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The use of a mass-action model to validate the output from a stochastic simulation model of bovine viral diarrhoea virus spread in a closed dairy herd

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Abstract

The spread of bovine virus diarrhoea virus (BVDV) in a closed dairy herd maintained under typical management conditions is studied using two approaches. In the first instance a stochastic computer model is used to simulate the month-to-month changes in the infection status of each animal. These results are contrasted with the results of a mass-action model which uses three differential equations. A comparison of the two approaches indicates that the results are in broad agreement. The stochastic approach has the benefit of providing an estimate of the probability of the infection becoming extinct and the herd becoming BVDV-free for different herd sizes. Published by Elsevier Science B.V.

Keywords: BVDV; Bovine viral diarrhoea; Modelling; Simulation; Differential equation

1. Introduction

Infection with the agent for Bovine Viral Diarrhoea (BVD) occurs world-wide, and causes important losses to the farming economy (Meyling et al., 1990; Bennet and Done, 1986). The virus (BVDV) occurs in two distinct forms: cytopathogenic and non-cytopathogenic (Horzinek, 1990). Most infections are with the non-cytopathogenic form, and usually cause only a mild disease or are clinically inapparent. The virus can pass the

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placental barrier to produce infection of the foetus which sometimes results in foetal abnormalities or abortion. If foetal infection occurs during the first trimester, i.e. before the onset of immunocompetence, the virus persists and the calf is born persistently infected (PI) (Brownlie, 1990). Such PI animals are asymptomatic carriers of the virus, shed large quantities of the virus into the environment, and are usually considered as the main source of infection. If PI animals are subsequently infected with a serologically-similar, cytopathic isolate of BVDV, they succumb to mucosal disease and will almost certainly die (Baker, 1990; Brownlie et al., 1987).

Although infections with BVDV are often asymptomatic, detection of serum antibodies can be used as an indicator of previous exposure to the virus. It is estimated that 25% to 30% of susceptible cows in the UK national herd seroconvert each year and that 70% of animals have seroconverted by 4 years of age (Harkness et al., 1978). It is an important economic disease in the UK national herd. Modelling such a disease provides understanding and allows the effects of altering management and control regimen on the level of infection within a herd to be determined.

The use of modelling techniques in the study of disease has a long history (Bailey, 1975). Most early models were mass-action models, in which individuals were ignored, and animals within any one group were presumed to act as a unit. An example of such a model is a differential equation, where the rate of change of the number in any one group may depend on several factors, some of which may be static, and some may vary with time. This approach has been widely used by Anderson and May in the study of parasitic disease of humans (Anderson and May, 1991). More recently the availability of digital computers has led to the widespread use of stochastic simulations. In a stochastic simulation, computer-generated pseudo-random numbers are used to determine the fate of individuals where two or more possible outcomes exist, according to the probability of the various outcomes.

Computer simulations are complex programs and difficult to verify. Sorensen et al. (1995) described the use of a case report to verify a model used to investigate the economic consequences of BVDV infection in a herd. In our paper we describe a deterministic model based on differential equations which we used to approximate the results from a computer program that was written to undertake a stochastic simulation of the spread of BVDV through a herd. The simpler approach of the deterministic model enables the output of the computer program to be compared with the known dynamics of the differential equations. In order to compare the two models, the computer simulation must conform to the conditions associated with the deterministic model. We assume that when these conditions are removed, the computer model will still embody the dynamics of the deterministic model.

2. Materials and methods

In order to model the disease in a closed herd, three groups of animals of distinct immunological status were considered:

- Susceptible: these are animals which have not encountered the virus and have no circulating antibodies. Infection with virus leads to transient illness and the animals become immune.

- Immune: these are animals which have encountered the virus and mounted an immune response. For simplicity, immunity is considered to be lifelong and complete; these animals are no longer susceptible to infection.
- Persistently infected (PI): these are animals which have encountered the virus in utero during the first trimester of pregnancy (either because their dam was PI or because their dam was acutely infected at this stage). PI animals remain so for life and give birth to PI calves.

Animals may leave each of the groups as a result of culling or other causes of mortality. Replacements allow new individuals to enter each of the groups. In addition, a model must take into account the normal management factors that influence animal demographics on a farm. These factors include culling rate, age at first service and the proportion of animals that return to service.

The model must also incorporate a method for calculating the rate of seroconversion of susceptible animals. In order to be reasonably accurate whilst maintaining computational practicality, a rate of seroconversion that depends solely on the number of PI animals was chosen. The infection rate takes the form $(1-(1-r)^{NP})$ where r is the transmission rate between animals, N the total number of animals in the herd and P the proportion of the herd that is PI. Thus NP is the number of PI animals in the herd. This results in a value for the proportion of susceptible animals that seroconvert each month. This proportion can be considered as the probability of seroconversion and varies between 0 and 1. It is particularly sensitive to variations in NP when NP is small. This is similar to the method used to calculate the infection rate in the Reed-Frost chain-binomial epidemic model (see Bailey, 1975). The infection rate, r has the units per PI animal per month, and represents the proportion of susceptible animals that seroconvert each month in the presence of a single PI animal. It is therefore analogous to the basic reproduction ratio, R_0, the rate of producing new infectious individuals at the time of introduction of a disease into a wholly susceptible herd. This model is not typical of models of disease in that animals that become infected outside the womb do not contribute to the infectivity within the herd, and in that we are considering the proportion of susceptibles that seroconvert, not the number of animals.

3. Stochastic computer model for disease transmission

The computer model simulates the spread of infection within the herd. On a month-to-month basis (month: 28 days), numbers of animals within each immunological group change. Susceptible animals may seroconvert and move to the immune group. Calves born to susceptible dams will be susceptible and join the susceptible group. Calves born to immune dams will be temporarily immune and will join the susceptible group once immunity wanes. Calves born to PI animals remain members of the PI group. In addition, a proportion of calves born to animals that seroconvert during pregnancy will be born PI.

The numbers of animals in each group will change according to management practice. Animals which are culled because of their age or because they do not conceive are replaced by animals chosen at random from replacement heifers of the appropriate

age. A binomial probability distribution was used to randomly select animals which conceive at service.

Combining the herd-management details and the probability formulation described for seroconversion, the computer model was constructed using the C^{++} programming language. The model enables changes in the herd structure to be followed from month to month. In particular, for any naive herd of known size and composition, it is possible, once BVDV has been introduced, to predict whether or not the proportions of susceptible, immune and PI animals become stable.

The management conditions are such that female calves are kept for a period of 14 months after which enough animals are retained as heifers to replace those adults and heifers culled. Seventy percent of heifers and adults conceive at service. All non-PI animals are culled after their fifth lactation, PI heifers are culled after their second lactation and animals failing on three successive services are also culled.

The transmission rate is 0.03 per PI animal per month, equivalent to 0.30 of the susceptible herd seroconverting per year in the presence of a single PI animal. This is similar to the rate shown in the UK herd as a whole (Harkness et al., 1978). It has been shown elsewhere that the stochastic simulation is not particularly sensitive to transmission rates higher than 0.025 per PI animal per month (Innocent et al., 1994).

The initial herd structure is assumed to be 40% calves, 10% heifers and 50% adults. On day 1, a PI adult is introduced into the adult group and the rate at which susceptibles become immune or persistently infected is simulated over a 10 year horizon. The model is repeated for 1000 runs and the average numbers of susceptible, immune and PI breeding animals calculated. In addition, a 95% confidence interval is constructed for the mean number of PI breeding animals in the herd and the proportion of runs in which no PI animals are left is recorded. These values are calculated for a number of different herd sizes.

The computer simulation is further described in Innocent et al. (in press.) where it is used to investigate the effect of the duration of active immunity and the effect of differential loss of PI calves during the first year or so of life.

4. Deterministic mass-action model for disease transmission

One method of representing the flow of animals from one group to another is to use one or more differential equations (Maynard Smith, 1974). Here the rate of change of a value over time, denoted dX/dT for some variable X, such as the proportion of the herd that is susceptible, is equated to some function of constants and variables from the model. Two types of solution to a differential equation are of interest. In the more detailed one, it may be possible to determine how the variables change over time, given any specific starting conditions, i.e. find an equation relating how X varies with time in our example above. Unfortunately this is not always possible. It is often possible, however, to produce an approximation to this using numerical methods and computer software packages, but our reason for using a differential-equation model was to determine whether our software developed for the stochastic simulation model was working correctly, and so this may not be suitable.

A second approach is to find the equilibrium solution for the model. If dX/dT is positive then X is increasing over time; if dX/dT is negative, X is decreasing; and if dX/dT is zero then X is not changing. The point at which all the differential equations of the model are 0 is said to be an equilibrium point: since without external influences the system will remain at this point indefinitely. A model may have no equilibrium points or many.

The movement of animals from one group to another is illustrated by the compartmental representation in Fig. 1. Only the adult and heifer herd is considered, as these are the only reproductively-active animals in the herd. S represents the proportion of the herd that is susceptible, I the proportion immune and P the proportion PI. N represents the total herd size. α, β and γ are the culling rates for susceptible, immune and PI animals respectively. $f(S,P,N)$ and $g(S,P,N)$ are functions of S, P and N which determine the rate at which seroconversion of susceptible animals takes place and the rate at which PI animals are used to replace culled animals respectively. The ratio of $g(S,P,N)$ to $\alpha S + \beta I + \gamma P$ at any point in time represents the proportion of replacements that are PI.

The rates of change of susceptible, immune and persistently infected animals with time are described by the following differential equations:

$$\frac{dS}{dT} = \beta I + \gamma P - f(S,P,N) - g(S,P,N)$$

$$\frac{dI}{dT} = f(S,P,N) - \beta I$$

$$\frac{dP}{dT} = g(S,P,N) - \gamma P$$

In practice, $g(S,P,N)$ will be of the form $\theta(\phi f(S,P,N) + P)$ where θ denotes the proportion of PI calves kept as replacements per unit time and ϕ the proportion of

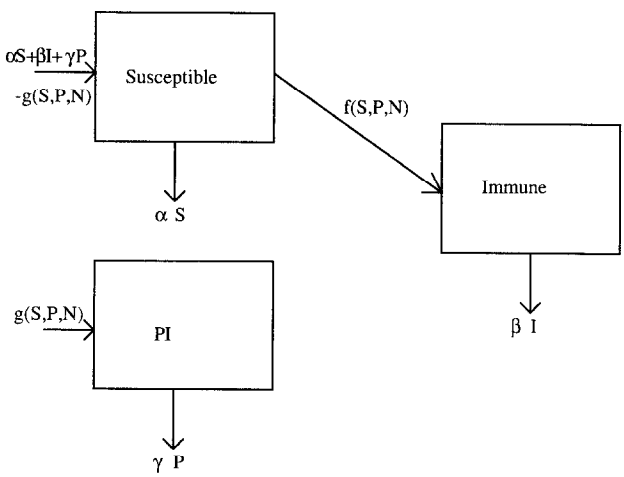

Fig. 1. A simplified representation of the flow of animals between susceptible, immune and PI groups used to formulate the mass action model.

newly-infected cows which give birth to PI calves; since *f(S,P,N)* is the number of newly-infected cows, and all PI cows give birth to PI calves. In order to maintain mathematical simplicity, all replacements are considered to be either susceptible or PI.

Because the herd is closed and the herd size is maintained constant by replacement of culled animals from the female calves, the sum of the above three rates of change is zero. It is therefore sufficient to investigate the rates of change of the PI animals and the immune animals. Analytical solutions for changes in the numbers of PI and immune animals over time are not known, but the eventual behaviour of the herd can be obtained from equilibrium solutions (Bailey, 1975).

In a equivalent manner to the simulation model it is therefore possible to set *f(S,P,N)* equal to $S(1-\epsilon^{NP})$, where ϵ is $1-r$. This means that the rate at which animals seroconvert depends solely on the number of PI animals. In order to determine the equilibrium values of P and I, denoted $\hat{P}$ and $\hat{I}$, it is necessary to solve the simultaneous equations:

$$\frac{dP}{dT} = 0$$

$$\frac{dI}{dT} = 0$$

Note that $\hat{S} = 1 - \hat{P} - \hat{I}$, since $S + I + P = 1$ at all times. This provides the following, at equilibrium:

$$\hat{P} = \frac{\theta\phi\beta(1-\epsilon^{N\hat{P}})}{\theta\phi\beta(1-\epsilon^{N\hat{P}}) + (\gamma-\theta)(\beta+1-\epsilon^{N\hat{P}})} \quad \text{(i)}$$

$$\hat{I} = \frac{(\gamma-\theta)\hat{P}}{\theta\phi\beta} \quad \text{(ii)}$$

Eq. (ii) shows that for any equilibrium value, $\hat{P}$, there is a single corresponding $\hat{I}$ value. The solutions to Eq. (i) give all the possible values for $\hat{P}$, and thus define the number of equilibrium points of the model.

We are thus interested in the number of solutions to Eq. (i) which lie in the interval $0 < \hat{P} < 1$, since $\hat{P}$ represents the proportion of the herd that is PI, so all sensible solutions must lie in this interval. One way to consider this is to equate the two sides of Eq. (i) to some dummy variable, Y:

$$Y = \hat{P} \quad \text{(iii)}$$

$$Y = \frac{\theta\phi\beta(1-\epsilon^{N\hat{P}})}{\theta\phi\beta(1-\epsilon^{N\hat{P}}) + (\gamma-\theta)(\beta+1-\epsilon^{N\hat{P}})} \quad \text{(iv)}$$

Where these two lines cross represents the solutions to Eq. (i). Eq. (iii) is a straight line, passing through the origin, of Slope 1. Eq. (iv) can be shown to be equal to 0 when

$$\hat{P} = 0$$

, is monotonically increasing for $0 < \hat{P} < 1$, with its slope monotonically decreasing, and it takes a value less than 1 when $\hat{P} = 1$. Therefore $\hat{P} = 0$ is always an equilibrium point,

there may be at most one further equilibrium point, and this only exists when the slope of (iv) is greater than 1 at $P = 0$. This occurs when:

$$N > \frac{\theta - \gamma}{\theta\phi \ln(\epsilon)}$$

Local-stability analysis investigates the behaviour of a system when it is close to an equilibrium point. In particular, an equilibrium point is said to be locally stable if, for any small disturbance from the equilibrium point, the system will return to that equilibrium point. It is therefore possible to determine under what conditions infection will die out within a herd.

Use of local-stability analysis indicates that the equilibrium point ($\hat{P} = 0$, $\hat{I} = 0$, $\hat{S} = 1$) is locally stable providing the following inequality holds:

$$N < \frac{\theta - \gamma}{\theta\phi \ln(\epsilon)}$$

The model predicts that in small herds infection will die out. Otherwise the group sizes converge towards the non-zero equilibrium point, i.e. a stable, endemic state is reached. In such situations the model indicates the proportions of the herd that will eventually become persistently infected, immune and susceptible.

The rate parameters were chosen to be comparable with the situation specified in the stochastic simulation model. In particular, the culling rates β for immune and γ for PI animals were set to 0.25 and 0.33 per year respectively. This is equivalent to keeping PI animals for 3 years, since they are kept for one year as heifers, then for a further two lactations. Immune animals are estimated to become immune on average after their first lactation and are then kept for a further four years, to be culled after their fifth lactation, thus one quarter of immune animals are culled each year. The equations representing the herd dynamics are independent of α, the culling rate of susceptibles. The replacement rate for PI calves, θ, and the proportion of cows to have PI calves, ϕ, are 0.17 per year and 0.25 respectively. Seroconversion depends on the number of PI animals. The transmission rate r is set to 0.3 per PI animal per year and so ϵ is 0.7.

5. Results

Results for the equilibrium numbers in the herd for a range of herd sizes can be obtained using the solutions derived using the mass action model. The non-zero equilibrium results for susceptible, immune and infected animals are dependent on the herd size as illustrated in Fig. 2.

In order for the stochastic simulation model to be equivalent to the mass-action model it was required that the seroconversion rate of calves in the simulation model be zero, and to only consider the adults and heifers in the herd. This was necessary because the mass action model presumes that all animals are reproductively active, and ignores the presence of calves in the herd. Results obtained from the simulation after a period of 10 years were examined as it was considered that the group numbers had reached a steady state by this time.

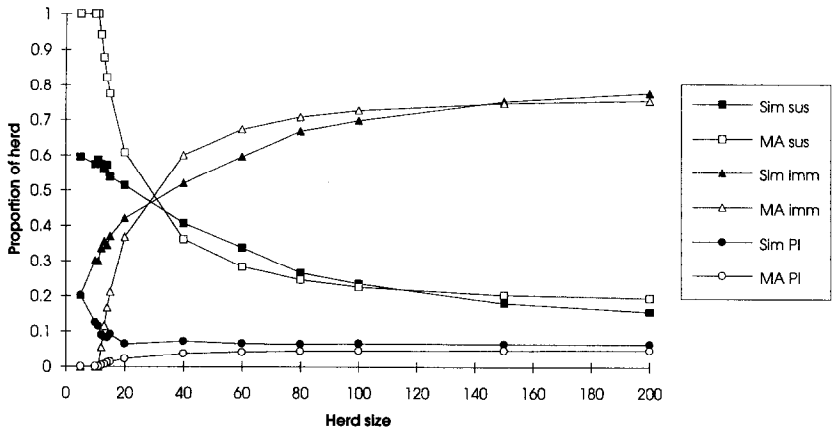

Fig. 2. Comparison of the proportion of the cows and heifers that are susceptible, immune or PI against herd size for the equilibrium point of the mass action model (open points) and the mean state after 10 years for 100 runs of the simulation model (solid points).

For a number of herd sizes, Table 1 shows the equilibrium numbers of PI animals within the herd predicted using the mass-action model. Note that PI animals are present in the equilibrium state providing the herd size (excluding calves) exceeds 11 animals. Otherwise, the number of PI animals becomes zero and the herd reverts to being susceptibles only.

For all herd sizes, the mass-action model predicts a lower number of PI animals than the mean obtained using the simulation model, and a higher number of susceptible animals (Fig. 2, Table 1). However, in all herd sizes the number of PI animals predicted by the mass-action model is within the 95% confidence interval of the stochastic simulation (Table 1). For herd sizes greater than 40, the proportion of the herd that is susceptible and the proportion immune are similar for both models (Fig. 2).

The mass-action model predicts very low numbers of PI animals as it allows fractions of PI animals to exist, unlike the simulation model which deals with animals as individuals. For example, at herd sizes of 20 or less the simulation model predicts a high chance of the herd becoming BVDV-free whereas the mass-action model predicts values for PI animals of less than a single individual, and that the herd will become BVD free without any cognisance of random variation if the herd size is less than 12. Furthermore, when the herd size is greater than 150, the simulation model indicates that the chance of the herd becoming BVDV-free is around only 1%, whereas it is 29% for a herd of size 5.

The mass-action and stochastic-simulation models are in close agreement for large herd sizes. This is because the random effects of an individual animal have less effect in a large herd than in a small one. Thus, the mass action model approximates to the stochatic-simulation model. There is still a discrepancy in the number of PI animals predicted by the two models, since both models predict low numbers of PI animals and therefore each individual is a large proportion of the total number of PI animals in the

Table 1
Comparison of the number of persistently infected animals in the herd at equilibrium predicted by the mass-action model with the mean and 95% confidence interval of the number of PI animals, and the probability of the herd becoming BVDV free by 10 years for various herd sizes as predicted by the simulation model run 1000 times

Herd size	Number of PI animals predicted by mass-action model	Mean number of PI animals after 10 years of simulation model	95% Confidence Interval of number of PI animals after 10 years of simulation model		Probability of herd becoming BVD free by 10 years
200	9.46	12.75	4	20	0.012
150	7.02	9.65	2	17	0.010
100	4.55	6.47	0	13	0.020
80	3.54	5.10	0	11	0.033
60	2.53	3.90	0	11	0.056
40	1.50	2.87	0	9	0.085
20	0.46	1.29	0	5	0.187
15	0.20	1.37	0	4	0.225
14	0.15	1.15	0	4	0.195
13	0.09	1.08	0	4	0.184
12	0.04	1.06	0	5	0.205
11	0.00	1.24	0	5	0.250
10	0.00	1.23	0	5	0.281
5	0.00	1.00	0	4	0.293

herd. In addition, both models confirm that once the herd size becomes 'large', the proportion of the herd that is PI is not greatly influenced by the herd size.

6. Discussion

Most previous attempts to model the effects of bovine viral diarrhoea virus have relied on relatively-simple, deterministic models to estimate the financial losses within a herd (Hartley and Richards, 1988; Houe et al., 1992 and Pasman et al., 1994). The use of a stochastic simulation similar to that described in this paper has been used by Sorensen and Enevoldsen (1994) and Sorensen et al. (1995). However, their simulation was an adaptation of a stochastic simulation designed to model various management factors on the economic output of a farm, overlaid with a simplified model for the spread of the disease. The model appears not to take into account the level of infection in a herd, but assumes a static seroconversion rate of 20% of susceptible animals per week. This level of seroconversion is higher than that which has been suggested in the UK (Harkness et al., 1978) and that used in our study.

The mass-action model is an approximation to the more-precise dynamics contained within the stochastic-simulation model. However, computer algorithms are difficult to validate in all but the simplest of cases. We therefore decided to produce the simpler mass-action model in order to compare its output with that of the simulation. The simulation model is able to deal with stochastic variability. It is therefore able to determine more accurately the behaviour of subpopulations of animals within the herd when the numbers become small or zero. It is also able to provide a measure of the variability of any output from the model. The two models compare well for large herd sizes; although the mass-action model consistently gives higher estimates of the number of susceptible, and lower estimates of the number of PI animals than the stochastic simulation. The discrepancy is due to the simplicity of the dynamics inherent in the mass action model. In particular, it assumes that animals which seroconvert are evenly distributed throughout pregnancy. In the stochastic simulation, however, heifers are introduced to a infectious adult herd at the same time that they are bred, and therefore a large proportion are likely to seroconvert early in their first pregnancy. This in turn will lead to a large number of PI births. Because the two models agree well with large herd sizes and because the general trend of the three groups with different herd sizes agrees fairly well (especially for large herds), we felt that the comparison represents a good indication that the computer simulation is working in the way in which it was intended.

Both models predict high proportions of immune animals in large herds. Thus, if it is proposed to detect infection in a herd by looking for antibodies in a relatively small proportion of the herd, it is likely that small herds will be declared BVDV-free when they are in a stable, endemic state. Furthermore, the stochastic simulation predicts that small herds are more likely to become BVDV-free than large ones in the absence of intervention. Indeed only around 1% of herds of 150 animals or more are likely to become BVDV-free within 10 years compared to almost 20% of herds of 20 animals. However, this prediction is for a completely-closed herd. It may be that in smaller herds, replacements are more likely to be bought in. These bought-in animals have a probability of being PI and therefore may re-infect the herd. It is therefore important that any attempt to eradicate or detect the level of infection in a herd should take into account the size of the herd and whether or not it is completely closed.

We feel that the computer simulation model is a useful and accurate tool for exploring the effects of various factors on the epidemiology of BVDV (such as the role of the sweeper bull) (Meyling and Jensen, 1988), and the effect of the duration of immunity (both from natural infection and vaccination). The mass-action model is a simplification of the dynamics believed to occur in an infected herd. In particular, it considers the numbers of animals in any group within the herd to be continuously variable within certain limits. It is, however, relatively simple to formulate and solve, using tried and trusted methods. Alternatively, formulation of a stochastic simulation is relatively complex, but allows the dynamics within the herd to be modelled fairly accurately. In particular, the stochastic simulation allows us to investigate the random effects of individuals within the herd. In this paper we have shown that the two modelling approaches do produce similar results. The findings provide evidence that the simulation program is producing results that are compatible with the known dynamics of the system.

Acknowledgements

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