Monitoring programmes for paratuberculosis-unsuspected cattle herds, based on quantification of between-herd transmission

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Keywords: cattle, paratuberculosis, surveillance, certification, mathematical model, transmission.

SUMMARY

A mathematical model was developed to calculate the between-herd transmission of paratuberculosis, expressed as the reproduction ratio $R_h$, which is the average number of new infected herds caused by one (initial) infected herd. In a monitoring programme herds are visited regularly and a certain number of animals is sampled and tested.

The model developed here to design effective monitoring programmes consists of three parts: (a) within-herd dynamics of the infection after (accidentally) introducing the infection in a herd, (b) the detection probability of the infected herd, and (c) the final equation for $R_h$. The model is age structured. The most important input for part (a) is the within-herd reproduction ratio ($R_0$) of the infection, assumptions about the infectious period, culling rate of cattle, herd size, and time between subsequent visits. Output is number of infected cattle at each visit. For part (b) input is number of infected animals in the herd at each visit, number (and age) of animals sampled, and the (infection-age dependent) sensitivity of the diagnostic test. For part (c) $R_h$ is calculated by multiplying the detection probability at a certain visit by the cumulative number of infected cattle at that moment, accumulated for all visits of the herd in time, and then multiplied with the rate with which animals are sold from one herd to another. This yields the average number of infected animals sold from the infected herd (before detection) to other herds, i.e. $R_h$.

The current monitoring programme in the Netherlands for paratuberculosis-unsuspected herds (yearly pooled faecal culture of all cows ≥ 2 year) yields an $R_h$ value of 0.58, which is sufficiently below 1. Other effective alternatives will be shown. Testing all animals ≥ 1 year with the pooled faeces test every two years is an attractive, because cheaper, alternative for which $R_h$ is sufficiently below 1 as well.

INTRODUCTION

Certified unsuspected cattle herds are important in a national paratuberculosis control programme as a source of purchase of animals. To maintain the unsuspected status of these herds, it is necessary to monitor the herds on a regular basis. In a successful monitoring programme, an unsuspected but infected herd has to be detected before it infects on average more than one other herd. Otherwise, the infected herd will lead to a cascade of new infections in other herds, and the pool of unsuspected herds will increase in time.

In the Netherlands the current certification programme was developed in 1998, in which herds are divided into status 'unknown', 'participant prevention', and followed by the unsuspected status 6 to 10 (1). Status 'participant prevention' can be reached after filling in a questionnaire about farm management together with the local veterinarian each year. Subsequently status 6 can be reached by serological testing of all cattle of 3 years and older. Then status 7 to 10 can be reached by yearly testing all cattle of 2 years and older with the pooled faecal culture (4). Maintenance of status 10 is monitored in the same way. A positive pooled faecal culture will be followed by individual faecal culture of the five animals. In case of positive animals, the current status can be maintained after immediate slaughter of these animals, when their number does not exceed 2 animals or 5 % of adult cattle in the herd.

However, the current monitoring scheme for unsuspected herds as described above is found too expensive by farmers. Therefore, alternative schemes were evaluated with two models. The simulation model Johne$\text{SSim}$ (3) for the within-herd transmission and economical
aspects of control was used for the progression from status 6 to status 10. This model for closed herds will be presented by Weber et al. (this volume). One of the outputs of the model is the invisible, because still undetected, prevalence of paratuberculosis in the herd when reaching status 10 (6). The analytical Rₙ-model for between-herd transmission is used for evaluation of test schemes to maintain status 10. This model is presented here and calculates the average number of new infected herds by an (accidentally) infected herd in a pool of unsuspected herds, i.e. the reproduction ratio Rₙ. Important parts of this model are the within-herd dynamics of the infection and of the cattle population, the detection probability of the infected herd, and the movement (trade) of animals between herds. For a successful monitoring programme, Rₙ has to be lower than 1. A comparable approach was followed by Graat et al. (2) for IBR in cattle.

MATERIALS AND METHODS

Several alternative test schemes for monitoring status of 10 herds were evaluated with the Rₙ-model (Table 1). This model calculates the between herd transmission of paratuberculosis in a pool of unsuspected herds were animal contacts are possible through animal trade.

The Rₙ model is an analytical age-structured model. For paratuberculosis transmission models, the age structure of the cattle population of the herd is very important, because the time lag between the moment of infection and becoming infectious of an individual is relatively long compared to their life time. Because of this, many infected animals are culled before becoming infectious (and becoming ‘visible’ due to clinical symptoms). This age structure is recognised in the equations of the Rₙ model by characterising each individual at time t with a certain age a.

The analytical model is built up by mathematical expressions for several processes and is not a simulation model. With the model a value for the between-herd transmission Rₙ is calculated. Rₙ is the average number of new infected herds generated by one initially infected herd. In this paper the most important aspects of the model will be described in words and not in mathematical expressions, to explain the principal idea. Details which often complicate the mathematics are left out here. The model consists of three parts: 1) the dynamics of the infection within the herd, 2) the probability of detection of an infected herd, and 3) the final expression for Rₙ.

1) Dynamics of the infection within the herd. The infection process is of the S - I type, so animals are distinguished in Susceptible and Infected, which can not recover from infection. Animals are assumed to be susceptible from 0 to 0.5 years of age. The period between infection and becoming infectious (latent period) is considered to be long. Contacts between animals within the herd (direct or indirect through manure) are assumed to be random. Animals leave the herd through slaughter. Every adult cattle (≥ 2 year) has a certain probability to be culled (non-selective cull). It is assumed that at a certain age (Aₘₐₓ) infected animals are culled because of clinical signs, whether or not specific for paratuberculosis, like lower milk production, loose of weight, etc. The infectivity (expressed as the transmission parameter β) of an infected animal is assumed to increase linearly between 2 years of age until age Aₘₐₓ. Below the age of 2 years it is assumed that an infected animal is not infectious. The transmission parameter β is the number of new infections (infected animals) caused by one infected animal per time, and the reproduction ratio R₀ is the total number of new infections caused by that animal (in a susceptible population). In the model Rₙ is an input parameter for the within-herd transmission of paratuberculosis, and β(a) (β as function of age a) will be calculated (see later). Rₙ is based on longitudinal observations of 21 infected herds (van Roermund et al. this volume).

The number of new infections in the herd at time t is calculated by multiplication of β(a) with the number of infected animals of age a at that moment (using the integral over all ages), and with the fraction of susceptible animals in the herd (S/N). So because of the presence or introduction of the first infected animal in the herd, the number of I-animals will increase in time. The value for the input parameter Rₙ, and thus for β, accounts for the rate with which this happens. After a certain time an equilibrium will develop in the number of infected animals in the herd, because the number of culled infected animals (by non-selective cull and selective cull at age Aₘₐₓ) will equal the number of new infections per time. The cumulative number of I animals in the herd since first infection until detection of that herd, is a measure for the infection risk to other herds (see later, expression for Rₙ).

2) The probability of detection of an infected herd. At each visit of a herd, a certain number of animals is tested for paratuberculosis. The probability to detect k animals is described by the binomial distribution. If p is the probability to detect an infected animal in the herd (expected number of detectable animals divided by herd size) and X animals will be sampled, the probability to detect the herd (i.e. to detect one or more infected animals) becomes:

\[ P_{\text{detection herd}} = 1 - (1 - p)^X \]
The probability $p$ to detect an infected animal in the herd is derived by multiplication of the number of infected animals $I(a)$ (since the introduction of the infection) with the age-dependent sensitivity of the diagnostic test $\text{sens}(a)$. This yields the expected number of detectable animals, which is then divided by herd size $N$. Then the above equation is adapted for $K$ subsequent visits of the herd, where the probability of no detection of the herd after $K$ visits equals the product of the probabilities of no detection per visit $(1 - p)^K$. Of course the number of infected animals in the herd (and thus $p$) increases per subsequent farm visit (until the equilibrium), due to the longer time since the introduction of the infection. One minus this final probability gives the chance to detect the herd after $K$ visits.

3) Expression for $R_h$, the between-herd transmission ratio. It is assumed that a paratuberculosis infection can be introduced on a farm solely by purchase of live animals. The cumulative number of infected animals $I_{\text{cum}}$ since introduction of the infection in the herd until detection of that herd plays an important role here. These animals could have transmitted the infection to other herds, if they were sold. This number of infected animals multiplied with the chance of an animal being sold (i.e. the fraction of the herd sold per year) results in the number of infected animals of one herd sold to other herds. A worst case scenario is assumed here, in that each animal is sold to a different herd. Then this number equals the value for $R_h$, as $R_h$ is the number of new infected herds caused by one initially infected herd. Thus:

$$R_h = \text{fraction of herd sold per year} \times \sum_{k=1}^{K} [P_{\text{detection herd}} \times I_{\text{cum}}]$$

Where:

- $P_{\text{detection herd}}$: probability of detection of the herd at $K$th visit
- $I_{\text{cum}}$: cumulative number of infected animals at that $K$th visit

The most important input parameters of the $R_h$ model are given in Table 2.

RESULTS

The between-herd transmission was calculated with the $R_h$-model for a pool of unsuspected herds which had contact among each other by animal trade. Figure 1 shows the calculated $R_h$ values at different values for animal trade. Animal trade is expressed here as fraction of herd size, i.e. number of animals sold to other unsuspected herds per year, divided by the herd size (adult cattle). For 87 status 9 and 10 farms in the Netherlands, a value of 0.006 was observed in 1998-2000 (see Table 2). $R_h$ is the average number of new infected herds by one infected herd, and has to be lower than 1. At an animal trade of 0.006, $R_h$ is smaller than 1 for the current monitoring scheme (Standard) and for the alternative schemes $F_1A_1$ and $A_1$ (see Table 1 for explanation).

Table 1. Monitoring schemes for maintaining unsuspected status 10, evaluated with the $R_h$-model.

<table>
<thead>
<tr>
<th>Test scheme</th>
<th>Test</th>
<th>Time between visits (D)</th>
<th>Number of animals tested (X)</th>
<th>Age of animals tested (AgeX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>St$^{(1)}$</td>
<td>PFC$^{(2)}$</td>
<td>1 year</td>
<td>all</td>
<td>$\geq 2$ year</td>
</tr>
<tr>
<td>St+c</td>
<td>PFC + IFC$^{(3)}$</td>
<td>1 year</td>
<td>all</td>
<td>$\geq 2$ year</td>
</tr>
<tr>
<td>F</td>
<td>PFC</td>
<td>1 year</td>
<td>all</td>
<td>$\geq 2$ year</td>
</tr>
<tr>
<td>N$_1$</td>
<td>PFC</td>
<td>1 year</td>
<td>30 youngest</td>
<td>$\geq 2$ year</td>
</tr>
<tr>
<td>N$_2$</td>
<td>PFC</td>
<td>1 year</td>
<td>30 oldest</td>
<td>$\geq 2$ year</td>
</tr>
<tr>
<td>A$_1$</td>
<td>PFC</td>
<td>1 year</td>
<td>all</td>
<td>$\geq 1$ year</td>
</tr>
<tr>
<td>A$_2$</td>
<td>PFC</td>
<td>1 year</td>
<td>1-3 year</td>
<td>$\geq 1$ year</td>
</tr>
<tr>
<td>$F_1A_1$</td>
<td>PFC</td>
<td>2 year</td>
<td>all</td>
<td>$\geq 1$ year</td>
</tr>
</tbody>
</table>

(1) St: Standard monitoring scheme in the Netherlands.
(2) Pooled faecal culture (4).
(3) Pooled faecal culture followed by confirmation of positive pools by individual faecal culture of the five animals.

Figure 1. Between-herd transmission $R_h$ as function of animal movements (trade) between herds, for several monitoring schemes. For explanation of schemes, see Table 1.
For a number of important input parameters a sensitivity analysis was carried out. The input parameters $R_0$ (within-herd transmission of the infection) and $A_\text{max}$ (maximum age of an infected animal) have no or little effect on the calculated $R_0$. The effect of the parameter animal trade is shown in Figure 1. This has a strong effect on the value of $R_0$. The alternative monitoring schemes are in fact also effective ($R_0 < 1$) when the number of animal movements between herds is sufficiently low. At a value of animal movement < 0.003 (i.e., less than 0.3 animals per year for a herd with 100 adult cattle) all evaluated monitoring schemes result in $R_0 < 1$ (Figure 1).

One of the most sensitive input parameters in the model is the test sensitivity. Test sensitivity is assumed to increase linearly with age $a$ of the infected animal (see regression equation in Table 2). When this sensitivity is increased by an absolute value of 5% (i.e., the curve is shifted upwards: $\text{sens}(a) = 0.0348 \times a - 0.0169 + 0.05$ for the pooled faecal culture), the $R_0$ decreases from 0.58 to 0.37 for the standard monitoring scheme, which is a large relative change. Decreasing the test sensitivity by 5% (and avoiding negative values) changed the $R_0$ value even more: from 0.58 to 1.3.

### DISCUSSION

The current monitoring scheme for paratuberculosis-unsuspected cattle herds in the Netherlands is a yearly pooled faecal culture of all cattle $\geq 2$ year. With the observed rate of animal trade among unsuspected herds, this monitoring scheme results in an $R_0$-value of 0.58, which is sufficiently below 1. So a not-yet detected infection in this pool of herds will be detected in time, without causing a cascade of new infections in other herds. This means that the total number of certified herds in the country will increase in time. Of course not-yet detected but infected herds will loose their certificate after a few test rounds, but more herds will enter and stay in the pool.

However, at the moment Dutch farmers find the costs for testing too expensive. Benefits for maintaining a certificate are still very limited. For an overview of costs of these monitoring schemes, see (6) or Weber et al. (this volume, pag. 376). Other effective monitoring schemes which yield an $R_0$ value below 1, are $F_1 A_1$ and $A_1$, i.e., testing all animals $> 1$ year with the pooled faecal culture every year or every two years. Especially the last one is an attractive, because cheaper, alternative. Although the test

### Table 2. Input parameters of the $R_0$-model.

<table>
<thead>
<tr>
<th>Input parameter</th>
<th>Parameter value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herd size $N$</td>
<td>60 cows + 42 young stock</td>
<td>Number of animals in the herd</td>
</tr>
<tr>
<td>Culling rate $\mu$</td>
<td>0.35 per year</td>
<td>Non-selective cull animals $\geq 2$ years</td>
</tr>
<tr>
<td>$A_{\text{max}}$</td>
<td>6.5 year</td>
<td>Maximum age of infected animal</td>
</tr>
<tr>
<td>Mult $^{(1)}$</td>
<td>0.006 per year</td>
<td>Fraction animals of herd sold</td>
</tr>
<tr>
<td>$R_0^{(2)}$</td>
<td>10</td>
<td>Within-herd transmission</td>
</tr>
<tr>
<td>$X$</td>
<td>see Table 1</td>
<td>Number of animals tested per visit</td>
</tr>
<tr>
<td>AgeX</td>
<td>see Table 1</td>
<td>Age of tested animals</td>
</tr>
<tr>
<td>$D$</td>
<td>see Table 1</td>
<td>Time between 2 subsequent visits</td>
</tr>
<tr>
<td>Sens(a) $^{(5)}$</td>
<td>see text below</td>
<td>Sensitivity of test</td>
</tr>
<tr>
<td>Prevalence $^{(7)}$</td>
<td>see text below</td>
<td>Prevalence when reaching status 10</td>
</tr>
</tbody>
</table>

(1) Taken identical to the model JohneSSim (6) when status 10 is reached.
(2) Represents the adult cattle age distribution in the Netherlands.
(3) The value of $A_{\text{max}}$ is based on simulations with JohneSSim (6). At age 5-5.5, 6-6.5 and 7-7.5 year a difference becomes clear between the age distribution of infected and not-infected animals in the herd.
(4) Based on observations on 87 status 9 and 10-herds in the Netherlands in 1998-2000. According to this parameter value, a herd with 100 adult cattle sells on average 0.6 animals per year to other unsuspected herds.
(5) Weighted average of $R_0$ as simulated by JohneSSim for 8 farm types (risk profiles concerning paratuberculosis based on management practices). JohneSSim was validated (see (3)) with the observed $R_0$ (see von Roermund, this volume) for 14 farms with risk profile 4-5. Through $R_0$, the infectivity $\beta(a)$ of an infected animal is calculated in the $R_0$-model. A linear increase is assumed from $\beta(a) = y$ at age $a$ to age $A_{\text{max}} = 6.5$. The level $\beta(a)$ is chosen based on comparison with JohneSSim (6). The value for $y$ is calculated with $R_0$ and the survival probability of an animal at age $a$.
(6) Based on simulations (thus same assumptions) with JohneSSim (6), the following regression equations were fitted. For the pooled faecal culture (5 individuals) $\text{sens}(a) = 0.0348 \times a - 0.0169$, where $a$ is age of the infected animal, and for the individual faecal culture $\text{sens}(a) = 0.036 \times a - 0.0158$. This means that the sensitivity is 0% at age 0.5 year and increases to about 20% at age 6.5 year. For the standard monitoring scheme (pooled faecal culture) followed by confirmation of positive pools with the individual faecal culture $(St + c$, see Table 1), independence of tests was assumed and the two sensitivities were multiplied.
(7) According to JohneSSim, 11% of the unsuspected herds are not free of infection when reaching status 10 (6). However, most of these infected herds have only one or a few infected animals. Thus the effect of these infected animals already present in the herd on the estimate of $R_0$ is low. The mathematical expressions for the effect on $R_0$ can be found in (5).
sensitivity of the pooled faecal culture for infected animals between 1 and 2 years of age is quite low in the model (see regression equation in Table 2), this result shows that it is worthwhile and important to aim at detecting infected animals at a young age, even with a poor test.

The test sensitivity of the pooled faecal culture of an (average) infected animal of old age (6 years) is quite low in the model, about 20% (see regression equation in Table 2). This is based on the assumption that it is about 90% for high shedders, but the proportion of high shedders in a population of infected animals of old age is low (15% according to simulations with JohneSSim, see (3)). Because the value of the input parameter test sensitivity is very important in the $R_0$-model, more experimental work on a cohort of infected animals during several years is needed. Especially for paratuberculosis it is important to look at the effect of age or infection-stage (latently infected, low or high shedder) of the animal in this respect.

REFERENCES