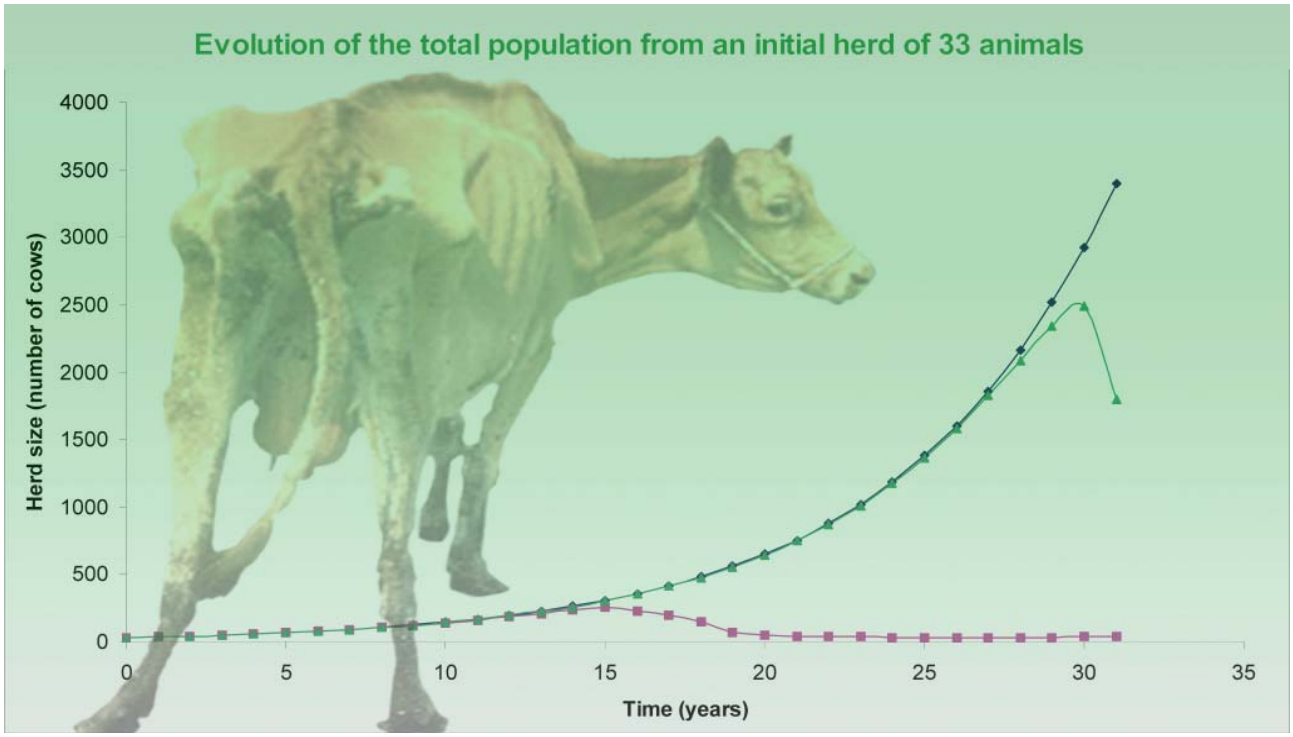
ALP science 2006, No. 497

THEORETICAL DISTRIBUTION OF JOHNE'S DISEASE STAGES IN INDIVIDUAL HERDS AND SIMULATION OF CONSEQUENCES TO RISK MANAGEMENT OPTIONS

Technical-scientific information



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Contents

ALP science

Title
Theoretical distribution of Johne's disease stages in individual herds and simulation of consequensces to risk management options

First edition

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Publisher
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Layout
Helena Hemmi

Publication frequency
Several times yearly at irregular intervals

ISBN 3-905667-38-X
ISSN 1660-7856 (online)

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THEORETICAL DISTRIBUTION OF JOHNE'S DISEASE STAGES IN INDIVIDUAL HERDS AND SIMULATION OF CONSEQUENCES TO RISK MANAGEMENT OPTIONS

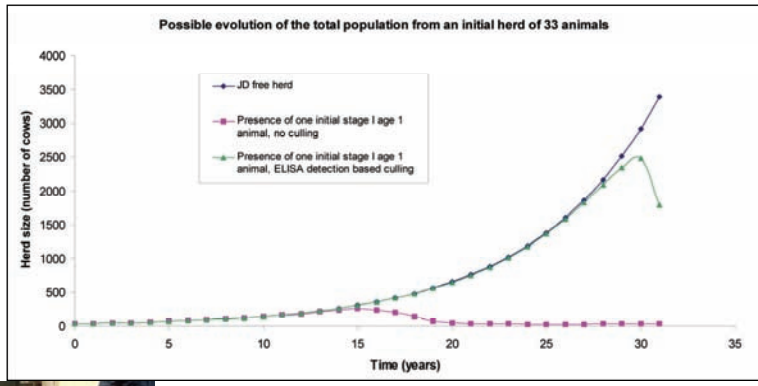
Abstract

The present work presents a model of the propagation of Johne's disease (JD) in individual herds in order to allow for the simulation of consequences of herd management options for disease control or eradication.

Sources for model parameterization were a qualitative description of JD based on 4 distinct disease stages, literature data and expert estimates. Modelling was based on the Susceptibility-Exposition-Infection-Retrieval (SEIR) model combined with the Leslie population model.

The model comprises an iterative process with matrices for initial conditions and transition between stages. The initial conditions matrix depends on the actual health status of the herd and is derived from the modelling of the distribution of JD and analytical data. The transition matrix depends on country and the specific expert knowledge of herd parameters, i.e. death and birth rates, contamination at birth, and duration of stages. The corresponding estimates may easily be reexamined. For a shorter duration than any JD stage duration, the matrix describes the changes in animals classes. Without this condition, the model is redefined between iterations.

An upper limit of 3 stage III animals, 9 stage II animals and 27 stage I animals and a lower limit of 2 stage III, 4 stage II and 8 stage I animals were implemented in order to estimate the initial stage values. For that reason, simple hypotheses concerning duration of stages and considered intervals of time were also implemented in order to test the combined model. Moreover, parameters such as births, contaminations and deaths were set as uniformly distributed. Output may be expressed as a user-friendly spreadsheet in which different scenarios could be tested.



Keywords: SEIR-Model
LESLIE-Model
Stages of Johne's disease
Factors influencing Johne's disease
Herd risk management

1 Introduction

Mycobacterium avium subspecies *paratuberculosis* (MAP) causes Johne's disease (JD, also named *paratuberculosis*). Discovered a century ago, MAP is found worldwide in numerous mammals and birds. Ruminants, especially cows, are particularly susceptible. JD positive cows produce less milk, less meat and have shorter lifespans [2]. The prevalence of Johne's disease is globally increasing in animal husbandry [10]. JD positive animals transmit MAP in faeces, intestinal tissue, lymphatic nodes, blood, colostrum and milk. The infected animals transmit the bacteria directly to the foetus [16], but also to the calves through colostrum and milk [15] and indirectly through faeces [18], [15], [7]. Cow to foetus transmission is a rare event. Transmission through colostrum and milk has three characteristics: it is diffuse (bacteria spread everywhere), continuous (bacteria is often found in the milk) and of low contamination level when compared with the indirect source of JD. The indirect transmission is occasional and with high MAP levels.

Six stages have been described to elucidate the evolution of JD [15]-[19] (Stage 0 is the MAP-free status. Stage I corresponds to the incubation time, separating the inoculation and the first immunological response of the animal. Stage II is the time span of increasing immune response to JD. Some shedding of MAP may happen during this stage [19]-[13]. The response of the immune system reaches a plateau value during stage III. MAP appears in the faeces at low contamination levels. At stage IV, infected animals show clinical signs [4]. Stage V is defined as the final stage during which JD induces death of the animal.

JD causes reduced milk production, loss of body weight in cattle sold for slaughter and premature culling [9]. Strategies to eliminate MAP have included repeated testing, vaccination of animals and development of genetically MAP-resistant animals. Each of these strategies is time consuming and cost intensive. Therefore a mathematical model of JD allowing rational estimation of disease development within a herd and an estimation of the expected costs would be useful. Based upon herd population dynamics and expert knowledge, our model allows rationalisation of dispersed information, i.e. the evolution of lactation as well as predictions about the effects of different management strategies.

2 Materials and methods

Modelling assumptions

For modelling purpose, MAP is assumed to be transmitted from an infective animal to susceptible animals either by intra-uterine contamination or by contaminated faeces and/or colostrums and milk. Then, JD evolution is time dependent and expresses itself in different stages (see above). These stages are to be taken into account. Susceptibility to JD lowers with age; older animals may not have time to fully develop the disease. Thus, age must be taken into account. The age of animals is measured in years.

Lactation is related to birth rates, so this parameter must also be considered. The first lactation period is assumed to take place during the third year after birth of the animal.

Model SEIR

Per definition, the SEIR mathematical model (http://www.biology-online.org/dictionary/seir_model, accessed 17.05.05) distributes the JD disease stages (0 to V) in our model herd. Independently from JD stages, Leslie's population model [5, 12] distributes ages, birth and death rates within the same herd. Thus, the Leslie model implies a varying total number of animals in the herd. Combining the models allows for the testing of interactions between both models. Correspondence is drawn between stage 0 and susceptible animals (S, can become infected), stage I and exposed animals (E, contaminated, but non infective), stages II, III and IV and infective animals (I, contaminated and infective), as well as stage V and retrieved animals (R, can no longer be contaminated). Contamination is understood as the change from stage 0 to stage I and depends on contacts between susceptible S and infective I animals.

SEIR models basically are differential equations systems that describe changes in the numbers of S, E, I, R during the small time interval dt. Variation in the number of susceptible animals is given by $\frac{dS}{dt} = B - \beta SI - \mu S$ (1) and depends on arrivals of newborn MAP-free calves B and a number of departures symbolized by βSI. Thus, the product SI represents interactions between the two subgroups in the herd during the time interval dt. The rate at which encounters between S and I animals create new stage I [or exposed E] animals in the herd is symbolised by β. Another source of departures is μS, the number of susceptible animals that die during the time interval dt.

The number of exposed animals E changes during the time interval dt accordingly to the relation (2). In this relation the group of exposed animals receives a number of newly exposed cows from equation (1) equal to βSI and loses a number of animals μE proportional to the number of exposed animals during the time interval dt. Another source of loss is given by the limited duration of stage I symbolised by λ_1. The exposed animals will disappear at the rate of $\frac{1}{\lambda_1}$. The relation (2) is thus

$$\frac{dE}{dt} = \beta SI - \frac{E}{\lambda_1} - \mu E \qquad (2)$$

Similarly, the change in number of the infected and infective animals is given by the loss through change of state in equation (2), a second form of change in state of the animals is given by $\frac{I_t}{\lambda_I}$, and the death rate $\mu_I I_t$, i.e. the relation (3) is

$$\frac{dI}{dt} = \frac{E}{\lambda_1} - \frac{I_t}{\lambda_I} - \mu_I I_t \qquad (3)$$

Finally, the number of retrieved animals is modified by the arrivals through deaths from stages S, E and I. This is summed up in relation (4) $\frac{dR}{dt} = \mu S + \mu E + \mu I$ (4).

Discretization of the SEIR model

Any derivative of the form $\frac{df(t)}{dt}$, where $f(t)$ is a continuous time dependent function, is the limit of a difference divided by the length of the time interval ($\frac{df(t)}{dt} = \lim_{dt \to 0} \frac{f(t+dt) - f(t)}{dt}$). Taking into account the numerator of the right hand term of this equality for a non-negligible time interval (denoted Δt), results in an approximation of this relation. The loss in precision is gained in calculability. Under such assumptions, equation (1) becomes

$$\frac{S(t+\Delta t) - S(t)}{\Delta t} = B(t) - \beta S(t) I(t) - \mu_S S(t) \qquad (1a)$$

or the iteration $S(t+\Delta t) = S(t) + \big(B(t) - S(t)\big(\beta I(t) - \mu_S\big)\big)\Delta t$

Analogously,

equations (2) to (4) become $\frac{E(t+\Delta t) - E(t)}{\Delta t} = \beta S(t) I(t) - \frac{E(t)}{\lambda_E} - \mu_E E(t)$ (2a)

$$\frac{I(t+\Delta t)-I(t)}{\Delta t}=\frac{E(t)}{\lambda_E}-\mu_I I(t) \tag{3a}$$

$$\frac{R(t+\Delta t)-R(t)}{\Delta t}=\mu_S S(t)+\mu_E E(t)+\mu_I I(t) \tag{4a}$$

Since JD is divided into the stages I, II, III and IV, the infective group is modelled as three distinct groups sequentially ordered in time. Exposed animals E become infective animals I. In the SEIR model, this situation is translated by the corresponding symbols (I_2, I_3, I_4). Each stage is either associated with a duration λ or with a dying rate μ. The equations for the infective groups are accordingly modified. This change justifies the renaming of the SEIR model as $SEI_2I_3I_4R$, i.e.

$$\begin{cases}
\dfrac{S(t+\Delta t)-S(t)}{\Delta t}=B(t)-\beta S(t)\big(I_2(t)+I_3(t)+I_4(t)\big)-\mu_S S(t)\\
\dfrac{E(t+\Delta t)-E(t)}{\Delta t}=\beta S(t)\big(I_2(t)+I_3(t)+I_4(t)\big)-\dfrac{E(t)}{\lambda_E}-\mu_E E(t)\\
\dfrac{I_2(t+1)-I_2(t)}{\Delta t}=\dfrac{E(t)}{\lambda_E}-\dfrac{I_2(t)}{\lambda_2}-\mu_2 I_2(t)\\
\dfrac{I_3(t+\Delta t)-I_3(t)}{\Delta t}=\dfrac{I_2(t)}{\lambda_2}-\dfrac{I_3(t)}{\lambda_3}-\mu_3 I_3(t)\\
\dfrac{I_4(t+\Delta t)-I_4(t)}{\Delta t}=\dfrac{I_3(t)}{\lambda_3}-\dfrac{I_4(t)}{\lambda_4}-\mu_4 I_4(t)\\
\dfrac{R(t+\Delta t)-R(t)}{\Delta t}=\mu_S S(t)+\mu_E E(t)+\mu_2 I_2(t)+\mu_3 I_3(t)+\mu_4 I_4(t)
\end{cases} \tag{5}$$

The Leslie model allows the introduction of differences in age in the $SEI_2I_3I_4R$ model by describing the herd as a squared matrix of any desired size. In our model, each of the six rows represents an age category and each of the six columns represents one stage of the disease (0 to V). Each matrix component, characterised by the indexes (.i;j), represents the number of animals of the i-th age and in the j-th stage of JD. The matrix itself is called a transition matrix.

Transition matrix

Basically, the transition matrix results from several modifications of a Leslie population model. It remains a Leslie matrix since it describes fertility and mortality rates in the herd.

The first modification in the transition matrix is the nonzero mortality and fertility rate for each matrix component. This modification is justified by the assumption that these rates are influenced by JD and by age.

Second, births are split into contaminated and non–contaminated animals. For any class indexed by (.i;j), fertility rates are denoted η_{ij} and contamination rates at birth γ_{ij} .

Products of the form $\gamma_{ij}\eta_{ij}I_{i,j}(t)$ represent the proportion of contaminated births found among the $\eta_{ij}I_{i,j}(t)$ births of the class indexed by (.i;j). Of course, the proportion of non-contaminated births is given by $(1-\gamma_{ij})\eta_{ij}I_{i,j}(t)$.

Third, the number of survivors of age .i in the unmodified Leslie model corresponds to a same age population containing all JD stages. In other words, each line of the matrix in the modified model is related to the Leslie model by the relation

$$k_{i-1}(t)(1-\mu_i)=S_i+E_i+I_{i2}+I_{i3}+I_{i4}+R_i$$

at the iteration t. (6)

Fourth, transitions from stage to stage branch either from susceptible to susceptible or from susceptible to exposed animals. When exposed, the disease evolves from stage II to stage V.

Contaminations are represented by products of the form $\beta_{i,0} S_{i,0}(t) \beta_{i,j} I_{i,j}(t)$. The tendency of susceptible animals to become MAP carriers when in contact with infective animals is described by its susceptibility $\beta_{i,0}$. Infectivity $\beta_{i,j}$ describes the tendency of infective animals to spread the disease. Finally, the transmission of JD is the result of the product of infectivity, the number of infective animals, the susceptibility, and the number of susceptible animals. For example, the one year old susceptible animals $S_{1,0}$ have a corresponding susceptibility $\beta_{1,0}$ and three year old stage II animals $I_{3,2}(t)$ whose infectivity is $\beta_{3,2}$ create $\beta_{i,0} S_{i,0}(t) \beta_{i,2} I_{i,2}(t)$ new members of the E group. Different values of infectivity and susceptibility result in different products. Therefore, the sum of all possible products replaces the expression of new cases in the SEIR model βSI. The number of survivors is then determined by multiplying the obtained results by the survival rate. The variation of susceptible animals from the t-th iteration to the $t + \Delta t$ iteration is thus expressed by

$$\frac{S_{i+1,0}(t+\Delta t) - S_{i,0}(t)}{\Delta t} = (1-\mu_{i,0}) \left(S_{i,0}(t) + B(t) - \sum_{i=1}^{N} \beta_{i,0} S_{i,0}(t) \left(\beta_{i,2} I_{i,2}(t) + \beta_{i,3} I_{i,3}(t) + \beta_{i,4} I_{i,4}(t) \right) \right) \quad (7)$$

Fifth, a contaminated animal may either grow older without changing its JD stage, i.e. $I_{i,j}$ to $I_{i+1,j}$, or grow older and change its JD stage, i.e. $I_{i,j}$ to $I_{i+1,j+1}$. When the actual time interval between two iterations is τ, the pertinent proportions of this branching event are defined by the factor $\frac{\tau}{\lambda_{i,1}}$. The time interval τ is chosen smaller than the duration of stages, i.e. $\tau \leq \lambda_{i,j}$ (for any .i;j.). Stage durations are assumed to depend on age and therefore the matrix $(\lambda_{i,j})_{i=0,\ldots,N;\, j=0,\ldots,5}$ is defined. This new term modifies the equation in the system (5) for the exposed animals E to

$$\frac{E_{i+1,1}(t+\Delta t) - E_{i+1,1}(t)}{\Delta t} = \sum_{i=1}^{N} \beta_{i,0} S_{i,0}(t) \left(\beta_{i,2} I_{i,2}(t) + \beta_{i,3} I_{i,3}(t) + \beta_{i,4} I_{i,4}(t) \right) - \frac{E_{i+1,1}(t)}{\lambda_E} - \mu_{i+1,1} E_{i+1,1}(t) \quad (8)$$

and for the infective animals (I) to

$$\frac{I_{i+1,2}(t+\Delta t) - I_{i,2}(t)}{\Delta t} = \frac{E_{i,1}(t)}{\lambda_{i,1}} - \frac{I_{i,2}(t)}{\lambda_{i,2}} - \mu_{i,2} I_{i,2}(t) \quad (9)$$

Since the measures defining the iterations are points on the time line, the distribution of events between the measures is unknown. In our model, events are arrivals and departures of animals with a change in JD's stage considering any (.i;j) indexed class. The simplest distribution to use in that sense is the uniform one. This means that events are proportional to $\frac{\tau}{\lambda_{i,1}}$ and their non realization is proportional to $1 - \frac{\tau}{\lambda_{i,1}}$.
In both cases, the age number (.i) changes.
Finally, the retrieved animals R collect all dead animals from all columns.

3 Results

Stage 0

Age 0 $$\left(\sum_{i=0}^{6}\left[\sum_{j=0}^{4}(1-\gamma_{i,j})\eta_{i,j}I_{i,j}(t)\right]-S_{0,0}(t)\right)(1-\mu_{0,0})$$

Age 1 $$\left(S_{0,0}(t)\sum_{i=0}^{6}\left[\sum_{j=1}^{4}(1-\beta_{0,0}\beta_{i,j})I_{i,j}(t)\right]-S_{1,0}(t)\right)(1-\mu_{1,0})$$

Age 2 $$\left(S_{1,0}(t)\sum_{i=0}^{6}\left[\sum_{j=1}^{4}(1-\beta_{1,0}\beta_{i,j})I_{i,j}(t)\right]-S_{2,0}(t)\right)(1-\mu_{2,0})$$

Age 3 $$\left(S_{2,0}(t)\sum_{i=0}^{6}\left[\sum_{j=1}^{4}(1-\beta_{2,0}\beta_{i,j})I_{i,j}(t)\right]-S_{3,0}(t)\right)(1-\mu_{3,0})$$

Age 4 $$\left(S_{3,0}(t)\sum_{i=0}^{6}\left[\sum_{j=1}^{4}(1-\beta_{3,0}\beta_{i,j})I_{i,j}(t)\right]-S_{4,0}(t)\right)(1-\mu_{4,0})$$

Age 5 $$\left(S_{4,0}(t)\sum_{i=0}^{6}\left[\sum_{j=1}^{4}(1-\beta_{4,0}\beta_{i,j})I_{i,j}(t)\right]-S_{5,0}(t)\right)(1-\mu_{5,0})$$

Age 6 $$\left(S_{5,0}(t)\sum_{i=0}^{6}\left[\sum_{j=1}^{4}(1-\beta_{5,0}\beta_{i,j})I_{i,j}(t)\right]-S_{6,0}(t)\right)(1-\mu_{6,0})$$

A transition matrix is shown in order to illustrate the equations (7) to (9). Subsequently, some particularities of the stages are discussed in relation to the matrix. In order to write shorter formulas, the time interval is taken as one unit of time, i.e. ($\tau=\lambda_{i,j}=1\ year$). For the same reason, the use of $K(t)=\sum_{i=1}^{6}\beta_{i,2}I_{i,2}(t)+\beta_{i,3}I_{i,3}(t)+\beta_{i,4}I_{i,4}(t)$ proved to be useful.

Stage 0 subpopulation arrivals occur by uncontaminated births (class (0;0)) from all other classes. On the other hand, departures from stage 0 are caused by either contaminations or deaths. In order to stay in the stage 0 subpopulation, the animals must avoid contamination by all subpopulations of infective cows (defined by coefficients of the form $(1-\beta_{4,0}\beta_{i,j})I_{i,j}(t)$) and survive during the time interval of the iteration (survival is defined by coefficients of the form $(1-\mu_{5,0})$).

Stage I	Stage II	Stage III
$\left(\sum_{i=0}^{6}\left[\sum_{j=0}^{4}\gamma_{i,j}\eta_{i,j}I_{i,j}(t)\right]-E_{0,1}(t)\right)(1-\mu_{0,1})$	0	0
$(\beta_{0,0}S_{0,0}(t)K(t)-E_{1,1}(t))(1-\mu_{1,1})$	$(E_{0,1}(t)-I_{1,2}(t))(1-\mu_{1,2})$	0
$(\beta_{1,0}S_{1,0}(t)K(t)-E_{2,1}(t))(1-\mu_{2,1})$	$(E_{1,1}(t)-I_{2,2}(t))(1-\mu_{2,2})$	$(I_{1,2}(t)-I_{2,3}(t))(1-\mu_{2,3})$
$(\beta_{2,0}S_{2,0}(t)K(t)-E_{3,1}(t))(1-\mu_{3,1})$	$(E_{2,1}(t)-I_{3,2}(t))(1-\mu_{3,2})$	$(I_{2,2}(t)-I_{3,3}(t))(1-\mu_{3,3})$
$(\beta_{3,0}S_{3,0}(t)K(t)-E_{4,1}(t))(1-\mu_{4,1})$	$(E_{3,1}(t)-I_{4,2}(t))(1-\mu_{4,2})$	$(I_{3,2}(t)-I_{4,3}(t))(1-\mu_{4,3})$
$(\beta_{4,0}S_{4,0}(t)K(t)-E_{5,1}(t))(1-\mu_{5,1})$	$(E_{4,1}(t)-I_{5,2}(t))(1-\mu_{5,2})$	$(I_{4,2}(t)-I_{5,3}(t))(1-\mu_{5,3}))$
$(\beta_{5,0}S_{5,0}(t)K(t)-E_{6,1}(t))(1-\mu_{6,1})$	$(E_{5,1}(t)-I_{6,2}(t))(1-\mu_{6,2})$	$(I_{5,2}(t)-I_{6,3}(t))(1-\mu_{6,3})$

From stage I to stage IV, the evolution of the disease is forced. When entering stage I, the cow successively passes all other stages. The coefficients of the form $(1-\mu_{3,1})$ define the proportion of survivors for a given iteration. The time intervals between iterations and the stage duration were set equal. Therefore, every animal in a (.i;j) class at the t-th iteration will leave its class for a (.i+1;…) class. The symbols $-E_{3,1}(t)$ and $-I_{4,2}(t)$ follow this relation. The arrivals into a new stage of JD are either due to contaminations (the coefficients of the form $\beta_{2,0}S_{2,0}(t)K(t)$) or to transition from the preceding stage and preceding iteration. For example, the stage II subpopulation at the age 3 receive the exposed animals (stage I) from age 2, i.e. in the class with the indexes (3;2) the arrivals are given by the coefficient $E_{2,1}(t)$. The last considered source of contamination is birth, whose size is calculated by the expression

$$\sum_{i,j=0}^{N}\gamma_{i,j}\eta_{i,j}I_{i,j}(t) \qquad (10)$$

$\gamma_{i,j}$ gives the proportion of contaminated births among $\eta_{i,j}I_{i,j}(t)$. If $\gamma_{i,j}$ relates to susceptible animals its value is set to zero.

When the time intervals between two iterations and the JD stages duration are different, some animals will not change their JD stage but will change their age (given by the coefficients of the form $\left(1-\frac{1}{\lambda_{3,1}}\right)E_{3,1}(t)$ representing arrivals in the (4, 1) class). Some animals in this class will change stage (denominated by the expressions $\frac{E_{4,1}(t)}{\lambda_{4,1}}$, representing departures in the same class). The remaining arrivals are from the preceding stage and preceding age . The proportion of survivors is still given by the $(1-\mu_{4,1})$ coefficient. In conclusion, these considerations result in formulas like

$$\left(\beta_{3,0}S_{3,0}(t)K(t)+\left(1-\frac{1}{\lambda_{3,1}}\right)E_{3,1}(t)-\frac{E_{4,1}(t)}{\lambda_{4,1}}\right)(1-\mu_{4,1}) \qquad (11)$$

instead of the formula $(\beta_{3,0}S_{3,0}(t)K(t)-E_{4,1}(t))(1-\mu_{4,1})$ used above in the stage I of JD at the age of 4.

Current contaminations under the uniform distribution hypothesis divide the herd in four subpopulations:

- The susceptible animal subpopulation ready to become JD positive E is given by the sum of the coefficients $\beta_{i,0}S_{i,0}(t)$
- The susceptible animal subpopulation not becoming JD positive is given by the sum of the coefficients $(1-\beta_{i,0})S_{i,0}(t)$
- The infective animal subpopulation infecting susceptible animals is the sum of the coefficients $\beta_{i,j}I_{i,j}(t)$
- Infective animals not infecting susceptible animals are related to $(1-\beta_{i,j})I_{i,j}(t)$.

Contact between animals among subpopulations are represented by products resulting in the number of non contaminated animals for a given initial population, i.e

$$(1-\beta_{i,0})S_{i,0}(t)\sum_{i=1,j=1}^{i=6,j=5}(1-\beta_{i,j})I_{i,j}(t)+(\beta_{i,0})S_{i,0}(t)\sum_{i=1,j=1}^{i=6,j=5}(1-\beta_{i,j})I_{i,j}(t) \qquad (12)$$
$$+(1-\beta_{i,0})S_{i,0}(t)\sum_{i=1,j=1}^{i=6,j=5}(\beta_{i,j})I_{i,j}(t)=S_{i,0}(t)\sum_{i=1,j=1}^{i=6,j=5}(1-\beta_{i,0}\cdot\beta_{i,j})I_{i,j}(t)$$

and the total number of contaminations for the same initial population, i.e. $(\beta_{i,0})S_{i,0}(t)\sum_{i=1,j=1}^{i=6,j=5}(\beta_{i,j})I_{i,j}(t)$

The presented example includes simplifications. Noteworthy is the consideration of classes with indexes (.i;j) without animals 0, where arrivals from precedent age or stage classes are considered impossible.

Stage IV	Stage IV
0	$\mu_{0,0}S_{0,0}(t)+\mu_{0,1}E_{0,1}(t)$
0	$\mu_{0,0}S_{0,0}(t)+\mu_{1,1}E_{1,1}(t)+\mu_{1,2}I_{1,2}(t)$
0	$\mu_{2,0}S_{2,0}(t)+\mu_{2,1}E_{2,1}(t)+\sum_{j=2}^{3}\mu_{2,j}I_{2,j}(t)$
$(I_{2,3}(t)-I_{3,4}(t))(1-\mu_{3,4})$	$\mu_{3,0}S_{3,0}(t)+\mu_{3,1}E_{3,1}(t)+\sum_{j=2}^{4}\mu_{3,j}I_{3,j}(t)$
$(I_{3,3}(t)-I_{4,4}(t))(1-\mu_{4,4})$	$\mu_{4,0}S_{4,0}(t)+\mu_{4,1}E_{4,1}(t)+\sum_{j=2}^{4}\mu_{4,j}I_{4,j}(t)$
$(I_{4,3}(t)-I_{5,4}(t))(1-\mu_{5,4})$	$\mu_{5,0}S_{5,0}(t)+\mu_{5,1}E_{5,1}(t)+\sum_{j=2}^{4}\mu_{5,j}I_{5,j}(t)$
$(I_{5,3}(t)-I_{6,4}(t))(1-\mu_{6,4})$	$\mu_{6,0}S_{6,0}(t)+\mu_{6,1}E_{6,1}(t)+\sum_{j=2}^{4}\mu_{6,j}I_{6,j}(t)$

4 Discussion

An important goal of this work is to produce a user-friendly spreadsheet-based tool that may be applied by herd managers. To this end, two problems are to be addressed. One, numerical calculus allows divergences between difference equations and differential equations. These divergences have to admit a supremum. Second, the parameter values and the initial distribution of age and stages must be known.

The close relation between our model and the Leslie model is established in case of a MAP-free herd, in which all coefficients related to JD are zero. The transition matrix becomes then the Leslie matrix, i.e.

	Stage 0	Stages –I – II – III –IV	Stage V
Age 0	$\sum_{i,j=0}^{N}\eta_{i,j}(i;j,t)(1-\mu_{0,0})$	0	$\mu_{0,0}S_{0,0}(t)$
Age i	$\sum_{i=0}^{6}S_{i-1,0}(t)(1-\mu_{i,0})$	0	$\mu_{i,0}S_{i,0}(t)$

(13)

Since each subpopulation defined by its age is related to the Leslie model by the relation (7), divergence in the combined model is controlled by the behaviour of the Leslie variables. They admit a supremum.

Moreover, the results of our combined model have to be consistent with the SEIR model, where infectivity and susceptibility are neither separated nor considered. The sum of all susceptible animals, separated in age classes represents the susceptible population of the SEIR model, i.e. $\sum_{i=0}^{6} S_{i,0}(t) = S(t)$ The beta coefficient β of the SEIR model can be redefined from the combined model. A general susceptibility coefficient $\overline{\beta}$ is defined using the sum of all possible products of susceptible classes multiplied by their corresponding susceptibility coefficients. $\overline{\beta}$ is the unknown in the first degree equation $\sum_{i=0}^{6} \beta_{i,0} S_{i,0}(t) = \overline{\beta} \cdot S(t)$. By analogy, a general infectivity coefficient $\overline{\overline{\beta}}$ can be defined with the relation $\sum_{i=0,\, j=2}^{6} \beta_{i,j} I_{i,j}(t) = \overline{\overline{\beta}} \cdot I(t)$. The loop to the SEIR model is closed by summing the two preceding relations giving the number of new cases in the SEIR model, i.e.

$$\sum_{i=0}^{6} \beta_{i,0} S_{i,0}(t) \sum_{k=1,j=2}^{k=6,j=5} \beta_{k,j} I_{k,j}(t) = \overline{\overline{\beta}} \cdot \overline{\beta} \cdot S(t) I(t) = \beta S(t) I(t) \quad (14)$$

Other simplifications are true in the SEIR model. For instance, JD stages are summed up in the E and I animal state. Expressions like become . Similarly, expressions like $\left(\beta_{3,0} S_{3,0}(t) K(t) + \left(1 - \frac{1}{\lambda_{3,1}}\right) E_{3,1}(t) - \frac{E_{4,1}(t)}{\lambda_{4,1}}\right)$ become $\left(\beta S(t) I(t) - \frac{E(t)}{\lambda}\right)$.

Similarly, expressions like $\left(\frac{E_{1,1}(t)}{\lambda_{1,1}} + \left(1 - \frac{1}{\lambda_{1,2}}\right) I_{1,2}(t) - \frac{I_{2,2}(t)}{\lambda_{2,2}}\right)$ become $\left(\frac{I(t)}{\lambda}\right)$.

Finally, the number of retrieved animals in the SEIR model is the sum of all stage V (i.e. dead) animals in the combined stage of stage- and age classes model.

Since the general behaviour of the herd is controlled by the differential equations (1 to 4), its functions grow within any finite time interval. Stage– and age classes that build the entire herd are therefore maximised. During a considered finite time interval, these classes behave within a finite interval of finite values without singularities, which is in agreement with the behaviour of a differential equations system.

Duration of stages and iteration time interval

The duration of a JD stage is defined as the time interval between the start and the end of that stage. Relating this duration to the interval between two iterations is problematic. If the time interval between two iterations τ for given .i and j is longer than each stage duration, i.e. $\tau \geq \lambda_{i,j}$, then the sum of the duration between two consecutive stages is considered. If the time interval between iterations is shorter than the sum of the stage durations, $\tau \leq \lambda_{i,j} + \lambda_{i,j+1}$, and the corresponding probabilities are uniformly distributed, then the evolution of the class $I_{i,j}(t)$ will lead to the classes $I_{i+1,j+1}(t)$ and $I_{i+1,j+2}(t)$, where

$$I_{i+1,j+1}(t) = \left(1 - \frac{\tau}{\lambda_{i,j} + \lambda_{i,j+1}}\right)(1 - \mu_{i,j} - \mu_{i,j+1}) I_{i,j}(t)$$

and $$I_{i+1,j+2}(t) = \frac{\tau}{\lambda_{i,j} + \lambda_{i,j+1}}(1 - \mu_{i,j} - \mu_{i,j+1}) I_{i,j}(t)$$

Underlying the uniform distribution, a continuous creation and disappearance of members of the class $I_{i,j+1}(t)$ will be observed. Therefore, the number of visible members of the class (.i;j+1) will be proportional to the ratio between the stage duration and the inter iteration time interval to the proportion of survivors and to the number of animals coming from the preceding JD stage, i.e. $I_{i,j+1}(t) = \frac{\lambda_{i,j}}{\tau}(1 - \mu_{i,j}) I_{i,j}(t)$.

If one ignores stage duration or at least its relation to the time interval between iterations τ , all possible relations must be considered. The forced evolution of JD animals in five stages combined with an unknown iteration time interval implies the necessity of calculating 2^4 different matrices, or, considering age dependent durations and different ages (N), $N*2^4$ different matrix are possible. Since each matrix contains 6*N equations, $6*N^2*2^4$ different equations should be defined, whereby only one of the matrices would be the correct one. Thus, for the best solution, a practical application would be to measure the durations of the different stages and to determine the initial matrix according to the chosen time interval τ . Another important feature is that the time interval between iterations τ is not necessarily constant. In this case, the transition matrix has to be redefined for each time interval between iterations.

Parameters

Our model must be transformed into a system of equations that is useful in herd management practice. Writing this system implies that values are assigned to the parameters of the equations. For our model, rough estimates could be accepted on first trials. When available from field studies, more accurate parameters may be introduced.

The proportion of calves that a cow delivers during a time interval between two iterations is called the fertility rate. Before the first lactation, cows have a fertility rate of zero. The stage V animals are dead and by definition have also a fertility rate of zero. As an estimate, the fertility rate of the cows will decrease proportionally to their age and to the evolution of the disease.

The proportion of death in a given group of animals for a given time interval is the death rate. In our stage–age model, the death rates will expectedly increase as age and stage classes of diseased animals evolve. On the other hand, susceptible animals will supposedly follow a normal pattern.

Initial state matrix

Defining the state of the herd at a given time is a further difficulty. Generally, JD in a herd is discovered by the identification of one or two clinical cases (http://ianrpubs.unl.edu /animaldisease/g977.htm, accessed 09. 09. 2004). Herd owners usually initiate precautionary measures when clinical symptoms are discovered. A starting point for action is to be able to describe the physiological status of the herd, i.e. the number of animals in each stage of JD.

An approximation of the initial state of a herd can be deduced from a few literature sources. Assuming 100% specificity as well as 100% sensitivity of a testing regimen, and analysing 9 positive animals from several positive herds, Meylan [6] observed the following distribution of infected animals: 2 stage IV, 5 stage III and 2 stage I or II. On the other hand, Streeter et al.[15] examined a herd with a significant number of animals (n > 100) and found a total of 36 MAP positive animals including light and heavy shedders. Meylan's relation of 2 stage IV and 5 stage III animals was also recognized in a different herd from the American continent. Stehman et al. [14] found 6 light and 3 heavy shedders in a population of 112 cows. The relation 2: 1 for light versus heavy shedders was found in Australia.

The proportion of calves born with a MAP infection, i.e. in stage I of JD, is defined as the 'at birth' contamination. We assume that only stage IV cows can bear contaminated calves ([3] for instance).

The rate at which a group of contaminated cows transmits the disease to susceptible animals is the contamination rate. The rate at which JD free animals become infected is the susceptibility rate. The susceptibility rate of the youngest MAP-free animals is the highest. This susceptibility is denoted by the symbol $\beta_{0,0}$. Therefore Muskens et al. [8] stress the importance to protect calves. Susceptibility rates for others groups of animals will be much smaller. The exposed animal column or the E column are denoted by susceptibility- or infectivity rates equal to zero. These animals are neither susceptible, nor infective. In the other classes of the herd, infectivity is assumed to grow with age and stage.

In another continent again, [17] observed a relation that is very similar to Meylan's in a small population of JD positive animals. Whitlock and Buergelt [17] propose the "iceberg effect", namely that for each stage IV animal (advanced clinical disease) 1 – 2 animals in stage III (clinical disease), 4 – 8 animals in stage II (subclinical disease, adult carrier), and 10 – 14 animals in stage I (silent infection, calves, young livestock, adults) will be found. Ratios from one stage to its preceding stage vary from 1 to 3.5 with the most accepted value being 2. Taking the middle of theses intervals, the same ratios lay between 1 and 2 with a clear preference for 2. The literature reveals a clear tendency that for each stage IV animal 2 - 3 stage III animals may be found and so forth. Thus, admitting 2.5 as factor of increase of infected animals between the stages seems reasonable, especially when considering the sensitivity of actual testing regimens. The body's serological response to MAP can be detected by ELISA tests. The sensitivity of ELISA tests towards MAP was found to be 21.7 % (stage I), 39.7 % (stage II), 58.6 % (stage III) and 85.8 % (stage IV; [1]). The sensitivity of stage I is 21.7 % meaning that almost 8, out of 10 diseased animals, will result in false negative analysis. For modelling purpose, this fact implies a serious underestimation of stage 1 infected animals. This underestimation of diseased

animals diminishes with the progress of JD through the consecutive stages and is set to zero for stage 4 animals, which are clearly detectable.

A recognized value of ELISA specificity is 98% [11]. Thus, specificity will not contribute to analytical problems. The specificity of 98% means that among 100 positive animals, 2 will be analysed as false negative. The important fact is that JD at stage 4 is readily detected, while preceeding stages of JD may be underestimated and the initial stage is seriously underestimated.

Assuming a constant contamination ratio between consecutive stages (derived from [6]) as well as a common duration for every stage, the contamination rate reaches 1.7 carriers per infective cow. Interpreted as a uniform distribution of contamination events through time, stage IV cows have more time to contaminate other animals. Our model implies that stage IV cows contaminate more animals than do less critically ill animals. Our model applies this rule to all stages and maintains the contamination rate between states between 1.7 (min.) and 2.5 (max). Performing the calculation, any detected stage IV cow within a herd results in an upper limit of 3 stage III animals, 9 stage II animals and 27 stage I animals and a lower limit of 2 stage III, 4 stage II and 8 stage I animals. Adequate analysis as well as better knowledge of the JD stages, contamination rates and duration of stages would also improve the results. For the moment, the initial stage matrix can be filled in by educated guesses.

5 Conclusions

JD was modelled according to the state of the animals. The states are defined by their ages and their stage in the evolution of the disease. The equation system may be executed in a simple spreadsheet. An estimate of the initial herd condition has been discussed for the case of the presence of one stage IV animal within a herd. In the near future, detection methods will improve and exact parameters will be available from literature and analytics. This model could then be a useful tool when applied to a set of probable scenarios in order to define optimum cost strategies to deal with JD.

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