Johne’s Disease (Paratuberculosis)

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Summary

- Johne’s disease (paratuberculosis) is a chronic intestinal disease that predominantly affects ruminants. It is characterised by severe weight loss, loss of body condition and diarrhoea (in cattle) culminating in death.

- The disease is caused by infection with a bacterium called *Mycobacterium avium* subspecies *paratuberculosis* (referred to as *Map*), which is a very slow growing organism that can survive for long periods in the environment.

- The disease is spread mainly by the ingestion of faeces from an infected animal. Infected animals can also pass on the infection in colostrum or milk and across the placenta to unborn animals. The organism can be found in the semen of infected bulls, but it is thought that this is of negligible importance in the spread of the disease.

- Young animals are more susceptible to infection than adults.

- The disease has a long incubation period of 2 to 4 years during which time the animal may show no clinical signs of disease and shed *Map* intermittently. Animals in this stage of the disease are said to be ‘subclinically infected’ and act as ‘carriers’ of the disease.

- The disease is usually introduced to a farm through the purchase of subclinically infected stock that show no sign of the disease.

- Different strains of *Map* can infect a broad range of hosts including cattle, deer, sheep, goats and some wildlife species.

- The diagnosis of Johne’s disease is problematic and there is no single diagnostic test that can detect all stages of the disease. Subclinically infected animals are particularly difficult to diagnose and test results may be negative.

- Diagnostic tests are available to detect *Map* in faeces and milk. These are faecal smears, bacteriological culture and polymerase chain reaction (PCR). There are also diagnostic tests that detect circulating antibodies to *Map* in infected animals. The most common test is the enzyme-linked immunosorbent assay (ELISA).

- There are two main objectives in the control of Johne’s disease.
  - Prevent the introduction of the infection by purchasing uninfected stock.
  - Reduce the impact of the disease in infected herds and move towards freedom from the disease.

The fine detail of control varies with the species and the production system, but biosecurity and reducing the amount of faecal contamination that young stock are exposed to are central to any control programme.

- Implementing a Johne’s disease control programme after consultation with your veterinary surgeon will help to protect your animals against Johne’s disease.
Introduction

Johne’s disease, also known as paratuberculosis, is a chronic infectious intestinal disease caused by *Mycobacterium avium* subspecies *paratuberculosis* (often abbreviated to *Map*). It is a disease that affects ruminants predominantly although *Map* can infect a broad range of animals including wildlife such as rabbits. Johne’s disease occurs worldwide and causes considerable economic losses through decreased productivity, increased wastage of adult animals as well as the cost of control, monitoring and diagnosis.

The prevalence of Johne’s disease is difficult to estimate and there is very little data for the situation in the UK. It has been estimated that the proportion of infected dairy herds in the UK is greater than 20% and because many beef herds have sourced replacement stock from the dairy herd then a similar proportion of infected beef herds is likely. A higher prevalence of infection has been associated with certain breeds of cattle although no survey work has ever been carried out to investigate this aspect of the disease. While good national disease data on this disease does not exist, information from the veterinary investigation service (Veterinary Laboratory Agency in England and Wales and Scottish Agricultural College Veterinary Service in Scotland) has shown that the number of laboratory diagnoses of Johne’s disease in cattle has increased more than two fold in the years 2000 to 2005 to a figure of 2582 diagnoses. This increase is likely to be the result of increased awareness within stock farmers and the veterinary profession as well as improved diagnostic tests. However it seems unlikely that an increase of this magnitude could be due to these factors alone and it suggests that the disease may be becoming more widespread.

The situation is even less clear in the sheep flocks of the UK. Johne’s disease is a relatively unusual diagnosis in sheep in this country and very few flocks are affected in the way that cattle herds can be. For example in 2005 a laboratory diagnosis was made 107 times in sheep in Great Britain. A further complication lies in that the disease is much more difficult to diagnose in sheep as they can be infected with few organisms and strains that are very difficult to culture.

Johne’s disease is also a particular problem in goat herds throughout the world. No reliable data exists on the situation in this country, but the veterinary opinion is that the national goat herd is no different in this respect to elsewhere in the world.

There is no information available regarding the prevalence of Johne’s disease among farmed deer in the UK. A survey of 1235 free-living deer in Scotland estimated the prevalence of *Map* infection to be 2%. There also have been reported incidences of Johne’s disease among farmed alpacas in the UK.

The Disease

In an infected herd or flock it is believed that most animals are infected in the first few months of life. All the research work done on Johne’s disease has shown that young animals are more susceptible to *Map* infection than adults, but the precise mechanisms that allow this remain unclear. Once ingested, the organisms pass to the small intestine where they are taken up by specialized cells called M cells.
Young animals have more M cells than adults, which is one reason why they may be more susceptible to infection. Another possibility is that in newly born ruminants the milk bypasses the immature rumen so the organism is delivered directly to the primary site of infection. *Map* is discharged from the M cells and is engulfed by macrophages (a type of white blood cell that can kill microorganisms and stimulate the action of other immune system cells).

The tendency then is for the very slow development of sites of infection dominated by the cellular response of the infected animal. These sites are known as granulomas and ultimately they will spread and join together to have an adverse effect on the digestive process of the intestine. However, infection is not restricted to the digestive tract alone and the infected macrophages carry the organism around the body via the blood and lymphatics systems.

*Map* has evolved very effective ways of resisting the killing mechanisms of the macrophages to allow it to survive. During these early stages of infection, it is very difficult to detect the bacterium and the animals show no clinical signs of disease. These animals are said to be ‘subclinically infected’ and can act as ‘carriers’ for the disease.

The infection rate within a herd or flock may be high, but it is believed that many animals will eliminate the infection at an early stage, and animals with a healthy immune system can control the infection but a proportion of infected animals (10-15%) develop clinical disease. The progression of disease is usually very slow with the majority of animals becoming clinically ill from between two and six years of age. Deer can differ in this respect as they can develop clinical signs of the disease from six months onwards and once clinical signs are evident they die within a few weeks. *Map* slowly replicates within the cells in the intestine and stimulates inflammatory and cellular immune responses. The intestines become thickened, absorption of nutrients is impaired and the animal loses weight through malnutrition. Eventually the animal dies.

**Clinical Signs**

As the disease develops there is a progressive loss of function in the small intestine in particular. The first impact that this has is to reduce the productivity of the infected animal. In the dairy herd this is principally seen as a loss of milk yield, resulting in cows failing to reach their lactation potential. Interference with the energy balance due to the impaired digestion and absorption of nutrients also reduces fertility. Therefore, animals in the pre-clinical phase of the disease may be culled because of poor productivity or infertility. Harder to explain is the increased incidence of diseases such as metritis, mastitis, displaced abomasums and even lameness in animals infected with Johne’s disease compared to uninfected animals within the herd. The consequence of the effects of the pre-clinical phase of the disease is that in many dairy herds the early stages of herd infection may go unrecognised other than an increased culling rate for apparently unrelated reasons.

The beef cow is usually under less production pressure than the dairy cow and the pre-clinical phase is not so well recognised. However poor calf growth rates consequent to reduced maternal milk yield and infertility all occur in the infected beef herd.
The pre-clinical phase in deer is likely to be similar to that in cattle although further research is necessary to determine whether a similar economic loss is being experienced in the deer industry due to preclinical Johne’s.

The pre-clinical phase of the disease in the sheep flock has similar characteristics to the disease in the beef herd. One important observation is an increased susceptibility to parasitic gastroenteritis. Therefore where ewes are seen to be heavily infected with stomach worms out with the period around lambing the possibility of an underlying Johne’s disease problem should also be considered.

As more of the intestine is affected by the disease the animal progresses from the pre-clinical to the clinical phase of the disease. Here loss in body condition becomes obvious and progressive. Cattle with Johne’s disease develop diarrhoea, sometimes graphically described as “hosepipe” or “pipestream diarrhoea”. A proportion of infected deer show no apparent weight loss or diarrhoea but may show carcass lesions at slaughter while others may develop the full range of clinical symptoms. Diarrhoea is less common in sheep and goats with Johne’s disease, although they may develop a softening of the faeces. The progressive loss of protein through the diseased intestine and the failure to digest and absorb protein efficiently ultimately leads to severe protein deficiency, often seen as bottle jaw.

Where these clinical signs are observed Johne’s disease must be considered along with other conditions such as liver fluke, parasitic gastroenteritis, poor nutrition and dental problems. However it must be remembered that animals suffering from the later stages of Johne’s disease will also lose their ability to resist fluke and worms.

**Transmission**

Infected cattle, deer, sheep and goats shed Map in their faeces and the number of bacteria shed increases as the disease progresses. In subclinically infected animals shedding can be intermittent. The primary route of infection is through the ingestion of contaminated food and drink. Young animals can be infected by ingesting faeces contaminating the teats and udders of the dams or from contaminated pasture and feed. Infected dams can also pass on the infection via contaminated Colostrum or milk. It is believed that the practice of pooling and feeding of Colostrum and feeding waste milk may have been a significant factor in the recent apparent upsurge of this disease in the dairy herd. The infection can also cross the placenta to unborn animals and this occurs at a high rate in the later stages of the disease. It has been shown that Map can be present in the semen of infected sires. It remains unclear how important this is as a transmission factor, but breeding from infected animals or their offspring should be avoided.

Map survives well in slurry and water and there is the potential for high transmission rates in cattle herds where contaminated water sources are the major source of water at pasture. Studies done several decades ago showed that the simple expedient of providing water from mains sources significantly reduced the clinical problem in infected herds. Fencing off slow moving and stagnant water therefore needs to be considered in any control programme.
Composting of straw and faecal material progressively kills *Map* and therefore introducing a composting stage into manure management will have an important effect on reducing the amount of *Map* recycled onto pasture. What is less clear is the impact of *Map* surviving on pasture grazed by infected cattle. With the weathering of faecal pats most of the infection will be leached into the soil and be unavailable to infect other animals. What is unknown is the time taken for this process to result in “safe” pasture where the amount of *Map* falls below that, which has the potential to lead to new infections.

The spread of Johne’s disease between farms is almost always the result of unwittingly introducing subclinically infected animals as replacement stock or sharing breeding animals between farms. Therefore, biosecurity is a key element in a Johne’s disease prevention strategy, but here lies one of the most difficult aspects of the disease.

Young animals in the early stages of infection are very likely to test negative using the available diagnostic tests to the extent that screening purchased animals offers very little assurance that infected animals will be detected. There are assurance programmes for cattle and the best practice is to buy only from herds in an assurance programme that have effectively demonstrated freedom from infection according to the rules of the scheme. Theoretically, any breach in biosecurity that allows contaminated faeces onto a farm e.g. Vehicles, equipment or clothing contaminated with faeces could result in introduction of the disease. But perhaps of greater importance is the practice of purchasing colostrum from dairy herds to use as a reserve top-up in the beef herd.

There is no Johne’s disease assurance programme for deer, sheep or goats in the UK and therefore effective biosecurity cannot be achieved for this disease in these species where significant numbers of replacements are purchased.

Studies of *Map* isolates from the UK suggest that the majority are capable of infecting cattle, deer and sheep so co-grazing infected animals with non-infected animals of any susceptible species or grazing at different times on the same pasture may be a risk factor for spreading Johne’s disease. A pigmented strain has been isolated from sheep but has not been found in cattle in the UK. Some *Map* strains have been found in wildlife such as rabbits suggesting that wildlife could be involved in spreading the disease. Reducing contact with wildlife and controlling rabbits on infected farms should be considered as part of a control programme.

**Diagnosis**

The diagnosis of Johne’s disease is problematic and there is no single diagnostic test that can detect all stages of the disease. Diagnosis is also more difficult in small ruminants such as sheep and goats compared with cattle. In general, clinically affected animals are much easier to diagnose than subclinically infected carriers. The diagnostic tests available either detect the bacterium or the animal’s immunological response to infection.
1) Detection of *Map*

The cheapest and simplest test to detect *Map* is to take a faecal smear and use a special acid fast staining technique (called Ziehl Nielsen or ZN staining) to visualize the bacteria. The test is very quick but not very sensitive so there needs to be a lot of *Map* in the faeces sample. Also, there are other related organisms that stain in this way so the test is not specific for *Map*. This test is only used for clinical disease where it may be expected to pick up only one third of cases. It cannot be used as a screening test to detect animals in the pre-clinical phase of the infection.

Culture is often considered the “gold standard” method for diagnosis of Johne’s disease. Although specific, it also has low sensitivity, is slow, expensive and requires specialized media. Some strains of *Map* are extremely difficult to grow in the laboratory, particularly sheep and goat strains, and culture is difficult where few organisms are present such as in the early stages of the disease. Conventional culture can take up to 16 weeks for cattle and deer strains and 18 months for some sheep strains. New liquid culture systems are a little faster at 7 weeks for cattle strains. Consequently, while faecal culture can be used to identify infected cattle, it is rarely used for the diagnosis of ovine Johne’s disease in the UK.

More recently a new test for detecting *Map* has become available using a technique called the polymerase chain reaction (PCR). This is a highly specific technique that is being used to detect *Map* in faeces and bulk milk samples. It can detect low numbers of bacteria including strains that are difficult to grow and the results are available in 1-2 days. However, the test is not without its problems and inhibitors present in the clinical samples can reduce test sensitivity. The test is sometimes used to confirm the identity of isolates cultured from faeces.

When testing faeces samples it should be remembered that a negative result is not a guarantee that the animal is free from Johne’s disease. An infected animal can shed *Map* intermittently so it is advisable to repeat faecal testing of suspected cases when a negative result is obtained.

2) Blood Tests

Blood tests detect the immune responses of infected animals. During infection with *Map*, animals develop both a cell-mediated immune (CMI) response and an antibody response at different times during disease progression. Generally speaking, the CMI response occurs early in infection and in subclinically infected animals. The antibody response develops as the disease progresses and the highest titres are produced during the clinical stage. The blood tests that are commercially available for the diagnosis of Johne’s disease detect circulating antibodies to *Map*. The most commonly used test for cattle is the enzyme linked immunosorbent assay (ELISA). This test will detect the clinically infected animals in a herd, which will be those that are shedding large numbers of *Map* and that pose the greatest risk to the rest of the herd. It will detect subclinically animals if they have started to develop antibodies, although they may be scored as “suspect” or “borderline” if the levels of circulating antibodies are low. The ELISA can be used very successfully with faecal culture in control programmes as described later. The current commercially available ELISAs do not perform as well in other host species such as sheep, goats or deer.
This may be because the ELISAs have not been optimized for these species or that the immune response to *Map* is different in these other hosts. A group in New Zealand has developed an ELISA specifically for deer (*Paralisa™*), which has greatly improved sensitivity in this species.

Currently, there is not a test commercially available to detect a CMI response in *Map*-infected animals. A blood test called the gamma-interferon (γIFN) ELISA has been developed for detecting the CMI response of animals infected with *Mycobacterium bovis* for the diagnosis of bovine tuberculosis. This test could be modified for the diagnosis of Johne’s disease if suitable *Map*-specific antigens could be found. This test would be extremely useful for detecting subclinically infected animals, particularly prior to introduction on a new farm or prior to breeding.

3) Post mortem examination

If the above tests have been inconclusive, it may be necessary to confirm Johne’s disease in a herd or flock by performing a post mortem examination on a suspected case. Animals with severe Johne’s disease have a thickened gut sometimes with a corrugated appearance and enlarged mesenteric lymph nodes which can be observed at post mortem. Samples of tissue can be taken for both microscopic examination and culture. Post mortem examinations are more commonly used for diagnosing Johne’s disease in sheep and goats where culture and blood tests yield negative results.

Two types of pathology are seen in sheep and goats; paucibacillary or tuberculoid characterized by the absence or presence of very few *Map* in the tissues and multibacillary or lepromatous characterized by large numbers of *Map*. These two conditions correlate with different immune responses; paucibacillary disease being associated with a predominant CMI response and multibacillary disease with a predominant antibody response.

Treatment

Johne’s disease is invariably fatal and treatment is only considered for valuable animals such as prime breeding stock or rare breeds. Treatment requires prolonged use of antimicrobials and is expensive. *Map* is resistant to many antibiotics and the antimicrobials used for the treatment of Johne’s disease are the same as those used for the treatment of tuberculosis or leprosy in humans.

Protecting your animals from Johne’s disease

The control measures that can be implemented for Johne’s disease will be determined by the type of farm. Your veterinary surgeon will be able to advise you on the best control strategy for your farm. The main goals are for herds/flocks that do not have the disease to maintain that position by ensuring that measures to prevent the introduction of the disease are built into the biosecurity module of their health plan. And for herds/flocks that have the disease to reduce the number of new infections that are occurring.
Biosecurity:
- Wherever possible minimise the purchase of replacement breeding stock.
- Source breeding stock from herds that are in a Johne’s disease assurance programme and have accredited status.
- Where this is not possible and large numbers of replacements are required for rapid herd expansion look to buy from one herd and test the whole herd.
- Consider screening cull cows and poor yielders in order to detect the disease at an early stage.

Dairy Herds:
- Keep cows clean during the dry period to ensure that the teats and udder are free from faecal contamination.
- Clean out calving pens and sick pens after each animal has left.
- Keep the calf with the cow for the minimum period only until it has sucked colostrum and been licked dry.
- Do not feed pooled colostrum or waste milk.
- Ensure that all water troughs for all ages of stock can be cleaned out easily to prevent cattle drinking faecally contaminated water.

Beef Herds:
- Control is as for dairy herds where appropriate, but in addition in rough grazing fencing off stagnant water or slow moving water should be considered.

Sheep Flocks and Goat Herds:
- Control programmes are as for dairy herds. Vaccination may also be appropriate.

Deer:
- The control programmes for cattle are appropriate for deer farms.

Formalised Control Programmes:
The Cattle Health Certification Standards (ChECS) has unified the existing formalised control programmes in the UK and licensed the providers. The programmes provide an assurance system to demonstrate freedom from Johne’s disease through regular whole herd testing. Animals purchased from herds accredited as free of Johne’s disease provide the lowest risk of introducing infection to a herd. In addition the ChECS Johne’s disease control programme offers a framework for control of the disease based on testing the herd annually and excluding positive animals and the offspring of positive females from the breeding herd. This is supported by a hygiene programme.
Clearing the herd of infection is a long term objective only achieved after many years, however the programme will in most herds result in a significant reduction in wastage from the disease and new infections after at least three years.

There are no similar programmes for deer, sheep or goats in the UK, but Johne’s disease programmes for these species do exist in other countries.

**Vaccination**

Vaccines are available for Johne’s disease but they have limitations. They prevent clinical disease thereby minimising losses through poor condition and premature culling but they do not prevent infection. This means that vaccinated animals introduced to other farms can still constitute a risk of infection. The vaccines lessen transmission by reducing shedding of *Map*. Once animals have been vaccinated they develop a protective antibody response to *Map* and it is not possible to distinguish between vaccinated and naturally infected animals with the available tests. Current vaccines sensitize animals to common antigens shared by *Map* and *Mycobacterium bovis* and cause cross reactions in the tuberculin skin test for bovine tuberculosis and for this reason they are not generally used for cattle or deer. Another drawback is that they sometimes produce a reaction at the site of inoculation and self-injection can be potentially hazardous. Nevertheless, vaccination can be used effectively to control Johne’s disease particularly in sheep and goats where diagnosis is so difficult and test and cull is not a viable option.

The Veterinary Laboratories Agency ceased the manufacture and supply of the ‘Weybridge vaccine’ for Johne’s disease in 2005 and at the time of writing there is no vaccine authorized for use in the UK. A killed vaccine (Gudair) manufactured and licensed in Spain, is available through Virbac Ltd.

If you are interested in vaccinating against Johne’s disease, you need to speak to your vet who will need to apply for a Special Import Certificate from the Veterinary Medicine Directorate to purchase the vaccine. The company is currently working towards gaining a licence for use in cattle.

**Crohn’s Disease**

Johne’s disease has some similarities to the human illness Crohn’s disease and *Map* has been suggested as a causative agent. Crohn’s disease is a chronic debilitating gastrointestinal disease affecting approximately 1 in 1000 people in the UK. There is a genetic susceptibility to the disease. However, no conclusive evidence has been presented which confirms *Map* is a cause of Crohn’s disease. A European Scientific Committee assembled in 1999 to investigate possible links between Crohn’s disease and Johne’s disease concluded: “The currently available evidence is insufficient to confirm or disprove that *Map* is a causative agent of at least some cases of Crohn’s disease in man”. Studies conducted since then have provided no additional information to refute this conclusion.
Current and Future Research

Research on Johne’s disease is particularly challenging due to the difficulties associated with the growth characteristics of *Map* and the prolonged incubation period of the disease. We have a poor understanding of how and why *Map* causes disease and this knowledge is crucial for developing new and improved diagnostics and for controlling spread of the disease. The Moredun Research Institute has a well established, internationally recognised research group studying the pathogenesis of *Map*. The research uses the most up to date technologies available and works closely with farmers and the veterinary investigation services. Johne’s disease is very difficult to induce experimentally in animals and the Moredun group is extremely grateful to the farmers who donate clinical cases for research.