Leptospirosis: Efficacy and place of a 7in1 vaccine

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This paper examines the efficacy of a 7in1 combination leptospiral and clostridial vaccine, recently registered for use in sheep at the dose of 1.5ml, and best practice recommendations for its use.

Introduction

Leptospirosis is an important zoonotic disease of all major livestock species including sheep, cattle, pigs and deer. In sheep while clinical leptospirosis occurs at a low incidence (Heuer et al. 2012a), it can cause abortions in ewes and kidney damage (redwater) and death in lambs. Recent studies through Massey University have found that 97% of sheep farms have evidence of infection with leptospira hardjobovis or pomona, with 51% of individual sheep seropositive (Dreyfus 2013).

It is estimated that 10-20% of sheep in NZ are shedding leptospires at any time (Dreyfus 2013, Heuer et al. 2012a, 2013).

Effects on production and reproduction in sheep are also being studied, so far indicating reductions in the growth rate of lambs, but only when infected very early around docking. (Vallee et al. 2013). However, reports have occurred of jaundice in lambs, and lamb loss after flooding and high rainfall resulting in losses of 5-15% (Dorjee et al. 2005).

Rates of leptospirosis vaccination in sheep are currently low, estimated at 0.6% (Dreyfus 2013). Farmers who have had problems with redwater and deaths in lambs, or abortion in ewes, may begin a vaccination program to prevent similar losses in future. In situations where sheep are managed intensively or have high human contact, such as milking sheep or lifestyle blocks, owners may wish to manage the risk of workers or family becoming infected. Similarly, public liability risks have prompted some regional councils to vaccinate sheep in their regional parks to manage potential public health risks.

Very little trial work has been conducted in sheep with leptospiral vaccines. Immunity to leptospirosis is a combination of both humoral antibodies and cell mediated immunity. Measuring immunity against leptospirosis is complicated as antibodies do not correlate well with protection and measuring cell mediated immunity is difficult. Following vaccination in cattle and sheep, antibodies are generated and detected in serum within 2-4 weeks after booster vaccination. Individual animal responses in terms of titre and duration of antibody response are highly variable. Typically, vaccinated animals become seronegative within a few months, however challenge studies have shown animals are still immune to leptospiral infection in spite of the absence of detectable antibodies at the time of challenge. In cattle and sheep, there is no correlation between antibody levels and protection in the vaccinated animal. Challenge studies are recognised as the only gold standard measure of protection using virulent field strains via a natural route of infection such as conjunctival or vaginal (OIE 2008). Validation studies that have used artificial challenge via intramuscular or intravenous routes have been found to not always be as protective against field challenge that occurs by conjunctival, nasal/oral or vaginal routes (OIE 2008).

New Zealand has little trial work describing the efficacy of leptospirosis vaccines in sheep. The only previous challenge study was reported by Marshall et al. (1979).
The study showed 78% protection against urinary shedding to artificial challenge with *L. hardjobovis* (intramuscular and intraperitoneal challenge) at six weeks post vaccination with Leptavoid 2 (A1948, MSD).

To our knowledge, challenge studies with *L. pomona* in sheep have never been reported before.

**Ultravac® 7in1 challenge study**

To this end, Zoetis instigated a challenge study in sheep to determine the efficacy of a leptospirosis vaccine, Ultravac 7in1 (A6935), against *L. hardjobovis* and *L. pomona*.

Prior to the challenge study beginning, a suitable sheep dose of Ultravac 7in1 had to be determined. Ultravac 7in1 contains the five core clostridial antigens used in “5in1” vaccines in NZ, Cl. tetani, chauvoei, novyi, perfringens type D and septicum. A 1.5ml dose was trialled in sheep and proven to elicit an effective immune response to all five clostridial antigens that was at least equivalent to the registered sheep dose of 1ml for Ultravac 5in1 (A3585) clostridial vaccine.

The challenge study trial was conducted by Estendart, Massey University, in 2012/13 on a Manawatu farm. The challenge and sampling phase was conducted in a secure containment facility at Massey University.

48 Romney cross lambs were allocated randomly to treatment and control groups. The vaccinates were given two 1.5ml doses of Ultravac 7in1, the first vaccination at 9-11 weeks of age and a booster four weeks later. At the same times, control lambs received saline placebo injections. Lambs were bled for MAT antibodies at regular intervals throughout the study. Four months after the second vaccination the lambs were challenged with approximately 10⁹ leptospires by conjunctival and intranasal administration, once daily for three days, with NZ strains of either *L. pomona* or *L. hardjobovis*. This challenge method mimics a natural route of infection and had been validated previously at the Massey Leptospirosis Unit. Following challenge, urine samples were collected weekly for six weeks. After six weeks the lambs were slaughtered and their kidneys collected. Urine and renal samples were cultured for leptospires – the results are shown in Table 1.

<table>
<thead>
<tr>
<th><strong>Table 1. Urine and renal samples.</strong></th>
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<tbody>
<tr>
<td><strong>Lamb urine or renal culture Ppositive</strong></td>
</tr>
<tr>
<td><strong>L. Hardjobovis</strong></td>
</tr>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>8/12</td>
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<tr>
<td>100% p=0.001</td>
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<tr>
<td>Ultravac 7in1</td>
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<td>0/12</td>
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66% and 75% of the controls were renal or urine culture positive for *L. hardjobovis* or *L. pomona* respectively on one or more occasions, while none of the vaccinated lambs were positive for kidney or urine culture at any time point. Vaccine efficacy was 100%.

**Discussion**

The vaccinated sheep showed a transient leptospiral antibody response post vaccination and were seronegative just prior to challenge – in spite of this, they were all protected against challenge. After challenge the controls showed a marked increase in leptospiral antibody titres, whereas the antibody response in vaccinates was minimal. We speculate that this may mean that in vaccinated sheep the infection is dealt with very early in the disease process, at the mucosal surface or early in the leptospiroemic phase.

Maternal transfer of leptospiral antibody to lambs in colostrum has not been investigated, however some predictions can be made based on the post vaccination antibody response recorded in this and other studies.
Colostrum antibody concentrations in ruminants are directly related to the level of circulating antibody in the dam’s serum immediately prior to parturition. The transient antibody response observed post vaccination in this study would suggest that ewe vaccination in late summer/autumn would not maximise colostral leptospiral antibody transfer to lambs born to ewes in the late winter/spring. Therefore if a goal was to maximise leptospiral colostrum antibodies, then a typical pre-lamb booster timing, 2-4 weeks before lambing, would be ideal. This timing may be desirable in some situations, for example to protect prime lambs against redwater, who in all likelihood will not themselves be lepto vaccinated before slaughter. Pre-lamb vaccination with Ultravac 7in1 would also be convenient in that it will also cover the annual clostridial ewe vaccination.

However from an epidemiological point of view, late summer/autumn vaccination of ewes may be considered best practice - boosting immunity prior to the time of greatest leptospiral survival and transmission (at least in most parts of the country with typical summer dry and autumn rains). If so, it would be more economical to use a straight leptospiral vaccine in the autumn, such as Leptoshield® (A3734, leptospiral only vaccine) at 1.5ml dose, with normal pre-lamb 5in1 vaccination, and Ultravac 7in1 vaccination for the lambs from docking.

A full farm leptospirosis control programme in all stock classes may reduce infection pressures enough to manage the risk to any unvaccinated prime lambs without the need to shift from late summer autumn to pre-lamb ewe vaccination. However if the source of infection is from an unmanageable source, e.g. L. pomona from wild pigs or shared waterways, then this may not hold true.

**When to use?**

Ultravac 7in1 vaccine is very efficacious in sheep. But when and how do you incorporate a leptospiral vaccine programme into the sheep management calendar?

Before instigating a programme, the disease risks need to be ascertained and the objectives of vaccination determined. For example, is vaccination undertaken due to OSH concern, suspicion or diagnosis of abortion caused by leptospirosis, clinical signs of redwater or known deaths due to leptospirosis in lambs? Once the main objective is known, then the best time to vaccinate can be determined.

Regardless of the reason, animals need to be vaccinated as early as possible prior to exposure. The recommendations for Best Practice (Heuer *et al.* 2012b, 2013) suggest first vaccination at tailing and the second 4-6 weeks later. The animals should then be given a third vaccination in autumn, prior to the time of greatest risk, and also in case of maternally derived antibody (MDA) interference at the time of first vaccination. It is now generally accepted that cattle and sheep should have completed their primary vaccination course by six months of age.

Most beef, deer and sheep farms are defined as high risk due to the high prevalence of leptospirosis positive farms/animals. In this case, young stock should be vaccinated early, at about 4-6 weeks of age then receive a booster 4-6 weeks later. Similar to the dairy cattle protocol, sheep should then ideally receive another booster at six months or at the time of the annual whole-flock booster. This will align them with the ewe flock and to ensure there is adequate immunity in the event of MDA interference with the primary vaccination.

In low-risk environments, such as flocks with a history of continued vaccination, lambs may receive their first vaccination from 4-12 weeks of age, i.e. a few weeks later than for high risk farms. The first course of vaccination should be completed before lambs are six months old. For continued immunity, these animals must be vaccinated annually at the same time as the ewe flock booster vaccination. On a low risk farm it is possible the second booster vaccination will coincide with the annual flock booster, thus a third shot won’t be required in the first year.

For adult stock, annual vaccination is best given prior to the time of greatest risk, i.e. autumn/winter. Thus the most practical time may be 2-4 weeks pretup, which will be around February/March for most NZ farms. Alternatively, vaccination could be given after tupping, although this could leave some animals exposed to infections in an “early leptospirosis season”, i.e. a year with high summer/autumn rainfall.

In situations where lambs are unlikely to get vaccinated, such as for prime lambs, vaccinating ewes pre-lambing should boost MDA in the colostrum and help protect lambs early in life, potentially for many, until slaughter. While pre-lamb booster timing is not ideal from an epidemiological point of view, it can achieve several goals if
7in1 vaccine is used: to protect the ewes and lambs against clostridial diseases in the periparturient period, boost leptospiral MDA in colostrum for prime lambs, and potentially protect the ewe through the peak leptospirosis season of autumn/winter. However, 12 month duration of immunity studies have not been undertaken with any leptospiral vaccines in sheep. One can extrapolate from cattle work (Zoetis data on file) that demonstrated that calves vaccinated with Ultravac 7in1, beginning at 6-8 weeks of age and boosted six weeks later, have immunity that lasts for at least 12 months. However, this may or may not be the case with sheep.

**Option 1: High risk farms**

Lambs get their first and second vaccinations as early as practical (tailing then weaning), then a third to align with the flock in autumn. Ewes are boosted pre-tup.

**Late Summer/Autumn Annual Booster - High Risk**

<table>
<thead>
<tr>
<th>Lambs 3rd shot flock alignment 7 in 1 or Lepto</th>
<th>Lambs 1st shot @ tailing 7 in 1 or Lepto</th>
<th>Lambs 2nd shot @ weaning 7 in 1</th>
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<thead>
<tr>
<th>Ewes pretup Lepto</th>
<th>Ewes Prelamb 5 in 1</th>
<th>Topping</th>
<th>Lambing</th>
<th>Tailing</th>
<th>Weaning</th>
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<tbody>
<tr>
<td>Feb</td>
<td>Mar</td>
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Advantage of this programme: the annual booster is prior to the period of maximum species survivability and transmission.

Disadvantage – unlikely to maximise MDA leptospiral protection for unvaccinated lambs.

**Option 2: Low risk farms**

First and second lamb vaccination can be delayed another 4-6 weeks. This results in the second vaccination aligning with the annual flock vaccination so a third injection is not required.

**Late Summer/Autumn Annual Booster - Low Risk**

<table>
<thead>
<tr>
<th>Lambs 2nd shot &amp; flock alignment 7 in 1 or Lepto</th>
<th>(5in 1)</th>
<th>Lambs 1st shot @ weaning 7 in 1</th>
</tr>
</thead>
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<table>
<thead>
<tr>
<th>Ewes pretup Lepto</th>
<th>Ewes Prelamb 5 in 1</th>
<th>Topping</th>
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**Option 3: Pre-lamb ewe booster**

Vaccinate ewes prelamb, then vaccinate replacement lambs at weaning and 4-6 weeks later. These lambs will need a third vaccination as yearlings to align with the ewe flocks annual pre-lamb booster.

**Prelamb Annual Booster Option**

<table>
<thead>
<tr>
<th>Lambs 2nd shot 7 in 1</th>
<th>Lambs 3rd shot &amp; 7 in 1 or Lepto</th>
<th>Lambs 1st shot @ weaning 7 in 1</th>
</tr>
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<table>
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<tr>
<th>Ewes pretup Lepto</th>
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Advantages: the convenience of combined leptospiral and clostridial vaccination in a single injection for the ewes and maximise leptospiral MDA for any unvaccinated lambs.

Disadvantage: not ideal annual booster timing.

Summary
This paper discusses the efficacy and practical recommendations of leptospiral vaccination in sheep. There are several reasons that farmers may wish to vaccinate their flock against leptospirosis and it is the veterinarians’ expertise in analysis of the risks in conjunction with the desires of the farmer that will determine the best vaccination protocol for the farm. Should vaccination be required, Ultravac 7in1 has known and excellent efficacy, proven in challenge studies to protect against leptospirosis, that can be used with confidence in sheep. The recommendations outlined above are in alignment with those of the Massey/NZVA Best Practice recommendations for leptospirosis vaccination.

References


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