# Dairy Cattle Intervention Model Paratuberculosis

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**ABSTRACT**

A mathematical continuous time, state transition model was developed to evaluate the economic effect of interventions for the control of paratuberculosis (ParaTB) in New Zealand dairy herds. Interventions covered by this report include early calf removal from the dam, pasture spelling, complete grazing separation of replacement calves from adult cows, and test and cull (T&C) by annual ELISA and/or PCR of adult cows. Outcome criteria are the infection prevalence of cows, the annual clinical incidence of ParaTB and the difference of benefits and cost (BC) of production.

Moderate, high and very high prevalence of infection was associated with 6, 9, and 15% loss of net-returns, respectively. Early calf removal had no effect and pasture grazing/spelling periods of 4 vs 1 month marginal effects on ParaTB and CB. Complete separate grazing of calves from cows reduced the clinical ParaTB incidence within 10 and infection prevalence within 15 years of starting the intervention when the prior annual incidence was 2 per 100 cows (moderate level of prevalence). T&C had similar effects on prevalence and incidence but could not compensate for the initial and annual recurrent investment during 80 years of simulation. It is concluded that the seasonal calving pattern with same-age cohorts of replacement calves raised on pasture – i.e. the New Zealand system – offers the opportunity of effective, low cost control of ParaTB whereas T&C does not appear to be a financially attractive intervention.

## 1. Purpose

A 4-year JDRC intervention phase was far too short for evaluating disease control interventions in the field. In addition to lack of time, funding was insufficient to instigate field intervention studies for controlling Johne's disease (JD= ParaTB) in dairy herds. Thus, modelling was used instead. The intention was to develop a deterministic model of disease dynamics combined with production cost and benefits. The model aimed to describe the economic impact of ParaTB on dairy herd productivity and detect relative merits and trends about the financial feasibility of controlling ParaTB in a dairy herd by reducing transmission or by test and cull (T&C). At this stage however, it was not aimed to predict financial returns for individual farms. This could be implemented later by adding stochastic functionality to the current deterministic model and allowing farmers to enter their own farm details such as herd size, pasture and calf management, and the annual incidence of clinical ParaTB cases observed on-farm.

## 2. Model description

A deterministic, continuous time Marcov-chain state transition model was developed. The focus was on medium term (20 years) and long term trends (100 years). A period of 100 years was chosen to allow the model to converge to equilibrium prevalence for sufficiently long time to reflect the 'final state' at equilibrium.

### *2.1 Transmission routes*

A constant true dam-daughter vertical transmission probability of 0.04 was set independent of the level of shedding or clinical state (Mitchell et al 2016). The pseudo-vertical transmission probability of MAP immediately after calving was 0.15 for low-shedding cows and 0.45 for high shedding cows (Benedictus et al. 2008, Whittington and Windsor 2009). This was assumed for the situation when calves were left on pasture with their dam for 4 days. If calves were removed earlier, the pseudo-vertical transmission was varied proportionally, e.g. removal 1 day earlier than 4 days, i.e. after 3 days, reduced the pseudo-vertical transmission by ¼ = 25%. After removal from pasture, calves were transferred to group pens for 3 months where some infected calves started shedding. Through this transient shedding, calves could infect pen mates. After 3 months, replacement calves were either grazed on pasture that was grazed by infected adult stock, or on a 'run-off' pasture block without grazing contact to pasture previously grazed by adult cows. In the first instance, 4-12 months old calves were exposed to MAP in the environment, which did not occur in the second instance. The susceptibility of 6-12 months old calves was 0.09 times the susceptibility of 0-6m old calves (Marce et al. 2011). However, recent studies of Koets et al (2016, personal communication) suggested that age may not be associated with susceptibility during the first year of life. Therefore, susceptibility was assumed to be constant in a sensitivity analysis. The infection parameter by environmental transmission (beta) was calibrated to the infection prevalence and clinical incidence observed in the field. Environmental infection was based on an exponential probability distribution based on dry matter intake and the number of infectious disease on pasture. Calves older than 12 months were assumed to be resistant to infection. While MAP infection of heifers and cows is possible, it is generally accepted to be a rare exception and hardly contributing any significant amount to ParaTB disease dynamics in dairy herds.

Respiratory infection through aerosols of dust contaminated with MAP was not considered as only one experimental infection has been reported for this transmission pathway (Eisenberg et al. 2011), and dust is unlikely an important fomite in pasture based dairy cattle.

### *2.2 Model structure*

The structure and all parameters were as in the model for beef cattle described by Verdugo et al. (2013), with the exception that calves were not grazed with their dams for 6 months but removed latest by 4 days. Briefly, animals were in four age groups, calves 0-6 months, replacement calves 7-12 months, heifers 13-24 months of age and adult cows older than 24 months. Susceptible calves 0-12 months could be born vertically infected or become infected by intermittently shedding calves while in group pens or while on calf-pasture, or by grazing pasture contaminated by adult infected cows. Susceptible calves could either become transient shedders or remain latently infected and remain in a slow-progression course of MAP infection. Transiently infected calves entered a latent, non-shedding phase before developing into low and eventually high shedders. High shedding resulted in clinical Johne's disease, and after 5.5 months, death or removal. Other than being subjected to regular culling, cows could be removed when they were found (correctly or false) positive by either ELISA or PCR.

### *2.3 Herd production economics*

The regular culling rate of cows was kept constant at 20% per year. The birth rate was allowed to vary based on the number of calves required to hold herd size constant. Average milk production was set to 1.6 kg milk solids (MS) per day for 280 days of lactation, sold at \$4.5/kg MS. The calving rate was 90%. After accounting for 20% bobby calves sold at \$40 each (i.e. removed almost immediately after birth), and 10% calves sold for beef production at \$200 each, any remaining female replacement calves were sold for breeding at \$350 each. Feed cost were \$0.20 per kg dry matter(DM) for pastureof which 2.5 kg DM/cow+day were required for maintenance, 2kg/d for maintenance and growth of calves 0-6m, 4kg/d for calves 7-12m, and 8kg/d for maintenance, growth and pregnancy of heifers 13-24m. Based on a market price of \$2,500 for a pregnant heifer, the annual cost of replacement were \$1,250/year. Miscellaneous other cost were assumed to be \$20/cow (AI, hired labour for milking, health, fence/race maintenance etc.) and \$5 per animal in other age and production groups. A regularly culled cows was sold at a salvage value of \$800, a low shedding cow at \$200 and a high shedding cow in poor clinical condition due to ParaTB at \$20.

The cost of lost milk production due to ParaTB was recently estimated in a New Zealand dairy herd (O'Brian et al. 2016, personal communication). Their data showed a 9% decrease of milk production in low shedding and 14% in high shedding cows compared to the average non-shedding cow.

## 3 Intervention scenarios

### *3.1 Herd level ParaTB*

Four levels of MAP prevalence and clinical ParaTB incidence were simulated using a range of beta parameters, resulting in a low (3%, 0.25), moderate (27%, 2.1), high (42%, 3.2), and very high (66%, 5.0) MAP infection prevalence and annual clinical incidence of ParaTB cases per 100 cows, respectively (Table 1).

### *3.2 No intervention*

Herd management of the baseline scenario included calf removal at 3 days after birth, one-month pasture spelling, i.e. the interval between grazing of cows and subsequent grazing by susceptible calves, and no test&cull intervention. The comparison of low, moderate, high and very high transmission of MAP

### *3.3 Early calf removal*

Calves were removed from dams 3 days after birth as a baseline. This was reduced to 1 day to evaluate the impact of early calf removal on ParaTB prevalence, incidence and production loss.

### *3.4 Pasture spelling*

In the baseline scenario, calves were exposed to pasture grazed by adult cows after a spelling interval of one month. This was compared to 4 months of spelling.

### *3.5 Grazing calves on paddocks not previously grazed by adult cows*

After the first 3 months when calves were in contact with each other in group-pens, they were transferred to pasture blocks without contact to adult cow pasture ('run-off'). Here it was assumed that they had no contact to pasture contaminated by older stock. Hence the only ways to become infected was vertically, by their dam short after calving or by transiently shedding calves in group pens. No extra cost was associated with this intervention.

### *3.6 Test and cull (T&C)*

Three options of T&C were compared with the baseline, (i) once-annual testing of all adult cows by ELISA ($10/cow), (ii) one-annual testing by PCR ($35/cow), and (iii) once-annual testing by both ELISA and PCR ($45/cow). To demonstrate changes over time, the model was simulated for 20 years without T&C to achieve equilibrium at moderate prevalence, and then T&C started and was continued every year for 80 years to evaluate the maximum achievable effect on prevalence, clinical incidence and financial returns. In addition to the final annual return per cow, the cost to achieve a reduction in clinical incidence to below 0.2 cases per 100 cows was calculated which was equivalent to no tangible production loss (Table 2). This was estimated as the cumulative financial cost from the start of T&C to the earliest time by which the maximum return was achieved. Likewise, the number of years until reaching this point was extracted from the model.

Parameters of test accuracy (sensitivity, specificity) were adapted from the model of Verdugo's PhD thesis (2013) listed in Table 1.

Table 1: Test accuracy parameters assumed by the model (Verdugo 2013)

| | | Sensitivity | Specificity |
|---|---|---|---|
| ELISA | | | 98% |
| | Latent (non-shedding) adults | 15% | |
| | Low Shedders | 30% | |
| | High Shedders | 71% | |
| PCR | | | 99% |
| | Latent (non-shedding) adults | 0% | |
| | Low Shedders | 80% | |
| | High Shedders | 95% | |

## 4 Results

### 4.1 Production loss due to Johne's disease

A low level of MAP transmission did not result in any significant production loss. At equilibrium, the prevalence of MAP infection was 3.3% and 1 clinical case occurred each year for every 400 cows in the herd. Moderate and high levels of prevalence and incidence decreased financial returns by 6% and 9%, and an extremely high ParaTB problem reduced returns by 15% (Table 2). The assumed constant values of cost and revenues had little if no impact on these relative comparisons.

Table 2: Level of MAP infection prevalence and incidence of clinical cases (% cows/year) and the associated loss of income (revenue – cost) due to Johne's disease evaluated at a long term equilibrium prevalence.

| Prevalence level | Prevalence at Equilibrium | Incidence at Equilibrium | % Income change rel. to zero prevalence |
|---|---|---|---|
| Low | 3.28% | 0.25% | 0.00% |
| Moderate | 27.18% | 2.07% | - 5.83% |
| High | 42.34% | 3.22% | - 9.39% |
| Very high | 65.72% | 5.00% | -14.68% |

### 4.2 Early calf removal (3 *vs.* 1 day)

Reducing the time that newly born calves remained in close contact with their dams on pasture, i.e. were exposed to pseudo-vertical transmission if the dam was shedding, from 3 days to 1day had no effect on prevalence (Figure 1;'Calf rem.1d'), clinical incidence (Figure 2), or financial returns (Figure 3). This lack of effect was independent of the initial prevalence level. No extra cost was attributed to early calf removal. The consideration of additional labor cost would have caused a financial loss additional to the loss of the baseline scenario.

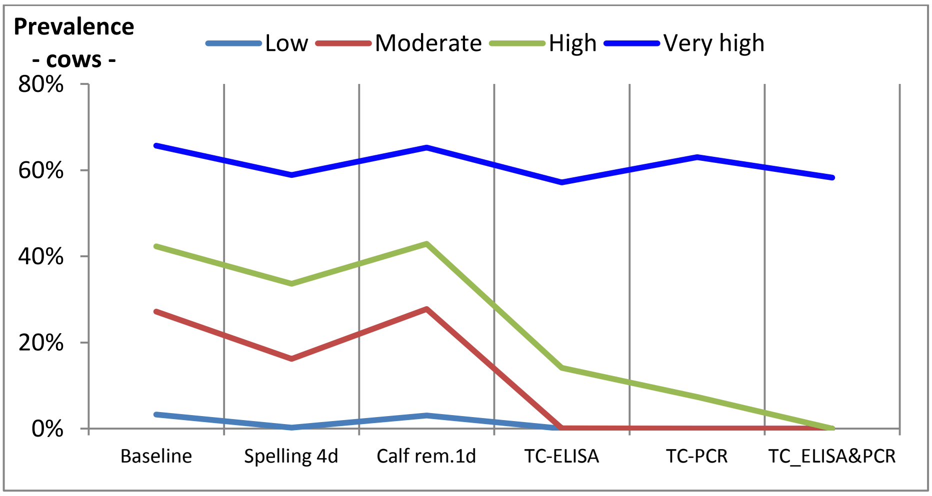


**Figure 1: Effect of interventions on the MAP infection prevalence of cows after long term intervention (80 years)**

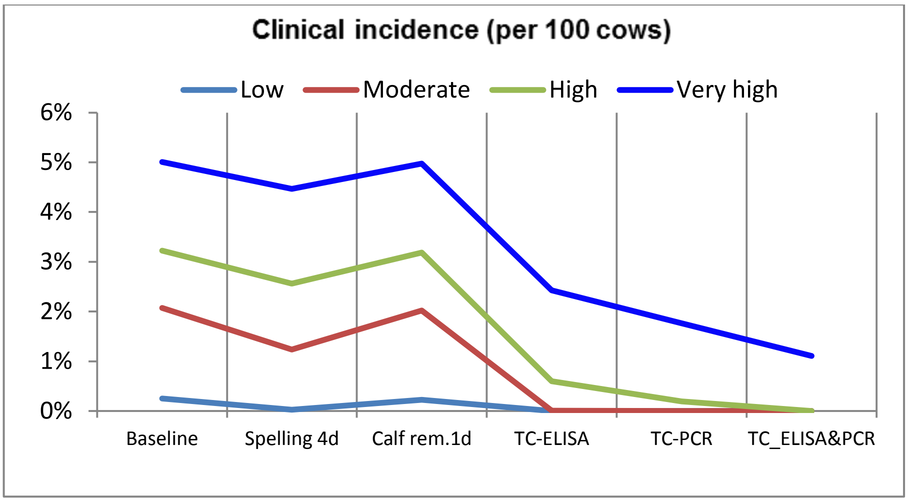


**Figure 2:** **Effect of interventions at four levels of initial prevalence (low, moderate, high, very high) on the incidence of clinical cases (per 100 cows) after long term intervention (80 years)**

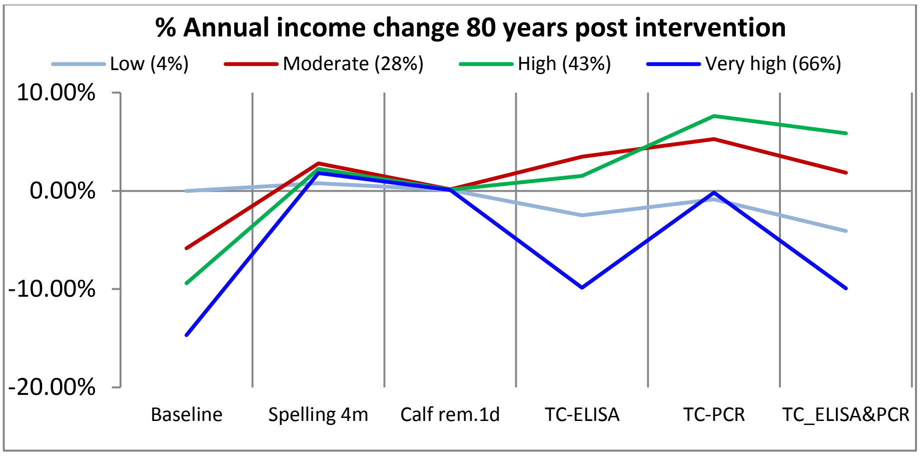


**Figure 3: Effect of interventions on the achievable change in annual income (revenues – cost) after long term interventions (80 years)**

### 4.3 Pasture spelling (1 vs. 4 months)

Increasing the period between grazing a pasture block from 1 to 4 months ('Spelling 4m') significantly reduced the MAP contamination of grass and soil but hardly decreased prevalence and incidence. It only increased financial returns marginally (Figures 1-3). These changes were similar at all levels of ParaTB transmission from moderate to very high.

### 4.4 Grazing calves on paddocks not previously grazed by adult cows

Moving calves from pens to a 'run-off' pasture not contaminated by shedding cows eliminated the clinical incidence within 10 and prevalence of cows within 15 years (Figure 4). Since no cost was associated with this intervention, the net-return increased by 6% within 15 years. Thus, this intervention eliminated all production loss associated with ParaTB at a moderate level of a-priori infection. A high level of initial MAP infection increased the time to achieving <0.2% clinical incidence by further 10 years, but was also highly cost effective.

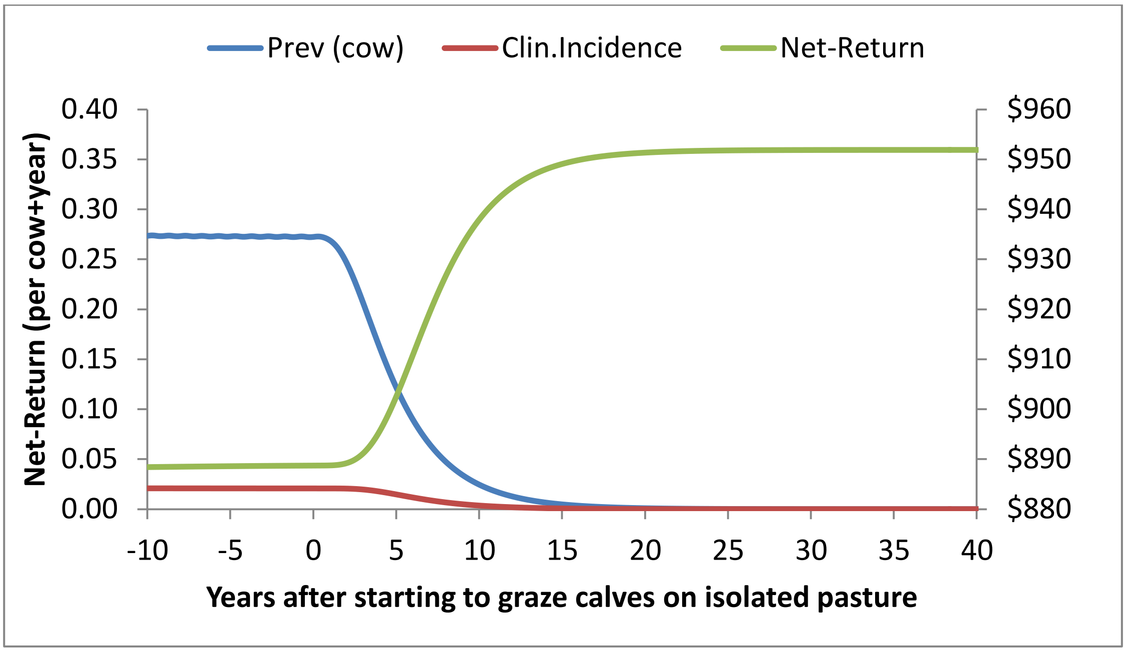


**Figure 4:** Effect of grazing calves without contact to adult cows on the prevalence of MAP shedders, the annual incidence of clinical cases and the net returns (per cow+year). The intervention started in year 0.

### 4.5 Test and cull (T&C)

In a moderately affected herd, T&C by either ELISA or PCR reduced the annual clinical incidence to <0.2% within 15 (PCR) to 25 (ELISA) years. However, annual ELISA testing and removal of positive cows reduced but did not eliminate the MAP infection prevalence or clinical incidence when ParaTB occurred at a high level (>3 cases per 100 cows). Such high prevalence and incidence is within the range reported by Voges et al. (2009). On farms with that high initial prevalence level, PCR had stronger effects than ELISA but could not eliminate MAP or clinical ParaTB either (Figures 1+2). At a very high level of affection, the MAP infection prevalence remained almost unaffected by T&C with any test, whereas the incidence of clinical cases reduced substantially. This seems to agree with field observations where farmers do not observe clinical cases any more once cows are tested and sero-positive or shedding cows are removed regularly once a year. It implies that ParaTB is likely to re-appear as soon as T&C has stopped.

Consequently, farms that are severely affected by ParaTB are very unlikely control ParaTB and achieve positive financial returns from T&C. At moderate and high MAP infection levels, annual financial returns from T&C compared to no-control were marginally positive, especially when only a PCR was used (Figure 3, green and red lines).

**Table 2**: Summary of the impact of tes-and-cull (T&C) on the time required to achieve no or only marginal production loss (i.e. incidence <0.2 cases/100 cows+year), the MAP infection prevalence at that point, the time until the maximum achievable financial return (benefit (B) minus cost (C)), the marginal gain compared to no intervention at equilibrium (per cow and year) and the total cost incurred over time to achieve the maximum achievable gain.

| | T&C_ELISA | T&C_PCR | T&C_ELISA+PCR |
|---|---|---|---|
| Years to <0.2% ParaTB cases/100 cows | 25 | 16 | 7 |
| MAP Prevalence of cows at <0.2% ParaTB cases/100 cows | 4.2% | 6.0% | 6.6% |
| Years to max. achievable B-C | 94 | 78 | 48 |
| Marginal gain/cow+year at max. achievable B-C | $8.00 | $6.50 | -$100.00 |
| Cumulative B-C to <0.2% ParaTB cases/year (herd) | -$10,328,961 | -$5,632,893 | -$8,283,043 |
| Cumulative B-C to 80 years (herd) | -$9,324,865 | -$3,871,269 | -$38,626,883 |

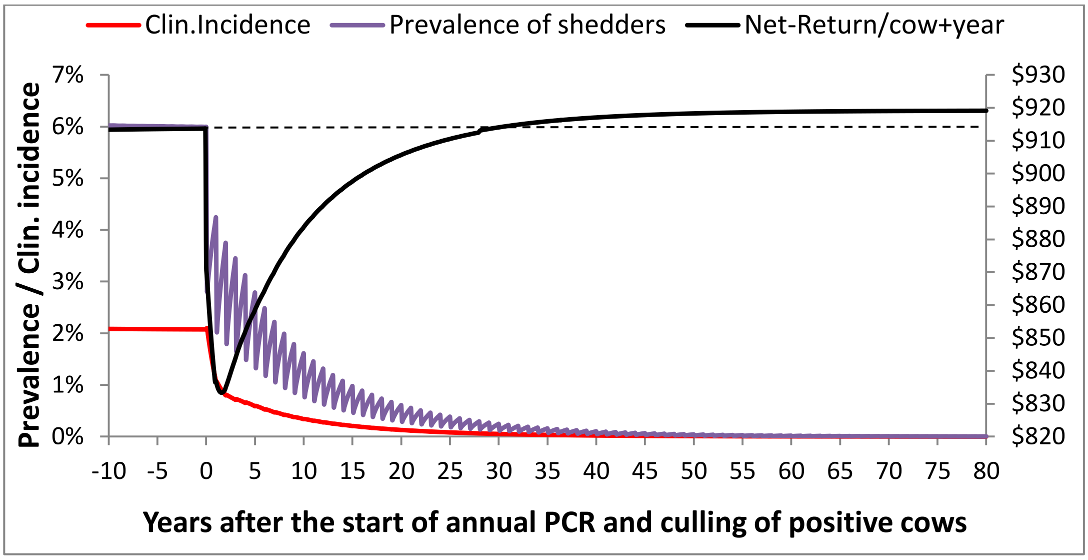


**Figure 5:** Effect of test-and-cull by annual PCR on the prevalence of MAP shedders, the annual incidence of clinical cases and the net returns (per cow+year). The intervention started in year 0.

However, the time of continued investment required for achieving positive financial returns outweigh the economic benefits. Even 80 years of continued T&C by PCR did not result in positive returns. T&C by annual PCR for 16 years in a herd with 1,000 dairy cattle (677 cows) had lost $5.6 million when achieving a no-loss incidence of

<0.2 cases/100 cows. The maximum net-return (benefit – cost) of $6.5 per cow and year only reduced this loss to $3.8m within the following 20 years. Any intervention using ELISA only or both tests combined would perform even poorer (Table 2). These relationships are shown in Figure 5 over time.

## 5. Discussion

Four age groups were differentiated in the demographic part of the model: calves 0-6 months, calves 7-12 months, heifers 13-24 months and adult cows >24 months. The age-split of calves complied with earlier models to appreciate an age specific susceptibility (Marce et al. 2011). The model was based on recently published transmission studies summarized by Mitchell et al. (2015). Published parameters simulated vertical transmission, pseudo-vertical transmission during the time calves were left with their dam, intermittent shedding of calves until 1 year of age, and the probability of an infected animal to enter a paucibacillary progressor state. To this point, the model was described in detail by Verdugo (2013) which derived the structure and some parameters from Mitchell et al. (2008) and other parameters from Marce et al. (2011). To adapt Verdugo's beef-cattle model to NZ dairy systems, components were added to simulate early calf removal from a maximum of 4 days, and grazing calves on pasture previously grazed by potentially shedding adult cows. In the latter, a default spelling period of one month was assumed before calves entered a pasture block. An additional grazing options was introduced to simulate grazing of calves 4-12 months old on a separate 'run-off' that was never grazed (i.e. contaminated) by adult cows. The test-and-cull options assumed by Verdugo et al. were used in the dairy model, i.e. culling of cows positive by an annual ELISA, annual PCR or both.

Mathematical simulation cannot accurately predict on-farm loss. It needs to be validated by testing in the field. But modelling can evaluate the relative merit of different scenarios. The evaluation criteria for the described scenarios included the prevalence of cows and low/high shedders, the annual clinical incidence of ParaTB, and the net-return of the total dairy enterprise calculated as benefits minus cost of production. The relative loss of milk production was informed by a recent, yet unpublished study by O'Brian et al. (2016, personal communication) in one NZ dairy herd. Here, the milk production loss associated with low shedding was 9% (sub-clinical loss), and that associated with high shedding and clinical disease as 15%. This was similar to 5% and 13%, respectively, found by Smith et al. (2016) in intensive US dairy systems. All other parameters used for calculating production economics were based on the DairyNZ Economic Survey 2014-15[1].

**The most significant finding** of this simulation exercise was that, despite ample opportunity for MAP for being transmitted from the dam and during group-pen housing, MAP transmission to 4-12 months old calves while grazing pasture contaminated by adult cows was sufficient to sustain herd infection. Consequently, grazing calves at this age on a separate pasture block that was never fertilized by cow

[1] http://www.dairynz.co.nz/media/4291790/dairynz-economic-survey-2014-15.pdf

manure or grazed by infected cows, turned out to be a low cost intervention that was able to completely control the circulation of MAP in the herd. The effect of this intervention was almost independent of the initial prevalence/incidence level (low/moderate/high/very high), except that the time to reach low levels was longer in high prevalence hers. While this does not necessarily mean MAP could be eradicated, the model suggested that the prevalence of shedders and the occurrence of clinical ParaTB in the herd would reduce to low levels within 10-15 years (at moderate-high prevalence). At such low levels, there would be no tangible production loss in the herd due to ParaTB.

Therefore, the recent suggestion that pseudo-vertical dam-daughter transmission through colostrum or faeces may be unimportant relative to environmental transmission (Eisenberg et al. 2015) is consistent with the findings of the model. This obvious as the infection dynamics of the model were mainly driven by the uptake of MAP from pasture grazed by adult cows.

The sensitivity analysis of the assumption that susceptibility may or may not be independent of the age of calves during the first year of life resulted in substantial differences in absolute estimates of prevalence and clinical incidence (data not shown). It would therefore have required setting different values for beta, the transmission parameter for infection from pasture. However, these differences did not alter any of the relative findings and conclusions about the comparative effect of interventions.

On the other hand, annual test and cull interventions by ELISA and/or PCR – while effectively reducing prevalence and eliminating clinical ParaTB – did not offer any positive financial returns with 80 or even 120 years of simulation.  Moreover, severely affected farms may not benefit from T&C at all as neither prevalence nor clinical incidence reached low levels even after 80 years of T&C. ParaTB control on such farms would have to start with measures to reduce contact between replacement calves and adult cows.

## References

**Benedictus A, Mitchell RM, Linde-Widmann A, Sweeney R, Fyock T, Schukken YH, Whitlock RH.** Transmission parameters of Mycobacterium avium subspecies paratuberculosis infections in a dairy herd going through a control program. Preventive veterinary medicine 83, 215-227, 2008.

**Eisenberg SWF, Koets AP, Nielen M, Heederik D, Mortier R, De Buck J, Orsel K.** Intestinal infection following aerosol challenge of calves with Mycobacterium avium subspecies paratuberculosis. Veterinary Research 2011, 42:117, 2011.

**Eisenberg SWF, Rutten VPMG, Koets AP.** Dam Mycobacterium avium subspecies paratuberculosis (MAP) infection status does not predetermine calves for future shedding when raised in a contaminated environment: a cohort study. Veterinary Research:46:70, 2015.

**Marce C, Ezanno P, Seegers H, Pfeiffer DU, Fourichon C.** Predicting fadeout versus persistence of paratuberculosis in a dairy cattle herd for management and control purposes: a modelling study. Veterinary Research 42, 2011.

**Mitchell RM, Whitlock RH, Stehman SM, Benedictus A, Chapagain PP, Grohn YT, Schukken YH**. Simulation modeling to evaluate the persistence of Mycobacterium avium subsp. paratuberculosis (MAP) on commercial dairy farms in the United States. Preventive Veterinary Medicine 83, 360-380, 2008.

**Mitchell RM, Whitlock RH, Gröhn YT, Schukken YH.** Back to the real world: Connecting models with data. Prev.Vet.Med. 118:215–225, 2015

**Smith RL, Wolfgang DR, and Schukken YH**. The effects of progressing and nonprogressing Mycobacterium avium ssp. paratuberculosis infection on milk production in dairy cows. J.Dairy Sci. 99:1383–1390, 2016.

**Verdugo C.** Epidemiology of *Mycobacterium avium* subspecies *paratuberculosis* infection on sheep, beef cattle and deer farms in New Zealand. *PhD thesis*, Massey University, Palmerston North, New Zealand, 2013

**Voges H, Back P, Nash M, Trotter T.** Evaluation of a JD bulk milk ELISA as a herd screening tool in NZ dairy herds *Proceedings of the 10th International Colloqium on Paratuberculosis, Minneapolis, Minnesota*, 2009

**Whittington RJ, Windsor PA.** In utero infection of cattle with Mycobacterium avium subsp paratuberculosis: A. critical review and meta-analysis. Veterinary Journal 179, 60-69, 2009.