Simulation model of Johne’s disease transmission in multi-species pastoral systems in New Zealand

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I) Introduction.

Johne’s disease (JD), caused by Mycobacterium avium subspecies paratuberculosis (MAP), is a chronic granulomatous enteric infection that occurs worldwide and affects domestic ruminant species including deer, sheep and cattle (Harris and Barletta, 2001; Whittington and Sergeant, 2001; de Lisle, 2005). JD is characterized, in clinical cases, by weight loss and diarrhoea, which do not respond to treatment, leading to emaciation and death. In spite of MAP’s worldwide distribution, there is scarcity of information about prevalence, strain diversity, infection sources, or transmission pathways, especially between livestock species on-farm and between livestock and wildlife. This lack of information is mainly explained by the absence of reliable diagnostic methods, characterized by poor test sensitivity and culture isolation difficulties. Moreover, JD has a long incubation period in sheep and cattle. MAP can circulate for several years on a farm before the onset of clinical cases. In recent years, an association between MAP and Crohn’s disease, a chronic inflammatory bowel disease in humans, has been hypothesised raising concerns in meat and milk industries about markets restrictions or decreasing demand due to public concern (Harris and Barletta, 2001).

In New Zealand, multi-species pastoral systems are common, where beef cattle, sheep or deer are often co-grazed, either concurrently or successively. This implies the necessity to develop a multi-species approach to the research of JD in New Zealand, where pastoral management could play a key role in the disease epidemiology and control. This contrast with major part of previous researches around the world, where JD has been studied in isolated species; commonly not taking into account the interaction with other ruminants, specially in the United States or Europe, where livestock is commonly kept under confined conditions.

Considering the difficulties and cost involved in conducting large studies on JD, simulation modelling approaches has become increasingly popular in recent years, offering a methodological framework to gather available information on JD, and study possible control options. Simulation modelling is a useful tool for analyzing the spread and control of economically important livestock diseases (Bennett, 1992; Dijkhuizen and Morris, 1997; Jalvingh et al., 1999; Bates et al., 2003; Carpenter et al., 2004). However, most of JD models are based on core aspects of our understanding of the epidemiology of JD (Sergeant, 2005), and despite uncertainties about a number of key input parameters, their outputs have been used to inform the design of control and certification schemes.
Available models have addressed a general cattle herd (Pouillot et al., 2004; Ezanno et al., 2005), dairy cattle (Collins and Morgan, 1991; Groenendaal et al., 2002; Kudahl et al., 2007; Mitchell et al., 2008), beef cattle (Humphry et al., 2006) and sheep flocks (Sergeant and Whittington, 2000). Models have been used for a number of different purposes, including: a) to investigate the epidemiology and dynamics of the disease in infected herds (Pouillot et al., 2004; Mitchell et al., 2008); b) to evaluate alternative strategies for management and control of JD in infected herds (Groenendaal et al., 2002; Van Schaik et al., 2002; Dorshorst et al., 2006); c) to evaluate national or industry-wide strategies for cost-effective test strategies, herd-certification or disease management (Weber et al., 2004; Tavornpanich et al., 2006; Tavornpanich et al., 2008); and d) to predict flock sensitivity for sheep abattoir surveillance (Abbott and Whittington, 2003).

The first transmission model, simulate JD spread at herd level, was developed by Collins and Morgan (1991) using deterministic equations to keep track of four different disease stages (susceptible, non-infected, infected, and culled), in this model was assumed that young animals remained susceptible up to 1 year age, when uninfected animals move to resistant category and infected animals became latent (subclinical and non-infectious), calves from infected dams had the same risk of infection as all other calves, and at 2 years old, latent animals become infectious for the remaining time in the herd. Groenendaal et al (2002) developed a more complex model, introducing stochastic equations to estimate the prevalence at each category, incorporating the uncertainty associated to several parameters used by the model. This model assumes three adult-shedding categories (low, high and clinical), an exponential decay in susceptibility of animals up to 1 year of age, being fully resistant at 1 year old, and the probability of a successful infectious contact increased as infected animals moved from low-shedding to high-shedding and then to clinical status. In this two simulation models, shedding status was only assigned to infected adult animals and based the incidence on the number of infectious adult animals present. Additionally, the transmission of MAP in these models also considered the infection of young calves, via infection in-utero, in colostrum/milk, or exposure to infected faeces. Finally, Mitchell et al (2008) develop a frequency dependant simulation model, rather than density dependant as the previous ones, that incorporated current knowledge of MAP epidemiology, exploring three new possible transmission dynamics: a) presence of a high-shedding compartment that reflects a much greater difference in shedding levels than previously assumed; b) all infected adults producing infected...
calves (not just restricting this transmission to high-shedding adults); c) and young animals shedding MAP rather than being latent.

The three JD model, previous mentioned, focuses in different possible forms of direct MAP transmission (animal to animal), which is a fair assumption for the simulated systems, dairy farm in the United States or Europe, where animals are commonly confined. However this assumption is not applicable to New Zealand pastoral systems. Humphry et al (2006) simulated JD spread in a beef cattle herd, under pastoral conditions, this model assumed the environment as the primary source of infection, reflecting a consensual understanding of the disease under pastoral conditions; taking into account the density of the infectious agent in the environment but without an explicit modeling of the MAP dynamic at farm level.

Based on available JD models, the objective of this study is to develop appropriate components to build up species specific models for New Zealand pastoral system, simulating prevalence over time and economic outcomes. These models will consider the presence of multiple susceptible species and MAP strain diversity, assessing the feasibility and cost effectiveness of available control methods, for the reduction of sub-/clinical JD.

II) Model description

Based on the framework proposed by Mitchell et al. (2008), a deterministic transmission model of JD, in beef cattle and sheep livestock, under pastoral conditions has been developed. The model simulates the disease dynamic in these two species plus a MAP environment-survival component, in order to model the indirect transmission, in a pasture based production system with multiple susceptible species. The model assumes two hypothetical all-female-closed-populations, a whole year simultaneous co-grazing, with random mixing between the two species, and a homogenous distribution of MAP in the effective farm area
text. All transmission not due to vertical/pseudo-vertical sources is assumed to be due to indirect transmission from environment contaminated with MAP.

In the Figure 1, a diagram of the model structure is presented, representing the relationship among the two compartment models, the MAP dynamic at paddock level, and the parameters that

* Area grazable by livestock.
described the epidemic. Where $\beta$, is the indirect transmission parameter from susceptible ($X_1$) to transient ($Tr$) or latent ($H$), depending of the species simulated. Animals can enter directly to the $Tr$ (or $H$) stage at a rate $\gamma$. Transition from $Tr$ to $H$, from $H$ to Low Shedders ($Y_1$), from $Y_1$ to High Shedders ($Y_2$), and from $Y_2$ to Clinical Cases ($Y_3$) occur at rates $\Phi$, $\sigma$, $\nu$, $\omega$ respectively. MAP is shed into the environment at a $\theta$ rate with decay rate of $\psi$. 
Figure 1. Diagram of the model structure representing the relationship among the environment, the two epidemic models and the parameters that described the JD outbreak pathways.
III) Differential equation

A description of the variables and parameters used by the model is presented in Table 1. The system is defined by a total of 19 equations. Below are presented the equations that define the most complex model (beef cattle), plus the environmental component. Equations (1) to (7) calculate the rate of entry and exit from each compartment. In equations (1) and (3), a modification of the Holling type II equation (Berryman, 1992) was included in order to define a maximum bacteria intake per unit of time \(\kappa\), avoiding an exponential epidemic growth, non compatible with observed disease manifestation, at field level. However, \(\kappa\) cannot be directly defined because it depends on the epidemic dynamic. Equation (12) indirectly estimates \(\kappa\), calculating the amount of bacteria diluted in the maximum dry matter intake per animal, per unit of time. In equations (8) and (9), the environment MAP dynamic is simulated, the first one calculates the number of bacteria available to infect a particular species, taking into account the agents shed by that species, as well as those coming from another species, adjusting them by a susceptibility factor \(\pi\). Equation (9) estimates the total bacterial load at farm level.

The replacement rate \((\mu, (10))\) take into consideration, the expected normal mortality \((\mu_{d(j)})\) as well as an extra mortality rate \((\alpha_{d(j)})\) due to the clinical manifestation, and an extra culling rate \((\delta_{d(j)})\) for active removing of positive animals. In this way, the introduction and exit rate are equals, keeping the population size constant during the entire simulation. Equation (11) calculates an adjusted introduction rate, directly into \(Tr\) (or \(H\)), weighting the number of animals in each disease stage and the probability of transmitting the disease to their offspring \((\gamma_{d(j)})\).

\[
\frac{dX_{1(b)}}{dt} = (\mu_b - \gamma_b)N_b - (\mu_{d(b)} + \rho_{b})X_{1(b)} - \frac{\beta_{b}B_{1}X_{1(b)}}{1 + B_{1}\kappa_{b}}
\]

\[
\kappa_{b} = \frac{1}{\eta \tau} \frac{B_{1(b)}}{e_{(b)}(j)}
\]

\[
\frac{dX_{2(b)}}{dt} = \rho_{b}X_{1(b)} - \mu_{d(b)}X_{2(b)}
\]

\(\eta\)  
Dry matter (DM) production per hectare

\(\tau\)  
Effective farm area

\(e_{(j)}\)  
Maximum pasture consumption per unit of time per animal \((j =\text{species})\)

\(B_{i(j)}\)  
Available bacteria for species \(j\) \((i = 1)\)

Total bacteria load in effective farm area \((i = 2)\)
\[
\frac{dT_{r(b)}}{dt} = \frac{\beta_{(b)}B_{1}X_{1(b)}}{1 + B_{1}\kappa_{(b)}} + \gamma_{(b)}N_{(b)} - (\phi_{(b)} + \mu_{d(b)})T_{r(b)}
\]  
(3)

\[
\frac{dH_{(b)}}{dt} = \phi_{(b)}T_{r(b)} - (\sigma_{(b)} + \mu_{d(b)})H_{(b)}
\]  
(4)

\[
\frac{dY_{1(b)}}{dt} = \sigma_{(b)}H_{(b)} - (\nu_{(b)} + \delta_{1(b)} + \mu_{d(b)})Y_{1(b)}
\]  
(5)

\[
\frac{dY_{2(b)}}{dt} = \nu_{(b)}Y_{1(b)} - (\omega_{(b)} + \delta_{2(b)} + \mu_{d(b)})Y_{2(b)}
\]  
(6)

\[
\frac{dY_{3(b)}}{dt} = \omega_{(b)}Y_{2(b)} - (\delta_{3(b)} + \mu_{d(b)} + \alpha_{(b)})Y_{3(b)}
\]  
(7)

\[
\frac{dB_{1(b)}}{dt} = \theta_{1(b)}T_{r(b)} + \theta_{2(b)}Y_{1(b)} + \theta_{3(b)}Y_{2(b)} + \theta_{4(b)}Y_{3(b)} + \pi_{b}(\theta_{1(s)}Y_{1(s)} + \theta_{2(s)}Y_{2(s)} + \theta_{3(s)}Y_{3(s)}) - \psi B_{1(b)}
\]  
(8)

\[
\frac{dB_{2}}{dt} = \theta_{1(b)}T_{r(b)} + \theta_{2(b)}Y_{1(b)} + \theta_{3(b)}Y_{2(b)} + \theta_{4(b)}Y_{3(b)} + \theta_{1(s)}Y_{1(s)} + \theta_{2(s)}Y_{2(s)} + \theta_{3(s)}Y_{3(s)} - \psi B_{2}
\]  
(9)

Where,

\[
\mu_{(b)} = \mu_{d(b)} + \frac{\delta_{1(b)}Y_{1(b)}}{N_{(b)}} + \frac{\delta_{2(b)}Y_{2(b)}}{N_{(b)}} + \frac{(\alpha_{(b)} + \delta_{3(b)})Y_{3(b)}}{N_{(b)}}
\]  
(10)

\[
\gamma_{(b)} = \frac{\mu_{(b)}[\gamma_{1(b)}(T_{r(b)} + H_{(b)} + Y_{1(b)}) + \gamma_{2(b)}Y_{2(b)} + \gamma_{3(b)}Y_{3(b)}]}{N_{(b)}}
\]  
(11)
\[ \kappa_{(b)} = \frac{1}{B_{(b)}} \frac{B_{(b)}}{\eta \tau} \varepsilon_{(b)} \]
### Table 1. Definition of variables and parameters used in the model

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Beef cattle</th>
<th>Refer</th>
<th>Sheep</th>
<th>Refer</th>
<th>Environment</th>
<th>Refer</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_{ij}$</td>
<td>Susceptible animals ($i = 1$)&lt;br&gt;Resistant animals ($i = 2$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{ij}$</td>
<td>Transiently shedding animals</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$H_{ij}$</td>
<td>Latent animals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Y_{ij}$</td>
<td>Low shedder animals ($i = 1$)&lt;br&gt;High shedder animals ($i = 2$)&lt;br&gt;Clinical animals ($i = 3$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$B_{ij}$</td>
<td>Available bacteria for a particular species ($i = 1$)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>$\mu_{ij}$</td>
<td>Herd/flock replacement rate</td>
<td>TBC$^2$</td>
<td>TBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_{ij}$</td>
<td>Vertical &amp; pseudo-vertical transmission for $T_{ij}$, $H_{ij}$, and $Y_{1ij}$ ($i = 1$)</td>
<td>0.15</td>
<td>a</td>
<td>0.01</td>
<td>i</td>
<td></td>
<td></td>
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<tr>
<td>$Y_{2ij}$ ($i = 2$)</td>
<td>0.17</td>
<td>a</td>
<td>0.05</td>
<td>i</td>
<td></td>
<td></td>
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<tr>
<td>$Y_{3ij}$ ($i = 3$)</td>
<td>0.21</td>
<td></td>
<td>0.10</td>
<td>i</td>
<td></td>
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<tr>
<td>$\mu_{dij}$</td>
<td>Expected average mortality rate (normal)</td>
<td>0.018583</td>
<td>b</td>
<td>0.05</td>
<td>b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\rho_{ij}$</td>
<td>Rate of exit due to aging</td>
<td>0.083/animal/month</td>
<td>c</td>
<td>0.083/animal/month</td>
<td>c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_{ij}$</td>
<td>Indirect transmission rate due bacterial intake</td>
<td>0.2501e-10</td>
<td>d</td>
<td>0.0197e-9</td>
<td>d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\kappa_{ij}$</td>
<td>Maximum bacterial intake per unit of time</td>
<td>TBC</td>
<td>TBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Phi_{ij}$</td>
<td>Rate of exit from transient stage</td>
<td>0.083/animal/month</td>
<td>e</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{ij}$</td>
<td>Rate of exit from latent stage</td>
<td>0.0556/animal/month</td>
<td>f</td>
<td>0.0556/animal/month</td>
<td>j</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\nu_{ij}$</td>
<td>Rate of exit from low shedding stage</td>
<td>0.0278/animal/month</td>
<td>f</td>
<td>0.1111/animal/month</td>
<td>j</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\omega_{ij}$</td>
<td>Rate of exit from high shedding stage</td>
<td>0.111/animal/month</td>
<td>g</td>
<td>0.1167/animal/month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\delta_{ij}$</td>
<td>Additional cull rate for $Y_{1ij}$ ($i = 1$)</td>
<td>0.00</td>
<td>UD$^3$</td>
<td>0.00</td>
<td>UD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha_{ij}$</td>
<td>Extra death rate from clinical animals</td>
<td>0.50</td>
<td>f</td>
<td>0.33</td>
<td>k</td>
<td></td>
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</tr>
<tr>
<td>$\pi_{ij}$</td>
<td>Strain susceptibility from MAP coming from another ruminant species at farm level</td>
<td>0.08</td>
<td>n</td>
<td>0.08</td>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\eta$</td>
<td>Dry matter (DM) production per hectare</td>
<td>535/kg/month$^2$</td>
<td>a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\tau$</td>
<td>Effective farm area</td>
<td>501.5 ha$^2$</td>
<td>a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\psi_{ij}$</td>
<td>Maximum pasture consumption per unit of time</td>
<td>309.59/kg/month</td>
<td>a</td>
<td>56.76/kg/month</td>
<td>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta_{ij}$</td>
<td>Shedding rate for $T_{ij}$ ($i = 1$)</td>
<td>1.125e+08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Y_{1ij}$ ($i = 2$)</td>
<td>2.25e+08</td>
<td>h</td>
<td>2.4e+7</td>
<td>l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Y_{2ij}$ ($i = 3$)</td>
<td>5.64e+08</td>
<td></td>
<td>2.4e+10</td>
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<td></td>
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<td></td>
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<tr>
<td>$Y_{3ij}$ ($i = 4$)</td>
<td>1.689e+10</td>
<td></td>
<td>2.4e+11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\psi$</td>
<td>Bacterial decay rate</td>
<td>0.25/bacteria/month</td>
<td>m</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

---

$^2$ Based on farm herd size of 500 cattle and 2000 sheep ($^3$Charteris et al., 2000)
1j=(b)eef cattle, j=(s)heep. 2To be calculated (TBC) by the model. 3User defined. 4Whitlock et al., 2005. 5Charteris et al., 2000. 6Calculated from available data. 7Estimated targeting a 50% true prevalence in 25 years without intervention. 8Ranking, 1961. 9van Schaik et al., 2003. 10Nielsen & Toft, 2006. 11Crossley et al., 2005. 12Sweeney, 1996. 13Eppleston et al., 2001. 14Whitlock & Buergelt, 1996. 15Whittington et al., 2000. 16Rowe et al., 2006. 17Moloney & Whittington, 2008.
IV) Simulation

The model was implemented in the software R version 2.10.1 using the odesolve package to solve the differential equation system, using the Runge-Kutta algorism. A 25 year period with a monthly time step was simulated, after the introduction of a single low shedder animal (Y1), in each of the two populations. Herd size was defined as 500 beef cows and 2,000 sheep, targeting a final true prevalence of 50%, in a herd/flock without any control measure.

V Preliminary results

Below simulation results are presented for the epidemic simulation without any control measure. Three graphs show the disease dynamic in each species and the total MAP load at farm level.