# Review

# An Assessment of Vaccination as a Control Tool for the Management of Johne's Disease in New Zealand

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# 1 Short Summary

Johne's disease (JD) or "paratuberculosis", is a sub-acute to chronic wasting disease of sheep, cattle, deer and goats. This arises from local invasion of the bowel by the organism *Mycobacterium avium* subspecies *paratuberculosis*. Most herds and flocks in NZ are infected (50% to 60% or more), but clinical cases are generally recognised in less than 10% of total herds/flocks. It appears that the deer industry has fairly recently emerged from what could be termed an "epidemic" phase of JD.

JD vaccines (live or inactivated with oil) have been in use for close to 100 years. Overall they have proved to be cost-effective with respect to reducing production losses arising from clinical disease, but not totally protecting against infection nor the establishment of all shedding. Of note is the risk of developing clinical disease is reduced after both pre-exposure and post-infection vaccination; as MAP can be widespread in the environment this "dual action" is important.

Across the world the use of these vaccines in some species has been "patchy" because of undesirable side-effects, especially interfering with the diagnosis of tuberculosis in cattle and, from both an animal welfare and a carcase quality perspective, severe tissue reaction in at the site of inoculation. However, they have played a significant role in some countries, for example controlling clinical disease in sheep in Iceland. A live vaccine (Neoparasec™) was available in New Zealand between 1987 and 2004. In sheep it appears to have been effective, but there was much concern about the amount of tissue damage and follow-on effects; e.g. fly strike.

Currently there are two JD vaccines registered in New Zealand; Gudair™ for sheep and Silirum™ for cattle and deer. Both contained inactivated MAP in oil. The use of Silirum™ is restricted to finishing deer destined for slaughter.

Gudair™ has a pivotal role in the current management of Johne's disease in sheep in Australia. Trials in New Zealand and Australia have demonstrated that Silirum™ reduces the risk of lesion development in deer and cattle. The side-effects referred to above are seen with these vaccines. Tissue damage is less than seen with Neoparasec™; most consider it acceptable but some consider there is still an animal welfare issue.

The managers of the national tuberculosis control programme (i.e. OSPRI) consider that from a technical perspective a limited number of vaccinated herds (with some expected diagnostic "complications") could now be safely handled. Vaccinated animals would have to be permanently identified.

In my opinion, there is a place for vaccination in sheep and in capital stock in deer and cattle in the JD control "tool box", especially where there is a high incidence of clinical disease. In these circumstances, test-and-management tactics (i.e. without vaccination) in deer and cattle would probably be very expensive and have uncertain outcomes. A programme which integrates testing, management and vaccination might be the best option.

There are currently a number of independent groups working on new vaccine prototypes that appear very promising. However, development of a new product for field use will take a long time, possibly as much as 8 to 10 years, and will be expensive. Many consider it important that the sheep, cattle and deer industries are involved in these developments in order to facilitate early adoption.

## 2 Long Summary

This document describes the outcome of an assessment of vaccination in the control of Johne's disease (JD) in New Zealand (NZ). The purpose is to assist the livestock industries establish a position on vaccination, having regard both to its effectiveness and to any untoward impacts on both animals and products.

The assessment was based on expert opinion and published literature including peer reviewed papers, conference proceedings and workshop notes.

JD is a sub-acute to chronic wasting disease of ruminants (including sheep, cattle, deer and goats) resulting from destruction of sections of the bowel as a result of a granulomatous enteritis. This arises from a local invasion of the organism *Mycobacterium avium* subspecies *paratuberculosis* (MAP). The disease is also called paratuberculosis.

Currently in NZ JD vaccines are not used in cattle, and are used only in a restricted manner in deer, primarily because of the potential interference with tests used to identify animals infected with bovine tuberculosis. A vaccine is used in sheep to a limited degree, but there are a number of animal welfare, product inspection and product quality issues that are of concern.

A brief overview of the pathogenesis, immunology and epidemiology is presented. MAP is maintained within cattle and deer herds and in sheep flocks via the transfer of infection from older animals to the incoming birth cohort. The main route of transmission is faecal-oral, but intra-uterine transmission and infection via milk also occurs. However, as MAP can survive in the environment for prolonged periods indirect transmission is also important.

In most animals infection is either eliminated or effectively controlled. In some, MAP is not controlled and the result is a progressive granulomatous lesion eventually leading to clinical JD. The ability of an animal to control MAP infection is associated with strong specific cellular immunity. Alternatively, the development of the disease is generally associated with high antibody levels. A notable aspect is that this "inability to control of MAP" is seen in most cases after many years. However, in some instances, for example deer, it has been seen much earlier (10 to 12 months).

Concerning the mode of action of JD vaccines, of importance is that the risk of developing clinical disease is reduced after both pre-exposure and post-infection vaccination. The former is sometimes called "prophylactic vaccination" and the latter "therapeutic vaccination".

It has been shown that the dynamics of MAP infection in herds and flocks is affected by many factors and these are the basis for so-called "test-and-management" control programmes; i.e. without vaccination.

JD in livestock is the primary focus nationally and internationally, but there is good evidence that the ecology of MAP extends beyond this.

A note is included concerning two issues which frequently came up during interviews. The first concerned setting what the objective of control should be; e.g. eliminating clinical disease or, additionally, subclinical disease or, alternatively, to focus on reducing MAP faecal shedding and product contamination (this in response to serious concerns about the association between MAP and

Crohn's disease in humans). The second issue concerned establishing, with appropriate scientific rigor, whether or not various interventions were effective.

A summary of the status of JD in sheep, beef cattle, dairy cattle and deer is presented. In all cases there is good evidence that most herds and flocks in NZ are infected (50% to 60% or more). With the exception of deer, clinical cases are generally recognised in less than 10% of total herds/flocks. Deer appears exceptional with around 30% of herds having clinical cases. However, the current figure for deer may be much less as it seems that the deer industry has fairly recently emerged from what could be termed an "epidemic" phase of JD. In herds or flocks in which clinical cases are seen, the annual incidence of cases per herd is generally very low (dairy 1 case per 200 cows, deer 4 per 200 and sheep less than 2 per 200), but in some exceptional cases 15% (30 per 200 head, or even more) of a herd or flock have been affected.

Concerning the efficacy of test-and-management programmes all the experts consulted agreed that eradication of MAP infection from cattle and deer herds is not practicable. However, there were different opinions concerning their impact and cost-effectiveness. There are "clinical" reports of successful outcomes, and some targeted interventions appear to have been very successful. For example, the detection of "pre-clinical" cases via milk tests in dairy cattle and serology in deer.

The general history of the international use of vaccines to control JD is described.

JD vaccines appear to have been first used, on a small scale, in NZ in the 1970's. In 1987 the French vaccine Neoparasec™ was licensed in New Zealand for use in cattle, sheep and goats. This was a live vaccine and although it was reputedly effective, it resulted in considerable tissue damage at the inoculation site. It was withdrawn from the market in 2004.

Currently there are two JD vaccines registered in NZ; Gudair™ for sheep and Silirum™ for cattle and deer. The use of Silirum™ is restricted to finishing deer destined for slaughter. Trials of Gudair™ have been conducted in merino sheep in Australia; JD mortality was reduced by 90% and faecal shedding was similarly considerably reduced. In NZ Silirum™ has been trialled in cattle and deer for shorter periods; with statistically significant evidence of a reduced risk of lesion development.

Silirum™ vaccination is not without some problems in deer and cattle. First, operator safety associated with self-inoculation, and second, interference with diagnostic tests used in tuberculosis control and in the current JD test-and-management programmes.

Concerning tuberculosis the most serious possible outcome is a reduced (by 50% to 70%) ability to identify infected animals. Concerning JD, the current vaccines result in prolonged high antibody which would interfere with the very useful technique of eliminating "dangerous" animals (i.e. currently (or likely to be) shedding large numbers of organisms).

The managers of the national tuberculosis control programme (i.e. OSPRI) consider that from a technical perspective a limited number of JD vaccinated herds (with some expected diagnostic "complications") could now be safely handled. Vaccinated animals would have to be permanently identified. In some locations, herds might be subject to special testing policies, for example no serial testing. There would also need to be discussion on any additional costs that might arise from such herds.

In the literature covering the use of Gudair™ and Silirum™ there are no statements of concern about animal welfare. "Tissue reaction" occurs, but, it seems, not to a degree that was unacceptable from an animal welfare perspective. Despite this a small number of the experts consulted considered that there is still an unacceptable welfare issue associated with the use of these MAP oil-adjuvanted vaccines.

Compared to Neoparasec™, Silirum™ and Guadair™ result in very much smaller inoculation site lesions. After 6 to 12 months, only minor problems have been reported by slaughter-house personnel. Because of this a non-invasive inspection procedure for sheep JD vaccinates has been introduced in NZ. The Ministry for Primary Industries intends to do likewise for cattle and deer. Despite this, a third of sheep processors still either refuse or are reluctant to accept JD vaccinates. Feedback from meat processors indicates there is confusion about the inspection requirements.

An in depth investigation of the economics of JD vaccination in sheep in NZ has been conducted. The "break-even point" was 1% mortality in ewes. There is conflicting data on the economics of vaccination in dairy herds. However, vaccination in heavily infected dairy herds in the Netherlands was reported as being both very effective and high highly profitable, but it should be noted that this was in an environment without the complication of tuberculosis infection as seen in NZ.

An overview of future JD vaccines is presented. Specialists in this area are optimistic that new vaccines will be developed that will be more efficacious than the current ones, will not interfere with tests for tuberculosis and will not cause tissue reactions. Examples of sub-unit vaccines are given; all are at an advanced stage of development.

My conclusions are as follows:

- The management of JD is very challenging as outcomes are affected by many factors and may not come to the fore for many years. From an operational perspective, this supports the continuing programme of developing a cadre of well-informed advisors who can analyse the situation existing in a herd or on a farm and develop appropriate short to long term control measures.
- It appears that the deer industry has quite recently moved out of what could be termed an "epidemic phase" of JD. Some herd owners and their animal health advisors faced very difficult situations and one can understand the frustration of being denied access to vaccines for use in capital stock.
- Looking at the results of the trials of Gudair™ and Silirum™, the performance is consistent with that seen with vaccines of this type: "cost-effective with respect to reducing production losses caused by MAP infection, but not totally protecting against infection nor the establishment of all shedding".
- The issue of "uncertainty of an outcome" needs to be considered when comparing test-and-management (i.e. without vaccination) and vaccination. In my opinion vaccination is superior, but there is a lack of solid data for the various alternatives.
- The animal welfare issue arising from the tissue damage caused by these MAP oil-adjuvanted vaccines is somewhat unresolved. Those involved experimentally and operationally have not recorded their concern, but some of the experts consulted considered this is not acceptable.

- I recommend that the current restriction that Silirum™ can only be used in "finishing deer destined for slaughter" should be removed and that vaccination of capital stock be permitted. In the rare cases of "epidemic" JD that might occur nowadays in either cattle or deer, the option of using this tool should be considered, especially for financial reasons. A combination of vaccination and test-and-management might be the best option.
- Silirum™ vaccination of dairy and deer herds would need to be undertaken cognisant of the attendant risks to JD management and tuberculosis eradication. I think it prudent that prior to any herd being vaccinated the risks are explained to the herd owner, and a written agreement to proceed signed with whoever is advocating this action.
- Although the current vaccines, used as directed, do not markedly affect carcase quality, there is a "hang-over" among processors from the earlier use of Neoparasec™. There is also confusion about the current inspection requirements for JD vaccinated stock.
- At this time the only useful National Animal Identification & Tracing (NAIT) function would be providing a more efficient method of alerting slaughter house management that cattle and deer have been vaccinated.
- Given the diverse opinions about the impact and cost-effectiveness of the test-and-management control strategies for dairy cattle and deer, careful thought should be given to establishing an ongoing programme of assessment and monitoring. The major assumptions that the control strategies are based on should be tested.
- It may well be that a major milestone in the development of more effective JD vaccines has been reached. There are currently a number of independent groups (e.g. in Denmark, United Kingdom, the Netherlands and NZ) working on prototypes that appear very promising, both from an efficacy and absence of undesirable side-effects for cattle and deer. However, development of a new product for field use will take a long time, possibly as much as 8 to 10 years, and would be expensive.
- Given the complexity of the epidemiology of MAP infection, it would advantageous to trial any new vaccines in NZ. A number of features, but especially the shorter pre-clinical period, makes trials in young deer an attractive option; industry should consider supporting this.
- A successful vaccine will probably require both an effective prophylactic and an effective therapeutic effect. The latter has not received adequate attention and should be a research priority.

# 3 Introduction

This document describes the outcome of an assessment of vaccination in the control of Johne's disease (JD) in New Zealand (NZ). The purpose is to assist the livestock industries establish a position on vaccination, having regard both to its effectiveness and to any untoward impacts on both animals and products.

Currently, in New Zealand, Johne's disease vaccines are not used in cattle, and are used only in a restricted manner in deer, primarily because of the potential interference with tests used to identify animals infected with bovine tuberculosis (*Mycobacterium bovis*). A vaccine is used in sheep to a limited degree, but there are a number of animal welfare, product inspection and product quality issues that are of concern.

The review was commissioned by the "Johne's disease Research Consortium" (JDRC) of NZ (see Appendix 1).

JD is a sub-acute to chronic wasting disease of ruminants, arising from destruction of sections of the bowel as a result of a granulomatous enteritis. This arises from a local invasion of the organism *Mycobacterium avium* subspecies *paratuberculosis* (MAP). In NZ, paratuberculosis, as it is also called, is seen in sheep, cattle and deer. MAP infection can be widespread in flocks and herds, but usually only a small number of animals progress through to "wasting". For most livestock owners JD has a minimal effect on productivity and it is not seen as a problem economically. However, with all three species there are a small number of farms where the disease is severe and there are significant losses; in these circumstances some sort of intervention to improve the situation is often sought.

The Terms of Reference of this project required that the industry stakeholders, technical managers of the NZ cattle and deer tuberculosis control programme and of the national livestock tracing programme (OSPRI), the current distributor of JD vaccines (Zoetis) and relevant groups within the Ministry for Primary Industries (MPI) should be consulted. In addition, it was requested that the views of a range of research and operational groups should be included in the report.

It is important to note that this is not a traditional review that one might undertake for the purpose of publishing in a scientific journal. In addition to material published in the peer reviewed scientific literature, it contains the views of those interviewed, including some speculation. I have also quoted from sources such as conference and workshop proceedings and other non-peer reviewed articles.

Most of the interviews were conducted face-to-face during December 2014. A number of telephone interviews were conducted during January 2015. All but two interviews (due to the noisy environment) were recorded and reviewed shortly after.

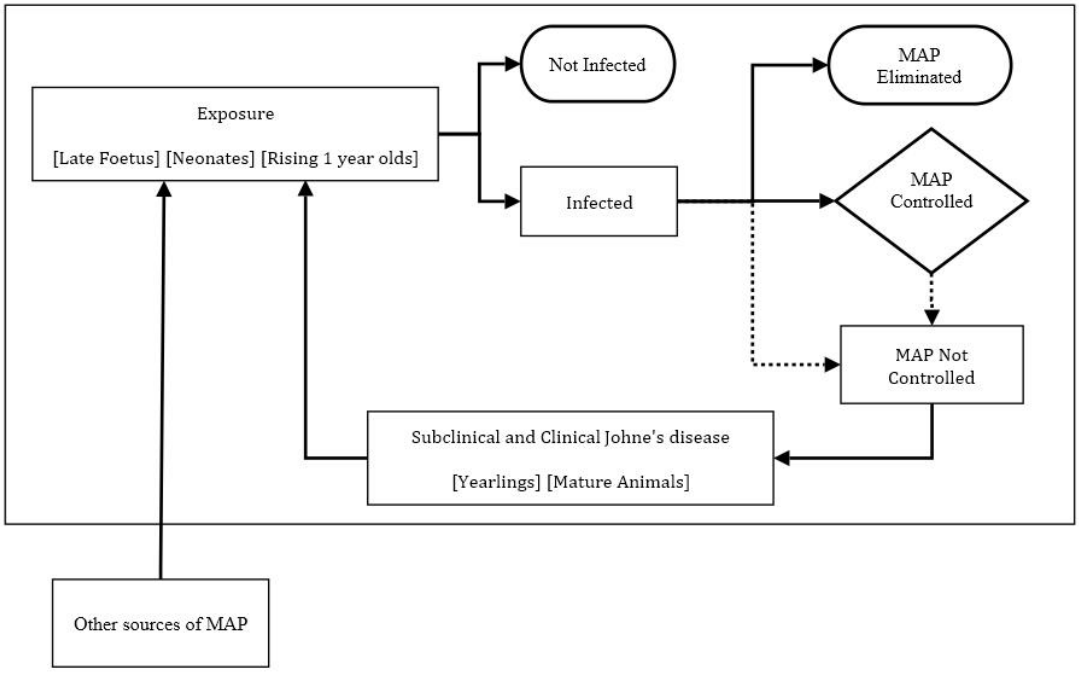
# 4 Johne's disease: pathogenesis, immunology & epidemiology

There are many publications that contain full descriptions of the pathogenesis, immunology and epidemiology of JD. The book "Paratuberculosis" which was published in 2010 is a collection of 30 papers by internationally recognised experts[1]. Shorter but containing the key elements are the workbooks developed by Solis Norton (2009) and Jamie Hunnam (2014) for veterinary practitioner training [2, 3]. Lying between these extremes is the widely used textbook "Veterinary Medicine"[4].

To establish the context in which vaccination might or might not be considered, a brief overview is presented in this section.

MAP is maintained within cattle and deer herds and in sheep and goat flocks via the transfer of infection from older animals to the incoming birth cohort. The main route of transmission is faecal-oral, but intra-uterine transmission and infection via milk also occurs. Contaminated colostrum from clinically affected cows may be a key contributor. Neonates are the most susceptible; over the 12 to 18 months resistance to infection gradually ensues. This process is illustrated diagrammatically in Figure 1, with the herd/flock dynamics shown within the border of the rectangle. Parallels can be drawn to some other infectious agents, such as the maintenance in cattle herds of *Leptospira hardjo* (via organisms shed in urine) and *Brucella abortus* (via uterine discharges and milk). However, as MAP can survive in the environment for prolonged periods (in contrast to *L.hardjo* and *B. abortus*), arguably of much greater significance in the maintenance of infection is indirect exposure from outside the herd or flock.

Figure 1 A schematic representation showing the MAP status of animals and the pathways of infection. Animals with the herd or flock are inside the rectangle




As is noted in the Introduction, in most herds and flocks clinical disease (i.e. chronic wasting with or without diarrhoea) is very uncommon. In most animals infection is either eliminated or effectively

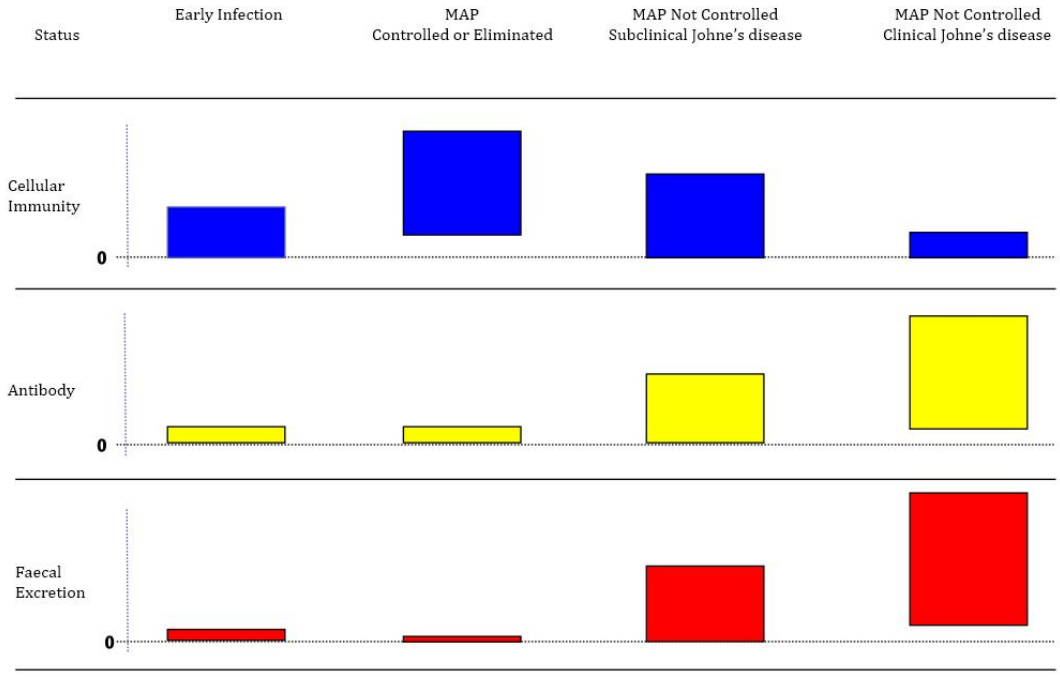
controlled. In some, MAP is not controlled and the result is a progressive granulomatous lesion which destroys the integrity of sections of the bowel. Subclinical or clinical JD is the outcome

A notable aspect is that this "inability to control of MAP" is seen in most cases after many years. However, in some instances, for example deer, it has been seen much earlier (10 to 12 months).

That JD control should be viewed at the level of the herd or flock and not of individual animals or even groups of animals was emphasized by many of those interviewed. Over time there will be marked changes, especially following the initial introduction of MAP [5-7] and ideally there should be repeated assessments of the status of a herd or flock. However, the cost of such surveillance might be prohibitive.

The ability of an animal to control MAP infection is associated with strong specific[a] cellular immunity. Alternatively, the development of the disease is generally associated with high antibody levels. As one might expect the level of shedding of MAP in faeces is also associated the development of gut lesions. Early in infection both cellular and humoral peripheral blood assays are generally negative, but this does rule out that there are local immune processes[8]. In Figure 2 these associations are illustrated. There is considerable variability and this is also shown schematically.

Figure 2 A schematic representations of the immune status and degree of faecal MAP excretion for each infection status




The interaction between the host and MAP at the cellular level is complex. However, there was general agreement between the experts working in this area that the inability of macrophages to "deal" with MAP is at the centre [6-9]. Paul Coussens *et al.* in their review of this topic[1][b] have some pertinent comments, as follows.

[a] i.e. directed at MAP
[b] Chapter 11

*"…it is apparent that infected cattle initially develop an early and effective pro-inflammatory immune response to MAP. However, this response typically declines in cattle that progress to clinical disease, favouring [one] which leads to antibody production but does not control infection. Why this reduction in pro-inflammatory response occurs and the molecular mechanism behind it are critical questions that must be addressed if we are to develop effective vaccines and better diagnostics to control JD. Thus, two of the most pressing questions in MAP patho-biology are: (i) how does this organism survive in macrophages cells; and (ii) why does the immune response against MAP switch from an appropriate [one] to an ineffective [one]."*

It has been shown that the dynamics of MAP infection in herds and flocks is affected by many factors. These are listed in Table 1, under the headings "host"," agent" and "environment", the traditional epidemiological division of these so-called disease determinates.

Table 1 Primary and secondary determinates that are known to influence the occurrence and nature of Johne's disease in a herd or flock

| Host | | Agent | | Environment | |
|---|---|---|---|---|---|
| Genome | Species | Type | Sheep | Climate | MAP Survival |
| | Susceptibility / Resistance | | Cattle | Management practices | MAP Survival Exposure |
| Age | Susceptibility / Resistance | Exposure dose | | Other hosts Livestock Wildlife | Exposure |
| Physiological Status | Nutrition / Energy balance | Virulence factors | Not established | | |
| | Other diseases | | | Contaminated water sources | Alternative exposure |
| Vaccination Status | Pre-exposure | | | Soil pH | MAP Survival |
| | Post-Infection | | | | |

The subject of this review is vaccination and this is described in detail below; it is of note that the risk of developing clinical disease may be reduced after both pre-exposure and post-infection vaccination [6, 8, 9]. The former is sometimes called "prophylactic vaccination" and the latter "therapeutic vaccination". Interestingly, with tuberculosis infection, post infection exposure to mycobacterial antigens, such as tuberculin, can exacerbate the disease[9].

Current control strategies used in deer and cattle, applied over varying periods, utilise these determinates[2, 3].

The magnitude of exposure of young animals to MAP is a risk factor, in terms of both the incidence of infection and the probability of progressing to subclinical and clinical JD. For this reason it is recommended that clinical cases are culled as quickly as possible. Further, an assay of systemic antibody (i.e. a serological or a milk test), with or without faecal MAP counts, may be used to identify potentially "dangerous animals"[6, 10].

It might be asked how important the removal of clinical and subclinical animals is. In the publication "Paratuberculosis" [1] Marie-Eve Fecteau and Robert Whitlock[c] present data concerning the infective dose for young calves (i.e. $10^3$ to $10^4$ organisms) and the number of organisms shed by adult cattle.

[c] Chapter 14

Assuming a daily faecal output of 12 kg [11] the potential "calf doses" per day and the amount of faeces containing a single dose can be calculated (Table 2). Clearly, this suggests that the top rated shedders, even though likely to be few in number, could have a huge impact on JD incidence in the future. This situation has been confirmed in the field in NZ[6].

Table 2 Shedding of MAP in cattle, an estimate of the number of calf doses per day and amount of faeces containing one calf dose

| Category | Calf doses / day | | Weight faeces containing one calf dose (g) | |
|---|---|---|---|---|
| | mean | $5^{th}$ & $95^{th}$ percentile | Mean | $5^{th}$ & $95^{th}$ percentile |
| Low | 5 | 1 to 9 | 1500 | 250 to 4,500 |
| Medium | 30 | 10 to 50 | 225 | 50 to 550 |
| High | 5,000 | 550 to 5,500,00 | 2.9 | 0.20 to 10 |
| "Super" | 5,000,000 | 450,000 to 9,000,000 | $4x10^{-3}$ | $2x10^{-4}$ to $10^{-2}$ |

Finally, there is evidence there are other MAP mammalian hosts [1][d] including wildlife. Further, that MAP may exist for long periods in the environment; e.g. MAP contamination of water supplies for a Welsh city [12]. It would appear, therefore, that there is still much to understand about the ecology of MAP, and this should be factored into disease control goals. In particular, the question "is long term eradication from a herd possible"?

# 5 Some important issues

## 5.1 Preclinical, subclinical or clinical Johne's disease versus MAP infection[e]

The goal of the review is to "assess the use of vaccination as a control tool for JD". During the interviews there was debate as to how this would be measured.

Although there is general agreement about the pathogenesis of MAP infection in ruminants there are differences in the way the outcome (i.e. the observed state of animals) is classified. To a large degree this appears to have arisen from attempts to link the underlying pathology and effects on the current or future productivity. But it has the potential to confuse. For example, it is generally accepted that a subclinical infection is nearly or completely asymptomatic (no signs or symptoms). However, in various publications there are statements that in both deer and dairy cattle during the subclinical phases there can be "significant" decreases in production. Conversely, a situation of a seemingly heathy animal with the history of high productivity having medium to high MAP antibody is, apparently, not uncommon. The term "preclinical"[13] rather than subclinical has been applied to such animals, as examples of some of them collapsing into clinical JD after a stressful event, such as parturition, were also described to me[6, 10].

In their review of the prevalence of JD in NZ, Bryan and Cresswell [14] addressed these issues, along with the problem of using diagnostic tests which, depending on the disease state (which is dynamic), may be highly inaccurate. They conclude that:

[d] see Chapters 17 and 18

[e] i.e. an animal harbouring the organism, with or without faecal excretion

*"The goal of any control and management programme should ultimately be to reduce the risk of MAP in the food chain and enhance consumer confidence in the product".*

That MAP infection (or, possibly, MAP infection with faecal shedding), because of the association of MAP with Crohn's disease in humans, should be the focus was also put strongly by some of those interviewed.

In his review of "Ruminant Aspects of Paratuberculosis Vaccination[f]" in Paratuberculosis[1] Geoffrey de Lisle suggests that a MAP vaccine should, at least, "prevent clinical disease in uninfected animals". Ideally it would also "prevent clinical disease in already infected animals". Better it would also "prevent the establishment of infection", which would eventually lead to eradication of MAP in the herd or flock.

Concerning the top two outcomes, his rationale is that while subclinical paratuberculosis can result in reduced productivity, these losses are minor compared with those accruing from clinical disease. With reference to MAP density in faeces over the course of paratuberculosis (Table 2) one could also argue that by focusing on clinical disease the issue of product contamination is also largely being addressed.

A long time worker in the field of JD, agrees there is confusion in the literature over the use of terms relating to infection and clinical disease. The important point is that the terms are defined [8].

## 5.2 Is this intervention having an effect?

Among the experts there were many different opinions concerning whether or not various interventions were, in fact, resulting in the control of paratuberculosis.

In areas like disease control in livestock, establishing cause-effect relationships can be problematic as it is often not practicable, usually because of costs, to use a classical experimental designs based on randomisation, replication and reducing/balancing noise from other factors. Instead one may be faced with simply observing the effects of field interventions and programmes.

Much has been written about this issue, as epidemiology relies primarily on observational studies; e.g. Dohoo *et al.* 2003[15]. Their position is that epidemiology is a pragmatic discipline and the key for disease prevention is to identify the causal factors that can be manipulated regardless of the level of organisation at which they act.

Dohoo *et al.* support the views of Karl Popper who suggests that we should gather data to test rigorously whether a hypothesis (e.g. a putative causal factor) is true; *"Investigations which start from a clear hypothesis are inevitably more focussed and more likely to result in valid conclusions than those on unfocused recording of observations".* Some of those interviewed made similar points.

There is no easy solution to this, and without doubt there will be continuing different opinions on the merits of various interventions and programmes.

[f] Chapter 29

# 6 Johne's disease in New Zealand

Over many years a number of reports have been published concerning MAP infection in NZ. Unfortunately, until recently the data that was collected, either passively or actively, cannot be used to estimate national figures; the datasets are either incomplete or contain bias's. However, investigations conducted over the last decade, many supported by JDRC, have generally been well designed.

The information presented in the following sections is derived from a JDRC commissioned review of JD in livestock[14] and from the information and opinions of the experts interviewed or from other publications as indicated.

## 6.1 Dairy Cattle

More than 50% of herds are infected, possibly as high or higher than 70%[10].

Livestock Improvement Corporation (LIC) farmer returns suggests that in 8% to9% of total herds JD clinical cases occurred, with a median of 2 JD culls per herd; i.e. 0.5% (1 case per 200 cows) of the herd or 0.0055% (2,2024/3.66 million) of the total dairy cow population.[16]. Note: The average was around 4 per herd, indicating a skewed distribution with some high outliers. Cases of some herds having many more JD clinical cases (50 to 100) have apparently occurred recently, but I have not been able to confirm this.

The greatest number of cows culled were 5 or 6 years old (32% of all JD culls) with 60% of JD culls aged between 4 and 7 years. A negligible number of JD culls were recorded amongst heifers under 2 years old.

JD risks were significantly greater in the South compared to the North Island.

Jersey breed was associated with significantly higher JD culling than Friesian, although it remains unclear if this is due to differences in susceptibility.

## 6.2 Beef Cattle

There is recent evidence that between 30% and 40% of beef herds are infected with from 2% to 5% having clinical cases annually [14, 17].

When beef cattle, sheep and deer are grazed together, statistically significant differences in the incidence of clinical cases have been observed as follows[18]:

- Beef cattle and sheep co-grazed, the infection risk increased 3 to 4 times in each species.
- Co-grazing of beef cattle and deer increased by 3 times the risk of infection on deer.
- Co-grazing beef cattle with sheep, or beef cattle with deer, also was associated with increased clinical incidence in these species.
- Conversely, the co-grazing of sheep and deer was associated with a lower clinical disease incidence in both species.

## 6.3 Deer

Reports published over the last 5 years suggest around 60% of deer herds are currently infected.

Many of those interviewed commented that the nature of clinical disease in deer herds has changed considerably over recent years. For example, in 1998 MacKintosh and de Lisle [19] reported as follows:

*"Sporadic cases of JD have occurred in all ages and classes of deer. However, recently outbreaks in young deer have become more common. Initially the farmer is likely to notice that there are 5-10 % of a mob of deer which fail to thrive, have low growth rates or are in poor condition. In spring they may fail to lose their winter coats or have a patchy or "moth- eaten" appearance. They start to scour and develop obvious soiling with green faecal material around the tail, hind quarters and hocks, and they start to lose weight. The disease course can be from days to months but generally it appears that the younger the animal, the quicker the progression to emaciation and death. In outbreaks, the most common age of onset is 8 to 20 months, compared with 2-4 years in cattle and sheep. Recent outbreaks have had mortality rates of up to 12% in rising yearlings."*

In Bryan's and Cresswell's [14] opinion the best available evidence suggests that 34% of deer herds are affected by clinical JD.

In 2008 Glossop *et al.* [20] published the results of a survey of the owners of deer herds regarding the prevalence of clinical cases. In herds clinically affected during 2005 they reported that the median prevalence in various stock classes was between 0.9% and 2.0%, but in all cases there were very high maximums (Table 3). The number of herds with one or more deer with clinical JD and the within-herd prevalence of clinical JD both increased over the period from 2005 to 2007.

Table 3 The prevalence of clinical JD in deer, an estimate of the median, minimum and maximum[20]

| Stock Class | Clinical JD Prevalence (%) | | |
|---|---|---|---|
| | Median | Minimum | Maximum |
| Weaners | 1.2 | 0.1% | 21.5 |
| Yearling hinds | 2.0 | 0.2 | 20.0 |
| Yearling stags | 2.0 | 0.2 | 13.2 |
| Adult hinds | 0.9 | 0.1 | 20.8 |
| Adult stags | 1.3 | 0.2 | 8.9 |

Nowadays, high incidence outbreaks are rarely reported and, in general, "a steady state" generally prevails. Sudden increases in cases are seen in some herds occasionally, but the situation is far less dynamic than it was [21].

Some consider that the events of the 1980's and 1990's were the result a naïve population being exposed to MAP and, as a result, "resistance to MAP" of farmed deer, via acquired immunity and genetics, has been shifted considerably.

## 6.4 Sheep

Recent studies suggest that around 68% of sheep flocks are infected, with 20% of farmers reporting clinical JD over a 3 year period. Interestingly studies during in the 1980's and 1990's found that clinical cases occurred in 7% of flocks each year.

JDRC has commissioned a study of ewe losses due to JD in the upper South Island. In a recent report[22] the interim data were released, as follows:

Table 4 Estimated ewe mortality (%) due to Johne's disease on farms in the upper South Island

| Breed | Mortality (%) |
|---|---|
| Romney | 0.5 |
| Composite | 0.65 |
| Corriedale | 1.58 |
| Merino | 1.67 |

# 7 Can Johne's disease be controlled without vaccination?

Current JD vaccines result in animals having altered responses to the commonly used tests for tuberculosis infection. As tuberculosis control in cattle and deer is a high priority in most countries, JD vaccination is generally not permitted in these species. JD control has therefore been formulated around other determinates (see Table 1) that can manipulated, over a short, medium or long term.

There is, very clearly, a profound "genetic" influence on the outcome of MAP infection, perhaps contributing as much as 50% of the overall observed variation between animals [6]. However, this is not considered further.

Putting aside the issue of re-infection from extrinsic sources, all the experts consulted agreed that, currently, eradication of MAP infection from cattle and deer herds is not practicable.

As noted above (Section 4.1) there is debate about what the objective of control should be. Assuming that it is simply to reduce and then maintain the prevalence of MAP infection at a low level (and as a consequence reduce the incidence of clinical cases) there were considerable differences in the opinions of the experts concerning the value of interventions in management such as those outlined in NZ for deer[2] and dairy cattle [3]. Some were confident that the NZ programmes had achieved or could achieve this; others considered that, especially in deer, the "biology" of the situation (e.g. a pathogen entering a naïve population and the subsequent events) was main influence; while others considered there was insufficient information to resolve if these programmes were effective.

From a clinical perspective, there are reports of management intervention being effective, both in NZ [23] and overseas [24-27].

Some targeted interventions appear to have been very successful. For example, the detection of "dangerous" cases (i.e. heavy shedders and "pre-clinicals") via milk tests in dairy cattle[10] and serology in deer[6]. In deer this activity has been extensive, with around 250,000 deer from more than 500 farms being tested with the Paralisa® (antibody) assay. Herd owners culled some or all of the test-positive animals and many consider this programme, coupled with changes in management, made a major contribution to reducing the losses from JD in their herds [6].

Finally, computer models of MAP infection in deer [28]and dairy herds[29] suggest that "management intervention" is a necessary component of a JD control strategy. For example, "test & slaughter" is largely ineffective if nothing is done to limit transmission pathways.

The most important issue regarding the effectiveness of control measures is whether or not they are cost effective [8]. However, this is somewhat difficult to assess as both the benefits and costs are

very variable; e.g. the incidence of clinical cases and the parts of the control programme that are adopted. Norton *et al.* (2011) investigated this, via modelling, in dairy herds; they concluded that *"control strategies involving any significant amount of investment were not cost effective in most herds but could be in high prevalence herds" [29].*

In an earlier economic analysis [30] Elizabeth Brett concluded that:

- *The key to controlling the [JD} is to have a range of disease control options available to livestock producers. The level of infection in individual herds/flocks determines whether any control is required, and which option would provide the most appropriate form of disease control.*
- *Ultimately, the control option which best suits individual producers depends on the primary focus of the enterprise. The circumstances of each enterprise need to be considered in determining whether any disease control program is appropriate.*

# 8 Vaccination

The objective of vaccination of an animal or human is to induce a high level of "protective immunity" against a potential pathogen, without harming the individual. To achieve this there has been huge advances in the formulation and application of vaccines. Obviously, vaccines must contain an antigen which will induce the specific immune response, but it has also been shown that other materials, so called adjuvants, also play an important role. Further, it has been shown that efficient and targeted delivery of antigen to appropriate cells is a critical element [9].

## 8.1 Early JD vaccines

In Paratuberculosis[1], Geoffrey de Lisle[g] provides a history of use of vaccines for controlling JD; briefly:

- In the 1920's a vaccine containing live MAP with adjuvants of olive oil, paraffin and pumice powder was produced.
- To date all paratuberculosis vaccines that have been used on a significant scale have contained live or dead MAP in an oil adjuvant.
- There has been very patchy uptake of vaccination for the control of JD, as a result of significant deficiencies in the vaccines. However, in some circumstances, where other controls measured have failed, vaccines have proven to be cost-effective with respect to reducing production losses caused by MAP infection. For example widespread vaccination of sheep in Iceland virtually eliminated clinical JD.
- Extensive use of vaccination was reported to be effective in controlling clinical JD in cattle in France, the Netherlands and the United Kingdom. It was discontinued because of concern about interference with testing for tuberculosis, the failure to prevent infection, and the large tissue reaction at the site of injection.

A live MAP vaccine, with both oil and powdered pumice, was imported in to New Zealand from the MAFF Weybridge Laboratory, United Kingdom in 1973 [31]. It appears that this was in response to

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problems in a specific dairy herd, diagnosed as being due to MAP infection, located in the Manawatu. In 1986 the herd was re-assessed and the report was as follows:

*"Results indicate that a combination of careful management to control JD, a change in the breed of cattle from Jersey to Friesian, the introduction of artificial breeding and vaccination of all replacement calves ……has resulted in the suppression of clinical signs of JD. However, infection of cows with JD has still occurred, nine cases being definitely diagnosed in vaccinates between 1980 and 1983."*

It is difficult to draw conclusions concerning the role that JD vaccination might have had.

In 1987 the French vaccine Neoparasec™ was licensed in New Zealand for use in cattle, sheep and goats. This was a freeze-dried live vaccine[h] with an oil-based adjuvant. I have been unable to find any reports on the efficacy of this vaccine in New Zealand livestock. One of those interviewed remembers that in sheep, post-vaccination mortality due to JD was considerably reduced[32]. However, there are reports of problems in both sheep and cattle.

- In lambs vaccination not only resulted in a tissue reaction at the site but also in the draining lymph node. The reactions were often sufficiently large to require carcases to be extensively trimmed, and occasionally condemned. The authors also warned that lambs were more susceptible to fly strike[33].
- In dairy cattle after 2 years 37% (57/157) of the vaccinates had injection site nodules greater than 10 cm diameter. Forty five percent (45%, 68/152) were test-positive to the standard caudal fold skin test. All vaccinates were test-negative to the comparative cervical skin test[34].

Neoparasec™ was withdrawn from the market in 2004 [35, 36].

## 8.2 Current JD vaccines

### 8.2.1 General

Two JD vaccines are currently licenced for use in NZ; Gudair™ for sheep and Silirum™ for cattle and deer. Both are manufactured by "CZ Veterinaria", Spain and marketed in NZ by the company Zeotis New Zealand Limited.

Although Silirum™ is licenced for use in cattle and deer, the label states that *"Silirum is for use ONLY in finishing deer destined for slaughter"*.

Both vaccines contained inactivated MAP[i], adjuvanted with mineral oil in a multiple emulsion. The composition of both is very similar [37].

The Gudair™ leaflet includes the following:

*"The dose for sheep and goats (greater than 1 month of age) is 1 ml. Further vaccine (booster) doses are not required."*

*"In infected or at-risk flocks vaccination can be carried out on all the flock, including adult animals."*

[h] Weybridge 316F strain
[i] also strain 316F

*"It is recommended that all replacement animals be vaccinated at a young age. When vaccination is commenced at between 1 and 4 months of age, faecal shedding may be prevented for 12 months or longer post-vaccination."*

The Silirum™ leaflet includes the follow"

*"The dose for cattle (from 1 month of age) is 1 ml, and for deer from 3 months of age is 0.5 ml."*

### 8.2.2 How effective are the current JD vaccines?

#### 8.2.2.1 Sheep

The reported results of a 5 year study of Gudair™ vaccination for the control of JD in Australian merino sheep was as follows [38, 39]:

- *The vaccine stimulated cell-mediated and humoral immune responses.*
- *Gudair™ reduced mortalities due to ovine JD (OJD) by 90% and delayed faecal shedding for the first year post-vaccination. Thereafter, the prevalence of shedders among vaccinates was reduced by 90%. The numbers of MAP excreted by the vaccinated groups were also reduced by at least 90% at most sampling times.*
- *However, high levels of excretion by vaccinates occurred on some occasions, and although only 7 of 600 vaccinates died from OJD, all had multibacillary disease. Thus there remains a risk that some vaccinated sheep could transfer the disease.*
- *Small reductions in liveweight gain were found in vaccinated lambs in the first year post vaccination, but there was little effect on condition score or wool production.*
- *Vaccine injection site lesions were detected in almost 50% of sheep 2 months post vaccination, and these persisted for at least 4 years in 20-25% of vaccinates*.

Data from this trial enabled the registration of Gudair™ in 2002 and underpins the pivotal role of vaccination in the current management of JD in sheep in Australia.

In NZ around 100 flocks, mostly either merino or corriedale, have been vaccinated [37]. In some cases the vaccine has been applied intermittently, rather than as recommended, making it difficult to assess the efficacy [40].

The authors of the current JDRC supported study of ewe productivity [22] reported that *"vaccination against OJD has not resulted in lower observed OJD but was associated with lower ewe death rates than farms not using vaccination. But such inference is likely to be biased by farm management as suggested by the differences between farms. For example, farms using OJD vaccine may well have had a greater OJD problem previously"*.

#### 8.2.2.2 Deer

There has been one experimental[41] and one field [42] trial in NZ of the efficacy of Silirum™ vaccination for JD in young deer.

In the experimental study, 6 to 8 week old fawns were vaccinated and then challenged 10 weeks later. They were killed after 59 weeks and subject to a full pathological examination. No clinical cases were observed in either the vaccinated or control (unvaccinated) groups; but, at slaughter, more gross lesions in intestinal lymph nodes were observed in control (20%) than vaccinated animals (0%; $P<0.05$).

This latter group also had less severe histopathological lesions in samples of intestines and lymph nodes compared with the control group (P<0.05).

In the field study, on six farms vaccination was carried out in four-month-old deer. The vaccinates (and controls) were slaughtered between 11 and 20 months of age. Clinical disease was confirmed in 18 controls and seven vaccinates, representing a vaccine efficacy estimate of 60 per cent (95% CI 3 per cent to 83 per cent, P=0.04). Forty-seven percent (95% CI 38 per cent to 56 per cent) of faecal samples from vaccinates and 55 per cent (95% CI 46 per cent to 64 per cent) from controls were MAP positive (P=0.5). Average daily live weight gain did not differ between the groups. At slaughter, 1.4 per cent of vaccinates and 4.5 per cent of controls had gut pathology.

#### 8.2.2.3 Cattle

In Victoria, Australia, a long term investigation of the results of Silirum™ vaccination in two dairy herds chronically infected with MAP was started in 2005. The study, which will end in 2016, is co-sponsored by Pfizer Animal Health (now Zoetis) and the Victorian Department of Primary Industries.

Zeotis NZ Limited has kindly given me access to a 2011 interim progress report. Some key outcomes are as follows:

- *In all age groups vaccinated in the first year of this study, including new-born calves vaccinated between 3 and 6 weeks of age, administration of a single dose of Silirum™ Vaccine induced a cell-mediated immune response, as measured by the mean gamma Interferon response to both avian tuberculin and Johnin antigens. Silirum™ Vaccine also induced a humoral (antibody-mediated) immune response in all age groups except new-born calves.*
- *All the clinical JD cases have been from cohorts aged 12 months or more at the start of the study; i.e. likely to have been infected. The incidence in the vaccinated group is less than the non-vaccinated group, but at this stage statistical significance has not been met (P = 0.12).*
- *No animal enrolled as a new-borns calf, either in 2005 or subsequent years, has been culled due to clinical JD at this stage of the study.*
- *With the exception of those vaccinated as adults, MAP faecal excretion was lower among vaccinates. Using faecal culture positive on at least two occasions as a standard, the percentage reduction in vaccinates compared to the controls was 77% for 2-year-old heifers, 61% for yearling heifers and 67% for new-born calves (2005-2007).*
- *Vaccination resulted in some animals reacting to the caudal fold skin test for tuberculosis. However, the follow-up comparative cervical tests were negative (also see below)*

The authors concluded that the 5-year interim results of this field efficacy study support the use of a single dose of Silirum™ Vaccine for the active immunisation of cattle aged 3 weeks or over against MAP as an aid in the control of Bovine Johne's disease.

## 8.3 What are the problems with the current vaccines?

### 8.3.1 Operator Health & Safety

With Gudair™ and Silirum™ there are warnings on the product leaflets that the vaccines are "*reactive*" substances and that a safety vaccinator that has a protective shroud should be used.

There is also advice that medical attention should be sought if the product comes into contact with the body (e.g. self-injection, needle scratch). Further, it states that *"PROMPT surgical attention may be required if [the vaccine] enters the body".*

### 8.3.2 Animal Welfare

This is a difficult area as *"The boundary between acceptable and unacceptable treatment of animals – whether farmed, companion, working or wild – is continually evolving"* [43]. Further, with an intervention such as vaccination one needs to balance any untoward side-effects with the aim of reducing the risk of disease.

The reports of the pathology that resulted from Neoparasec™ indicate that many had misgivings about this product, and, in particular, that the suppurating lesions could lead to serious other problems, such as fly-strike [33].

I have screened the various papers and reports of the use of Gudin™ and Silirum™ and have not found statements of concern about animal welfare. Certainly, there was "tissue damage" (see Section 7.3.4), but, it appears, not to a degree that was unacceptable from an animal welfare perspective. Despite this a small number of the experts consulted considered that there is still an unacceptable welfare issue.

### 8.3.3 Tuberculosis (*M.bovis*) control diagnostics

Being members of the same genus, it is not surprising that MAP and *Mycobacteria bovis* have antigens that will cross-react. This can result in the accuracy of tests being reduced.

A number of studies of this issue have been undertaken, as follows:

#### 8.3.3.1 Effects on test accuracy

##### 8.3.3.1.1 Silirum™ in cattle

Fifty 6 month old Friesian bulls were randomly allocated into treatment and controls groups (n=40 and n=10, respectively). After vaccination with Silirum™ they were skin tested (caudal fold, standard interpretation, I presume) four times over ~80 weeks. Caudal fold test-positive animals were serially tested with the Bovigam™ assay and the "Special Antigen" assay. The results of skin testing are shown in Table 5 and Figure 3. All the follow-up Bovigam™ tests were negative, as were all but one of the Special Antigen tests. The control animals remained negative throughout the study.

Table 5. Percent of calves caudal fold test-positive in a Silirum™ vaccinated and a control (non-vaccinated) groups over 77 weeks.

| Weeks post-vaccination | 0 | 11 | 20 | 41 | 77 |
|---|---|---|---|---|---|
| Vaccinated, % positive | 0 | 53 | 35 | 20 | 13 |
| Control, % positive | 0 | 0 | 0 | 0 | 0 |

Serum samples were also submitted and tested for MAP antibody (ELISA, Parachek®). In Figure 4 the percent positive over 40 weeks is shown. All were negative prior to vaccination. Post-vaccination 80% to 85% were positive.

Figure 3. Percent of calves caudal fold test-positive in a Silirum™ vaccinated group over 77 weeks

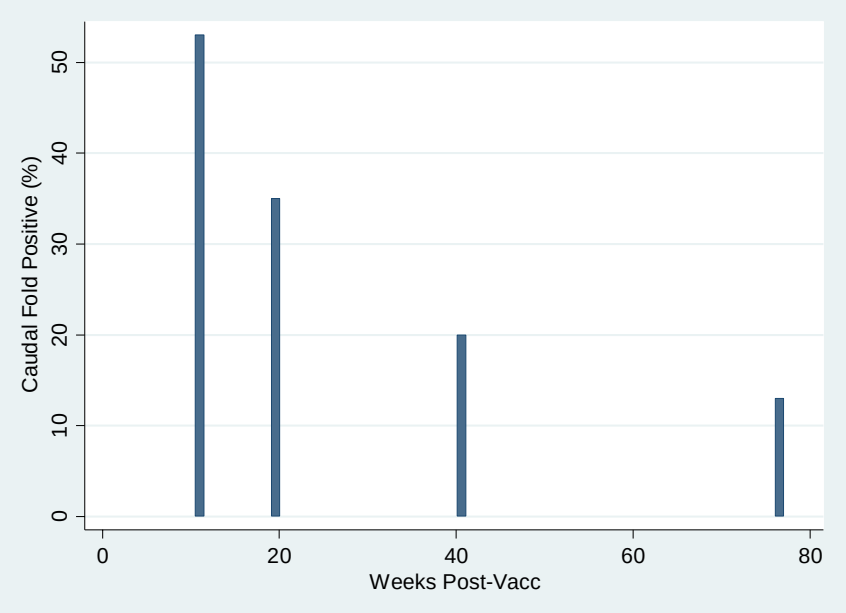
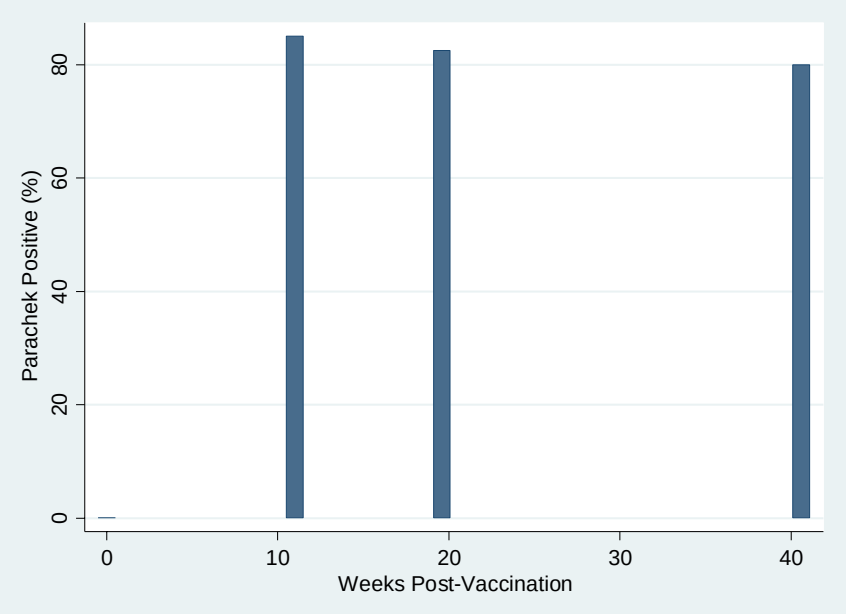



Figure 4. Percent of calves ELISA test-positive-positive in a Silirum™ vaccinated group over 41 weeks week




#### 8.3.3.1.2 Gudair™ in deer[41][j]

In this trial 30 6 to 8 week old red deer fawns were vaccinated. Ten weeks later all the animals in the trial (including the controls) were challenged with MAP. The mid-cervical skin test (MCT) was conducted at 23 weeks, followed by comparative cervical tests (CCT) at 37 and 57 weeks. An antibody assay, Paralisa®, was also performed at various points. A *M. bovis* antibody test was also conducted.

[j] There is no explanation by Gudair™ is used instead of Silirum™

In over 90% of all the animals (including *the* controls) the MCT was positive. With the exception of 1 or 2 the follow-up CCT's were negative. However, a much larger proportion of the Gudair™ vaccinated animals exhibited antibody responses, to both the MAP and the *M. bovis* antigens.

#### 8.3.3.1.3 Silirum™ in deer[44]

This trial took place in commercial herds which were known to be infected with MAP. Around twice the proportion of vaccinates failed the MCT (44% (79/180) and 23% (42/181) respectively). Two of the vaccinates also failed the follow-up CCT.

The author concluded that *"infection with MAP and vaccination increased the chances of MCT [false-positives] in deer herds. [The current follow-up tests] are effective tools to address [this]. However, where use of these tests is not permitted [for example in herds where there is a risk of tuberculosis] there is likely [to be some confusion].*

#### 8.3.3.1.4 Silirum™ in deer challenged with *M.bovis* [45]

The interesting aspect of this trial is that it demonstrates a potential for an increase in false-negatives (i.e. reduced test sensitivity) in a tuberculosis infected herd. In the above cases, the problem has been presented as false-positives which can be resolved using one of the serial supplementary tests.

In this trial the animals were vaccinated and then challenged with *M. bovis* after 20 weeks. All the vaccinates were shown to be infected at the end of the trial (week 47). When they were tested (MCT) during week 32 all were positive. Likewise when tested during week 44, all had a significant skin reaction at the "bovine" site. However, when the CCT criteria was applied to this (i.e. bovine ≥ avium), the outcome was only 57% positive. After 72 hours this dropped to 36% positive.

A similar outcome in cattle, using BCG vaccination, has also been reported [46].

### 8.3.3.2 The National Bovine Tuberculosis Pest Management Strategy

After two decades or more of intensive work, the prevalence of bovine tuberculosis in cattle and deer has been reduced considerably. At the end of the 2013/2014 year there were only 69 cattle and 3 infected deer herds; over the prior 12 months only 166 tuberculous cattle and no tuberculous deer were identified at slaughter.

From a technical perspective a limited number of JD vaccinated herds (with some expected diagnostic "complications") could be handled. Vaccinated animals would have to be permanently identified. There would also need to be discussion on any additional costs that might arise from such herds [47].

There are some policies that would impinge on JD vaccinated herds; as follows:

- With all primary tests the sensitivity should not be compromised; i.e. a comparative cervical test could not be used for deer and standard interpretation would be applicable with the caudal fold test in cattle.
- The special antigen test can only be used in low risk herds; i.e. herd status C5 or more and in vector free areas.
- In some areas special policies are sometimes applied. For example in some herds on the West Coast serial retesting might not be permitted.

One the other hand, OSPRI is endeavouring to enhance field operations via new technology. For example more accurate diagnostic tests that would not cross react with MAP.

Currently it is a legal requirement for JD vaccinated cattle and deer to be earmarked; i.e. an earmark in either ear as a rimcut in a forebit or backbit position depending on which position leaves the clearest possible identifying mark. The mark should not be an earmark placed as a punch hole, rip or quarter.

The recently established "National Animal Identification & Tracing" (NAIT) system, seemingly offers an alternative more efficient identification method. Further, to assist field staff, when deciding the fate of animals, additional information, such as the prior testing results, could be presented at testing.

OSPRI staff explained that the primary purpose of NAIT is to determine at any given time where an animal, currently limited to cattle and deer, is located and the farms on which the animal has been on. Associated with each animal there are treatment fields with, if needed, a withholding period. An animal could therefore be registered as having been vaccinated. However, NAIT and the tuberculosis "Disease Management System" (DMS) are separate systems and currently there is no easy way of linking the data [48].

At this time the only useful NAIT function would be providing a more efficient method of alerting slaughter house management that cattle and deer have been vaccinated (see below).

### 8.3.4 Tissue reactions to the current vaccines

#### 8.3.4.1 Sheep

Clough and Booth presented a report to the NZ meat industry in 2013 on lesions resulting from Gudair™ [36].

Data from an Australian study of 3,199 cull ewes and 122 lambs was included. The prevalence of injection site lesions was high (66%) in lambs slaughtered within 6 months of vaccination, but was low (18%) in "mutton sheep" vaccinated 12 months or more before. The size of the lesions is shown in Table 6.

Table 6 Injection site lesions and enlargement of the prescapula lymph node following Gudair™ vaccination in lambs within 6 months and in mutton sheep 12 months or more.

| Class | Number | Lesion Diameter (mm) | | | Total with lesions | % with lesions | No. (%) with enlarged prescap lymph nodes |
|---|---|---|---|---|---|---|---|
| | | <10 | 10 to 25 | >25 | | | |
| Mutton | 3199 | 177 | 201 | 207 | 585 | 18 | 93 (3%) |
| Lamb | 122 | 38 | 25 | 16 | 79 | 65 | 0 |

The authors said that *"The value of the trim removed was insignificant, the labour cost of its removal was nil and no carcase was downgraded to a lower value grade."*

Some data from NZ was also included in this report; lesions observed in ewes following vaccination when lambs with Gudair™ (Table 7). The lesions were graded with 1 = minor with few scattered gritty bits, 2 = moderate obvious lesion with some tracking and 3=severe with tracking into scapula regions and prescapular lymph nodes affected.

Table 7. Injection site lesions and enlargement of the prescapula lymph node following Gudair™ vaccination. The lesions were graded with 1 = minor with few scattered gritty bits, 2 = moderate obvious lesion with some tracking and 3=severe with tracking into scapula regions and prescapular lymph nodes affected.

| Total Vaccinated | Total with Lesions | Prevalence of Lesions (%) | Prevalence of Lesions by Score (%) | | |
|---|---|---|---|---|---|
| | | | 1 | 2 | 3 |
| 470 | 66 | 14.0 | 12.8 | 1.3 | 0 |

#### 8.3.4.2 Deer

In the trial of Silirum™ described above, approximately eight months after vaccination a group was slaughtered and the vaccination sites of 486 were examined. This revealed 181 (38 per cent) with palpable subcutaneous lesions. The reaction size ranged from 5 to 39 mm (mean 14.4, sd 5.93). Most were firm circumscribed lesions, although two discharging sinuses were found. Meat inspection staff reported that although vaccination site reactions were evident, these were generally circumscribed and were removed with the hide or were easily trimmed. No difficulties were experienced with access to export markets, nor was there any apparent loss of carcase value of vaccinated deer due to injection site lesions.

#### 8.3.4.3 Cattle

In the trial described above, in which 6 month old calves were vaccinated with Silirum™, the animals were slaughtered 18 months after they had been vaccinated. A sample (n = 18) was examined for inoculation site lesions. Twelve (67%) had no visible lesion or the lesion was very small (2mm). One had a 20mm by 20 mm lesion. Four had lesions up to 30 mm across. Four had lesions up to 60 mm and one had a 5 mm by 70 mm lesion (Table 8 ).

Table 8 Dimensions of inoculation site lesions found in a 18 animal sample

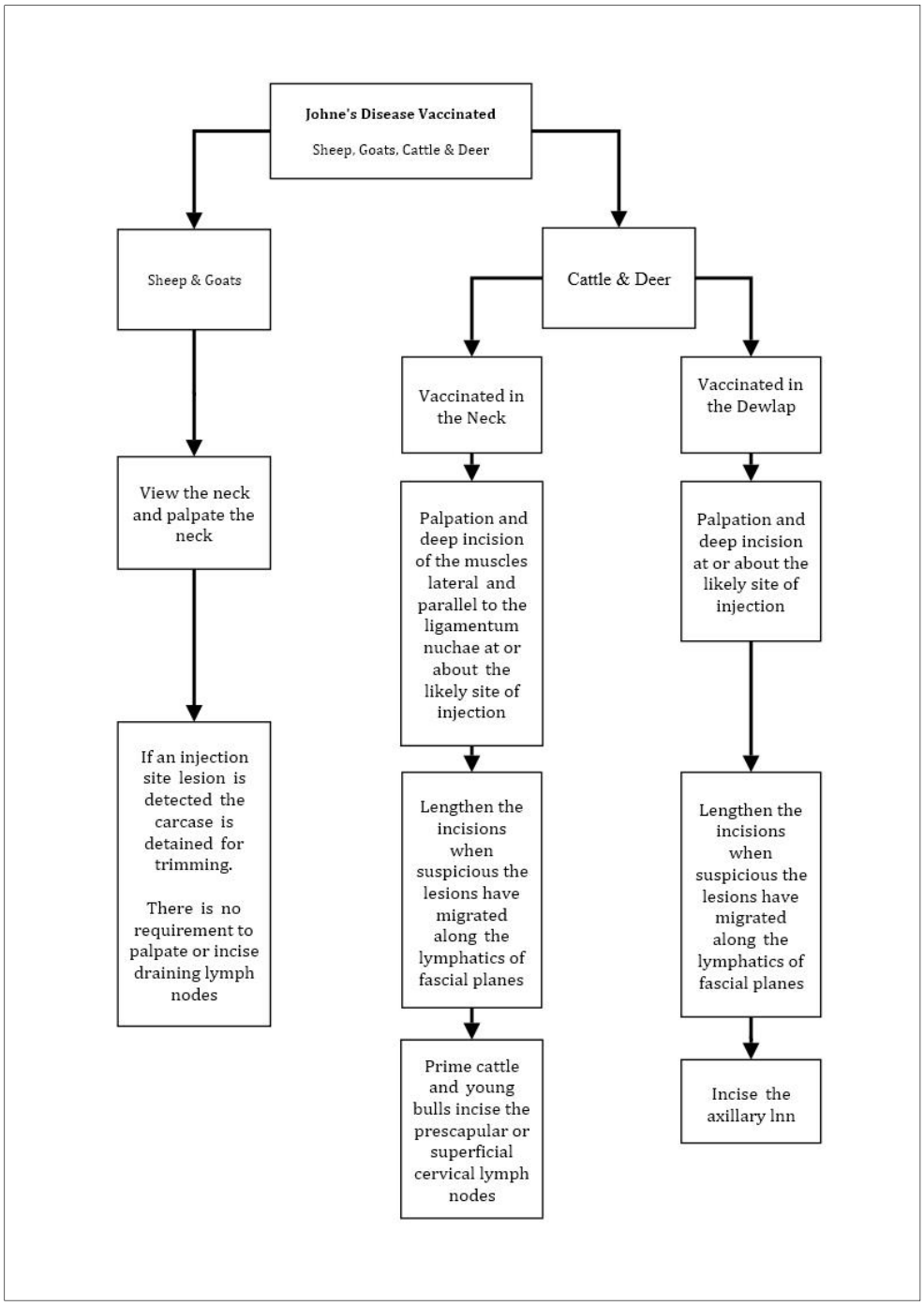
| Dimension (mm) | Number |
|---|---|
| 0 to 2 | 12 |
| Up to 20 mm | 1 |
| Up to 30 mm | 4 |
| Up to 60 mm | 4 |
| 5 mm by 70 mm | 1 |

### 8.3.5 NZ meat inspection requirements

The current inspection requirements for livestock which have been vaccinated against JD is shown in Figure 5 [49, 50]. In essence, an invasive procedure is required for cattle and deer, while in sheep the instruction is to view and palpate the neck.

It is the intention of the Ministry for Primary Industries (MPI) to revoke the current specific procedure for JD vaccinated cattle and deer. Instead it would be included in the sections dealing with injection site issues [49].

Figure 5. A flow diagram showing the Ministry for Primary Industries current inspection requirement for sheep, goats, cattle and deer that have been vaccinated against Johne's disease




The Animal Products (Specifications for products intended for human consumption) notice 2004 included directions for the identification of farmed mammals treated with Johne's disease vaccine (part 9; Sec 35, 36). These applied to the farmers who administered the vaccine and described both the earmark and the position it was to be placed [51].

To allow for the optimum processing time to be arranged and to alert inspection staff, it is a requirement to notify the processor of any livestock lines that have been vaccinated [51]. This is currently provided via the "Animal Status Declaration". An alternative for cattle and deer would be the "National Animal Identification and Tracing" (NAIT) system (see Section 7.3.2.2).

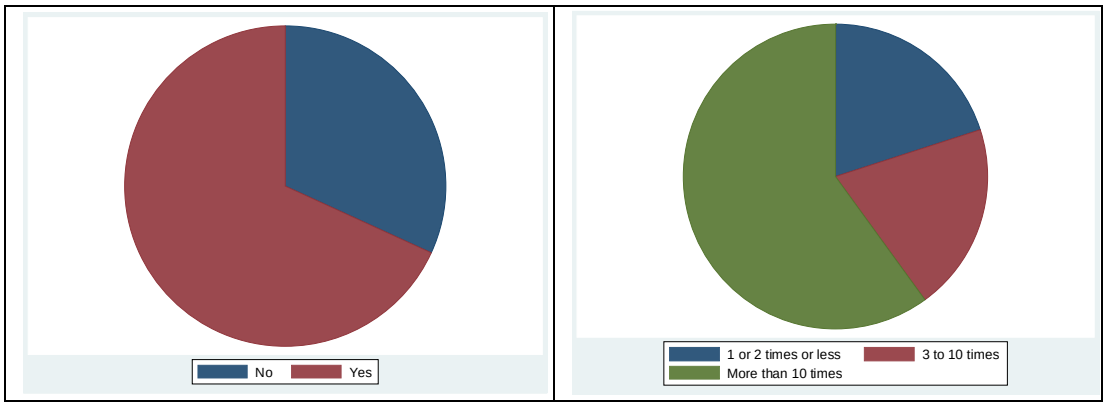
There appeared to be some confusion about the current MPI requirements, especially for sheep. In addition, instances of processors refusing to accept JD vaccinated stock have been reported. To clarify this, a survey of processors was conducted, the objectives being to ascertain

- whether or not processors were aware of the current inspection requirements, and
- if processors discriminated against processing JD vaccinated stock.

The results were as follows:

- replies from 22 processors were received
- 68% (15/22) correctly identified the current MPI requirement for either sheep or deer (Figure 6).
- one sheep processor stated they refused to accept JD vaccinated sheep, 5 other were reluctant; i.e. a third (33%, 6/18) of sheep processors either refused or were reluctant to accept JD vaccinates.
- around 50% of the sheep processors who discriminated against vaccinates had to deal with this 10 or more times a year (Figure 6).
- none of the deer processors (n = 4) were reluctant to accept vaccinates.

Figure 6. Pie graphs showing (left) the proportion of processers who correctly or incorrectly identified the current inspection requirements and (right) the number of times per year that those who were reluctant to process JD vaccinates had to deal with this issue.



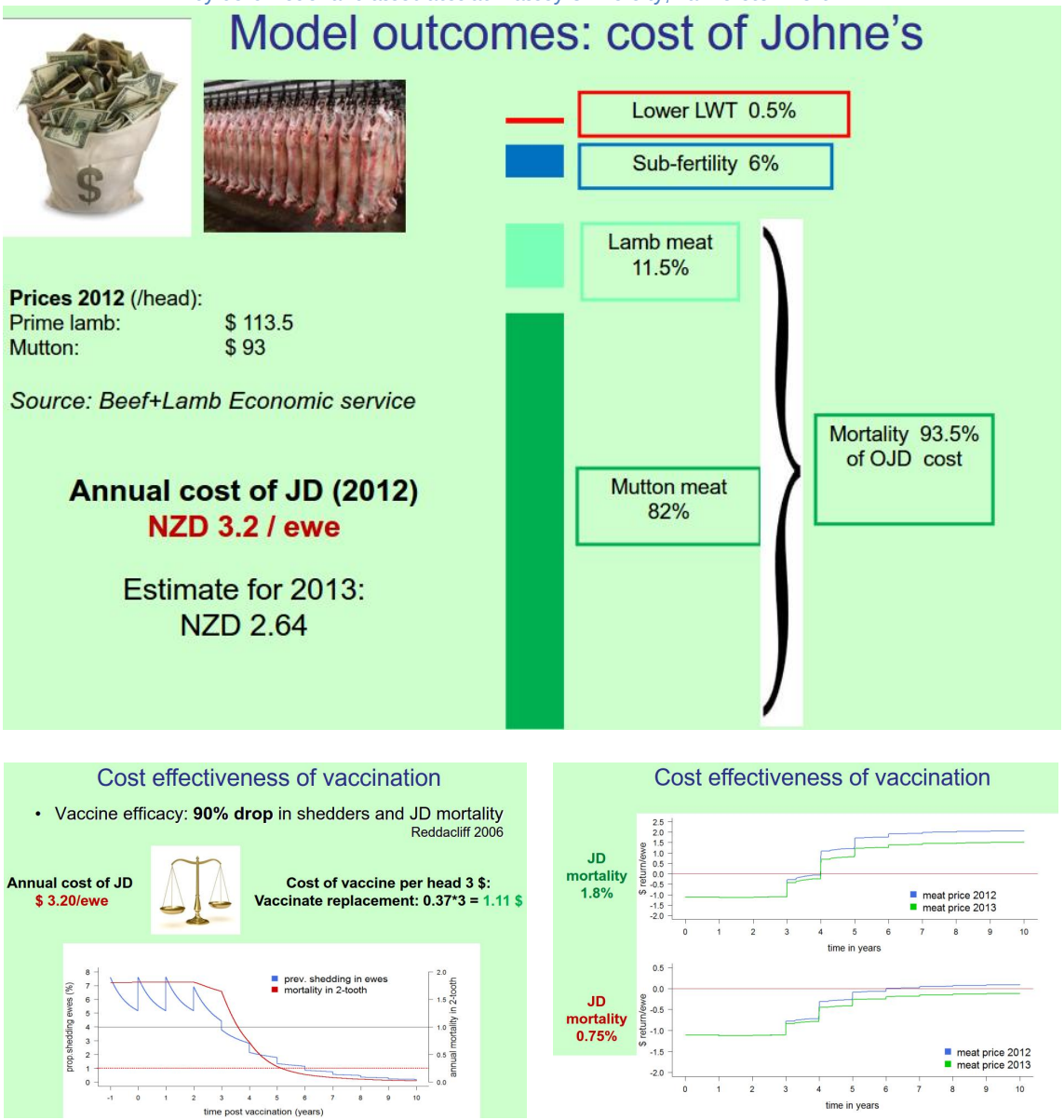

## 8.4 The economics of vaccination

There appears to have been only two investigations of the economics of JD vaccination in NZ. An in-depth study of the effects of JD in sheep was conducted by Cord Heuer and associates at Massey University. The other, "A Stimulation Study of Johne's disease for New Zealand Dairy Herds", also involved people at Massey University 2011 [29].

There appears to be no published report on the sheep study, but Cord Heuer[52] has kindly given me access to a presentation illustrating the key economic issue (Figure 7). The crux of the model was that over 90% of the costs of JD on NZ sheep farms arose from the deaths of ewes. Lower growth rates and lower fertility were responsible for only around 6% to 7% of the loss. The effect of vaccination was assumed to be as reported in Australia; i.e. a 90% drop in shedders and JD mortality [39]. The

main conclusion was that the "break-even" point was around 1% ewe mortality, but that a return on the investment of vaccination took 4 to 5 years.

Figure 7 Summaries of the inputs and outputs of a cost-benefit analysis of Johne's disease vaccination in sheep by Cord Heuer and associates at Massey University, Palmerston North




In the study of dairy herds, it was assumed that vaccination results in "an increase in the average period between infection and entering the highly infectious stage from five to seven years". With reference to the published results of Silirum™ in cattle (see above), this seems to be a considerable under-estimate of what one would expect. The authors concluded that

- vaccination was relatively inexpensive but failed to drive prevalence to a very low level.
- manipulating farm management to reduce the effective contact rate between calves and MAP was by far the best strategy for controlling Johne's disease

In contrast to this, in a 1996 publication[53] it was reported that in 12 Dutch dairy herds after five years [of vaccination]

- the rate of disposal of [cows] because of the clinical form of paratuberculosis-was reduced from 11 per cent in 1984 to less than I per cent in 1989
- the numbers of subclinically infected animals was also reduced
- Partial budgeting showed that vaccination against paratuberculosis was highly profitable

However, it should be noted that this was in an environment without the complication of tuberculosis infection in livestock as seen in NZ.

## 8.5 Future JD vaccines

In Paratuberculosis[1] Kris Huygen, Tim Bull and Desmond Collins[k] offer a vision of possible future JD vaccines that will be more efficacious than the current ones, will not interfere with tests for tuberculosis and will not cause tissue reactions.

With reference to the modes of action of MAP vaccines, they suggest that *"exposure [of livestock] to MAP is often inevitable and that eradication [or control] programmes that include vaccination may not be successful unless the vaccine used [has both a prophylactic and therapeutic effect]"*. In other words livestock may become infected prior to being vaccinated and thus as well as protection against infection, protection against developing clinical disease would be required.

They consider that there are both live and MAP sub-unit options (Table 9).

Table 9. Development of new Johne's vaccines: potential candidates, Kris Huygen, Tim Bull and Desmond Collins in Paratuberculosis[1]

| Vaccine Type | Sub-Type | Notes |
|---|---|---|
| Live | Attenuated strains of MAP | The use of well-characterised MAP mutant strains as vaccines remains attractive as they would be cheaper than sub-unit based vaccines and may offer better protection. |
| | Live vectors expressing subunits | A complex area, but recently there have been some promising results with respect to therapeutic and prophylactic effects (see below). |
| Sub-unit | Immunodominant antigens | Candidate antigens have been identified. Cross-reactivity with *M. bovis* may, in some cases, still be a problem. |
| | Protein subunit candidates | A number of proteins have been identified and some initial studies are very promising (see below). |
| | DNA vaccines | These have been shown to be very effective in small rodents in inducing humoral and cellular immunity responses need for protection against intracellular mycobacterial pathogens. However, one expert consulted thought developing a MAP DNA vaccine for livestock would present many challenges[9]. |

Some recent reports suggest that there are a number of promising developments, as follows.

- Jungersen *et al.* from the Technical University of Denmark presented a paper "Developing a recombinant vaccines against *Mycobacterium paratuberculosis*" at the recent Paratuberculosis Colloquium (Parma, Italy).

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This is an example of a sub-unit protein vaccine. Of note, was that the animals (cattle and goats) were vaccinated after challenge with MAP. Intestinal MAP in the vaccinated animals was significantly reduced compared to non-vaccinated animals. The immune responses corroborated the observed vaccine efficacy; in particular and in contrast to the non-vaccinates, most of the vaccinated animals did not sero-convert. All the vaccinated calves were test-negative to the single [bovine] tuberculin test, in contrast to the whole cell vaccinates all of which were test-positive. The authors concluded that the vaccine could be used to accelerate eradication [or control] of paratuberculosis while surveillance or test-and –mange control for tuberculosis and paratuberculosis remain in place.

- An evaluation of a live vector vaccine expressing sub-units has recently been published by Bull *et al.* [54] Vaccination was based on the delivery of MAP specific antigens via two viruses. The vaccinated calves showed no cross-reactivity with tuberculin and were provided a degree of protection against challenge evidenced by a lack of faecal shedding. The authors concluded that the vaccine shows excellent promise as a new tool for improving the control of MAP infection in cattle.
- Work on a novel vaccine based on attaching MAP subunit proteins on "biobeads" is about to start at the Hopkirk Institute , AgResearch, Palmerston North [9]. This "construction" has been shown, with other antigens, to enhance responses 100 fold. The antigen combination has been previously shown to reduce MAP infections by 87.5% in experimentally challenged goats. It is likely that the biobeads subunit vaccine will not interfere with the current bovine tuberculosis test.
- In the Netherlands a putative subunit vaccine Hsp70/DDA has been developed, and again without compromising diagnosis of bovine tuberculosis or paratuberculosis [55].
- Under the USA based Johne's Disease Integrated Program (JDIP) initiative, promising vaccine candidates have been identified.

To date, sub-unit vaccines for tuberculosis have not shown much promise. However, the immune mechanisms involved in MAP infection appear to be different; sub-unit vaccines appear to be effective and, potentially, offer a supplementary tool for MAP control [9].

Despite this progress it needs to be remembered that development of a new vaccine to the stage of field use will take a long time, possibly 8 to 10 years, and will be expensive. Ideally for registration purposes there should be efficacy data from field trials for the different hosts; for cattle such trials would take 5 or more years [8].

# 9 Conclusions & Recommendations

Many of those consulted suggested that I would need to consider cattle, sheep and deer separately because of the different situations presented. I would take this further, as it is apparent that even within each species there is a potential for a wide range of patterns of disease. JD is a complex disease, being significantly influenced by a wide range of determinates. Further, it is very challenging to manage as the outcomes may not come to the fore for many years. Currently, there is no simple single solution that could be applied across all species and within each species. From an operational perspective, this supports the development of a cadre of well-informed advisors who can analyse the situation existing in a herd or flock, or on a farm, and then develop appropriate control measures.

From what I was told and have read, it appears that the deer industry has quite recently moved out of what could be termed an "epidemic phase" of JD. A number of herd owners, and their animal health advisors, were faced with explosive outbreaks especially in yearlings but also in hinds and other stock classes. With 15% to 20% having clinical JD and recognising that this was just the "tip of the iceberg", one can understand the frustration of being denied access to vaccines for use in capital stock. After all there was the earlier example of Neoparasec™ success in sheep (albeit with tissue reaction issues) and there were the reports of vaccination being very effective in merino sheep in Australia. Some practitioners had also observed the devastating effects of failure to vaccinate[l] during the brucellosis eradication campaign. Finally, there is the well-established principle of vaccinating in the face-of-an-outbreak which has been shown, in many circumstances, to be an effective way of curtailing an epidemic.

Looking at the results of trials of Gudair™ and Silirum™, they are consistent with the historic performance of what some see as fairly crude vaccines, as described by Geoffrey de Lisle in Paratuberculosis [1]; i.e. cost-effective with respect to reducing production losses caused by MAP infection, but not totally protecting against infection nor the establishment of shedding. Despite these deficiencies, where other control measures have not been successful, they have proved to be very useful control tools, as seen for example in Australia in merino sheep.

The issue of "uncertainty of an outcome" needs to be considered. In Section 6, the efficacy of the test-and-management programmes (i.e. without vaccination) is addressed. Among the experts consulted there was a range of views. And, with such programmes, providing "evidence", in a classical sense, of cause-and-effect poses some difficulties (see Section 4.2). In contrast, with vaccination there is the ability to set up a trial with "treatments and controls". Clearly, the design of a trial is critical, as are such issues as reference populations, sampling frames, sampling methods etc. However, I suggest that an advantage of the "vaccination" pathway to control JD is this ability to progressively build up such "evidence". This does not rule out a combination of vaccination and test-and-management. Some of new vaccines (see below) are compatible with this.

In my opinion the current restriction that Silirum™ can only be used in "finishing deer destined for slaughter" should be removed and that vaccination of capital stock be permitted. In the rare cases of "epidemic" JD that might occur nowadays in either cattle or deer, the option of using this tool should be considered, especially for financial reasons. Vaccination of capital stock is a once-in-a-lifetime event. Test-and-management might require years of work and therefore ongoing costs. Vaccination might also be part of a long term programme to bring JD under control. Whether or not it is used should be looked at from a cost-benefit perspective and additional research on this, using the results of vaccination trials, would be very helpful. However, some other issues would also need to be considered.

With regard to JD control, Silirum™ vaccination undoubtedly would result in prolonged high antibody levels and would therefore eliminate what appears to be a very effective method of identifying current and potential high and "super" shedders [6, 7, 10]. In recent years this "tool" has been refined and the feedback from herd owners has been very positive; e.g. in dairy herds post-parturition losses due to clinical JD have been reduced or even eliminated. This is also used as the basis of some regional or

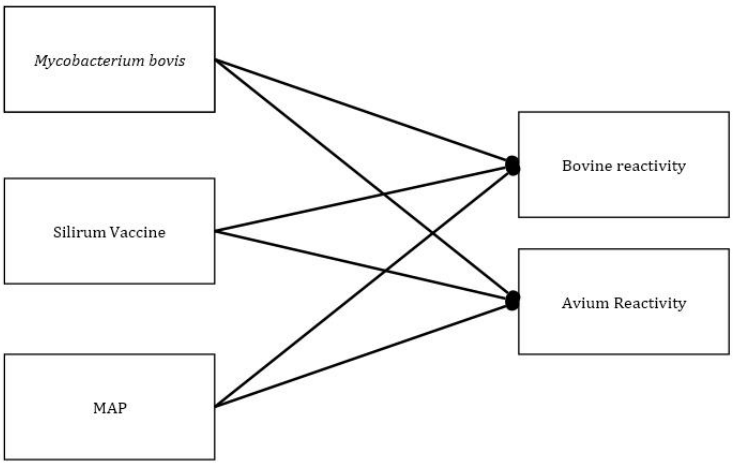
[l] i.e. *B. abortus* strain 19

even national control in some countries [9] and could be considered in NZ. Thus, vaccination would, most likely, remove the ability to impose such "targeted control". Of note, however, is the observation that new born calves vaccinated with Silirum™ did not produce antibody (see section 7.2.2.3 above). This is worthy of further investigation.

Silirum™ vaccination would complicate tuberculosis testing in both cattle and deer herds. Interestingly it is not the issue of false-positives (i.e. specificity) that is the risk; skin test-reactivity decreases over time and can be resolved using one of the serial tests, either skin or blood. The main threat is failure to identify *M. bovis* infection, if it exists. The situation is shown schematically in Figure 8. The net result in deer, as reported by Mackintosh *et al.* [45], would be that only half or less of the tuberculosis-infected animals would be CCT-positive. In this circumstance, it would have to be assumed that any animal that exhibited "bovine reactivity" was infected. Failure to do this could lead to tuberculosis spreading through the herd.

This risk of not identifying tuberculosis in a herd, which nowadays is very low, could be further reduced by not vaccinating herds in which there is evidence of recent infection, herds located in a vector risk area etc. However, of some concern is the recent occurrence of sporadic breakdowns in dairy herds in vector free areas; this suggests "leakage" via animal movements from infected foci. It is unfortunate that NAIT and DMS are not integrated as this would allow one to generate a risk profile of all the members of a herd.

Figure 8. Schematic representation showing influences on the bovine and avium reactivity in diagnostic tests in animals infected with both MAP and *M. bovis* (TB) and also vaccinated against Johne's disease




Thus, Silirum™ vaccination of dairy and deer herds would need to be undertaken cognisant of the attendant risks to JD management and tuberculosis eradication. I think it prudent that prior to any herd being vaccinated the risks are explained to the herd owner, and a written agreement to proceed signed with whoever is advocating this action.

Considering the problem of inoculation site lesions, the data presented indicates that the current vaccines (Gudair™ and Silirum™) result in only minor problems after approximately 12 months. However, the results of the survey of processors suggest that the problems that arose from Neoparasec™ are still having a marked influence. Part of this is, most likely, the result of a misunderstanding about the modified inspection requirements for sheep; i.e. from invasive to view

and palpate. On the other hand, the four deer processors who gave feedback were not concerned about the current invasive procedure.

Of course, the apparent confusion about current inspection requirements is of concern. The documentation provided to processors and inspectors is not clear. I understand that MPI are taking steps to improve this [49, 50].

As a background, a brief description of the status of JD in sheep, cattle and deer was presented (Section 5). There have been calls for more work on the prevalence and incidence of JD and MAP within the national [dairy] herd, for example by Bryan and Cresswell [14]. Given the potentially dynamic nature of MAP infection, the many unknowns concerning the ecology of this ubiquitous organism and the limitations of current diagnostics, I think little would be gained doing this. This was also the opinion of experts from the dairy industry [10, 56].

In my opinion, some careful thought should be given to a continuing assessment or monitoring of the manage-and-test programmes that have been developed for deer and dairy herds. The major assumptions that the control strategies are based on should be tested. I recognise that this is a challenge and would require on-going funding, but in my view it is essential as there are examples of major disease control programmes going down spurious pathways. An example from the NZ National Brucellosis Eradication Programme is described in Appendix 2 A feature of the very successful "NZ Bovine Tuberculosis Control Strategy" was a robust wide-ranging research programme in which the determinates of *M. bovis* infection in cattle and deer were rigorously investigated. Good examples are the work that was done to establish the role of various wild animals in the epidemiology of bovine tuberculosis and epidemiological surveillance using *M. bovis* markers.

It may well be that a major milestone in the development of more effective JD vaccines has been reached [9]. There are currently at least five independent groups working on prototypes that appear very promising, both from an efficacy and absence of undesirable side-effects in cattle and deer. They may be very useful adjuncts to the current test-and-manage programmes. Given the complexity of the epidemiology of MAP infection, it would advantageous to trial new vaccines in NZ. A number of features, but especially the shorter time to clinical disease, makes trials in young deer an attractive option; industry should consider supporting this.

Despite these very positive developments, the release of a new product for field use will take a long time, possibly as much as 8 to 10 years, and it would be expensive process.

Having regard to the statement by Kris Huygen, Tim Bull and Desmond Collins In Paratuberculosis[1][m] that a successful vaccine will probably require both an effective prophylactic and an effective therapeutic effect, it appears that the latter has not been well defined. For example is there an age effect? Some experts believe there is [8] and this might be a critical success factor. Clearly, understanding why the apparent immune dysfunction which is responsible for the development of disease and thus the maintenance of JD occurs would be a major step forward.

[m] Chapter 30.

# 10 Appendix 1. The Johne's disease Research Consortium.

JDRC was established in 2008 to undertake a coordinated program of research to develop practical and cost effective tools for the management of JD in New Zealand. Partners in the Consortium include Beef+Lamb New Zealand, DairyNZ, DEEResearch Limited, AgResearch, Livestock Improvement Corporation, Massey University and the University of Otago, with observers from the Ministry of Business Innovation and Employment, Dairy Companies Association of New Zealand and the Meat Industry Association. Landcorp Farming Limited, Johne's Management Limited and NZ Merino Limited are all associated with the Consortium through the Research Programme.

# 11 Appendix 2. Brucellosis problem herds, carrier animals or lack of vaccination?

In the late phases of the national brucellosis eradication scheme in NZ, it was observed that in "problem herds" sero-negative but bacto-positive late abortions occurred. This led to a wide-spread belief that in these herds there were sero-negative "carrier" animals which year-after-year excreted *B. abortus* at calving. Thus, the only way to detect them was screening the whole herd for *B. abortus* at calving. This was done in many herds at great cost. However, when this hypothesis was tested, quite simply by re-testing these animals shortly after calving, it was found they were sero-positive and usually the titres were very high. It was also found that there was a very strong association between such cases and that they had not been vaccinated as calves. It turned out that these cows were acute abortions and that there had been insufficient time for the late antibody that the standard test (i.e. CFT) was based on (i.e. IgG) to develop. Attention to this, via culling unvaccinated animals prior to calving or the use of low dose strain 19 resolved the problem.

# 12 Appendix 3. Terms of Reference

The aim of this review is to provide an assessment of vaccination as a control tool for Johne's disease in New Zealand for the purpose of informing industry positioning considering:

- The effectiveness of vaccination as a control tool
- The identifiable impact and consequences of vaccine use on both animals and product

The review should:

- Assess the use of vaccination as a control tool for the management of Johne's disease in New Zealand in sheep, cattle and deer
- Inform industry positioning on vaccination as a control tool for JD in New Zealand
- Indicate if any specific research is required in New Zealand to inform industry about the use of vaccination as a control tool.

The review should provide and/or describe, from a New Zealand based context:

- A summary regarding the status of Johne's disease for each species
- Background information regarding vaccination, it's history, current and future state, as a control tool for the management of Johne's disease in each species
- Technical information regarding the use and efficacy of currently available vaccines

- The historical and current information regarding issues associated with the use of JD vaccines in New Zealand (including technical, regulatory and perception based matters) and any changes that have impacted arguments for and against the use of vaccines
- An assessment of the cost effectiveness of vaccination as a control tool for each species (where data is available)
- Comment and recommendations for industry positioning on vaccination given the current understanding of issues and recent changes
- An analysis of any gaps in understanding that may require further research

Acknowledge and comment on:

- Gaps in the analysis
- Limitations in the data, methodologies and analysis
- Assumptions

This review should be based on information from JDRC, any relevant organisations (e.g. OSPRI, Zoetis, DairyNZ, Beef+Lamb NZ, Deer Industry NZ) and published data.

Expected output from the review

A confidential paper for the JDRC Board, assessing the status of vaccination as a control tool for the management of Johne's disease in New Zealand, for the purpose of informing industry positioning on the use of vaccination.

The paper is to be reviewed by the Johne's Advisory Group, signed off by the JDRC board and distributed to the Boards of JDRC's participant organisations as an information paper. The paper will be made available to other organisations and the public at the discretion of the JDRC Board.

Management of the review

An independent Johne's disease veterinary expert or group will be engaged by JDRC to complete this review. The expert will be responsible to the Consortium Board via the Consortium Manager for the delivery of the analysis.

The review must be carried out in consultation with the following groups:

- OSPRI (TB free programme management)
- Zoetis, New Zealand (vaccine manufacturer)
- JDRC Industry Stakeholders (B+LNZ, DairyNZ, Deer Industry NZ, DCANZ, MIA)
- Ministry of Primary Industries (MPI)

And it is recommended that the following groups be consulted during the review

- Johne's Management Limited (experts in control and management of JD in deer)
- Massey University (Published field trials for Silirum® in Deer; Evaluation of Vaccination as a control tool for sheep)
- AgResearch Limited (expertise in development of vaccines and field trials for Silirum® in Deer)
- Other Johne's disease research experts (including Otago University, LIC)

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