Mycobacterial infections in domestic and wild animals due to *Mycobacterium marinum*, *M. fortuitum*, *M. chelonae*, *M. porcinum*, *M. farcinogenes*, *M. smegmatis*, *M. scrofulaceum*, *M. xenopi*, *M. kansasii*, *M. simiae* and *M. genavense*

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**Summary**

The epidemiology and the natural distribution of *Mycobacterium marinum*, *M. fortuitum*, *M. chelonae*, *M. porcinum*, *M. farcinogenes*, *M. smegmatis*, *M. scrofulaceum*, *M. xenopi*, *M. kansasii*, *M. simiae* and *M. genavense* are described. In addition to the bacteriological, biochemical and genetic characteristics, the authors review the pathology of these species, including the natural and experimental diseases and the accompanying lesions, diagnosis, antibiotic sensitivities and treatment of animal infections caused by these mycobacteria.

**Keywords**

Antibiotics – Diagnosis – Domestic animals – Epidemiology – Mycobacteria – Pathology – Wild animals.

**Introduction**

The 'atypical' or non-tuberculous mycobacteria (NTM) are mycobacteria belonging to species other than those classified in the *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti* and the newly described *M. canetti*). These mycobacteria have been long recognised as potential pathogens for animals and humans. Some species are opportunistic pathogens for animals (*M. scrofulaceum*), some are primary pathogens for animals (*M. genavense* for birds) and some are agents of zoonosis (*M. marinum*). The importance of NTM in human pathology has dramatically increased due to the epidemic of acquired immune deficiency syndrome (AIDS). These mycobacteria are frequent pathogens of patients with underlying immunodeficiency. The pathology resulting from infections due to these mycobacteria is most often expressed as a chronic granulomatous disease associated with lymphadenopathy, although acute disease can also be a feature. The intracellular localisation of these pathogens is reflected well in the pathology of these pathogens.

*Mycobacterium marinum*, *M. fortuitum* and *M. chelonae* are the only described NTM pathogens of fish, although the organisms can also be found in other animal species. In contrast, *M. xenopi* for which water is the proven reservoir, has not yet been implicated in diseases of fish, despite descriptions of infection by this mycobacterium in toads. *Mycobacterium scrofulaceum*, *M. xenopi*, *M. kansasii*, *M. simiae* and *M. porcinum* are mainly isolated from lymph nodes of animals post mortem. The role of *M. farcinogenes* in bovine farcy still requires clarification. Finally, infections due to *M. genavense* in birds can be considered as a new emerging disease caused by a newly discovered agent.
Progress in nomenclature and identification methods has improved the recognition of the incidence of the diseases caused by NTM. Any change in health status or in medical procedures for humans or in breeding conditions for animals can result in the appearance of new infections due to NTM, as a result of the ubiquity of these mycobacteria in most of the environmental niches (water, soil, sphagnum and wild animals) (123, 209). Food and occupational safety concerns in developed countries strengthen the impact of NTM on the health of humans and animals. New methods have been developed to detect and characterise these mycobacteria, especially polymerase chain reaction (PCR) assays which are easily applicable and more rapid than culture (49, 120, 121, 205). These methods also provide a new alternative for the diagnosis of NTM mycobacterial infections. These PCR assays are not systematically mentioned here, but have been described in the literature for most of the species included in this paper (16, 49, 50, 120, 121, 205). However, due to the wide distribution in the environment of most species of NTM, a definitive diagnosis of infection due to these mycobacteria cannot be based solely on culture and PCR. Pathological and histopathological findings are required to establish a definitive diagnosis that can discount the possibility of contamination from the environment. Extensive and excellent papers covering all aspects of these mycobacteria, including systematics, ecological distribution, epidemiology and disease in humans, have been published in the last decade and are cited in this paper (61, 62, 261). These reviews are highly recommended to those interested in mycobacteria.

**Mycobacterium marinum**

**Epidemiology**

*Mycobacterium marinum* was first described as a pathogen of fish under the names *M. marinum*, *M. platyspeciosus* and *M. balnet*, before these species were recognised as synonyms and named *M. marinum* (271). This species is distributed worldwide in fresh and salt water and also in sphagnum moss (209). The organism has also been detected in unpasteurised milk (96). In humans, *M. marinum* produces an infection of the skin, specifically of the extremities in contact with contaminated water. This pathology was termed 'fish tank granuloma', but the name 'water related occupational granuloma' is preferable, given the various sources of human contamination (54, 61). However, *M. marinum* can be considered a zoonotic agent, since infected fish can transmit the infection to humans directly or indirectly through water.

The distribution of *M. marinum* in animals corresponds to the optimal physiological temperature of the organism, which is below 37°C. *Mycobacterium marinum* is one of the principal pathogens of cultured, ornamental and wild fish living in densely populated habitats. Temperature and water quality appear to be crucial factors for the development of *M. marinum* infection (35).

The natural distribution of *M. marinum* correlates well with the fact that many species of fresh and salt water fish have been reported infected, including Chinook salmon (*Oncorhyncus tshinyaytkscha*) (5), striped bass (*Morone saxatilis*) (88), cod (*Gadus morhua L.*) (47), tilapia (*Oreochromis mossambicus*) (161), European sea bass (*Dicentrarchus labrax*) (118), rabbitfish (*Siganus nivulatus*) living close to caged striped bass, sturgeon (*Acipenser spp.*), angelfish (*Pomacanthus paru* and *P. arcuatus*), rock beauty (*Holacanthus tricolor*), cherubfish (*Centropyge argi*), princess parrotfish (*Scarus taeniopterus*), blue chromis (*Chromis cyaneus*), balloonfish (*Diodon holocanthus*), whitespot filefish (*Canthurines macroceros*), doctorfish (*Acanthurus chirurgus*), reef butterflyfish (*Chaetodon sedentarius*), foureye butterflyfish (*Chaetodon capistratus*) (131) and numerous species of ornamental fish (71, 92, 134). Contaminated fish pellets produced from fish products have been incriminated as the source of epidemics in fish.

Domestic animals such as pigs and cattle are rarely infected with *M. marinum* (33, 162). However, *M. marinum* infections have been described in exotic animals (Amazonian manatee [*Trichechus inunguis*] (157) and wild animals (European hedgehog [*Erinaceus europaeus*]) (226) as well as cold-blooded animals (235). Fatal outbreaks of *M. marinum* infection occurred in a commercial bullfrog (*Rana catesbeiana*) colony (8) and in American toads (*Bufo americanus*) (55, 216).

**The agent**

*M. marinum* is a photochromogenic species which grows at 30°C on primary isolation, but becomes adapted to 37°C on subcultures. Although mycobacteria are usually recognised as either slow or rapid growers according to whether colonies are produced on solid media in less than five to seven days, *M. marinum* is considered as a slowly growing species by Wayne (258) and Rastogi et al. (184) or a rapidly growing species by Jenkins et al. (103). The difference in classification is based on the different cut-off point of five or seven days selected by the authors. *Mycobacterium marinum* usually requires five to seven days to grow on solid media. If checked at five days, colonies may be not well developed and the strain considered as a slow grower, although strains regularly form colonies at seven days. *Mycobacterium marinum* gives rise to smooth colonies that acquire a lemon-yellow colour after photoinduction. Smear microscopy reveals short acid-fast bacilli. In most strains, the catalase activity is weak and thermolabile, a characteristic which easily differentiates *M. marinum* from the other photochromogenic species. Additional differential tests are the absence of nitrate reductase and the presence of urease.

In common with *M. kansasi*, *M. marinum* accumulates alpha-, methoxy- and keto-mycolates. High-performance liquid chromatography (HPLC) allows the recognition of a characteristic pattern that is adopted as the final identification in some laboratories (231). Also in common with *M. kansasi*, additional differential tests are the absence of nitrate reductase and the presence of urease.
M. marinum synthesises a phenolic glycolipid, a rare property among the genus Mycobacterium. Phenolic glycolipids are cell wall components consisting of a lipid core, identical for all molecules of this class, linked to a variable, species-specific osidic part. Interestingly, all mycobacterial species able to synthesise phenolic glycolipids share the alpha-, methoxy- and keto-mycolate profile. In M. marinum, the osidic part is limited to a single sugar. The molecule is almost identical to the phenolic glycolipid synthesised by M. bovis, differing only in the position of the methyl group esterifying the hydroxyl positions 2 or 3 of the sugar (180).

The 16S ribosomal ribonucleic acid (rRNA) structure of M. marinum adds to the discussion of whether the species should be classified as a slow or a rapid grower. The phylogenetic tree based on 16S rRNA shows M. marinum close to M. ulcerans in the vicinity of M. tuberculosis. Moreover, the molecule presents a 27-base long helix 18 (positions 451 to 482 of the Escherichia coli numbering system), a signature specific to the slowly growing species (220). Mycobacterium marinum possesses only one copy of the gene encoding the 16S rRNA, a common feature in slowly growing mycobacterial species; most rapidly growing species have two copies of the gene (11). Interestingly, M. marinum and M. ulcerans possess nearly homologous 16S rRNA gene sequences. The two hypervariable sequences identified in mycobacterial 16S rRNA molecules do not allow differentiation between the two species. Definitive identification is performed by investigation of nucleotide positions outside these two hypervariable regions (115). The investigation of eight housekeeping and structural genes of M. marinum and M. ulcerans confirmed the close genetic relationship inferred from the 16S rRNA data and revealed evidence of recent divergence between the two species (221). Similarly to M. kansasii, M. xenopi, M. ulcerans and M. leprae, M. marinum displays a GyrA protein splicing element, uniformly present at the species level (204). No genomic marker has been described for the molecular epidemiological study of the species.

**Clinical presentation and lesions**

The clinical signs of M. marinum infections in fish are not always pathognomonic. Signs include exophthalmia, cachexia, changes in pigmentation, ulcerative dermal necrosis, skeletal changes, and a swollen abdomen. Diseased fish have lesions on the anterior part of the head, ulcerated body sores, fin and tail rot, and a heavy mucus coating on the body surface (131). The disease is usually chronic. Mycobacterium marinum eventually invades and colonises the internal organs. The usual course of the disease is the appearance of weak and emaciated fish that eventually die (mortality can reach 50%) over a long period (88), although sudden mass deaths can sometimes occur after the purchase of new fish, especially in aquaria (92). In fish cultured in cages or in hatcheries, the disease can be present for many years (5). At post-mortem examination, the main findings are visible granulomata and nodular lesions containing acid-fast bacteria in all major organs (skin, gill, spleen and kidney) (71, 88, 92). In tilapia, in addition to the symptoms of piscine mycobacteriosis, melanotic foci were described in the skin and spleen, due to the presence of melanomacrophages (161).

In frogs and toads, M. marinum infection can be localised as an ulcerative dermatitis and cellulitis (55) or can be invasive and fatal with the presence of disseminated granulomata (8).

**Experimental disease**

Natural M. marinum infection has been reproduced successfully in various species of fish and in leopard frogs. In addition, M. marinum infection in mice has been widely used as a model of temperature restricted mycobacteria infection, such as M. leprae infection.

Sea bass (38), Congo tetra (Phenacogrammus interruptus), tilapia (Saoherodon or Oreochromis esculentus), firemouth cichlid (Cichloma meeki) (207) and goldfish (Carassius auratus) (224) develop either a chronic or an acute fatal M. marinum infection, depending on the dose injected. The acute form of the disease is characterised by a systemic mycobacterial infection, severe peritonitis, tissue necrosis, and a short median survival time. The chronic form of the disease is characterised by granuloma formation in all organs and a longer survival time (224). The granulomata develop rather rapidly and can be observed in the spleen, four to six weeks after the initial infection (38).

Infection of M. marinum in frogs induces a chronic granulomatous disease similar to the natural disease of amphibians. Immunosuppression of the frogs with hydrocortisone results in an acute lethal disease. This model that mimics a spectrum of tuberculosis-like disease has been proposed for the dissection of the genetic basis of mycobacterial pathogenesis (181).

Finally, because M. marinum infection mimics aspects of M. leprae infection, the former has been often used in mice to study the pathophysiology of an intracellular organism whose metabolism is temperature dependant. The multiplication of M. marinum is limited by the body temperature of the mouse, as M. marinum, similarly to M. leprae, prefers cooler sites such as the skin (160). The viability of M. marinum introduced into the footpads of mice declines within thirty days, but small numbers of viable bacilli can be recovered from the footpads of these mice up to eighteen months after initial inoculation (37, 156).

**Diagnosis**

The presence of skin and internal granulomata with acid-fast bacteria is sufficient to suspect M. marinum infection in fish. However, culture of the granulomata followed by the biochemical identification of the growing mycobacteria are necessary for a definitive diagnosis. Polymerase chain reaction tests based on 16S ribosomal deoxyribonucleic acid (rDNA) sequences have been proposed for a more rapid diagnosis that...
can be applied to purified DNA, a simple colony preparation or infected fish tissue (118, 223).

**Antibiotic sensitivity and treatment**

*In vitro,* among the new quinolones, levofloxacin exhibited a higher efficacy in reducing bacterial colony forming units (CFUs) in infected macrophages than ofloxacin (203). In humans, the recommended protocol for treatment is based on minocycline and doxycycline associated with trimethoprim-sulphamethoxazole or rifampin, ethambutol and amikacin (61). Clarithromycin (72) or various combinations including the above-mentioned antibiotics plus ciprofloxacin (130) have also been recommended. In an experimental model in mice, amoxicillin/clavulanate has been shown to significantly reduce the lesions caused by *M. marinum* (28).

Treatment of fish has not been very successful and is not recommended in cultured fish. Feeding diseased fish with rifampin (6 mg/100 g food for sixty days) was not an effective treatment (38, 88) and in experimental studies, this antibiotic only partially reduced the bacterial load of diseased fish (17).

**Mycobacterium fortuitum**

**Epidemiology**

*Mycobacterium fortuitum* is a ubiquitous species broadly present, world-wide in various habitats such as lakes, surface water, potable water and soil (61, 271). In addition, *M. fortuitum* has been detected in the environment of pig farms (sawdust bedding and feed) (44, 45), unpasteurised milk (58, 113), and in houseflies (*Musca domestica*) which may carry *M. fortuitum* from the environment or infected animals to healthy animals (176).

*Mycobacterium fortuitum* has been frequently isolated from wild animals including reptiles, amphibians and invertebrates (235), wild boar (*Sus scrofa*) (108), a swamp buffalo (*Bubalus bubalis*) (85), seals (*Phoca vitulina*) (12, 265) and captive armadillos (*Dasypus novemcinctus*) (52).

In humans, *M. fortuitum* is an opportunistic pathogen found in infections following cardiac bypass surgery, mammoplasty or in disseminated infections in immunocompromised patients (61). *Mycobacterium fortuitum* isolations are not uncommon in normal or diseased domestic and pet animals. The organism has been isolated from skin and diseased organs and also from fluids (bronchial washes or semen) and excretions of dogs, cats, horses, cattle (105, 119), pigs and nearby birds (44), pet birds (95) and fish (134) including guppies (*Poecilia reticulata*), oscars (*Astronotus ocellatus*), discus (*Symphysodon discus*) (21) and salmonids (97).

**The agent**

*Mycobacterium fortuitum/Mycobacterium peregrinum*

The taxonomy of *M. fortuitum* is closely related to biochemically related species including *M. chelonea* and *M. abscessus*, as described by Rastogi et al. in this issue (184). Literature has to be interpreted cautiously, as references to *M. fortuitum* may include *M. peregrinum*, especially in studies published before 1992 when *M. peregrinum* was formally described.

The differentiation of the *M. fortuitum* group from the other rapidly growing mycobacteria was principally based on the strong and early positive arylsulphatase test in these mycobacteria. In 1986, a mycolic acid analysis of the *M. fortuitum* group showed that the arylsulphatase-positive rapidly growing mycobacteria corresponded to three groups defined by three different mycolic acid patterns, namely, *M. fortuitum*, *M. chelonea* and a third group (137). The present nomenclature was modified according to DNA-DNA hybridisation studies, which demonstrated the taxonomic validity of the species *M. fortuitum*, *M. peregrinum* (previously *M. fortuitum* subsp. *peregrinum*), *M. chelonea* and *M. abscessus* (127, 137). The third group fits the properties of *M. mucogenicum*, an extensively investigated species, formally described in 1995 (219).

*Mycobacterium fortuitum* is a non-chromogenic rapidly growing species, able to grow at 30°C, 37°C and 42°C. The biochemical differentiation from other rapidly growing species, in addition to pigmentation and temperature range, relies on positive arylsulphatase activity, a positive nitrate reductase activity, inability to grow on capreomycin and ability to use levulose as a sole carbon source. *Mycobacterium peregrinum* and *M. fortuitum* share all the properties listed above, except that *M. peregrinum* does not grow at 42°C. In addition, *M. peregrinum* is able to grow on media containing mannitol as the sole carbon source, whereas *M. fortuitum* is not (136, 215).

*Mycobacterium fortuitum* accumulates alpha- and epoxy-mycolates, similarly to several other species including *M. peregrinum*, *M. smegmatis*, *M. senegalense* and *M. chitae*. In HPLC analysis of mycolate content, no differences were described between *M. fortuitum* and *M. peregrinum* (73). In *M. fortuitum*, a peculiar peptidoglycolipid with a C-mycoside-like structure has been identified. The core of the molecule differs from that synthesised by *M. avium* in that the oligosaccharide is branched to the lipoprotein by the residue alaninol (the residue is threonine in *M. avium*). Moreover, a sulphate residue has been identified in the oligosaccharide moiety (141).

Biovariants of *M. fortuitum* are distinguished on the basis of sequence differences in 16S rRNA and hsp65 genes (50, 115, 195). An IS6100 (insertion sequence), belonging to the IS6 family, has been identified in *M. fortuitum*. Isolated from a single strain, this IS presents a transposon-like organisation responsible for the natural sulphonamide resistance of the strain (147). Transposition ability has been confirmed in *M. smegmatis* and used for insertional mutagenesis (82).
Circular plasmids have been detected in *M. fortuitum* (7, 129), including pAL5000, a widely used tool for genetic manipulation (129). Linear plasmids have also been detected (171). However, the epidemiological uses of these extra-chromosomal elements have not been investigated. Pulsed-field gel electrophoresis (PFGE) applied to *M. fortuitum* has allowed the identification of isolates involved in independent nosocomial outbreaks, in which water was identified as the source of infection (87).

**Clinical disease and lesions**

*Mycobacterium fortuitum* can be detected in asymptomatic animals or in animals with unrelated pathology. The organism has been isolated from swabs of the nasal cavity of healthy horses (146). Strains of *M. fortuitum* were isolated from one of fifteen dogs and two of nine cats with chronic or recurrent diarrhoea (56). Although this finding suggests a potential role of *M. fortuitum* as an aetiologic agent of chronic diarrhoea, it may only indicate a passive but rather frequent presence of *M. fortuitum* in the digestive tract of these animals.

In dogs and cats, diseases due to *M. fortuitum* have two presentations, namely: a pulmonary disease and a skin disease. *Mycobacterium fortuitum* pneumonia has been reported in dogs (100, 243) as well as an acute suppurative bronchopneumonia with productive cough in a young dog (98). Similar symptoms were also associated with a hypertrophic osteopathy (273). Following bites or wounds, *M. fortuitum* infection progresses to a skin cutaneous granuloma in dogs (80, 218) and cats (51, 126, 155, 268). The skin infection can be chronic, with cutaneous vesicopustular or nodular lesions that can ulcerate, and with fistulous draining tracts. This condition can worsen and evolve to disseminated multiple subcutaneous abscesses on the neck, trunk and limbs (66). A similar skin disease with multiple nodules and fistulas has been described in Southern sea lions (*Otaria byronia*)/South American sea lions (*Otaria flavescens*) and seals (12, 139, 265).

In cattle, the main pathology of *M. fortuitum* is a chronic mastitis (166). In the United States of America (USA), twenty-one strains of *M. fortuitum* were isolated from 2,035 samples of mastitic milk (119). *Mycobacterium fortuitum* has also been frequently isolated from unpasteurized milk (58, 113). However, *M. fortuitum* can be easily killed by regular pasteurisation. The organism does not survive heating to 63.5°C for 30 min under conditions equivalent to the standard holder pasteurisation method (77).

The occurrence of chronic fibrosing mastitis due to *M. fortuitum* is usually associated with the use of large doses of intramammary antibiotics (267). This chronic mastitis does not respond to treatment and cows must be culled (266). Disinfection is difficult due to the inhibition of chemical disinfectants by organic matter (173). The isolation of *M. fortuitum* from the lymph nodes of a swamp buffalo which gave a positive result in a tuberculin test (85) underlines the wide distribution of this bacterium and the problems of cross reaction with bovine tuberculosis. Similarly, in two studies in the People's Republic of China, nine strains of *M. fortuitum* were isolated from the lymph nodes of 321 slaughtered cattle; the cattle were either healthy or positive reactors (86, 257).

*Mycobacterium fortuitum* was isolated from the fluid in swollen stifle and hip joints of three of four pneumonic and arthritic pigs (30). Most of the isolations of *M. fortuitum* in pigs are post-mortem findings from healthy animals or animals presenting a defined pathology (inflamed lymph nodes). *Mycobacterium fortuitum* was rarely isolated from porcine tissues sent to Veterinary Services during a three-year period (1971 to 1974) in the USA; only three strains of *M. fortuitum* were isolated, out of nearly 1,600 mycobacterial strains, most of which were *M. avium* (232). In contrast, *M. fortuitum* was very frequently isolated from lymph nodes of healthy pigs in Brazil; of seventy-nine mycobacteria isolated from 200 mesenteric lymph nodes, sixty-five strains were *M. fortuitum* (65). The organism has been detected in the direct environment of pig breeding facilities, in two of nine samples of sawdust bedding and in three of seven feed samples (44), therefore these may constitute sources of contamination other than water for pigs.

*Mycobacterium fortuitum* is the second most frequently isolated mycobacteria in fish (after *M. marinum*). The bacterium can produce a fatal disease in aquarium fish with skin ulceration and ascites (249). *Mycobacterium fortuitum* has been isolated in freshwater salmonid hatcheries in Australia (97). The bacterium was also isolated from oscars, guppies and discus fish in South Africa and produced high mortality in a guppy farm (21). Isolations have also been made from diseased organs of species of wild marine fish (134).

Surprisingly, *M. fortuitum* has been rarely isolated from birds and exotic animals (234), and has principally been revealed through post-mortem findings rather than in a defined pathology (93, 95). *Mycobacterium fortuitum* was among the mycobacterial species most frequently isolated from the lungs and stools of a large number of armadillos presenting disseminated leprosy infection. However, the bacterium was not found in non-*M. leprae* infected armadillos (52). Dhople *et al.* suggested that the close correlation between the development of disseminated leprosy infection and the occurrence of cultivable mycobacteria in the lungs and stools was perhaps due to the depression of the immune system in these animals in the later stages of infection (52).

With regards to laboratory animals, *M. fortuitum* is naturally pathogenic for mice, producing internal organ abscesses and spinning disease (271).
**Experimental disease**

Experimental infection with *M. fortuitum* has been successfully reproduced in mice, which developed a chronic dermatisis and necrotising granulomatous lymphadenitis with intracellular localisation of the organism; rabbits developed necrotising suppurrative granulomatous lesions only (138). Cats inoculated subcutaneously in the inguinal area developed a pyogranulomatous parnniculitis identical to the naturally occurring disease (138). Oral administration of *M. fortuitum* to cattle induces only mild lesions (microgranulomata in mesenteric lymph nodes) (106, 213). However, the bacterium can produce mastitis when injected into the mammary gland of cows and sheep (166, 193).

Finally, goldfish (*Carassius auratus*) experimentally infected with *M. fortuitum* develop a characteristic chronic granulomatous response similar to that associated with the natural infection (225).

**Diagnosis**

Isolation from lesions and bacterial characterisation of *M. fortuitum* are the only reliable means of definitive diagnosis. A PCR assay that can be applied to a bacterial colony or to infected tissue has been proposed for a rapid diagnosis of *M. fortuitum* infections in fish (223).

**Antibiotic sensitivity and treatment**

*Mycobacterium fortuitum* is susceptible to amikacin, ciprofloxacin, cefotaxin, imipenem (61) and the new macrolides such as clarithromycin (89). However, when administered alone, resistance to ciprofloxacin can develop rapidly (254). Canine pneumonia has been successfully treated by antibiotics with or without pneumonectomy, using a combination of amoxicillin trihydrate-clavulanate potassium and kanamycin (243), or by intravenous gentamicin and cephalaxin followed by an oral course of ciprofloxacin (98). In canine skin infections, surgical resection of lesions was generally of little benefit (126) and antibiotic treatment (enrofloxacin or clofazimine) produced the best results (152, 222). Cefoxitin or cefotetan administered to mice inoculated intravenously with *M. fortuitum* suppressed spinning disease and reduced the severity of renal lesions and the number of organisms in the kidneys and liver, but not in the lungs or spleen (202). Cefoxitin or cefotetan administered to mice inoculated intravenously with *M. fortuitum* suppressed spinning disease and reduced the severity of renal lesions and the number of organisms in the kidneys and liver, but not in the lungs or spleen (202).

**Mycobacterium cheloneae/Mycobacterium chelonae/Mycobacterium abscessus**

**Epidemiology**

*Mycobacterium cheloneae*, which was also described as *M. chelonei* or *M. abscessus* until 1972, is widely distributed in the environment, notably in sphagnum moss, and especially in fresh water sources (rivers, ponds, lakes, drinking water and aquaria) (42, 61, 165), and consequently can contaminate many reagents, materials and medical equipment. As a result, the diseases related to *M. cheloneae* in humans are very varied (skin infection, corneal infection, infection of solid-organ transplant recipients with cutaneous lesions of the extremities, tenosynovitis and joint infection (61, 251)). Not surprisingly, *M. cheloneae* is principally a pathogen of fish, although originally isolated from a turtle (235). The bacterium was isolated in epidemics of fish ‘tuberculosis’ (chronic inflammatory granulomatous disease) in freshwater fish such as the yellow perch (*Perca flavescens*) (48), marine species such as the Atlantic salmon (*Salmo salar*) (24) and ornamental fish (134, 143). In addition, *M. chelonae* was isolated in granulomatous diseases of snakes, turtles (235) and mice (145) and from a fur seal (*Arctocephalus australis*) and a sea lion (*Otaria flavescens*) (12). Rare bovine tuberculosis-like disease (124) and outbreaks of bovine mastitis due to *M. cheloneae* have also been reported (151). Finally, the ubiquitous distribution of this bacterial species is confirmed by the scarce but scattered reports of *M. chelonae* infections in pigs (69, 233), cats (238), dogs (80), a golden hamster (*Mesocricetus auratus*) (111), numbats (*Myrmecobius fasciatus*) (70), an Amazonian manatee (14) and presence of the organism in cryopreserved bovine semen (105).

*Mycobacterium abscessus* (formerly named *M. chelonae* subsp. *abscessus*) had been isolated from various fish species including black acaras (*Cichlasoma bimaculatum*), goldfish, firemouth cichlid, oscar and Japanese medaka (*Oryzias latipes*) (74, 229).

**The agent**

*Mycobacterium cheloneae/Mycobacterium abscessus*

The *M. cheloneae* and *M. abscessus* species are closely related. The history of the nomenclature of these species is rather complicated and confuses the understanding of the literature. The two species were previously confounded in the single species *M. chelonei*, which was part of the *M. fortuitum* complex. In 1972, numerical taxonomic analysis demonstrated the distinction between *M. fortuitum* and *M. cheloneae* and two subspecies were proposed, *M. cheloneae* subsp. *abscessus* and *M. cheloneae* subsp. *chelonae* (122).

*Mycobacterium cheloneae* and *M. abscessus* are non-chromogenic rapidly growing species, able to grow at 30°C and 37°C. Biochemical differentiation from other rapidly growing species, in addition to pigmentation and temperature range, relies on positive arylsulphatase activity, negative nitrate reductase activity and the ability to grow on capreomycin and use levulose as a sole carbon source. These properties do not allow differentiation between *M. cheloneae* and *M. abscessus*. *Mycobacterium cheloneae* is inhibited by 5% sodium chloride and can grow with sodium citrate as a sole carbon source, whereas *M. abscessus* presents the opposite phenotype in this respect (136, 215).
Mycobacterium chelonae and M. abscessus share a peculiar 
mycolate pattern with only alpha- and alpha'-mycolates 
(136), a profile found in only one other mycobacterial species, 
M. agr. However, Tsukamurella spp. show the same mycolate 
pattern. This is the unique instance of a possible confusion 
between mycobacteria and other genera based on thin-layer 
chromatography analysis of mycolic acid. Using HPLC, 
Glinkenm et al. were able to identify 96% of the M. abscessus 
strains, 97% of the M. chelonae and 100% of the Tsukamurella 
included in the study (73). Alkali-stable glycopeptidolipids 
(i.e. related to the C-mycoside family encountered in 
M. avium) have been detected in M. chelonae and M. abscessus 
(83). The molecules gave strong cross-reactions with sera 
against members of the two species as well as sera against 
M. peregrinum.

Unlike the other rapidly growing mycobacteria, and similarly 
to the slowly growing mycobacterial species, M. chelonae and 
M. abscessus have only one 16S rRNA copy. The 
polymorphism of the 16S rRNA sequences is restricted in 
M. abscessus and M. chelonae. The part of the molecule that 
usually shows a high polymorphism and signature sequences 
for the identification of mycobacterial species does not differ 
between the two species (116, 127). However, the conserved 
gene hsp65 shows a high diversity. The different hsp65 alleles 
of M. chelonae and M. abscessus allow differentiation between 
the two species and the identification of sequevars within each 
species (195). The polymorphism of the sequences may be 
readily displayed by the digestion pattern of the hsp65 
alleles according to the PCR-restriction fragment length 
polymerism (RFLP) technique (also known as PCR restriction 
analysis [PRA]) (50, 227).

Circular plasmids of a large range of molecular weights have 
been detected in both M. chelonae and M. abscessus (129, 
253), but the epidemiological value of these extra-chromosomal elements has not been investigated. The 
PFGE technique has been successfully applied for 
epidemiological study of infections due to M. chelonae. The 
technique allowed the demonstration of the identity of a 
colony of M. chelonae isolates and traced the environmental 
source of infection (255). However, the same technique 
alone was not sufficient as a sole means of diagnosis. 
Mycobacterium chelonae infection in fish generally progresses 
towards a chronic inflammatory granulomatous disease. At 
post-mortem examination, infected organs (liver, spleen and 
kidney) show focal granulomatous lesions with multiple 
dense greyish-white miliary nodules containing abundant 
acid-fast bacteria (24, 134). A severe granulomatous 
peritonitis can also be observed (48). Infected fish may be 
asymptomatic or may present (as M. chelonae-diseased fish) 
one or more of the following symptoms: loss of appetite, 
swollen abdomen and visible granulomatous lesions. The 
infection can readily spread within a water tank and from tank 
to tank (229).

In cats, dogs and turtles, the presentation of M. chelonae 
pathology is a skin infection (abscess) with or without 
dissemination to internal organs in the turtle, in which the 
organ and spleen can be the site of granuloma (80, 190). 
Mycobacterium chelonae was also isolated from caseous 
lesions in the neck muscle of a pig (233).

In 3 of 141 cases of bovine tuberculosis diagnosed at a 
slaughterhouse, M. chelonae was isolated in pure culture from 
lungs and lymph nodes (124), suggesting a potential 
pathogenicity for the cow. In a large dairy herd in Quebec, 
M. chelonae was the aetiological agent of an outbreak of 
bovine mastitis characterised by many cows with severely 
inflamed, indurated and therapeutically incurable quarters. 
Approximately 40% of the milking cows in this herd 
developed chronic mastitis (151). Spontaneous disseminated 
mycobacteriosis was observed in a pet golden hamster with 
severely enlarged feet and lymph nodes. This enlargement resulted from non-purulent granulomatous inflammation with intracytoplasmic acid-fast bacteria that were 
characterised as M. chelonae. Microscopic focal lesions in the spleen, liver and lungs were of the same type (111). In 
immunocompromised mice, M. chelonae was associated with 
a series of granulomata of the tail (145).

Experimental disease
An experimental disease was reproduced in salmon injected 
with M. chelonae. The fish remained subclinically infected, 
demonstrating the chronic nature of the disease (24). 
Mycobacterium chelonae is pathogenic for mice, producing 
internal organ abscesses and spinning disease (271). The 
disease was also transmitted experimentally to hamsters, but 
not to rats, by inoculation of a tissue preparation from a foot 
lesion containing M. chelonae (111).

Diagnosis
Infection with M. chelonae is ideally diagnosed by assessment 
of gross and microscopic pathology together with isolation of 
the organism. A review of clinical signs (skin infection) is 
necessary but insufficient as a sole means of diagnosis. 
Bacterial cultures must be followed by biochemical and
molecular identification of M. chelonae (195). Specific PCR assays have been developed and can be applied to the pure cultures or to infected tissues to detect the presence of M. chelonae and M. abscessus (212, 223, 275).

Skin testing with purified protein derivative (PPD) is not an effective diagnostic tool, since studies have demonstrated that M. chelonae-infected animals have reacted to PPD from both M. avium (PPD-A) and M. bovis (PPD-B) (12). Experimental infection with M. chelonae can even desensitise M. bovis-infected cows (237).

**Antibiotic sensitivity and treatment**

*Mycobacterium chelonae* is resistant in vitro to pefloxacin, norfloxacin, ofloxacin and ciprofloxacin (230), but susceptible to the new macrolides (clarithromycin and azithromycin) (78), amikacin, tobramycin and imipenem (61). Livestock are not treated, but abscesses in a cat were apparently treated with a combination of systemic rifampicin and local rifamycin (238).

**Mycobacterium farcinogenes**/**Mycobacterium senegalense**/**Mycobacterium porcinum**

**Epidemiology**

Bovine farcy is a pathology found in Africa which is characterised by inflamed superficial lymph nodes with a productive suppuration associated with local induration of lymphatic vessels. This pathology can evolve into a more disseminated form with the development of nodules and tubercules on internal organs. The aetiology of this disease has been attributed to *Nocardia farcinica, Mycobacterium farcinogenes* and *M. senegalense* (29). The latter agent has been also detected in tuberculosis-like pathology of cattle in Africa (154). Whether a single agent is responsible for bovine farcy is still unclear, although Chamoiseau considered *M. farcinogenes* var. *senegalense* and *M. farcinogenes* var. *tchadense* to be the sole agents of bovine farcy (29).

*Mycobacterium porcinum* has been isolated in Japan only, from submandibular lymph nodes of pigs with tuberculosis-like lymphadenitis (242).

**The agents**

*Mycobacterium farcinogenes* is a slowly growing species, whilst *M. senegalense* is a rapidly growing species. Both species are putative agents of bovine farcy. Both species were first described by Chamoiseau from strains isolated from farcy lesions in Africa (29). The author described two geographical variants, *senegalense* and *tchadense*, and proposed to name the strains from Chad *M. farcinogenes* and the strains from Senegal *M. senegalense*.

*Mycobacterium farcinogenes* produces colonies characterised by a honey yellow colour and a stable mycelium, a unique property in the mycobacteria. The organism grows at 30°C and 37°C, but not at 42°C. The species presents nitrate reductase activity and very unusual amidase patterns, similar to the rapidly growing mycobacteria. The classification of this species as a slowly growing species has not been further investigated.

*Mycobacterium senegalense* produces non-pigmented, rough colonies. The species presents few biochemical characteristics that allow differentiation from the other rapidly growing species related to the *M. fortuitum* complex. The species is characterised by a nitrate reductase activity, the ability to grow in the presence of 5% sodium chloride, and to use citrate or mannitol as sole carbon sources (215).

*Mycobacterium porcinum* is very similar to *M. fortuitum*, but grows more rapidly (in three days) on egg media at 28°C to 42°C, but not at 45°C, and differs biochemically by failing to reduce nitrate in 24 h, and by using benzoxate and benzamide as a sole source of carbon (242).

Numerical taxonomic and phylogenetic studies based on 16S rRNA sequences cluster *M. senegalense* and *M. porcinum* with *M. fortuitum* and *M. peregrinum* (115, 175, 194). *Mycobacterium farcinogenes* and *M. senegalense* were demonstrated to present the same 16S rRNA sequence (116). The hsp65 gene shows a polymorphism that allows the differential identification of *M. senegalense* from the other mycobacterial species, whereas *M. porcinum* presents a PCR-RFLP pattern that is very similar to *M. peregrinum* (50).

Very few strains of these three species have been investigated. More extensive study is required for a better understanding of the taxonomy of these organisms.

**Mycobacterium smegmatis**

**Epidemiology**

This common environmental mycobacterium and rare pathogen was named by Gordon and Smith (79), based on the first isolation of the organism, which was from smegma. Subsequently, *M. smegmatis* was isolated from milk, soil, water, reptiles and invertebrates (235). Rare cases of skin and soft tissue infections have been reported in humans, perhaps due to the similarity of *M. smegmatis* to *M. fortuitum* and the resulting confusion in bacterial identification (252). Two fatal infections in infants (disseminated and pulmonary diseases) have been reported (125, 172) in addition to the previous reports. *Mycobacterium smegmatis* has been isolated occasionally from diseased animals, including a dog (79), cats (222, 269), and more frequently, from cattle (192, 210).
The agent

*Mycobacterium smegmatis* is a rapidly growing species that forms non-pigmented colonies which may accumulate a yellow to orange pigmentation on ageing (258). Strains are thermophilic and able to grow at temperatures up to 45°C. The catalase is usually thermolabile, nitrate reductase is strongly positive and the arylsulphatase test at three days is negative. These properties allow the differentiation of *M. smegmatis* from the other rapidly growing mycobacteria.

*Mycobacterium smegmatis* accumulates alpha- and epoxymycocolates, in common with some other rapidly growing, non-chromogenic mycobacterial species, including *M. farcigenes*, *M. fortuitum* and *M. peregrinum* (46). *Mycobacterium smegmatis* accumulates alpha- and keto- and dicarboxy-mycolates, in common with *M. avium*, but 42°C, biochemically related to *M. scrofulaceum* (225). The sequence analysis of the 16S rRNA places *M. smegmatis* in a position far from the other rapidly growing potential pathogens, i.e. *M. farcinogenes* and the species previously named *M. fortuitum* complex (*M. fortuitum*, *M. peregrinum*, *M. cheloneae* and *M. abscessus*) (115). Similarly, hsp65 gene analysis by PCR-RFLP demonstrates a specific pattern (50, 227). Strains of *M. smegmatis* are widely used for genetic manipulation. Transposon mutagenesis experiments have contributed to the identification of several insertion sequences (179). The IS1096 is a specific *M. smegmatis* element which probably transposes in a random fashion, as most of the IS1096 copies are inserted into distinct loci (34). The IS6120 was also captured by a transposon trap system. This has been found in two to eight different loci in *M. smegmatis* and the host range extends to *M. aurum* (81). The IS1137, a member of the IS3 family, has been found in *M. smegmatis* and also in *M. chitae*, a non-pathogenic, rapidly growing species (68).

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Clinical signs and lesions

Mastitis is the principal presentation in cattle and *M. smegmatis* is usually subsequently recovered from the milk of diseased cows (210). In one dairy herd, following a treatment of subclinical streptococcal mastitis with cloxacillin, 59% of the treated cows developed acute clinical mastitis associated with *M. smegmatis* (236). Infected quarters were moderately hypertrophied and fine clots were present in the milk for three to four weeks. No cows presented systemic signs of illness. *Mycobacterium smegmatis* was isolated for three to four months in the milk and the affected quarters remained hypertrophied in most of the cows after one year (236). In cats, cases of opportunistic infections of the skin and soft tissues (222), and a primary case of pyogranulomatous panniculitis have been described (269). Finally, a single case of *M. smegmatis* systemic infection has been reported in a dog with abdominal lymphadenopathy resulting from a chronic granulomatous hepatitis and lymphadenitis (79).

Experimental disease

*Mycobacterium smegmatis* mastitis has been successfully reproduced experimentally in cattle and sheep (193). Goldfish were also demonstrated to be susceptible to an experimental challenge with various strains of *M. smegmatis*. Following inoculation, the fish developed a chronic granulomatous response similar to that associated with natural *M. fortuitum* infection (225).

Antibiotic sensitivity and treatment

Isolates of *M. smegmatis* are resistant to isoniazid and rifampin, but susceptible to ethambutol, doxycycline, sulphonamide, ciprofloxacin, imipenem and amikacin (252). Enrofloxacin was successfully used to treat opportunistic infection with *M. smegmatis* in cats (222).

Diagnosis

Acid-fast staining of suspicious material, followed by bacteriological culture, biochemical characterisation and genomic identification of the agent based on conserved genes (16S rRNA and/or hsp65) is the only reliable means of specific diagnosis.

*Mycobacterium scrofulaceum*

Epidemiology

*Mycobacterium scrofulaceum* is widely distributed in temperate surface water (61, 76), unpasteurised milk, dairy products and soil (271). In humans, a scrofula or cervical adenitis is generally produced, primarily found in young children. *Mycobacterium scrofulaceum* has been isolated world-wide and frequently from lymph nodes of cattle (41, 257), buffaloes (9), farmed deer (140), swine (109, 133, 201, 232), feral pigs (40), patas monkeys (*Erythrocebus patas*) (189), fish (134) and mice (244). In most of the cases, the animals were reactors to tuberculin and especially to PPD-A. The isolation of *M. scrofulaceum* from faeces of tuberculin positive cattle (188) and of mice (244) emphasises that the disease can spread by oral contamination.

The agent

*Mycobacterium scrofulaceum* is a slowly growing, scotochromogenic mycobacterial species, able to grow at 42°C, biochemically related to *M. avium*, but characterised by a strong urease activity. *Mycobacterium scrofulaceum* accumulates alpha-, keto- and dicarboxy-mycocolates, in common with *M. avium* and other biochemically related
species (46). High-performance liquid chromatography lacks accuracy for the identification of M. scrofulaceum that can be misidentified as M. avium or M. intracellulare. Similarly, some M. avium or M. intracellulare strains could be misidentified as M. scrofulaceum (73). Cell-free antigens have been detected through seroagglutination tests according to the procedure developed by Schaefer (206). Mycobacterium scrofulaceum was attributed serovars 41 to 43. Chemical analysis revealed that the structure of C-mycoside peptidoglycolipid is related to the family of molecules identified in M. avium, that are responsible for the Schaefer agglutination tests (6).

Comparisons of base sequences of 16S rRNA demonstrate a deep branched separation between M. scrofulaceum and other mycobacteria (199). The hsp65 gene reveals a characteristic sequence for the species that can be readily demonstrated by PCR-RFLP (50, 227). Mycobacterium scrofulaceum may be identified using a commercial kit that includes a probe covering the 16S-23S rRNA spacer region (153).

Circular plasmids have been detected in M. scrofulaceum in a high percentage of strains, especially in strains isolated from humans, but also those from water and dust (150). Plasmid presence was associated with resistance to mercury. Falkinham and colleagues demonstrated cross-hybridisation between plasmids from M. scrofulaceum and M. avium (107, 150). No epidemiological marker has been developed for M. scrofulaceum.

Clinical signs and lesions

Mycobacterium scrofulaceum infection is asymptomatic in cattle, deer, buffaloes, pigs and fish. The bacilla is detected, after the slaughter of PPD-positive animals suspected of tuberculosis (33), in nodular thelitis (214), tonsils, submaxillary, preparotid, retropharyngeal (132) and mesenteric lymph nodes (65). The lymph nodes can display tuberculoid lesions (109) or appear normal. The presence of M. scrofulaceum in healthy patas monkeys was accompanied by no clinical symptoms. A positive tuberculin test justified the euthanasia of these animals. Miliary tuberculosis and lung granulomata were detected at autopsy and M. scrofulaceum was isolated from these lesions (189). Finally, in immunosuppressed nude mice, M. scrofulaceum produced a more invasive infection with colonisation of the mesenteric lymph nodes and the spleen. Bacteria were also isolated from the faeces of the infected mice (244).

Experimental disease

Cows inoculated experimentally, either subcutaneously or into a mesenteric lymph node, presented a chronic infection with inflamed draining lymph nodes, at the site of the inoculation (39). The tuberculin test performed with PPD-B or PPD-A in the experimentally infected animals was transiently positive.

Diagnosis

The diagnosis of M. scrofulaceum infection is based on the post-mortem isolation and biochemical characterisation of the agent. A commercial kit and the PCR-RFLP analysis applied to the hsp65 gene provide a species-specific identification for M. scrofulaceum (50, 153, 227).

Antibiotic sensitivity and treatment

The primarily asymptomatic presentation of M. scrofulaceum infection in animals precludes any indication for a treatment.

Mycobacterium xenopi

Epidemiology

The prevalence of M. xenopi varies geographically. Mycobacterium xenopi infection in humans is rare, with a pulmonary presentation in non-immunosuppressed patients, and resembling M. avium infection in patients with human immunodeficiency virus (61, 148). Four clinical syndromes account for nearly all cases in humans: pulmonary disease, lymphadenitis, skin or soft tissue disease and disseminated disease in AIDS patients. Mycobacterium xenopi has been found in hot water systems more often than in cold water systems and has been associated with pseudo nosocomial epidemics in hospitals (26, 217, 256). Mycobacterium xenopi was originally isolated from a toad (211), and later on from bird droppings (271), a cat (239), a healthy cow (132), and more frequently, from pigs (101, 232, 270). Out of 96 strains of mycobacteria isolated from 751 feral pigs examined in Australia, two strains were identified as M. xenopi (40). Mycobacterium xenopi is principally a pathogen of pigs; in one study, M. xenopi was isolated from 316 (44%) of 721 mesenteric lymph nodes with tuberculosis-like lesions (84). The natural reservoir and principal source of contamination for animals and humans seems to be water (61); one strain was detected in a sphagnum sample in Madagascar (209).

The agent

Mycobacterium xenopi is a slowly growing species (258). Colonies are compact, smooth, shiny and usually exhibit a fringe of short branching filaments at the periphery when examined, an aspect that is unique to M. xenopi. Colonies are pale yellow, although young colonies may be non-pigmented, as the pigmentation slowly accumulates. Classically, M. xenopi is classified as a non-photochromogenic species. However, the species is truly scotochromogenic. The morphology of the bacilli may be very characteristic; long, thin, weakly acid-fast bacilli may be observed in loose aggregates. Mycobacterium xenopi is a thermophilic species, unable to grow at 28°C. The optimal growth temperature is 42°C, but strains continue to grow at 45°C. Strains produce a weak thermostable catalase. The standard biochemical tests performed for mycobacterial identification are all negative except the aroyl sulphatase which is early and strongly positive.
The mycolate profile is composed of alpha- and dicarboxy-mycolates which release a C26 ester under pyrolysis conditions (46). The secondary alcohol esterifying the dicarboxy-mycolate may be used as a specific marker for identification using gas-liquid chromatography (142). This property is unique to M. xenopi. Similarly, a unique mycolate pattern is displayed by HPLC (73, 231). Mycobacterium synthesises neither phenolic glycolipid as found in M. hansasi, nor glycopeptidolipid of the C-mycoside class, as found in M. avium. However, a peculiar class of molecules, named glycopeptidolipids with serine, has been identified only in M. xenopi (197). The lipopeptidic core of this peptidoglycolipid is composed of a linear fatty acid in C-12 covalently linked through an amide link to a tetrapeptide L-Ser-L-Ser-L-Phe-D-alloThr. The oligosaccharide part of the molecule is branched on the Ser residue (198). Unlike the other complex glycolipids identified in mycobacteria, the oligosaccharide chain of this class of glycopeptidolipid harbours fatty acids, which contribute to the hydrophobic nature of the molecule. The structure of the oligosaccharide part may vary among strains of M. xenopi (13). Sequence analysis of the 16S rRNA gene demonstrates that M. xenopi is isolated in a deep branch on the phylogenetic tree of the genus Mycobacterium (199). The hsp65 PCR-RFLP allows a straightforward identification of the species (50, 227). Methods have been developed for the molecular identification of M. xenopi. These consist of PCR tests relying on the amplification of either a non-rRNA-directed nucleic probe or a 16S rRNA sequence followed by a luminescent sandwich hybridisation assay (63, 166). A commercially available kit based on the polymorphism of the 16S-23S rRNA spacer region, allows the identification of M. xenopi (153). Similarly to some other mycobacterial species, M. xenopi presents an intein (intervening protein sequence) in gyrA (228). This intein, consisting of a 198 amino-acid in-frame insertion in the gyrA gene of M. xenopi, is the smallest known naturally occurring active protein splicing element. Comparison with other mycobacterial gyrA inteins suggests that the M. xenopi intein underwent a complex series of events, including a large deletion that removed the conserved motifs of the endonuclease activity and the addition of a linker of unrelated residues required for splicing. A specific insertion sequence IS1395 has been described in M. xenopi (168); this 1,323 base-pair (bp) element encodes a putative transposase that displays sequence homology with the Staphylococcus aureus IS256 family. Members of this family have been identified in some mycobacterial species. These include IS1081 in the M. tuberculosis complex, IS1245-IS1311 in M. avium, IS6120 in M. smegmatis, IS1407 in M. celatum and IS1408 in M. gordani. Before the description of IS1395, Collins showed the possibility of typing M. xenopi strains with the IS1081 from M. bovis used as a probe (36). The cross hybridisation between IS1395 and IS1081 reflects the high similarity of their nucleotide sequences (up to 86%) (168). Strains of M. xenopi possessed a copy number for IS1395 that varied from three to eighteen copies, with a median of fourteen. However, the potential of the discrimination index is reduced by the existence of numerous common bands. The IS1395-RFLP typing of unrelated M. xenopi strains revealed relatively similar patterns. Similarly, Dral PFGE analysis showed a reduced discrimination among strains. These results, based on two independent techniques (IS1395 has no Dral restriction site), stress the high homogeneity of the M. xenopi genome among various strains.

Linear plasmids of a wide range of sizes (from 20 kbp to 160 kbp) have been detected in M. xenopi (170). These elements, the first described in the Mycobacterium genus, present an invertron structure, as found in Streptomyces, with covalently attached proteins at the 5' termini (171). The similarity in the structure and terminal nucleotide sequences of mycobacterial linear plasmids and the termini of linear replicons of Streptomyces and Rhodococcus species indicated a conservation of these elements within the Actinomycetales. Linear plasmids have also been detected in the related species M. celatum and M. branderi, and also in M. avium. The elements cross-hybridise, suggesting either inter-species genetic exchange or a common ancestry. Interestingly, a copy of IS1395 has been detected on a linear 140-kbp plasmid (171).

Clinical signs and lesions

The first strain of M. xenopi was isolated from a granulomatous lesion of the skin of a toad (211) and of a cat (239). The bacillus was also isolated from a cat presenting parotitis associated with lymphadenitis (144). In pigs, M. xenopi produces a lymphadenitis similar to the widely recognised M. avium-intracellulare pig lymphadenitis (270). A study of slaughtered pigs from one farm in Eastern Europe between 1990 and 1993, resulted in the isolation of M. xenopi from 316 (44%) of 721 mesenteric lymph nodes with tuberculosis-like lesions (84). However, in the USA, only one strain of M. xenopi was isolated among the 1,591 mycobacterial strains isolated (principally M. avium and M. intracellulare) from 2,036 porcine tissues submitted to the laboratories of the Veterinary Services over a three-year period from 1971 to 1974 (232). Mycobacterium xenopi can be isolated from lymph nodes (consils submaxillaries, preparotid, retropharyngeal and mesenteric lymph nodes) of asymptomatic animals such as feral pigs (40) and cattle (132).

Experimental infection of beige mice has been used to study the in vivo efficacy of antibiotic treatments (117).

Diagnosis

As M. xenopi infection has no real specific clinical symptoms, the culture of the bacteria from clinical samples is critical to enable the diagnosis. Biochemistry (148), gas chromatography (3) and DNA methods can be used to identify M. xenopi. Several specific PCR and hybridisation
assays have been developed for the identification of M. xenopi (49, 120, 153, 167, 212).

**Antibiotic sensitivity and treatment**

The disease caused by M. xenopi is usually diagnosed retrospectively, therefore antibiotic treatment is not practical and is not recommended for animals. Minimum inhibitory concentrations (MICs) against roxithromycin used alone and in combination with ethambutol, rifampin, amikacin, ofloxacin and clofazimine were defined in an extensive study by Rastogi et al. (183). Clarithromycin, rifabutin and sparfloxacin have been used to treat immunosuppressed patients (208).

**Mycobacterium kansasii**

**Epidemiology**

*Mycobacterium kansasii* has been isolated in Africa, Europe, Asia and America. The species has been detected in wild animals and in water, which may be the natural reservoir (123, 158). *Mycobacterium kansasii* was one of the first species shown to be responsible for non-*M. tuberculosis* pulmonary infections, thereafter termed atypical mycobacterial disease, in humans (23). The impact of this important pathogen in human infection has been thoroughly reviewed (61, 261, 271).

In contrast, *M. kansasii* is a relatively rare pathogen of animals. The presence of the bacteria has been rarely reported from asymptomatic wild or domestic animals such as birds (158), wild deer (262), pigs (1.2% of 250 healthy nodes of healthy pigs) (201), dogs (248) and squirrel monkeys (*Saimiri sciureus sciureus*). Infection with *M. kansasii*, accompanied by inflamed lymph nodes or pneumatic lesions, has been described in rhesus monkeys (*Macaca mulatta*) (99, 245), squirrel monkeys (22), cattle (102), a llama (104), a goat (1), camels (60), and domestic and feral pigs (40). *Mycobacterium kansasii* has been also isolated occasionally from unpasteurised cow milk (4).

The close relationship between the two species *M. kansasii* and *M. gastri*, suggested by their common lipid content, is confirmed by the analysis of sequences of the gene encoding the 16S RNA. Based on 16S rRNA sequences, *M. gastri* and *M. kansasii* cannot be differentiated, whereas the polymorphism of the gene hsp65 allows differentiation by PCR-RFLP analysis (2, 169, 199). In common with other mycobacterial species (among others *M. leprae*, *M. marinum*, *M. ulcerans* and *M. xenopi*), *M. kansasii* presents an intein, ensuring protein splicing of the precursor protein gyrA (67, 204). The gyrA intein is a taxonomic characteristic specific at the species level, although some *M. kansasii* strains have gyrA genes without inteins. Several repetitive elements have been identified in *M. kansasii* (179), including the polymorphic GC-rich repetitive sequence (PGRS), the major polymorphic tandem repeat (MPTR), and an insertion sequence, IS1052 (90, 200, 274). The PGRS and MPTR elements share some similarities in their nucleotide consensus sequence, high copy number, polymorphism and stability. The mycobacterial host range of PGRS corresponds roughly to the species listed above with alpha-, methoxy- and keto-mycolates able to synthesise phenolglycolipids, suggesting a common phylogenetic descent. The MPTR mycobacterial host range is restricted to the *M. tuberculosis* complex, *M. gordonae* and *M. kansasii*. The IS1652 is species specific.
specific. The elements PGRS, MPTR and IS1652 may be used as epidemiological markers for the differentiation of *M. kansasii* strains. Five different subspecies were described in *M. kansasii*, based on various molecular markers including MPTR-RFLP, IS1052-RFLP as well as PCR-RFLP of the hsp65 gene, PFGE and amplified fragment length polymorphism (AFLP) (169). No subspecies was found to be particularly more virulent, as all subspecies contained clinical and environmental strains. The use of PFGE and AFLP produced polymorphic patterns within each subspecies. The presence of IS1652 was revealed in two subspecies only. The use of IS1052-RFLP produced polymorphic patterns in one subspecies with two to six copies per strain, whereas the other subspecies contained a single copy carried by a unique fragment (169). A further analysis demonstrated that the three subspecies with no IS1652 copy possessed a GyrA intein, whereas the two subspecies with IS1652 did not (2). These data confirm the observation that the distribution of GyrA inteins is not random, but specific at a species or subspecies level (204).

**Clinical signs and lesions**

Infection with *M. kansasii* can be asymptomatic or symptomatic. In the asymptomatic form, regardless of whether animals react with tuberculin or not, pathological lesions can be found post mortem in submandibular, mediastinal, mesenteric and bronchial lymph nodes and in the lungs (tuberculosis-like lesions). Caseous lesions and micro abscesses with some calcified areas have been found post mortem in the lymph nodes, lungs and liver of pigs (177), feral pigs (40), camels (60), goats (1), cows (102, 272) and squirrel monkeys (22). In the symptomatic form, similar lesions are found in a clinical tuberculosis-like disease with pulmonary involvement. Emaciation, lack of appetite and gut stasis were the principal clinical signs in a llama prior to death. Autopsy revealed an excess of clear peritoneal fluid, greatly enlarged mesenteric lymph nodes with irregular outlines and caseous lesions with some calcification, multiple irregularly shaped pale caseous lesions in the liver and small lesions in the lungs (104). In rhesus monkeys, *M. kansasii* produces a disease which resembles tuberculosis but is less acute. Caseous lesions in lungs, cavitation, and involvement of inguinal and iliac lymph nodes with dissemination to the spleen and liver can be observed post mortem (99, 245).

**Experimental disease**

In common with most of the mycobacteria, *M. kansasii* is an intracellularly multiplying bacterium, producing inflammatory lesions in the lymph nodes and the reticuloendothelial system in general (spleen, liver, etc.) and in the lungs. Infections with *M. kansasii* have been established in mice, rabbits, hamsters, guinea-pigs and dogs (271). In the mouse, the multiplication of *M. kansasii* in macrophages reduces the expression of major histocompatibility complex (MHC) class II molecules (immune response-associated proteins: Ia) (159). An aerosol of *M. kansasii* can induce a severe lung infection in mice that can be prevented by BCG vaccination (163). Calves infected orally with *M. kansasii* developed a full cell- and antibody-mediated response within six weeks. Histopathology revealed microgranulomata in the mesenteric lymph node, from which the bacteria could be reisolated four months after inoculation (106).

**Diagnosis**

Cross reactions prevent the use of the PPD test for a definitive diagnosis (1). Clinical signs are not pathognomonic and therefore the isolation of *M. kansasii* from lesions followed by bacteriological and molecular identification (as described above) is the only definitive method to diagnose the infection.

**Antibiotic sensitivity and treatment**

The treatment of diseased animals is not recommended for both medical reasons (lack of specific diagnosis in living animals) and economic reasons and also to avoid the development of strains resistant to antibiotics used in human therapy. *Mycobacterium kansasii* is susceptible to aminoglycoside (streptomycin, gentamicin), rifabutin, quinolones (ofloxacin, ciprofloxacin, levofloxacin and sparfloxacin) and to macrolides (azithromycin and clarithromycin) (117, 128, 240).

*Mycobacterium kansasii* can survive heating to 63.5°C for 30 min (equivalent to holder pasteurisation), therefore higher temperatures are necessary to kill these bacteria from pasteurised milk (77).

**Mycobacterium simiae**

**Epidemiology**

*Mycobacterium simiae* has been isolated from humans in Europe, the USA and Asia, mainly in immunocompromised hosts (61, 247, 261, 271). The geographical distribution of this mycobacterium also includes Africa and Madagascar. *Mycobacterium simiae* was first isolated from healthy *Macacus rhesus* imported from India by Karasseva *et al.* (110). It was subsequently isolated from both imported tuberculin negative *M. rhesus* and Cercopithecus *etios* monkeys (264). *Mycobacterium simiae* was also isolated in rhesus monkeys infected with simian immunodeficiency virus (SIV) and presenting intermittent diarrhoea (53). Transmission between animals in captivity appears possible in addition to transmission from animals to humans (271). The isolation of *M. simiae* has been reported from the liver and spleen of wild and ornamental fish (134). In Madagascar, sphagnum samples were contaminated with *M. simiae*, indicating a large environmental reservoir for this species (207); the bacterium has also been isolated from water (135).

**The agent**

*Mycobacterium simiae* is usually defined as a photochromogenic species able to produce niacin, an unusual property among non-tuberculous mycobacteria. However, these properties, although usually reproducible within the
genus Mycobacterium, are highly variable in M. simiae, even for a single strain (256). Mycobacterium simiae grows optimally at 37°C and most strains fail to grow at 42°C. Biochemical tests (absence of Tween 80 hydrolysis, absence of nitrate reductase activity and positive urease test) demonstrate the close relationship between M. simiae and M. scrofulaceum. The designation M. habana used for some strains associated with human lung disease, is synonymous with M. simiae (263).

The analysis of mycolate composition allows easy differentiation from M. scrofulaceum and biochemically-related species. The M. avium complex, including M. scrofulaceum, accumulates alpha-, keto- and dicarboxymycolates, whereas M. simiae presents alpha-, alpha'- and keto-mycolates, like M. genavense or M. malmoeense. A straightforward identification of the specific fatty acid content can be obtained by HPLC (231). Cell-free antigens have been detected through seroagglutination tests according to the procedure developed by Schaefer (206), but the chemical structure of these antigens has not been precisely investigated. Structures related to C-mycolides, the peptidoglycolipids identified in M. avium as responsible for the Schaefer agglutination tests, could be involved, as some strains of M. simiae have been found to react with M. avium serotype 18 antisera (191). Two M. simiae serotypes are recognised. The division into two subspecies has been suggested by some authors, although never formally proposed, and not supported by the tertiary semantide catalase (260).

The phylogenetic tree based on the 16S rRNA shows M. simiae in a separate branch in the vicinity of M. genavense (199). The position of the branch is intermediate between the two clusters of rapidly and slowly growing mycobacteria. Mycobacterium simiae is characterised by a short 21-base loop in helix 18 (positions 451 to 482 in E. coli), a signature specific to the rapidly growing species (220). Investigation of the hsp65 polymorphism by PCR-RFLP showed two subgroups defined by different alleles of the gene (50). However, no serotype study was performed in parallel with the PCR-RFLP, preventing any conclusion as to a possible correlation between serotypes and hsp65 alleles.

Clinical signs and lesions

Naturally infected monkeys do not present a specific pathology. After experimental SIV infection, one rhesus monkey developing a progressive immunosuppression, presented a gastrointestinal disease due to M. simiae, very similar to the clinical and pathomorphological features of Johne's disease caused by M. avium subsp. paratuberculosis (53). Pathological findings in SIV-infected rhesus monkeys were considered to be primary SIV-induced (SIV enteropathy, giant cell disease) or secondary, caused by opportunistic agents such as M. simiae (112).

Experimental disease

Mycobacterium simiae is virulent and multiplies in mice and in a limited manner in guinea-pigs and rabbits (264, 271). Mice vaccinated with BCG are not protected against a challenge with M. simiae (165).

Diagnosis

The isolation and identification of M. simiae by biochemical tests and HPLC of fatty acids (231) allow a definitive diagnosis; analysis of the polymorphism of conserved genes such as 16S rRNA and hsp65 can also be used.

Antibiotic sensitivity and treatment

Mycobacterium simiae is resistant to streptomycin, isoniazid, p-aminosalicylate and rifampin, but is sensitive to cycloserine (264). Azithromycin and clarithromycin were demonstrated to be active against M. simiae in vivo, in a beige mouse model, and in combination with other agents, could be useful for the therapy of M. simiae infections in humans or monkeys (117). In normal outbred mice, M. simiae infection was controlled by the use of clarithromycin combined with ofloxacin, or clarithromycin combined with ethambutol (246).

Mycobacterium genavense

Epidemiology

Mycobacterium genavense is a newly described atypical, difficult-to-grow mycobacteria (18, 20) which has been isolated from AIDS patients and from immunocompromised patients (15). In regards to animals, M. genavense is now recognised as the most frequent aetiological agent of avian mycobacteriosis (cutaneous and disseminated) in pet birds and especially in Passeriformes and Psittaciformes (93, 178). The organism has also been detected in Coraciiformes, Piciformes and Galliformes, and more specifically in Amazon parrots (Amazona ochrocephala), canaries (Serinus canaria), budgerigars (Melopsittacus undulatus), orange-winged parrots (Amazona amazonica), blue-and-white flycatchers (Cyanopitilla cyanomelana) and zebra finches (Taeniopygia guttata). Mycobacterium genavense has been isolated in Europe, Australia and the USA. Mycobacterium genavense infections can represent up to 10% of the disseminated infections caused by mycobacteria in AIDS patients.

Epidemiological data on M. genavense are scarce due to the difficulty in culturing this mycobacteria. Pet birds and dogs have been reported as potential sources of contamination of humans. The mode of transmission among birds remains unclear. However, potential environmental reservoirs such as tap water have been identified (91) and could be the source of the bacteria for infections of animals and humans.

The agent

Mycobacterium genavense has unusual fastidious growth requirements and shows poor and variable growth in vitro.
The first description of the taxon was based on molecular biology techniques, and amplification and sequencing of the 16S rRNA; cultural or biochemical characteristics could not be evaluated (19). Considerable efforts have been made to improve in vitro growth of M. genavense. Realini et al. inoculated nude mice to obtain large amounts of bacilli in order to test different growth conditions (185). The authors demonstrated that acid pH (pH 6.0) significantly enhanced growth of bacilli. A Middlebrook 7H12 medium, without any additive, at pH 6.0 was recommended as providing the ideal conditions for primary cultures. Moreover, low oxygen tension, of 2.5% to 5%, was shown to allow detection of growth of very small inocula (25 bacilli/ml) and should replace the standard 21% oxygen concentration recommended by the manufacturer for cultures using the BACTEC 460-TB (186). The optimal solid medium for primary cultures is the Middlebrook 7H11 medium acidified to pH 6 and supplemented with charcoal and blood. Colonies are observed within six to twelve weeks of incubation (187). Colonies are usually dysgonic and non-chromogenic, but as agar cultures age, eugonic, either dense and creamy or flat and dry colonies can be observed (20). Strains grow at 30°C, 37°C and 42°C. The species is biochemically related to M. simiae, with no hydrolysis of Tween 80, no nitrate reductase or arylsulphatase activity, but positive results for urease.

**Mycobacterium genavense** produces alpha-, alpha'- and ketomycocytolates, similar to M. simiae and M. malmoense (20). The presence of cis-10-hexadecenoic acid detected in gas-liquid chromatography and the absence of cis-11-hexadecenoic acid contributed to the differentiation between M. genavense and M. simiae (32, 43). In 1992, M. genavense was misidentified as M. fortuitum using a commercial microbial identification system based on fatty acid analysis by gas-liquid chromatography (43). However, analysis of mycolic acid cleavage products showed that the ratio of tetracosanoic acid to hexacosanoic acid was distinct in M. genavense (ratio <1) and M. fortuitum (ratio >3) (32). Patterns obtained from HPLC of M. genavense closely resembled those of M. simiae, but could be used for a species-specific identification (196, 241).

Sequencing of 16S rRNA revealed a specific sequence for M. genavense which was used for the formal description of the species (19, 20). The phylogenetic tree based on 16S rRNA sequences showed that M. genavense and M. simiae are closely related, on the same branch, rooted deeply from the basis of slowly growing mycobacteria. Because of the fastidious growth of M. genavense, molecular methods are especially useful for identification of the species. In particular, efforts have been made to develop specific probes. Molecular probes may consist of a single specific DNA fragment present in M. genavense only, easily detected with specific primers in a PCR test (31). Alternative methods rely on the amplification of conserved genes. Independent systems have been developed based on selective PCR amplification with primers specific to the genes coding for 16S rRNA. Both systems used biotinylated species-specific oligonucleotides and capturing probes attached to nitrocellulose membranes including probes specific for the genus Mycobacterium and various mycobacterial species (49, 121). The systems were adequate for the detection of M. genavense directly in intestinal tissues (57) or from clinical specimens from various sources (121). The polymorphism of the hsp65 gene within a 360-bp region was also found to be adequate for the specific identification of M. genavense by automated sequencing (164).

### Clinical signs and lesions

**Mycobacterium genavense** is the cause of a wasting illness in patients with AIDS (18). In birds, the clinical signs associated with the disease are similar to any mycobacteriosis and are not specific (i.e. sudden death without any symptoms or following a wasting syndrome and emaciation [severe muscular wasting], acute respiratory distress [94] and sometimes diarrhoea). Granulomatous dermatitis caused by M. genavense has also been described in two psittacine birds (*Trichoglossus haematodus* and *Amazona albifrons*) showing featherless, non-painful, non-pruritic nodules. Histopathological studies of skin biopsies from both cases demonstrated the presence of a diffuse granulomatous dermatitis with acid-fast organisms that were identified as *M. genavense* (64). In one of the birds, generalisation of the process to internal organs (intestinal and hepatic serosa) was observed. In general, the evolution of the disease is more rapid than that of *M. avium* infection.

In a dog, severe hind limb weakness and enlarged cervical lymph nodes were associated with *M. genavense* infection (114).

Gross post-mortem findings are non-specific. In birds, *M. genavense* infection is associated with an enlarged spleen and liver, and thickening of the intestinal wall (95, 182), trachea and lungs (114, 178). If present on internal organs, inflammatory nodules are non-caseous and infiltrated by large macrophages. In the intestine, the mucosal area is generally heavily infiltrated, suggesting an intestinal origin of the infection. Severe muscular wasting, cutaneous nodules and subcutis granuloma can be also observed (94).

### Experimental disease

Gamma-interferon-gene-deficient BALB/c mice are the most satisfying experimental model for the multiplication of *M. genavense* in infected animals (59). *Mycobacterium genavense* multiplied and persisted in the liver and spleen of intravenously inoculated animals and induced a chronic inflammatory response, resulting in splenomegaly, granulomatous lesions in the liver and extensive lymphadenopathy.

### Diagnosis

The diagnosis of the disease and the agent is based on the detection of acid-fast bacilli after staining the lesions found by histopathology, followed by culture of the bacteria on special
media for six to twelve weeks (187), or detection of the bacteria by DNA methods (149). The final identification of the bacteria can be performed by computerised mycolic acid analysis using HPLC that distinguishes the mycolic acid profile of *M. genavense* from those of all other organisms (196). Alternatively, gas-liquid chromatography of the fatty acids and mycolic acid cleavage products may be employed (32, 174). Many PCR assays have been developed to remedy the difficulties encountered in growing this organism. Polymerase chain reaction assays can be applied directly to infected tissues and to cultures in liquid medium (203), with (31, 49, 57) or without (16, 121) an additional step of DNA probing.

**Antibiotic sensitivity and treatment**

No antibiotic treatments have been used for *M. genavense* infections in animals. The species appears to be susceptible to clarithromycin (27), and in experimentally infected mice, amikacin, ethambutol, clarithromycin and rifabutin were able to reduce the number of CFU in the spleen, whereas ciprofloxacin had no effect (250).

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**Infections mycobactériennes chez les animaux domestiques et sauvages dues à Mycobacterium marinum, M. fortuiitum, M. chelonae, M. porcinum, M. farcinogenes, M. smegmatis, M. scrofulaceum, M. xenopi, M. kansasii, M. simiae et M. genavense**

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**Résumé**

Les auteurs décrivent l'épidémiologie et la distribution naturelle de *Mycobacterium marinum, M. fortuitum, M. chelonae, M. porcinum, M. farcinogenes, M. smegmatis, M. scrofulaceum, M. xenopi, M. kansasii, M. simiae* et *M. genavense*. Outre les caractéristiques bactériologiques, biochimiques et génétiques, les auteurs examinent la pathologie de ces espèces lors d'infections naturelles et expérimentales, ainsi que les lésions résultantes de l'infection, le diagnostic, la sensibilité aux antibiotiques et le traitement des infections animales dues à ces mycobactéries.

**Mots-clés**

Infecciones micobacterianas debidas a *Mycobacterium marinum*, *M. fortuitum*, *M. chelonae*, *M. porcinum*, *M. farcinogenes*, *M. smegmatis*, *M. scrofulaceum*, *M. xenopi*, *M. kansasii*, *M. simiae* y *M. genavense* en animales domésticos y salvajes

H. Bercovier & V. Vincent

**Resumen**

Los autores describen la epidemiología y distribución natural de *Mycobacterium marinum*, *M. fortuitum*, *M. chelonae*, *M. porcinum*, *M. farcinogenes*, *M. smegmatis*, *M. scrofulaceum*, *M. xenopi*, *M. kansasii*, *M. simiae* y *M. genavense*. Además de repasar las características bacteriológicas, bioquímicas y genéticas de estas especies, los autores exponen su patogenia en el transcurso de enfermedades tanto naturales como experimentales, las lesiones que acarrean y el diagnóstico, la sensibilidad a los antibióticos y el tratamiento de esas infecciones micobacterianas de los animales.

**Palabras clave**


**References**


