An independent review of leptospirosis vaccination guidelines

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Motivation
Leptospirosis continues to place a significant disease burden on rural New Zealanders. A sheep and beef farmer and a deer farmer, both with renal and hepatic failure were recently admitted to the intensive care unit at Waikato Hospital (Dr. Chris Mansell; clinical microbiologist Waikato District Health Board; personal communication April 2012). In September 2010 there was a cluster of three cases of leptospirosis in staff at a lower north island dairy farm. Two staff were hospitalised. An annual vaccination programme had been carried out on the dairy farm since 2003; however the Department of Labour investigation identified deficiencies in the programme (Department of Labour 2011).

Seventy cases of leptospirosis were notified in 2011 of which 38 of 66 (58%) were hospitalised (Institute of Environmental Science and Research Limited 2012). *Leptospira* species and serovars (sv) were recorded for 57/70 of these, the most commonly identified serovar was *L. borgpetersenii* sv Ballum (35%, 20/57 cases), followed by *L. borgpetersenii* sv Hardjo (26%, 15/57 cases) and *L. interrogans* sv Pomona (23%, 13/57 cases). In 2010 sv Ballum emerged as the most frequently notified serovar in human cases. This rise in Ballum is coincident with an increase in the proportion of farmers represented among notified cases (Figure 1). In 2011 36 of the 62 cases with occupation recorded were identified as farmers or farm workers, with 10 of the 62 working in the meat industry.

An observational pilot study of vaccine efficacy in dairy herds with a history of regular vaccination was carried out in 2010/2011 (Parramore et al. 2011). There was evidence of leptospiral shedding in 30% of the herds and

![Figure 1. Proportion of notified leptospirosis cases infected with serovar Ballum (solid line) and associated with farming occupation as a function of time. Data sourced from ESR annual surveillance reports and Thornley et al. 2002.](image-url)
in 13% of animals from positive herds. Age at first vaccination was the only significant factor associated with the probability of shedding at the herd level. The results suggest that leptospiral challenge of calves at an early age still exists on dairy farms using vaccines. Vaccinating already infected animals may not be effective, as it appears that vaccination after natural challenge reduces vaccine efficacy (Hancock et al. 1984). Neither vaccine type nor the number of serovars included (2 vs 3) altered the shedding probability. However it is important to note that no serological data were available from the sampled animals, information about vaccination timing from farmers appeared somewhat uncertain, and tests employed may not be 100% accurate. Therefore, the results are preliminary and require further confirmatory work.

Motivated by the above information, the New Zealand Veterinary Association (NZVA) commissioned us to develop a systematic review of leptospirosis vaccination. The review aims to determine ‘Best Practice’ protocols for ruminant vaccination for leptospirosis with the primary goal of vaccination being the protection of humans. There are multiple other benefits from ruminant vaccination such as reduction of clinical disease and sub-clinical health effects, but these are not the primary focus of this work. The review remains work in progress with an estimated completion date of June 1 2012. This paper outlines the scope of the report, search methodology and details our key findings and recommendations with regard to the age at first vaccination (using the example of cattle). When the review is finalised it will be made available on the NZVA website.

Scope of the review

The review evaluated the following key areas with regard to the use of leptospirosis vaccines in New Zealand:

- The type and measurement of the immune response to infection or vaccination;
- The measurement of vaccine efficacy;
- The likely presence and interference of a maternally derived immune response;
- The age at first vaccination to prevent urinary shedding;
- The effect of vaccination before and after natural exposure;
- The duration of vaccine induced immunity;
- Environmental and management factors interacting with the response to vaccination.

Based on the results, the review subsequently derives best practice recommendations for the use of leptospirosis vaccines in dairy cattle, beef cattle, deer and sheep.

Search Methodology

Pubmed and the Web of Knowledge data bases were searched using the following key words: Lepto* OR Weil; Cattle OR Bovine, Deer OR Cervine, Sheep OR Ewe*, Human OR People OR Worker* OR Farmer*; Vacc* OR Prophy OR Immun* OR Protect*; Efficacy OR Effecti* OR Shedd* OR Serolog* OR Antibod*. Firstly, titles and abstracts of all returned articles were scanned to select relevant articles by one author (JS). A relevant article was defined as one that contained information that would inform the report as scoped above. Unpublished literature and data from Massey studies and from New Zealand pharmaceutical companies (MSD Animal Health, Pfizer Animal Health and Virbac Animal Health) also formed a substantial part of the review process.

Age at first vaccination

The uncertainty about when to first vaccinate calves remains a key question for veterinarians and farmers. The major conflict here is the balance between managing interference from maternally derived antibodies (MDA) and concerns about leaving calves unprotected in the face of challenge.

MDA are potentially present in offspring either when there is (1) a high level of natural challenge (Hellstrom 1978), or when (2) the dam has been vaccinated (Ayanegui-Alcerreca 2006). Vaccinating cows close to calving may result in interference with vaccination (Ankenbauer-Perkins 2000) or may not (Bolin 1989). There is evidence suggesting that efficacy of live vaccine may NOT depend on an absence of MDA (Woolums 2007). However, this inference may not be equally valid for killed vaccines such as all currently available leptospirosis vaccines. Thus vaccination of offspring in the presence of MDA may (or may not) reduce vaccine efficacy.

Following a high level of natural challenge, the decay of naturally acquired maternal antibody, as measured by the microscopic agglutination test (MAT), was described in detail by Hellstrom (1978). Over 90% of calves, birthed to a population of dams with high endemic levels of *Leptospira* sv. Hardjo and Pomona, acquired MDA after suckling sero-positive dams. Titres declined with a half-life of 15-17 days, most calves were MAT sero-negative at 100 days of age, and all were negative at 190 days. This was equivalent to a decay rate of 3.5% per day.
Calf cohorts were followed until new infections were detected by MAT, with most infections occurring at about 12 months of age Hellstrom (1978). New, natural infection resulted in high titres within 14 days of exposure which decayed down to 38% in the first, to 11% in the second year after exposure, and by 5% per year thereafter.

However, if a continuously-high natural challenge of new born calves is assumed under these circumstances, the proportions of susceptible, MDA-protected and infected calves from birth to two years of age would be as shown in Figure 2. Colostrum-acquired MDA decays to 100 days of age; most infections occur from about 100–200 days with 20% of calves being infected at about 3.5 months of age. Consequently, the peak of susceptibility if this is associated with loss of MDA and therefore most vulnerable time for infection would be around 40–110 days of age. Assuming that MDA negatively affects vaccine efficacy, vaccination would be scheduled at about 60-90 days for optimal efficacy (as indicated by the horizontal line labelled 1 to 3.5m in Figure 2). However, the true susceptible age may be somewhat later: Hellstrom’s data (1978) indicated that calves resisted experimental challenge up to three months after the loss of MDA-induced, MAT-detectable titres.

In endemic environments where MDA are assumed to be present, calves appear to be susceptible to infection as early as three months of age. In an observational study on age at first natural challenge, MAT titres of 1:96 and higher in 13 calf mobs of 11 vaccinated dairy herds were evaluated. The calves were between three and six months of age and had not yet been vaccinated. Titres were too high to be considered due to maternally derived antibodies (MDA) and calves were considered too old (>3 months) to still have MDA. The natural challenge was suspected to have occurred in mobs while grazing at run-offs at external farm locations. No antibodies were found in age-equivalent calves at the home farm (Pegram 1998). A 1980 study found five 6-months old calves that were already shedding leptospires in urine before first vaccination when screening calves for a vaccine efficacy study (Flint and Liardet 1980).

Discussion and recommendations
An important finding of the systematic review has been that there is a scarcity of robust scientific evidence to answer the following key questions:

• For how long does maternally-derived immunity protect against leptospiral challenge and urinary shedding?
• How does MDA influence vaccine efficacy in field management conditions and with natural challenge?
• What is the field efficacy of vaccine in sheep?
• How long does vaccine protection last - beyond 12 months?
• What are the quantifiable production effects of vaccination in cattle and sheep?
However, using current knowledge the following recommendations may be implemented while the data required to fully inform vaccination strategies in individual species and on mixed-species farms are acquired and evaluated.

In high challenge situations or when farmers perceive that the risk of human exposure is high, (for example in a beef herd) cattle should be vaccinated early, e.g. at 1-2 month of age. However, in low challenge situations, or when farmers perceive the human infection risk to be low, or when vaccination has been applied according to label for a number of years, (for example in a long-term vaccinated dairy herd) young stock may be vaccinated later, e.g. at 3-4 months of age.

Hence, our general ‘Best Practice’ vaccination guideline differentiates two situations:

1. Vaccination when there is high challenge

This situation applies when there is high risk of human or animal exposure and/or confirmed clinical cases have occurred and/or serological data from young stock exist that objectively demonstrate a high level of challenge at an early age.

We suggest an estimated first vaccination age of approximately six weeks followed by a booster at three months. This is illustrated in Figure 3, a timeline of events in a representative New Zealand beef herd. In order to ensure maximum vaccine efficacy, animals should get a second booster at six months of age followed by annual re-vaccination in 12 month intervals. One vaccine producer recommends that the 6-month booster be another full course of 2-vaccinations at a 4-6 week interval. No conclusive data currently exist in favour or against this claim.

It is understood that deviations from this recommendation will be unavoidable. Due to variable times of calving and practicalities on-farm, a recommended age of six weeks (boostered at three months) will effectively be a large range around this anticipated mean (or median) age.

2. Routine vaccination

In all other instances, it is recommended to complete the first course of two vaccinations within 4-6 weeks up to six months of age followed by annual whole herd vaccination.

References


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