Zoonotic Tuberculosis in Mammals, including Bovine and Caprine Tuberculosis

Infections caused by Mycobacterium bovis, M. caprae, M. pinnipedii, M. orygis and M. microti

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Importance

Several closely related bacteria in the *Mycobacterium tuberculosis* complex cause tuberculosis in mammals. Each organism is adapted to one or more hosts, but can also cause disease in other species. The two agents usually found in domestic animals are *M. bovis*, which causes bovine tuberculosis, and *M. caprae*, which is adapted to goats but also circulates in some cattle herds. Both cause economic losses in livestock from deaths, disease, lost productivity and trade restrictions. They can also affect other animals including pets, zoo animals and free-living wildlife. *M. bovis* is reported to cause serious issues in some wildlife, such as lions (*Panthera leo*) in Africa or endangered Iberian lynx (*Lynx pardinus*). Three organisms that circulate in wildlife, *M. pinnipedii*, *M. orygis* and *M. microti*, are found occasionally in livestock, pets and people.

In the past, *M. bovis* was an important cause of tuberculosis in humans worldwide. It was especially common in children who drank unpasteurized milk. The advent of pasteurization, followed by the establishment of control programs in cattle, have made clinical cases uncommon in many countries. Nevertheless, this disease is still a concern: it remains an important zoonosis in some impoverished nations, while wildlife reservoirs can prevent complete eradication in developed countries. *M. caprae* has also emerged as an issue in some areas. This organism is now responsible for a significant percentage of the human tuberculosis cases in some European countries where *M. bovis* has been controlled. It was also found recently in China and North Africa, suggesting its distribution probably extends beyond Europe.

Etiology

In mammals, tuberculosis is caused by members of the *Mycobacterium tuberculosis* complex, which are Gram positive, acid-fast bacterial rods in the family Mycobacteriaceae. The organisms maintained in animals include *Mycobacterium bovis* (bovine tuberculosis), *M. caprae* (caprine tuberculosis), *M. pinnipedii*, *M. orygis* and *M. microti*. *M. caprae*, *M. pinnipedii* and *M. orygis* were members of *M. bovis* before being designated separate species. Two other agents, *M. tuberculosis* and *M. africanum*, are maintained in humans but occasionally affect animals. One poorly-understood organism, *M. canettii*, has only been found in humans in Africa, but it is not thought to be maintained in people. Its reservoir is unknown. Some authors also recognize additional species, such as *M. mungi* in banded mongooses (*Mungos mungo*) or *M. suricattae* in meerkats (*Suricata suricatta*).

The taxonomy of the *M. tuberculosis* complex can be controversial, and *M. bovis* and *M. caprae* are sometimes called *M. bovis* subsp. *bovis* and *M. bovis* subsp. *caprae*, respectively. Other authors argue that all of the agents in the *M. tuberculosis* complex should be considered a single species, due to their close genetic relationships. Under this system, *M. bovis* and *M. caprae* would be renamed *M. tuberculosis* subsp. *bovis* and *M. tuberculosis* subsp. *caprae*.

Species Affected

Mycobacterium bovis

Cattle are the primary hosts for *M. bovis*, but it can probably infect most or all mammals and marsupials. Susceptibility to illness might vary. Clinical cases have been described in sheep, goats and their relatives; pigs and other Suidae; horses and other equids; camels and South American camelids; dogs and other canids; cats and various wild felids; many wild ruminants and cervids; other ungulates such as elephants, rhinoceroses (*Ceratotherium simum*, *Diceros bicornis*) and giraffes (*Giraffa camelopardalis*); and diverse other hosts including ferrets, mink, banded mongooses, meerkats, otters (*Lutra lutra*), raccoons (*Procyon lotor*), coatis (*Nasua nasua*), opossums, hares (*Lepus* sp.), rabbits, nonhuman primates, bears and many rodents. Although most organisms previously reported in seals and sea lions are now classified as *M. pinnipedii*, *M. bovis* has been identified in grey seals (*Halichoerus grypus*), suggesting that marine mammals are probably susceptible to it as well.

Cattle are the usual maintenance hosts for *M. bovis*, but it can also be maintained in goats, captive cervids and some free-living wildlife. A species can be a maintenance host in one location and a spillover host at another, depending on its population density and other factors that facilitate transmission. Elk (*Cervus canadensis*) and white-tailed deer (*Odocoileus virginianus)* are both thought to be maintenance hosts around Riding Mountain National Park, Canada, though elk play the principal role. However, elk are spillover hosts in Michigan, where white-tailed deer maintain *M. bovis*. Neither species currently seems to be infected with this organism in other parts of the U.S. or Canada. Similarly, wild boar are thought to be important maintenance hosts in Mediterranean climates on the Iberian Peninsula in Europe, but they seem to be spillover hosts in Atlantic Spain and some other parts of Europe. Other maintenance hosts include wood bison (*Bison bison athabascae*) around Wood Bison National Park, Canada, feral swine in parts of Hawaii, brush-tailed opossums (*Trichosurus vulpecula*) in New Zealand, European badgers (*Meles meles*) in the United Kingdom and Republic of Ireland, red deer/elk (*Cervus elaphus*) in parts of Europe; and African buffalo (*Syncerus caffer*) and Kafua lechwe (*Kobus leche kafuensis*) in Africa. Greater kudu (*Tragelaphus strepsiceros*) and warthogs (*Phacochoerus aethiopicus*) have also been suggested as possible maintenance hosts in Africa, but their role is still debated. Determining whether a wildlife species is a maintenance host or a spillover host can be difficult. At one time, feral ferrets (*Mustela furo*) were proposed as maintenance hosts in New Zealand, but they now appear to be spillover hosts in which *M bovis* can cycle for a long time but eventually disappears. Ecosystems where *M. bovis* circulates in wildlife usually have diverse spillover hosts ranging from rodents and small mammals to carnivores and ungulates.

Tuberculosis in birds is usually caused by *M. avium*, which is not a member of the *M. tuberculosis* complex. However, there are a few reports of birds affected by *M. bovis*, including parrots, an ostrich and a black swan (*Cygnus atratus*). *M. bovis* replicated in pigeons (*Columba livia*) after oral or intratracheal inoculation, and budgerigars (*Melopsittacus undulatus*) after intramuscular inoculation. Clinical signs developed in the budgerigars but not the pigeons; however, a few pigeons occasionally shed the organism in feces. American crows (*Corvus brachyrhynchos*, starlings (*Sturnus vulgaris*), Mallard ducks (*Anas platyrhynchos*) and wild turkeys (*Meleagris gallopavo*) seem to be resistant to experimental infection.

Mycobacterium caprae

M. caprae is an important cause of tuberculosis in goats. Clinical cases or infections have also been documented in cattle, sheep, pigs, wild boar, red deer, red foxes (*Vulpes vulpes*), and some animals in zoos including a Siberian tiger (*Panthera tigris altaica*), wild Bactrian camels (*Camelus bactrianus ferus*), a dromedary camel (*Camelus dromedarius*), a Borneo elephant (*Elephas maximus borneensis*) and American bison (*Bison bison*). Although goats are the usual maintenance hosts, *M. caprae* has been found in cattle herds that have no apparent contact with small ruminants. In Europe, it seems to be maintained in free-living red deer and possibly in wild boar.

Mycobacterium microti, M. pinnipedii and M. orygis

M. microti is maintained in wild rodents and insectivores (e.g., shrews), and causes tuberculosis in these species. Commonly infected species such as field voles (*Microtus agrestis*), bank voles (*Myodes glareolus*), wood mice (A*podemus sylvaticus*) and shrews (*Sorex araneus*) might be maintenance hosts. Wild boar are also proposed to maintain this organism. Some recognized spillover hosts include cattle, goats, pigs, South American camelids, cats, dogs and ferrets, as well as free-living or captive wildlife such as badgers, meerkats, otters and nonhuman primates (squirrel monkeys, *Saimiri sciureus*; marmosets, *Callithrix jacchus*).

M. pinnipedii, which causes tuberculosis in pinnipeds, has been isolated from several species of seals and sea lions. There are occasional reports of this organism in other hosts including cetaceans (Hector's dolphin, *Cephalorhynchus hectori;* bottlenose dolphin, *Tursiops truncatus*), cattle, llamas, Bactrian camels, at least two species of tapirs (*Tapirus* sp.) and nonhuman primates (e.g., gorillas, *Gorilla* sp.). Mycobacterial infections in a captive snow leopard (*Panthera uncia*) and Amur leopard (*Panthera pardus orientalis*) at one zoo may also have been caused by *M. pinnipedii*.

M. orygis was first isolated from East African oryx (*Oryx beisa*). Since then, it has been found in a number of other ungulates including cattle, Arabian oryx (*Oryx leucoryx*), waterbuck (*Kobus ellipsiprymnus*), African buffalo, Indian rhinoceros (*Rhinoceros unicornis*), spotted deer (*Axis axis*), blue bull (*Boselaphus tragocamelus*) and nonhuman primates.

Zoonotic potential

M. bovis, *M. caprae, M. orygis*, *M. pinnipedii* and *M. microti* can all cause tuberculosis in humans.

Geographic Distribution

A limited number of countries (e.g., Australia, Iceland, Greenland, Singapore, some European nations, Israel) are completely free of *M. bovis;* however, infected livestock herds are now uncommon in Europe, Canada, the United States, New Zealand and some other locations. Wildlife reservoirs are known to exist in Wood Bison National Park and Riding Mountain National Park in Canada, Hawaii and northeastern Michigan in the U.S., some European countries and New Zealand. Bovine tuberculosis is still common or relatively common in cattle in parts of Africa, Asia, the Middle East and Latin America including Mexico.

M. caprae has mainly been reported in Europe; however, it was recently described in a few cattle in North Africa (Algeria, Tunisia), and sheep and reindeer in China, suggesting that it may be more widely distributed. *M. orygis*

has been found in Africa, southern Asia and the Middle East. Isolated cases identified in humans in the U.S. and New Zealand were probably acquired in Asia. *M. pinnipedii* has been described in marine mammals in many locations, including the coasts of Europe, New Zealand, Australia and South America. *M. microti* also seems to be widespread, with reports of indigenously acquired clinical cases in Europe, Africa and South America. It seems likely that some of these organisms also circulate in other areas.

Transmission

Most information on the transmission of the zoonotic mycobacteria comes from studies of *M. bovis*. Depending on the sites where it has localized, this organism may be found in respiratory secretions, exudates from lesions (e.g., draining lymph nodes, some skin lesions), urine, feces, milk, vaginal secretions and semen. Shedding can occur intermittently and differs between individuals. *M. bovis* is more likely to be transmitted when the respiratory tract is affected and in the late stages of the disease, when lesions are more extensive. Close contact in confined spaces facilitates its spread. It has also been cultured from the oral secretions of some animals, including ferrets, which may facilitate transmission in bites.

Animals can become infected by inhalation, ingestion or direct contact through the mucous membranes or breaks in the skin. Much larger numbers of organisms are generally needed to establish an infection by ingestion than inhalation. The importance of the various transmission routes differs between host species. Cattle are often infected via aerosols during close contact. Ingestion is less important in this species, except in calves that nurse from infected cows. Cutaneous, genital (sexual) and congenital transmission are possible but seem to be uncommon in cattle. Respiratory transmission is also thought to predominate in some other hosts such as camels, nonhuman primates and badgers. However, ingestion is thought to be the most common route in ferrets, cats, deer and horses. Percutaneous transmission is mainly seen in species that tend to hunt or fight, such as cats and badgers. Cats might also inoculate organisms onto mucous membranes when they wash after eating. Dogs with kidney lesions were thought to have transmitted *M. bovis* in urine in a kennel. Nosocomial transmission has been reported in at least two small animal veterinary clinics. In one instance, organisms from an infected cat were transmitted to healthy feline surgical patients, probably on hands or clothing.

Humans can be infected by the same routes as animals, including inhalation, ingestion and direct contact with mucous membranes or breaks in the skin. Ingestion is a common form of exposure when dairy products are not pasteurized. Viable *M. bovis* may also be found in raw or undercooked meat and other animal tissues. Animal bites have been linked rarely to human cases. Person-to-person transmission is possible, especially when the respiratory tract is affected. These incidents usually involve people in close contact, such as families, but at least one investigation suggested the possibility of respiratory transmission of *M. bovis* during casual contact in the community. Possible human-to-human transmission was also suggested for *M. microti*. Rare cases of probable or possible human-to-animal transmission have been documented for M. *bovis* and *M. orygis*. The organism was probably transmitted in aerosols in most of these cases, but urine-contaminated hay was thought to be involved in one incident in cattle.

The environmental survival of *M. bovis* and closely related mycobacteria are affected by the temperature, humidity, exposure to sunlight, fluctuations in moisture and temperature, competition with other microorganisms and initial numbers of bacteria. *M. bovis* can persist for up to several months in soil and other material (e.g., feed, feces), particularly in cold, dark and moist conditions; however, it sometimes disappears within days or weeks, especially when exposed to direct sunlight, higher temperatures and dry environments. There are a few reports of extended survival for a year or more, generally in feces or soil under optimal laboratory conditions. One study, which tested soil, water, hay and shelled corn kept outdoors in open containers, found that the number of viable *M. bovis* declined significantly during the first 2 weeks, but a small number of organisms survived longer. *M. bovis* is infrequently isolated from soil or pastures grazed by infected cattle, but whether this is due to inactivation of the organism or difficulties in isolating it from sites with competing bacteria, which grow more readily in culture, is not always clear.

Disinfection

The members of the *M. tuberculosis* complex are relatively resistant to disinfectants. Some agents effective against *M. tuberculosis*, which is more resistant than *M. bovis*, include phenol-based disinfectants, povidone iodine (but not iodophors), sodium hypochlorite, peracetic acid, glutaraldehyde, formaldehyde, orthophthaldehyde ethylene oxide, and a mixture of 7.5% hydrogen peroxide and 0.85% phosphoric acid. Some of these agents may require a longer contact time or higher concentrations than normally used for other microorganisms. In one report, a 70% alcohol solution could only inactivate *M. tuberculosis* in the absence of sputum; however, alcohols may be a valuable component in multi-step disinfection procedures for equipment.

M. bovis and *M. caprae* are both destroyed by standard HTST pasteurization of milk. Mycobacteria can also be killed by exposure to UV light, heating to greater than 65°C (149°F) for at least 30 minutes, or autoclaving (moist heat of 121°C/ 250°F for at least 15 minutes).

Infections in Animals

Incubation Period

Tuberculosis usually has a slow onset, with clinical signs often taking several months or more to develop. Infections can also remain latent for years and later reactivate. Unusually short incubation periods have been seen occasionally, including in 2 cats accidentally infected via surgical incisions, which became ill after 14 and 42 days.

Clinical Signs

Bovine tuberculosis (Mycobacterium bovis)

Tuberculosis is usually a chronic, debilitating disease in cattle, although acute and rapidly progressive cases are possible. The onset is typically insidious, initially with few or no signs of illness. Common clinical signs in this species include weight loss (emaciation may become severe in the terminal stages), weakness, inappetence, a low-grade, fluctuating fever, lymphadenopathy and respiratory involvement with a moist, intermittent cough that is worse in the morning, or during cold weather or exercise. Dyspnea or tachypnea may also be seen, and involvement of the gastrointestinal tract can result in intermittent diarrhea and constipation. The superficial lymph nodes can be palpably enlarged, and sometimes rupture and drain. The retropharyngeal lymph node is often affected in this species. Enlargement of deeper lymph nodes occasionally obstructs blood vessels, airways or the digestive tract. Ocular disease (e.g., anterior uveitis, choroidal infiltrates, subretinal exudates), repeated abortions and infertility caused by lesions in the uterus, and other syndromes have also been reported. Skin lesions are uncommon in cattle.

Tuberculosis is generally similar in other species, but the predominant syndromes or course of the disease may differ. Abdominal organs are affected more often than the respiratory tract in equids and some other hosts, while elephants tend to have few signs until the lesions are extensive. Syndromes reported in farmed cervids range from cases that progress slowly, over a period of years, with abscesses of unknown origin in isolated lymph nodes, to disseminated disease with a rapid, fulminating course. Skin lesions are sometimes seen in cervids. Subclinical infections seem to be prevalent in pigs, but disseminated disease can also be seen, especially in young animals. Osteomyelitis and meningeal involvement are reported to be relatively common in this species. Respiratory disease is a common form of tuberculosis in both badgers and brush-tailed opossums, but it tends to be chronic in badgers, which may survive for years, while opossums often die within a few months. Wildlife with advanced tuberculosis are sometimes found when they display abnormal behavior (e.g., opossums wandering around in the daytime).

Localized or generalized tuberculosis can be seen in cats. The submandibular lymph node is often enlarged in this species. In addition to lymphadenopathy, cats with generalized disease usually have nonspecific signs of illness (e.g., weight loss, persistent or fluctuating low-grade fever) and, in some cases, respiratory signs (coughing, dyspnea) or episodes of vomiting or diarrhea. Central nervous system (CNS) signs, enlargement of abdominal organs (e.g., liver, spleen) and joint or bone involvement are also possible. Skin and subcutaneous lesions are common in cats, and may appear as a soft swelling, firm nodule or flat ulcer. Skin lesions often result from direct inoculation of the organism, and tend to affect the face, neck, shoulders and extremities. Progressive lesions may sometimes expose and destroy the bones of the nose and face. Some infected cats have unilateral or bilateral eye lesions, either alone or accompanied by other syndromes. Common ocular lesions include panuveitis or anterior uveitis, conjunctivitis, and granulomas in ocular tissues (e.g., cornea, choroid, retina), the eyelid or periorbital tissues. As in other species, tuberculosis normally progresses slowly in cats. However, fulminant disease is possible. In one instance, two cats accidentally infected through their surgical wounds became severely ill within 2-3 weeks. Tuberculosis in lions seems to resemble the illness in cats.

There are usually no distinctive features of bovine tuberculosis in dogs, but one outbreak in a foxhound kennel was characterized by an unusual fulminant course with nonspecific signs including weight loss and lymphadenopathy, together with polyuria and polydipsia from kidney involvement.

Clinical cases caused by *M. bovis* are rare in birds, and few descriptions are available. Sudden death was reported in a black swan affected by this organism, and nonspecific signs of illness were seen in experimentally infected birds. This appears similar to avian tuberculosis, which is caused by organisms such as *M. avium* and is characterized mainly by poor body condition and other nonspecific signs, although skin lesions, ocular involvement and signs related to lesions in the internal organs are also possible.

Tuberculosis caused by other organisms

In terrestrial mammals, clinical cases caused by other organisms are usually indistinguishable from those caused by *M. bovis*. However, a clinical picture that consists of firm, raised skin lesions and submandibular lymphadenopathy is common in cats infected with *M. microti*, either with or without the involvement of other organs. *M. microti* can also cause other syndromes in cats, including pulmonary disease, arthritis, ocular signs and disseminated disease. Lethargy, anorexia, weight loss and respiratory signs are common in pinnipeds infected with *M. pinnipedii.*

Post Mortem Lesions

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Mammals

Tuberculosis is characterized by the formation of granulomas where bacteria have localized. The classic lesion is the tubercle, a yellowish-white or grayish-white granuloma typically enclosed in a capsule of varying thickness. Its interior is usually caseous, caseo-calcareous or calcified in cattle, small ruminants, pigs and a number of other species. However, tubercles in some species of cervids are often poorly encapsulated, tend to resemble abscesses and may have purulent centers. Tubercles vary in size. Some are small enough to be missed unless the tissue is sectioned; others may form coalescing, confluent lesions that affect most of the organ. In cattle and other species that tend to inhale the organisms, lesions are typically found in the lungs and lymph nodes of the head and thorax. They are more likely to occur in the abdominal organs and lymph nodes (e.g., mesenteric lymph nodes) of animals infected by

ingestion. Many other tissues and organs including the skin, bones, joints and CNS can also be affected.

Classic tubercles are less common in some hosts such as cats, dogs and horses. Instead, the lesions tend to appear as diffuse granulomatous infiltration, which can resemble neoplasia, or multiple small uncalcified nodules or caseous foci. Smooth, gray infiltrative lesions in the spleen and liver, are characteristic of primary tuberculosis lesions in horses. Small caseous foci may sometimes be found within these lesions. Diffuse granulomatous infiltrates are also common in disseminated disease, including cases in hosts that normally form classic tubercles at the primary infection site. Miliary tuberculosis, the most common form of disseminated disease in cattle, appears as small gray, white or yellowish-white caseous foci scattered throughout a tissue.

In cattle, dissemination of *M bovis* to the pleura, pericardium or peritoneum results in multiple small, sessile, pedunculated or cauliflower-like tubercles, which eventually calcify. They are said to resemble pearls, and can sometimes be so numerous that they cover the serosa. Dissemination to serosal surfaces is reported to be infrequent in sheep, goats and pigs, but horses sometimes have nodular serosal lesions. Pleuritis, peritonitis and pericarditis also be seen in some cats and dogs, but the serosa is usually thickened by granulation tissue rather than forming nodules. Some other lesions that may be found in tuberculosis include straw-colored or serohemorrhagic fluid in the body cavities or pericardium; ulcerative lesions in the trachea, bronchi or intestines; osteomyelitis; and various abnormalities in the joints, including proliferative lesions and joint capsule mineralization. Some infected animals do not have any visible lesions.

Birds

Mycobacterium sp. do not form classic encapsulated tubercles in birds; instead, the internal organs usually contain pale yellow, white or tan nodules and granulomatous infiltration. Small nodules are usually not caseated; larger nodules may be caseous but do not usually mineralize. Some birds with mycobacteriosis have no visible lesions.

Diagnostic Tests

Tuberculosis can be diagnosed by detecting either the causative organisms or the immune responses to these organisms. Animals that react in either type of test are generally treated as having an active infection. In some species, diagnostic tests may be supplemented with x-rays or other imaging techniques to visualize abnormalities in the internal organs.

Tuberculin test

The tuberculin skin test, which detects cell-mediated immune responses (CMI), is the primary screening test in cattle and some other species. Tuberculin, a mixture of bacterial proteins, is injected intradermally and the site is examined 48-96 hours later for an inflammatory swelling (delayed hypersensitivity reaction). The elapsed time affects the test's sensitivity and specificity. Livestock tests normally use antigens from *M. bovis*, but they can also detect infections with other members of the *M. tuberculosis* complex. A comparative test that evaluates relative reactivity to *M. bovis* and environmental mycobacteria (*M. avium*) can be used to decrease false positive reactions. False negative tests are also possible, especially during the first few weeks after exposure, in animals with suppressed immune responses, including those that have recently calved, and late in the course of the disease, when CMI may diminish.

The primary tuberculin tests used in cattle are the caudal fold test (CFT), the single cervical intradermal test (CIT) and the comparative cervical test (CCT). The CIT is generally considered to have higher sensitivity and specificity than the CFT; however, the CFT uses a site that can be more convenient to inject and examine. The U.S., Canada and some other countries use the CFT for preliminary screening of cattle, and re-test reactors with the CCT. Some European countries use the CCT; others start with the CIT and confirm reactors with the CCT.

The tuberculin test is also used in other animals, but it must be validated in each species, and the injection site can differ. The CCT and CIT are common tests for tuberculosis in captive cervids. Tuberculin tests have also been evaluated and/ or used in goats, water buffalo, guinea pigs and a limited number of wildlife hosts (e.g., lions infected with *M. bovis*, captive sea lions infected with *M. pinnipedii*). There is relatively little research on these tests in sheep, and some authors report that false negatives are common unless the animal has extensive lesions. Tuberculin tests have relatively poor sensitivity and specificity in llamas and alpacas, and they are often supplemented with *in vitro* CMI tests or serology for better accuracy. They are considered to be unreliable, due to inadequate sensitivity and/or specificity, in cats, dogs, horses, European badgers and brush-tailed opossums. Practical considerations, including the need to recapture the animal to read the test, can also preclude their use. Tuberculin tests cannot be employed in pachyderms due to the nature of their skin.

In vitro tests of cell-mediated immunity

Gamma-interferon (IFN- γ) release assays measure CMI using blood samples. Most of these tests are in the ELISA or ELISPOT format. Comparative assays that evaluate reactivity to *M. bovis* and environmental mycobacteria (*M. avium*) may be available in some laboratories. IFN-γ release tests can be used instead of skin tests in animals that are difficult to capture or handle. They have also been combined with skin tests to increase sensitivity or specificity.

IFN-γ release tests developed for cattle do not necessarily work in other animals. As of 2019, these tests have been used or evaluated in a limited number of species including goats, sheep, South American camelids, cats, badgers and lions. They were also employed, in conjunction with serology, during an outbreak in dogs. Samples for this test must be

transported to the laboratory promptly, as it must be started within 24-30 hours of blood collection.

The lymphocyte proliferation test, another blood test for CMI, has mainly been used in wildlife and zoo animals. It is not a commonly used test.

Serology

Antibodies to *M. bovis* usually develop later than CMI, and titers tend to increase as the disease progresses. The most commonly used serological tests are ELISAs and lateral flow immunochromatographic assays, but other methods (e.g., immunoblotting or a multiantigen print assay) may also be available. Serological tests have only been validated for a small number of hosts. However, they have been used to help diagnose tuberculosis in South American camelids, farmed cervids, dogs, elephants, and a number of captive or free-living wildlife infected with *M. bovis*, and in pinnipeds infected with *M. pinnipedii*. At one zoo, gradually increasing antibody titers preceded positive tuberculin skin tests in a *M. bovis*- infected onanger (*Equus hemionus onager*) and gemsbok (*Oryx gazelle gazelle*). Serology may occasionally be useful in cattle or goats in the late stages of tuberculosis. There are a few reports of these tests being used to monitor responses to treatment (e.g., in elephants). Cross reactions to other bacteria, especially environmental mycobacteria, can complicate test interpretation.

Tuberculin skin tests can boost serological responses in deer and South American camelids, and combining these tests can reveal infected animals that do not respond in the skin test. This technique needs to be validated in each species. An attempt to use it in elephants resulted in a high rate of false positive reactions.

Detection of the organism

In live animals, members of the *M. tuberculosis* complex are sometimes found in exudates, biopsy samples from affected tissues, sputum and other secretions and excretions. Trunk washes to collect sputum are a routine diagnostic test in elephants, as there are few other antemortem tests in this species. Sputum is also collected in captive pinnipeds that may be infected with *M. pinnipedii*, and bronchoalveolar lavage fluid has occasionally been employed in lions or other animals. More often, tuberculosis is confirmed in tissue samples from affected organs, taken at necropsy. Infections can sometimes be found in animals with no apparent lesions. In cattle with no visible lesions, the recommended minimum sample is pooled lymph nodes from the head and thorax. Collecting additional tissues may be helpful. A recent study found that, in cattle with no visible lesions that were infected by ingestion, *M. bovis* is more likely to be found in the abdominal (e.g., mesenteric) lymph nodes.

A presumptive diagnosis can be made by histopathology and/or the demonstration of acid-fast bacilli in smears from tissues, exudates or body fluids. Some lesions contain abundant bacteria; others have very few. Concentration methods can increase the chance of visualizing the organism. Direct smears for microscopy can be stained with Ziehl-Neelsen stain, a fluorescent acid-fast stain (e.g., auramine) or immunoperoxidase techniques. *M. microti* is distinctive in that the rods may appear curved in fresh specimens. This characteristic is usually lost after culture.

Tuberculosis can be confirmed by isolating the causative organism on selective culture media such as modified Middlebrook 7H10 or 7H11 agar, or Stonebrink's or Lowenstein–Jensen egg-based medium. While colonies may occasionally appear as early as 2 weeks, the median time on solid media is 4-5 weeks, and some samples may require up to 12 weeks or longer. Recovery is reported to be faster in automated liquid broth culture systems. Because these slow-growing organisms can be overgrown by contaminants, samples for culture should be collected as aseptically as possible. If necessary, culture can incorporate a decontamination step, where the samples are treated with a toxic agent to which members of the M. *tuberculosis* complex are relatively resistant (e.g., cetylpyridinium chloride, sodium hydroxide or oxalic acid). However, decontamination also decreases the recovery of mycobacteria. Culture is not always successful in infected animals. *M. microti* is especially difficult to isolate.

A cultured organism's identity can be confirmed with biochemical tests, or PCR and other genetic techniques (e.g., commercial DNA probes; sequencing of certain genes). Biochemical methods are slow and labor-intensive and may occasionally give ambiguous results, and molecular methods are generally preferred if they are available. At least one commercial genetic test can distinguish *M. bovis*, the vaccine strain *M. bovis* BCG, *M. caprae*, *M. tuberculosis*, *M. africanum* and *M. microti*. However, it cannot reliably differentiate some organisms, such as *M. pinnipedii* and *M. africanum*. Genetic techniques such as spoligotyping, multilocus variable number tandem repeat typing (MLVA) or whole genome sequencing) can be used for epidemiological purposes such as tracing outbreaks.

PCR can sometimes identify the causative organism directly in clinical samples. It has the advantage of speed, and can also be helpful when organisms are difficult to grow. However, it is less sensitive than culture if the sample has few bacteria.

Animal inoculation is possible but rarely done.

Treatment

Antibiotics have been used to treat some animals with tuberculosis, especially pets and zoo animals. However, the possibility of clinical improvement without bacteriological cure must be kept in mind. Some animals that responded initially later relapsed, especially with inadequate treatment (e.g., too short treatment or the use of a single drug). The risk of shedding organisms, hazards to humans (especially if the respiratory tract is infected or there are draining lesions), and potential for the development of drug resistance make treatment controversial. Treatment is not permitted in some countries.

Members of the *M. tuberculosis* complex are not susceptible to many common antibiotics; they can be treated only with a limited number of tuberculocidal agents. Treatments for animals are usually patterned after successful protocols used in humans, and employ two or more drugs, given simultaneously for months. When selecting antibiotics, it should be kept in mind that, except in rare cases, *M. bovis* is intrinsically resistant to pyrazinamide, a common "first line" drug for tuberculosis. This drug can, however, be used in animals infected with *M. caprae*. One protocol for cats, which are unusually sensitive to some of the commonly used tuberculocidal drugs, combines rifampicin, a fourth generation fluoroquinolone such as pradofloxacin, and clarithromycin or azithromycin.

Surgery is occasionally used to remove small masses, treat ocular tuberculosis (e.g., enucleation), or amputate an infected joint, in combination with tuberculocidal drugs. Drug treatment alone seems to have poor results in cats that have significant osteomyelitis or joint involvement.

Control

Disease reporting

Veterinarians who suspect an animal is infected with a member of the M. *tuberculosis* complex should follow their national and/or local guidelines for disease reporting. Although most regulations are written for *M. bovis* or *M. caprae* in livestock, some nations stipulate that other members of this complex or infected pets (e.g., cats with tuberculosis in the U.K.) must also be reported. State authorities should be consulted for regulations in the U.S.

Prevention

Sanitation and disinfection, open air housing rather than confinement, and avoidance of crowding might reduce the spread of tuberculosis within a herd. Rodent control decreases the risk that these animals may disseminate the organism. Keeping cats indoors can help protect them in areas endemic for *M. bovis*, *M. caprae* or *M. microti*. In endemic areas, barrier nursing precautions and tuberculocidal disinfectants should be considered in veterinary hospitals when animals have signs consistent with tuberculosis.

Control programs are usually targeted at bovine tuberculosis in cattle, but some programs may include *M. caprae*. In these programs, animals are tested periodically with the tuberculin skin test and/or other assays. If an infected herd is found, the reactors are removed and the herd is quarantined until all animals test negative. Where testing is done regularly, most herds contain only a few infected cattle. Reactors are generally slaughtered, but some countries may employ test-and-segregation programs at first, and later switch to test-and-slaughter. Entire herds can also be depopulated, though this is generally rare. Once eradication is nearly complete, slaughter surveillance, with tracing of infected animals, may be a more efficient use of resources. However, it is relatively insensitive, and can miss infected animals with few or no visible lesions. Screening programs may sometimes include species other than cattle (e.g., farmed deer); however, in most cases, these animals are only found by passive surveillance or epidemiological investigations of infected cattle.

The occurrence of *M. bovis* and *M. caprae* in wildlife reservoirs complicates eradication efforts. Transmission from these animals to livestock can be reduced with biosecurity measures such as wildlife barriers around feed storage areas, or solid metal barriers and gates to exclude badgers from cattle pens. Some countries have also established control programs targeted at the principal maintenance host(s). Culling may decrease their population density below the level needed to sustain transmission. However, each situation must be assessed individually, as culling may have unanticipated effects if it encourages infected animals to disperse. Capture and testing programs, with the release of uninfected animals, have sometimes been used in badgers and African buffalo. Some control programs include bans on feeding deer and elk, to reduce transmission between congregating animals and discourage transmission on fomites. Elimination of organisms mainly found in wildlife, such as *M. pinnipedii*, *M. orygis* and *M. microti*, is impractical.

Vaccines, including some that contain the Bacillus Calmette Guerin (BCG) strain of *M. bovis*, are being evaluated for possible use in livestock and farmed deer, and as an aid in controlling tuberculosis in wildlife reservoirs. IFN-γ release assays and tuberculin skin tests that can distinguish BCG-vaccinated livestock from animals infected with *M. bovis* have been published. As of 2019, the only licensed vaccine is a parenteral BCG vaccine for badgers in the U.K. Test-negative badgers are vaccinated before release in some control programs.

Morbidity and Mortality

Possible outcomes after exposure to a member of the *M. tuberculosis* complex include elimination of the organism by the immune system, persistent asymptomatic infection with or without limited lesions, or the development of a chronic and eventually fatal disease. Some subclinically infected animals become ill only if they become debilitated or stressed, or in old age. There are also reports of *M. bovis* lesions resolving in experimentally infected animals, with or without the elimination of the organism; however, this is thought to be rare. Factors that may influence the outcome of an infection include the animal's species, the species of *Mycobacterium*, the dose of organisms, the site of inoculation and the individual's general health. Clinical cases also seem to be more severe in young animals. Genetic resistance to *M. bovis* has been identified in some hosts including cattle, farmed red deer and African buffalo. Zebu cattle (*Bos indicus*) are reported to be more resistant to bovine tuberculosis than the Ankole or Holstein breeds of *Bos taurus*.

Mycobacterium bovis

In two studies of *M. bovis* transmission in naturally infected cattle, 0-40% of susceptible contacts reacted in tuberculin tests, and 0-10% developed gross lesions. Sheep

are thought to be more resistant to *M. bovis* than cattle or goats, but underdiagnosis could be an issue, as reports of tuberculosis in sheep seem to be rising. It is possible that management (e.g., less intensive rearing) or behavior helps protect sheep from exposure. Rabbits also seem to be relatively resistant; most clinical cases have been reported in animals exposed to heavily contaminated environments.

Tuberculosis was seen regularly in pigs, horses, cats and dogs in the first part of the 20th century, when infected cattle with extensive lesions were more common. Only sporadic cases have been reported in dogs or horses in recent years. During one recent outbreak in a working English Foxhound kennel, approximately 8% of the dogs were infected, and 8 of the 14 infected dogs became ill. Ferrets, guinea pigs and cats seem to be relatively susceptible to *M. bovis*. At one time, infections were estimated to occur in 7% of the cats in Switzerland, and about half of the cats exposed to infected cattle herds in Pennsylvania. Later, in the 1970s, a Swiss study found evidence of tuberculosis in 0.2% of feline necropsies. However, recent reports did not detect any infected cats on farms with bovine tuberculosis in Michigan or the U.K., probably because the number of infected cattle was low and the lesions were not extensive. In the U.K., infected rodents and other wildlife now seem to account for most cases of tuberculosis in cats. Occasional infections in indoor cats probably result from exposure to other infected cats or people in the household. A commercial raw food with venison was also implicated in a number of recent cases. Most cats with tuberculosis are not infected with immunosuppressive viruses, and were previously healthy.

M. bovis infection rates in wildlife spillover or maintenance hosts generally range from ≤ 5% to 20%, but there are reports of localized clusters with higher prevalence. High animal density, social structures that encourage contact between individuals, and artificial concentration of animals (e.g., supplemental feeding of deer) increase the probability that a species will maintain *M. bovis*. Spillover hosts sometimes act as temporary reservoirs that can reinfect maintenance hosts.

Other organisms

Research on *M. caprae* is limited, but many aspects of its morbidity and mortality are probably similar to *M. bovis*. Some evidence suggests that *M. caprae* tends to be less virulent than *M. bovis* in goats, although it can also cause severe disease. *M. pinnipedii* is thought to be widespread in pinnipeds, and *M. microti* is common in some wild rodent populations. Among domestic animals, clinical cases and lesions caused by *M. microti* have been reported relatively often in cats and wild boar, and sporadically or rarely in some mammals such as cattle. This organism is challenging to culture and it may be underdiagnosed. Some reports suggest that tuberculosis in cats tends to be less severe when it is caused by *M. microti* than *M. bovis*.

Infections in Humans

Incubation Period

Systemic signs can develop months to years after exposure in humans, or the infection may remain latent until many years later when waning immunity allows the organisms to reactivate. Tuberculous chancre, a type of skin lesion, typically appears 2-4 weeks after cutaneous exposure.

Clinical Signs

In humans, tuberculosis is characterized by nonspecific signs such as fever, malaise and weight loss, and various symptoms caused by lesions in the lymph nodes, lungs, skin, bones, joints, genitourinary system, intestinal tract, CNS and/or a variety of less frequently involved sites. In one unusual case caused by *M. bovis*, the primary sign of infection was a tooth abscess. Pulmonary involvement, with fever, chronic weight loss, coughing, chest pain and hemoptysis, is common in people infected with the anthroponotic organism *M. tuberculosis*, which is usually acquired by inhalation. Because zoonotic organisms are often ingested, many of these cases tend to involve extrapulmonary sites instead. Cervical lymphadenopathy of the jugulodigastric (tonsillar) and preauricular lymph nodes is a common presentation in children who drink infected milk. These nodes sometimes suppurate and drain to the skin, resulting in chronic skin lesions. Pulmonary involvement is, however, common when zoonotic mycobacteria cause disseminated disease or the organisms in latent infections reactivate. It can also be seen when zoonotic organisms are inhaled.

The skin lesions that occur in some cases of tuberculosis have been given various names (e.g., scrofuloderma, lupus vulgaris) depending on their appearance, origin and typical course. They can result from direct inoculation of organisms into the skin, or by the extension of an infection from another site. Some are also caused by hypersensitivity reactions to small numbers of organisms in cutaneous blood vessels. Cutaneous lesions may appear as papules, ulcers and/or suppurative lesions; soft, gelatinous plaques with central atrophy; reddish-brown, gradually enlarging subcutaneous nodules; or vegetative lesions that can resemble a tumor. One common localized form of tuberculosis, called tuberculosis verrucosa cutis or "butcher's wart," results from direct inoculation of the organism into the skin, often on the extremities, and typically appears as one or more painless verrucous and tuberous papules. Tuberculosis verrucosa cutis usually evolves slowly, does not ordinarily spread to the lymph nodes or other organs, and tends to be self-limiting. Another localized form called tuberculous chancre, which appears as a shallow, painless, nonhealing ulcer, may regress spontaneously, persist or evolve into other forms, and sometimes spreads to other parts of the body.

CNS disease and disseminated disease are particularly serious forms of tuberculosis. Patients with CNS disease can have meningitis, meningoencephalitis or a focal infection, either with or without the involvement of other organs. Chronic meningitis, the most common form of CNS

disease, has an insidious onset and is most often seen in young children, people who are immunosuppressed and older adults. Meningoencephalitis has been reported in all ages, and patients can deteriorate fairly quickly. Disseminated disease usually affects both pulmonary and extrapulmonary organs, and occasionally includes widespread skin lesions. Patients with this form of tuberculosis are severely ill, and may die soon after the onset of clinical signs. Disseminated tuberculosis is particularly common in immunocompromised patients, and also has an elevated incidence in young children.

Diagnostic Tests

Tuberculin skin tests, IFN-γ release assays, direct microscopy for acid-fast bacilli, culture, and PCR or other nucleic acid assays, combined with imaging studies such as chest x-rays, are used to diagnose tuberculosis in humans. In people, the tests that evaluate immune responses are interpreted in conjunction with evidence of bacterial replication and disease. Unlike in animals, the diagnosis is not a binary assessment of whether the person is infected or not, but also considers possibilities such as a latent infection or exposure without persistence of the bacterium. Vaccination with BCG or sensitization by periodic skin testing can complicate the interpretation of some tests of CMI. Comparative tests that evaluate immune responses to environmental mycobacteria are employed only rarely in humans.

Human diagnostic laboratories sometimes use PCR-based systems to screen sputum samples for tuberculosis, either routinely or when they contain acid-fast bacilli. These tests are more sensitive than microscopic examination of the sample, but less sensitive than culture. Zoonotic mycobacteria, which often cause extrapulmonary tuberculosis, are not always found in sputum. Diagnostic testing for tuberculosis in people does not necessarily identify the species of organism except as a member of the *M. tuberculosis* complex. This is especially common in some impoverished countries, where acid-fast smears are widely used for diagnosis, and culture may be unavailable. The inability to identify *M. bovis* might influence the effectiveness of treatment.

Treatment

Commonly-used first line agents for tuberculosis in humans include rifampicin, isoniazid and pyrazinamide; other (second-line) drugs are employed for drug-resistant isolates. Multidrug-resistant strains of M. bovis (defined as resistance to at least isoniazid and rifampicin) have been identified occasionally, and there have been a few strains resistant to second line drugs. Antibiotic resistant strains of M. bovis are mainly thought to arise during tuberculosis treatment in humans, rather than circulating in animals.

Active tuberculosis is usually treated for a minimum of 6 months with two or more agents, used simultaneously. The standard first line tuberculosis treatment for *M. tuberculosis* can usually be employed for cases caused by *M. caprae;* however, *M. bovis* is intrinsically resistant to pyrazinamide and the recommended length of treatment for this organism is currently 9 months. Compliance can be an issue, and some researchers have been investigating whether shorter treatment periods would also be effective. Surgery might occasionally be considered for some isolated forms of tuberculosis such as cutaneous disease.

Prevention

The risk of contracting zoonotic tuberculosis can be decreased by controlling the organisms in domestic animals. Pasteurization destroys the members of the *M. tuberculosis* complex in dairy products. Thorough cooking is effective in meat and other animal tissues; however, some organisms may survive in undercooked (e.g., rare) meat. Carcasses with lesions should not be eaten. People who must handle infected animals or their tissues should use gloves and other personal protective equipment (PPE), including respiratory protection where aerosolization could be an issue. Any open wounds should be covered. Hunters should also use PPE in areas where wildlife may be infected. The use of high pressure hoses for cleaning animal facilities has been associated with some infections, probably by aerosolizing bacteria.

Some countries administer a BCG vaccine, which contains an attenuated strain of *M. bovis*, to infants. It can protect young children from severe tuberculosis, especially disseminated disease and CNS disease; however, its efficacy differs between individuals, the protection wanes early in adolescence, and revaccination does not seem to be helpful. The BCG vaccine is expected to be protective against *M. bovis* as well as *M. tuberculosis*.

Morbidity and Mortality

M. bovis

Current understanding of human tuberculosis suggests that, in some cases, the organisms are eliminated from the body after a few weeks, while, in others, they may proliferate either with or without clinical signs, or establish a latent infection. Infected individuals can move between these states. The typical course of events is for inapparent infections to become symptomatic, or latent infections to become reactivated when immunity wanes. However, spontaneous improvement or recovery is also possible, even after the development of clinical signs. While there are no data for *M. bovis*, approximately 5-10% of humans infected with *M. tuberculosis* become ill during the first 2 years. The risk of reactivation in latent *M. tuberculosis* infections is estimated to be 5-10% in healthy people over their lifetime, and about 10% per year if the person is significantly immunocompromised.

In healthy people, clinical tuberculosis is often a slowly progressive disease with low mortality if it is treated. However, disseminated disease and CNS involvement are more likely to be fatal. In a small number of studies, case fatality rates were 18-72% in various forms of CNS tuberculosis, and about a third of the surviving patients had permanent neurological deficits. Mortality rates are also elevated in people who are immunocompromised, regardless

of treatment, and in young children. Childhood mortality from tuberculosis was about 1% in recent years. Without treatment, however, historical reports suggest case fatality rates of 22% in all children and 44% in those under the age of 5 years. Only a few studies have specifically examined tuberculosis mortality due to *M. bovis*. In at least two reports, it appeared to be higher in patients infected with this organism than *M. tuberculosis*; however, patient characteristics, including underlying illnesses, may not have been comparable. Two studies found case fatality rates of 10-14% in people with uncontrolled HIV infections and tuberculosis caused by *M. bovis*.

Groups at elevated risk of infection with *M. bovis* include farmers, abattoir workers, veterinary personnel, zoo staff and others who may handle infected animals or tissues, and those who drink unpasteurized milk. The incidence of tuberculosis due to this organism is poorly understood, as the causative organism is not always identified. Approximately 25-30% of all tuberculosis cases were thought to be caused by *M. bovis* before the advent of milk pasteurization and bovine tuberculosis control programs, at a time when close contact with livestock was also more common. Newer studies estimate that this organism is responsible for < 1% to 5-10% or more of the tuberculosis cases in various countries, and usually < 2% of the cases in developed nations with good bovine tuberculosis programs (e.g., approximately 230 cases in the U.S. each year). In endemic areas, clinical cases are especially common in children, who are more susceptible than adults and may be exposed to *M. bovis* in unpasteurized milk products. However, most cases in developed countries now occur in elderly or immunosuppressed individuals, as the result of reactivated infections acquired in childhood, and in immigrants from endemic regions. Small clusters of *M. bovis* infections seem to be caused by person-to-person transmission, especially among people in close contact (e.g., families). Healthy people, as well as those who are immunocompromised, have been affected in these incidents.

Organisms other than M. bovis

M. caprae is uncommon in humans but it may represent a significant fraction of the zoonotic cases where *M. bovis* has been controlled. In Europe, this organism was responsible for <1% to 70% of the tuberculosis cases in various surveys. Risk factors seem to be similar to those for *M. bovis*, and both goats and cattle have been associated with human infections. Clinical cases caused by *M. microti* and *M. pinnipedii* are thought to be uncommon in humans. However, infections with *M. microti* may be underdiagnosed, as this organism is common in wild rodents in some areas, but it is difficult to culture and clinical suspicion is low.

Internet Resources

Canadian Food Inspection Agency.Bovine Tuberculosis

Centers for Disease Control and Prevention, United States. Tuberculosis

European Centre for Disease Prevention and Control. Tuberculosis

European Union Reference Laboratory. Bovine Tuberculosis

Michigan Bovine Tuberculosis Eradication Project

The Merck Manual

The Merck Veterinary Manual

Public Health Agency of Canada. Pathogen Safety Data Sheets and Risk Assessment

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests for Aquatic Animals

WOAH Aquatic Animal Health Code

United States Department of Agriculture, Animal and Plant Health Inspection Service (USDA APHIS) National Tuberculosis Eradication Program

World Health Organization. Tuberculosis

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