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Ovine Paratuberculosis

Transmission Dynamics and Cost- Effectiveness of Interventions

A thesis presented in partial fulfilment of the requirements for the degree of Doctor of
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Abstract

This thesis aimed at enhancing the knowledge about the epidemiology and control of paratuberculosis caused by infection with *Mycobacterium avium* subsp. *paratuberculosis* (MAP) in the New Zealand farming system, with a primary focus on sheep.

The potential for pathogen transmission between farms was explored in two studies. Four years of livestock movement records to and from 112 corporately owned farms in New Zealand, involving 1.15 million sheep, cattle and deer were analysed using social network analysis. In the first study, topologic features favouring pathogen spread in this network of farms were established. Hub-farms were identified as targets for risk-based movement control strategies to effectively decrease the potential for large epidemics. Inferences about movement control were not specific to MAP, so could apply to any pathogen transmission. In a second study, the potential for MAP transmission between farms was evaluated. In 2010, cross-sectional MAP screening using faecal culture and genotyping of cultures was performed on a subset of 102 farms in this network at the herd/flock level. These data were merged with the data about livestock movements. Multiple regression methods adapted to network data showed associations between past livestock movements and current strain type distribution in this population of farms. Farms in the same livestock movement network community were found to be twice as likely to share the same strains of MAP compared to farms in different communities ($p=0.033$). These studies showed that livestock movements between farms favour pathogen transmission and likely contribute to the high level of MAP infected farms in New Zealand. Results suggest that MAP can establish in a flock following the introduction of infected animals, and that biosecurity applied to trade may reduce the spread of MAP.

In a second part, a compartmental infection model was developed to simulate paratuberculosis on a typical self-replacing Romney sheep farm in New Zealand. This was preceded by a review of the literature on the physio-pathology of MAP infection in sheep, clinical outcomes and pathways following MAP infection to inform the model structure. A review of MAP enumeration methods *in vitro* identified comparative biases in estimating MAP doses in experimental studies. Subsequently, a systematic review and meta-analysis of experimental infection of sheep with MAP quantitatively estimated parameters for the simulation model, and identified relevant challenge-dose effects. The meta-analysis also enabled to integrate the effect of age at exposure, strain of MAP and type of inoculum on the

outcomes of experimental infection with MAP. It determined that MAP is highly infectious, with only 76 live ingested organisms required to cause histological lesions in the small intestine in 50% of inoculated sheep. However, 8.9×10^6 MAP organisms were necessary to cause progression to clinical disease in 50% of sheep infected as lambs or hoggets, and 7.7×10^9 in sheep infected as adults.

Simulations using the model were carried out for a range of clinical incidence scenarios, to study the impact of ovine Johne's disease (OJD) on a New Zealand pastoral sheep farm and the cost-effectiveness of interventions, *e.g.* vaccination. The impact of OJD is low on the majority of NZ pastoral sheep farms. These would not economically benefit from vaccination. However, vaccination with Gudair™ drastically reduced OJD mortality in flocks with high (1%) to very high (2%) annual clinical incidence of OJD in ewes, and was cost-effective. At a level of 1% OJD cases/annum in the ewe flock, the time to positive return on investment was 23 years, dropping to five years for 2% OJD cases/annum. After 30 years, farms with 2% OJD could expect NZD 2.4 return (net present value) for each dollar invested, with a total net profit of NZD 2,435 per 100 ewes in the flock. Meat price fluctuations had a strong impact on the economic evaluation.

Besides, annually replacing 1% of the flock with infected ewes tended to negate the beneficial impact of vaccination on reducing clinical disease incidence, through maintaining high levels of pasture contamination. The movements of MAP-infected animals can thus jeopardize the success of vaccination strategies. In the current context of high endemic prevalence of MAP infection in New Zealand farms, and given evidence about transmission between farms, it seems unrealistic to prevent MAP re-/introductions on farms in the absence of a certification program.

The network analysis undertaken in this thesis enhanced the understanding of the role of livestock movement in transmission of MAP. Combined with the simulation model, this work provides options to support farmers' decision-making and veterinary advice for managing sheep flocks with high OJD mortality.

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List of Abbreviations

AIC	Akaike Information Criterion
AGID	Agar Gel Immunodiffusion
CI	Confidence Interval
CFU	Colony Forming Unit
Ct	Cycle threshold
DNA	Deoxyribonucleic Acid
FMD	Foot-and-Mouth Disease
GAMM	Generalised Additive Mixed Models
GLM	Generalised Linear Models
GOF	Goodness-of-fit
GSCC	Giant Strongly Connected Component
GWCC	Giant Weakly Connected Component
IFN _γ	Interferon Gamma
IL	Interleukin
JD	Johne's disease
LC	Landcorp
MAP	<i>Mycobacterium avium</i> subsp. <i>Paratuberculosis</i>
<i>M. bovis</i>	<i>Mycobacterium bovis</i>
MC	Monte Carlo
MPN	Most probable Number
<i>M. tb</i>	<i>Mycobacterium tuberculosis</i>
NAIT	National Animal Identification and Tracing Scheme

NZ	New Zealand
NZD	New Zealand Dollar
OD	Optical Density
ODE	Ordinary Differential Equation
OJD	Ovine Johne's Disease
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PTB	Paratuberculosis
qPCR	quantitative Polymerase Chain Reaction
RFLP	Restricted Fragment Length Polymorphism
SNA	Social Network Analysis
SSR	Short-Sequence-Repeat
TB	Tuberculosis
Th1	T helper 1
Th2	T helper 2
VNTR	Variable-Number Tandem-Repeat
WGS	Whole Genome Sequencing

List of Journal Publications

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