Mycobacterium avium and Mycobacterium intracellulare infection in mammals

M.-F. Thorel (1), H.F. Huchzermeyer (2) & A.L. Michel (3)

(1) Agence française de sécurité sanitaire des aliments, 22 rue Pierre Curie, B.P. 67, 94703 Maisons-Alfort Cedex, France
(2) P.O. Box 12499, Onderstepoort 0110, South Africa
(3) Agricultural Research Council-Onderstepoort Veterinary Institute, Private Bag X05, Onderstepoort 0110, South Africa

Summary

Mycobacterium avium subsp. avium and M. intracellulare are ubiquitous organisms in the environment. The reservoir of M. avium subsp. avium is generally accepted to be environmental, in particular, water and soil are sources of the organism. In contrast to M. avium infection in wild and domestic birds, M. avium infection in mammals occurs only sporadically and is rarely transmissible. Generalised disease is usually uncommon, owing to the non-progressive, chronic character of the infection. However, some cases of disseminated disease have been reported, e.g. in captive non-domestic hoofed animals as well as in immunosuppressed dogs and cats. The majority of M. avium and M. intracellulare infections in livestock are detected at slaughter and the diagnosis is confirmed by bacteriological procedures. Condemnation of affected portions of the carcass can result in significant economic losses, although gross lesions are mostly restricted to lymph nodes close to the alimentary tract. Successful treatment with antibiotics in combination with surgery has been reported in some affected domestic cats, but is not considered to be effective or economical in other species. In the past, differentiation of M. avium bacteria from the closely related M. avium subsp. paratuberculosis was based on the mycobactin dependence and prolonged incubation period of the latter. More recently, amplification of the genomic insertion sequence IS900 has proved to be a powerful tool for identification of M. avium subsp. paratuberculosis. The potential zoonotic importance of M. avium infections has been indicated, but requires clarification.

Keywords


Introduction

The M. avium complex is comprised of M. intracellulare and three subspecies of M. avium, namely: M. avium subsp. avium, M. avium subsp. paratuberculosis and M. avium subsp. silvaticum. A discussion of Johne’s disease (infection with M. avium subsp. paratuberculosis) is presented in the papers by Manning and Collins (82) and Kennedy and Benedictus (68), and will not be addressed in this paper. Unless otherwise specified, the mycobacterial species under discussion will be M. avium subsp. avium or M. intracellulare.

Aetiology

Mycobacterium avium and M. intracellulare are acid-fast, slow growing organisms, which produce effuse growth or discrete colonies of approximately 1 mm in diameter after nine to twenty days incubation (see Rastogi et al. in this issue [107]). The colour of the colonies may be pearly grey or lemon yellow and occasional colonies may be bright yellow (44). Most colonies emulsify easily, and microscopically, the bacilli are small, approximately 1 µm × 0.5 µm, almost resembling cocci (44). Mycobacterium avium strains grow at 45°C, while
M. intracellulare strains can grow only up to a temperature of 42°C (38). Several environmental mycobacteria will not grow at 37°C in primary culture, but will grow at temperatures between 28°C and 33°C (138). This variability in optimal growth temperature may be one reason for failures to grow mycobacteria from the environment. In laboratory media, the optimum pH for growth of M. avium organisms is pH 5 to 5.5 (104). Mycobacterium avium subspp. avium and M. intracellulare comprise twenty-eight serovars (147). Serotypes 1-6 and 8-11 are strains of M. avium, and serotypes 7 and 12-20 and 25, strains of M. intracellulare (62, 111, 147). The most widely used method of differentiating amongst strains of M. avium and M. intracellulare is seroagglutination (113, 130, 144). However, many strains autoagglutinate or are non-reactive with currently available sera (22). Culture and biochemical tests cannot distinguish between M. avium and M. intracellulare. Various serotypes can be identified if deoxyribonucleic acid (DNA) probes specific for the two species are used (111). Mycobacterium avium organisms have been divided into three subspecies according to genetic and cultural characteristics, namely: M. avium subspp. avium, M. avium subspp. silvaticum and M. avium subspp. paratuberculosis (103, 139).

Tools developed more recently to investigate the relationship between isolates of M. avium and M. intracellulare are restriction fragment length polymorphism (RFLP) typing with the insertion sequences IS1245 or IS901, pulsed-field gel electrophoresis (PFGE) and multilocus enzyme electrophoresis (MEE). These techniques have helped to identify members of M. avium and M. intracellulare (1, 13, 39, 46, 69, 73, 98), but references to serotypes are still found in the literature.

Host spectrum

Mycobacterium avium and M. intracellulare cause infection and disease in a wide range of mammals, including humans (38, 40, 44, 49, 62, 72, 129, 134, 151). The widespread occurrence and significance of localised infection in the form of lymphadenitis in pigs has been documented in a large number of case reports and reviews published world-wide (136), including Europe (32, 71, 72, 76, 94, 95, 100, 112, 114, 120, 128, 148), Australia (39), New Zealand (37), Japan (89, 90), North America (18, 20, 129, 136), South America (5) and Africa (70, 91). In cattle, as in pigs, infection with M. avium and M. intracellulare does not usually lead to clinical disease. The veterinary importance of the infection lies in the development of a sensitisation to purified protein derivative from M. bovis culture (PPD-B), and thus an interference in surveillance for infection with M. bovis if the single skin test is performed (7, 28, 67). Cervids are naturally susceptible to infections with M. bovis, M. tuberculosis and M. avium (27). In farmed deer, the population density and therefore the likelihood of these infectious diseases is increased considerably (3, 27, 45, 61, 109, 123, 143).

In horses, mycobacterial disease is considered to be uncommon, although several cases have been described (15, 21, 41, 47, 55, 75, 118, 149). Mycobacterium avium infections are rarely encountered in sheep and goats, but can cause intestinal lesions and generalised disease (141).

Cases of localised pathological changes associated with the skin, and generalised disease have been reported in domestic cats (29, 31, 48, 64, 66, 74, 81, 86, 93, 125, 145). Dogs are reportedly more susceptible to infection with M. tuberculosis and M. bovis, but relatively resistant to M. avium and M. intracellulare (53). However, sporadic reports of dogs naturally infected with M. avium have occurred during the 1980s and 1990s (9, 56, 119, 150).

Naturally acquired infections with M. avium and M. intracellulare are reported to be rare in non-domestic species such as non-human primates and exotic hoofed animals (140, 141). However, M. avium has been isolated from several species of mink (Mustela vison) (40, 50), free-living hedgehogs (Erinaceus europaeus) (84) and a ferret (Mustela furo) (117). Mycobacterium intracellulare has been isolated from wallabies (Macropus parma) (101, 116) and the isolation of M. avium complex was reported in kangeroos (Dendroagus matschieti) (87, 132) and macaques (Macaca arctoides) (43, 60) without further differentiation of the mycobacterial species.

Clinical findings

In deer, infections with M. avium are characterised by loss of condition, diarrhoea, faecal staining of the perineum, low serum albumin and total protein. In other cases, the infection is clinically inapparent (26, 79). In one case, ataxia and weight loss were observed in an eighteen-month-old deer (99).

In pigs and non-cervid ruminants, clinical signs characteristic of infection by M. avium and M. intracellulare are rarely observed. The small lesions of 1 mm-10 mm in diameter, in a few lymph nodes of the intestinal tract or head and neck, as seen in swine at slaughter, will not cause detectable clinical signs (30) (Fig. 1). In cattle, infections due to M. avium and M. intracellulare are usually self limiting and may not be detectable (33).

Mycobacterium avium infection in horses involves principally the intestinal tract, similar to Johne’s disease in cattle, and clinical signs are moderate or persistent weight loss, intermittent diarrhoea and anorexia (21, 47). Inappetence and hypoproteinaemia (15) may also be observed. In other cases, clinical signs reported in horses as a consequence of infection with M. avium complex organisms were spontaneous abortion, weight loss, intermittent diarrhoea, a chronic lingual ulcer and increasing blindness occurring in both eyes (21, 55, 75). A skin condition consisting of localised swelling of one or more extremities, and in some cases also the forehead, was
Fig. 1
Tuberculous lymphadenitis in a porcine mesenteric lymph node
*Mycobacterium avium* complex was isolated from this node
Bar = 10 mm

Mycobacterium avium complex was isolated from this node

Mycobacterium avium infection in cats and dogs may be localised to the skin (31, 81, 85, 125) or may progress to disseminated disease involving the alimentary and/or the respiratory tract (31, 74, 102). Anaemia and anorexia are the most frequent abnormalities observed in cats with disseminated *M. avium* infections (88, 125). In both species, mild to progressive weight loss with depression, lethargy and weakness may be observed. Inappetence and, in the cat, sporadic vomiting after eating are described (74, 102). Spleno- and hepatomegaly have been noted in both species, in addition to enlargement of lymph nodes. The liver is frequently involved in canine mycobacteriosis (Fig. 2). Involvement of the skin and the eye due to infection with *M. avium* or *M. intracellulare* is more frequently observed in cats than in dogs, while the liver is more frequently affected in canine *M. avium* infections (81, 121). Rare abnormalities, such as a subcutaneous lump behind the jaw (125) and a subcutaneous swelling on the nasal bridge (126), both due to *M. avium*, as well as a discrete raised lesion of the right cornea caused by *M. intracellulare* (29) were also encountered in cats.

In tree kangaroos (*Dendrolagus* sp.) kept in a zoo, lethargy, anorexia and weight loss and sometimes coughing were observed (87) and in Parma wallabies (*Macropus parma*), disorders in locomotion were also detected (116). A pet ferret showed anorexia, vomiting and diarrhoea (117).

**Diagnosis**

The ante-mortem detection of infection depends on the demonstration of delayed-type hypersensitivity to purified protein derivative from *M. avium* culture (PPD-A) or detection of specific antibodies by serology. Diagnosis of clinical disease is made at necropsy, based on the detection of pathognomonic lesions, either grossly or histologically, bacterial culture of *M. avium* and polymerase chain reaction (PCR) testing. The choice of tests depends on the circumstances and the degree of sensitivity required at individual animal or herd level. The animal species is also a factor, for swine, cattle and deer, different laboratory tests can be applied, whilst for horses, cats, dogs and wild animals, the diagnosis relies principally on clinical examination.

Microscopically, a diffuse granulomatous infiltrate with borders of epithelioid cells and multinucleated giant cells can be observed (58, 129). Many acid-fast bacilli can usually be observed in Ziehl-Neelsen stained smears. Lesions caused by serovars 4, 8 and 10 usually contain fewer acid-fast bacilli than those caused by serovars 1 and 2 (135). Histopathological differentiation of mycobacterial lymphadenitis caused by *M. tuberculosis* complex, *M. avium*
or *M. intracellulare* is not possible without the use of mycobacterial species-specific immunohistochemical reagents.

Demonstration of acid-fast organisms followed by culture is the conventional method of detecting the causative bacterium. However, several weeks may be required to obtain the results. More recent techniques, for example PCR, which is based on the amplification of the target DNA, provide a more rapid test result (11, 12, 23, 92, 96, 103). A nested PCR assay and subsequent restriction enzyme analysis is a fast, sensitive and reliable method for routine detection and identification of *M. bovis*, *M. avium* and *M. intracellulare* in paraffin-embedded tissues (6). However, false-positive results due to interference from the biologic sample have hampered some of these assays.

A diagnosis of *M. avium* and *M. intracellulare* infections in swine is based on the use of tuberculin skin tests using PPD-A, but routine testing is not commonly performed in pigs. The presence of *M. avium* infection is generally detected in swine at the slaughterhouse (2). The skin test is performed by injecting 0.1 ml PPD-A (containing approximately 2,500 International Units/0.1 ml [97]) into the dorsal surface of the ear. Test sites should be observed at 48 h post injection. The response may be swelling, induration or oedema of 30 mm in diameter. In the case of disseminated disease, evidence of generalised infection, such as elevated temperature, anorexia and weight loss may be observed (135). Serological tests to detect circulating antibodies in the sera of infected pigs are also in use, for example the slide agglutination test (ELISA) (65) and the enzyme-linked immunosorbent assay (ELISA) (65, 133).

Following infection, cattle mount an immune response which may result in the elimination of organisms. Some cattle develop a positive tuberculin skin test result; this non-specific skin reaction may disappear with time (28, 142). These animals should be retested with the comparative cervical skin test. Those animals infected with *M. avium* or *M. intracellulare* will usually react more strongly to PPD-A than to PPD-B (28, 124).

Following the subcutaneous or oral inoculation of twelve sheep and eleven goats with a suspension of *M. avium* serotype 2, comparative intradermal tuberculin tests showed a positive reaction to PPD-A twenty-three to thirty days after inoculation. At slaughter eighty to 176 days after experimental infection, macroscopic lesions were detected only at the infection sites and the adjacent lymph nodes (54).

In deer, the single cervical skin test was used on farmed fallow deer in Tasmania, to determine the specificity of this test. Increases in skin thickness of 1 mm and 2 mm were arbitrarily used as significant responses. One lymph node each from two of nine reactors contained mycobacteria identified as *M. avium* and *M. scrofulaceum*. This report emphasises the difficulties associated with the use of the single cervical skin test for certifying freedom from infection with *M. bovis* in deer (77). Given the increasing economic losses due to paratuberculosis in deer, it is important to note that neither the comparative skin test nor the currently available serological tests are able to differentiate between disease due to *M. avium* subsp. *paratuberculosis* and a similar condition caused by *M. avium* (79).

The gamma interferon (IFNγ) assay is another test for diagnosis of *M. avium* and *M. intracellulare* infections in cattle and several other members of the family Bovidae. The test is based on the release of IFNγ from lymphocytes sensitised with antigen from mycobacteria. The relative amount of IFNγ is quantified by a sandwich ELISA that uses two monoclonal antibodies to bovine IFNγ (110). This assay has been used more in the research setting than for standard diagnostic purposes.

Among the few reports on *M. avium* complex infections in horses, a diagnosis of placentitis and abortion was based on the histological association of numerous acid-fast bacilli with placental lesions and isolation of *M. avium* complex organisms (55). The tuberculin skin test is unreliable in the horse, as tests may be positive in 70% of clinically normal horses (80).

In cats, radiographic examination of the thorax and histological examination of biopsied lymph nodes were found useful in combination with amplification of mycobacterial DNA by PCR (145). In dogs, clinical diagnosis is difficult because the primary clinical signs are non-specific. Chronic respiratory problems, pleural effusion and large numbers of acid-fast bacilli on Ziehl-Neelsen stained smears should suggest mycobacteriosis. In a male miniature schnauzer showing these signs, periodic acid-Schiff (PAS) and acid-fast (Ziehl-Neelsen) stains demonstrated high numbers of moderately PAS-positive, strongly acid-fast intracytoplasmic bacilli within macrophages. *Mycobacterium avium* was identified using PCR and subsequent hybridisation of the amplified product using a DNA probe on formalin-fixed tissue from the liver (34). Generalised mycobacterial infection was diagnosed, based on enlarged lymph node aspirates and the tissue biopsies from spleen and colon which demonstrated large numbers of acid-fast organisms (119).

In non-domestic mammals, the clinical protocol for infections with *M. avium* and *M. intracellulare* includes physical and radiographic examinations, and haematological and serum chemical analyses (87).

**Epidemiology**

In general, *M. avium* and *M. intracellulare* infections cause localised rather than generalised pathology in mammals, with lesions mostly restricted to the lymph nodes, as previously
These include birds (24), water (146), contaminated litter reported in pigs. As a consequence, infection does not spread such as wood shavings or sawdust (24, 25, 70, 115, 122), soil (70), feed (25), peat (32) and compost (35). Engel et al. demonstrated that granulomatous lymphadenitis could be induced by feeding compost to pigs (35). As compost is now heat-treated, the likelihood of it containing viable mycobacteria and acting as a source of infection is minimised (72). Mycobacteria were also isolated from a wide range of arthropods in various sites such as stables and pastures (10, 36). Sawdust not only carries the infection, but aids the invasion, as mechanical injury of the mucus membranes by sawdust helps mycobacteria to become established (127, 148). Kleeberg and Nel demonstrated in South Africa that M. avium serovars multiplied in woodshavings but not in clean timber before contact with soil (70). This finding provides a possible explanation for an outbreak of M. intracellulare serotype 4 in pigs kept on sawdust that originated from whole trees as opposed to rough-hewn planks in the United Kingdom (148).

However, pigs themselves could be a possible source of environmental contamination (76, 148), since swine with systemic infection can harbour M. avium and M. intracellulare in the contents of the gastrointestinal tract.

Outbreaks of M. avium infections in young deer in New Zealand were believed to be caused by exposure to contaminated feed and water while the deer were kept indoors or in feedlots. As previously mentioned, these outbreaks were unusual in that multiple animals were clinically affected and mortality was high (79).

A continuous cycle of infection has been suggested for cattle. The results of oral infection tests with M. intracellulare suggest that a temporary persistence of M. intracellulare occurs in cattle, often in the mesenteric lymph nodes, followed by the elimination of the organisms and the contamination of the environment (142). This would lead to further infection of susceptible animals which would explain the persistence of M. intracellulare or perhaps other organisms of this mycobacterial group in some cattle herds (142). Clinical investigations into the source of infection in pigs often prove difficult because the disease usually remains undetected until pigs are slaughtered, by which time the source may have disappeared. Three to four months are required for bacon pigs to reach slaughter weight (148) and by that time the infection may be well established in a herd and difficult to eliminate (20, 24). The distribution of serotypes responsible for mycobacteriosis in pigs seems to differ considerably among countries with different environments (62). This probably reflects diverse risks of exposure derived from climatic and environmental factors in different areas and different systems of farming, rather than differences in host-range specificity of determined genotypes (98, 144). With regard to the prevalence of M. avium and M. intracellulare infections in pigs, data can usually only be obtained from meat inspection records (2, 18, 30, 42, 72, 83, 120, 128, 135). However, when 79,452 pigs in Croatia were skin tested using PPD-A, 773 (0.97%) reacted positively and pathological changes characteristic for tuberculosis were detected in 67.5% of the reactors. Mycobacterium avium serovars 8 and 2 were isolated which correlated with those isolated from the environment. Apart from soil, sawdust and water, faeces of sparrows that had contaminated the pig feed was also considered a source of the infection in this study (25). In recent investigations in the Netherlands, the average prevalence of caseous lesions due to M. avium in slaughtered pigs was 0.5% (72). Duerrling et al. report from Germany that the prevalence of lesions caused by M. avium in the mesenteric and portal lymph nodes varied between 0.6% and 37.7%, depending on the origin of the slaughtered pigs (32). In pigs from farms that experienced high prevalence, higher condemnation figures of up to 70% have been reported. In another slaughterhouse survey, the intestines of 10% of the slaughtered pigs were condemned because of mycobacterial lesions in the mesenteric lymph nodes. In this investigation, peat was determined as the source of the M. avium infection (32).

The role of environmental sources appears even more important given the prolonged survival time and environmental hardiness of M. avium and M. intracellulare. Charette et al. proved that M. avium could be isolated from woodshavings kept in paper bags for over one year in a room in which temperatures varied from -20°C to over 30°C (20). In sawdust contaminated with a laboratory strain and kept at 18°C to 22°C, M. avium has been reported to survive for up to seven months (115). Some mycobacteria are relatively resistant to chlorine, which is why some disinfectants are ineffective in killing these organisms (146). The organism has been found in hospital water supplies and municipal drinking water systems comprised of galvanised pipes. These findings are in keeping with the report that the number of M. avium organisms detected is directly correlated with the concentration of zinc in the water (38, 146).

In countries where the prevalence of M. tuberculosis infection in the human population is high, lymphadenitis caused by M. tuberculosis also occurs in pigs. On macroscopic examination, the lesions cannot be distinguished from those caused by M. avium or M. intracellulare. In the experience of the authors, the lesions are mainly detected in the submaxillary lymph nodes. Approximately 20% of mycobacteria isolated from tuberculous lesions in pig lymph nodes were identified as M. tuberculosis (H. Huchzermeyer, unpublished findings). Identification of the causative species of Mycobacterium is relevant for public health reasons.
Control of infection

Control of M. avium and M. intracellulare infections and their spread is of particular importance in countries with a large pig production industry. Control should be based on thorough cleaning and disinfection of equipment and buildings. Cresylic or substituted phenolic compound disinfectants should be used in concentrations of 2%-5% to kill mycobacteria (135). A vaccine designed to enhance cell-mediated immunity could help to prevent infection and disease. The efficacy of two vaccines was evaluated in swine challenged with virulent M. avium serovar 2; the first vaccine was a 'whole cell' M. avium serovar 2 bacterin and the other a subunit vaccine (macrophage inhibitory factor A3). Results indicated that neither vaccine prevented infection in challenged pigs, although the 'whole cell' killed bacterin reduced the severity of gross and microscopic lesions by 47%. However, to prevent the potential for food-borne zoonotic disease, the elimination of the causative mycobacteria is essential (59).

Molecular epidemiology

During recent years, a number of methods have been used to study the molecular epidemiology of M. avium' and M. intracellulare infections, in particular to gain an understanding of the sources of infections in humans.

Seroagglutination with polyclonal sera was previously used to subgroup strains of M. avium and M. intracellulare into twenty-eight different serovars. No major differences were found among the serovars infecting acquired immune deficiency syndrome (AIDS) patients and those infecting non-AIDS patients, either in this study or in a study conducted in the United States of America. Restriction fragment length polymorphism analysis using the insertion sequences IS901, IS2245 and IS901 was used to characterise M. avium strains isolated from domestic and wild birds and mammals including human patients (8, 108). The IS2245 was found to be a useful tool for the differentiation of M. avium strains and a considerable degree of polymorphism among strains was observed. However, the large number of IS2245 copies in strains of M. avium and the many fragments of apparently identical or similar lengths complicate the interpretation of the results. In New Zealand, Collins et al. used RFLP with IS901, IS901, IS1245 and IS1311 as DNA probes to characterise reference strains, isolated from cattle, deer, pigs, sheep and humans (22). The IS901 was detected only in strains of M. avium subsp. paratuberculosis. All strains of M. avium and M. intracellulare contained IS1245 and the majority of those from lesions in cattle, deer and pigs also contained IS901. All animal strains containing IS901 had the same RFLPs, with IS901, IS1245 and IS1311. These results indicate that a very closely related group of M. avium and M. intracellulare strains cause the majority of non-paratuberculosis lesions in animals in New Zealand. A study using MEE and PFGE in Australia suggested that certain strains of M. avium may be transmitted between birds and pigs, but no clear evidence was found of transmission from birds to humans (39).

According to Bono et al. (13) and Ritacco et al. (108), bird isolates carried IS901 and a few copies of IS1245 and pig isolates showed features previously described in human isolates, namely: the absence of IS901 and a high copy number of IS1245. Novel allelic variants of M. avium in isolates from both pigs and humans were found in Brazil (16). Recently O'Grady et al. (98) performed an RFLP investigation using probes derived from IS901, IS1245 and IS1311 on M. avium isolates from humans, deer, pigs and cattle in Ireland. Forty-two of the cervid isolates and two of the bovine isolates contained IS901, while this insertion sequence was absent from all of the human and porcine isolates. The IS901-negative isolates exhibited highly polymorphic IS1245 and IS1311 hybridisation patterns which differentiated the human and porcine isolates into a wide diversity of strain types.

Comparative pathology

When M. avium and M. intracellulare bacilli gain entrance into the host, the most likely route of penetration is the intestinal mucosa (62). The bacilli are ingested by the macrophages within which they grow intracellularly without inhibition (33, 137). The development of disease depends on the ability of the bacilli to survive and to replicate in the host macrophages and to induce a host response. The bacilli are able to resist the intracellular killing mechanisms of macrophages by inactivating superoxide radicals generated by the host cell. The fusion of phagosome and lysosome is inhibited, thus preventing contact with proteolytic enzymes (62, 106). The localised formation of granulomas appears to contain and control the infection in many animals. Characteristics of the organism and the host immune response are thus both responsible for the outcome of the infection.

In mammals, the route of infection with M. avium and M. intracellulare is mainly via the alimentary tract, and lesions develop in lymph nodes of the cervix and intestine. One or several lymph nodes may be involved. Systemic disease develops through pulmonary or gastrointestinal tract invasion, while localised infection of the skin is thought to develop through contamination of penetrating wounds (125).

Microscopically, M. avium and M. intracellulare infections in most mammals are characterised by a diffuse granulomatous, inflammatory reaction involving large numbers of epithelioid macrophages, but without necrosis, fibrosis or calcification. Multinucleated giant cells of the Langhans' type may be present. The number of organisms in lesions is variable (135).
In pigs, the granulomatous lesions detected in the lymph nodes are usually small yellow-white foci of 1 mm-10 mm in diameter, although involvement of an entire lymph node or a number of lymph nodes may occur (30, 57, 135). Lesions are usually detected in the lymph nodes of the head and neck and/or in the mesenteric lymph nodes, indicating that the infection occurs by the oral route. Generalised disease caused by M. avium or M. intracellulare is rare in swine, but has been reported (135). The lesions are proliferative, lardaceous, neoplastic-like granulomas without distinct encapsulation (78, 83). Caseous necrosis and mineralisation are seldom seen (129). Detectable lesions develop three to four months after infection (15). In an investigation in South Africa, Kleeberg and Nel observed that piglets and adult pigs, mainly sows, very rarely presented lesions (70). The authors speculated that piglets must first be sensitised before they will react by producing necrotic lesions and that adult pigs probably overcome the infection because of low virulence and high natural resistance, and are able to reabsorb the necrotic tissue. The absence of live mycobacteria in a third of the lesions indicated that pigs do overcome the infection. In contrast, Thoen et al. detected mycobacterial lymphadenitis caused by M. avium serotype 2 in brood sows and slaughter pigs in Iowa (131).

In cattle, lesions due to M. avium are probably transient (142) and indistinguishable from those caused by M. bovis, grossly and microscopically (28, 135). These lesions are granulomatous with a central area of caseous necrosis that undergoes dystrophic calcification. The central part is surrounded by epithelioid and Langhans’ giant cells and in the periphery by lymphocytes, macrophages and fibrosis. Ziehl-Neelsen staining reveals varying numbers of intracellular acid-fast bacilli (33). Mycobacterium avium has also been isolated from apparently normal lymph nodes (11, 19). When investigating a cattle herd with non-specific skin reactors, De Lisle et al. found that most cattle infected with M. avium serotype 2 were young animals under the age of two years (28). In another investigation, the non-specific reactors were all under the age of four years (4). Hejlick and Treml infected three bulls and two cows subcutaneously with a suspension of M. avium (51, 52); granulomatous lesions were detected only in the subscapular lymph nodes and at the site of inoculation. After repeatedly exposing bulls and cows to faeces from M. avium infected poultry, lesions were detected only in the mesenteric lymph nodes, from which M. avium was isolated. The authors concluded that oral challenge of cattle with faeces from M. avium-infected poultry rarely led to lesions, and if lesions did appear, they were confined to the lymph nodes of the intestine. The authors further suggested that lymph nodes are capable of arresting the infection, as demonstrated by the results of the subcutaneous infection of cattle. The same authors isolated M. avium from the semen of one bull and also from the faeces of another bull after repeated oral exposure of these bulls to poultry faeces. Inoculation of the blood of the experimentally infected bulls into chickens resulted in a PPD-A reaction in the fowl. Mycobacterium avium was not isolated from the semen of naturally infected bulls.

Mycobacterial disease is uncommon in horses, probably due to a lower exposure to infection and a more pronounced natural resistance compared to other species (47). The alimentary tract represents the most common route of infection (15). The infection results in granulomatous enteritis, colitis and mesenteric lymphadenopathy (15, 149). Airborne infection may also occur (47). A case of ocular lesions due to M. avium infection in a horse with disseminated disease was unusual; caseous necrosis was present in the centre of several of the large foci. Acid-fast organisms were detected in most lesions, including those in the eyes. The localisation of the lesions in both eyes indicates that the spread may have been haematogenous (75). Abortion in mares caused by M. avium complex has been described (21, 55).

Cats and particularly dogs seem to be intrinsically resistant to M. avium infection (88). Lesions of the infrequent M. avium infection in cats include localised fluctuant nodules in the skin and subcutaneous tissue with or without involvement of the lymph nodes (74, 81, 86, 125). The route of infection in feline skin disease is thought to be via contamination of existing wounds (e.g. fight wounds). Disseminated disease with granulomas which spread through many organs may also develop in cats and dogs (14). Some breeds of cats and dogs appear to be more susceptible to disseminated M. avium infection. A Siamese cat with severe necrotising and granulomatous lymphadenitis, multifocal necrotising hepatitis and diffuse interstitial pneumonia was reported (31). Similar lesions were observed in three other Siamese cats (64). It is possible that the three cats were predisposed to M. avium infection by an underlying immune system defect. However, a genetic predisposition to intracellular pathogens is more probable, as all three cats were Siamese and two of the cats were related (64). A similar predisposition to M. avium and M. intracellulare infection is reported in the Basset Hound (17) and in the Miniature Schnauzer (34, 85). Hejlick and Treml concluded that healthy dogs have considerable resistance to infection by oral exposure, based on an unsuccessful attempt to infect dogs by feeding the animals large numbers of M. avium organisms (53).

Lesions in deer contained, on average, more acid-fast bacilli, more epithelioid macrophages and fewer Langhans’ giant cells than lesions from which M. bovis was isolated. The majority of the isolates were cultured from retroparyngeal and mesenteric lymph nodes, suggesting that environmental sources were involved. The relatively high incidence of lesions associated with M. avium in deer may be due to an innate susceptibility to infection with M. avium or may in part be due to a reduction in immunity associated with stress in farmed deer (27, 105).
Tree kangaroos are known to be more susceptible to *M. avium* complex infections than true placental mammals (87). The animals develop primary progressive disease with disseminated lesions throughout all tissues, but principally in the lung and long bones. Histologically, pyogranulomatous inflammation and necrosis with large numbers of acid-fast organisms are observed. In a pet ferret, granulomatous inflammation of the pylorus, small intestine, mesenteric lymph nodes, liver and spleen, with the presence of acid-fast organisms was described (117).

**Zoonotic potential**

*Mycobacterium avium* infections in humans have increased during the 1980s and 1990s, principally in human immunodeficiency virus-infected patients. *Mycobacterium avium* can cause pulmonary infections in adults and submandibular lymphadenopathies in children, while disseminated infections occur frequently in the late stages of AIDS (62, 63). There is growing consensus that strains of *M. avium* can cause disseminated disease in humans, including bacteraemia and tissue infection; mortality is primarily caused by selected strains (62). Whether infected mammals play a role in the epidemiology of human mycobacteriosis caused by *M. avium* still needs to be defined (128, 136). Studies in several countries have shown that the serotypes of *M. avium* and *M. intracellulare* and the distribution of these serotypes are similar in pigs and humans. More recent genetic characterisation of isolates in Western Australia (39) and the Netherlands (72) demonstrated an extensive conformity between *M. avium* isolates of human origin and isolates from pigs. Investigations in Switzerland revealed that *M. avium* isolated from humans and animals shared several genotypic characteristics, namely: the absence of IS901, a high copy number of IS1245 and marked polymorphism by PFGE (13, 46). These findings may indicate either the presence of epidemiological links between infected pigs and humans or infection from common sources. A recent report from Denmark suggested that peat used as potting soil for plants may be a source of *M. avium* infection for humans and animals or that animals and peat are potential sources of infection for humans (8). It is most probable that a common environmental reservoir of infection exists, or that pigs and inadequately heated pork products are a vehicle for infection of susceptible humans (13, 98). In addition, a proportion of the human *M. avium* and *M. intracellulare* isolates may represent other groupings within the total spectrum of *M. avium* and *M. intracellulare*, presumably reflecting the fact that humans have sources of infection not shared with pigs (72), and also that both species may have a high susceptibility to a wide range of *M. avium* genotypes (8). In conclusion, more evidence is required to demonstrate the conditions and possibilities of transmission of strains of *M. avium* and *M. intracellulare* from pigs to humans. To achieve this aim, long term epidemiological studies need to be implemented (72).

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**Infections dûes à Mycobacterium avium et à Mycobacterium intracellulare chez les mammifères**

M.-F. Thorel, H.F. Huchzermeyer & A.L. Michel

**Résumé**

*Mycobacterium avium* subsp. *avium* et *M. intracellulare* sont des micro-organismes ubiquistes présents dans le milieu naturel. Il est généralement admis que le réservoir se situe dans l'environnement, en particulier dans l'eau et dans le sol. Contrairement à l'infection due à *M. avium* chez les volailles sauvages et domestiques, l'infection se déclare chez les mammifères de manière sporadique et n'est que rarement transmissible. La généralisation de la maladie est peu fréquente, en raison du caractère chronique non évolutif de l'infection. Cependant, certains cas de dissémination de la maladie ont été signalés, par exemple chez des ongulés non domestiques vivant en captivité ou chez des chiens et des chats immunodéprimés. Chez les animaux d'élevage, la plupart des
infections à *M. avium* et à *M. intracellulare* sont décelées à l'abattoir avec confirmation du diagnostic au moyen d'examens bactériologiques. La saisie des parties de carcasses infectées entraîne de lourdes pertes économiques, bien que les lésions macroscopiques se concentrent en général aux ganglions lymphatiques à proximité du tube digestif. L’antibiothérapie ajoutée à une intervention chirurgicale a donné de bons résultats chez des chats domestiques infectés, mais elle n’est pas jugée efficace ni économique chez d’ autres espèces. Par le passé, la différentiation entre *M. avium* et *M. avium* subsp. *paratuberculosis*, bactéries étroitement apparentées, se basait sur la dépendance à la mycobactine et sur la durée d’incubation plus longue de ces dernières. Plus récemment, l’amplification de la séquence d’insertion génomique *IS900* a fait la preuve de son efficacité pour l’identification de *M. avium* subsp. *paratuberculosis*. Le risque de zoonose lié aux infections dues à *M. avium* a été signalé, mais requiert une investigation plus poussée.

**Mots-clés**
Mammifères domestiques — Mammifères non domestiques — Mycobacterium avium — Mycobacterium intracellulare — Tuberculose.

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**Infección de mamíferos por Mycobacterium avium y Mycobacterium intracellulare**

M.-F. Thorel, H.F. Huchzermeyer & A.L. Michel

**Resumen**
*Mycobacterium avium* subesp. *avium* y *M. intracellulare* son microorganismos ubicuos en el medio natural. Es opinión extendida que *M. avium* subesp. *avium* tiene su reservorio en el medio ambiente, y más concretamente en el agua y el suelo. A diferencia de lo que ocurre en aves tanto salvajes como domésticas, la infección de mamíferos por *M. avium* es esporádica y rara vez transmisible. Dado el carácter crónico y no progresivo de la infección, los casos de enfermedad generalizada de la enfermedad son poco frecuentes. Se han descrito sin embargo algunos casos de diseminación, por ejemplo entre ungulados no domésticos cautivos o perros y gatos inmunosuprimidos. La mayoría de las infecciones de ganado por estas micobacterias se detectan en el momento del sacrificio, tras lo cual suele confirmarse el diagnóstico por métodos bacteriológicos. El descarte de las partes afectadas de la canal puede ser causa de importantes pérdidas económicas, aunque las lesiones macroscópicas se circunscriben principalmente a los ganglios linfáticos cercanos al tracto digestivo. Pese a que en algunos gatos domésticos se ha tratado con éxito la infección combinando el uso de antibióticos y la cirugía, tal procedimiento no se juzga eficaz ni rentable en otras especies. La dependencia de la micobactina y el prolongado período de incubación de *M. avium* subesp. *paratuberculosis* servían, en el pasado, para distinguir a este taxón de su pariente cercano, *M. avium*. Recientemente se ha comprobado que la amplificación de la secuencia genómica de inserción IS900 es una poderosa herramienta para identificar a *M. avium* subesp. *paratuberculosis*. Aunque se ha indicado la posible importancia zoonótica de las infecciones causadas por *M. avium*, tal extremo queda aún por aclarar.

**Palabras clave**
Mamíferos domésticos — Mamíferos no domésticos — Mycobacterium avium — Mycobacterium intracellulare — Tuberculosis.
References


