Paratuberculosis

Johne's Disease

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IOWA STATE UNIVERSITY
College of Veterinary Medicine

World Organisation for Animal Health
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Importance

Paratuberculosis is a chronic intestinal disease, caused by *Mycobacterium avium* ssp. *paratuberculosis,* that primarily affects ruminants and camelids. When this organism exists in a herd and no control measures are employed, animals usually become infected early in life, many become asymptomatic chronic carriers, and a few carriers develop overt disease, usually after several years. Symptomatic animals generally die from cachexia or are culled due to the illness. None of the currently available drugs seems to be able to eliminate *M. avium* ssp. *paratuberculosis* from an infected animal. Unless testing is done, paratuberculosis can exist undetected in a herd for years. Clinical cases can be particularly difficult to recognize in sheep, which often have more subtle clinical signs than cattle. In herds or flocks with uncontrolled paratuberculosis, the prevalence of infection tends to gradually increase, and greater numbers of animals become sick. This disease can also cause production losses, such as decreased milk yield.

M. avium ssp. *paratuberculosis* can infect animals other than its usual hosts, but the significance of these infections is still mostly unclear. This organism has been proposed to have a causative role in Crohn's disease, a chronic enteric disease of humans. While this is still controversial and unproven, concerns about a potential zoonotic role have helped stimulate the development of control programs for paratuberculosis. To date, these programs have generally been more successful in reducing the prevalence of infection and clinical cases than in eliminating the organism from a herd.

Etiology

Paratuberculosis results from infection by *Mycobacterium avium* subspecies *paratuberculosis*, an acid-fast rod in the *M. avium* complex of organisms, within the family Mycobacteriaceae, order Actinomycetales. Its name is frequently abbreviated as MAP. Former names for this organism include *Mycobacterium paratuberculosis* and *M. johnei*.

M. avium ssp. *paratuberculosis* strains have been divided into at least two groups, which seem to have some degree of host preference. Type II strains (which are also known as type C) were originally identified in cattle, but they have a broad host range that includes sheep, goats, camelids and both ruminant and nonruminant wildlife. Type I (type S) strains are found most often in small ruminants; however, they have increasingly been reported in other species including cervids, South American camelids and camels, as well as in some cattle in close contact with sheep. Type III strains were once a separate "intermediate" group, but are now considered to be a subtype of type I. There are also two different bison type (B) strains, one in North America and the other in Asia. The latter is a sublineage of type II, and is known as "Indian Bison type." It has been found in cattle, water buffalo, sheep, goats, deer, bison, rabbits, wild boar and other animals, and is the predominant strain in some parts of Asia. A goat-specific strain was proposed to exist in Norway, where paratuberculosis mainly seems to affect goats, and only sporadic infections have been reported in cattle and sheep. One genetic analysis found evidence for a distinct goat strain, but other studies have been unable to confirm this, and management factors or breed-related resistance in cattle could also explain the situation in Norway.

Species Affected

Paratuberculosis mainly affects ruminants and camelids. Some animals reported to develop clinical signs include cattle, sheep, goats, water buffalo, South American camelids, dromedary (*Camelus dromedarius*) and Bactrian (*Camelus bactrianus*) camels, moose, reindeer (*Rangifer tarandus*), bison (*Bison bison*), wild relatives of small ruminants (e.g., bighorn sheep, *Ovis canadensis*; Rocky Mountain goats, *Oreamnos americanus*) and various species of deer, antelope and elk. *M. avium* ssp. *paratuberculosis* infections have also been reported in captive or wild ruminants and camelids not (yet) reported to have clinical signs. Domesticated ruminants are thought to be the primary reservoirs for this organism. Wildlife mostly seem to become infected from domestic herds, although a few wild cervid populations may maintain this organism locally.

M. avium ssp. *paratuberculosis* has also been found in diverse other hosts, i.e., members of families other than the Ruminantiae and Camelidae. Some species reported to be susceptible to infection include European rabbits (*Oryctolagus cuniculus*), wild hares (*Lepus europaeus*), dogs, cats, horses, pigs, wild boar (*Sus scrofa*), red foxes (*Vulpes vulpes*), stoats (*Mustela erminea*), Eurasian otters (*Lutra lutra*), weasels (*Mustela nivalis*), beech marten (*Martes foina*), Egyptian mongooses (*Herpestes ichneumon*), badgers (*Meles meles*), skunks (*Mephetis mephetis*), brown bears (*Ursus arctos*), raccoons (*Procyon lotor*), armadillos, coyotes (*Canis latrans*), opossums (*Didelphis virginiana*), and various species of nonhuman primates, Australian marsupials, rodents and shrews. Rabbits have been proposed as possible reservoir hosts in some areas. Illnesses and/or gross lesions consistent with paratuberculosis have been reported in wild rabbits, nonhuman primates, pigs and dogs, as well as in experimentally infected horses inoculated intravenously, but a causative role was not always proven (see Clinical Signs section for details). *M. avium* ssp. *paratuberculosis* has also been found in some birds, including members of the Corvidae (jackdaws, rooks, crows), starlings, house sparrows (*Passer domesticus*) and gulls.

Zoonotic potential

M. avium ssp. *paratuberculosis* can be found in the intestinal tract of some healthy people. This organism is also proposed to have a role in causing Crohn's disease, a chronic intestinal illness of unknown etiology. There is evidence both for and against this hypothesis, and a causative role is currently unproven (see Public Health). Some investigators have suggested that *M. avium* ssp. *paratuberculosis* might play a role in the onset or progression of a variety of other diseases (e.g., sarcoidosis, diabetes mellitus types 1 and 2, multiple sclerosis, HIV infection, Hashimoto's thyroiditis), based mainly on the presence of antibodies to this organism. One review described weak but consistent evidence for a possible association with diabetes mellitus type 1 in some studies, but not all. For the other diseases, any role appears to be speculative at this time.

Geographic Distribution

M. avium ssp. *paratuberculosis* is thought to occur worldwide. Some countries report never having detected this organism. However, only Sweden and some states in Australia are currently proven to be paratuberculosis-free. An unusual situation exists in Norway, where this disease affects goats but infections in other species seem to be uncommon.

Transmission

M. avium ssp. *paratuberculosis* is transmitted mainly by the fecal-oral route. Some asymptomatic and sick animals shed large numbers of organisms in the feces. Others may shed bacteria intermittently, transiently or not at all during the subclinical stage. Nucleic acids have been detected in the saliva of cattle, but the significance of this finding is currently unclear. The offspring of a number of species, including cattle, sheep, red deer and chamois, can be born infected. In cattle and sheep, this is more likely if the dam is in an advanced stage of paratuberculosis. However, prenatal transmission is reported to be very high in both symptomatic and asymptomatic red deer. Animals can also shed *M. avium* ssp. *paratuberculosis*, to varying degrees, in colostrum and milk. Shedding appears to be more common in clinically affected than asymptomatic animals, and bacterial numbers seem to be highest during the first 2 months of the lactation. *M. avium* ssp. *paratuberculosis* has been detected in semen.

Although young animals can be born infected, most cattle and sheep are thought to acquire *M. avium* ssp. *paratuberculosis* during the first few months after birth, probably when they nurse (via colostrum, milk or fecal contamination of the udder) or are housed in contaminated pens. Animals can also become infected later in life, including as adults, but susceptibility (and/or the ability to control the infection) seems to decrease with increased age. In cattle, susceptibility appears to be highest in calves < 6 months of age, and lowest in adults > 1 year. Calves are considered to be at greatest risk when they are exposed to the feces of infected adults, but infected calves sometimes shed the organism and can transmit it to each other.

M. avium ssp. *paratuberculosis* can be spread on fomites, and some animals might be infected via aerosolized contaminated dust. This organism is common in the environment, especially on contaminated farms; however, it does not multiply outside a living host. It can survive for a year or more on some pastures, although infectivity is reported to decrease significantly within a few months. Survival is greatest in full shade and lower in sunny areas. *M. avium* ssp. *paratuberculosis* has also been reported to persist in some water sources for maximum periods ranging from 9 months to nearly 2 years; in barn dust for at least several weeks; and in bovine feces for up to 8-11 months. Uptake into plants has been demonstrated, although one field study suggested that this organism is more likely to persist in soil than harvested crops. Some data suggest that it could become dormant for a limited time in the environment. *M. avium* ssp. *paratuberculosis* has been reported to form spore-like structures that may help it survive adverse conditions. It might also survive (and possibly multiply) in free-living amoebae, but whether this occurs to any significant extent in nature is currently unclear. Insects have been proposed as possible mechanical vectors.

Little is known about the transmission of *M. avium* ssp. *paratuberculosis* in nonruminant hosts, but fecal-oral spread is probably important. In rabbits, this organism has been isolated from the feces and milk, and from fetuses and the testes. Both horizontal and vertical transmission seems to occur in wild rabbit populations. Predation might be a route of transmission to carnivores or omnivores.

Disinfection

M. avium ssp. *paratuberculosis* is resistant to most disinfectants, and tuberculocidal agents should be employed.

Some disinfectants reported to be effective against members of the *M. avium* complex include sodium hydroxide, chlorine dioxide, ethylene oxide, 0.35% peracetic acid and orthophthalaldehyde. *M. avium* ssp. *paratuberculosis* may survive drinking water treatment, including chlorination.

While pasteurization of milk kills large numbers of *M. avium* ssp. *tuberculosis*, some reports indicate that a small percentage of the organisms might survive, depending on their initial numbers and the specific combination of heat and time. Other reports suggest that pasteurization is effective, and unrealistically high initial pathogen concentrations or defects in the pasteurization conditions could account for most studies reporting treatment failures.

Standard heat treatments for colostrum, such as 56-59°C (133-138°F) for 60 minutes, can significantly decrease the number of *M. avium* ssp. *paratuberculosis*, but they do not necessarily kill all of the organisms. Complete destruction may not be achievable, as colostral antibodies must be preserved and the colostrum should not become too viscous to feed.

Incubation Period

The incubation period for paratuberculosis ranges from months to years. Incubation periods of 2-5 years are common in cattle, which rarely show clinical signs before they are 2 years old. In rare cases, the incubation period may be as long as 15 years. Paratuberculosis can appear sooner in small ruminants, cervids and some camelids. In these species, it is not unusual to see clinical cases in animals that are less than a year old. Some cervids may become ill as soon as 5-8 months of age.

Clinical Signs

Ruminants and camelids

Paratuberculosis typically presents as sporadic clinical cases in most species, including cattle and small ruminants. However, it can appear as an outbreak in cervids, affecting even young animals.

In cattle, the major clinical signs are diarrhea, typically without blood, mucus or epithelial debris, and wasting. The initial signs can be subtle, and may be limited to weight loss, decreased milk production or roughening of the hair coat. Diarrhea can be intermittent at first, but it becomes more constant and severe over weeks or months. Tenesmus is not seen. Some cattle also develop subcutaneous edema, especially submandibular and/or ventral edema, as the result of decreased plasma protein concentrations. Body temperature and appetite are usually normal, and animals are alert. Paratuberculosis is progressive; affected animals become increasingly emaciated and usually die with terminal cachexia and dehydration.

While the clinical signs are generally similar in other ruminants and camelids, there can be some differences, particularly in the presence and extent of diarrhea. Weight loss and exercise intolerance are prominent signs in sheep and goats, and affected animals may trail the flock. Diarrhea

is less common than in cattle, it is more likely to appear as soft feces than frank diarrhea, and it may be intermittent. Some small ruminants have submandibular edema ("bottle jaw") without other evidence of edema, and the wool is often damaged and easily shed. Anemia is also reported to be common. South American camelids may also have no apparent diarrhea despite other signs of advanced paratuberculosis. However, diarrhea is a common sign in some cervids, and it is reported to be severe in some camels. The course of the illness may be unusually rapid in both cervids and camels.

Other species

The effects of *M. avium* ssp. *paratuberculosis* on other hosts are still largely unknown. Many infected animals were identified during surveillance for this organism, and either did not have clinical signs or were not observed before death (e.g., surveys of hunter-killed animals). Intestinal lesions consistent with paratuberculosis and/or illnesses have been reported in a few species.

M. avium ssp. *paratuberculosis* can cause diarrhea and weight loss in orally inoculated rabbits, but whether it affects naturally infected animals is controversial. Some studies have found gross lesions in wild rabbits, but others only detected microscopic lesions. This organism was also found in a South African dog that had a fever, progressive weight loss and debilitation, associated with granulomatous ileitis, splenomegaly and abdominal lymphadenopathy. A survey found nucleic acids in intestinal biopsies from some dogs with gastrointestinal signs due to food allergies or inflammatory bowel disease, as well as some dogs that had mild or no lesions and might have been affected by non-GI causes of vomiting and diarrhea.

Reports of paratuberculosis in pigs and horses are rare, and date from before the advent of nucleic acid methods (e.g., PCR) for definitive identification of this microorganism. A pig suspected to have paratuberculosis had intestinal lesions ("hyperplastic enteritis") containing acid fast bacilli; however, other *M. avium* serotypes can cause granulomatous enteritis in pigs, and the organism's identity was not confirmed. In a later report, a mycobacterium was found in a herd of asymptomatic pigs with lymph node lesions, and the organism's identity was established by experimental inoculation into calves. Experimentally infected pigs appeared to be unaffected in one study, but grew more slowly than control pigs, without obvious clinical signs, in another report. Pigs developed lymph node lesions (caseous nodules) in both studies. One of the studies reported that they also had intestinal lesions consisting of diffuse areas of granulomatous inflammation in the small intestine and infrequently the large intestine.

A report of *M. avium* ssp. *paratuberculosis* in a horse described the isolation of a mycobacterium from the mesenteric lymph nodes, but did not mention any clinical signs. The isolated organism produced paratuberculosis lesions when it was inoculated into calves. This article also mentioned that MAP-like organisms were found in the

mesenteric lymph nodes of a farm horse with profuse diarrhea and a corrugated small intestine in 1913. Experimentally infected horses developed intestinal lesions (granulomatous inflammation), lymph node lesions and clinical signs (weight loss, rough hair coat, transient diarrhea) after intravenous inoculation. However, horses fed bacteria had no lesions or signs of illness.

Post Mortem Lesions   Click to view images

The carcasses of animals with advanced disease are usually thin or emaciated. There may be dependent edema and/or fluid in the body cavities.

The characteristic lesion in cattle is a thickened, often corrugated, intestinal wall, most apparent in the distal small intestine. In some advanced cases, lesions may extend from the jejunum to the colon. Discrete plaques may be present early in the disease, and can sometimes be detected by holding the intestines up to a light source. The intestinal mucosa is not usually ulcerated. The mesenteric lymph nodes and other regional nodes (e.g., ileocecal nodes) are often enlarged and edematous, and subserosal lymphatics tend to be prominent. Gross lesions are usually absent or subtle in subclinical carriers, and they are occasionally absent or minimal in clinical cases. The lesions in South American camelids are reported to be similar to those of cattle, but there may also be lymph node necrosis and mineralization.

Affected areas of the intestines are often only slightly thickened in sheep, and may appear normal even in sick animals. Certain type I (S) strains of *M. avium* ssp. *paratuberculosis*, which are more common in sheep than cattle, produce a pigment that stains the intestinal lesions yellow or brownish–yellow. Caseated or calcified foci are sometimes found in the intestines and associated lymph nodes of sheep, goats and cervids. Some goats have lesions that are similar to those of sheep, with little or no thickening of the intestinal wall. However, there are also reports of naturally infected goats with severe, diffuse intestinal lesions that are especially prominent in the proximal jejunum. Reported lesions in some of these animals included a thickened intestinal wall; mucosal lesions described as "cobblestone-like," with hyperemia, ulcerations and fibrinous exudates; and fibrous peritoneal adhesions and intestinal strictures in some cases. Some experimentally infected goats developed typical paratuberculosis lesions (e.g., caseous nodules or segmentally thickened, corrugated small intestinal mucosa). Others had crater-like lesions, which sometimes progressed to become confluent, in the small intestines. Granulomatous lesions have also been noted occasionally in other organs, especially the liver, of sheep, wild small ruminants, cervids, South American camelids and captive saiga antelope (*Saiga tatarica*).

Limited information is available for nonruminant species. Thickened, often corrugated, intestinal walls, and enlarged, edematous, and granulomatous to abscess-like tuberculous lesions in the regional lymph nodes have been reported in rabbits. Intestinal lesions are reported to be most common in the cecal appendix, sacculus rotundus and cecum in this species. Microscopic lesions have sometimes been reported in other species including foxes and stoats; however, gross lesions are usually mild or absent. Few or no lesions have been reported in wild birds and rodents.

Diagnostic Tests

The best tests to identify infected animals can vary depending on the stage of the disease. Animals in the early stages of the infection may not be recognizable with any of the current tests.

Ziehl–Neelsen stains can be used for a presumptive diagnosis in clinical cases; clumps of small, strongly acid-fast bacilli in the feces suggest that the signs might be caused by *M. avium* ssp. *paratuberculosis*. Organisms may also be found in smears from the intestinal mucosa or the cut surfaces of lymph nodes. Bacteria can be sparse or absent in some infected animals. Histopathology can also be helpful in diagnosis. Immunostaining methods can detect organisms in tissue samples, but the antibodies may cross-react with other mycobacteria.

M. avium ssp. *paratuberculosis* or its nucleic acids can be found in the feces, intestinal tract and associated lymph nodes at necropsy. Commonly recommended samples for culture include the ileum, mesenteric and ileocecal lymph nodes and liver, although the organism may also be detected at other sites. Posterior jejunum and the ileocecal lymph nodes were the most valuable necropsy samples for detecting mild lesions in subclinically infected red deer. Biopsies of the ileum and regional lymph nodes may occasionally be useful in valuable domesticated animals. Milk can also be tested, and environmental sampling is sometimes used to detect infected herds.

M. avium ssp. *paratuberculosis* may grow on a number of specialized culture media, but some strains, such as those belonging to type I (S), are more difficult to isolate. One group found that a number of type I and type II strains all grew on Middlebrook 7H10 and 7H11 media with mycobactin J, although some did not grow on other commonly-used media. Some authors suggest culturing organisms on more than one medium. *M. avium* ssp. *paratuberculosis* grows slowly, and depending on the strain and culture medium, results may not be available for several weeks or months.

PCR assays are rapid, and are often used for diagnosis. Loop-mediated isothermal amplification (LAMP) methods have also been published. Specialized genetic techniques, such as pulsed-field electrophoresis and restriction fragment length polymorphisms, are useful for epidemiological investigations, and can distinguish type I and II strains.

Serology can be useful for the presumptive identification of infected animals, or to help confirm paratuberculosis in animals with clinical signs. Enzyme-linked immunosorbent assays (ELISAs), complement fixation and agar gel immunodiffusion tests are available. ELISAs are more sensitive and more likely to detect subclinically infected cattle, but CFT and AGID are also useful in clinical cases. ELISAs that detect antibodies in milk

are available. Detectable titers are slow to develop in infected animals: serum titers usually appear 10-17 months after infection, but may take longer. Serological responses can be weak in some infected animals that are not shedding bacteria. Conversely, animals that have cleared the infection may be seropositive. False positive reactions can be caused by other mycobacteria and some other organisms.

Intradermal testing with johnin or avian purified protein derivative tuberculin can detect delayed-type hypersensitivity (DTH) reactions to *M. avium* ssp. *paratuberculosis*; however, this test is insensitive and nonspecific reactions are common. The gamma interferon assay, an *in vitro* test that detects cell-mediated immunity to *M. avium* ssp. *paratuberculosis*, can identify some subclinically infected animals before antibodies can be found in serological tests. Cross-reactivity with other organisms can result in false positive reactions in both tests.

Both antibody levels and cell-mediated immunity can diminish or become undetectable in advanced disease.

Treatment

There is no known cure for paratuberculosis. A few animals have been treated with various drugs including isoniazid, rifampin, clofazimine, aminoglycosides and other agents. The use of probiotics has also been explored. Treatment may result in clinical improvement and prolong the animal's life, but lifelong treatment is thought to be necessary, and some animals nevertheless relapse. Milk or meat from treated animals should not be used for human consumption.

Control

Disease reporting

Veterinarians who encounter or suspect paratuberculosis should follow their national and/or local guidelines for disease reporting. Paratuberculosis is a reportable disease in many U.S. states; state regulations should be consulted for more specific information.

Prevention

M. avium ssp. *paratuberculosis* is usually introduced into a herd in an infected animal and persists in breeding stock. While it may be useful to test herd additions, diagnostic tests on individual animals are unreliable for ensuring freedom from infection, especially in animals < 3 years of age. For this reason, farmers should buy replacement animals from test-negative herds with good records and management practices. Multiple tests, conducted over a prolonged period, are often necessary to determine whether *M. avium* ssp. *paratuberculosis* exists in a herd or flock. Control programs, such as the voluntary Johne's Disease Herd Status Program in the U.S., can identify herds at low risk for being infected. Minimizing contact between wildlife and livestock decreases the risk that a wild animal might infect a MAP-free herd, or (more likely) that an infected herd will transmit paratuberculosis to wild species.

Once paratuberculosis has entered a farm, the basic control techniques are 1) to protect animals from exposure to infectious manure, colostrum and milk while they are young and most susceptible to infection, and 2) to decrease overall exposure to *M. avium* ssp. *paratuberculosis* in the herd. While these measures may not eliminate the organism, they can decrease the prevalence of infection and result in fewer animals with clinical signs.

Test and removal programs reduce the level of exposure by periodically testing a herd or flock, and separating and/or culling the infected animals, especially those shedding large numbers of organisms. The offspring of infected dams, particularly dams that are sick, may also be considered for removal. Good manure management and disposal are expected to help reduce environmental exposure. Manure build-up should be prevented, and surfaces should be kept clean. Food and water troughs may be elevated to reduce contamination. Piped water is less likely to be contaminated than ponds. Occasionally (e.g., in disease-free countries), entire herds may be culled and restocked with uninfected animals. One study found that high pressure washing, disinfection and a 2-week waiting period reduced environmental contamination below detectable levels.

In infected dairy cattle herds, management practices help protect calves during the period when they are most susceptible to *M. avium* ssp. *paratuberculosis*. Cows should give birth in clean, dedicated maternity pens to minimize their offspring's exposure to infectious feces at birth. One study suggested that individual calving pens are more effective than group pens. Calves are also removed from their dams at birth, fed colostrum from cows free of *M. avium* ssp. *tuberculosis* (or colostrum replacement products) and raised separately from the adult herd. Milk replacer or pasteurized milk, rather than raw milk, should be fed until the calves are weaned. (Because this organism might still be present in some pasteurized milk, milk replacer is thought to be safer.) U.S. paratuberculosis programs recommend that calves remain separated from adult cattle for at least their first year. Some authors suggest it would be ideal to also separate calves of different infection status; however, this may be impractical or even impossible to accomplish. Chemoprophylaxis with monensin has been investigated in some calves.

Similar management measures can be used in young animals of other species, to the extent that they are practical. The practice of feeding bovine colostrum to some neonatal alpacas has been mentioned as a possible risk factor in this species. In all species, feeding pooled milk or colostrum increases the risk that young animals will be exposed to an adult shedding *M. avium* ssp. *paratuberculosis*.

Vaccines are available in some countries for cattle, sheep and goats, and they have also been investigated in red deer. Vaccines can decrease the incidence of clinical signs, and may also reduce shedding of the organism. They are an important component of some control programs in sheep. Consistent vaccine use in this species, generally in young replacement animals, appears to reduce the prevalence of infection within a flock. Some countries restrict vaccine use, usually due to concerns about interference with tuberculosis testing.

Control programs for paratuberculosis have been established in a number of countries. They range in size and scope from small independent programs to large government-run initiatives. Most programs assist farmers in identifying and maintaining paratuberculosis-free herds and/or help infected farms reduce the prevalence of infection. Eradication is the eventual goal of a few national programs, such as those in Denmark and the Netherlands. A few countries have strict programs that keep herds in paratuberculosis-free regions from becoming infected.

Morbidity and Mortality

M. avium ssp. *paratuberculosis* is common in many dairy-producing countries, where approximately 20-50% or more of the dairy cattle herds are often infected. This organism can also be a significant problem in sheep, goats and captive red deer. Its overall prevalence is usually much lower in beef cattle; nevertheless, paratuberculosis can be a health issue in some beef herds. A number of zoos have reported finding *M. avium* ssp. *paratuberculosis*, including some that have detected it in exotic ruminants. This organism has been described in pigs, but infections seems to be uncommon in this species. Its prevalence also tends to be low in most wildlife populations, although reservoirs do seem to exist in some regions.

Most cattle and sheep that are exposed to *M. avium* ssp. *paratuberculosis* either eliminate the organism or become asymptomatic carriers, while a minority develops clinical signs. Affected animals eventually die. Clinical cases tend to be sporadic in most species, and the mortality rate is approximately 1% in most dairy cattle herds. However, captive deer can experience outbreaks of rapidly progressive disease, with morbidity rates up to 20% reported in some herds of red deer. In a newly infected cattle herd, *M. avium* ssp. *paratuberculosis* usually spreads for years before the first clinical cases appear. If no preventive measures are taken, the number of infected animals tends to gradually rise, young animals are exposed to increasing doses of bacteria, and clinical cases appear more frequently – first in older animals and later, as the exposure level increases, also in younger animals. In herds where the organism is widespread, clinical signs can be seen in second- and first-calf cows, and even in springers or bred heifers. Paratuberculosis can also cause production losses, including reduced milk yield, in subclinically infected cattle. The extent of milk production losses is controversial. One recent study suggested that milk yield might return to normal in cattle that are able to control the infection, and the most significant losses occur in animals that will progress to develop clinical signs.

What proportion of carriers will eventually develop clinical signs is still uncertain; however, some studies suggest that most infected cattle and sheep are able to control the organism and do not become ill within their expected lifetimes. In calves, lambs and red deer, progression to disease seems to be more likely if they are infected when young. While experimentally infected cattle can repeatedly start and stop shedding high numbers of mycobacteria, one recent study suggests that only a small percentage of naturally infected cattle (<10%) become high shedders, and these animals usually die or are culled within a year. In this study, animals that continuously shed *M. avium* ssp. *paratuberculosis* were likely to become high shedders, even if the numbers of organisms were initially low. Animals that shed organisms intermittently and in low numbers appeared less likely to progress to clinical signs. There is also some evidence that genetic background may influence disease progression in cattle and red deer; however, the genes involved are not well understood.

Public Health

Possible association with Crohn's disease

M. avium ssp. *paratuberculosis* has been proposed to have a role in some human diseases. In particular, some studies suggest that this organism might be involved in Crohn's disease, a chronic enteritis of humans. Crohn's disease is characterized by periods of malaise, abdominal pain, chronic weight loss and diarrhea, with remissions and relapses. It often begins between the ages of 16 and 25 years, and persists lifelong. The cause of Crohn's disease is not known; however, it may result from several interacting factors including a genetic predisposition, an abnormal immune response, and environmental factors such as responses to intestinal microorganisms.

M. avium ssp. *paratuberculosis* can be found in both healthy people and Crohn's disease patients. However, some studies suggest that the organism itself, its nucleic acids and/or serological evidence for exposure are more common in people with Crohn's disease. These studies vary in their methodology and quality, and not all show a link. One issue with the MAP hypothesis is that recent studies could not find an association between Crohn's disease and living on a farm, contact with infected domesticated animals, or the consumption of dairy products. Nevertheless, it should be kept in mind that wider environmental or food sources could also be sources of exposure. Another issue is that studies to date have not been able to demonstrate a direct or indirect causative role for *M. avium* ssp. *paratuberculosis* in the pathogenesis of Crohn's disease. Even if this organism is common in patients, it might simply be an "innocent bystander" that is more likely grow in an inflamed intestinal wall. Therefore, whether *M. avium* ssp. *paratuberculosis* plays a role in Crohn's disease is currently unclear, but the possibility cannot be discounted.

Vaccine safety

Paratuberculosis vaccines, which are oil-based, can cause severe local reactions including tissue sloughing, chronic synovitis and tendonitis, if they are accidentally injected into humans. The severity of the reaction may depend on the amount of vaccine injected and amount of tissue damage. Some cases can require surgery.

Internet Resources

International Association for Paratuberculosis

Mycobacterial Diseases of Animals

The Merck Veterinary Manual

University of Wisconsin School of Veterinary Medicine Johne's Information Center

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

WOAH Terrestrial Animal Health Code

Acknowledgements

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