Modelling Johne's disease control in deer

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Abstract

This study aimed to develop a mathematical model describing the dynamics of paratuberculosis (PTB) in red deer (Cervus elaphus) under pastoral farming conditions in New Zealand. The model examined infectivity differences between ovine and bovine strains of *Mycobacterium avium* subspecies *paratuberculosis* (MAP) and seasonality of MAP survival. We also evaluate variable use of pasture and the effect of management interventions on the infection prevalence and annual clinical incidence of PTB. A state-transition model was developed and calibrated to observed data on both prevalence of infection and incidence of clinical PTB. To accommodate specific PTB features for deer, the model included a fast and a slow track for progression of infection to disease. MAP on pasture was the source for horizontal transmission and infected dams for vertical transmission. In the presence of a single strain, an infectivity reduction of up to 80% allowed MAP to persist in the herd (R0>1). For mixed infection by two strains however, a 30% reduction in infectivity of one strain was sufficient to outcompete a strain with lower infectivity, suggesting that mixed infection of MAP strains with different infectivity may not be common in deer. The model showed that seasonal variation of MAP survival on pasture had little impact on transmission dynamics, and that rotational grazing with pasture spelling versus permanent grazing of the same paddock reduced both infection prevalence and clinical PTB by about 50%. Based on model outputs, early detection of young deer in a high-shedding state was the most effective means of controlling PTB among the tested scenarios.

KEY WORDS: *Paratuberculosis, Mathematical model, Deer, Strain type, Management*

Introduction

Clinical paratuberculosis (PTB) is a chronic-progressive enteric disease caused by Mycobacterium avium subspecies paratuberculosis (MAP). Evaluating interventions to control PTB through randomised trials incurs high cost due to long study periods and large numbers of herds required to achieve adequate statistical power.

A low-cost alternative to expensive field studies is mathematical modelling of disease dynamics. Modelling can help to understand the driving forces for disease transmission and the impact of disease control on the prevalence of infection and incidence of clinical disease. Modelling intra-herd transmission of PTB in dairy cattle has been reviewed and proposed as an alternative to costly infection experiments and intervention trails (Marce *et al*. 2010). Such models were not available for deer populations.

Deer are grazed on fenced pastures throughout the year, often in succession following or grazed together with sheep or cattle. Pasture blocks may be grazed for limited intervals allowing re-growth of grass in the absence of grazing animals, or they may be grazed by the same herd of animals over an entire production season. Due to the system of mixed species farming and year-round grazing, the major source of horizontal MAP transmission is considered to be the environment (pasture). Deer, sheep, cattle, and to some extent wildlife (rabbit, possum, hedgehog), may contribute to pasture contamination with MAP, potentially causing transmission across species. Deer are considered to be susceptible to infection by both ovine and bovine strains of MAP, but the infectivity for deer of bovine MAP strains appears to be greater than that of ovine strains (O'Brien *et al*. 2006, Mackintosh *et al*. 2007). Due to contact with sheep, which are mostly infected with ovine strains, or contact with cattle, which are mostly infected with bovine strains, strain type may be an important determinant for infection, MAP transmission characteristics and clinical disease. Thus, strain type should be taken into account in a mathematical model of MAP transmission in deer.

This study intended to evaluate the impact of interventions (e.g. test and cull, rotational grazing), seasonal effects on MAP survival on pasture, and infection with either a single or multiple MAP strains with different infectivity using a modelling approach. The model developed in this study considered the specific infectivity of MAP in deer, allowing for an extension to mixed-species pastoral farming conditions involving deer, and infectivity differences of species-specific MAP strain types in deer in a deterministic state-transition fashion. For validation, model outputs were compared to observed data of MAP prevalence and clinical PTB incidence.

Material and methods

A state-transition model was developed that included a susceptible (state S) and an age-dependent resistant state (state R). Susceptibility to infection was assumed to wane from 12 months of age (Mackintosh *et al*. 2010). Susceptible deer could become infected with sheep-type (s) or cattle-type (c) strains and enter either the 'fast' or the 'slow' tracks (Figure 1). Fast-track infected deer started shedding (State Y) soon after infection (Y1c,Y1s) and became high shedders/clinical within six months (Y2c,Y2s), whereas slow-track infected deer became latent (State L) infected with either cattle or sheep strains (Lc, Ls), and progressed to low-shedding (aY1c,aY1s) and subsequently high-shedding states (aY2c,aY2s) at very low rates (Table 1). The probability (ξ) of newly infected susceptible deer (S) entering the fast track was assumed to be 0.3 (Mackintosh *et al*. 2007). The impact of all parameters on prevalence and incidence was tested in a sensitivity analysis. Parameters were modified to fit simulation results to both experimental data and survey estimates of prevalence and incidence.

Horizontal transmission depended on dry matter intake (DMI), the colony forming units (cfu) of MAP organisms on pasture, and the transmission parameter (β) which encompasses both rate of contact (between susceptible animals and MAP in the environment) and infectiousness of contacts. These parameters were combined to render the proportion (Pc, Ps) of susceptible deer calves getting infected per unit time as follows:

$Pc = \xi * [1 - \exp(-\beta * \text{path-c} * MAPc * DMI/(\text{pasture area}*DM \text{ growth}))]$

$Ps = \xi * [1 - \exp(-\beta * \text{path-s} * MAPs * DMI/(\text{pasture area}*DM \text{ growth}))]$

where ξ was the probability of an infected animal to enter the fast track, MAPc and MAPs were the total number of MAP bacteria of type s and c, respectively, on pasture, and the expression DMI/(pasture area*DM growth) was the proportion of total dry matter (DM) consumed by one animal, thus equivalent to the proportion of total bacteria on pasture ingested by one animal. We assume a DMI per month of 87.6kg for all age groups including susceptible young animals 0-12 months old. Probabilities (Pc, Ps) had a logistic S-shape association with the number of MAP organisms on pasture at the logarithmic scale. The shape suggested that the infection risk increased slowly at low exposure to MAP and increased exponentially (or linear at normal scale) at critical levels to a threshold of one at high level of bacterial load on pasture. Thus, the relationship mimics a dose response effect of exposure to MAP. The parameters path-c/path-s in equations (1) and (2) were weighting factors for the transmission parameter (β) to explore MAP-strain dependent infectivity in scenarios where one factor was kept constant (path-c=1) and the other variable (path-s = 0, 0.1, 0.2… 1… 5). Since no published evidence on mixed infections exists, the model excluded mixed infection of individual animals with both strains.

The time unit for rates in parameter estimates was one month. The model was updated for up to 80 years (1000 months) using a time step changes of 0.3 days (0.01*1 month). A fourth order Runge-Kutta approximation (RK4) was applied in Berkeley Madonna to solve the ordinary differential equations listed in the annex. Since animals (not proportions) were calculated for each time step, this was a density type model (Begon *et al*. 2002) where stocking density was held constant.

Model validation

Available information indicated that the annual incidence of clinical PTB was highest (2%) in yearling hinds and stags (1-2 years old) and about half as high in adult hinds and stags (1%) (Glossop *et al*. 2008). Moreover, observed incidences of 3-5% in weaners and 2% in adults were not uncommon and a few herds experienced incidences of up to 20% in individual age groups (Glossop *et al*. 2008). Based on the population prevalence of culture positive mediastinal lymph nodes (45%, 95% confidence interval 30-60%) of carcasses of mostly clinically normal 12-months old deer and an estimate of the herd infection prevalence of 59% (Stringer, 2011), the prevalence of tissue-culture-positive carcasses was approximately 75% in yearling deer in infected herds. By varying the transmission parameter (β), transition rate ($\nu 2$) from latent (L) to low shedding (Y1), rate ($\nu 3$) from low to high shedding clinical state, and proportion (ξ) splitting the infected into fast and slow tracks, the default model was calibrated to approximate these rates after reaching the equilibrium state where prevalence and incidence would remain stable over time.

The sensitivity of prevalence and incidence to changes in these parameters was tested by repeated model runs varying one parameter at a time. Additionally, a possible dependence of prevalence and incidence on a range of values for the vertical transmission rate (γ) for calves born from moderate shedders ($\gamma 1$), or high shedders ($\gamma 2$), was evaluated where $\gamma 1$ was assumed to be a quarter of the value of $\gamma 2$. The range of values and the relationship between $\gamma 1$ and $\gamma 2$ was based on findings in foetuses from serologically and culture positive, slaughtered hinds (Thompson *et al*. 2007). The study reported a much higher rate of vertical transmission (75%) than reported from cattle. In cattle, vertical transmission was reported as 25% from dams with clinical PTB and 18% from dams with subclinical PTB (Whitlock 2005).

Model scenarios

Critical outcome criteria were (1) the change in MAP infection prevalence, (2) the number of shedding animals and (3) the annual incidence of clinical PTB. In addition, the number of MAP on pasture was evaluated to demonstrate the impact of the seasonal variation of MAP survival or the change in MAP infectivity.

The following scenarios were evaluated:

1. Effect of rotational grazing vs. permanent use of pasture (set-stocking).
2. Seasonal variation of MAP survival on pasture.
3. Effect of the presence of two MAP-strains with equal or different infectivity on the persistence of the lesser virulent strain.
4. Early detection and removal of high shedding/clinical animals.

Results

Model development

The basic model resulted in a MAP infection prevalence of 62% and clinical annual PTB incidence of 5.3% in weaners/yearlings and 3.8% in adult deer. At equilibrium, there were 6% susceptible, 31% resistant, 38% latent, 25% low or high shedding animals, and 1.2% calves were infected vertically. All subsequent permutations started with the model at equilibrium state.

Model validation

The model-predicted endemic infection prevalence of 63% was somewhat below the prevalence of 70-75% expected from observations in slaughter stock (Stringer 2011) and a field study (Glossop *et al*. 2008), but was well within expected confidence limits of carcass infection prevalence of 30-60% at a given average herd prevalence of 59% (Stringer 2011), thus resulting in a wide within herd prevalence of infected herds of 51-100%. The predicted annual clinical incidence rates were about 2-fold higher than observed rates in table 2, allowing for an assumed lack of sensitivity of farmer detected PTB. The predicted MAP prevalence and PTB incidence outputs of the base model were therefore within acceptable limits of the natural pattern of PTB of deer on pastoral farms in New Zealand.

A sensitivity analysis of the impact of model parameters used for calibration on prevalence and incidence outputs revealed that the two major determinants were the transmission parameter (β) and the proportion of young deer entering the fast track of rapid progression to clinical state (ξ). A transmission parameter of 2.5 x 10-11 was selected for the base model because it resulted in outputs that reflected observed prevalence and incidence data best. In the base model, the transmission parameter was the same for slow and fast track animals and for both strain types (c, s). The proportion of horizontally infected deer entering the fast track was necessary to be greater than 0.3, else the clinical PTB incidence was larger in adult than 8-12 months-old deer. This would be contrary to the observed incidences. A value of 0.3 was

therefore selected providing the best fit. Higher values of ξ caused an exponential increase of PTB in weaners/yearlings, far higher than the observed incidence.

Two combinations of vertical transmission (VT) probabilities from low (γ1) and high shedding dams (γ2) were evaluated: in the first instance, γ1 was calculated to be a quarter of γ2, and in the second, γ1 was half of γ2. The relative size of γ1/γ2 had no measurable impact on model outputs of prevalence/incidence. Vertical transmission from high shedding dams had a four-fold greater effect on PTB incidence in weaner/yearling deer than on PTB incidence in adult deer but overall, PTB incidence did not change by more than 14% when VT was as extreme as 0 or 1 compared to the default value of 0.5.

A moderate impact on prevalence and clinical PTB incidence was attributable to transition rates from latent to low shedding adults (ν2), and low to high shedding adults (ν3) in slow track. The rates were calculated as the inverse of the duration of animals being in these states. Both durations had little impact on infection prevalence and moderate impact (change of -9 to +32% compared to the base model) on PTB incidence of weaners/yearlings. However, both parameters had strong impact on PTB incidence in adults causing a change of +119% when reducing the latent period from the default of 60 to 12 months, and of -30% when increasing the latent period from 60 to 96 months.

Model scenarios

1. Effect of rotational grazing vs. permanent use of pasture: The model predicted that PTB infection caused an almost two-fold higher MAP contamination of pasture when deer were kept on the same paddock permanently compared to bi-monthly grazing rotation. A change from permanent grazing of pasture to rotational grazing led to a 50% reduction in the number of MAP after approximately 2-3 years. The impact on prevalence and incidence was similar: MAP infection prevalence decreased by one half from 61% to 30%, and clinical incidence from 7.6% to 3.0% in weaners/yearlings and 3.6% to 1.8% in adult deer. An oscillating prevalence pattern developed that was attributable to rotational grazing where MAP loads decreased by decay during re-growth of pasture.
2. Seasonal variation of MAP survival on pasture: seasonally changing MAP survival had only a very small impact on seasonal infection prevalence. The long term effect was caused by the change from the endemic default situation of permanent grazing at time zero to rotational grazing. There was no notable effect of seasonal MAP survival on clinical incidence of young or adult deer under typical climatic conditions in New Zealand.
3. Effect of the presence of two MAP-strains with equal or different infectivity on the persistence of the lesser virulent strain: the basic reproduction ratio increased linearly when the infectivity was increased from 0, indicating complete absence of infectivity, to 1, indicating full infectivity of strain ‘c’. At a value of 0.2, R0 was 1.15, thus higher than the epidemic threshold of R0=1, suggesting that a MAP would persist in the herd. In a population with dual infection where infectivity of the ‘c’ strain was 1, persistence of strain ‘s’ was predicted to be possible as long as the infectivity of strain ‘s’ was above 0.8 (Figure 2). At infectivity of 0.8 or lower, strain ‘s’ was out-competed by strain ‘c’. Strain ‘s’ persisted at a lower prevalence than strain ‘c’ when the virulence of strain ‘s’ was smaller than that of strain ‘c’ (path-s <1). Because both strains were present in these situations. the total MAP prevalence was 10% higher than in the absence of strain ‘s’, and approached but did not increase over a level of 0.86 (Figure 2). Annual clinical PTB incidence of yearling and adult deer infected with one of the two strains followed the patterns of change in prevalence with increasing infectivity of type ‘s’ (not shown).
4. Early detection and removal of high shedding/clinical animals: rapid detection and removal of clinically affected weaners/yearlings had substantial effects on overall prevalence and incidence (Figure 3). The overall prevalence decreased from 63% in the default situation, when clinical PTB was detected after eight weeks in 8-12 months-old deer, to 4% when clinical cases were left in the herd for an average of only one week. Correspondingly, clinical incidence decreased, facilitated by a lower risk of new infection, from 7.9% to 0.5%. On the contrary, early detection of clinical cases among adults had relatively little effect on overall prevalence and clinical disease incidence (not shown).

Discussion

To our knowledge, this was the first mathematical model of an infectious disease in red deer. We intended to consider that a herd could be infected with two strains where strains were competing for hosts. The inclusion of a second competing strain was motivated by observations of epidemiological and experimental studies and an infection study of cell cultures: a survey of deer herds resulted in lower rates of clinical PTB when deer were in contact with sheep (usually infected with ovine MAP), and higher rates of clinical PTB when in contact with cattle (usually infected with bovine MAP) compared to deer in isolation (Glossop *et al*. 2011); patho-histological lesion scores were lower in yearling deer experimentally infected with ovine strains than in deer infected with bovine strains (Mackintosh *et al*. 2007); and infecting bovine monocyte-derived macrophages with bovine MAP resulted in stronger cytopathic effects than infection of such cells with ovine MAP (Gollnick *et al*. 2007). Those observations led to the hypothesis that the infectivity of MAP strains may vary. It is not clear however, whether infectivity affects infection per se or also impacts on progression to high shedding and clinical disease. Our model assumed total cross-immunity between two strains against infection, and that progression to disease was the same in deer infected with one or the other strain. Total cross-immunity might be sufficient to explain a decrease in clinical disease incidence when a deer herd infected with high-virulent bovine strain is super-infected with a low-virulent ovine strain, for example through contact with co-grazing sheep. In fact, an additional consideration of virulent dependent disease progression resulted in similar changes in clinical disease incidence and infection prevalence as in a situation with only infectivity being strain dependent (results not shown).

The next question was whether a low-infectivity strain would successfully compete with a highly virulent strain for susceptible hosts when assuming complete cross immunity. Epidemic models generally do not allow two strains of a pathogen with different R0 to persist in a population (White *et al*. 1998). However, our model relied on indirect transmission with a bacteria-dependent force of infection dependent on total volume of infectious material, hence allowed two strains with different R0s, both higher than the threshold value of 1, to survive at endemic equilibrium.

Infectivity was parameterised as the proportional infectivity of an ovine relative to a bovine strain with respect to the transmission of infection. A basic reproduction ratio was calculated for both strains at increasing levels of ovine MAP infectivity. In this situation, a strain would cause persistent infection in a fully susceptible herd when its infectivity was at least 20% of that required to achieve an endemic level of infection and clinical disease similar to that observed in the population. However, if a herd was already infected, a lower infectivity strain would have to be about 80% as virulent as a fully virulent (bovine) strain in order to compete successfully and persist in a deer herd with dual infection. Thus, a relatively small reduction in infectivity caused the dominant strain to outcompete a second strain. A similar relationship was found in a two-strain/one-host model comparing the relative competitiveness of genetically engineered viruses to be used as environmentally benign insecticides vs. wild-type strains (Dushoff and Dwyer 2001). Our model also suggested that the total prevalence of infection increased by up to 10% in the presence of two highly virulent strains.

Mixed infections of deer herds with MAP may not be uncommon when contact with other species exists such as in the pastoral farming systems in New Zealand. Survey and slaughter data from studies in New Zealand showed that deer herds had a higher risk of being infected or to show PTB-like lesions at slaughter when other ruminant livestock were present on farm than on deer-only farms (Verdugo *et al*. 2008, Heuer 2010).

Conclusions

This study has developed and tested a model for PTB dynamics in farmed deer based on a New Zealand farming environment, with MAP infection prevalence and clinical disease as outcomes. Inclusion of two MAP strains with different infectivity suggested that coexistence of two strains was possible when their infectivity was within approximately 20% of each other. The model showed that prevalence and incidence fell rapidly when rotational grazing compared to continuous grazing was adopted. It showed that early culling of high shedders resulted in a rapid decline in infection and prevalence.

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Figure 1. Two-MAP-strain model for infection dynamics of PTB in red deer (see text for abbreviations and indices)

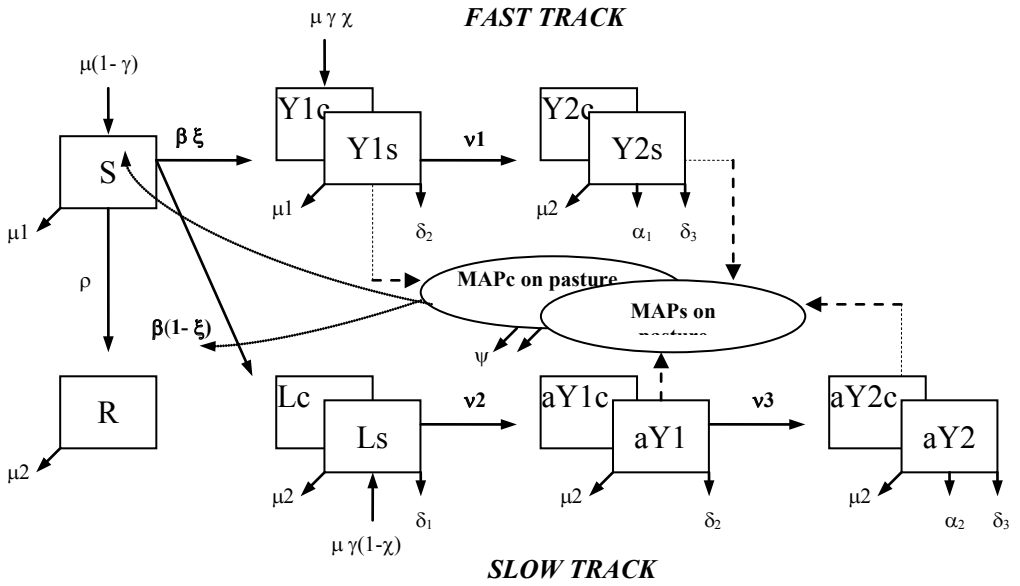

Figure 2. Effect of two strains (s = sheep, c = cattle) with relatively different virulence on strain specific and total prevalence of infected deer

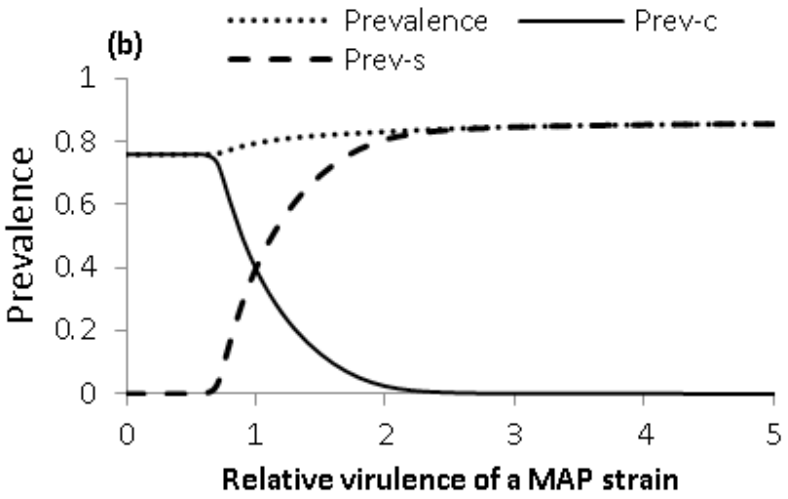

Figure 3. Effect on prevalence of PTB of detecting and removing clinically affected yearling deer earlier than eight weeks after the start of high shedding