Yersiniosis: Resistance, susceptibility and vaccination

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Abstract

Laboratory and clinical reports confirm that yersiniosis outbreaks in herds of young deer are still common. Some outbreaks occur in deer even after vaccination with "Yersiniavax". Data from field studies of vaccine efficacy in at-risk herds confirm that vaccination significantly reduces clinical incidence and mortality rates but does not totally eliminate disease. Mortality rate averaged 0.8% in vaccinated deer and 2.1% in unvaccinated herd mates. Data also suggests that vaccination may not reduce the incidence of sporadic cases, suggesting individual animal susceptibility.

During research into vaccine development it was observed that, with heavy experimental stress/challenge, clinical disease incidence rates varied 14-85% and mortalities 0-37% between sire groups. This suggests that genetic factors may influence susceptibility to yersiniosis.

A recent outbreak of yersiniosis in a mob of 136 vaccinated weaner deer was investigated. Of five animals that died, four were progeny of one sire and the fifth was a second generation progeny of that sire. Eight sire groups were involved. The seven surviving progeny of the suspect sire, along with seven from each of two unrelated sires, were blood sampled and re-vaccinated with "Yersiniavax" and blood sampled again 21 days later. Samples were analysed by ELISA for OI, OII and OIII, pure V and crude V *Yersinia pseudotuberculosis* antigens, and for cellular reactivity. Statistical analysis showed no difference in cellular reactivity but a significant difference between sire groups in the ELISA response with the OI and OII antigens. The suspect sire group consistently produced the lowest immunological responses.

This paper reviews existing information showing that yersinia vaccination will reduce morbidity and mortality rates in outbreaks and that sire-related immunological factors may place some progeny lines at higher risk than others.

1. Introduction

Yersinia pseudotuberculosis (*Y. pstb*) was first diagnosed as the bacterium involved in outbreaks of diarrhoea in deer herds in 1978 (Beatson and Hutton, 1981). Having made the link between clinical disease outbreaks and *Y pstb*, this disease was soon diagnosed elsewhere (Hunter, 1981) and rapidly became regarded as one of the most serious and common infectious diseases of farmed deer in New Zealand (Mackintosh and Henderson, 1984). In 1983 alone, 335 cases were diagnosed in animal health laboratories and mortality rates were high (Beatson, 1984). Cases are frequently reported by animal health laboratories (Orr, 1995). The epidemiology of yersiniosis has been reviewed by Mackintosh and Henderson (1984) and Mackintosh (1992).

Previously, *Y pstb* was most frequently isolated from canaries, other cage birds and guinea-pigs, with some sporadic isolations from sheep, cattle and cats (Beatson and Hutton, 1981). *Y pstb* will survive in the environment for long periods of time in cold, wet conditions. The

organism can be isolated from all deer herds, with or without the clinical occurrence of yersiniosis (Henderson and Hemmingsen, 1983). Research on a clinical model for yersiniosis (Mackintosh *et al.* 1990, 1991) found it necessary to expose deer to transport stress before significant clinical disease occurred. Those authors also noted a relationship between the severity of disease and the challenge dose of *Y. pstb* organisms. This, along with other epidemiological evidence, proves that the precipitation of the disease state is associated with a complex interrelationship involving challenge dose and environmental and animal factors. Mackintosh *et al.* (1990, 1991) also noted a different disease and mortality incidence between sire progeny groups, suggesting that genetic differences in animal response to the organism and/or stress influenced the establishment of a disease state.

By the mid-1980s preliminary investigations into immunological responsiveness to a trial vaccine had begun (Mackintosh *et al.* 1986). Further studies at Invermay involving artificial challenge and vaccination were reported subsequently (Mackintosh *et al.* 1990, 1991). Evaluation of the efficacy of "Yersiniavax" under field conditions was reported by Mackintosh *et al.* (1992). The development of a vaccine against yersiniosis in deer is reviewed by Mackintosh (1993).

This paper re-examines the issue of clinical outbreaks of yersiniosis with particular reference to those in vaccinated herds. It addresses the question of what is a realistic expectation of "Yersiniavax", reviewing existing evidence, and providing further evidence for a sire line susceptibility to the disease related to immunological responsiveness.

2. Clinical outbreaks and vaccination status

There is little published data on the current incidence rate of yersiniosis in commercial deer herds. Table I contains a summary of recently published mortality rates of yersiniosis on some commercial deer farms. Quarterly reviews of diagnostic cases reported in *Surveillance* over the past few years have indicated that yersiniosis outbreaks are still commonly diagnosed in farmed deer herds. Some affected herds contained vaccinated animals.

Table 1. Recently published mortality rates caused by yersiniosis on commercial deer farms

Reference	No herds studied	No herds with yersiniosis	Mortality rate % (range)	
			Non-vaccinated	Vaccinated
Mackintosh *et al* (1992)+	17	13	2 1 (0-22)	0 8 (0-8 5)
Audigé (1995)	16	4/2 yrs	1 09* (0-30)	
Langdon and Hutton (1998)	1	1	10	4

* confirmed cases only Rate = no cases/100 deer-years
+"at-risk" herds

Mortality rates in non-vaccinated deer can be as high as 30% of a mob. Earlier estimates of 1% average mortality may be conservative since the data of Audigé *et al.* (1995) showed an average of almost 1.1% for confirmed cases only. If "suspected" cases were included, the

figure would be higher since some cases are likely to have been confirmed, had investigations been undertaken. Data of Mackintosh *et al.* (1992) were from herds that had been selected by veterinary practitioners as being "at risk". Further, the 2.1% mortality rate was confounded by the vaccination of half of the deer in the herd. This would have altered the epidemiology of the disease, particularly the challenge rate. Thus, the mortality rate would probably have been higher in those herds had vaccination of half the deer not been undertaken. It is therefore a reasonable assumption that the national average mortality rate is between 1 and 2% per annum.

This evidence, together with clinical observations by practitioners and anecdotal evidence of farmers, suggests that yersiniosis is still an important disease of farmed deer, despite apparent advances in herd management, and the availability of the vaccine. However, anecdotal information suggests that possibly only 30-40% of deer farmers vaccinate their deer, and that some veterinarians do not actively recommend vaccination. Figure supplied (Brenton-Rule, AgVax developments, pers com) suggest that about 55% of weaner deer are vaccinated! It therefore seems that vaccine usage may be more common in larger herds. There is also evidence that the vaccine is often not used as recommended, with some farmers using less than the recommended 2 ml dose, only giving one dose of vaccine and vaccinating either too early when colostral interference may occur, or too late when an outbreak is already underway.

3. Vaccine efficacy

The pack insert claims that "Yersiniavax" ... "promotes an immune response against *Yersinia pseudotuberculosis*". The indication for yersiniosis vaccination is ... "to protect deer against clinical yersiniosis caused by *Yersinia pseudotuberculosis*". In a promotional brochure, advice includes the following:

- aim to reduce the effect of common stress
- vaccinate with yersinia vaccine to prevent clinical disease
- use "Yersiniavax" to enhance, rather than to substitute for, good management.

While these statements may give some the impression that the yersinia vaccine is fully protective, veterinarians should view this information in context of the published information from studies of yersiniosis vaccine efficacy to achieve a realistic expectation of the rate that this vaccine plays in deer herd disease risk management. These data are summarised in Table 2.

Studies of Mackintosh *et al.* (1990, 1991) described the response of red deer weaners to artificial challenge followed by exposure to transport stress to precipitate clinical disease. Two challenge dose rates were applied. In both experiments a high proportion of non-vaccinated animals succumbed to the disease. The disease incidence in vaccinated animals was approximately half that of non-vaccinated animals. Reference was made to mortalities but rates were not provided in those papers. These data are summarised in section 4 of this paper.

Table 2. Summary of published data from studies of yersiniosis vaccine efficacy

Study	Design	No deer	No deer affected			
			Non-vaccinated control		Vaccinated	
			*yers(%)**	*died(%)†*	*yers(%)**	*died(%)†*
Mackintosh *et al* (1992) Vaccine/challenge	1 dose + stressor	139	54	N R	31	NR
Mackintosh *et al* (1991) Vaccine/challenge	2 adjuvants 2 doses stressor	128	60	N R	28**	NR
Mackintosh *et al* (1992) Field trials	2 doses	Total 4958	162 (3 2)	106 (2 1)	57 (1 1)	39 (0 8)
	Outbreak farms					
	1	299	33 (22)	33 (22)	10 (6 7)	10 (6 7)
	2	520	88 (34)	55 (21 2)	10 (4)	10 (6 7)
	3	304	22 (14)	3 (2 0)	13 (8 5)	3 (2 0)
	Sporadic case farms					
	4-13	2742	18 (0 7)	15 (0.5)	24 (0 8)	23 (0 8)
	No cases					
	14-17	1093	0	0	0	0
Langdon and Hutton (1998)		NR	NR	NR (10)	NR	NR (4)

* = Morbidity rate
† = Mortality rate
N R = Not stated
** = Both adjuvants combined because not significantly different

Field trials of 17 "at risk" herds (Mackintosh *et al.* 1992) indicated an overall incidence rate of yersiniosis in non-vaccinated deer of 3.2% compared with 1.1% in vaccinated deer. A number of the clinically affected deer died of the disease and the overall mortality rate in non-vaccinates was 2.1% and in vaccinates 0.8%. Data for individual herds where outbreaks occurred (farms 1-3) showed consistent and statistically significant reduction in incidence rate in vaccinated groups. However, in 10 herds where only sporadic cases were observed there was no difference in the incidence rate between vaccinated and non-vaccinated deer.

A recent laboratory diagnostic case report (Langdon and Hutton, 1998) described a 10% mortality rate of unvaccinated deer compared with a 4% mortality rate in vaccinated deer in a clinical disease outbreak. However, no details were given.

These are the only data available describing "Yersiniavax" efficacy, and probably represent a worst-case scenario because only half of most herds studied were vaccinated. The conclusions that can be drawn from this data are:

- Vaccination with "Yersiniavax" reduces the incidence rate of clinical yersiniosis in outbreaks by at least 66%; and probably considerably more;
- Vaccination reduces the mortality rate in outbreaks by at least 60%, and probably more;

- Vaccination may not reduce the incidence rate of sporadic or individual cases of yersiniosis,
  Since there have been no surveys of the incidence rates of yersiniosis in vaccinated *vs* non-vaccinated herds, it can only be speculated that the vaccine may prevent the occurrence of outbreaks when all deer are vaccinated.

4. Vaccine prescription

"Yersiniavax" is a Prescription Animal Remedy Class I. There is currently a concern amongst some deer farmers as to the effectiveness of the vaccine. Data presented suggests that concern may be based on an unrealistic expectation of the vaccine. However, veterinarians, being familiar with that data, are uniquely placed to advise on the expectation of the vaccine. The concept of black and white treatments and cures is not appropriate to this situation; the concept of risk management is.appropriate. Veterinarians should advise clients of the likely outcomes on the basis of existing knowledge; firstly, vaccination is likely to reduce the risk of an outbreak *per se.*, *secondly*, if an outbreak were to occur, the risk of clinical disease and mortalitieswould be reduced by at least 60-70%. Failure to properly inform the deer farmer of these expected outcomes, and therefore failure of the vaccine to live up to an expectation, albeit unrealisable, by the farmer may result in the vaccine being discredited. This could lead to a reduction in usage, and potentially threaten the availability of a product that currently provides significant benefits to the deer industry, in financial and welfare terms. Reducing mortalities from 2.1 to 0.8%, as shown for "high risk" herds, means that, on a simplified economic basis, a farmer could spend 1.3% of the average value of a deer on vaccination. This calculation does not include the cost of investigation and treatment of clinical cases.

Why is vaccine protection not 100%?

Firstly, few vaccines, if any, are 100% effective. The first step in the process of evaluating disease in vaccinated deer on an individual farm is to investigate the circumstances of vaccination including age of animal when sensitised, the interval between sensitiser and booster, the vaccination – disease interval, stress factors, vaccine dose and handling, vaccination technique etc.

Disease susceptibility and resistance is a complex interrelationship between the organism, host and environment, and there are many excellent reviews on this topic in the literature. There are complex immunological interactions when a subcutaneous immunisation is given for a disease that is primarily gastrointestinal. The degree of *Y pstb* challenge described by Mackintosh *et al.* (1990, 1991) affects the onset of clinical disease. In an experimental situation a low challenge in unstressed deer produced little clinical disease. Conversely, a high challenge coupled with the stress of transport, fasting and handling resulted in high clinical disease incidence and mortality rates.

There are individual animal differences in immunological response. These may account for sporadic cases. In addition, there is a significant inherited basis for immunological responsiveness, ie: resistance or susceptibility to disease. This will be discussed below.

5. Evidence for a sire line susceptibility to yersiniosis

5.1 Previous research observations

Data in Table 3 details outcomes by sire from the research described by Mackintosh *et al.* (1991,1992). In the first study, 14-50% of progeny from various sires were affected with yersiniosis. In Study 2, 25-85% of progeny were affected. For both studies the sire effect was statistically significant.

Table 3. **Clinical disease and mortality rates of progeny of different sires after challenge with *Y. pstb* with or without vaccination (C G Mackintosh. Data)**

	Sire	No challenged	Clinical (%)		Died (%)		Total affected %
			Vacc	*Non-vacc*	*Vacc*	*Non-vacc*	
STUDY 1	1	7		14		0	14
	2	12		17		0	17
	3	11		27		0	27
	4	18		22		11	33
	5	11		27		9	36
	6	14		43		0	43
	7	14		29		14	43
	8	18		28		22	50
	9	15		47		7	53
STUDY 2	1	13	28	50	28	16	62
	2	20	50	62	25	37	85
	3	12	0	43	0	0	25

5.2 Commercial farm yersiniosis outbreak investigation

An opportunity arose to study immunological responsiveness in a commercial deer herd in which an outbreak of yersiniosis occurred and there appeared to be a sire-line susceptibility. The following describes the outbreak and the immunological investigations.

5.2.1 History.

The sequence of events related to this outbreak is presented in Table 4. Note that type OIII *Y. pstb* was cultured from 2 deer in this outbreak.

Table 4. Sequence of events related to the yersiniosis outbreak and investigation

March	3	Mob	Weaners from a run-off were joined with those of the home farm
March	17	Mob	Vaccinated with ""Yersiniavax"", drenched with oral "Ivomec"
April	14	1 deer	Found dead – no investigation Signs of scouring
April	19	Mob	Vaccinated with ""Yersiniavax"", drenched with "Ivomec"
	21	1 deer	Found dead – no investigation Signs of scouring
	26	1 deer	Scouring farmer treatment Terramycin died 27 April Vet PM - yersiniosis confirmed
May	1	1 deer	Died scouring Diagnosis Yersiniosis
May	2	Mob	Treated with oral Neomycin
May	7	1 deer	Died scouring Presumed Yersiniosis
May	15	1 deer	Scoured, treated, recovered *Y pstb* cultured
	18	21 selected	Blood sample (7 of progeny test sire, 7 progeny of sires 1 and 3 - see Table 7)
		Mob	Vaccinated with "Yersiniavax", oral "Ivomec"
June	8	21 selected	Repeat blood sample

The farm is 40 hectares and is in the Pahiatua district. In 1998 it wintered 85 adult velvetting stags, 95 breeding hinds and 136 weaner males and females, progeny of eight breeding sires. The weaner mob in question was grazed on perennial ryegrass/white clover pastures of green leaf quality and a minimum residual grazing height autumn and early winter of 8 cm.

This herd is a well managed herd, and during the Deer Herd Health and Production Profiling survey (Audigé, 1995) was at the 50 percentile for reproductive outcomes, at the 75th percentile for growth rates and at the 100 percentile for velvet antler production. Mortality rates compared with other farms in that study are presented in Table 5. It should be noted that the first dose of vaccine was given in mid March and the second was given 5 weeks later, 5 days after the first case of suspected yersiniosis occurred.

Table 5. Mortality rate(/100 deer years) on study farm compared with other farms during a deer herd health and production profiling study (Audigé, 1995)

		All farms	
	This farm	Mean	Range
Weaners	2 52	5 87	0 35 - 30 30
Yearling and adult hinds	2 34	1 77	0 27 - 4 33
Yearling and adult stags	1 82	2 56	0 99 – 4 44

Available bodyweights of the affected progeny against herd means and ranges are presented in Table 6. This data shows that most of the affected deer had bodyweights below average in late January, suggesting that they were born late. Unfortunately no weights at the time of the outbreak were available. It is known that both bodyweight and bodyweight percentile are both risk factors for yersiniosis (Audigé, 1995).

Table 6. Weights of affected deer and mean and range of weights of mob

Status	ID Affected deer	Sex	Sire*	Weight (kg) 20/1/98
Died	7556	F	4	21 9
	7560	F	4	20 1
	7561	F	8	19 7
	7026	M	4	32 1
	7048	M	4	27 7
Recovered	7562	F	3	31 22
	7021	M	1	30 3
	7065	M	8	18 7
Herd mean (range)		F		27 9 (18-36)
		M		31 5 (18-41

*See Table 7 Sire 4 is the suspect sire, sire 8 is progeny of 4

The five deer that died were related directly to one sire (see Table 7). Four of 11 progeny of sire 4 died of yersiniosis while two other affected deer were the offspring of a sire that was a progeny of sire 4. Two of 8 cases were from sires not related to sire 4. Both recovered.

Table 7. Numbers and % (in brackets) of progeny from each sire group on study farm and mortalities over the study period

Sire	Progeny			Scoured but died		Scoured but recovered	
	Total	M	F	M	F	M	F
1	59	32	27			1(3%)	
2	28	15	13				
3	16	6	10				1(10%)
4*	11	5	6	2(40%)	2(33%)		
5	9	4	5				
6†	8	3	5				
7	3	2	1				
8†	2	1	1		1(100%)	1(100%)	

*Test stag
†Son of test stag

This pattern, relating disease to sire group, prompted a preliminary investigation of immunological responsiveness.

5.2.2 - *Immunological investigation*

The seven remaining progeny of sire 4, along with 7 progeny of unrelated sires 1 and 3, were blood sampled and re-vaccinated with "Yersiniavax" (Batch #9801.11) on May 18, and blood sampled again on June 8 as described in Table 4. Blood samples were couriered immediately to the Deer Research Laboratory, University of Otago, where ELISA using O antigens I, II and III and a crude (unfractionaed) V (virulence) and pure protein V antigens were undertaken, along with tests of cellular reactivity.

Statistical analysis of the pre- *vs.* post-vaccine antibody (ELISA OD (optical density)) or cellular immune response measured by uptake of radiolabelled nucleotides and the difference between them was undertaken by multiple analyses of variance. The differences in OD or counts pre- and post-booster vaccination responses, and the pre-post difference for ELISA crude and pure antigens and all cellular reactivity tested were not statistically significant.

Mean ELISA optical density readings and the difference between pre- and post-booster means for antigens OI,II and III and statistical analysis are presented in Table 8. Differences in pre-booster immunisation ODs indicate baseline differences between progeny of sire groups. For antigens OI and OII there is a statistically significant difference in magnitude of the pre- *vs* post-booster response of progeny of sire 1 compared with those of sires 3 and 4, ie. there is significant difference between groups in immunological response to the vaccine. The sire (No. 4) with the greatest number of progeny affected with yersiniosis had consistently the lowest immunological responsiveness. Note that the standard errors for progeny of sire 1 are large. One progeny of that sire showed a mild clinical case of yersiniosis.

While the responsiveness of progeny of sire 4 to vaccination were low, it should be noted that these animals were those which survived the yersiniosis outbreak. One can only speculate on the likely immunoresponsiveness of those that died. It should be noted also that every progeny of that sire which developed yersiniosis died.

Table 8. Mean (± SE) ELISA optical density reading, and the pre- post "Yersiniavax" booster difference, for offspring (n = 7) of 3 sires

	Antigen								
	O I			O II			O III		
Sire*	*Pre-*	*Post-*	*Diff*	*Pre-*	*Post-*	*Diff*	*Pre-*	*Post-*	*Diff*
1	32 (5 7)	105 (12 5)	73	25 (3 0)	66 (8 7)	41	59 (12 1)	92 (14 7)	33
3	25 (1 9)	60 (6 0)	35	25 (2 3)	44 (5 7)	19	42 (4 9)	68 (5 7)	26
4	23 (5 7)	54 (6 4)	33	21 (2 3)	38 (7 2)	17	29 (2 3)	48 (6 4)	19
P value	NS	< 001	<0 001	NS	<0 05	<0 05	05	<0 -5	NS

*Same sire numbers as Table 7 4 = Test sire

These results, albeit with small numbers, suggest an immunological basis for sire differences in the incidence rate of yersiniosis in progeny.

Further research needs to be undertaken to evaluate the role of immunological responsiveness in apparent genetic susceptibility to yersiniosis. Further investigations are underway to

evaluate the relative risk of other diseases in progeny of the apparently susceptible sire *vs* other sire on the present property, and on a second property which also contains progeny of sire 4. Interestingly, the second property has reported no yersiniosis cases. Environmental and/or dam effects may be involved.

6. Conclusions

This review of available literature has shown that the vaccine will significantly reduce the clinical incidence rate and the mortality rate of yersiniosis.

Review of available literature and research data combined with the present clinical investigation provide strong evidence for a sire-related difference in susceptibility to yersiniosis. Results from the case study suggest an immunological basis for that difference.

These observations suggest that further evaluation of genetic susceptibility to yersiniosis is warranted. Ultimately, selecting sires with desirable resistance characteristics or enhanced response to prophylaxis, which may be identified by genetic markers, may reduce the risk of yersiniosis.

Acknowledgements

The encouragement of Tony Brenton-Rule, AgVax Developments Ltd., with both the Invermay and Massey studies reported in this paper is gratefully acknowledged. AgVax New Zealand Ltd. contributed financially to the collection and analysis of samples from the case study reported. Statistical analyses were undertaken by Carola Sauter Louis.

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