animals infected at birth and a group that can be described by a fixed probability distribution of age at infection. Thus we arrive at a two dimensional 'age at infection' space, spanned by a delta 'function' $\delta_a = \delta_0 = 0$ for maternal infections and the function $\beta(a)\mathcal{F}_s(a)$, for horizontal, diagonal en environmental infections.

For the two types of infected animals we separately determine the expected number of new infections that they will induce during their whole infectious period (by the two types of infection routes). We denote the expected number of infections via a type i route caused by an animal that was itself infected through a type j route as q_{ij}. Explicit formulas for q_{ij} can be derived.

A first step in formulating q_{ij} is constructing a survival function $\mathcal{F}_s(a)$, which describes the probability for a susceptible animal to survive until at least age a:

$$\mathcal{F}_s(a) = e^{-\int_0^a \mu(\alpha)d\alpha} \qquad (4.1)$$

The infection survival function $\mathcal{F}_i(\tau)$ describes the probability of an infected cow to survive until at least infection age τ, under the condition that the animal will be culled only due to BSE signs, i.e. neglecting the possibility of normal cull.

$$\mathcal{F}_i(\tau) = e^{-\int_0^\tau \nu(\alpha)d\alpha} \qquad (4.2)$$

Then the survival function of infected cattle under normal farming conditions (including normal cull) is represented by $\mathcal{F}_s(a + \tau)\,\mathcal{F}_i(\tau)$, where a represents the age at infection, and the true age of the animal becomes $a + \tau$.

Here q_{11} represents the expected number of new feed infected individuals from one (average) feed infected individual. Next, q_{21} represents the expected number of new maternally infected individuals from one (average) feed infected individual. One (average) feed infected animal is distributed over all possible ages at infection according to the density.

$$\frac{\beta(a)\mathcal{F}_s(a)}{\int_0^\infty \beta(\alpha)\mathcal{F}_s(\alpha)d\alpha} \qquad (4.3)$$

Now q_{11} is calculated as the probability of cull μ at age $(a+\tau)$ and ν at infection-age τ, multiplied with the fraction of its infectious load $\gamma(\tau)$ that enters rendering (c_1 and c_2), the rendering reduction factor (k_1) and the fraction fed to cattle (k_2). Thus $c_1\mu(a+\tau)+c_2\nu(\tau)$ is the fraction of the infectious load (prions) of an infected animal entering the rendering process, and multiplication with k_1k_2 gives the fraction that survives rendering and is fed to cattle. This expression then has to be multiplied with the probability of an infected animal to survive, $\mathcal{F}_s(a+\tau)\mathcal{F}_i(\tau)/\mathcal{F}_s(a)$, and also has to be multiplied with the infectious load $\gamma(\tau)$ at infection-age τ. Accumulating this over all possible combinations of age and infection age at cull (integral over a and τ), we find the expected number of infectious doses in feed taken up by cattle. Multiplying this with the age dependent susceptibility $\beta(a)\mathcal{F}_s(a)$ yields the total number of new infections. After dividing by a factor to normalize the relevant distributions we obtain the expected number of new feed infections that will be caused by the 'average' feed infected cow of 'average' age. The ω for the other horizontal infection also needs to be incorporated for the various age groups. The calculation takes account of both the age of the infectious animal (α) and the age of a newly infected animals (a) for the feed infection route. The other three partial ratios (q_{ij}) can be derived likewise, leading to

$$q_{11} = \cfrac{\displaystyle\int_0^\infty \int_0^\infty \beta(\alpha)\left((c_1\mu(\alpha+\tau) + c_2\nu(\tau))k_1 k_2 + \omega\right)\mathcal{F}_s(\alpha+\tau)\mathcal{F}_i(\tau)\gamma(\tau)d\tau d\alpha}{\displaystyle\int_0^\infty \mathcal{F}_s(a)da}$$

(4.4)

$$q_{21} = \cfrac{\displaystyle\int_0^\infty \int_0^\infty \beta(\alpha)b(\alpha+\tau)\mathcal{F}_s(\alpha+\tau)\mathcal{F}_i(\tau)m\gamma(\tau)d\tau d\alpha}{\displaystyle\int_0^\infty \beta(\alpha)\mathcal{F}_s(\alpha)d\alpha}$$

(4.5)

$$q_{12} = \cfrac{\displaystyle\int_0^\infty \beta(a)\mathcal{F}_s(a)da}{\displaystyle\int_0^\infty \mathcal{F}_s(a)da} \int_0^\infty \left((c_1\mu(\tau) + c_2\nu(\tau))k_1 k_2 + \omega\right)\mathcal{F}_s(\tau)\mathcal{F}_i(\tau)\gamma(\tau)d\tau$$

(4.6)

$$q_{22} = \int_0^\infty b(\tau)\mathcal{F}_s(\tau)\mathcal{F}_i(\tau)m\gamma(\tau)d\tau$$

(4.7)

From these four partial reproduction ratio's by infection type, the overall reproduction ratio R_0 of BSE in a cattle population can be calculated as the dominant eigenvalue of the 2x2 matrix, Q. The two components of the right eigenvector show the relative importance of the feed infection route and the maternal infection route.

$$R_0 = \frac{1}{2}q_{11} + \frac{1}{2}q_{22} + \frac{1}{2}\sqrt{(q_{11}^2 - 2q_{11}q_{22} + q_{22}^2 + 4q_{12}q_{21})}$$

(4.8)

To stop the epidemic, several measures can be taken. The rendering method can be improved, brains and spinal cord can be removed from rendering, and feeding of MBM to cattle can be minimized. In the model we can calculate the effect of these measures on R_0 by adjusting the relevant parameters, such as c_1, c_2, k_1 and k_2 (see Section 4). In this way one can draw up a set of regulations to minimize the risk of a major epidemic given the costs of following these regulations, or regulations that lead to a fast decline in the number of new infections, given that an epidemic has started (see section 2.5).

4.2.5 Characterization of growth rate r.

Analogous to the derivation of the reproduction ratio R_0, we can derive an equation for the per capita growth rate r of the infection at the initial (exponential) phase of the epidemic. This derivation is slightly more complicated.

The real-time evolution of the infection is described by

$$I(a,t,0) = \overline{S}(a)\beta(a) \int_0^\infty \int_0^\infty \theta_{11}(\alpha,\tau)\,I(\alpha,t-\tau,0) + \theta_{12}(\alpha,\tau)I(0,t-\tau,0)d\tau d\alpha$$

$$I(0,t,0) = \int_0^\infty \int_0^\infty \theta_{21}(\alpha,\tau)\,I(\alpha,t-\tau,0) + \theta_{22}(\alpha,\tau)I(0,t-\tau,0)d\tau d\alpha \qquad (4.9)$$

which is the continuous-time counterpart of the next-generation operator Q on which the expression for R_0 is based. Here, $I(a,t,0)$ denotes the feed-induced incidence of new cases with age a arising at time t (then infection age $\tau = 0$) and $I(0,t,0)$ denotes the maternally induced incidence with age $a = 0$ at time t. $\overline{S}(a) = F_s(a)/\int_0^\infty F_s(\alpha)d\alpha$ denotes the age distribution arising from the demographic steady state of the cattle population (held constant by the farmer) and $\beta(a)$ denotes the age dependent susceptibility. The transmission kernel $\Theta(a,\tau)$ is given by a two-dimensional matrix with elements $\theta_{ij}(a,\tau)$:

$$\theta_{11}(a,\tau) = ((c_1\mu(a+\tau) + c_2\nu(\tau))k_1k_2 + \omega)\frac{F_s(a+\tau)}{F_s(a)}\mathcal{F}_i(\tau)\gamma(\tau)$$

$$\theta_{12}(a,\tau) = b(a+\tau)\frac{F_s(a+\tau)}{F_s(a)}\mathcal{F}_i(\tau)m\gamma(\tau)\beta(a)$$

$$\theta_{21}(a,\tau) = \frac{\int_0^\infty \beta(a)\mathcal{F}_s(a)da}{\int_0^\infty \mathcal{F}_s(a)}(c_1\mu(\tau) + c_2\nu(\tau))k_1k_2 + \omega)\,\mathcal{F}_s(\tau)\mathcal{F}_i(\tau)\gamma(\tau)$$

$$\theta_{22}(a,\tau) = b(\tau)\mathcal{F}_s(\tau)\mathcal{F}_i(\tau)m\gamma(\tau) \qquad (4.10)$$

We write $i(a,t)$ for the vector $(I(a,t,0), I(0,t,0))^{\mathsf{T}}$ and can then rewrite system (4.9) as

$$i(a,t) = \begin{pmatrix} \overline{S}(a)\beta(a) & 0 \\ 0 & 1 \end{pmatrix} \int_0^\infty \int_0^\infty \Theta(\alpha,\tau)i(\alpha,t-\tau)d\alpha d\tau \qquad (4.11)$$

To derive the growth rate r, we look for exponential solutions to (4.11), i.e. solutions

of the form:

$$i(a,t) = F(a)e^{rt}$$

where $F(a) = (f(a), f(0))^{\mathrm{T}}$. Substitution into equation (4.11) leads to a relation for the vector $F(a)$:

$$F(a) = \begin{pmatrix} \overline{S}(a)\beta(a) & 0 \\ 0 & 1 \end{pmatrix} \int_0^\infty \int_0^\infty \Theta(\alpha,\tau) F(\alpha) e^{-r\tau} d\alpha d\tau \qquad (4.12)$$

One can show that this operator has a two-dimensional range and that we can re-formulate the eigenvalue relation (see Diekmann & Heesterbeek, 2000, section 5.3.3) as stating that the value of r we are looking for should be such that the dominant eigenvalue of the following 2*2-matrix is one:

$$\begin{pmatrix} \int_0^\infty \int_0^\infty \theta_{11}(\alpha,\tau)\overline{S}(\alpha)\beta(\alpha)e^{-r\tau}d\alpha d\tau & \int_0^\infty \int_0^\infty \theta_{12}(\alpha,\tau)e^{-r\tau}d\alpha d\tau \\ \int_0^\infty \int_0^\infty \theta_{21}(\alpha,\tau)\overline{S}(\alpha)\beta(\alpha)e^{-r\tau}d\alpha d\tau & \int_0^\infty \int_0^\infty \theta_{22}(\alpha,\tau)e^{-r\tau}d\alpha d\tau \end{pmatrix}.$$

This leads to an equation for r which can be solved numerically.

From the available data (see Section 3) we find that $\theta_{12}(\alpha,\tau)$ and $\theta_{22}(\alpha,\tau)$ are small relative to $\theta_{11}(\alpha,\tau)\overline{S}(\alpha)\beta(\alpha)$, so the second component of the eigenvector (vertical transmission) will be rather small relative to the first. Therefore we restrict ourselves to the horizontal-infection routes we get a simple relation from which r can be estimated:

$$f(a) = \overline{S}(a)\beta(a) \int_0^\infty \int_0^\infty \theta_{11}(\alpha,\tau)f(\alpha)e^{-r\tau}d\alpha d\tau$$

If we define the operator K_r by the right-hand side of this relation, then r is defined as the value for which $f(a)$ is an eigenvector of K_r corresponding to eigenvalue 1. Note that K_r has a one-dimensional range and $\overline{S}(a)\beta(a)$ is the only eigenvector corresponding to a non-zero eigenvalue. Substituting this into the eigenvalue relation leads to an implicit relation:

$$1 = \int_0^\infty \int_0^\infty \theta_{11}(\alpha,\tau)\overline{S}(\alpha)\beta(\alpha)e^{-r\tau}d\alpha d\tau \qquad (4.13)$$

which can be shown to have a unique solution r, which can be computed by, for example, a Newton algorithm. We will make this restriction for the remainder of this paper.

4.3   Estimation of Parameter values

4.3.1   Demographic parameters

In most developed countries the replacement rate of cattle older than two years is approximately $1/3$ to $1/4$ per year, and rather constant over ages. Young stock are submitted to higher culling rates, about 0.5 per year with peaks in the first half year and at about 18 months. Culling of young stock is normally done to control the size of a local herd, so it depends on both the culling rate of adult cattle and the birth rate.

We assume a constant per capita culling rate per year for cattle older than two years. For the Netherlands that culling rate of adult cattle is $\mu_a = 0.3$ and for the UK it is somewhat lower, i.e. $\mu_a = 0.25$. In cattle younger than two years BSE has rarely been detected (0.002%) and therefore this age group is supposed to hardly contribute to the spread of the infection. Thus, the precise shape of the survival function up to two years old is of minor importance. We simplify the culling rate of young stock to a constant, μ_y. Cattle reproduce from two years of age onwards, and produce on average one calf per cow per year ($b = 1$). Assuming a constant population size and stable age distribution, the fraction $\mathcal{F}_s(2)$ of cattle surviving until at least two years of age can be calculated as the adult culling rate (μ_a) divided by the birth rate b, since $b\mathcal{F}_s(2)/\mu_a$ should equal one, at a constant population size. Thus we estimate the culling rate of young stock (μ_y) from $\mathcal{F}_s(2) = e^{-2\mu_y} = \mu_a/b$. In summary, we use:

$$b(a) = \begin{cases} 0 & \text{if} \quad a < 2 \\ 1 & \text{if} \quad a \geq 2 \end{cases}$$

$$\mu(a) = \begin{cases} 0.55 & \text{if} \quad a < 2 \text{ in NL} \\ 0.3 & \text{if} \quad a \geq 2 \text{ in NL} \end{cases}$$

$$\mu(a) = \begin{cases} 0.6 & \text{if} \quad a < 2 \text{ in the UK} \\ 0.25 & \text{if} \quad a \geq 2 \text{ in the UK.} \end{cases}$$

4.3.2   Probability of becoming infected

Recently, various models (e.g. [60]) for the infectious behaviour of prions were developed, generally involving polymerization of prions and giving very plausible explanations of some features found in infectious load development and dose response relations. We will focus on one of the simplest models for infection, assuming that BSE infection is spread by many small infectious particles (prions or small clusters of prions), which all have an extremely low probability p to induce infection (single hit theory). This leads to the following dose-response relation: (See also [45])

$$\text{response} = 1 - (1 - p)^{\text{dose}} \tag{4.14}$$

Here response is defined as the probability for an animal to become infected by the dose of infectious material ingested (expressed in grams of brain material) and this is estimated from the fraction of animals that respond (get infected) in a bioassay. Because p is very small, this relation can be approximated by:

$$\text{response} = 1 - e^{-p \cdot \text{dose}} \tag{4.15}$$

For different amounts of infectious material ingested (dose) we visualized this relation in Figures 1. Using (4.14), we analyzed titration data from mouse bio-assays of Taylor [79],[78] and Schreuder et al. [75] for the effect of heating and rendering on prion survival. Generalized linear modelling (GLM, see [61]) with a binomial distribution and a complementary log-log link function is applied to the data using GENSTAT v5, which estimates the constant p and its standard error. Our results are generally the same as the original analysis with the Kärber method, with this differencem that the latter expresses the results in terms of ID50, i.e. dose that is infectious for 50% of a test group.

This dose response relation is also used to describe the transmission of the infection in the population. In the population the incidence of BSE is generally low and infectious contacts are spread widely over the population due to the processing steps of MBM-rendering, feed processing and feed distribution. Therefore, the infectious dose per individual animal will remain low. For low individual dose, the dose response relation can be linearized, which leads to a constant probability for each particle to induce infection:

$$\text{response} = 1 - e^{-p \cdot \text{dose}} \approx p \cdot \text{dose}$$

dose as the amount of infectious material, that is expected to induce one new infection

in a population. In the linearized model, it does not matter whether this material is spread over one herd or a hundred herds, it is still expected to induce one new infection. If such an infectious dose unit would be fed to one animal (relatively high dose), the linearization of the model is not valid any more, in that case the probability of infection for that one animal is estimated from the above to be 63%.
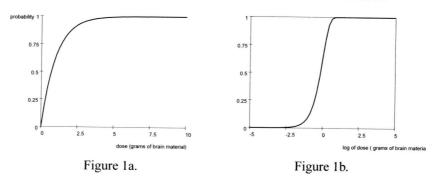

Figure 1a.   Figure 1b.

Figure 1. Dose-response curve for TSE's on a lineair (1a) and on a logarithmic scale, i.e. titre (1b).Next we define the unit of infectious

4.3.3   Infectious load in the animal

The infectious load of an infected animal is assumed to increase exponentially during the infectious period, as there is no knowledge of any inhibiting immune reaction to the BSE agent. Infectious load means the amount of the infectious agent that accumulates in the infected animal in time. Dose-incubation time analysis for cattle yields a shortening of the incubation time by 22 weeks for a 10 times higher dose, which suggests a doubling time of the infectious agent of about 6 weeks (oral exposure experiment, unpublished data from VLA, Weybridge, UK). Thus, assuming a doubling of BSE infectiousness over 6 weeks time (i.e. 0.12 year), we estimate and use a growth rate of the infectious load of 6 per year.

The oral infectious dose for cattle of 4 months old was estimated from the same oral exposure study which consists of 4 groups of 10 cattle (unpublished data, VLA), using the previously described dose response analysis. Analysis with the dose response relation as suggested above yields an estimated oral infectious dose unit of 1.9 grams of brain material of a cow with clinical BSE symptoms (equaling an ID50 of 1.3 grams). An average brain weighs 600 to 800 grams and the spinal cord weighs about 250 grams. Other parts of the carcass contain a very small infectious load compared to these parts. This leads to an estimate of the total infectious load of a BSE infected

cow in the last stage (when clinical BSE signs have developed and τ can be assumed 4.5 years) of about five hundred infectious dose units.

The infectious load as a function of infection age, can be derived by calculating backwards from the infectious load at the time clinical symptoms show ($\tau = 4.5$ years) and using an exponential growth rate of 6 per year:

$$\gamma(\tau) = 10^{-9}e^{6\tau} \qquad (4.16)$$

4.3.4 Other infection related parameters

We assume that cattle of all ages receive equal amounts of feed. The exact shape of the decreasing function that describes the age-dependent susceptibility is not known. We assume an exponential decrease to 10% of the susceptibility of 4 months old cattle and a relative rate of decrease of 2 per year. The susceptibility of calves of 4 months old is by definition equal to 1, and the age dependent susceptibility of cattle is given by (Figure 2):

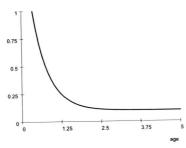$$\beta(a) = 0.1 + 1.8 \cdot e^{-2a} \qquad (4.17)$$

Figure 2. Age dependent susceptibility of cattle for BSE, relative to the susceptibility of a four months old calf.

We assume that clinical signs of BSE (and thus also the infection-age dependent culling rate) increase with the infectious load of a cow. At present in the UK, farmers and veterinarians will be more experienced in recognizing BSE than before 1990. Before 2000 most other countries were as unexperienced as Britain was in the early stage of the epidemic. We estimate the average infection age of clinically diagnosed BSE cattle (incubation period) at 4.5 years for the UK since 1989 and in other countries as well as in the UK prior to 1989, diagnosis is assumed a few months later, 4.8 years.

Given an average incubation period of 4.5 and 4.8 years, we determined the infectionage dependent culling rate (per year) as:

$$\nu(\tau) = \begin{cases} 10^{-12}e^{6\tau} & \text{UK since 1990} \\ 5 \cdot 10^{-12}e^{6\tau} & \text{otherwise (Figure 3)} \end{cases} \qquad (4.18)$$
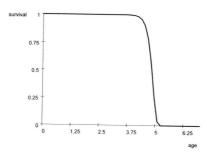

Figure 3. survival function of BSE infected cattle, when culling will be limited to clinical BSE.

To model the feed infection route we have to follow the infectious material from the infected animal up to the moment of new infection and estimate the reduction of infectivity in each step in the material, by keeping track of the total infectious load. For animals which were culled without signs of a neural disease (even though they may have been infected), the normal slaughter process will be applied. The fraction of the infectious load of a cow that enters the rendering process is called c_1. For the UK before 1989, it was estimated that almost 70% of the infectious material (mainly brains and spinal cord) of a beef carcass entered the rendering process ($c_1 = 0.7$, Table 1). Animals which were culled due to signs of a neural disease, may have been treated differently. For these animals we assume a fraction c_2 of the infectious load of a cow entering the rendering process. Before 1987, BSE was not recognized as such. About 50% of cattle with neural diseases was not used for human consumption and was therefore fully rendered, therefore we assume c_2 to be slightly higher than c_1: 0.85 (Table 1).

The reduction of infectious load during the process of rendering, k_1, is determined in mouse bioassays. Taylor et al. ([79],[78]) tested a continuous vacuum rendering process with high fat content, which was commonly used in the UK since the 1970s. Schreuder et al. ([75]) tested several different treatments to quantify the efficacy of various rendering processes in TSE reduction. He found similar results for the at-

mospheric process and also quantified processes as applied in the Netherlands (see Table 1).

Next, from the total amount MBM that is produced from the rendered cattle material, a fraction of about $k_2 = 0.20$ is used in the production of cattle feed, whereas the major part is used in pig, pet and chicken feed. These species are far less susceptible to the BSE agent than cattle (there are only a few reports of cats infected with TSE), and this is considered to be a dead end route for the spread of the infectious agent among cattle.

parameter	UK 1986	UK 1991	UK 1995	UK 1998
k_1	0.1	0.1	0.1	0.1
k_2	0.2	0.02	0.005	0.002
c_1	0.7	0.05	0.05	0.01
c_2	0.85	0.05	0.05	0.01
$\nu(\tau)$	$5 \cdot 10^{-13}e^{6\tau}$	$10^{-12}e^{6\tau}$	$10^{-12}e^{6\tau}$	$10^{-12}e^{6\tau}$

parameter	NL 1986	NL 1991	NL 1995	NL 1998
k_1	0.01	0.01	0.001	0.001
k_2	0.2	0.1	0.01	0.005
c_1	0.7	0.7	0.7	0.05
c_2	0.85	0.85	0.85	0.05
$\nu(\tau)$	$5 \cdot 10^{-13}e^{6\tau}$	$5 \cdot 10^{-13}e^{6\tau}$	$5 \cdot 10^{-13}e^{6\tau}$	$5 \cdot 10^{-13}e^{6\tau}$

Table 1. The parameter estimates underlying the estimate of R_0.

Table 1 gives an overview of the parameter values, that were separately estimated for the UK and the Netherlands. These estimates were made in four different time periods, 1986, 1991, 1995 and 1998. In 1986, BSE control was unknown, differences between countries lie only in the rendering and feeding methods: UK uses low temperature atmospheric systems whereas in the Netherlands mostly pressurized high temperature methods were applied (different value of k_1). Before 1991 both countries introduce a ban to feed MBM to ruminants (reducing k_2) and in the UK specified risk materials, SRMs, are defined and removed to be incinerated (reducing c_1 and c_2). In the period between 1991 and 1995, the feedban is extended and inspection for compliance with the ban follows, leading to a further reduction of k_2. Furthermore in the Netherlands rendering temperatures and pressure are slightly increased (EU regulations affecting k_1) and in the UK clinical diagnosis improves ($\nu(\tau)$). Between 1995

and 1998, especially in the UK inspection into compliance with all bans is extended and risk of cross-contamination becomes clear, leading to separate production lines and flush batches (further reducing k_2). In the Netherlands the SRM removal is introduced, reducing c_1 and c_2.

A maternal transmission study [30] gives an estimate of 10% $\pm5\%$ maternal transmission when a cow gives birth at the highly infectious last stage of the infection (when the infectious load $\gamma(4.5)$ is estimated at 2000 infectious dose units, see the previous). Maternal infection is assumed to be lower for cows in earlier stages of the infection, according to the infectious load $\gamma(\tau)$ of the mother. With this information we estimate the maternal transmission rate for a calf (relative to the mothers infectiousness): $m = 0.1/\gamma(4.5) = 0.1/2000 = 0.5 \cdot 10^{-4}$.

The last parameter that remains to be estimated is very difficult to quantify. It describes the combined transmission rate for direct horizontal contact infection, ω_h, diagonal infection, ω_d and indirect infection via the environment, ω_i. These three parameters can not be estimated separately from any data presently available, so we cluster them into one parameter ω. The following argumentation leads to a quantification of this parameter.

During the initial stage of the outbreak in the UK, these "other" transmission routes were negligibly small compared to the feed infection route. However, when infection via the feed infection route is minimized, due to the feed and SRM bans, ω may become visible in the development of the epidemic. It can explain why it has been impossible to bring BSE transmission to a complete stop immediately. The parameter was estimated from the observed data of infections after the feed ban (new cases during 1993 until 1997). Assuming that the feed infection route was fully closed in that period, we estimated backwards from the exponential decay rate of the epidemic at that time (using (4.13) and Figure 6) that ω is at most $3 \cdot 10^{-4}$.

Thus we derive a maximum estimate for ω, knowing that the feed ban was certainly not fully effective between 1990 and 1996. In the mean time we neglect a part of the environmental infection route, by only looking at short-term survival (in the order of months) of the material in the environment. Given enough time, infectious material will flow away from the soil with the rain and ground water, so this appears to be a reasonable assumption. Such infectious material may finally accumulate in lakes, seas and oceans where it is presently assumed to be harmless.

4.4 Quantifying R_0

4.4.1 Estimates

R_0 (upper 95%)	1986	1991	1995	1998
UK	14 (25)	0.1 (0.3)	0.05 (0.1)	0.03 (0.1)
NL	0.7 (1.3)	0.2 (0.5)	0.08 (0.1)	0.05 (0.1)

Table 2. Estimated reproduction ratio R_0 for the United Kingdom (UK) and the Netherlands (NL), during different periods depending on the implemented control measures. Numbers between brackets are the upper boundary of the confidence interval (alpha = 0.95), see section on sensitivity analysis.

Table 2 shows estimates of the reproduction ratio R_0 for the UK and the Netherlands over the last two decades. The impact of the first control measures, such as feed and SRM bans can clearly be seen in the strong decline of R_0. Later measures had little impact. The reproduction ratio was estimated to be below one in the Netherlands even before introduction of control measures. Therefore, a BSE epidemic was not to be expected. The difference in R_0 with the UK is almost completely due to differences in the rendering processes between these countries, affecting k_1 (see also Table 1). That the Netherlands actually still finds BSE cases in the indigenous population is mainly due to large imports of risk material and live animals. Since then very slow fade out of the infection started, but total eradication is not expected within another 5 to 10 years, depending especially on the level of infection via non-feed routes. Figures 4-6 show the development of the epidemic in these periods.
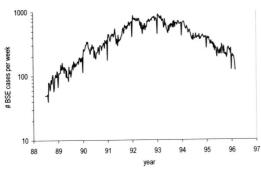

Figure 4. Increase and decrease of the number of new BSE cases per week during the outbreak in the United Kingdom.
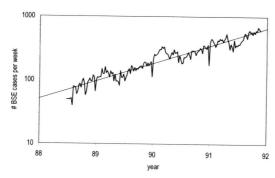
Figure 5. Linear regression on the data of the BSE outbreak from June 1988 until December 1991
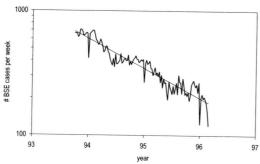

Figure 6. Linear regression on the data of the BSE outbreak from October 1993 until march 1996.

From the model, the growth rate of the infection was estimated at $r = 0.58$ per year in the initial exponential phase of the epidemic in the UK. Using linear regression on the case data from the beginning of 1988 (when reporting levels stabilized) up to halfway 1991, we find that the growth rate $r = 0.64$. For the decreasing phase of the epidemic, the data (end 1993 to beginning 1996) lead to an estimated growth rate of $r = -0.53$ per year.

In the UK, introduction of a feed ban and SRMban (ban on the use of SRMs in the rendering process) reduced the reproduction ratio from 14 to 0.1, a 100 fold reduction. Application of an initial feed ban in the Netherlands reduced the local reproduction ratio only about 10 fold. Later extensions on the feedban led to further decrease of R_0. In 1997 the Netherlands also introduced an SRMban, but at that point the impact was rather small because the feed infection route had already become small compared to the remaining infection routes.

4.4.2 Sensitivity analysis and confidence interval

The quality and accuracy of the estimate of R_0 depends heavily on the quantification of the ingredients. Whenever modelling and quantification are combined, one of the more difficult issues to deal with is the confidence interval associated with the estimated or calculated results. Due to high uncertainty in some of the parameter estimates in this study, the ensuing uncertainty in the estimated reproduction ratio is possibly high and we need to quantify this more precisely. We determine a 95% confidence interval from the known variance of the parameters for the model with the restrictions and assumptions as mentioned before. A good choice for the distribution of the uncertainty of the parameters and of the R_0 estimate are important for the final result. In constructing methods to quantify the variance of R_0, we distinguish transmission via food, and other transmission routes.

For the feed infection route the analysis is explained in detail below. For the other infection routes, little information is available, and we restrict ourselves to determining an upper 95% confidence level, leaning on the assumption that the highest possible value of the reproduction ratio through non-feed routes is equal to the lowest reproduction ratio to be determined from the data. This is estimated at $R_0 = 0.1$, and $r = -0.5$ which fits with the negative growth rate estimated from the case data between 1994 and 1996. We therefore determine the upper boundary of the 95% confidence interval for non-feed infections at 0.1. The total variance of the estimator is the sum of the variances of the two parts, and thus, the upper confidence boundary cannot get below 0.1, but can be (much) higher if the feed transmission route is non-zero.

For the calculation of q_{11} the estimates of infectious load, $\gamma(\tau)$ and the efficacy of the rendering process, k_1 are the most uncertain ingredients. This does not imply that R_0 is most sensitive to these ingredients. One could use e.g. latin hypercube sampling to determine the contribution of all ingredients to the uncertainty in R_0. Here we have chosen to analyse uncertainty only with respect to $\gamma(\tau)$ and k_1. These two factors are estimated using generalized linear modelling on titration of infectious material in cattle ($\gamma(\tau)$) and mice bio-assays (k_1). The efficacy of the rendering process is determined by titration of material before and after treatment. The high uncertainty in these parameter estimates is due to the limitation in the number of test animals. For k_1 the material before and after a rendering process needs to be analyzed, bringing two such parameters into the equation. Those parameters derived from the bio-assays are here denoted as $\widehat{x_i}$. Given the structure of q_{11}, we assume that:

$$\widehat{R_{feed}} = f(\widehat{x_1}, \widehat{x_2}, \widehat{x_3}) = c\frac{\widehat{x_1 x_3}}{\widehat{x_2}} \tag{4.19}$$

We will estimate the ensuing variance of $\widehat{R_{feed}}$, from the variance of the estimators $(\widehat{x_i})$. From the bioassay results the titre (10 log(dilution)) of the original material is determined. We assume a normal distribution for the titre with expected value μ and variance σ^2. Then the estimated infectious dose $\widehat{x_i}$ of that material follows a lognormal distribution. The expected value and variance of R_{feed} (for which we also assume a lognormal distribution) can then be analyzed as follows (see [53]):

$$E(x_i) = e^{(\mu + \frac{1}{2}\sigma^2)}$$

and

$$Var(\underline{x_i}) = e^{(\mu + \frac{1}{2}\sigma^2)}(e^{\sigma^2} - 1)$$

For independent variables x_i we know that

$$Var(\ln R_{feed}) = Var(\ln x_1) + Var(\ln x_2) + Var(\ln x_3) \qquad (4.20)$$

Now, using

$$Var(\ln x_i) \simeq \ln\left(1 + \frac{Var(x_i)}{E(x_i)^2}\right) \qquad (4.21)$$

we derive

$$Var(\ln R_{feed}) \simeq \ln\left(1 + \frac{Var(x_1)}{E(x_1)^2}\right) + \ln\left(1 + \frac{Var(x_2)}{E(x_2)^2}\right) + \ln\left(1 + \frac{Var(x_3)}{E(x_3)^2}\right)$$
$$(4.22)$$

which can be calculated from the data. Finally using (4.21) and (4.22) we derive the variance of R_{feed}

$$Var(R_{feed}) \simeq E(R_{feed})^2 e^{(Var(\ln R_{feed}) - 1)} \qquad (4.23)$$

The rules as explained above are applied to calculate the upper boundary of the 95% confidence interval as given in table 2.

4.4.3 Choice of functions/curves

The use of a different function for the age-dependent susceptibility may lead to very different results, especially for a cattle population with a rather unusual age distribution. We tested whether constant susceptibility over all ages would be a reasonable

assumption, but from the decreasing BSE prevalence at older ages (over 7 years) it is clear that this model does not fit the observed distribution in the UK so we did not calculate the effect on R_0. Infection only at birth or very young age would fit the data rather well, if the incubation period has a very long tail to the right, but that effect on R_0 is minimal (3 % at most). The assumed susceptibility curve of formula 25 results in a good fit with the data. From the data it is not yet possible to make an accurate estimate of the susceptibility as function of age (see also Ferguson et al., [36]).

The estimated R_0 is also sensitive to the age distribution of the cattle population. Extreme age distributions (resulting from very high or very low culling rates) may lead to more than a 10 fold difference in the estimated R_0. However, for the observed cases, UK and Netherlands, realistic variation in age distributions leads to less than 1% differences.

4.4.4   Comparison of the estimated R_0 with field data

The results from the present model can be compared to the observed case data of the UK outbreak. From the model with the parameters set at the estimated values for 1986 (Table 1), we calculate a reproduction ratio $R_0 = 14$ with an exponential increase of infection of $r = 0.58$ per year. From the UK case data, a growth rate of 0.64 ± 0.14 per year is directly estimated by use of linear regression on the logarithm of the number of BSE cases per week, in the period between the beginning of 1988 (when reporting levels stabilized) and mid-1991 (after which exponential increase slows down due to control measures). Cases in this period are born before the feed ban, and are therefore considered to be representative for the development of the epidemic without the ban. Thus, the model slightly underestimates the growth rate and the reproduction ratio of the infection in the UK in the 1980s, but the model result for the growth rate still lies within the confidence interval of the growth rate estimated from the field data. Ferguson et al. [37] quantify R_0 from a data driven model, and estimate it between 10 and 18 between 1983 and 1988, with some variation over the years. Valleron et al. [81] estimate a growth rate of 0.6 per year. All these estimates lie easily within our confidence interval (see below) and thus support our quantification.

The measured growth rate $r = 0.64$ can be mimicked with the model by calibrating some of the more uncertain parameter estimates, such as k_2. Such a calibrated model gives an estimate of R_0 equal to 19, leading to a good fit of the model to the observed UK data. However, given that it is unclear which parameters should be calibrated, in this paper we restrict ourselves to the original parameter estimates to quantify R_0.

4.5 Discussion

This paper describes the calculation of R_0 and r for BSE, where all ingredients are based on proposed underlying mechanisms of infection or estimated from data. A problem in modelling BSE (and other TSEs) is that much of the behaviour of the infectious agent is still unknown or uncertain. Some assumptions made in our calculation have a substantial influence. Especially the behaviour of the infectious agent according to the 'single hit theory' and to a lesser extent the exponential increase of the infectious load in an infected individual. Existence of a minimal infectious dose or polymer formation by prions will affect the transmission of BSE, and if proven, should lead to more accurate calculation of R_0. The single hit theory must be seen as a worst case scenario.

The confidence interval of the estimated reproduction ratio R_0 is wide, due to high uncertainty, especially in parameter values estimated from infectious dose quantification by bioassay. The estimate of k_1, the reduction of infectious load by the rendering process, also shows a high standard error. When, in the future, more advanced and precise tests are developed to measure the concentration of the infectious agent, the uncertainty in this factor may be reduced.

In our calculation we ignore spatial aspects of the infection, so local clustering of BSE cases, as observed in the UK data, is not explained in this model. Hagenaars et al. [41] give a nice overview of some spatial features of the BSE epidemic. It remains to be seen in how far ignoring clustering will affect our calculations. We also ignore infection of other species than cattle, and long-term persistence of infection in the environment. Although these two factors are worrysome for the future, they are unlikely to have a strong influence on the short-term analysis of the effect of BSE control.

We assessed the effect of different control measures and find that there are three major control measures: a feed ban on MBM to cattle, optimization of the rendering process and SRM removal and incineration. In most cases, to reduce R_0 below 1, it suffices to apply two of these measures, but faster reduction of the problem will be obtained by adding further controls. When the compliance to the control measures is difficult to maintain as was the case in the first decade of controlling the infection, extra measures should be taken to ensure fade out of the epidemic.

When these control measures are sufficiently in place, infection routes other than via feed will become the major remaining transmission routes. These remaining transmission routes will be much harder to control, and therefore, the reproduction ratio cannot be reduced to zero. However, the remaining transmission routes are definitely

too small to cause a major BSE epidemic, and under some basic control measures a decrease of 50% per year can easily be achieved. The maximum estimate of the reproduction ratio without feed transmission is 0.06, which leads to fast decrease of the number of BSE infections.

We conclude that countries which had a rather inefficient rendering industry with respect to BSE inactivation and where farmers tended to feed large amounts of MBM to cattle are presently at high risk concerning BSE in their cattle herd. Especially when such countries also imported cattle and/or MBM concentrated feeds from the UK. Countries with a rather efficient rendering and with low amounts of MBM in their cattle feed can expect a very low BSE prevalence, if at all.

Countries with a high BSE prevalence should close the feed infection routes as much as possible, thus minimizing the reproduction ratio and the growth rate, leading to a fast decrease of infection and disease. When the prevalence has become very low, these control measures may be relaxed, but these countries must be more careful in this respect than other countries, because of the unknown long-term survival of the infectious agent in the environment.

Chapter 5

Analysing BSE transmission to quantify regional risk

Aline de Koeijer

Abstract

Recently, due to consumer fears and political worries concerning BSE as a possible threat to human health, a need arose for more sensitive methods to detect BSE and more accurate methods to determine BSE prevalence. As a part of that, it is important to pinpoint groups in which BSE risk is higher. One of the well known risk factors for BSE is age, very young animals do not develop the disease, and very old animals are less likely to develop the disease. We analyse which factors have a strong influence on the age distribution of BSE in a population. In a next step, we develop a system to easily calculate the (risk of) BSE prevalence in a population. Data on imports and on the BSE control level over the last ten or twenty years are the required input data.

5.1   Introduction

The presence of BSE in the European cattle population led to decreased beef consumption in the late nineteennineties. Clearly consumers worry about the possibility that material from infected cattle may induce a new variant of Creutzfeld Jacob, a fatal and incurable disease in humans. For proper assessment of the human risk per region, it is important to estimate the local prevalence of BSE. This is not easy, because the infection can spread among cattle unnoticed for several years, as the disease develops very slowly, and early clinical symptoms are various and difficult to diagnose, especially by unexperienced people. This difficulty to diagnose can lead to major underreporting of the disease, as was shown to have happened in the UK and Switzerland in the beginning of their respective outbreaks. It has by now become clear that several European countries had BSE circulating in their population while still claiming freedom from the disease.

Especially in countries where few or no BSE cases are reported so far, active surveillance is far more effective than passive surveillance (mandatory reporting of clinical suspects) to assess the apparently low or zero prevalence. If the prevalence of BSE is low, large numbers of animals need to be tested to establish and quantify it. The number of tests could possibly be reduced if there would be a good method to focus on specific risk groups in the population and, thus, design an optimal surveillance program. Indeed, targeting of surveillance to specific risk groups may reduce the sample size needed to determine the prevalence of BSE, and if, according to a reliable risk assessment, there is negligible risk, this can be a good reason to refrain from an intensive surveillance program.

Doherr et al (1999) showed that, in Switzerland, BSE is found with a higher probability in fallen stock (5 times higher) and emergency slaughter (4 times higher), than it is in the normal slaughter line. Biased sampling from groups with higher risk can increase the sensitivity of a surveillance system. Thus, surveillance could be improved by concentrating on the fallen stock and emergency slaughtered animals. Quantitatively, this risk pattern is established for Switzerland. Relevant other information can be derived from the routine testing of all slaughter animals over 30 months and of some part of the fallen stock, which most EU countries started in 2001, confirms the higher BSE prevalence in fallen stock and emergency slaughter animals. However, given that large differences between countries have appeared, a more subtle method to extrapolate to other countries may be needed.

General patterns in the age distribution of BSE cases, as resulting from the local cattle population structure and from the local measures in BSE control are analysed

in DeKoeijer et al 2002. Here we will show in more detail how to develop a model to analyse such patterns and the effect of changing BSE control conditions over time. Using the available information on development of the infection, focussing specifically at regional conditions, and including information on import of risk animals and infectious material in the past, we strive for a good risk assessment of the infection. However, to do so, several difficult steps in modelling and calculation need to be made. In this paper, we introduce a basic deterministic BSE transmission model, which is then transformed into a rather simple calculation system, based on discrete time steps. This calculation system can be used to make a quantitative regional BSE risk assessment, that requires rather simple and straightforward input information. It also offers options to analyse the age distribution of detected BSE in a cattle population and evaluate the quality of historical information on import or control conditions from that. The results can be used to support discussion on trade safety, and can be applied to further target the BSE surveillance to a smaller group of cattle with relatively high risk of BSE.

5.2   Age Structured Model

According to basic theory, the number of new infections at some point in time depends on the infection pressure at that moment in time. The number of individuals suffering from the disease depends on the number of infected individuals some time ago (i.e. the incubation period ago); the precise dependence has to take account of processes like survival of the infected individual, see Diekmann and Heesterbeek (2000) [24]. For very slowly developing diseases like BSE, the delay introduced by the incubation period has a major impact on the prevalence of the infection in specific age groups.

In de Koeijer et al 2002 [14] it is shown that the age distribution of BSE cases is influenced by life history parameters of the population; for instance, a high culling rate of cattle leads to a lower average age of BSE cases. The control history also has a high impact; a region with bad BSE control measures will find BSE cases with a lower age (on average), than a region with good BSE control measures. This all follows from straightforward age structured modelling of the dynamics of the infection. However, a few important features are ignored in [14]. (1) the fact that conditions can change over time: most EU countries have introduced many new control measures over the last 15 years. (2) the lack of suitable input data.(3) the fact that cattle can become infected at an advanced age (preliminary results of Wang et al. [83]). Most of these features can be incorporated in a more careful mathematical formulation. We aim at a model that describes the number of BSE cases over time and age, based on parameters concerning

typical BSE cattle interactions, survival of cattle, and impact of BSE control measures.

We model the infection deterministically and assume that the fraction of susceptibles in the population remains close to 1. We define a BSE case as an animal that would give a positive result if tested for prions, and denote the number of BSE cases at time t by $c(t)$. New infections induced at time t will be referred to as $n(t)$, the infection cohort of time t. Assume a simple model with a fixed incubation period τ^*, where the animals will die as a result of the disease after the incubation period. In this case, the normal survival of cattle (not influenced by the disease), denoted by $\mathcal{F}(\alpha)$, determines which part of this infection cohort will live sufficiently long to become cases later on (for more details see Diekmann and Heesterbeek [21]), so

$$c(t) = n(t - \tau^*)\mathcal{F}(\tau^*). \qquad (5.1)$$

Animals in early stages of BSE infection hardly contribute to the transmission of BSE, so for practical purposes we neglect their contribution and assume that the infectiousness is concentrated in a very narrow time window centred around the moment when disease symptoms show. Therefore, $n(t)$ is proportional to $c(t)$, say $n(t) = \theta c(t)$. Combining this with (5.1) we obtain

$$c(t + \tau^*) = R_0 c(t), \qquad (5.2)$$

where R_0 is the basic reproduction ratio of the infection, given by $R_0 = \theta\mathcal{F}(\tau^*)$. In the context of BSE, we find that θ is actually time dependent, since behaviour and control measures are changing in the course of time. Here it is also relevant to realise that in general θ is mostly influenced by the major transmission route, i.e. transmission via cattle derived meat and bone meal (MBM) in cattle feed. Other factors also influence R_0 but are assumed to be small compared to the above. When R_0 is constant, the model in (5.2) is straightforward. When R_0 varies over time, strictly speaking we cannot interpret $R_0(t)$ as a reproduction ratio since the very concept doesn't make sense when environmental conditions change with time while generations overlap. In this paper we will make the more specific assumption that $\mathcal{R}(t)$ denotes a quantity that relates the number of cases at time t, to the number of cases in animals that got infected at time t and will become cases at time $t + \tau^*$. More specifically this means that

$$c(t + \tau^*) = \mathcal{R}(t)c(t). \qquad (5.3)$$

The BSE case data from the UK ([84]) indicate that infection mostly occurs at very

young age but cases display a large variation in the incubation period. Therefore, we extend the basic model into a very simple age structured model by adding a variable incubation period while assuming that BSE infections start at the birth of an animal. As a consequence, the length of the incubation period coincides exactly with the age of the case. Let $g(\tau)$ denote the probability density function of the variable incubation period τ. Note that the distribution of the incubation period of cases detected in the population will generally differ from $g(\tau)$, due to a lower probability for animals with a long incubation period to survive until the onset of the disease. We will now distinguish cases according to the variables time and age and define the relation between cases in the past and future by:

$$
\int_0^\infty c(t + \sigma, \sigma)d\sigma = \mathcal{R}(t) \int_0^\infty c(t, \tau)d\tau. \qquad (5.4)
$$

Here $c(t, \tau)$ is the number of cases at time t, with infection age τ. Then $\int_0^\infty c(t, \tau)d\tau$ is the number of cases at time t, while $\int_0^\infty c(t + \sigma, \sigma)d\sigma$ corresponds to all cases that became infected at time t. Previously, we saw that R_0 consisted of a time dependent factor $\theta(t)$ and survival $\mathcal{F}(\tau^*)$. With a variable incubation period, the survival influence is given by the average survival of a BSE case $\int_0^\infty g(\tau)\mathcal{F}(\tau)d\tau$. When quantifying the value $\mathcal{R}(t)$ from information on feeding patterns, population data and BSE control, the moment that these ingredients have their impact is important. For $\theta(t)$ this is simple, the effect will be timed around the moment of transmission, i.e. between death of a BSE case and infection of a susceptible young cow through MBM. When the survival function changes over time, it changes during incubation. Therefore, such changes in $\mathcal{R}(t)$ should be analysed using the $\mathcal{F}(\tau)$, that is valid for the birth cohort of time t. In general, the survival function does not depend on time, but major policy changes like the British OTMS (Over Thirty Months Scheme: cattle over thirty months old are not accepted for human consumption) may lead to substantial changes. In such cases carefull specification of the survival function for a given point in time becomes important.

The number of BSE cases at time t is distributed with respect to age. This distribution is influenced by three factors: (1) the distribution of the BSE incubation period as described by g, (2) the survival probability $\mathcal{F}$ which may vary between countries and over time, and (3) the way new infections in the past varied with time, which depends on the local epidemic history. Let k denote the normalisation constant of this distribution (so $k^{-1} = \int_0^\infty g(\xi)\mathcal{F}(\xi)d\xi$). We can now formulate the number of cases

in a cohort by

$$c(t + \tau, \tau) = k\, g(\tau)\mathcal{F}(\tau)\mathcal{R}(t) \int_0^\infty c(t, \xi)d\xi \qquad (5.5)$$

and find that the age distribution of cases at time t, denoted by $h(t, a)$, is given by

$$h(t, a) = \frac{c(t, a)}{\int_0^\infty c(t, \zeta)d\zeta} = k\, g(a)\mathcal{F}(a)\mathcal{R}(t - a)\frac{\int_0^\infty c(t - a, \xi)d\xi}{\int_0^\infty c(t, \zeta)d\zeta}. \qquad (5.6)$$

When $\mathcal{R}(t)$ is constant over time ($\mathcal{R}(t) = R_0$), a stable age distribution will be reached (see for example [21]), where the total number of cases grows (or declines) exponentially over time, with rate r:

$$\int_0^\infty c(t_0 + t, \xi)d\xi = e^{rt} \int_0^\infty c(t_0, \zeta)d\zeta \qquad (5.7)$$

For the method to calculate r, we refer to deKoeijer et al [13]. Substituting (5.7) in (5.6) we find that h is independent of time and given by

$$h(t, a) = k\, g(a)\mathcal{F}(a)R_0 e^{-ra}.$$

Note that the age distribution of the BSE cases displays the growth rate of the infection. An epidemic in a stage of fast growth will display a lower average age of the BSE cases than an epidemic in a stage of slow or negative growth. Real data and predictions derived from these can be found in deKoeijer et al. [14]. Such results can be applied to monitor the efficacy of BSE control measures in a country which recently started testing and has since detected enough BSE cases to determine the age distribution.

An abrupt change in R_0 at time t^* induces an abrupt change in the growth rate. Let r_1 denote the growth rate of the epidemic before change. Then, soon after the change, the age distribution of cases will show a running wave over time, and slowly settle into the new stable age distribution. As before, the age distribution of the older cases displays the growth rate of the infection before change:

$$h(t^* + t, a) = k\, g(a)\mathcal{F}(a)e^{-r_1 a} \qquad \forall a > t \qquad (5.8)$$

For younger cases, the age distribution can be calculated, but it will not immediately settle into the new stable distribution, because the infection pressure is changed

abruptly due to the new $\mathcal{R}(t)$, but the number of cases after change will still grow with the old growth rate for a while, because they are already incubating. It may take many years before the new age distribution will be visible in the case data. When $\mathcal{R}(t)$ is constantly changing, the model (Formula (5.6)) has to be applied to predict or analyse the age distributions that will appear in the data.

It is suspected that, although young cattle are far more susceptible, adults are also susceptible to the infection. Neglecting the low susceptibility of older cattle may not be warranted to answer some specific questions which involve the infection age. Therefore we introduce a variable age at infection, which is influenced by age dependent feeding and age dependent susceptibility. Let $f(\alpha)$ denote the probability density function for the age at infection by BSE in a test group of cattle with a uniform age distribution. In a production population of cattle the probability density function of the age at infection is then given (modulo normalisation) by $f(\alpha)\mathcal{F}(\alpha)$, because the lower survival of older cattle influences the effective age at infection. We assume that $g(\tau)$ is independent of the age at which an animal is infected.

Under this extended model, the incubation period is no longer the same as the age of a case. Formula (5.5) remains valid, but it can be extended by including the age of the animals separate from the incubation period. Let $\widetilde{c}(t, \alpha, \tau)$ denote the BSE cases at time t that were infected at age α and had incubation period τ. As before, (see Formula (5.4)), $\mathcal{R}(t)$ is defined by the balance of all the cases in an infection cohort and all the cases at the moment that cohort got infected. (An infection cohort is a group of animals that got infected at the same time.)

$$\int_0^\infty \int_0^\infty \widetilde{c}(t+\tau, \alpha, \tau) d\alpha d\tau = \mathcal{R}(t) \int_0^\infty \int_0^\infty \widetilde{c}(t, \zeta, \xi) d\zeta d\xi.$$

Next we derive the age distribution of the cases at time t, $h(t, a)$. New infections are distributed over the age groups according to $f(\alpha)\mathcal{F}(\alpha)$ and as before, the incubation period is distributed according to $g(\tau)\frac{\mathcal{F}(\alpha+\tau)}{\mathcal{F}(\alpha)}$. Thus, the cases at time t, that got infected at age α, and had incubation period τ, are given by

$$\widetilde{c}(t, \alpha, \tau) = \kappa f(\alpha)\mathcal{F}(\alpha)g(\tau)\frac{\mathcal{F}(\alpha+\tau)}{\mathcal{F}(\alpha)}\mathcal{R}(t-\tau) \int_0^\infty \int_0^\infty \widetilde{c}(t-\tau, \zeta, \xi) d\zeta d\xi,$$

where κ is now the normalisation constant for the distribution of the cases over α and τ ($\kappa^{-1} = \int_0^\infty \int_0^\infty f(\alpha) g(\tau)\mathcal{F}(\alpha+\tau) d\alpha d\tau$).

In the case data, the only available characteristics are the time and the age, whereas

the age at infection and the incubation period will not be detectable. Therefore, we denote cases by $c(t, a)$ and find

$$c(t,a) = \int_0^a \widetilde{c}(t, a - \sigma, \sigma)d\sigma =$$

$$\kappa \mathcal{F}(a) \int_0^a f(a - \zeta)\, g(\zeta)\mathcal{R}(t - \zeta) \int_0^\infty \int_0^\infty \widetilde{c}(t - \zeta, \sigma, \xi)d\sigma d\xi d\zeta$$

which, using that $\int_0^\infty c(t.a)da = \int_0^\infty \int_0^\infty \widetilde{c}(t, \sigma, \xi)d\sigma d\xi$, can also be written as

$$c(t,a) = \kappa \mathcal{F}(a) \int_0^a f(a - \zeta)\, g(\zeta)\mathcal{R}(t - \zeta) \int_0^\infty c(t - \zeta, \xi)d\xi d\zeta. \qquad (5.9)$$

The age distribution of cases is then given by

$$h(t,a) = \frac{c(t,a)}{\int_0^\infty c(t, \xi)d\xi} = \frac{\kappa \mathcal{F}(a) \int_0^a f(a - \zeta)\, g(\zeta)\mathcal{R}(t - \zeta) \int_0^\infty c(t - \zeta, \xi)d\xi d\zeta}{\int_0^\infty c(t, \xi)d\xi}.$$

When $\mathcal{R}$ is constant over time (R_0), the system reaches a stable age distribution given by

$$h(t,a) = \frac{c(t,a)}{\int_0^\infty c(t, \xi)d\xi} = \kappa \mathcal{F}(a) \int_0^a f(a - \zeta)\, g(\zeta)\mathcal{R}e^{-r\zeta}d\zeta,$$

which is independent of t.

5.3   Semi-discrete Model

A user of this model needs to specify all the relevant functions in quantitative terms. To facilitate the use of the model by people with little background in mathematics, we should make sure that the specification and the implementation is as straightforward as possible. Given the sort of information that is available in most European countries, the functions $\mathcal{F}(a)$, $f(a)$ and $g(\tau)$ may best be given as step functions with a one year step over time or age. The case data are often presented in statistics clustered by year of detection and by age group. These full-year steps have the advantage that seasonality patterns in the data disappear, and can therefore also be neglected in the

transmission model. Discretizing time into steps of one year brings the model into a form that can be implemented in a spreadsheet, and is therefore easy to apply by the animal and veterinary scientists, who can provide the input information.

Let $C(y, z)$ denote the number of detectable cases in the full calendar year y and having an age of z, when age is expressed in full years. Below we use δ to denote the part of the year that has passed since the first of January and we use ε to denote the time elapsed since the animals last birth day. So $0 \leq \{\delta, \varepsilon\} < 1$ and $\{y, z\} \in \mathbb{N}$. The step function assumption amounts to $\mathcal{F}(z) = \mathcal{F}(z + \varepsilon)$, $g(z) = g(z + \varepsilon)$ and $\mathcal{R}(y + \varepsilon) = \mathcal{R}(y)$.

Given that

$$C(y, z) = \int\limits_{y}^{y+1} \int\limits_{z}^{z+1} c(t, a)\,da\,dt,$$

using formula (5.5) we find that:

$$C(y, z) = \int\limits_{y}^{y+1} \int\limits_{z}^{z+1} k\, g(a)\mathcal{F}(a)\mathcal{R}(t - a) \int\limits_{0}^{\infty} c(t - a, \tau)\,d\tau\,da\,dt.$$

Now replace a and t by, respectively, z plus ε and y plus δ and separate into parts where ε is bigger or smaller than δ.

$$C(y, z) =$$

$$\int\limits_{0}^{1} \int\limits_{0}^{1} k\, g(z + \varepsilon)\mathcal{F}(z + \varepsilon)\mathcal{R}(y + \delta - z - \varepsilon) \int\limits_{0}^{\infty} c(y + \delta - z - \varepsilon, \tau)\,d\tau\,d\varepsilon\,d\delta =$$

$$\int\limits_{0}^{1} \int\limits_{0}^{\delta} k\, g(z + \varepsilon)\mathcal{F}(z + \varepsilon)\mathcal{R}(y + \delta - z - \varepsilon) \int\limits_{0}^{\infty} c(y + \delta - z - \varepsilon, \tau)\,d\tau\,d\varepsilon\,d\delta$$

$$+ \int\limits_{0}^{1} \int\limits_{\delta}^{1} k\, g(z + \varepsilon)\mathcal{F}(z + \varepsilon)\mathcal{R}(y + \delta - z - \varepsilon) \int\limits_{0}^{\infty} c(y + \delta - z - \varepsilon, \tau)\,d\tau\,d\varepsilon\,d\delta.$$

Next we can remove those functions from the integral, which are not dependent on

τ, ε and δ and analyse the remaining integral further.

$$
\begin{aligned}
C(y,z) \quad = \quad & k\, g(z)\mathcal{F}(z)\mathcal{R}(y-z) \int\limits_0^1 \int\limits_0^\delta \int\limits_0^\infty c(y+\delta-z-\varepsilon,\tau)d\tau d\varepsilon d\delta \\
& + k\, g(z)\mathcal{F}(z)\mathcal{R}(y-z-1) \int\limits_0^1 \int\limits_\delta^1 \int\limits_0^\infty c(y+\delta-z-\varepsilon,\tau)d\tau d\varepsilon d\delta
\end{aligned}
$$

The latter integrals cannot be written in terms of $\sum\limits_{i=0}^\infty C(y,i)$ and $\sum\limits_{i=0}^\infty C(y-1,i)$, unless we assume that $c(t,\tau)$ also behaves as a step function over t, i.e. all cases found in year y and with age z are detected with equal probability throughout that year. In that case $C(y,z) = c(y+\delta, z+\varepsilon)$ and we see that $\int_0^1 (1-\delta) \int_0^\infty c(y+\delta,\tau)d\tau d\delta = \int_0^1(1-\delta) \sum\limits_{i=0}^\infty C(y,i)d\delta = \int_0^1(1-\delta)d\delta \sum\limits_{i=0}^\infty C(y,i) = \frac{1}{2}\sum\limits_{i=0}^\infty C(y,i)$. Also using $\int_0^1 \int_0^\delta 1d\varepsilon d\delta = \int_0^1 \int_\delta^1 1d\varepsilon d\delta = \frac{1}{2}$, we find that

$$
C(y,z) = \tag{5.10}
$$

$$
k\, g(z)\mathcal{F}(z)\frac{1}{2}\left(\mathcal{R}(y-z)\sum_{i=0}^\infty C(y-z,i) + \mathcal{R}(y-z-1)\sum_{i=0}^\infty C(y-z-1,i) \right).
$$

Thus, the cases in year y, and having age z are partly born in $y-z$, and partly born in year $y-z-1$.

Obviously, in some cases a discrete version of the extended model can be applied best, so we will also transform the model with a variable age at infection into a semi-discrete model. We use all definitions as given above and already include the assumption that cases develop as a step function over time. Then we use (5.9) and argue as follows:

$$
C(y,z) = \int\limits_y^{y+1} \int\limits_z^{z+1} c(t,a)da\,dt =
$$

$$
\int\limits_y^{y+1} \int\limits_z^{z+1} \kappa\mathcal{F}(a) \int\limits_0^a f(a-\zeta)\, g(\zeta)\mathcal{R}(t-\zeta) \int\limits_0^\infty c(t-\zeta,\xi)d\xi d\zeta dt da
$$

$$C(y,z) = \kappa \int\limits_0^1 \int\limits_0^1 \int\limits_0^{z+\varepsilon} f(z+\varepsilon-\zeta)\, g(\zeta)\mathcal{F}(z+\varepsilon)\mathcal{R}(y+\delta-\zeta) \int\limits_0^\infty c(y+\delta-\zeta,\xi)d\xi d\zeta d\delta d\varepsilon$$

and replace the functions where possible with the discrete values,

$$C(y,z) = \kappa\mathcal{F}(z) \int\limits_0^1 \int\limits_0^1 \int\limits_0^{z+\varepsilon} f(z+\varepsilon-\zeta)\, g(\zeta)\mathcal{R}(y+\delta-\zeta) \int\limits_0^\infty c(y+\delta-\zeta,\xi)d\xi d\zeta d\delta d\varepsilon.$$

Now we can split the right-hand size of the equation for various values of ζ, to obtain functions that can be rewritten in a discrete version. To do so we let $\zeta = x + \phi$, where $x \in \mathbb{N}$ and $0 \le \phi < 1$ and formulate and we split the equation up further into

$$C(y,z) =$$

$$\kappa\mathcal{F}(z) \sum_{x=0}^{z-1} \int\limits_0^1 \int\limits_0^1 \int\limits_0^1 f(z + \varepsilon - x - \phi)\, g(x + \phi)\mathcal{R}(y + \delta - x - \phi)$$

$$\int\limits_0^\infty c(y + \delta - x - \phi, \xi)d\xi d\phi d\delta d\varepsilon$$

$$+ \kappa\mathcal{F}(z) \int\limits_0^1 \int\limits_0^1 \int\limits_0^\varepsilon f(\varepsilon - \phi)\, g(z + \phi)\mathcal{R}(y + \delta - z - \phi)$$

$$\int\limits_0^\infty c(y + \delta - z - \phi, \xi)d\xi d\phi d\delta d\varepsilon$$

Move f and g out of the integrals, and separate the case where $\delta < \varepsilon$, from the case where $\delta > \varepsilon$, which leads to

$$C(y,z) =$$

$$\kappa\mathcal{F}(z)\sum_{x=0}^{z}g(x)f(z-x)\int_0^1\int_0^\varepsilon\int_0^\delta\mathcal{R}(y+\delta-x-\phi)\int_0^\infty c(y+\delta-x-\phi,\xi)d\xi d\phi d\delta d\varepsilon$$

$$+\kappa\mathcal{F}(z)\sum_{x=0}^{z}g(x)f(z-x)\int_0^1\int_0^\varepsilon\int_\delta^\varepsilon\mathcal{R}(y+\delta-x-\phi)\int_0^\infty c(y+\delta-x-\phi,\xi)d\xi d\phi d\delta d\varepsilon$$

$$+\kappa\mathcal{F}(z)\sum_{x=0}^{z}g(x)f(z-x)\int_0^1\int_\varepsilon^1\int_0^\varepsilon\mathcal{R}(y+\delta-x-\phi)\int_0^\infty c(y+\delta-x-\phi,\xi)d\xi d\phi d\delta d\varepsilon$$

$$+\kappa\mathcal{F}(z)\sum_{x=0}^{z-1}g(x)f(z-x-1)\int_0^1\int_0^\varepsilon\int_\varepsilon^1\mathcal{R}(y+\delta-x-\phi)$$

$$\int_0^\infty c(y+\delta-x-\phi,\xi)d\xi d\phi d\delta d\varepsilon$$

$$+\kappa\mathcal{F}(z)\sum_{x=0}^{z-1}g(x)f(z-x-1)\int_0^1\int_\varepsilon^1\int_\varepsilon^\delta\mathcal{R}(y+\delta-x-\phi)$$

$$\int_0^\infty c(y+\delta-x-\phi,\xi)d\xi d\phi d\delta d\varepsilon$$

$$+\kappa\mathcal{F}(z)\sum_{x=0}^{z-1}g(x)f(z-x-1)\int_0^1\int_\varepsilon^1\int_\delta^1\mathcal{R}(y+\delta-x-\phi)$$

$$\int_0^\infty c(y+\delta-x-\phi,\xi)d\xi d\phi d\delta d\varepsilon$$

Now we can simplify $\mathcal{R}$ and c to their semi-discrete versions, and move both $\mathcal{R}$ and summation over c out of the integration. Then the remaining part of the integrals

can be calculated and we find all six of them to be equal to $\frac{1}{6}$. Thus we arrive at

$$
\begin{aligned}
C(y, z) = {} & \frac{1}{3} \kappa \mathcal{F}(z) \sum_{x=0}^{z} g(x) f(z - x) \mathcal{R}(y - x) \sum_{i=0}^{\infty} C(y - x, i) \\
& + \frac{1}{6} \kappa \mathcal{F}(z) \sum_{x=0}^{z} g(x) f(z - x) \mathcal{R}(y - x - 1) \sum_{i=0}^{\infty} C(y - x - 1, i) \\
& + \frac{1}{6} \kappa \mathcal{F}(z) \sum_{x=0}^{z-1} g(x) f(z - x - 1) \mathcal{R}(y - x) \sum_{i=0}^{\infty} C(y - x, i) \\
& + \frac{1}{3} \kappa \mathcal{F}(z) \sum_{x=0}^{z-1} g(x) f(z - x - 1) \mathcal{R}(y - x - 1) \sum_{i=0}^{\infty} C(y - x - 1, i).
\end{aligned}
$$

Thus the semi discrete version of the extended model is also derived. Obviously it is far more complicated than the earlier model, because the sum over all possible ages at infection continuously complicates the model. This system can be very well applied and fully calculated from a given starting situation, and calculations forwards in time are no problem. For calculations backwards in time, this model is less suitable, because of the far more complicated dependence of a new value of C on many others, earlier in time.

5.4 Applications

In the above, we developed several versions of a case cohort model, that relates incidence and infection pressure in the past to incidence and infection pressure in the future. The first, continuous time models (5.5) are exact, given the assumptions on BSE and cattle behaviour, but it is very hard to quantify the various continuous time functions included in the model accurately, unless extra assumptions are included on their general form. The semi-discrete versions of these models overcome such practical problems. They require a limited amount of input, which links well to the type of information that can generally be obtained. The method typically fits the sort of data that can be found in statistics describing a cattle population and their management. But most importantly, the semi discrete model allows for easy use in a spread sheet to calculate the behaviour of a regional cattle BSE situation. Therefore, little is required in terms of computer software to do the analysis, which will be very valuable if there are no mathematicians involved in the risk assessment study.

This paper focusses on deriving an easy-to-apply method for quantitative BSE risk

assessment, with a secondary aim in predicting the age distribution of BSE, which can be used to target age specific surveillance. However, once available, such a model can be applied in many ways. Three typical ways to apply the model are explained here. One way uses the model and case data over a long period of time, to estimate the previous infection pressure, and from that, calculate the historical reproduction ratio in the country. Obviously, this method can only be applied to countries with a sufficiently large number of BSE cases over at least a decade and a good record on the changes in disease notification. The model takes account of the known number of cases, but can only be related to the real number of cases, when a good estimation of disease notification can be made, including its development over time. This method of analysis is very suitable for countries like the UK, Switzerland and Portugal. We will not address this method any further, because similar work has been done with more sophisticated continuous time models, and is explained with much more detail by Donnely and Ferguson [31]. This method can be used to analyse the history of the BSE epidemic in a country and, within limitations, it also allows for forward extrapolation to predict future development of the epidemic. However, for those scientists who would like to do such an analysis themselves, our method is more accessible and easier to apply than those more detailed models.

The other two ways to apply the model are fit for analysing BSE prevalence in countries with few BSE cases. In such countries a case data based model can not be applied, and therefore other available data sources must be analysed to assess the local prevalence. The semi-discrete model can be applied to such countries for two main purposes, prediction of undetected and future prevalence and quantification of parameters.

The model focusses on making a quantitative risk assessment of the BSE prevalence, but at the same time it supplies information that can be used to target the disease surveillance more efficiently and it offers future predictions on prevalence of the infection. The effectivity of present and intended control measures can also be calculated and predicted. This may then be used to support a cost-benefit analysis.

Quantification of parameters can be used to make an analysis of the efficacy of the BSE control over the last few decades. Recent results of active BSE surveillance can be used to calculate the BSE prevalence earlier on. Thus, the efficacy of control measures can be quantified. Control measures can include a feed ban, import ban on live cattle, etc. This method can also be used to quantify disease specific characteristics like the distribution of the incubation period, by applying it to a large data set of BSE cases. (UK case data would be the best.) The extended model is used to quantify $f(a)$ by Wang et al [83].

A disadvantage of the extended model is that it is not easy to apply as a backwards calculation model, but as a forward model it works fine and is hardly more complicated to use. However, we found that the results differ little from the first model that assumes infection at birth. Therefore, the simplest model may be preferred for most problems.

5.5 Example quantitative risk assessment

A quantitative risk assessment for countries with few or no BSE cases can best be built on an analysis of the main risk factors and prevention of import and transmission. The model we have just developed, does not take account of the effect of import or export of infection into and from the population addressed. However, without an initial import, very few countries would have had a problem with BSE. Therefore, the above model on transmission of BSE over time, needs to be combined with the aspects of the (continued) import of risk material.

The European Union has developed a good method to analyse the combination of these two factors in their Geographical BSE Risk assessment, which makes a qualitative analysis of BSE propagation (i.e. transmission), with results ranging from very unstable ($\mathcal{R} > 1$) to a very stable system (little propagation, $\mathcal{R} > 1$). Next, this is combined with the assessed internal challenge (i.e. local prevalence of infection) and external challenge (i.e. import of risk material) into the system each year. Obviously, due to the qualitative level of the assessment, the dynamics of the interactions cannot be incorporated completely, but for rather short term analysis, the method works very well.

We will explain how to extend the simple version of the semi-discrete model to do just that, but quantitatively. (Given the expected accuracy of the input data, it seems that use of the extended model with $f(a)$, will not contribute much to the accuracy of the result, but will complicate the assessment very much.) We start by quantifying all the relevant functions, $g(\tau)$, $\mathcal{F}(a)$ and $\mathcal{R}(t)$, where the last may prove to be quite a big job in most cases (methodology is explained in deKoeijer et al. [13]). To quantify $g(\tau)$, we use the UK case data of a few cohorts as explained in [14] and correct for the age dependent survival of cattle in the UK, $\mathcal{F}(a)$ should be quantified based on the regional statistics and when the extended model is chosen, we need to quantify $f(a)$, which is done best by Wang et al (in prep.)[83]. Analysing the UK data on BSE cases with this model, he estimates that the probability for older cattle to get infected is about 10 times lower than that of calves (0 to 11 months).

Subsequently, risk imports need to be analysed in terms of the expected number

of cases they will induce in the exposed cohort of cattle. Thus we derive a starting distribution of BSE cases, due to the first import of BSE. The expected prevalence of BSE due to imports must be added to the BSE prevalence, resulting from internal BSE transmission and we obtain the following equation. Let $I(y, z)$ denote the expected number of BSE cases per year y, and per age group z, directly resulting from import of live cattle and MBM in previous years. Then we extend equation (5.10) and derive:

$$
C(y, z) =
$$

$$
k\, g(z)\mathcal{F}(z)\frac{1}{2}\left(\mathcal{R}(y - z)\sum_{i=0}^{\infty} C(y - z, i) + \mathcal{R}(y - z - 1)\sum_{i=0}^{\infty} C(y - z - 1, i)\right)
$$
$$
+\, I(y, z)
$$

To determine $I(y, z)$, lots of factors need to be taken into account. For instance MBM imports in year y will lead to cases in the birth cohort of year y, and they will distribute over $I(y + z, z)$ for random z. Imports of live cattle can only lead to direct cases in those imported animals. The age of the imported animals and the purpose of import will affect the distribution of cases over $I(y, z)$. Imports often consist of calfs for slaughter which will lead to a very small import risk, but cattle imported for breeding are mostly 1 or 2 years old and will have a longer life expectance than local stock. Finally, to determine $I(y, z)$ one will need to assess the prevalence of infection in the exporting country, and bearing the previous in mind, then determine the age distribution for cases due to these imports. We refer to the EU-GBR methodology [34] for further details on the many factors that can influence the age distribution of the cases, as it is somewhat beside the scope of this article.

This method for risk analysis has been applied in a quantitative risk assessment of BSE in Norway. A scientific publication of that work is in preparation [51]. We find that this model offers an easy to apply calculation, and find that most of the actual work now goes to assessing the input parameters of the model, but given their straight forward definition, they can be determined within the limits set by the available data. We conclude that a quantitative BSE risk assessment of a country is a major job to fulfill, and note that the reports of the EU GBR are a good starting point for each country that would be interested in applying this method.

5.6 Discussion and Conclusions

We have derived a method of calculation that can be applied to assess regional BSE risk in quantitative terms. Given that it follows the general lines of the European Geographical BSE Risk (EU-GBR) Assessment, it may be of interest to the EU, and to those countries, that want to extend quantitatively on the results of the EU-GBR work. Furthermore, so far, this is the only systematic approach to BSE risk assessment that is suitable for low and zero prevalence countries. Because of the easy-to-apply methodology, it may even be of interest for countries with a lot of cases, as a tool to easily explore the effect of specific control measures and the effect of changing the surveillance programme.

The model has been applied to the Netherlands and Norway [51], and it becomes clear that for optimal accuracy, one actually needs to assess all countries where the imports originate. Fortunately, a quick assessment may suffice, for slightly lower accuracy, but the results of the assessment will always depend on the quality of the assessed BSE risk in other countries. For the Netherlands, this is not so much of a problem when assessing the period up to 1995, because the majority of imports originate from the UK. In the last ten years, imports from Germany dominate the statistics. This should not be a problem, given that their BSE prevalence is presently of the same order of magnitude. However, whereas BSE control in the Netherlands leans a bit more on the quality of the rendering system, the German BSE controls tend to lean a bit heavier on the feed ban. Therefore, MBM produced in Germany used to carry a slightly heavier risk than Dutch MBM, which, through cross-contamination, could still lead to a higher risk of new BSE infections in the Netherlands, a higher risk than in Germany itself. Thus, even imports from countries with similar BSE prevalence may have a negative effect on the BSE risk. Clearly the recent total ban on the use of MBM for all animal husbandry feeds has ended the effect mentioned before. For Norway we found that the very limited imports came from other Scandinavian countries, which all have low to zero BSE prevalence. The risk of BSE being imported in Norway therefore depends very strongly upon the BSE prevalence in those countries. For a good assessment of the BSE risk in any European country, it would be best to assess most other EU countries too. We suggest that a joint European study to quantify BSE prevalence and risk will contribute to the present discussion on the safety of cattle and cattle derived products.

Finally we note that a human BSE exposure assessment must always be based upon a good BSE risk assessment of the cattle population. Therefore, we expect that linking of this model with existing human exposure models that use an estimated

BSE prevalence in the slaughter population can improve the results of those models in making them more accurate.

Chapter 6

Factors that influence the age distribution of BSE cases.

Potentials for age targeting in surveillance.

Aline de Koeijer
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Abstract

Recently, due to consumers fears concerning BSE and vCJD, the need arose for methods to detect BSE, to estimate the present prevalence of BSE among cattle and to predict future BSE prevalence. As a part of that set of urgent questions, it has become important to indicate groups in which BSE risk is higher or lower. One of the well-known risk factors for BSE is age: very young animals do not develop the disease, and very old animals are less likely to develop the disease. Using age structured modelling, three factors influencing the age distribution of BSE were found to be important: 1) the incubation period of BSE, 2) age structure of the cattle population, and 3) the local risk history: methods of rendering, feeding of compound feed containing Meat and Bone Meal (MBM), and the development of BSE control. The EU has considered these three risk factors to be the most important for BSE risk assessment. So far, this EU risk assessment method has been proven right by several countries detecting BSE after being classified as "BSE is most likely present here". The age distribution of BSE seems to vary a lot between countries and regions. When information on these three factors is available, the expected age distribution of BSE in different countries can be calculated. Our calculations show that in countries where, until very recently, the reproduction ratio was high, (i.e.BSE risk factors were high), the BSE prevalence is expected to be highest in 4-year-old cattle. In countries with low reproduction ratio for BSE, (i.e. BSE control at a very high level) for more than 5 years, the prevalence will be highest in the 6- to 8-year-old cattle. Thus, surveillance could be targeted specifically at the age groups with the highest BSE risk. For each country, a short assessment shows in which age group BSE is most likely to be found.

6.1 Introduction

The presence of Bovine Spongiform Encephalopathy (BSE) in the European cattle population led to consumers fear that the eating of food products from infected cattle may induce a new variant of Creutzfeld Jacob (nvCJD), a fatal and incurable disease in humans. Since BSE-infected cattle are still present in the population in Europe, a proper assessment of the risk for consumers has to be made. For an adequate assessment, it is important to estimate the local prevalence of BSE in a region or country. However, the infection can spread among cattle unnoticed for several years, the disease has a long incubation period, and early symptoms are difficult to diagnose, especially by inexperienced people. Therefore, a proper assessment of human risk is difficult to make.

The difficulty to diagnose can lead to major underreporting of the disease, as was shown for the UK and Switzerland in the beginning of their respective outbreaks ([1], [7]), and it is now clear that several countries had BSE circulating in their population while they were still claiming freedom from the disease. Especially in countries where few or no BSE cases are reported, active surveillance appears to be a suitable way to assess the presence of BSE.

For the risk assessment it is necessary to estimate the prevalence of BSE in each country or region. The prevalence is the percentage animals of the population that is BSE-positive. If the prevalence of BSE is low, a large number of animals should be tested to accurately quantify this prevalence. The large number of tests can be reduced if groups with high BSE-risk are identified within the population. Especially if the surveillance is meant to determine whether the infection is present or not, targeting a surveillance program to such high-risk groups can reduce the sample size needed to establish the presence of BSE. An optimal monitoring program can thus reduce the costs without loosing sensitivity. For surveillance to better quantify the prevalence of the infection, the certainty of the risk history parameters must be followed throughout the surveillance, by also analysing some lower risk age groups.

For Switzerland, [27] showed that BSE was found more often in fallen stock and emergency slaughter than during the normal slaughter procedure. This finding indicates that an accurate BSE control surveillance could focus on the fallen stock and emergency slaughter. However, although this pattern is established for Switzerland, and the first results from the slaughter line testing in the EU indicate similar results, it is not yet clear, whether this pattern is the same in other countries. We concentrated on another factor that increases the BSE risk, i.e. the risk of age for developing disease. Analysing the age distribution of BSE in a population will enable more efficient

focusing of the BSE surveillance to certain age groups of cattle, which can reduce the number of sampling and maximises the probability of finding infected animals.

In this paper we explain the use of age-structured modelling to predict the age distribution of BSE in the cattle population. We explore factors that influence the age distribution of BSE and we apply these methods to analyse the expected age distribution of BSE in the Netherlands. Finally we determine the age at which most BSE cases are expected to be found in total and the age with the highest probability per individual animal to show BSE if tested, which is not necessarily the same age.

6.2   Methods: the age-structured Model

6.2.1   Data analysis

Mathematical modelling is very useful in analysing dynamic infection processes in populations. By formulating functions to describe the key dynamic processes in the cattle population and the pathogen-host interaction, the age distribution of cases can be predicted for any sort of conditions.

Basic population dynamical analysis is used to assess the BSE data from the UK epidemic, to make them independent of the local conditions, and fit for extrapolation to other countries. Dr J. Wilesmith of the British Veterinary Laboratory Agencies kindly supplied us with the essential information from their BSE database.

Figure 1

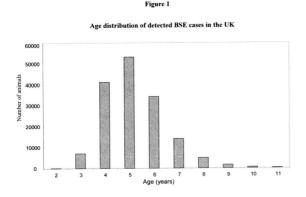**Age distribution of detected BSE cases in the UK**

Figure 1 shows the age distribution of all reported and confirmed BSE cases in the UK until the beginning of 1997. We suspect that local conditions may affect the detailed shape of this distribution, and we will therefore look into more detail at the data. It

can be seen easily from Figure 2 that the age distribution of cases detected in 1988 (Figure 2a) differs from the age distribution of cases detected in 1996 (Figure 2b). Basic age-structured modelling of a BSE infection in a cattle population can explain this characteristic (see also [77]).

Figure 2a

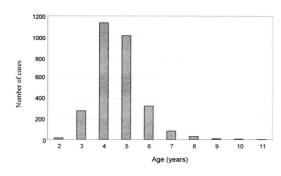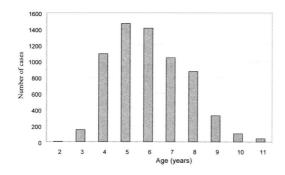**Age distribution of BSE cases in the UK in 1988**

Figure 2b

Age distribution of detected BSE cases in the UK in 1996

6.2.2   Modelling

Two typical characteristics of the population dynamics of the host and pathogen inter-action are expected to appear in this type of data. The first characteristic is the survival of cattle. Very few animals will reach a high age (over ten years). Since BSE has a very long incubation period, animals that are infected with BSE are not very likely to survive long enough to become a clinical BSE case (less than 25% would survive

more than 4 years, given an annual replacement of about 30%). The longer the incubation period, the less likely that the animal lives to develop clinical BSE. Thus, older animals are relatively underrepresented in the case data. Information on the survival and age distribution of cattle in the normal population is essential to correct for this feature.

The second important characteristic is the force of infection, i.e. the probability for an animal in the population to become infected. Generally, the force of infection increases exponentially over time in the early, exploding phase of an epidemic. Thus, it is assumed that the force of infection of BSE in the UK increased more or less exponentially between 1980 and 1988. This is supported by the exponential increase in BSE cases until 1991 (Figure 3). Thus, before 1988, the number of newly infected animals increased each year (with about 60%). Assuming that BSE only infects cattle at a very young age, the incubation period would be approximately equal to the age distribution of cases from a birth cohort.
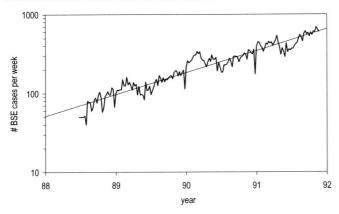

Figure 3. BSE cases between 1989 and 1992

However, when the epidemic grows exponentially, the age distribution of cases per year differs from the distribution of the incubation period. This implies that animals with a very short incubation period would be over-represented in the annual age distribution of BSE cases. This is, because animals that become a BSE case at young age also got infected later in time, that is, when the infection pressure had increased. Many more animals became infected at that later stage in time. Therefore the age distribution of BSE-cases in the nineteen-eighties would peak at a younger age as compared to the distribution of the incubation period in itself. (See Figure 2a.) The inverse effect is seen when BSE control measures have reduced the exponential growth rate to a negative growth: an exponential decrease of new infections. Due to the decreasing force of infection, the age distribution of BSE-cases then shifts to older

ages (Compare Figure 2a and 2b).

6.2.3 Mathematical calculation

Mathematical modelling is very useful in analysing problems that deal with the interaction of age, survival and real time. By formulating functions to describe the key dynamic processes in the cattle population and the basic pathogen-host interaction, the age distribution of cases can be predicted under all kinds of conditions.

First, assuming that cattle get infected at a very young age, the incubation period would be distributed according to the age distribution of the detected BSE cases, but corrected for the survival of cattle. Thus, let $g(t)$ denote the distribution of the incubation period, let $\mathcal{F}(a)$ denote the survival probability of cattle and let $\phi(a)$ be the age distribution of all BSE cases in an infection cohort. Then we derive

$$\phi(a)g(a)F(a). \tag{6.1}$$

Next, we can calculate the distribution of BSE cases in the nineteen-eighties, which will be equal to the distribution of the incubation period multiplied by the force of infection at the time of birth of those animals and multiplied with the survival function (age distribution) of cattle. In mathematical notation the following terminology could be applied:

Let r denote the exponential growth rate of the BSE epidemic in the early 1980s. Then the expected age distribution of BSE cases $C(a)$, (which is valid under a given time period with BSE growth rate r), is described by

$$C(a) = g(a)e^{r(-a)} \ \mathcal{F}(a) = \phi(a)e^{r(-a)} \tag{6.2}$$

Stochastic influences in the infection process and underreporting may lead to small differences in the age distribution of the detected case data. A Poisson distribution is expected to fit such stochastic influences.
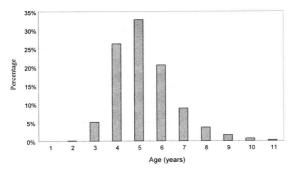
6.2.4 Quantifying the functions

The function $\phi(a)$ can be estimated from the BSE cases in a cohort. To derive the best possible estimate, we use several birth cohorts. All BSE cases detected in animals born between July 1985 and June 1991 contribute to this estimate. Thus, the effect of the force of infection on the age distribution of cases is removed by looking at all animals born in the same year. Data on animals born before 1985 were not used

here, because the effect of major underreporting before 1988 can strongly reduce the number of cases in the younger age groups. Data on animals, born after 1991 were excluded, because older cases are still expected to show the disease in these cohorts. The age distribution of BSE cases is not exactly constant over those five cohorts, but the differences are small (2%). This may suggest that other effects (like infection of cattle at older age) have a small impact on the age distribution of BSE cases. The data derived estimate of function $\phi(a)$ is graphically represented in Figure 4.

Figure 4

Age distribution in cattle born July 1982 until June 1986

Assuming that dairy cattle in the UK have on average about 4 productive years, that means that about one quarter of the productive (adult) cattle will be replaced each year. This replacement is rather constant over all ages, although it increases slightly with age. This means that the adult cattle population is rather well described by an exponential decrease over age. The survival function of adult cattle could thus be described by

$$\mathcal{F}(a) = e^{-(0.25a)}.$$

6.3   Results

Using formula (6.1) we can derive an estimate $g(a)$ of $g(a)$, which is graphically represented in Fig. 5. This is a function that appears to be typical for the infection, and has little dependence of the UK conditions under which the BSE epidemic developed. Therefore, this function will be used to extrapolate UK BSE information to other countries with different circumstances.

Figure 5

Distribution of BSE incubation period

Time (years)

6.3.1   Extrapolation to other regions

Now, we can predict the case age distribution of BSE in all kinds of situations. We will give the two extreme examples. Let us look at a country with a high annual turnover of adult cattle (removal rate is 35% per year), and where the BSE epidemic is still growing exponentially (This description would fit many western countries about ten years ago). To estimate the exponential growth rate, we will use available estimates of the basic reproduction ratio of the infection. The basic reproduction ratio is the expected number of new infections that is induced by one "typical" initial infection. From this reproduction ratio we can derive the growth rate of the epidemic ([13], chapter 3 of this thesis).

Let us look at a country with a reproduction ratio of BSE being about equal to the UK in the initial phase of the epidemic, i.e. equal to about 16 (Ferguson et al., 1999). Then the exponential growth rate of the infection, r is approximately equal to 0.7 ([13], chapter 3 of this thesis). The distribution of the BSE cases that will be found that year can be predicted from formula (6.2), and we can quantify an estimate $\underline{C(a)}$ of $C(a)$ and find:

$$\underline{C(a)} = \underline{g(a)}e^{-(0.7a)}e^{-(0.35a)}$$

as shown in Figure 6. Clearly, this only indicates the distribution of cases over the ages. The absolute numbers remain unclear, as long as there is no indication of the actual prevalence in this country.

Figure 6

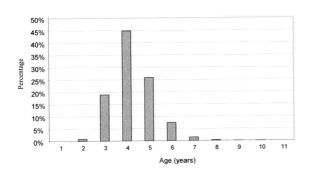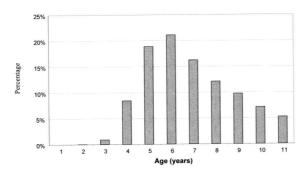**Age distribution BSE cases in fast growing epidemic**

Figure 7

BSE case age distribution in fast declining epidemic

The same is done for another extreme situation. Observe a country with a low annual removal rate of cattle (20%) and a very low reproduction ratio $R = 0.1$ for BSE. (This level is achieved when several control measures, for instance a feed ban and an SRM ban are implemented, see [13]; chapter 3 of this thesis). Then the growth rate of the epidemic can be estimated at $r = -0.5$ and the case age distribution will follow from:
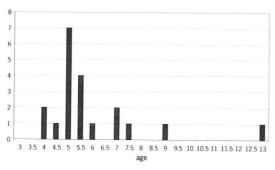
$$C(a) = g(a)e^{(0.5a)}e^{-(0.20a)}$$

as shown in Figure 7. With these extreme examples we see that the age distribution of the BSE cases can shift considerably, due to local conditions. Thus, if we want to monitor for BSE, it is useful to analyse the local population and it's history in BSE control. In that way, a targeted surveillance may improve BSE surveillance and reduce the number of samples needed for an adequate estimate of the local BSE prevalence.

For the Netherlands with a long history of BSE control, that would mean the following. Since a feedban was introduced (1989) and extended (1994) the reproduction ratio of BSE was slightly below 1 due also to the applied high temperature, pressurised rendering ([13], chapter 3 of this thesis). This reproduction ratio decreased further over time, due to more extended measures and inspection, but the strongest decreases will have come after 1996. Given a small rate of decrease of the infection and a high annual replacement of cattle (about 30%), for the Netherlands the most BSE cases are expected to be found in cattle of 5 years old, with extra low numbers in the age groups up to 4, due to an extra BSE control measures introduced halfway 1997 (SRM removal). The results of the Dutch BSE surveillance in 2001, testing (almost) all dead and slaughtered cattle over 30 months of age, confirm this pattern (See Figure 8).

Figure 8

Age distribution of BSE cases in the Netherlands in 2001

Finally, to apply such a targeted surveillance efficiently, we should not focus on the age group where the most cases are predicted. Better would be, to focus on the age group with the highest relative incidence, i.e. the most cases relative to the size of the age group. This is not necessarily the same, because younger age groups consist of far more animals than older age groups. Thus, the predicted distribution $C(a)$ should be corrected for the size of the age groups, which is described (again) by the survival function $\mathcal{F}(a)$. The removal of $\mathcal{F}(a)$ from the formulae, would give the relative distribution of BSE cases over the ages as

$$g(a)e^{r(-a)}.$$

For the two examples given, the predicted relative age distribution of BSE is given in Figures 9 and 10. Summarising: in countries with an exploding epidemic, BSE-cases are to be found mostly in 4-year-old cattle and the BSE prevalence is also ex-

pected to be highest in the 4-year-old population. However, in countries with a fast decreasing epidemic, BSE cases are mostly to be found in 5-year-old cattle, whereas BSE prevalence appeared to be highest in the 6-year-old animals.

Figure 9

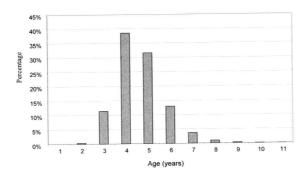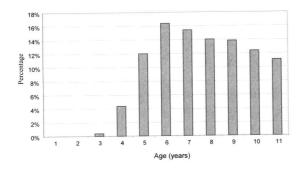**Age distribution of BSE relative to size of age group (at fast growth)**

Figure 10

Age distribution of BSE relative to size of age group (at fast decline)

6.4   Discussion and Conclusions

An adequate risk assessment for BSE requires the estimation of the local prevalence of BSE among cattle in a region or country. Targeting a surveillance program to such high-risk groups can reduce the sample size needed to estimate the local prevalence of BSE. In this paper we explained the use of age-structured modelling to predict the age distribution of BSE in the cattle population. We explored factors that influence the age distribution of BSE and we analysed the expected age distribution of BSE in

the Netherlands. Finally we determine the age at which most BSE cases are expected to be found in total and the age with the highest probability per individual animal to show BSE if tested, which is not necessarily the same age. Earlier published models for BSE ([31]; [50]) can be very valuable in answering these questions. Unlike the model described in this paper, these models are case-data-driven. These models use information on the development of BSE over the last ten years, to analyse what has happened and how the epidemic evolved. That has a major advantage, in the fact that the result will be very to the point and very exact, for the specific situation that is assessed. However, such models are not suitable for extrapolation to the future or to other countries, although limited extrapolation can be acceptable. The main disadvantage of such work is that it is not suitable for countries where the number of detected BSE cases so far is limited or zero. This gap is filled using the model addressed in this paper. This work has the advantage that no large numbers of cases are needed for predictions. Another advantage is that it is more suitable for future extrapolation.

One of the major weaknesses of the work in this paper is the assumption that all cattle get infected at birth (or very shortly after). The general opinion on the age-dependent susceptibility is based on epidemiological assessment of the data and physiological information on the transmission via the bowels. According to this hypothesis, most cattle will have become infected at a very young age, during the first year of their life. However, although it is clear that older animals are less susceptible ([31]), it remains unknown whether these older animals can get infected at all. The assumption of BSE-infection at birth leads to an overestimation of the incubation period. However, because most animals become infected at very young age, this overestimation will probably be minor.

The age distribution of BSE can be predicted rather easily for situations as described in this paper, i.e. for countries with a rather constantly evolving BSE infection (either increasing or decreasing). Age-structured modelling, indicating the age distribution of BSE within the population, is a very strong tool in applying a targeted surveillance. Moreover, risk assessment methods can be applied that are partially based on surveillance results. The results and effects of this modelling can even be strengthened by combining the age distribution of BSE in the population with a prediction on the distribution of BSE over different exit routes, as can be based on [27].

There are, however, a few warnings. First, the age distribution of cattle in the high-risk exit routes could be different from the general age distribution of removed (culled) cattle. Secondly, the regular change in BSE control measures and the regular introduction of new control measures over the last 10 years might disturb the calcu-

lations. This makes it rather unclear which set of control measures should be chosen for the model to determine the development of the epidemic. Thirdly, the import of BSE-contaminated feed and BSE-infected cattle can have a strong influence on the age distribution of BSE in a country when these imports fluctuated strongly in time. Clearly, years with major imports will strongly bias the age distribution of BSE later on. Thus, if there are reasons to expect such biases in the development of the epidemic, this should be included in the assessment of the age distribution. Models that include more detailed information can provide better calculations for these cases. Then, generally, the years of major imports and the years of implementation of the major control measures show up as the cohorts inducing most cases thus causing a peak in the age distribution.

Using age structured modelling, three factors influencing the age distribution of BSE were found to be the most important: 1) the incubation period of BSE, 2) age structure of the cattle population, and 3) the local risk history: methods of rendering, feeding of compound feed containing Meat and Bone Meal (MBM), and the development of BSE control. When information on these three factors is available, the expected age distribution of BSE in different countries can be calculated.

The age distribution of BSE seems to vary a lot between countries and regions. It appears that in countries where BSE risk factors were high and control measures were minimal until very recently, the BSE prevalence is expected to be highest in 4-year-old cattle. In countries where BSE control is at a very high level for more than 5 years, the prevalence may be highest in the 6- to 8-year-old cattle. Then, an adequate surveillance could be targeted specifically at the age groups with the highest BSE risk. For each country, the assessment shows in which age group BSE is most likely to be found. Obviously pure focussing on the predicted age group with the highest BSE prevalence is not optimal, because of the difficulty to quantify a risk history, but great economic gain can be made in focussing a part of the surveillance (for instance 50%) on the indicated risk group. Especially for countries that try to establish a so far undetected presence of the infection, this method can be very rewarding.

In countries with a very high turnover of cattle, the age distribution of BSE peaks at a slightly lower age than in countries where cattle have a very long production span. However, when we observe this incidence in relation to the size of the age groups, then this difference disappears and only the course of the epidemic remains as a major influence on the age distribution.

Chapter 7

Development of a surveillance program to decide about the status 'Freedom from Infection'

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Abstract

The paper describes the general principles underlying the concept of disease-free territory and the required statistical basis for the corresponding epidemiological surveillance operations. Among the essential points, it is emphasized that "disease-free" status should be assigned only under conditions substantiating the absence of infection (or infestation) and not simply on basis of a known low level of infection (or infestation). We also raise concerns about confusion that may arise between, on the one hand, the inevitable requirement to set a threshold on the level of detection of epidemiological surveillance tools, for economic reasons, and on the other hand the acceptance of a level of infection (or infestation) that is known, but occurring below the accepted threshold, when awarding the official status of "territory free from a given disease". In such a situation, it would be preferable to accord the status of "territory where the disease is in the process of eradication".

Surveillance programs are used to support the free from disease status of a country, but unfortunately, so far, these programs can only prove that the infection was below the threshold some time ago. The time that has elapsed since, offers infections the opportunity to develop a new epidemic when they are reintroduced in the area. This is generally not assessed quantitatively so far.

In this paper we describe a method to assess surveillance programs on all these issues. Repeated negative results of the surveillance proves freedom from infection of the country for the recent past, but they also allow us to calculate the expected time needed to detect a newly started epidemic, and the expected size of that epidemic. We suggest that this method can help to compare various surveillance programs, and will also offer further opportunities in setting standards in the prevention of importing and exporting infections.

7.1 Introduction

The expanding international trade in live animals and products of animal origin increases the risk of transmission of infectious diseases throughout the world. These risks apply not only to notifiable diseases (list A diseases of the Office Internationale des Epizooty (OIE)), for example foot-and-mouth disease (FMD) or classical swine fever, but also to other infectious diseases, e.g. OIE list B diseases such as Porcine Reproductive and Respiratory Syndrome (PRRS). Generally, infectious diseases of economic importance, which might result in an epidemic after introduction to populations free from these diseases, are of primary relevance.

Every country is aware of the risks of transmission of infectious diseases by trade, and tries to prevent the import (and even export) of diseases (or more precisely: the causative agents) by blocking the import of animals or animal products from countries where an infectious disease is present. On the other hand, many countries benefit from an open market, or from its export possibilities. Thus, to maximize exports many countries are interested in proving their 'free from disease' state. For infectious diseases, 'freedom from infection' is the real thing to prove, while the presence or absence of disease due to the infection is less relevant here.

The way to show that an area is free from a certain infection is a proper surveillance program (e.g. [28]; [35]; [67]). The claim 'free from disease' only has a meaning after evaluation of the test procedure. The OIE is an independent international organization that monitors these test procedures and certifies the 'free from disease' status (OIE, 2001). The surveillance programs should, with a specified level of certainty, guarantee freedom from disease or infection as appropriate. To do so, usually a percentage of a population is tested, generally by taking serum samples that are subsequently tested for the presence of antibodies. In practice, 'freedom from disease' means that the prevalence in a sampled population is below a certain, specified level (e.g. 2%). Most of the surveillance programs are supported by statistical methods to determine the appropriate sample size for the detection of a specified prevalence level. A statistical analysis, in combination with the test characteristics, shows the probability that the local prevalence is below that level. Such an assessment is generally accepted as an indication of the freedom from disease, particularly after repeated sampling with negative results.

The advantage of using serology for a surveillance program is that samples are easy to gather, the tests are relatively easy to perform, and can often be applied on a large scale. There are, however, also disadvantages to serological surveillance to assess the 'freedom from disease' status. One disadvantage is a matter of timing:

test results always lag behind reality. Other disadvantages of the methodology are that test methods and the assessment of the test results may vary between countries and regions, and that the biological interpretation of the test results with regard to the dynamic course of an infection in a population and the risk of transmission is not always clear.

In this paper we will focus on the time delay problem and the dynamic development of the infection throughout the population. We will combine mathematical modelling with statistical analysis to develop and compare surveillance methods that can be used to assess a 'freedom from disease' status. We will show that an integrated approach allows for a much more sophisticated assessment of the freedom from disease status, it can also include an analysis of the risk of re-occurring epidemics, which is not traditionally included in surveillance programs.

7.2 Critical aspects of serological surveillance related to time delay

The time delay problem is twofold. One is that serology gives a 'late' response to infection. For many infectious diseases, the interval between infection and a subsequent serological response, i.e. a detectable antibody titer in the blood, is at least one week. That means that a surveillance program that is based on serology, tells you what the situation was 'then' rather than what it is 'now'. Serological monitoring may therefore give a misleading perception of security, or may not be informative with respect to presence of the agent in sero-negative animals. Secondly, surveillance by random sampling with statistical assessment of prevalence is a static approach, whereas the spread of infection is a dynamic process, so in between surveillance rounds, an epidemic may develop unseen.

At the start of an epidemic (immediately after introduction) the prevalence will be very low, only few animals will be infected. The prevalence can be too low to be detected in a sample, especially if the applied test is not very sensitive (e.g. [67]), and when the serological test results lag behind a lot on infection. This implies that a starting epidemic may easily be missed in a surveillance program. The sensitivity of the test is very important in this context, since it will determine whether some of the - few - cases will be detected or missed. Depending on the contagiousness of the infection and its incubation period, the course of the infection may very soon lead to a high prevalence of the infection and therefore a high export risk, before it is detected in the (next) surveillance round. For instance the FMD epidemic in the UK in 2001

was exported to France before it was detected, and it is also thought that the infection was already, again, exported further into the Netherlands, before it was established that the disease was present in France.

With some basic epidemiological information and mathematical modelling it is possible to analyse this problem of exporting/importing infections.

To summarize: Four major factors are important for the assessment of the risk of exporting infection:

1.   The probability that the infection is introduced into the country (assessing import risk);

2.   The growth rate of an epidemic, if the infection is "successfully" introduced;

3.   The ability of the local surveillance program to detect new epidemics;

4.   The size of the exported population (per unit of time).

Assessment of the risk of missing an infection under a specific monitoring program is a very recent development in veterinary science. Mathematical models can help in analysing the dynamic processes of infectious diseases in relation to test characteristics and surveillance efforts. The purpose of this paper is to show the possibilities and advantages of combining mathematical modelling with statistical analysis in a 'freedom from disease' assessment. We combined the factors 2 and 3 into one method to assess the disease free status of a country, focusing on the risk of exporting a disease.

7.3   Model for evaluation of 'free from disease' status

Mathematical modelling may be used to incorporate the dynamical behaviour of infectious diseases into the assessment of a surveillance program. Such a comprehensive quantitative approach enables us to test whether a surveillance program suffices under some given criteria. It also allows us to compare the quality and reliability of different surveillance programs.

One way to apply mathematical modelling in the assessment of efficacy of a surveillance program is shown by Graat et al. [39], who calculated the critical sampling frequency and sampling intensity for BHV infection in a group of BHV free herds in the Netherlands. They used a model for the change in number of sero-positive cattle in a herd from bulk milk samples. They subsequently assessed the probability of detecting the infection in a herd before the infection has spread to (on average) more than 1 other (free) farm. Their method was applied to free herds based on the disease dynamics within a herd, between individual animals.

In the current study, the analysis focuses on the country level, whereas Graat et al. [39] focused on a small cluster of herds. The approach for analysis, however, is similar. We will, therefore, apply the same basic method for the evaluation of surveillance programs. Since a variety of diseases occur and several surveillance procedures are available, this framework is outlined with as much generality as possible. Here, we explain a method that would be suitable for viral infections that spread fast within a herd, while transmission between herds is relatively slow. We will look at the prevalence of such infections, meaning the fraction of infected herds in the national (or regional) population. In this case, a test is a screening method of a herd, to classify them either as infected or disease free. We will, for now, assume that the sensitivity of this herd test is constant over time. In section 6, we work this out with an example for Aujeszky's disease.

Let us assume that at some moment in time, t_0, some infection is introduced into a population of herds with prevalence i_0. It is assumed that the prevalence of this infection, $i(t)$, initially increases exponentially (deterministic description of an inherently stochastic system) with rate r. Hence

$$i(t) = \begin{cases} i_0 e^{r(t-t_0)} & t > t_0 \\ 0 & t \leq t_0 \end{cases}.$$

We assume an ongoing surveillance program in this population, with regular sampling points over time. During sampling, a fixed number of samples, x_m, are taken, and the time between two sequential sampling moments will equal Δ_m.

Let the sensitivity of the test be denoted by σ. The tested 'individual' can be an animal, a herd or a region, in this paper we generally use the term individual for a herd. Thus, sensitivity means herd sensitivity and sample size means the number of herds sampled.

Given that the infection is introduced into the country, at t_0, we will set the time to zero at the last sampling moment before introduction of infection. Note that $t = 0$ is not equal to t_0. The unknown moment of introduction of the infection, t_0, lies somewhere between $t = 0$ and $t = \Delta_m$. Assuming a uniform distribution of t_0 over this time interval, the expected prevalence of the infection, $i(t)$, can be calculated by averaging $i(t)$ over all possible introduction moments, thus deriving

$$\tilde{i}(t) = \frac{1}{\Delta_m} \int_0^{\Delta_m} i(t)dt_o \tag{7.1}$$

$$= \frac{i_0}{r\Delta_m} e^{rt}(1 - e^{-r\Delta_m}) \qquad \forall t > \Delta_m.$$

The probability to detect the infection, depends on the prevalence and on the test quality. The probability that a randomly sampled herd gives a negative test result at time step k, is one minus the probability of selecting an infected herd, (i.e., $\tilde{i}(t)$), but needs to be corrected for the sensitivity of the test.

For the time being, we assume the specificity of the test to be equal to 100% (neglecting false positive test results, for instance by confirming positive results with the gold standard). Thus, the probability of not detecting an introduced epidemic in k consecutive samples of x_m individuals, is given by

$$(1 - \sigma \tilde{i}(k\Delta_m))^{x_m} \approx e^{-x_m \sigma \tilde{i}(k\Delta_m)}.$$

The approximation is valid for all $\tilde{i}(t)\sigma \ll 1$, which fits the presumed low prevalence of a newly introduced exotic disease. The probability that a sequence of m samples after virus introduction give negative test results only (escape probability) is given by

$$P(m\Delta_m) = \prod_{k=1}^{m} e^{-\sigma \tilde{i}(k\Delta_m)x_m} \tag{7.2}$$

$$= e^{-\sigma x_m \sum_{k=1}^{m} \tilde{i}(k\Delta_m)}.$$

This formula is the basic tool to analyse the quality of a surveillance program: the lower the escape probability, the better the surveillance program. In the following paragraph, we explain some of the main features of surveillance programs on the basis of formula (7.2)

7.4   Main features of surveillance methods

Two typical features of a surveillance program can be shown easily. First we will put more emphasis on the time interval between sampling. The main question is: which interval is optimal? To answer this question, we have to reformulate the escape probability by substituting the total number of tests $x = mx_m$ and the total period $\Delta = m\Delta_m$ in the expression for $\widetilde{i}(k\Delta_m)$ (i.e. Formula 7.1), thus a key ingredient of Formula (7.2) can be rephrased as

$$\sum_{k=1}^{m} \widetilde{i}(k\Delta_m) = \sum_{k=1}^{m} \frac{i_0}{r\Delta_m} e^{rk\Delta_m}\left(1 - e^{r\Delta_m}\right)$$
$$= \frac{mi_o}{r\Delta}(e^{r\Delta} - 1)$$

and we derive

$$P(\Delta) = e^{-\sigma x i_0\left(\frac{e^{r\Delta}-1}{r\Delta}\right)} \tag{7.3}$$

Thus, the probability that the epidemic will not be detected in the full time period Δ, $(P(\Delta))$ does not depend on the time interval between sampling moments if the total number of samples, x, remains equal. This implies that it is irrelevant how often measurements are taken within the period Δ, as long as the sampling rounds are equally spaced over time and the total number of sampled individuals is constant. For example, twice the number of sampling occasions with half the sample size will lead to the same escape probability as the original.

Secondly, in Formula (7.3) we distinguish two sets of parameters, which influence the escape probability. These two sets of variables are $\{\sigma, x, i_0\}$ and $\{r, \Delta\}$. As a group these parameters are restricted, but single parameters from a group are free to choose, as long as they are compensated by the other parameter(s) in the group to maintain an acceptably low escape probability.

These observations can be very useful in an economic assessment of the surveillance program. If, for example, two tests are available, a cheap test with a low sensitivity and an expensive one with a high sensitivity, we can now easily calculate the optimal test, both for epidemiological aspects (earliest and most reliable detection) and for economical ones (financially optimal, depending on cost of sampling, costs of testing, costs of control and risk of an infection being re-introduced). The optimal test is not necessarily the test with the highest sensitivity, although that is generally called

the best test.

7.5 Quality of a surveillance program

A consequence of the non-zero escape probability is that, despite constant negative results in the surveillance, the real prevalence can still be above zero. A perfect surveillance program should determine the actual prevalence of the infection at sampling. Knowing that to be impossible, we suggest defining the quality of a surveillance program, taking account of the fast growth of an infection, using quantitative measures, which allow for comparison of alternative approaches. The quality of a surveillance program can be defined by two factors, (1) the escape probability, at a specific time period since introduction of an infection, and (2) the actual prevalence upon detection. If the prevalence and escape probability are high, the surveillance program has a low quality, and vice versa, since the time of detecting an infection is heavily influenced by the stochasticity of the process. Therefore, we propose to define the quality of the surveillance program using the expectation of the prevalence at detection :

$$\bar{i}(m\Delta_m) = \sum_{k=1}^{m} \tilde{i}(k\Delta_m) \left(P((k-1)\Delta_m) - P(k\Delta_m) \right).$$
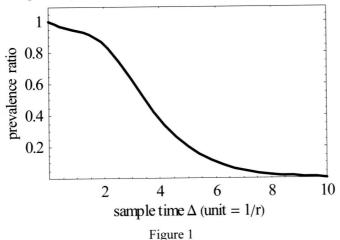
This is derived as follows: the probability of detecting the infection at sampling moment k is equal to the probability of detecting up to (and including) sampling moment k; $(1 - P(k\Delta_m))$ minus the probability of detecting it before sampling moment k; $(1 - P((k-1)\Delta_m))$, which results into $P((k-1)\Delta_m) - P(k\Delta_m)$. Substituting formula's (7.1) and (7.2), we derive that the expected prevalence at detection can be described by

$$\bar{i}(m\Delta_m) = i_0 \sum_{k=1}^{m} \frac{e^{rk\Delta_m} - e^{r(k-1)\Delta_m}}{r\Delta_m} \left(e^{-\sigma x_m i_0 \frac{e^{r(k-1)\Delta_m}-1}{r\Delta_m}} - e^{-\sigma x_m i_0 \frac{e^{rk\Delta_m}-1}{r\Delta_m}} \right)$$

$$(7.4)$$

This looks rather complicated, and the influence of separate parameters is difficult to determine. Therefore, we give a short overview of the typical characteristics that follow from this expression.

Let us start by scaling i_0 to one (multiplying i at both sides with the population size making it the number of infected herds instead of the prevalence of infected herds). Furthermore, assume that m (total time) goes to infinity. We want the expected prevalence at detection to remain sufficiently small, so that control of the epidemic will be

feasible. We suggest that a maximum of 10 infected individuals would be realistic for most infections. Now we will visualize the effect of the two relevant group-variables σ, x_m, i_0 and r, Δ_m on the expected prevalence at detection. Figure 1 shows that the multiplication of σ, x_m, and i_0 should remain above 0.2, while Figure 2 shows that the multiplication of r and Δ_m should remain below 3. Thus, as a rule of thumb, keeping both in the order of one would suffice the basic quality needs of a surveillance system aiming at early detection.

Figure 1

The steepness of the graphics in Figure 1 for values of σ x_m i_0 below 0.5 shows the fast decline of the quality of the surveillance program when this limit is passed. The constraint on r Δ_m is even stronger, which is clear from the exponentially increasing function in Figure 2.
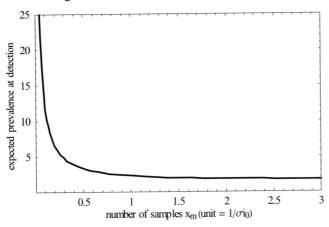

Figure 2

7.6   Application to Aujeszky's disease virus (ADV)

Aujeszky's disease is an infectious disease of swine, characterized by, in particular, respiratory distress and abortion. In 1993, the Netherlands started a campaign to eradicate the virus from the Dutch pig population by means of vaccination. The strategy was based on the application of a glycoprotein E (gE)-negative marker vaccine in combination with an ELISA that detects gE antibodies after infection with a wild type ADV strain (Stegeman 1997). This gE-negative vaccine reduced the transmission of the virus sufficiently (De Jong and Kimman, 1994), inducing a negative growth rate of infected herds and subsequent extinction in fade-out of the infection. The Netherlands may soon try to establish the status freedom from infection for ADV and end the vaccination program. An ongoing surveillance program will be needed to make sure that we remain free from the infection ([15]). Based on the methodology in this paper, we give an example of a surveillance program to guarantee that the prevalence of the infection is, with high probability, below a certain level.

A quick guestimate of the relevant parameter values is applied here to quantify the relevant parameters under non-vaccinating conditions, because it is merely meant as an example. Obviously, for a serious analysis of ADV, a more elaborate assessment of the parameter values will be needed, to obtain the required precision.

The herd will serve as the unit of infection in this case. Based on earlier studies ([15]), we estimate the growth rate of the infection $r = 0.3$ per week. The herd test sensitivity (gE ELISA) depends on the number of samples within the herd and the development of infections within. For now, we assume that the sample size within the herd is sufficiently large to obtain a high sensitivity of the herd test in the field, i.e. $\sigma = 95\%$. For the simplicity of the example, we will not make a full analysis of the herd test quality, but simply assume that the herd test is sufficiently sensitive to pick up the infection in an early stage (with 95% probability). Finally we assume that an epidemic will start with one infected herd in a free population (the Netherlands) of about 20 000 herds (Stegeman et al., 1999), i.e. $i_0 = 1/20000$.

For financial and logistic efficiency, we would like to combine this new surveillance program with an existing monitoring scheme (for other infections) in The Netherlands, where all pig herds are visited and sampled once every 4 months (is 17 weeks). Week will serve as unit of time, and we find that each week ($= \Delta_m$), $20000/17$ ($= x_m$) herds will be tested. We calculate the probability of detection over time using Formula (7.3) (see Figure 3) and the expected prevalence at detection using Formula (7.4). Calculations are performed using Mathematica® 4.1.
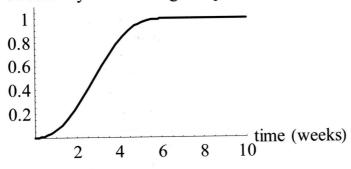
Probability of detecting an epidemic

Figure 3

We find that the given surveillance scheme and the parameter estimates, will lead to detection of the infection within about 2 months, on average about 4 weeks after introduction, with an expected prevalence at detection of 8 herds. These results are based on a perfect test in the sense that it detects infection immediately. Now from the Dutch point of view, the problem is controlling an epidemic, once infection has reoccurred. In that view, the result of this analysis is not impressive. It merely proves that the intensity of the chosen surveillance program is a bit low for ADV, because it will be hard to eradicate the infection, when on average 8 herds are infected at first detection of the epidemic.

In a more conventional analysis of the surveillance program, we would assess that we have a surveillance program that repeats every 4 months. We find that this surveillance system is very sensitive, it is able to detect the presence of infection in the country with 95% certainty, when more than 1 herd is infected. And indeed this analysis proves that the country is free from the infection, at least, it was so, 4 months ago. But it does not include an assessment of the likeliness of detecting a recently started new epidemic. How far can this epidemic develop before the surveillance picks it up? That is determined by the time between surveillance rounds, and the growth rate of the infection. Obviously, a gut feeling assessment of the growth rate of the infection is used to determine the time between surveillance rounds, which is usually quite sufficient, but that does not allow for a calculation of the possible size of the epidemic at detection as we describe in this paper.

Whereas the conventional assessment gives sufficient proof of a Freedom of Disease status, the method in this paper adds an analysis of what happens in the unlikely event that the infection was re-introduced recently: We expect to detect the

epidemic before the epidemic has infected 8 herds. Thus, the probability of importing ADV from the Netherlands is proven to be very small, even when the infection is re-introduced. This re-introduction probability of the infection in the Netherlands is not well quantified. However, the ability of the Netherlands to eradicate the infection with vaccination within five to ten years, and without detection of the infection for a few years in the surveillance as described above, shows that the reintroduction rate must be less than once per 2 years (104 weeks). The expected time between introduction and detection is estimated at 4 weeks, so the probability of importing infection from the Netherlands is now quantified to be less than $4/104 * 8/20000 = 1.5 \times 10^{-5}$ per exporting herd per 4 weeks. Depending on the situation, this may or may not be considered a sufficient guarantee.

Obviously, a better quantification of the introduction risk in the Netherlands could improve the numbers a lot, but so far, the period of disease freedom is too short to make a better estimate. At present, the Netherlands maintains a surveillance program for ADV and also has a quarantine system for export, according to OIE regulations. However, depending on the exact details, for some infections a more efficient strategy may be found in integrating the safety of exports in the national surveillance, without specifically separating surveillance and quarantine for export.

7.7   Discussion

In this paper, we showed the possibilities and advantages of combining mathematical modeling with statistical analysis to assess a 'freedom from disease' status, and we focused on the export of infections. Many surveillance programs are based on serological testing of a randomly chosen percentage of a population on a regular basis. This is usually done in live animals, but carcass screening at the slaughterhouse is also applied (e.g. [76]). The optimal sampling intensity depends on 1) an optimization of the surveillance program, to fulfill internationally agreed standards, which should preferably be based on export risk, and 2) an economic optimization that includes costs and quality of the surveillance program versus the (in-)direct costs of an epidemic. Thus conventional assessment of surveillance is very efficient in proving freedom of disease, but it does not assess the quality of the surveillance system in detecting new epidemics. When surveillance is (also) assessed with a dynamic model, it's ability to detect new epidemics can also be included in the results, and thus, a higher guarantee of safety of import/exports can be given.

The probability of exporting an infectious disease depends on the local prevalence

of the infection, and of the type of infection. For infections that induce sterile immunity, e.g. many viral diseases, sero-positive animals might be of no risk, although importing countries do not accept those sero-positive animals. However, carriers, latently or persistently infected animals, e.g. ADV-infected pigs or FMD- carriers are sero-positive and might be a risk for importing infectious agents. Therefore, sero-prevalence will be regarded as presence of the infection and seropositive animals are regarded as a potential risk. A low prevalence might not be detected when only a random sample of the population is examined, but after some initial random fluctuations with a possibility of spontaneous extinction of the infection, an epidemic can be expected to approximate exponential growth ([24]). Once the prevalence exceeds the detection limit, the presence of the infection will be detected at the next sampling. The probability of detecting the outbreak increases over time with each new sampling round.

The advantage of implementing the dynamic characteristics of infectious diseases in the design of a surveillance program is mainly found in the way the factor time is included in the analysis. Without a dynamic assessment, it is not possible to calculate the time between introduction and detection, i.e. the high risk period (HRP). The longer the HRP, the more animals are exported to other countries, and thus, the higher the probability of exporting the infection. A dynamic model immediately shows that the sampling intensity (or frequency) is essential in detecting the epidemic before it has reached a predefined level. So far, this has rarely been calculated properly in relation to the development of a possible epidemic or in comparing the quality of surveillance programs. The OIE Animal Health Code and the Manual on diagnostic tests ([69]) do not mention this topic at all. Proving freedom of disease is sufficient and the fact that the infection can be reintroduced in the country is neglected.

Conventional surveillance analysis calculates the detection level of a surveillance program, but neglects to analyse the development in between. Between rounds of testing, a large epidemic can develop, depending on the rate of transmission for that infection. Therefore, an analysis that includes the assessment of the size of such an epidemic gives a better idea of the safety of a surveillance system. Previously, the surveillance was mainly aiming at proving that a country has been free from the infection, and therefore, it most likely still is. With the basic methodology as explained in this paper we can now also analyse the risk of a recently reintroduced infection for export, and compare the quality of surveillance systems in other countries with respect to HRP and import risk.

The optimal sampling frequency is partly based on the costs of a surveillance program and the costs of an epidemic. Thus, one can set criteria for monitoring from

an economic assessment of surveillance costs against the costs of controling an epidemic. Especially, the time until detection has a very strong influence on the costs of controling the infection ([52]; [66]).

The example of ADV shows that an ADV epidemic will be detected by serological surveillance within 2 months after introduction. For comparison and validation, little is available in literature. The closest we can find is a study by Crauwels et al. [9], who investigated the effectiveness of serological surveillance for classical swine fever (CSF), based on a sampling interval of four months and assuming within-herd prevalence of 25%. To do this, they used the data of the CSF epidemic 1998-98 in the Netherlands, and a simulation model that was used to analyse that epidemic. They calculated that the probability of detection of a CSF case was very low. They further showed, that even sampling scheme of 60 samples per month, the probability of detection within 40 days was less than 40%. This supports our calculations about an ADV infection, which spreads somewhat slower, but is in most transmission aspects comparable to CSF. The sampling intensity of 60 herds per month is indeed far too low to detect the infection within a reasonable time frame. The advantage of our method is that the calculation for general situations is more straightforward, and the assessment is also faster, because it does not require the availability of a simulation model.

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Summary

For the eradication or control of infectious diseases, one needs knowledge of the spread of the infection between (groups of) animals. Models can easily be used to observe the efficacy of various control measures in fighting the infection. However, the availability of information and data to build and quantify these models is essential for applying such models in real life. In this thesis, models on the spread of infectious diseases in animals are always combined with data concerning the host, the infectious agent, their interactions and often also case data from epidemic or endemic disease situations. In some cases, the models are used to interpret data (Chapter 2 and 6), but mostly, the data are used to quantify the various model parameters. In some cases data on outbreaks or epidemics can also be applied to validate the models. Therefore, the results of such modelling studies can often be used to improve or optimise the disease control situation.

Two factors enable us to compare the efficacy of disease control measures, i.e. modelling and data. Careful representation of the contact patterns between host and infectious agent, but also between infected and susceptible hosts may have a large influence on the result. Good en recent data allow for increased insight in the important factors in the spread of the infection, and allow for reliable quantification of the results. Various methods in modelling, model analysis and quantification of models are addressed in this thesis, but typically, they will always be given with a real life example, where a disease situation poses a certain problem, that may be of environmental, ethical, or economical origin.

Careful consideration of the epidemiological situation (behaviour, time delays, etc.) in relation to the purpose of the study (understanding, optimising control, etc.) is needed to choose the best model to analyse the situation. For slow developing diseases, age structured models are often useful, because many animals may not survive long enough to become infectious. For animals living in herds, their clustering can be very influential in spreading the infection, and that behaviour should be incorpo-

rated in the model. For herpes viruses, it is important to see whether reactivation of the infection in previously infected hosts influences the dynamics of the infection in a population.

We show that for Phocine Distemper Virus (PDV) the data of the epidemic in 1988 show that clustering of animals has a strong influence on the transmission and survival of the animals. A previously applied model to analyse the seal situation did not fit the data very well, and further analysis of the seal behaviour, and the transmission options for the virus suggested that the virus will mainly be transmitted when the seals haul out on the sand banks. Due to their clustering, the death rate was higher than could be expected from the first model.

To control and eradicate Infectious Bovine Rhinotracheitis (IBR) it is known that the persistence of the infection in previously infected animals may cause a delay in eradication. We have quantified the probability for such a virus to reactivate in the field, and combined that with a model that calculates the expected time to extinction. Thus, control measures in the eradication process can easily be compared for efficacy and a time frame can be defined.

In the control of BSE, the major consumers fears have lead to extremely strict attempts to control the infection, after an initial neglect of the seriousness of the problem. By quantifying the transmission parameters, the various control measures can be compared, and it becomes clear that to end the epidemic, several options are available and may be interchangeable. Given the uncertainty of the human risk, maximum efforts have been put forward, but now that more information is available, both on surveillance and on control, optimisation of the methods can be introduced, based on the models as explained in this thesis. Based on the age distribution of BSE cases, much information becomes available on the efficacy of BSE control in the past, but also concerning the prevalence of the infection in the future. Risk assessment and modelling are especially important for countries without BSE cases, or to few cases to really describe an epidemic. Based on the models, surveillance can be aimed at higher risk groups in the population, thus improving the efficacy of the surveillance program.

Monitoring of an animal disease situation may have many purposes, for instance to prove freedom from infection for a certain farm or country. Such a status increases the value of animal in those herds or countries. However, there is never a full-proof method to show absence of the infection. This is caused by various reasons; 1) test quality, infected animals are not always detected by the test, 2) a sample of the animals is tested, and the few infected animals may be missed, and 3) the infection may be introduced after the sampling. In the last chapter of the thesis, we give an opening for extended modelling to quantify such risks. An integrated approach of transmission

models that include repeated sampling over time allow a calculation of the probability that an early epidemic escapes from detection. Thus a much more exact calculation can be given of the safety of the herd or herds concerning this infection.

Samenvatting

Om besmettelijke ziekten te kunnen beheersen of bestrijden is kennis nodig van het spreiden van de infectie tussen (groepen) dieren. Met behulp van modellen kan eenvoudig worden bestudeerd welke maatregel geschikt is om de infectie te bestrijden. Maar daarvoor dient wel voldoende informatie beschikbaar te zijn, om de modellen goed te kunnen kwantificeren. In dit proefschrift wordt het gebruik van modellen steeds gecombineerd met data, omtrent de gastheer, het infectieuze agens en de interacties daartussen. Bovendien worden er ook van data over de ontwikkeling van een epidemie of de incidentie van de ziekte in een endemische situatie gebruikt. Soms kunnen modellen gebruikt worden om de data te verklaren (hoofdstukken 2 en 6), in andere gevallen worden de data gebruikt om parameters in de modellen te kwantificeren en soms ook om de modellen te valideren. Hierdoor zijn de model resultaten vaak direct in de praktijk toe te passen voor het verbeteren of optimaliseren van de beheersing van de infectie.

Voor het vergelijken van de effectiviteit van bestrijdings- en/of beheersingsstrategieën van besmettelijke dierziekten zijn twee factoren heel belangrijk, modelformulering en dataverzameling. Het zorgvuldig weergeven van contactpatronen binnen modellen is vaak heel belangrijk voor het eindresultaat. Actuele en goede data geven veel meer inzicht in factoren die een rol spelen bij de verspreiding van besmettelijke ziekten. Daarmee kan zo'n model kwantitatief verder worden uitgewerkt. Verschillende methodes voor modelleren, analyseren van modellen en kwantificeren van modellen komen aan de orde, en worden dan altijd geplaatst in de context van een praktijk probleem, zoals bijvoorbeeld gekke koeienziekte of zeehondenziekte, waar verbetering van de ziektebeheersing wenselijk is.

Het is belangrijk om de epidemiologische situatie (snelheid, gedrag zieke dieren, etc) zorgvuldig te bestuderen, alvorens een definitieve keuze te maken voor bepaalde modellen, en de keuze hangt bovendien af van het doel, bijvoorbeeld vergelijken van de effectiviteit van verschillende bestrijdingsmaatregelen. Bij traag ontwikkelende

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infecties zijn leeftijdsgestructureerde modellen belangrijk, bij kudde dieren moet rekening gehouden worden met kudde gedrag. Bij herpes virussen kan reactivatie in dieren die hersteld zijn van de infectie belangrijk om mee te nemen.

Voor Pocine Distemper Virus (PDV, zeehondenziekte) blijkt uit toepassen van data, dat een eerder gebruikt model minder geschikt is voor het analyseren van een epidemie, maar dat voor zeehonden toch sterk rekening moet worden gehouden met kudde gedrag tijdens het rusten op de zandplaten. Daardoor verloopt de epidemie sneller dan verwacht, en is de sterfte onder de dieren ook hoger dan verwacht.

Bij de bestrijding en eradicatie van Infectious Bovine Rhinotracheitis (IBR, koeiengriep) blijkt dat het persisteren van de infectie in eerder besmette dieren sterke invloed kan hebben op de tijd die het duurt voor de infectie uit een kudde verdwenen is. Door het kwantificeren van de kans dat het virus weer reactiveert, kan worden berekend hoe lang het eradicatieproces onder bepaalde (extra) bestrijdingsmaatregelen zal duren.

Bij de bestrijding van BSE (gekke koeienziekte) heeft de angst onder consumenten geleid tot een zeer streng controlebeleid, nadat er in eerste instantie voor een wat voorzichtige aanpak was gekozen. Door het kwantificeren van de transmissieparameters kan de effeciviteit van de verschillende maatregelen zichtbaar gemaakt worden en blijkt dat een aantal maatregelen om de epidemie te stoppen uitwisselbaar zijn, maar niet efficient optellen. Door de onzekerheid over de voedselveiligheid was in eerste instantie een maximale veiligheid noodzakelijk. Nu veel meer duidelijkheid bestaat over zowel epidemie bij mensen als bij koeien, kunnen de controlemaatregelen en surveillance gerichter worden ingezet, op basis van model resultaten, zoals in dit proefschrift in detail wordt uitgelegd. De surveillance voor BSE kan efficiënter worden ingericht, door gebruik te maken van kennis over de leeftijd waarop BSE zichtbaar wordt. Bovendien kan door analyse van de leeftijden van BSE koeien een geschikte toekomst voorspelling van het voorkomen van de ziekte worden gemaakt, en kan ook de effectiveit van bestrijdingmaatregelen in het verleden beter geanalyseerd worden.

Monitoren van een dierziektesituatie kan met vele doelen gebeuren, onder andere wordt het toegepast om aan te tonen dat een bedrijf of land vrij is van een bepaalde infectieziekte. Om meerdere redenen is zo'n analyse nooit een 100%-bewijs dat de infectie afwezig is; 1) de test is meestal niet volledig betrouwbaar, 2) niet alle dieren zijn getest, maar slecht een sample, en 3) na het testen is de infectie binnengekomen. In het laatste hoofdstuk van het proefschrift wordt uitgelegd hoe deze problematiek in de toekomst beter kan worden aangepakt. Daarvoor is een geïntegreerde aanpak nodig, waarbij de spreiding van de infectie (indien aanwezig) en het tijdsverloop sinds de laatste test specifiek wordt meegenomen. Daarmee kan veel zuiverder dan voorheen worden berekend wat het risico is dat het bedrijf of land toch niet vrij is van de infectie.

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Curriculum Vitae

Aline de Koeijer was born at May 23rd 1967 in Schoondijke, the Netherlands. Between 1979 and 1986 a VWO-degree was obtained at Scholengemeenschap 't Zwin in Oostburg. Since 1989 and 1993, she studied Biology at Leiden University, the Netherlands, which resulted in a graduation as mathematical biologist with a thesis on modelling the spread of PDV virus in wild populations of harbour seals. She continued research in a PhD project at the Centre for Mathematics and Computer Sciences (CWI) in Amsterdam, concerning mathematical modelling in epidemiology, mainly focussing on theoretical aspects at population level. In 1997 she moved to more applied and quantitative epidemiology, in a new employment at the Dutch Institute for Animal Science and Health, later called ID-Lelystad, which by now, is part of the Animal Sciences Group, WageningenUR. The work in chapters 2 and 3 has mainly been done at CWI, the remaining part of the research has been done in the Quantitative Veterinary Epidemiology cluster of ID-DLO / ID-Lelystad

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