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A computer simulation of the transmission dynamics and the effects of duration of immunity and survival of persistently infected animals on the spread of bovine viral diarrhoea virus in dairy cattle

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SUMMARY

This paper describes a computer model that mimics the spread of bovine viral diarrhoea virus (BVDV) infection through a closed herd. The model is able to simulate the spread of infection when a persistently infected (PI) animal is introduced into an infection-free herd, and it is used to investigate the role of persistently infected animals, seroconverting animals, loss of PI calves and duration of immunity on the level of infection within the herd. Under typical management conditions one persistently infected animal poses a real threat to a herd, and the prospect of the herd becoming infection free in a 10-year period without intervention is remote. Seroconverting animals are found to be an important source of infection in herds with few immune animals. The increased loss of PI calves is likely to restrict the numbers of PI animals in a herd, and loss of immunity is important since it increases the possibility of a PI calf being born.

INTRODUCTION

Bovine viral diarrhoea virus (BVDV) infection is widespread throughout the world. In the UK it has been reported that 70% of the national herd have been infected with the virus by 4 years of age [1] and that infection results in major economic losses in the cattle industry [2, 3]. Most primary infections with non-cytopathogenic BVDV produce mild clinical symptoms. Transient diarrhoea or respiratory disease may accompany infection in calves and young stock, while infection in cows can result in a transient drop in milk yield [4]. Recently, more virulent strains of the virus have been identified, which cause acute haemorrhagic disease and mortality. Detection of serum antibodies can be used as an indicator of previous infection with BVDV.

The most significant clinical consequences of infections with non-cytopathogenic BVDV arise as a result of infection of pregnant animals. The virus is able to cross the placenta and infect the foetus. In the first and second trimesters of pregnancy this results in abortion or foetal abnormalities in a small proportion of animals. Infection of cows during the first trimester, before the foetus has acquired immune competence, results in the birth of calves that are persistently infected (PI) with the virus and immunologically tolerant to it. These animals remain asymptomatic lifelong carriers of the virus, unless mucosal disease intervenes. High levels of viraemia and virus shedding in nasal secretions can be demonstrated by virus culture or detection of viral antigen by ELISA. Thus PI animals represent a continual source of infection for susceptible animals. This is in contrast to immunocompetent animals undergoing primary infections, which shed virus for no more than 2 weeks [5]. PI animals are often smaller and show slower growth rates than their contemporaries. They are also prone to pneumonia and enteritis [6, 7].

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An important clinical syndrome associated with BVDV is mucosal disease, which occurs in PI animals that become super-infected with a cytopathogenic strain of BVDV that is antigenically related to the persisting non-cytopathogenic strain [8]. Mucosal disease occurs most commonly in animals 6–18 months of age and is characterised by ulceration of the gut mucosa and persistent diarrhoea, with death usually occurring within 10 days of the onset of signs. Cytopathogenic virus does not establish persistent infections in the foetus and may therefore have a limited capability of perpetuating infection within a herd [5]. Clearly, the risk of mucosal disease in a herd is related to the numbers of PI animals in the herd. This in turn is dependent on the numbers of pregnant cows that have been infected with BVDV in previous years. Indeed the occurrence of mucosal disease is often the first obvious sign that BVDV has been introduced into a herd [9].

Various methods have been proposed for the control of bovine viral diarrhoea (BVD) at the herd level. Two major approaches under consideration are the use of herd testing for the identification and removal of persistently infected animals and the use of live or killed vaccines. However, if these measures are only partially effective they could in the long term potentially increase the risk of mucosal disease, since introduction of a PI animal into a herd in which the virus has been eradicated could lead to a large number of PI births with a subsequent outbreak of mucosal disease. The development of a mathematical model of the transmission dynamics of the virus would provide a means of predicting the impact of various control measures. Herein we describe a modelling approach that simulates the transmission of BVDV within a typical dairy herd structure and explore parameters within the model that influence the steady state.

METHODS

Network flow of animals between disease groups

For the purposes of establishing a model representing the spread of BVDV amongst animals in a herd, four important groups can be identified:

(1) All susceptible animals are at risk to infection. Susceptible dams that do not become infected during pregnancy give birth to susceptible calves that join the **susceptible group**.

(2) Once a susceptible animal becomes infected and seroconversion takes place, the animal will become a member of the **immune group**. Immunity may be considered to be lifelong, in which case animals entering this group remain in the group; alternatively immunity may decrease with time, in which case when immunity is lost animals will join the susceptible group again. Calves born following *in utero* infection after 120 days of gestation acquire immunity and also join the immune group.

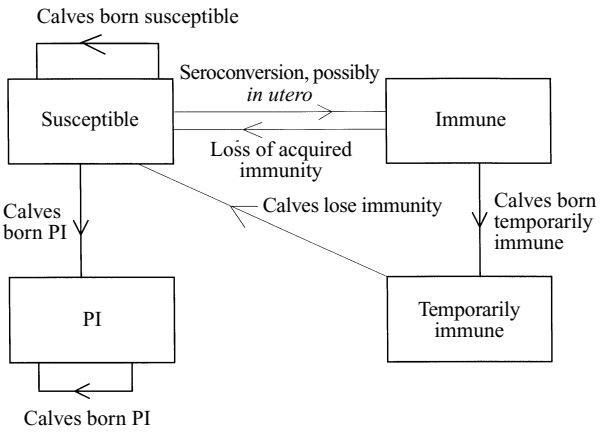

Fig. 1. A network representation of the flow of animals between susceptible, immune, temporarily immune and PI groups. Narrow lines represent the movement of animals from one group to another, heavy lines the birth of calves.

(3) Calves born of immune dams acquire colostral antibody and join the **temporary immune group**. Temporary immunity is considered to last for a period of 6 months after which the animals join the susceptible group.

(4) Infection of a susceptible dam during the first 120 days of pregnancy may result in abortion in a small percentage of cases or a persistently infected calf which becomes a member of the **persistently infected group**. Persistently infected animals are also born to persistently infected dams.

The network representation in Figure 1 illustrates the flows between the susceptible, immune, temporary immune and persistently infected groups. Animals may leave each of the groups as a result of culling or other causes of mortality, and replacements will result in new members joining the groups.

Network flow of animals according to husbandry

The network shown in Figure 2 illustrates a typical management life cycle for animals within a closed dairy herd. The network convention is such that boxes are used to denote a time delay in the flow of animals from one event to another and large circles are used to denote proportions of animals at one stage which move to another.

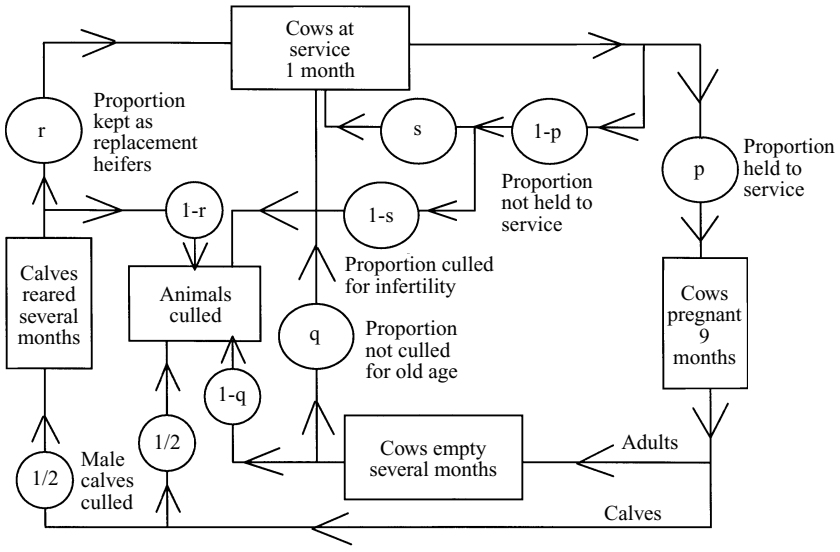

Fig. 2. A network representation of the flow of animals according to age and husbandry practice in a dairy herd.

When calves are born it is assumed that males are culled and female calves are kept until breeding age when a proportion is selected to become replacement heifers. Heifers are kept only to replace those cows or heifers that have been lost or culled that month. The replacement heifers and empty cows are taken to service each month. A proportion will not hold to service, and if an animal is not pregnant after a fixed number of services culling takes place. For those animals which do hold to service, pregnancy is assumed to last 10 months (280 days), a month being defined as 28 days, after which time calves are born. Heifers are considered to join the adult group once they have given birth to their first calf. Following the birth of a calf, cows are kept empty for a specified period before being returned to service. At this point cows are culled according to their age.

The small circle containing a plus sign in Figure 2 denotes the accumulation of animals that return to service as a result of two feedback loops. One feedback loop takes account of animals returning to service after pregnancy and the other feedback loop arises from animals not holding to a previous service.

There are several management factors that will vary from one producer to another. These include the period that calves are kept before being used as replacement heifers, the period that cows are kept empty before returning to service, the number of failed services before it is decided to cull an animal and the proportion of animals that hold to service. Specification of these herd parameters will in turn affect the number of replacement heifers to be kept, in order for the herd to remain in a steady, viable state.

Management conditions in the model have been chosen 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 per cent of heifers and adults hold to service, and all non-PI animals are culled after their fifth lactation. To take into account the reduced fertility and increased abortion associated with persistent infection, PI cows are culled after their second lactation. In addition, animals failing on three successive services are culled.

Infection during the first 120 days of pregnancy results in 10% of cows aborting and 64% of cows giving birth to PI calves. These figures are derived from those used by other authors (10).

Stochastic computer model for disease transmission

A computer simulation model is proposed which can take account of the interaction of infection and immune status as illustrated in the network in Figure 1 and husbandry practice as illustrated in the network in Figure 2. Combining these two networks results in ten classes of animal: susceptible calves, heifers and adults; immune calves, heifers and adults; temporary immune calves; and persistently infected calves, heifers and adults. In addition, details of the age and disease status of animals culled in any 1 month need to be maintained.

The simulation model follows the spread of disease within a previously virus-free herd after the introduction of one persistently infected adult. The parameters pertaining to replacement, return to

service, culling, etc. are specified for the herd along with the age structure on the day of introduction. A stochastic element is introduced into the model in several places. Animals are selected at random according to a Bernoulli distribution with parameter (p), for the proportion of animals that holds to service; susceptible animals are also selected according to a Bernoulli distribution, with a probability of seroconversion that alters depending on the level of infection within the herd (see below); animals to be retained as replacement heifers are chosen at random to replace culled animals; and the outcome of infection on the foetus is chosen at random, the probability of the foetus aborting or being born either PI or virus-free varies according to how far through pregnancy the foetus is infected.

The mode of transmission assumes that susceptibles become infected from persistently infected animals and that the probability of infection increases as the number of persistently infected animals increases. The infection probability takes the form $(1-(1-\epsilon)^{\Pi})$ where ϵ is the transmission rate between animals and Π is the number of persistently infected animals. In addition to persistently infected animals shedding virus, animals that are seroconverting are considered to represent a source of infection for a period of 10 days.

The simulation instructions have been implemented using the C^{++} object-orientated programming language. The model operates in steps of 1 month, each month being 28 days. Numbers of animals in each of the ten classes defined can be estimated over the management period of interest. In particular, the model can be used to plot changes in the numbers of susceptible, immune and persistently infected calves and adults. The pattern which evolves over a period of years represents the level of infection which can be expected to be present in the herd when the management practice is kept constant. The presence of a regular pattern is known as the steady state distribution. The model therefore gives insight not only into the steady state distribution but also to the early stages of the transmission of the virus.

By repeating a large number of simulations the effect of stochastic variation on the numbers of infected and uninfected animals can be assessed. In particular, it is possible to estimate the probability of the infection becoming extinct within the herd.

The stochastic simulation model has been used to study the dynamics of transmission in a closed dairy herd of 200 animals. The initial herd structure is assumed to consist of 80 calves, 20 heifers and 100 adults all of which are susceptibles. A persistently infected animal is introduced into the adult group during the first month and the rate at which susceptibles become immune or produce persistently infected calves is simulated monthly over a 10-year horizon. Immunity that is acquired subsequent to infection may or may not be lifelong. Calves born to immune dams will have temporary immunity from colostrum. PI cows are culled after their second lactation, non-PI cows after their fifth. This difference was introduced in order to take into account that PI animals may be poorer producers of milk, and thus culled at an earlier age.

The effect of altering the rate of spread of infection has already been described [11]. It was found that the transmission rate only had any great effect on either the rate of spread of infection or the final level of infection of the herd if it was small, below around 0·025 per PI animal per month. This transmission rate is equivalent to 0·025 of the in-contact, susceptible herd becoming infected for each month that a PI animal is present. Throughout the models described in this paper a transmission rate of 0·03 per PI animal per month has been used; this transmission rate is consistent with survey data of the UK herd (1).

The results from the following models are presented in this paper:

(1) PI animals are considered as the sole source of infection; natural, acquired immunity is considered to last the lifetime of the animal; and PI calves are no more likely to die or be culled than non-PI calves.

(2) As (1), except that seroconverting animals are considered to be infectious for 10 days. This is implemented by considering the number of infectious animals in any month to be the number of PI animals plus one third the number that seroconverted last month.

(3) As (2), except that 20% of the remaining PI calves are lost in each of the first 2 months of life, followed by 5% per month for the next 12 months, resulting in a total loss of around 65% of all PI calves before selection for heifers. Previous models have assumed that although PI cows are culled after their second lactation whereas non-PI animals are not culled until after their fifth lactation, there is an equal chance of a PI or non-PI heifer calf being chosen as a replacement. PI calves are generally more likely to be smaller and to succumb to intercurrent diseases than non-PI calves. They may also develop mucosal disease. Therefore, they are less likely to be kept as

replacements. The model has been used to simulate what happens when a PI heifer is more likely to be culled or die during the first year or so of life.

(4) As (2), except that 10% of the remaining PI calves are lost in each of the first 2 months of life, followed by 5% per month for the next 12 months, resulting in a total loss of around 50% of all PI calves before selection for heifers. This represents what we believe to be the lower estimate of PI calf loss.

(5) As (4), except that immunity wanes. The previous models assume that acquired immunity is lifelong. This may not be the case. Animals may become susceptible to infection once antibody levels wane. Moreover, two levels of immunity may exist. In the first, high levels of antibody are present and prevent infection without any further boosting of antibody levels. In the second, animals have low levels of antibody that are sufficient to prevent systemic infection with the virus, and so protect the foetus from infection, but limited local replication of virus results in boosting of antibody and immunity. In this model the duration of the high level of immunity is 6 months, as is the duration of the low level of immunity, resulting in a total duration of immunity of 1 year.

(6) As (5), except that the duration of the low level of immunity is increased to 18 months, resulting in a total duration of immunity of 2 years.

RESULTS

Transmission dynamics and sources of infection

It is generally considered that the major source of infection within a herd comes from PI animals. The situation where PI animals represent the only source of infection has been analysed and the results illustrated in Figure 3. In this model all animals that recover from infection have lifelong immunity. The results indicate the fluctuations obtained in the numbers of persistently infected, immune, temporary immune and susceptible animals. In order to simplify the presentation heifers have been included in the adult groups.

Following the introduction of a persistently infected animal into the herd there is a decline in the number of susceptible animals and an increase in the number of immune animals. Thereafter, an equilibrium is reached within about 5 years. The equilibrium consists of 18% susceptible animals, 75% immune animals and 7% persistently infected animals. At no point do the results present a perfectly smooth curve, due to the fact that a number of random elements are present within the model; namely the probability that a cow becomes pregnant following service, the probability that a susceptible cow becomes infected, the outcome of infection on the foetus and the probability that a heifer is kept as a replacement.

Animals that seroconvert also excrete virus whilst they are viraemic. If seroconverting animals are now considered as a source of infection for the 10-day period after they become infected then the results in Figure 4 are obtained.

Initially there is a faster decline in the number of susceptible animals than if only PI animals are considered as a source of infection. Thus, after 10 months the proportion of adults which is susceptible is around 67% as opposed to around 83% if only PI animals are a source of infection. Thereafter the decrease in susceptible animals slows down, reaching an equilibrium state after a total of about 4 years. However, the final ratio of susceptible, immune and PI animals is much the same as that obtained if PI animals are considered the only source of infection at 19% susceptible, 75% immune and 6% persistently infected animals.

The proportions of adults, heifers and calves that are susceptible, immune and PI at the end of the 10-year period are shown in Table 1. This is the expected state which a herd would eventually exhibit if infection becomes endemic. It can be seen that around 54% of the calves are immune, much of which is due to maternally-acquired immunity. This is lost after 6 months, but by the time that the animals become heifers a number have encountered the virus and become immune; so that in the heifer group around two thirds are immune, and under one third are susceptible. As the animals become older they are more likely to have encountered the virus and so become immune, hence in the adult cow population approximately 90% are immune and under 10% are susceptible. This is true whether or not seroconverting animals are considered to be a source of infection, indicating that the inclusion of seroconverting animals as a source of infection does not greatly alter the endemic state in the herd.

In order to determine the likelihood that random events would lead to eradication of the virus from the herd, the transmission dynamics within the herd was simulated over a 10 year horizon on 1000 occasions and the number of times the herd became BVDV free recorded. This provided an estimate of 0·032 for the probability of extinction of the infection within a herd when PI animals are the only source of infection. This

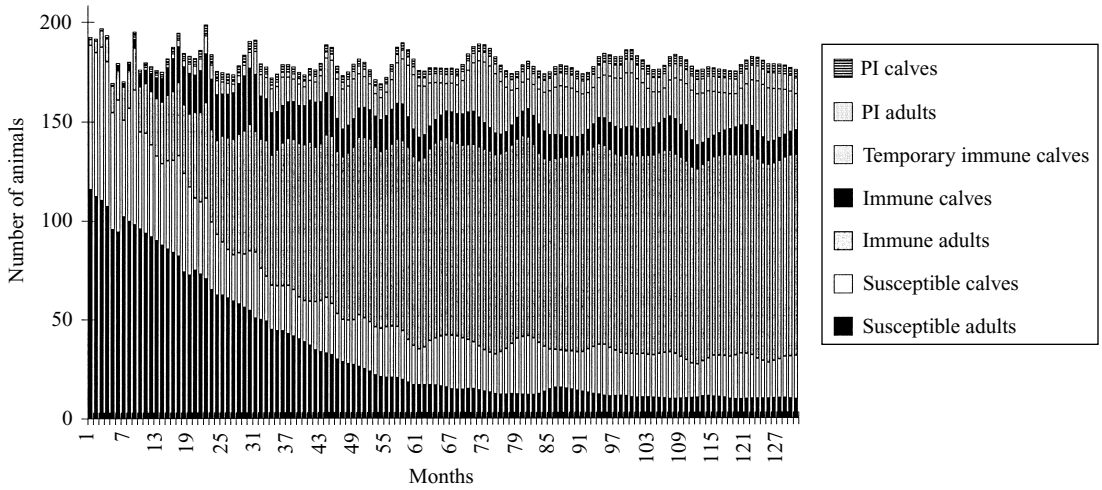

Fig. 3. Changes in the numbers of persistently infected, immune and susceptible animals within a closed susceptible dairy herd after the introduction of a persistently infected adult with infection rate dependent on the number of PI animals.

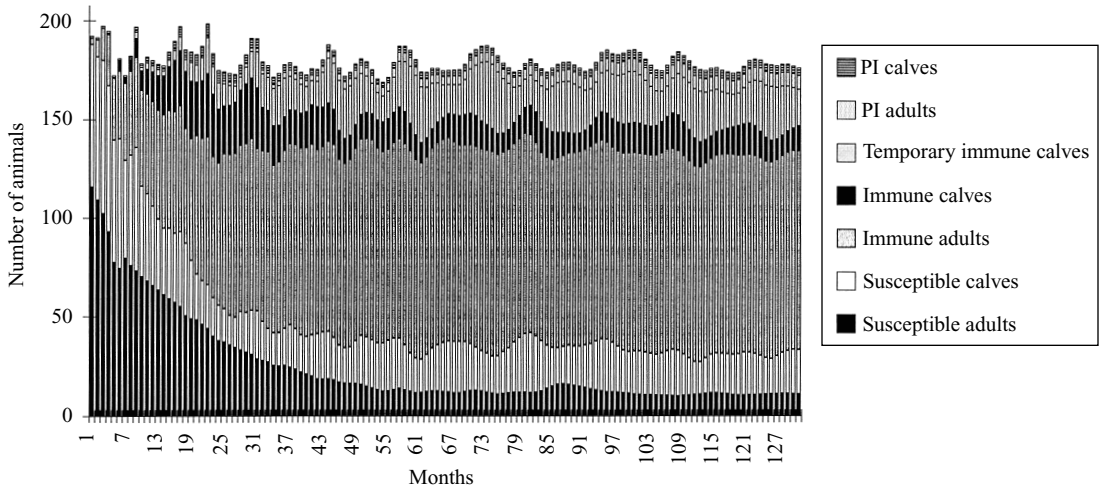

Fig. 4. Changes in the numbers of persistently infected, immune and susceptible animals within a closed susceptible dairy herd after the introduction of a persistently infected adult with infection rate dependent on number of PI animals and the number of animals seroconverting.

suggests that when a persistently infected animal is introduced into such a herd, on average in only 32 out of 1000 times will the herd become free of infection during the first 10 years. If seroconverting animals are included as a source of infection then the likelihood of extinction during the first 10 years is 0·033, i.e. almost identical to that when PI animals are considered the only source of infection.

Effect of differential loss of PI animals

Two scenarios are examined. In one there is approximately a 50% chance of a PI animal being lost during the first 12 months; in the second there is approximately a 65% chance of being lost in the first 14 months. The results from the first of these is shown in detail in Figure 5 and summary results for both scenarios are given in Table 1.

In both cases there is an initial drop in the number of susceptible animals during the first 3 years so that the proportion of the herd that is susceptible after 3 years is around 30%; thereafter there is a slight increase in the numbers of susceptible animals. If PI animals are lost at a rate of 10% during the first 2 months followed by 5% for the next 10 months then after 8 years the herd has reached a stable state in which there are on average 37% susceptible, 62% immune and 2% PI. If PI animals are lost at the higher rate then it takes around 10 years for the herd to reach a stable state at which time there is a lower level of infection in the herd, with 57% susceptible, 42% immune and 1% PI.

Table 1. *Influence of various parameters relating to infection and immunity on the outputs of the stochastic simulation model*

Parameters in model			Status of herd after 10 years				
Source of infection	Duration of immunity	Differential loss of PI animals	Probability of viral extinction	Animal group	Susceptible (%)	Immune (%)	PI (%)
PI	Lifelong	None	0·032	Calves	38	54	8
				Heifers	27	65	8
				Adults	4	89	6
				Total	18	75	7
PI + seroconverting	Lifelong	None	0·033	Calves	39	54	7
				Heifers	27	66	7
				Adults	6	89	6
				Total	19	75	6
PI + seroconverting	Lifelong	~ 65% in first 14 months	0·530	Calves	70	29	1
				Heifers	79	20	0
				Adults	45	54	1
				Total	57	42	1
PI + seroconverting	Lifelong	~ 50% in first 12 months	0·301	Calves	53	45	2
				Heifers	59	39	2
				Adults	22	76	1
				Total	37	62	2
PI + seroconverting	12 months	~ 50% in first 12 months	0·056	Calves	38	56	6
				Heifers	27	67	6
				Adults	30	66	4
				Total	33	63	5
PI + seroconverting	24 months	~ 50% in first 12 months	0·167	Calves	50	46	3
				Heifers	44	53	2
				Adults	34	64	2
				Total	41	56	3

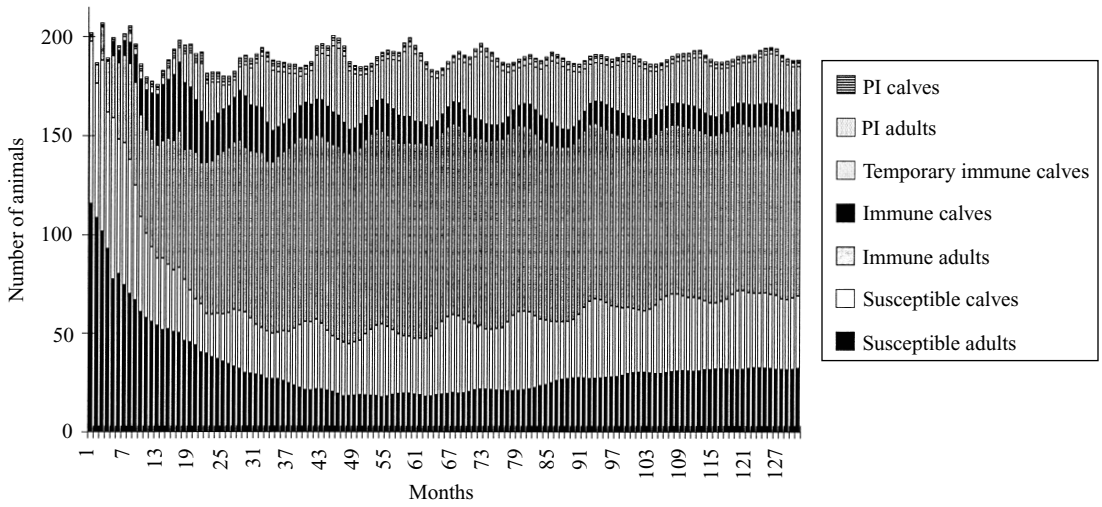

Fig. 5. Changes in the numbers of persistently infected, immune and susceptible animals within a closed susceptible dairy herd after the introduction of a persistently infected adult with infection rate dependent on number of PI animals and the number of animals seroconverting and with loss of PI calves during the first 12 months after birth.

If the probability of the herd becoming BVDV-free in 10 years is examined in Table 1 it can be seen that the probability is higher if PI animals are lost at the higher rate, as would be expected, with herds becoming BVDV-free 53% of the time when losses are at the higher rate as opposed to just over 30% at

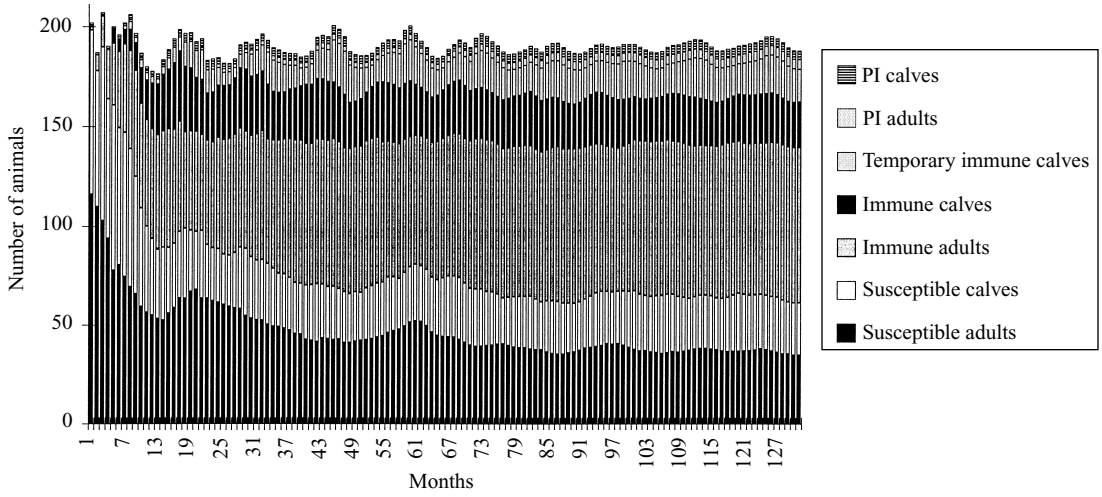

Fig. 6. Changes in the numbers of persistently infected, immune and susceptible animals within a closed susceptible dairy herd after the introduction of a persistently infected heifer with infection rate dependent on number of PI animals and the number of animals seroconverting and with culling of PI calves during the first 12 months after birth, and active immunity being temporary and lasting for twelve months.

the lower rate. As expected both probabilities are higher than that when PI animals are not lost during the first year or so of life.

Effect of duration of immunity

Two scenarios have been investigated. In the first, the animals are immune for a total of 12 months, during the last 6 months of which their immunity may be boosted. In the second scenario animals are immune for a total of 24 months, and immunity may be boosted during the last 6 months. In both instances a differential loss of approximately 50 % of PI animals is considered to occur in the first year. The result of the first scenario is illustrated in Figure 6.

When immunity is not considered lifelong there is an initial drop in the number of susceptible animals followed by a subsequent rise. This represents the loss of immunity by a proportion of those animals that were initially infected. After this there is once more a decrease in the number of susceptible animals followed by a small rise, as the herd approaches an equilibrium state. If immunity is presumed to last for just 1 year then the initial fall in the number of susceptible animals results in around 50 % being immune, the rise in susceptibles taking place around 1 year following the first introduction of a PI animal. If immunity is presumed to last for 2 years the rise in susceptible animals is delayed to around 2 years following the introduction of the PI animal, at which time there is only about 30 % of the herd susceptible.

From Table 1 it can be seen that although the proportion of adults that are susceptible is much the same whether immunity lasts for 1 or 2 years, there is a much larger proportion of heifers that are susceptible if immunity lasts for 2 years. Overall in the herd there are more immune animals if immunity lasts for 1 year than if it lasts for 2: this may reflect the higher numbers of PI animals in the herd if infection only lasts for 1 year. If immunity lasts for 2 years then there is a much higher likelihood of the herd becoming BVDV-free than if immunity only lasts for 1 year, although this is approximately half that if immunity is presumed to be lifelong.

DISCUSSION

This paper describes a stochastic computer model that simulates the spread of BVDV through a closed dairy herd. The model has been used to investigate the influence of parameters relating to source of infection, duration of immunity and survival of infected animals, on the prevalence and maintenance of infection within a herd. The presence of persistently infected animals as the sole source of infective virus was shown to be sufficient to maintain infection in a herd. Inclusion of acutely infected animals as an additional, transient source of virus, resulted in more rapid spread of infection through the herd and earlier establishment of a steady state (three years compared to four years). However, the status of the herd once the steady state was established was similar in both situations.

Differential loss of PI calves is known to occur because of their greater susceptibility to intercurrent disease and losses due to mucosal disease [4, 8, 9]. The rate of loss of PI calves in the first year of life was found to have a strong influence on the level of infection (seroconversion), the numbers of PI calves produced and the likelihood that infection is lost from the herd. However, even when about 50% of PI calves were lost, infection was maintained in a majority of herds. The duration of immunity following recovery from infection with BVDV is not known. In the initial investigations immunity was considered to be lifelong; a limited duration of immunity was shown to increase the numbers of PI calves produced and decrease the likelihood that infection is lost from a herd.

Serological surveys of prevalence of antibodies specific for BVDV have revealed levels of seropositivity of 53–72% [1, 12–17]. While these figures are within a similar range to that generated by the model described herein, most of the reported surveys will have included animals from herds that were BVDV-free or herds in which infection had not become endemically stable. Thus in the survey of Harkness and colleagues [1], which involved 1593 animals from 133 herds, 62·2% of animals were seropositive but 7·5% of the herds were seronegative. The level of seropositivity is, therefore, likely to be higher in individual herds in which infection with BVDV is endemic. In one study of a herd into which infection had recently been introduced, 73% of the adult animals had seroconverted in the first year. Of the animals that were seronegative at this time 35% had seroconverted after a further 3 months and 95% within a year [18]. These observations suggest that the values generated by the simulation model are an underestimate of the level of immunity (seropositivity) in infected herds. The transmission rate used in the model could potentially influence the steady state. In a preliminary investigation of the model [11] it was found that increasing the transmission rate above 0·025 per PI animal per month had only a minor effect on the final levels of immunity and persistent infection in a herd, assuming that immunity is lifelong. However, a higher rate of transmission may have a more pronounced influence on the levels of immunity obtained with the simulation model if immunity wanes after one or two years.

A number of management factors may also contribute to discrepancies between field observations and the results obtained with the simulation model. The model, as applied in this study, is based on a closed dairy herd structure in which calving occurs throughout the year and all male calves are removed at birth. In the field, many herds are not run as closed units, calving may be more seasonal and, in many instances, male calves are retained for 1 or 2 years. Moreover, there is usually some segregation of calves, heifers and adults in dairy herds whereas mixing of these groups commonly occurs in beef herds. Several of these parameters, e.g. retention of male calves and operation of an open herd, could influence the number of PI animals and hence the level of transmission of infection within herds.

Field surveys have reported variable levels of persistently infected cattle. Two surveys carried out in the UK, involving 924 and 3151 animals reported levels of PI animals of 0·4% and 1·8% respectively [12, 17]. A survey in the US involving 3156 animals from 66 herds revealed 1·7% PI animals [13] however, a large proportion of the positive animals in this survey were from two herds which clearly contained large cohorts of PI animals generated by recent introduction of the virus. These surveys are likely to have included some herds that were BVDV-free; in the survey by Edwards and colleagues [17] 5% of herds that submitted 10 or more samples showed no evidence of infection. Thus, the level of PI animals in endemically infected herds is probably higher than the values obtained from these surveys. Perhaps the most meaningful data are provided by a study of 19 herds in Denmark [6] PI animals were present in 10 of these herds and constituted 2·9% of the herd, with 87% of animals being seropositive. This value for PI animals is within the range of values generated by the simulation model when differential loss of PI calves and/or limited duration of immunity to BVDV were considered.

In conclusion, the results of this study demonstrate the importance of several factors in influencing the endemic stability of BVDV in closed herds of cattle. They point to the need for more accurate information on the transmission rate of the virus, the duration of immunity following infection and the survival of PI calves. Such information will enable the model to be refined and validated, using appropriate field data, so that it can be applied to studies of the potential impact of disease control measures.

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