Bovine Tuberculosis

Last Updated: October 2007

Minor Update: July 2009

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Importance

Bovine tuberculosis is a chronic bacterial disease of cattle that occasionally affects other species of mammals. This disease is a significant zoonosis that can spread to humans, typically by the inhalation of aerosols or the ingestion of unpasteurized milk. In developed countries, eradication programs have reduced or eliminated tuberculosis in cattle, and human disease is now rare; however, reservoirs in wildlife can make complete eradication difficult. Bovine tuberculosis is still common in less developed countries, and severe economic losses can occur from livestock deaths, chronic disease and trade restrictions. In some situations, this disease may also be a serious threat to endangered species.

Etiology

Bovine tuberculosis results from infection by *Mycobacterium bovis*, a Gram positive, acid-fast bacterium in the *Mycobacterium tuberculosis* complex of the family Mycobacteriaceae.

Species Affected

Cattle are the primary hosts for *M. bovis*, but other domesticated and wild mammals can also be infected. Known maintenance hosts include brush–tailed opossums (and possibly ferrets) in New Zealand, badgers in the United Kingdom and Ireland, bison and elk in Canada, and kudu and African buffalo in southern Africa. White-tailed deer in the United States (Michigan) have been classified as maintenance hosts; however, some authors now believe this species may be a spillover host that maintains the organism only when its population density is high. Species reported to be spillover hosts include sheep, goats, horses, pigs, dogs, cats, ferrets, camels, llamas, many species of wild ruminants including deer and elk; elephants, rhinoceroses, foxes, coyotes, mink, primates, opossums, otters, seals, sea lions, hares, raccoons, bears, warthogs, large cats (including lions, tigers, leopards, cheetahs and lynx) and several species of rodents. Most mammals may be susceptible.

Little is known about the susceptibility of birds to *M. bovis*, although they are generally thought to be resistant. Experimental infections have recently been reported in pigeons after oral or intratracheal inoculation, and in crows after intraperitoneal inoculation. Some avian species, including mallard ducks, appear to be resistant to experimental infection.

Geographic Distribution

Although bovine tuberculosis was once found worldwide, control programs have eliminated or nearly eliminated this disease from domesticated animals in many countries. Nations currently classified as tuberculosis-free include Australia, Iceland, Denmark, Sweden, Norway, Finland, Austria, Switzerland, Luxembourg, Latvia, Slovakia, Lithuania, Estonia, the Czech Republic, Canada, Singapore, Jamaica, Barbados and Israel. Eradication programs are in progress in other European countries, Japan, New Zealand, the United States, Mexico, and some countries of Central and South America. Although bovine tuberculosis has been eradicated from the majority of U.S. states, a few infected herds continue to be reported, and a few states may periodically lose their disease-free status. In particular, a focus of infection in wild white-tailed deer has complicated eradication efforts in Michigan. Similar problems exist with infected badgers in the U.K. and Ireland, and infected brush-tailed opossums in New Zealand. Bovine tuberculosis is still widespread in Africa, parts of Asia and some Middle Eastern countries.

Transmission

M. bovis can be transmitted by the inhalation of aerosols, by ingestion, or through breaks in the skin. The importance of these routes varies between species. Bovine tuberculosis is usually maintained in cattle populations, but a few other species can become reservoir hosts. Most species are considered to be spillover hosts. Populations of spillover hosts do not maintain *M. bovis* indefinitely in the absence of maintenance

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hosts, but may transmit the infection between their members (or to other species) for a time. Some spillover hosts can become maintenance hosts if their population density is high.

Cattle shed *M. bovis* in respiratory secretions, feces and milk, and sometimes in the urine, vaginal secretions or semen. Large numbers of organisms may be shed in the late stages of infection. Asymptomatic and anergic carriers occur. In most cases, *M. bovis* is transmitted between cattle in aerosols during close contact. Some animals become infected when they ingest the organism; this route may be particularly important in calves that nurse from infected cows. Cutaneous, genital, and congenital infections have been seen but are rare. All infected cattle may not transmit the disease. Ingestion appears to be the primary route of transmission in pigs, ferrets, cats and probably deer. In addition, cats can be infected by the respiratory route or via percutaneous transmission in bites and scratches. Nonhuman primates are usually infected by inhalation. Aerosol transmission also seems to be the main route of spread in badgers, but transmission in bite wounds can be significant. Badgers with advanced disease can shed *M. bovis* in the urine, and organisms have been found in the feces. Due to behavioral changes, badgers and possums are most likely to transmit *M. bovis* to cattle during the late stages of disease.

*M. bovi*s can infect humans, primarily by the ingestion of unpasteurized dairy products but also in aerosols and through breaks in the skin. Raw or undercooked meat can also be a source of the organism. Person-to-person transmission is rare in immunocompetent individuals, but *M. bovis* has occasionally been transmitted within small clusters of people, particularly alcoholics or HIV-infected individuals. Rarely, humans have infected cattle via aerosols or in urine.

M. bovis can survive for several months in the environment, particularly in cold, dark and moist conditions. At 12-24°C (54-75°F), the survival time varies from 18 to 332 days, depending on the exposure to sunlight. This organism is infrequently isolated from soil or pastures grazed by infected cattle. Although *M. bovis* can be cultured from artificially stored samples for nearly two years under some conditions, it appears to survive in natural pastures for, at most, a few weeks. In a recent study, *M. bovis* remained viable for 4 to 8 weeks in dry or moist soil samples in 80% shade [34°C (93°F)]. In another study, it was destroyed within four days on New Zealand pastures in either summer or winter.

Incubation Period

The symptoms of bovine tuberculosis usually take months to develop in cattle. Infections can also remain dormant for years and reactivate during periods of stress or in old age. Similarly, severe disease can develop in some deer within a few months of infection, while other deer do not become symptomatic for years. In kittens experimentally infected by the parenteral route, the incubation period is approximately three weeks; it is probably longer under natural conditions.

Clinical Signs

Tuberculosis is usually a chronic debilitating disease in cattle, but it can occasionally be acute and rapidly progressive. Early infections are often asymptomatic. In countries with eradication programs, most infected cattle are identified early and symptomatic infections are uncommon. In the late stages, common symptoms include progressive emaciation, a low–grade fluctuating fever, weakness and inappetence. Animals with pulmonary involvement usually have a moist cough that is worse in the morning, during cold weather or exercise, and may have dyspnea or tachypnea. In the terminal stages, animals may become extremely emaciated and develop acute respiratory distress. In some animals, the retropharyngeal or other lymph nodes enlarge and may rupture and drain. Greatly enlarged lymph nodes can also obstruct blood vessels, airways, or the digestive tract. If the digestive tract is involved, intermittent diarrhea and constipation may be seen. In cervids, bovine tuberculosis may be a subacute or chronic disease, and the rate of progression is variable. In some animals, the only symptom may be abscesses of unknown origin in isolated lymph nodes, and symptoms may not develop for several years. In other cases, the disease may be disseminated, with a rapid, fulminating course.

In cats, the symptoms may include weight loss, a persistent or fluctuating low-grade fever, dehydration, decreased appetite and possibly episodes of vomiting or diarrhea. If the respiratory tract is involved, the cat may have coughing, dyspnea and rales. Respiratory failure can occur with exertion, if there is significant pleural exudate. In the abdominal form, enlarged mesenteric lymph nodes may be palpable. Skin infections are also common in cats, and may appear as a soft swelling or flat ulcer, most often on the face, neck or shoulders. Draining fistulas or tracts may be seen. In some cats, bovine tuberculosis appears as a deformity of the forehead or bridge of the nose. In the late stages, these infections can expose and destroy the bones of the nose and face. An unusual form of tuberculosis in cats mainly affects the eyes. The first symptom may be blindness or abnormal pupillary responses. Retinal detachment may be seen, and webs of exudate can be found in the vitreous humor. When the anterior portions of the eye become involved, the iris is thickened and discolored, and lacework is found on the anterior surface of the lens. Pericorneal congestion and vascularization, and conjunctivitis can be seen the late stages of the disease. Abscesses can also occur in periorbital tissues.

In brush-tailed opossums, bovine tuberculosis is usually a fulminating pulmonary disease that typically lasts two to six months. In the final stage of the disease, animals become disoriented, cannot climb, and may be seen

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wandering about in daylight. In contrast, most infected badgers have no visible lesions and can survive for many years. In symptomatic badgers, bovine tuberculosis is primarily a respiratory disease.

Post Mortem Lesions

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Bovine tuberculosis is characterized by the formation of granulomas (tubercles) where bacteria have localized. These granulomas are usually yellowish and either caseous, caseo-calcareous or calcified. They are often encapsulated. In some species such as deer, the lesions tend to resemble abscesses rather than typical tubercles. Some tubercles are small enough to be missed by the naked eye, unless the tissue is sectioned.

In cattle, tubercles are found in the lymph nodes, particularly those of the head and thorax. They are also common in the lung, spleen, liver and the surfaces of body cavities. In disseminated cases, multiple small granulomas may be found in numerous organs. Lesions are sometimes found on the female genitalia, but are rare on the male genitalia. In countries with good control programs, infected cattle typically have few lesions at necropsy. Most of these lesions are found in the lymph nodes associated with the respiratory system. However, small lesions can often be discovered in the lungs of these animals if the tissues are sectioned.

In cervids, tubercles are most common in the lymph nodes of the head and thorax, particularly the medial retropharyngeal lymph nodes. Discharging sinus tracts from the cranial lymph nodes occur in some species. Large abscesses may also be fund in the mesenteric lymph nodes. In white-tailed deer, the medial retropharyngeal lymph nodes and tonsils are often involved, and sinus tracts are uncommon.

M. bovis tubercles are not usually calcified in cats or dogs. In cats, they can be found in the lymph nodes, lungs and other organs. Pleuritis, peritonitis and pericarditis may also be seen. In dogs, tubercles are common in the lymph nodes, lungs, liver, kidney, pleura and peritoneum, and straw-colored fluid may be found in the thorax.

Although some infected badgers have disseminated disease, many others may have minimal, localized lesions. Tubercles are found most often in the lungs and associated lymph nodes, but may also be found in other lymph nodes and visceral organs. In contrast, brush-tailed opossums tend to have extensive lung caseation and necrosis.

Morbidity and Mortality

In countries with control programs, bovine tuberculosis is often confined to one or two animals in a herd. In two studies of transmission from naturally infected reactor cattle, 0-40% of susceptible contacts became infected and 0-10% developed gross lesions. The severity of the disease varies with the dose of infectious organisms and individual immunity. Infected animals may remain asymptomatic, become ill only after stress or in old age, or develop a chronic, debilitating fatal disease. In developed countries, most reactors are detected during routine testing and mortality from tuberculosis is rare.

In maintenance hosts other than cattle, the prevalence of infection and the severity of the disease vary with the species. In Ireland, more than 40% of culled badgers have been found to carry *M. bovis* in some studies. Most of these animals remain unaffected: 50-80% of infected badgers have no visible lesions, and 5% or less develop generalized disease. In contrast, bovine disease is usually progressive and fatal in brush-tailed opossums in New Zealand. Although more than 50% of the opossums can be infected in localized areas, the prevalence of infection in this species is typically 1-10%. In the Michigan white-tailed deer population, the annual prevalence varies from 2% to 4%. In affected regions of Canada, the prevalence of *M. bovis* in wild elk appears to be approximately 1%, but mature males have a prevalence of nearly 5%.

When bovine tuberculosis is uncontrolled in cattle, a high incidence of disease may be seen in cats; up to 50% of the cats may be infected on affected farms.

Diagnosis

Clinical

Tuberculosis can be difficult to diagnose based only on the clinical signs. In developed countries, few infections become symptomatic; most are diagnosed by routine testing or found at the slaughterhouse. In cervids, tuberculosis should be considered in the differential diagnosis when abscesses of unknown etiology are found.

Differential diagnosis

The differential diagnosis includes contagious bovine pleuropneumonia, *Pasteurella* or *Corynebacterium pyogenes* pneumonia, aspiration pneumonia (which is often secondary to chronic wasting disease in cervids), traumatic pericarditis, caseous lymphadenitis or melioidosis in small ruminants, and chronic aberrant liver fluke infestation.

Laboratory tests

In live cattle, tuberculosis is usually diagnosed in the field with the tuberculin skin test. In this test, tuberculin is injected intradermally; a positive test is indicated by a delayed hypersensitivity reaction (swelling). The tuberculin test can be performed using bovine tuberculin alone, or as a comparative test that distinguishes reactions to *M. bovis* from reactions to environmental mycobacteria. The U.S. uses the caudal fold (bovine tuberculin) test for the preliminary screening of cattle; reactors are re-tested with the comparative cervical test. The single cervical test is used for preliminary screening of cervids. A comparative cervical test is used for the initial screening of cattle in Europe. False negative responses are sometimes seen soon after infection, in the late stages of the disease, in animals with poor immune responses and in those that have recently calved.

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A presumptive diagnosis can also be made by histopathology and/or the microscopic demonstration of acid-fast bacilli. Direct smears from clinical samples or tissues may be stained with the Ziehl/ Neelsen stain, a fluorescent acid-fast stain or immunoperoxidase techniques. The diagnosis is confirmed by the isolation of *M. bovis* on selective culture media. Mycobacteria grow slowly, and cultures are incubated for eight weeks; growth usually becomes visible in 3 to 6 weeks. The identity of the organism can be confirmed with biochemical tests and culture characteristics, or polymerase chain reaction (PCR) assays. PCR can also detect *M. bovis* directly in clinical samples. Genetic fingerprinting techniques (e.g. spoligotyping) can distinguish different strains of *M. bovis*. Animal inoculation is rarely done, but may be necessary if the histopathology suggests tuberculosis and cultures are negative. All procedures for bacterial culture should be done in a biological safety cabinet, as the bacteria may survive in heat-fixed smears or become aerosolized during specimen preparation.

Other assays are typically used as ancillary tests to the tuberculin test. The lymphocyte proliferation and gamma-interferon assays are blood tests that measure cellular immunity. The gamma-interferon assay is particularly useful in animals that are difficult to capture or handle, as they must be captured only once, rather than twice for the tuberculin test. The lymphocyte proliferation test is uncommonly used in cattle, but may be useful in wildlife and zoo animals. Enzyme-linked immunosorbent assays (ELISAs) measure antibody titers to *M. bovis*. ELISAs may complement tests of cellular immunity in anergic cattle. However, tests of humoral immunity are generally of limited utility in cattle, because titers are inconsistent and rise only in the late stages of infection. In deer, titers can rise earlier in the course of disease, and may be more predictable. ELISAs may also be useful in other wildlife and zoo animals. Radiographs are used for diagnosis in dogs and cats, together with culture.

For the use of various diagnostic tests in non-bovine species, see the review article "Review of tests available for use in the diagnosis of tuberculosis in non-bovine species" in Internet Resources.

Samples to collect

Bovine tuberculosis is a zoonotic disease; samples should be collected, handled and shipped with all appropriate precautions.

The tuberculin test is the standard method of diagnosis in live cattle and cervids, and the prescribed test for international trade.. Occasionally, the sputum and other body fluids may be collected from live animals for microbiological examination. Blood samples may also be taken for the gamma interferon or lymphocyte proliferation tests, and serum can be collected for ELISA. Samples for the gamma interferon test must be transported to the laboratory promptly, as this test must be started within 24 to 30 hours of blood collection.

At necropsy, samples for culture should be collected from abnormal lymph nodes and affected organs such as the lungs, liver, and spleen. These samples should be collected into clean, preferably sterile, containers; environmental mycobacteria grow more rapidly than *M. bovis* and contamination with these organisms can cause false negatives. Specimens should be shipped to the laboratory quickly; prompt shipment maximizes the chance of isolating *M. bovis*. If shipping must be delayed, the samples can be refrigerated or frozen. If refrigeration or freezing is not feasible, 0.5% (w/v) boric acid may be added for periods of a week or less. Specimens should also be collected for histopathology.

Recommended actions if bovine tuberculosis is suspected

Notification of authorities

Bovine tuberculosis is a reportable disease. State authorities should be consulted for specific regulations.

Federal: Area Veterinarians in Charge (AVIC):

www.aphis.usda.gov/animal_health/area_offices/

State Veterinarians:

www.usaha.org/Portals/6/StateAnimalHealthOfficials.pdf

Control

Bovine tuberculosis can be controlled by test-and-slaughter or test-and-segregation methods. Affected herds are re-tested periodically to eliminate cattle that may shed the organism; the tuberculin test is generally used. Infected herds are usually quarantined, and animals that have been in contact with reactors are traced. Only test-and-slaughter techniques are guaranteed to eradicate tuberculosis from domesticated animals. However, some countries use test-and-segregation programs during the early stages of eradication, and switch to test-and-slaughter methods in the final stage. Once eradication is nearly complete, slaughter surveillance, with tracing of infected animals, may be a more efficient use of resources. Sanitation and disinfection may reduce the spread of the agent within the herd. *M. bovis* is relatively resistant to disinfectants and requires long contact times for inactivation. Effective disinfectants include 5% phenol, iodine solutions with a high concentration of available iodine, glutaraldehyde and formaldehyde. In environments with low concentrations of organic material, 1% sodium hypochlorite with a long contact time is also effective. *M. bovis* is also susceptible to moist heat of 121°C (250°F) for a minimum of 15 minutes. Rodent control may also be advisable on affected farms; meadow voles and house mice can be infected experimentally, and voles shed *M. bovis* in feces.

The occurrence of *M. bovis* in wildlife reservoir hosts complicates eradication efforts. Culling to reduce the population density can decrease transmission. However,

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each situation must be assessed individually; culling may have unanticipated effects such as increasing the dispersal of the remaining members of a species. Prohibition of supplemental feeding and baiting (feeding of wild ruminants by hunters) can decrease transmission at feeding areas. Barriers can be used around hay storage areas to prevent wildlife access. In addition, biosecurity measures on farms decrease interactions between wildlife and domesticated animals.

Effective bovine tuberculosis vaccines are not currently available for cattle. New vaccines are being developed and tested, particularly for wildlife reservoirs.

Antimicrobial treatment has been attempted in some species, but the treatment must be long term, and clinical improvement can occur without bacteriological cure. The risk of shedding organisms, hazards to humans, and potential for drug resistance make treatment controversial. In some countries, it may be illegal.

Public Health

Human tuberculosis due to *M. bovis* has become very rare in countries with pasteurized milk and bovine tuberculosis eradication programs. However, this disease continues to be reported from areas where bovine disease is poorly controlled. The incidence is higher in farmers, abattoir workers and others who work with cattle. In addition, humans can be infected by exposure to other species; documented infections have occurred from goats, seals, farmed elk and a rhinoceros. Wildlife may be a source of infection, particularly in countries where bushmeat is eaten.

Some human infections are asymptomatic. In other cases, localized or disseminated disease can develop either soon after infection, or many years later when waning immunity allows the infection to reactivate. Localized disease can affect the lymph nodes, skin, bones and joints, genitourinary system, meninges or respiratory system. Cervical lymphadenopathy (scrofula), which primarily affects the tonsillar and pre-auricular lymph nodes, was once a very common form of tuberculosis in children who drank infected milk. In some cases, these lymph nodes rupture and drain to the skin; chronic skin disease (lupus vulgaris) may occasionally result. Humans infected through the skin can develop localized skin disease ("butcher's wart"), a form usually thought to be benign and self-limiting. Pulmonary disease is more common in people with reactivated infections than initially; the symptoms may include fever, cough, chest pain, cavitation and hemoptysis. Genitourinary disease can result in kidney failure. Bovine tuberculosis can be treated successfully with antimicrobial drugs, but untreated infections may be fatal.

Internet Resources

Cousins DV, Florisson N. A review of tests available for use in the diagnosis of tuberculosis in non-bovine species http://www.oie.int/eng/publicat/rt/2403/A_R2403_COUSINS.htm

Manual for the Recognition of Exotic Diseases of Livestock http://www.spc.int/rahs/*

Michigan Bovine Tuberculosis Eradication Project http://www.michigan.gov/emergingdiseases/0,1607,7-186-25804-74719--,00.html

The Merck Manual http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual http://www.merckvetmanual.com/mvm/index.jsp

Public Health Agency of Canada. Material Safety Data Sheets http://www.phac-aspc.gc.ca/msds-ftss/index.html

World Organization for Animal Health (OIE) http://www.oie.int

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

OIE Terrestrial Animal Health Code http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

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