
Prolonged persistence of bovine herpesvirus in small cattle herds: a model-based analysis

L. MOLLEMA^{1,2}, M. C. M. DE JONG^{1,2,3} AND M. VAN BOVEN^{1*}

¹ *Animal Sciences Group, Quantitative Veterinary Epidemiology, Lelystad, The Netherlands*

² *Wageningen University, Animal Sciences Group, Quantitative Veterinary Epidemiology, Wageningen, The Netherlands*

³ *Utrecht University, Faculty of Veterinary Medicine, Quantitative Veterinary Epidemiology, Utrecht, The Netherlands*

(Accepted 12 August 2004)

SUMMARY

Herpesviruses can remain dormant in once-infected hosts and, upon reactivation, cause such hosts to become infectious. This phenomenon of latency and reactivation may enable herpesviruses to persist for a long time in small host populations. To quantify the effect of reactivation on persistence, the time to extinction of bovine herpesvirus type 1 (BHV-1) in small cattle populations was calculated. For realistic parameter values the mean time to extinction is already more than 100 years in a population of 10 animals. In a population of 20 animals the time to extinction is approximately 2000 years. The effects of vaccination on persistence were also studied, revealing that continued vaccination of the whole population could result in much faster eradication. For instance, in an isolated herd of 20 animals BHV-1 could be eradicated in 44 years.

INTRODUCTION

Extinction of an infectious pathogen in any finite local host population is certain and has been observed and modelled [1–4]. The time to extinction of an infectious pathogen is dependent on its host–pathogen relationship. Measles, of which the extinction events have been well documented, cannot persist beyond the duration of a single epidemic even within fairly large local populations (<250 000 individuals) [1]. In a meta-population context like the cities of England and Wales [5], no extinction of measles was observed in the troughs between epidemics. This was probably due to a re-introduction of measles from one local

population with measles, to another local population where measles had already become extinct.

The reason why the persistence of herpesviruses [e.g. bovine herpesvirus type 1 (BHV-1), equine herpesvirus type 1, Marek's disease virus, varicella-zoster virus] is very different from the persistence of measles is because herpesviruses possess properties that enable them to survive in small host populations for a long time. Once individuals are infected with a herpesvirus they remain carriers of the virus for life [6, 7] and, under certain conditions the virus can reactivate and the carrier hosts become infectious again [7–10].

Recently De Koeijer et al. [11] developed a model for calculating the time to extinction of herpesviruses, which they subsequently applied to BHV-1 in cattle. Importantly, the model analysis necessitated a separation into two time-scales: (1) a short time-scale during which the infection and recovery processes

* Author for correspondence: Dr M. Van Boven, Animal Sciences Group, Quantitative Veterinary Epidemiology, PO Box 65, 8200 AB Lelystad, The Netherlands.
(Email: Michiel.vanBoven@wur.nl)

take place and (2) a long time-scale during which reactivation and birth events take place. This separation into short and long time-scales was possible because the infection and recovery processes occur on a much faster time-scale than the birth and reactivation processes. For instance, the time between infection and recovery of BHV-1 in cattle is approximately 1 week, whereas the lifespan of cattle and the time between reactivation events of BHV-1 in cattle is in the order of years. However, De Koeijer's model [11] does not account for all stochastic effects of the dynamics of BHV-1 in cattle. In particular, in the model: (1) only major outbreaks were taken into account, while minor outbreaks were ignored; (2) no stochasticity in the size of the outbreak was incorporated; and (3) stochasticity in the birth–death process was omitted, using a deterministic description of the host demography.

Yet, we believe that incorporation of the above stochastic effects may be vital to obtain more realistic calculations of the time to extinction in small populations. Here we studied the impact of demographic stochasticity and stochasticity in the size of the outbreak on the time to extinction of BHV-1. The dynamics were modelled using a fully stochastic extension of the model of De Koeijer et al. [11]. For the analysis of the model and its variants we used analytical results available on Markov chain models where possible. Those variants that could not be formulated as standard Markov models were studied by simulation. We studied the implications for management directed at eradication of BHV-1 within local populations, especially the effect on the time to extinction of population size and of vaccination.

MODEL STRUCTURE AND ANALYSIS

Model overview

Two separate time-scales were considered: (1) a short time-scale (days or weeks) during which infection and recovery events take place; and (2) a long time-scale (years) during which birth, death and reactivation events take place. Separation of the two time-scales can be safely done if the birth, death and reactivation rates are small compared to the infection and recovery rates. In essence, we assumed that epidemic outbreaks take place instantaneously on the long time-scale. This assumption greatly simplified the model as it kept the number of events small, and it enabled us to describe the dynamics of the long time-scale solely by the number of latently infected individuals (i.e.

individuals that have become carriers of the virus without being infectious). The dynamics of our model are governed by a discrete-time Markov chain. Hence, the probability of a population being in a particular state $m(t)$ on day, conditional on it being in state $k(t-1)$ on the previous day, was: (1) independent of the population's behaviour prior to day $t-1$; and (2) dependent only on the value $k(t-1)$ and not on t explicitly. The short time-scale was modelled by focusing on the probability distribution of outbreak sizes. Subsequently, the distribution of the outbreak sizes was incorporated into the long time-scale during which birth, death and reactivation events took place.

The short time-scale: outbreaks

We first considered the short time-scale during which outbreaks occur after a reactivation event of a latently infected individual. In the following, $S(t)$ denotes the number of susceptible individuals at time t , $I(t)$ denotes the number of infected and infectious individuals at time t , and $P(t)$ denotes the number of latently infected individuals at time t . Throughout, total population size is denoted by N and was assumed to be constant [i.e. $N = N(t) = S(t) + I(t) + P(t)$]. Thus, the population state during the short time-scale can be denoted by the pair $[I(t), P(t)]$, whereas the population state during the long time-scale is determined by $P(t)$ only, as infectious individuals are absent during inter-epidemic periods.

An outbreak starts with a reactivation event after which the population has amongst it a single infected and infectious individual. This infectious individual may infect a number of susceptible individuals, who in turn may infect other susceptible individuals. The outbreak ends when the infection chain has stopped, namely, when the number of infectious or susceptible individuals has dropped to zero. Figure 1 gives a schematic structure of the possible routes that the infection chain can take.

By standard arguments, it was assumed that susceptible individuals are infected at a rate $\beta(I/N)$, where $\beta(\text{time}^{-1})$ is the transmission rate constant. Infected individuals recover from infection at a rate $\alpha(\text{time}^{-1})$, so that $1/\alpha$ corresponds to the infectious period.

Note that the above model formulation entails the following assumptions: (1) all infectious individuals are equally infectious; (2) all susceptible individuals are equally susceptible; (3) each infected

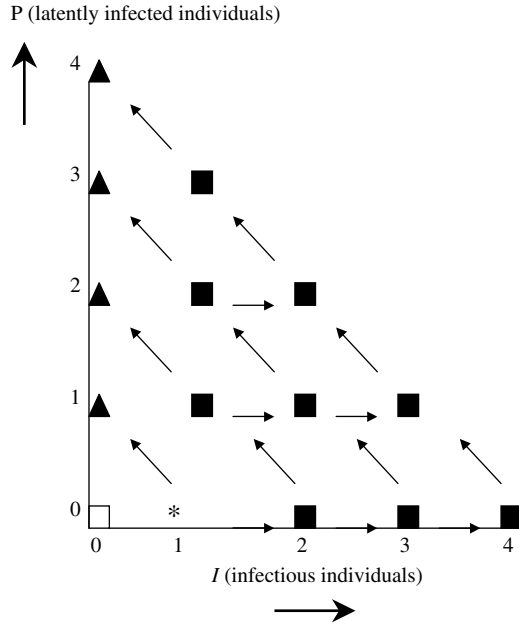


Fig. 1. Possible routes of the infection chain in a population of four animals. The population state is given by the number of infectious animals, I , and the number of latently infected animals, P . Each population state is a vertex of the grid in the (I, P) -plane. Starting from the vertex, marked by an asterisk, the population state will jump from one vertex to another until it reaches one of the absorbing states where $I=0$. Vertexes on this axis are the final population states, i.e. the states where there are no more infectious individuals [13, 14]. * Starting position; ■, intermediate position; ▲, end position; □, non-reachable position; ↖, recovery event; →, infection event.

individual poses an identical and independent risk of infection to each susceptible individual; and (4) the transmission rate parameter and the recovery rate are constant over time.

Given the above assumptions, the probability that an infection event occurs before a recovery event occurs is given by the infection rate $\beta(SI/N)$ divided by the sum of the infection rate and the recovery rate $\beta(SI/N) + aI$. Hence, the probability that an infection event will occur before a recovery event is given by: $R_1 S / (R_1 S + N)$, where $R_1 = \beta/\alpha$. Likewise, the probability that a recovery event occurs before an infection event is given by $N / (R_1 S + N)$, which is the recovery rate aI divided by the sum of the infection rate and the recovery rate. The parameter R_1 represents the reproduction ratio of a single outbreak, namely, the number of newly infected individuals infected by one infectious individual during one infectious period in a fully susceptible population. Note, the reproduction ratio R_1 does not depend on the population size N [12]. Using the above formulations we

can calculate the probability distribution of the final size of an outbreak [13, 14]. The final size gives the probability distribution of the number of initially susceptible individuals that have been infected and have become latently infected (P) at the end of the outbreak.

The long time-scale: demographic turnover and reactivation

On the long time-scale there are no infectious individuals and three types of events may occur: birth, death and reactivation. Our assumption that population size N remains constant requires that birth and death events are coupled so that a deceased individual is immediately replaced by a newborn susceptible individual. Birth–death events occur at a rate μ per individual. Thus, the total birth–death rate is given by μN . In practice only the death of a latently infected individual is of importance because the death of a susceptible individual results in an identical susceptible individual.

A seropositive latently infected individual reactivates at a rate ν . Hence, the total reactivation rate is given by νP . De Koeijer et al. [11] showed that the number of reactivation events per host lifetime is crucial to the time to extinction. The number of reactivation events of a latently infected individual during its lifetime is given by the geometric series

$$\frac{\mu}{\mu + \nu} \sum_{i=0}^{\infty} i \left(\frac{\nu}{\nu + \mu} \right)^i = \frac{\nu}{\mu}.$$

As explained in the previous section, a latently infected individual that re-excretes virus causes an outbreak, the size of which may vary. In the following we will denote by the element f_{ij} the probability that the population contains i latently infected individuals before a reactivation event, while it contains j latently infected individuals after the event. The outbreak size $j - i$ depends on the parameter values of the infection process (α and β), and on the number of susceptible individuals at the start of the outbreak ($S(t)$).

After having described the dynamics on the short and long time-scales we are now able to determine the overall reproduction ratio, R_0 , for a reactivating virus, which is defined as the number of newly infected individuals infected by one infectious individual during its lifetime in a fully susceptible population. The overall reproduction ratio (R_0) is equal to the reproduction ratio of a single outbreak (R_1) plus the expected number of times reactivation events take

place per host lifetime (ν/μ) times the reproduction ratio of a single outbreak (R_1)

$$R_0 = \left(1 + \frac{\nu}{\mu}\right) R_1.$$

As a consequence it is possible that $R_1 < 1$ while $R_0 > 1$. This will happen whenever the reactivation rate ν is high relative to the mortality rate μ .

Analysis of the model

With the Markov model at hand, several interesting properties such as the mean time to extinction can be

Illustration

To illustrate how the short and the long time-scales were integrated we present a specific example in which the total population contains four individuals ($N=4$). On the short time-scale, a 4×4 matrix \mathbf{F} contains the probability distribution of outbreak sizes [equation (3)]. This probability distribution of outbreak sizes is then subsequently incorporated into the 5×5 transition matrix \mathbf{M} , which describes the long time-scale [equation (4)]. For simplicity, the time-step Δt in the matrix \mathbf{M} is set at $\Delta t=1$. The two matrices take the following form

$$\mathbf{F} = \begin{pmatrix} \frac{4}{4+3R_1} & \frac{12R_1}{(2+R_1)^2(4+3R_1)} & \frac{96R_1^2(8+3R_1)}{(2+R_1)^2(4+R_1)^3(4+3R_1)} & \frac{3R_1^3(160+R_1(96+R_1(16+R_1)))}{(2+R_1)^2(4+R_1)^3(4+3R_1)} \\ 0 & \frac{2}{2+R_1} & \frac{16R_1}{(2+R_1)(4+R_1)^2} & \frac{R_1^2(8+R_1)}{(2+R_1)(4+R_1)^2} \\ 0 & 0 & \frac{4}{4+R_1} & \frac{R_1}{4+R_1} \\ 0 & 0 & 0 & 1 \end{pmatrix}, \quad (3)$$

$$\mathbf{M} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ \mu & 1-\mu-\nu(1-f_{11}) & \nu f_{12} & \nu f_{13} & \nu f_{14} \\ 0 & 2\mu & 1-2\mu-2\nu(1-f_{22}) & 2\nu f_{23} & 2\nu f_{24} \\ 0 & 0 & 3\mu & 1-3\mu-3\nu(1-f_{33}) & 3\nu f_{34} \\ 0 & 0 & 0 & 4\mu & 1-4\mu \end{pmatrix}. \quad (4)$$

calculated. The transition matrix, \mathbf{M} , containing the transition probabilities on the long time-scale can be partitioned so that a matrix \mathbf{Q} contains only the entries corresponding to the transient states. Then direct application of standard Markov chain theory teaches us that the so-called fundamental matrix \mathbf{K} is given by $\mathbf{K}=(\mathbf{I}-\mathbf{Q})^{-1}$ [15], where \mathbf{I} denotes the identity matrix.

If the initial distribution over the non-absorbing states is given by a row vector \mathbf{r} , then the mean time to extinction $E[T]$ is given by

$$E[T]=\mathbf{r} \cdot \mathbf{K} \cdot \mathbf{1}, \quad (1)$$

where $\mathbf{1}$ represents the vectors of ones. Likewise the variance of the time to extinction $\text{Var}[T]$ is given by

$$\text{Var}[T]=\mathbf{r} \cdot (2\mathbf{K}-\mathbf{I}) \cdot \mathbf{K} \cdot \mathbf{1} - (\mathbf{r} \cdot \mathbf{K} \cdot \mathbf{1})^2. \quad (2)$$

The dynamics are determined by the matrix equation

$$\mathbf{x}(t+1) = \mathbf{x}(t) \cdot \mathbf{M}, \quad (5)$$

where \mathbf{x} is a (row) vector containing the distribution of latently infected individuals over the various population states. The elements f_{ij} ($1 \leq i, j \leq N$) and m_{ij} ($0 \leq i, j \leq N$) of the transition matrices \mathbf{F} and \mathbf{M} represent the probabilities that the population contains i latently infected individuals before an event, while it contains j latently infected individuals after the event. Note that the indices i and j run from 1 to 4 in \mathbf{F} and from 0 to 4 in \mathbf{M} .

Simulation model

We also developed a simulation model to investigate the robustness of the results of the Markov model and to examine the impact of the assumption that

the host lifespan is exponentially distributed. To this end we extended the model by considering: (1) a fixed host lifespan; and (2) an exponentially distributed host lifespan with fixed maximum age (i.e. a truncated exponentially distributed host lifespan). For this comparison all simulations started with only latently infected individuals ($N=20$). Apart from different assumptions on the distribution of the host lifespan, the simulation model contained the same processes as the Markov model. Per parameter combination 1000 replicates were taken. The simulations were stopped when no latently infected individuals were left in the host population. The time-step in the model was chosen such that the probability of two events occurring at the same time was approximately 0.01.

Parameter values

Parameter values were derived from data of both feral and domestic cattle populations. The mean host lifespan was estimated from demographic data of the Heck cattle population in the Dutch nature reserve ‘De Oostvaardersplassen’ [16–19]. Because there was no data available on the dynamics of BHV-1 within feral cattle populations, data from field studies was taken describing the dynamics of BHV-1 [20] within domestic dairy cattle herds in The Netherlands. The reproduction ratio of a single outbreak of BHV-1 was estimated at 3.2 [20]. The reproduction ratio of a single outbreak under vaccination conditions was set at 0.45. The reactivation rate was calculated by De Koeijer et al. [11] from data of field studies done by Bosch et al. [20], and was estimated at 0.09 per year. The same value for the reactivation rate under vaccination conditions was used [11]. For the population size we referred back to the Heck cattle population. The Heck cattle population is a structured population. Various social units were distinguished in the Heck cattle population: (1) solitary animals; (2) bull groups; (3) mixed groups; and (4) cow groups. Mature bulls often stayed in small groups (2–30 animals), while cow groups could contain larger numbers of animals (20–100) [21]. These group sizes varied during the year. The default population size in this study was set at 20 individuals (range 2–50), referring to the Heck cattle population of ‘De Oostvaardersplassen’. As the initial condition we took the expected distribution belonging to the case in which the virus was already present in the population for a relatively long time (technically this distribution corresponds to the quasi-stationary distribution [22, 23]).

Table 1. *Default values and the range of parameters in the Markov model and simulation model**

Parameter	Default value (range)	Ref.
Population size (N)	20 (2–50)	[21]
Mortality rate (μ)	0.1 year ⁻¹ (0.1–0.5)	[16–19]
Reactivation rate (ν)	0.09 year ⁻¹ (0–0.5)	[11]
Reproduction ratio of a single outbreak (R_1)	3.2 (0.45–50)	[20]

* Data refers to a Heckcattle population in the Dutch nature reserve ‘De Oostvaardersplassen’ and to data of domestic dairy cattle herds in The Netherlands.

The initial population state vector was given by the quasi-stationary distribution with $R_1=3.2$. In a sense, the quasi-stationary distribution corresponds to a worst-case scenario. Table 1 shows the default parameters values and the range of values considered.

RESULTS

Default parameter setting

First, we considered the fate of the pathogen in a small population ($N=20$) in which initially one infectious individual is present while all remaining individuals are susceptible. Motivated by empirical data [20] we chose $R_1=3.2$ for the reproduction ratio of a single outbreak. Other parameters were as shown in Table 1. Figure 2 shows the results. Figure 2a gives the probability distribution just after the first outbreak. The probability distribution is markedly bimodal with peaks at $P=1$ and at $P=20$. A reactivation event in a latently infected individual resulted in a minor outbreak in approximately 35% of the cases in which only a minority of the susceptible individuals (say $1 < P < 8$) is infected. On the other hand, once a certain critical number of susceptible individuals have been infected, the remaining susceptible individuals are unlikely to escape infection. In fact, the probability that all susceptible individuals are infected (i.e. $P=20$ after the outbreak) is approximately 25%. Figure 2b–e shows the probability distributions after 1, 10, 100 and 1000 years. Figure 2b illustrates that the probability of extinction of the pathogen after 1 year is just 2%. The most likely outcome is that the population contains one latently infected individual ($P=1$) while the remaining individuals are susceptible. As time progresses the probability of extinction increases gradually, so that after 1000 years the probability of extinction is approximately 50%.

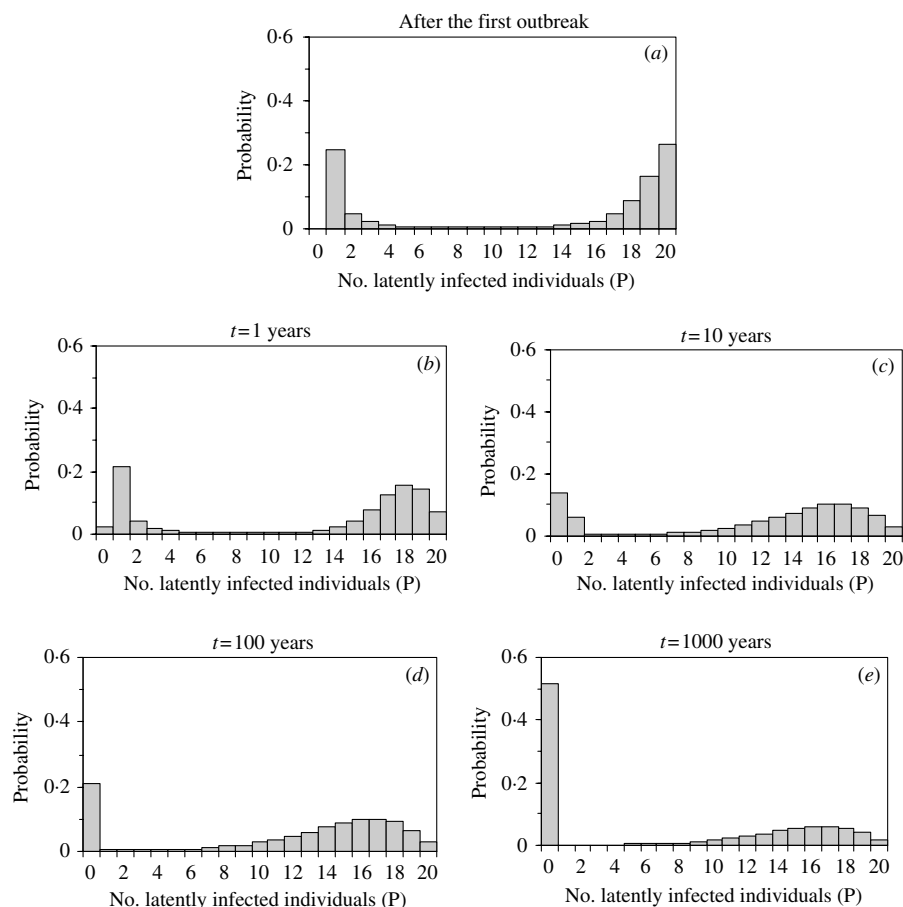


Fig. 2. Probability distribution of the number of latently infected individuals (P) in a population after (a) introduction of one infectious individual; (b) 1 year; (c) 10 years; (d) 100 years; and (e) 1000 years. The total population size is set at $N=20$. The number of latently infected individuals at the x -axis ranges from 0 to 20.

In case the pathogen has not become extinct after 1000 years, it is highly likely that 10–20 latently infected individuals are present (Fig. 2e). This is because once the population contains predominantly latently infected individuals it will take a very long time before all latently infected individuals have died in the population conditional on no new outbreaks having taken place. Roughly speaking the right-hand-sided peak in Figure 2 corresponds to the so-called quasi-stationary distribution. Even after 1000 years it is still highly probable that the population has not yet reached the absorbing state. In fact, with a probability of 0.48 the population contains predominantly latently infected individuals ($11 < P < 19$).

The initial conditions

To study the effect of the initial conditions on the time to extinction we considered three scenarios: (1) one individual is latently infected and the remaining

individuals are susceptible; (2) one individual is infectious and the remaining individuals are susceptible; and (3) the population distribution corresponds to the quasi-stationary distribution. Parameter values are as in Table 1, and Figure 3 shows the results.

As illustrated in Figure 3a, if the population contains one latently infected individual, the pathogen is quickly (within 10 years) driven to extinction with a probability of 0.49. On the other hand if the pathogen does not become extinct within this time-span, it may persist for a very long time ($> 10\,000$ years). The intuitive explanation is that the pathogen will become extinct in a short space of time only if the latently infected individual dies before a reactivation event takes place. If, on the other hand, a reactivation event leading to a major outbreak takes place before the latently infected individual dies, the population will contain mainly or exclusively latently infected individuals and extinction of the pathogen may take a very long time.

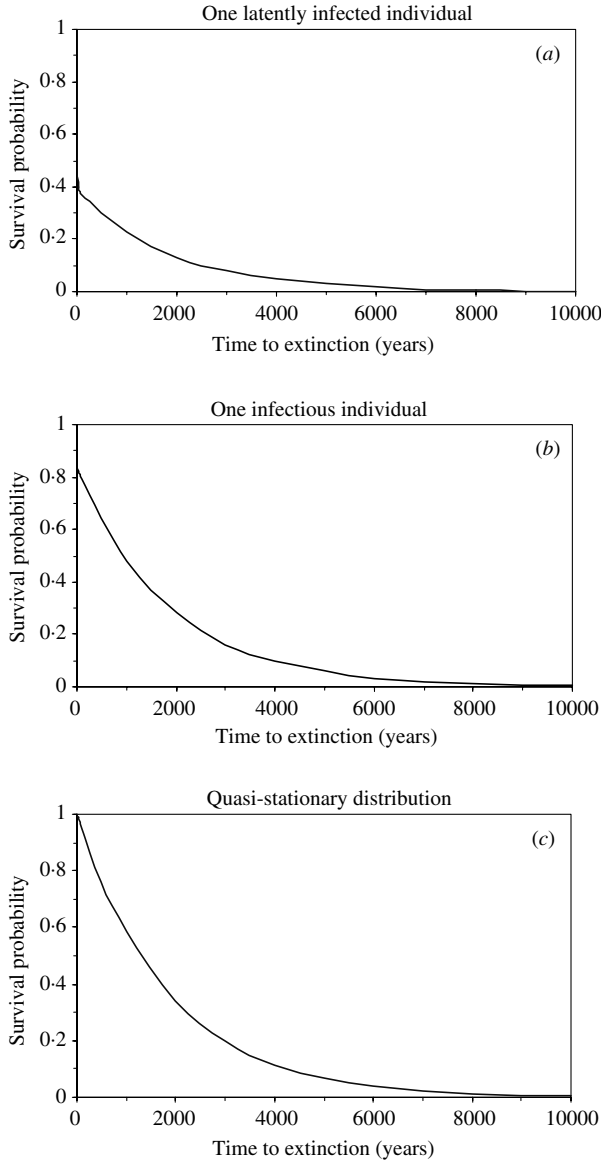


Fig. 3. The time to extinction against the survival probability of BHV-1 within a population of size $N=20$. We considered three different initial distributions: (a) one individual is latently infected and the remaining individuals are susceptible; (b) one individual is infectious and the remaining individuals are susceptible; and (c) the population distribution corresponds to the quasi-stationary distribution.

If initially a single infectious individual is present in the population, the probability of extinction within a short time-span decreases considerably. In fact, the probability of rapid extinction (within 10 years) is just 14%. The intuitive explanation is that there will be an immediate outbreak if an infectious individual is introduced.

Figure 3c shows the results of a case where, initially, the probability distribution over the population states is given by the quasi-stationary distribution. Here, it is

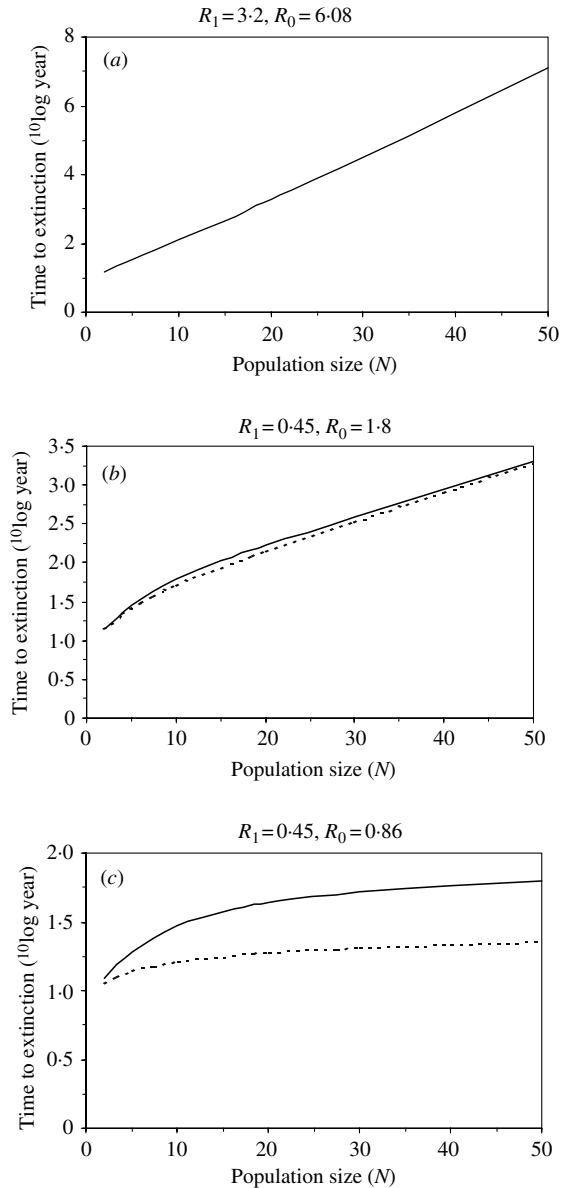


Fig. 4. The mean time to extinction as a function of population size (N) and three different scenarios for the reproduction ratios. (a) Both $R_1 > 1$ and $R_0 > 1$; (b) $R_1 < 1$, $R_0 > 1$ and $\nu = 0.3 \text{ year}^{-1}$; (c) both $R_1 < 1$ and $R_0 < 1$. In (a) the quasi-stationary distribution with $R_1 = 3.2$ was taken as the initial distribution and in (b) and (c) the quasi-stationary distribution with respectively $R_1 = 3.2$ (—) and $R_1 = 0.45$ (---) were taken as initial distributions.

very unlikely that the pathogen becomes extinct in a short time-span, as it is unlikely that the population has only one or a few latently infected individuals.

Population size

The impact of in the population size (N) on the time to extinction is illustrated in Figure 4. Figure 4a,b

refers to two different values of the reproduction ratio of a single outbreak (R_1), one well above the critical value 1 ($R_1=3.2$) and one well below 1 ($R_1=0.45$). In both cases R_0 exceeds 1. Figure 4c refers to the situation where both $R_1 < 1$ and $R_0 < 1$. In Figure 4a the quasi-stationary distribution with $R_1=3.2$ was taken as initial distribution and in Figures 4b,c the quasi-stationary distribution with respectively $R_1=3.2$ (smoothed line) and $R_1=0.45$ (dashed line) were taken as initial distributions.

If both $R_1 > 1$ and $R_0 > 1$ (Fig. 4a), then the mean time to extinction increases exponentially with increasing N . Even in relatively small populations the mean time to extinction may be high (e.g. 126 years if $N=10$). In larger populations (e.g. $N=50$) the time to extinction is in the order of millions of years.

If $R_1 < 1$ and $R_0 > 1$ (Fig. 4b), the time to extinction increases more or less exponentially for relatively large population sizes ($N > 20$) and increases less than exponentially for values of $N < 20$. Note, the initial distribution is of marginal importance for the time to extinction.

If both $R_1 < 1$ and $R_0 < 1$ (Fig. 4c), then the time to extinction increases less than exponentially for all values of N . The time to extinction increases marginally if N is large. Intuitively, this can be understood as follows. If $R_0 < 1$ an infectious individual will infect only a few susceptible individuals. As a consequence the time to extinction is hardly affected by population size.

Number of reactivation events per host lifetime

The effect of changing the number of reactivation events per host lifetime is illustrated in Figure 5. Population size N was fixed at $N=20$, and the lifespan of the host was kept constant at 10 years. The reactivation rate was varied systematically from 0 to 0.5 (year^{-1}), corresponding to 0–5 reactivation events per host lifetime. This implies that the overall reproduction ratio R_0 varied from $R_0=3.2$ to $R_0=19.2$ if $R_1=3.2$ (Fig. 5a), and from $R_0=0.45$ to $R_0=2.7$ if $R_1=0.45$ (Fig. 5b). In Figure 5a the quasi-stationary distribution with $R_1=3.2$ was taken as initial distribution and in Figure 5b the quasi-stationary distribution with respectively $R_1=3.2$ (smoothed line) and $R_1=0.45$ (dashed line) were taken as initial distributions.

The figures show that the time to extinction increases with an increasing number of reactivation events per host lifetime. If $R_1 > 1$ (Fig. 5a) then the

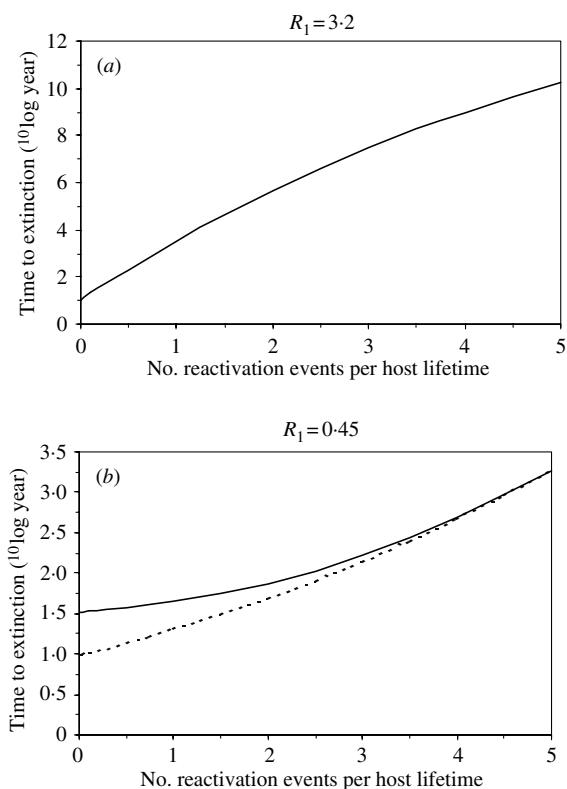


Fig. 5. The mean time to extinction as a function of the number of reactivation events per host lifetime (ν/μ) and two different values of the reproduction ratio of a single outbreak (R_1). Note in (a) R_1 is 3.2 and (b) R_1 is 0.45. In (a) the quasi-stationary distribution with $R_1=3.2$ was taken as initial distribution and in (b) the quasi-stationary distribution with respectively $R_1=3.2$ (—) and $R_1=0.45$ (- - -) were taken as initial distributions.

time to extinction increases less than exponentially whereas if $R_1 < 1$ (Fig. 5b) the time to extinction increases faster than exponentially. Thus the pathogen might still persist for a long time if the expected number of reactivation events per host lifetime is sufficiently large (> 3) to bring R_0 sufficiently above 1.

The reproduction ratio of a single outbreak R_1

The effect of changing R_1 on the mean time to extinction is studied and illustrated in Figure 6. The quasi-stationary distribution accompanying each value of R_1 was taken as the initial distribution. The figure shows that the time to extinction increases less than exponentially if R_1 increases. The impact on the time to extinction is larger for values of $R_1 < 10$ than for values of $R_1 > 10$. The time to extinction reaches an asymptote for large values of R_1 . Intuitively, this can be understood as follows. For relatively high values of R_1 the probability of a major outbreak goes

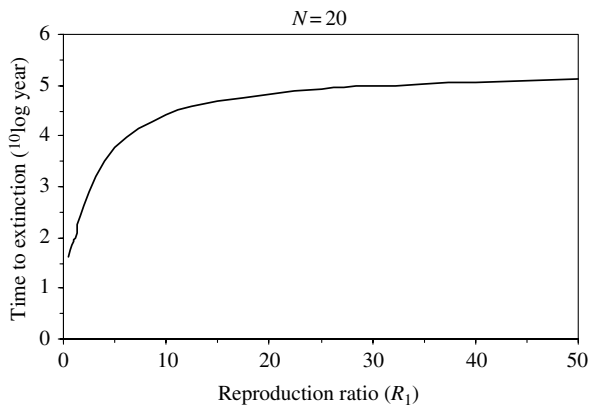


Fig. 6. The mean time to extinction as a function of the reproduction ratio of a single outbreak (R_1). The quasi-stationary distribution accompanying each value of R_1 was taken as the initial distribution. Other parameters were set at their default values.

to 1 and thus all susceptible individuals in the population will already be infected.

The distribution of the host lifespan

The simulation model allows us to explore the impact of various assumptions on the distribution of the host lifespan. Specifically we considered: (a) a fixed host lifespan; and (b) a truncated exponentially distributed host lifespan. To be able to make a fair comparison, the mean host lifespan was kept constant at 10 years in all scenarios. In the case of a fixed host lifespan each individual lives exactly 10 years. In the case of a truncated exponentially distributed host lifespan, the mortality rate was set at 0.05 year^{-1} and the maximum age at 14 years.

Table 2 shows the times to extinction in the case of an exponentially distributed host lifespan *vs.* a fixed host lifespan for different values of R_1 . For all values of R_1 the time to extinction is lower in a model with a fixed host lifespan than in a model with an exponentially distributed host lifespan. Intuitively this can be explained as follows. In the case of a fixed host lifespan all individuals live exactly 10 years whereas in the case of an exponentially distributed host lifespan some individuals live for a very short time and some individuals live relatively long. For those individuals that live relatively long there still remains the probability of a reactivation event during the time that the population contains latently infected individuals. In the case of a truncated exponentially distributed host lifespan and relatively small or large values of R_1 , the time to extinction lays in between

Table 2. The times to extinction in years (s.e.) in the case of an exponentially distributed host lifespan and in the case of a fixed host lifespan and for five different values of R_1^*

R_1	Exponentially distributed host lifespan	Fixed host lifespan
0.45	48.16 (0.85)	20.41 (0.35)
1.1	104.57 (1.44)	74.67 (2.67)
1.5	212.33 (5.16)	140.67 (4.81)
2.0	449.08 (12.96)	229.06 (4.13)
3.2	1899.56 (67.28)	492.24 (17.38)

* Three host lifetime distributions are compared with each other, namely, an exponentially distributed host lifetime, a fixed host lifetime and an exponentially distributed host lifetime with a maximum age. The mean time to extinction in years (s.e.) is given for two host lifetime distributions and for five values of the reproduction ratio of a single outbreak (R_1).

the values for the time to extinction in the case of an exponentially distributed host lifespan and a fixed host lifespan.

Demographic stochasticity and stochasticity in the size of the outbreak

To study the effect of demographic stochasticity and stochasticity in the size of the outbreak we compared our model, which included both types of stochasticity with the model of De Koeijer et al. [11], which did not include those types of stochasticity. Their analysis was based on the following assumptions: (1) only large outbreaks were taken into account, while small outbreaks were ignored; (2) outbreaks could only occur when the fraction of susceptible individuals reached a critical fraction (x_0) at which $R_1 > 1$; (3) the probability of a major outbreak was approximated by $1 - (1/xR_1)$ (where x is the fraction of susceptible individuals); and (4) stochasticity in the birth–death process was omitted. In our more realistic model with a finite population we did not make an artificial distinction between major and minor outbreaks. For technical reasons, the time to extinction in this section was calculated as the time until the last outbreak had taken place.

First, the impact of stochasticity in the size of the outbreak on the time to extinction was studied. Figure 7 shows the results. For a reproduction ratio of a single outbreak just above 1, the mean time to extinction in our model (smoothed line) was

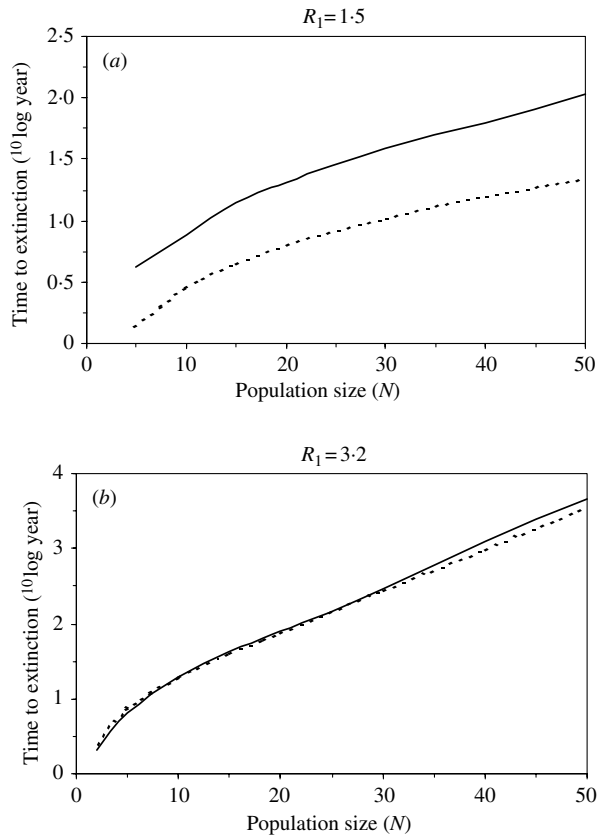


Fig. 7. The mean time to extinction determined with our model (—) compared with the model of De Koeijer et al. [11] (---) as a function of the population size. Note in (a) R_1 is 1.5 and in (b) R_1 is 3.2. The host lifespan was set at 5 years and other parameters were set at their default values. In both models we started with a number of susceptible individuals (S) equal to the critical density (x_0) times the population size N , and $N - S$ latently infected individuals (P).

substantially larger compared to the model of De Koeijer et al. [11] (dashed line), as is shown in Figure 7a. In our model, with an exponentially distributed infectious period, the probability of a minor outbreak is given by the inverse of the reproduction ratio of a single outbreak, assuming the density of the susceptible individuals is 1. For instance if $R_1 = 1.5$ the probability of a minor outbreak is given by $1/1.5 = 0.67$. For relatively small values of the reproduction ratio (R_1) the probability of a minor outbreak becomes higher. For larger values of the reproduction ratio ($R_1 > 3$) our results were similar to the results of De Koeijer et al. [11], as is shown in Figure 7b. Hence, we conclude that minor outbreaks can not be ignored for values of R_1 close to 1.

Second, we systematically studied the impact of the host lifespan and the reproduction ratio of a

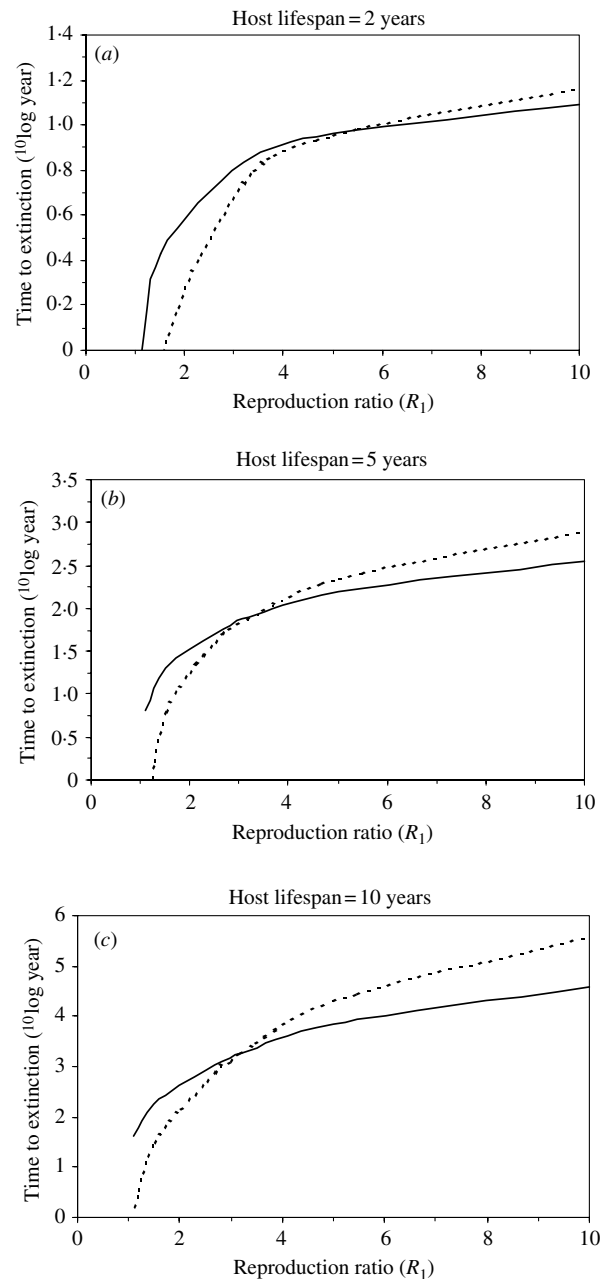


Fig. 8. The mean time to extinction determined with our model (—) compared with the model of De Koeijer et al. [11] (---) as a function of the reproduction ratio of a single outbreak (R_1). We considered three different values for the host lifespan namely, 2 years, 5 years and 10 years. In both models we started with a number of susceptible individuals (S) equal to the critical density (x_0) times the population size N , and $N - S$ latently infected individuals (P).

single outbreak on the time to extinction. Figure 8 shows the results. In short, the analysis showed that for values of R_1 near to or just above 1 the mean times to extinction were larger for reasons explained in

the previous paragraph. For large values of R_1 , on the other hand, the time to extinction in ref. [11] may be considerably larger than in our model. The intuitive reason is that in ref. [11] the fraction of latently infected individuals could reach very small values close to zero at which point major outbreaks could still take place, whereas in our model the last latently infected individual already would have died by chance.

DISCUSSION

Compared to other viruses herpesviruses have an eye-catching mechanism, which may enable them to survive for a long time in small populations. They have the possibility of reactivation after recovery of the host, which may have profound consequences for the eradication of the virus.

In this paper we calculated the time to extinction for BHV-1 in small closed cattle populations using a Markov model that takes into account demographic stochasticity and stochasticity in the size of an outbreak. Specifically, we examined the impact of the population size, mortality rate, reactivation rate, reproduction ratio of a single outbreak and the overall reproduction ratio on the time to extinction.

Our results indicate that for realistic parameter values the mean time to extinction is already in the order of 100 years in small populations ($N=10$). In larger populations (e.g. $N=50$) the mean time to extinction increases strongly, and can be in the order of millions of years. In fact, our results indicated that a relatively short time to extinction (say in the order of 60 years) can only be achieved if both R_1 and R_0 are below 1. Given the demography of the Heck cattle population this implies that the reactivation rate has to be relatively low ($\nu < 0.1 \text{ year}^{-1}$).

A reproduction ratio R_1 smaller than 1 might be achieved by vaccinating a sufficient part of the population. Vaccination might be a useful tool to achieve eradication of BHV-1. Suppose, for instance, that vaccines were available that were able to reduce the reproduction ratio of a single outbreak (R_1). If, hypothetically, by vaccination R_1 dropped from 3.2 to 0.45 then for a population of 50 animals the mean time to extinction decreases from several millions of years to approximately 60 years. For a population of 100 individuals the time to extinction becomes approximately 80 years and for a population of 1000 individuals the time to extinction becomes 150 years. For practical purposes this is, however, still a very long time.

Alternatively, vaccination could result in a decrease in the number of reactivation events per host lifetime. In fact, there is evidence that this can be achieved by: (1) vaccinating susceptible individuals with a gE-negative BHV-1 vaccine strain [24] or a latency-related (LR) mutant of BHV-1 [25]; or (2) by reducing the host lifespan of latently infected individuals. For sufficiently small values of the reactivation rate ($\nu = 0.01 \text{ year}^{-1}$) and $R_1 = 3.2$ the time to extinction can be decreased to 50 years even in a population of 50 animals.

Prior to 1998 BHV-1 infections in cattle were widespread in The Netherlands. For instance, a BHV-1 bulk milk survey in 1994 revealed that at least 84% of the dairy herds had seropositive cattle [26], while the young stock of these herds had on average a seroprevalence of 12% [26]. This led the Dutch authorities to introduce an integrated eradication campaign in 1998. From 1997 to 2000 the seroprevalence of milking cows in The Netherlands had decreased strongly (from 40% to 22%) as a result of the integrated eradication campaign. At the same time the total number of BHV-1-free certified herds had increased from 3000 herds in 1997 to almost 16000 herds in 2000 [27]. During the eradication campaign, the purchase of cattle to complement a certified BHV-1-free herd was only permitted from other certified BHV-1-free herds. All cattle over 3 months of age in herds not proved to be BHV-1-free had to be vaccinated twice a year.

For feral cattle, on the other hand, intervention measures such as vaccination may not be achievable. Furthermore the lifespan of feral cattle may be at least twice as long as that of domestic cattle, and population sizes can also be much larger. We have shown that a longer mean lifespan and a larger population size both increase the time to extinction to such an extent that for practical purposes the virus will persist indefinitely. To what extent circulation of BHV-1 in feral cattle possess a risk to commercial farms remains to be investigated.

ACKNOWLEDGEMENTS

The authors thank the Ministry of Agriculture, Nature and Food Quality for funding this work.

REFERENCES

1. Bartlett MS. Measles periodicity and community size. *J R Stat Soc A* 1957; **120**: 48–70.

2. Bartlett MS. The critical community size for measles in the U.S. *J R Stat Soc A* 1960; **123**: 37–44.
3. Grenfell BT. Chance and chaos in measles dynamics. *J R Stat Soc B* 1992; **54**: 383–398.
4. Keeling MJ. Modelling the persistence of measles. *Trends Microbiol* 1997; **5**: 513–518.
5. Grenfell BT, Bolker BM. Cities and villages: infection hierarchies in a measles population. *Ecol Lett* 1998; **1**: 63–70.
6. Gibbs EPJ, Rweyemamu MM. Bovine herpesviruses, Part I, Bovine herpesvirus 1. *Vet Bull* 1977; **47**: 317–343.
7. Ackermann M, Peterhans E, Wyler R. DNA of bovine herpesvirus type 1 in the trigeminal ganglia of latently infected calves. *Am J Vet Res* 1982; **43**: 36–40.
8. Sheffy BE, Rodman S. Activation of latent infectious bovine rhinotracheitis virus infection. *J Am Vet Med Assoc* 1973; **163**: 850–851.
9. Dennett DP, Barasa JO, Johnson RH. Infectious bovine rhinotracheitis virus: studies on venereal carrier status in range cattle. *Res Vet Sci* 1976; **20**: 70–83.
10. Hage JJ, Schukken YH, Barkema HW, Benedictus G, Rijsewijk FAM, Wentink GH. Population dynamics of bovine herpesvirus 1 infection in a dairy herd. *Vet Microbiol* 1996; **53**: 169–180.
11. De Koeijer AA, Diekmann O, De Jong MCM. Calculating the time to extinction of a reactivating virus, and in particular to bovine herpesvirus. *Math Biosci* (in press).
12. De Jong MCM, Kimman TG. Experimental quantification of vaccine-induced reduction in virus transmission. *Vaccine* 1994; **12**: 761–766.
13. Kroese AH, De Jong MCM. Design and analysis of transmission experiments. In: Menzies FD, Reid SWJ, eds. *Proceedings of a Meeting of the Society for Veterinary Epidemiology and Preventive Medicine*. Noordwijkerhout: The Netherlands, 2001: xxi–xxxvii.
14. Ball F. A unified approach to the distribution of total size and total area under the trajectory of infectives in epidemic models. *Adv Appl Prob* 1986; **18**: 289–310.
15. Kemeny JG, Snell JL. *Finite Markov chains*. New Jersey: D. Van Nostrand, 1960: 43–58.
16. Cornelissen P, Vulink JTh. Large herbivores in wetlands: evaluation of the grazing regime in 'De Oostvaardersplassen'. *Flevobericht*, 1996; **399**: 142 pp. [in Dutch].
17. Platteeuw M, Cornelissen P, Jans L. Vegetation, grazing and birds in a fresh water swamp: Monitoring programme 'De Oostvaardersplassen', 1996/1997. In: Report by the Institute for Inland Water Management and Waste Water Treatment, Lelystad, The Netherlands, 98.096X. 1998: 35–49 [in Dutch].
18. Platteeuw M, Jans L, Cornelissen P, Beemster N, Altenburg W. Vegetation, grazing and birds in a fresh water swamp: Monitoring programme 'De Oostvaardersplassen', 1997/1998. In: Report by the Institute for Inland Water Management and Waste Water Treatment, Lelystad, The Netherlands, 99.119X. 1999: 28–95 [in Dutch].
19. Platteeuw M, Cornelissen P, Beemster N, Altenburg W, Van Der Heide Y. Vegetation, grazing and birds in a fresh water swamp: monitoring programme 'De Oostvaardersplassen', 1998/1999. In: report by the Institute for Inland Water Management and Waste Water Treatment, Lelystad, The Netherlands, 2000.120X. 2000: 109 pp. [in Dutch].
20. Bosch JC, De Jong MCM, Franken P, et al. An inactivated gE-negative marker vaccine and an experimental gD-subunit vaccine reduce the incidence of bovine herpesvirus 1 infections in the field. *Vaccine* 1998; **16**: 265–271.
21. Vulink JTh. *Hungry Herds: management of temperate lowland wetlands by grazing* [dissertation]. University of Groningen, The Netherlands, 2001. Chapter 6.
22. Diekmann O, Heesterbeek JAP. *Mathematical epidemiology of infectious diseases: model building, analysis and interpretation*. Chichester: Wiley, 2000: 73–95.
23. Caswell H. *Matrix population models*. Sunderland: Sinauer Associates, 2001: 56–109.
24. Mars MH. *Vaccinology and Epidemiology of bovine herpesvirus 1 infections* [dissertation]. University of Utrecht, The Netherlands, 2000. Chapter 5.
25. Inman M, Lovato L, Doster A, Jones C. A Mutation in the latency-related gene of bovine herpesvirus 1 disrupts the latency reactivation cycle in calves. *J Virol* 2002; **76**: 6771–6779.
26. Van Wuijckhuise L, Bosch J, Franken P, Frankena K, Elbers AR. Epidemiological characteristics of bovine herpesvirus 1 infections determined by bulk milk testing of all Dutch dairy herds. *Vet Rec* 1998; **142**: 181–184.
27. Animal Health Service (Gezondheidsdienst voor Dieren), Deventer, The Netherlands (<http://www.gd-dieren.nl>).