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Zoonosis Update

Tuberculosis

John B. Kaneene, DVM, MPH, PhD, and Charles O. Thoen, DVM, PhD

Tuberculosis is a term that encompasses various diseases caused by bacteria of the *Mycobacterium tuberculosis* complex, including *M tuberculosis*, *M bovis*, *M africanum,* and other mycobacterial species. Whereas *M tuberculosis* infection is largely spread from human to human, *M bovis* infection has been identified as a zoonotic disease with most cases of human infection attributable to animal sources. The **mycobacteria other than tuberculosis complex (MOTT)**, which includes *M avium* subsp *avium* and *M avium* subsp *intracellulare* isolated from animals,[1,2] has been isolated from immunocompromised humans (ie, those with **human immunodeficiency virus [HIV]** infection), but seldom from immunocompetent humans.[3] Recently, there has been increased interest among public health officials in drug-resistant strains of *M tuberculosis*, *M bovis*, and *M avium* because several have been isolated from HIV-infected and nonimmunocompromised humans.[4]

Mycobacterium tuberculosis is the cause of most of the cases of tuberculosis in humans. Worldwide, more humans die as a result of tuberculosis each year than from any other infectious disease.[4] At present, more than a third of the world's population is infected with tubercle bacilli and more people are dying as a result of tuberculosis than ever in history. Ninety-five percent of the tuberculosis cases are reported in developing countries, and it has been estimated that the disease results in the deaths of 2 to 3 million people each year.

Infection with *M bovis* has been reported in humans[5-10,a,b] and causes pulmonary and extrapulmonary disease.[11,12] In the United States and other developed countries, extrapulmonary *M bovis* infections in humans have been almost eliminated following the introduction of food-production procedures such as pasteurization of milk and routine carcass inspection.[11,13] However, *M bovis* infection commonly occurs in less-developed countries and in specific demographic groups within developed countries in which consumption of unpasteurized dairy products is practiced. Although there is no active surveillance program for human cases of *M bovis* infection in the United States, most of the reported cases appear localized to states with large immigrant populations from countries with recognized *M bovis* infections in livestock.[10,a,b] For example, 7% of mycobacterial isolates from 1,931 cases of tuberculosis in San Diego were identified as *M bovis*. These infections were associated with ingestion of raw dairy products; 53% of these patients had extrapulmonary disease,[10,14] and 33% of isolates obtained from children were *M bovis*.[10,14]

Contact with infected animals is another source of *M bovis* infection for humans and is a recognized hazard for abattoir workers, veterinarians, and livestock handlers.[5-7,11,15-17] Among such workers who developed the disease, aerosol transmission was considered the most likely route of infection, but there are many occasions on which infection had been spread via cuts and abrasions (eg, butcher's wart).[16] Although many of the primary nonaerosol sources of *M bovis* infection in humans have been removed in industrialized countries, there has been an increase in the number of cases of pulmonary infection with *M bovis*, which may be due to several factors: the lung is the usual site of postprimary *M bovis* infection, regardless of the site of the primary lesion; cases of pulmonary *M bovis* infection may be the result of reactivation of previously quiescent (ie, nonclinical) primary lesions; and infection may be the result of human-to-human aerosol transmission.[16] Finally, aerosol transmission of *M tuberculosis* from humans to animals has been reported.[18,19] The disease has been reported in elephants, nonhuman primates, and several other species.[18-22,b]

The reemergence of *M bovis* infection in captive and free-ranging wild animals, with subsequent transmission of infection to domestic animals, is of concern to livestock producers and regulatory officials in the United States and in several other countries of the world.[23-26] In Michigan, the detection of tuberculosis in deer and other wild animals and the transmission of *M bovis* infection to beef and dairy herds have threatened the export of breeding stock and semen to other states and to countries outside the United States.[26] When an outbreak of tuberculosis in cattle is reported within a state, federal disease control officials remove the state's accredited-free status, causing economic hardships for the state's livestock industries.

With the effects of tuberculosis on animal health and zoonotic implications, eradication and control of disease caused by the bacteria that compose the *M tuberculosis* complex are high priorities. Despite efforts to control tuberculosis since its recognition in antiquity, the disease continues to be a problem in both human and animal populations.

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Etiology

Bacteria of the *M tuberculosis* complex are aerobic, nonmotile, non–spore-forming, slow-growing, acid-fast bacilli. Because they are slow growing, isolation of the bacteria can require 3 to 8 weeks of incubation.[27] Results of experimental studies[28,29] indicate that the strain of the organism, dose of the organism, route of inoculation, and prevailing conditions for growth of the organism may influence the time required to produce disease.

The natural and acquired immune response mechanisms of a host are often successful in limiting proliferation of tubercle bacilli and the development of progressive disease.[29] The susceptibility of certain animal species to different types of tubercle bacilli is variable. Nonhuman primates, swine, cats, and dogs are susceptible to *M tuberculosis*. Ruminants are quite resistant to infection by *M tuberculosis*; however, this organism may induce responses to *M bovis* **purified protein derivative (PPD)** tuberculin. Other mycobacterial infections including those involving *M avium* complex (*M avium-M intracellulare-M scrofulaceum*), *M kansasii, M fortuitum,* and *M avium* subsp *paratuberculosis* may induce skin sensitivity to tuberculin, but do not usually induce progressive pulmonary disease in cattle and other animals.[2] Cattle are susceptible to *M bovis*, yet they are comparatively resistant to infection with *M tuberculosis*.[30] Moreover, laboratory animals such as guinea pigs and rabbits are susceptible to *M bovis*, whereas chickens are resistant to that organism; this difference in observed susceptibilities may be associated with differences in body temperature.[31]

Pathogenesis

Mycobacterium bovis infection first results in the formation of a primary focus, which is usually located in the lungs.[31-33] In mammals, lymphatic drainage from the primary focus leads to the formation of caseous lesions in an adjacent lymph node; this lymph node lesion, together with the primary focus, is known as the primary complex. This primary complex seldom heals in animals.

Results of experimental investigations[30-33] involving exposure of animals to *M bovis* via IV, intratracheal, and IP injection and via the oral route have indicated that the nature and extent of the resultant disease vary with the route of exposure. In cattle and other animals, aerosol spread of tubercle bacilli frequently leads to involvement of lungs and thoracic lymph nodes, whereas exposure by ingestion of contaminated food and water often results in primary foci in lymph tissues associated with the intestinal tract.[30]

At sites of localization of the organisms, granulomas form and develop into tumor-like masses called tubercles in advanced cases.[29] Because of the continued growth of the organisms, these tubercles often enlarge to a considerable size. Large masses may develop on the serous membranes of the body cavities. As the granulomas increase in size, necrosis of their central portions may occur. Finally, these central portions are reduced to caseous masses, which have a tendency to undergo mineralization or liquefaction. In mammals, tubercles may become enclosed in dense fibrous tissue and the disease becomes arrested.

Advanced lesions associated with clinical disease include caseous nodules or cavities with liquefaction. Bacilli are transferred from the primary foci via lymph and blood vessels; they lodge in other organs and tissues, thereby establishing sites of additional tubercles. When the bloodstream is invaded by numerous tubercle bacilli from a local lesion, many tubercles develop in the major organs (such as the lungs). The acute form of generalized infection (known as miliary tuberculosis) is often rapidly fatal. If small numbers of bacilli enter the circulation from the primary complex, a few isolated lesions develop in other organs; these widely distributed lesions may become encapsulated and remain small for extended periods, usually causing no detectable clinical signs of disease.[30] The progression of the disease from early infection of macrophages to the development of caseous nodules that undergo calcification and liquefaction, as well as the regression, progression, or generalized spread of lesions, depends on the interrelation of the immune response of the host and the proliferation of the bacilli in macrophages.[29,31] The disease can take months to develop.

Epidemiology

The *M tuberculosis* complex is known to infect a wide variety of warm-blooded animals. Although occasional cases of *M tuberculosis* have been reported in animals such as cats, dogs, and elephants, the sources of these infections have commonly been traced to infected humans who have exposed susceptible animals to infection. In animals, most mycobacterial infections that are reported involve *M bovis*; therefore, infection with *M bovis* is of public-health and economic importance.

Several mammalian species are known to be susceptible to infection with *M bovis*, including hoofed mammals (Artiodactylae and Perissodactylae), marsupials, carnivores, primates, pinnipeds, lagomorphs, rodents, and other species. In addition to mammals, some avian species are also susceptible to infection, including parrot-like birds (Psittacciformes), rock doves, and North American crows. Humans are also susceptible to *M bovis*, and there are numerous instances of human infection resulting from contact with infected animals.[5-7,16,17,34-37] Throughout the world, the most commonly recognized hosts for *M bovis* are domesticated bovids. However, in recent years, several wildlife reservoir hosts have been identified, including brushtail possums in New Zealand,[38,39] European badgers in the United Kingdom,[40,41] white-tailed deer in Michigan,[42,43] and Cape buffalo[44] and several antelope species in South Africa.[36] Other species, such as elephants[45] and rhinoceros,[7,17] have been identified as hosts for *M bovis* infection in captivity. Although *M bovis* infection may be detected in other species, most of those affected animals are considered to be spillover hosts that require external sources of infection to maintain disease in their populations.

There are several routes of transmission for *M bovis* infection, but the primary routes of infection are via the respiratory and gastrointestinal tracts. Respiratory transmission via the inhalation of contaminated aerosols or fomites is the most efficient form of transmission, requiring a low number of organisms as an infective dose.[32] Respiratory transmission has been detected in herding animals, such as domestic cattle,[16,32] feral water buffalo,[46] and African cape buffa-

lo,[44] and in captive herds of various cervid species.[47-49] Transmission of *M bovis* via inhalation appears to be effective in wildlife species that are kept in confinement in zoos[7] and in free-ranging wildlife species that maintain social or familial groups in underground dens, such as European badgers in the United Kingdom[40] and brushtail possums in New Zealand.[38] Furthermore, respiratory transmission of *M bovis* has been detected in wildlife populations during periods when normal behaviors become altered (for whatever reason) and result in more frequent direct contact between animals, such as that which occurred among white-tailed deer in Michigan in association with winter feeding.[26,50]

Although respiratory transmission is the most important route of infection in groups of animals that remain in close contact, indirect transmission via feed contamination is another important route. For oral transmission to be accomplished, an uninfected animal has to consume feed or water contaminated with mucous or nasal secretions, feces, or urine that contain the infective organisms or receive milk from an infected dam; therefore, *M bovis* must be able to survive outside an infected host for sufficient time to be ingested by another animal. The environmental survival of *M bovis* is reduced by dessication, exposure to sunlight, and high temperature. Results of experimental studies have indicated that *M bovis* can survive for < 4 days on cotton strips[51] and for as much as several months in feces[52-55] or in animal carcasses that remain out in the field in South Africa.[56] Oral transmission of *M bovis* has been detected in several species: in cattle that graze pastures contaminated with the organism[57-60]; in feral swine in Australia[61] and Hawaii[62] that scavenge among infected animal carcasses; in wild carnivores in Africa, New Zealand,[63,64] and North America[65]; and in dogs and cats[66-68] that consume contaminated milk or scavenge contaminated carcasses. Consumption of infected feeds has also been implicated in interspecies disease transmission in which direct contact between species was not evident (eg, the transmission of *M bovis* between white-tailed deer and cattle in Michigan).[69]

Other routes of infection for *M bovis* have been identified. Transmission through biting has been identified in black-footed ferrets in New Zealand[63,70] and in domestic cats.[71] Vertical transmission has also been identified in some species, but many cases of what has appeared to be vertical transmission may be a result of infection via aerosolization of organisms from infected parent to offspring living in close quarters (eg, animal dens), direct contact associated with grooming of offspring by infected mothers, or consumption of contaminated milk.[72]

Outbreaks of *M bovis* infection and endemic infection have been reported in animal populations. Outbreaks are characterized by a rapid increase in infection rate over a short period within a population of animals; these can occur with the introduction of infected animals to a population (eg, a cattle herd) that has susceptible animals with the capacity for spreading the disease among herd mates. Such explosive increases in numbers of cases of infection are often easily identified through routine surveillance procedures that detect increases in the prevalence or incidence of infection, or as a result of the identification of sick animals that are not included in surveillance programs. An example of the latter is the detection of *M bovis* infection in free-ranging white-tailed deer in Michigan that was recognized after a hunter submitted a carcass with suspicious lesions to the state's Department of Natural Resources for investigation.[42]

Endemic mycobacterial infections are characterized by low rates of infection and have also been reported in animal populations. The extent of the disease is not sufficient to affect the survival of the population, but is sufficient to continue transmission of infection within the populations.[73] However, low rates of infection may be below detectable levels for some surveillance methods; the infection may be detected only when circumstances change to increase the number of cases of disease in the population or when a highly susceptible dead-end host is affected by infection from an endemically infected host species, with dramatic effect. These problems associated with detection of low rates of infection must be taken into consideration when evaluating the effectiveness of any surveillance program.

Clinical Findings

Clinical signs of tuberculosis vary depending on the extent and location of the lesions. Detection of enlarged superficial lymph nodes provides a useful diagnostic sign, whereas small lesions located in deep lymph nodes are of little or no value in establishing a clinical diagnosis. The principal sign of tuberculosis is wasting or emaciation that develops despite good nutrition,[30] and other general signs include weakness, anorexia, dyspnea, and low-grade fluctuating fever. In mammals, the organs of the thoracic cavity are usually involved; when the lungs are extensively affected, an intermittent hacking cough is commonly detected, mainly after exercise.

Diagnosis

Clinical diagnosis of tuberculosis is usually possible only after the disease has reached an advanced stage and, with the exception of miliary tuberculosis, is dependent on the site of lesions. At the time of diagnosis, most infected animals are shedding bacilli and are a source of infection for other animals.

Antemortem evaluations are a critical component of tuberculosis control programs throughout the world. At this time, one of the most reliable and practical methods of diagnosis (albeit tentative) in domestic animals is assessment via the tuberculin skin test. Animals infected with mycobacteria are allergic to the proteins contained in tuberculin and develop characteristic delayed-type hypersensitivity reactions when exposed to those proteins. The deposition of tuberculin intradermally in the deep layers of the skin usually elicits a local reaction characterized by inflammation and swelling in infected animals, whereas such reactions at the injection site fail to develop in uninfected animals. The sensitivity and specificity of the intradermal test often depend on the field conditions,

prevalence of infection, and other factors.[30,74] The intradermal tuberculin skin test may not be effective or practical for use in all species, but has been accepted by the USDA for identification of *M bovis* in cattle, bison, goats, and captive cervids.[75]

At present, most countries use *M bovis* for the preparation of PPD tuberculin for veterinary use; heat-concentrated synthetic-medium old tuberculin is infrequently used. The use of PPD tuberculin is preferable because it is easier to standardize and more specific than old tuberculin and is particularly useful in comparative tuberculin tests used to differentiate responses caused by *M bovis* or *M tuberculosis* and those induced by other mycobacteria. Most countries use PPD tuberculin at a dose of 0.1 mL (ie, 0.1 mg of protein) containing 5,000 tuberculin units in mammals and 0.05 mL containing 2,500 tuberculin units in chickens. When testing for avian tuberculosis, an *M avium*-PPD tuberculin must be used because animals infected with *M avium* react less to tuberculin made from the culture filtrate of *M bovis*.[30]

In the United States, 2 specific skin tests are serially applied to livestock herds for diagnosis of tuberculosis. Large mammals such as cattle, bison, or deer are usually injected in 1 of the folds at the base of the tail or in skin of the cervical region (the caudal fold test); swine are injected in the skin behind the ear or vulva, and chickens are injected in the skin of the wattle. The injection sites are examined by observation and palpation for characteristic swelling 48 hours after injection for swine and chickens and 72 hours after injection for cattle, sheep, and goats.[28,30,76] In general, animals for which test results are positive or suspect are removed from the farm and examined post-mortem for confirmation of mycobacterial infection, depending on federal and state testing regulations, which vary with species or the specific circumstances under which testing was undertaken. In cattle that are suspected to have *M bovis* infection, the comparative cervical skin test is administered by another caudal fold test. The comparative cervical skin test is performed by injecting biologically balanced *M avium* and *M bovis* PPD tuberculins into separate sites in the skin of the neck. The injection sites are examined by observation and palpation. The differences in the size of the resultant skin responses are compared on a graph, which indicates whether the observed tuberculin sensitivity is caused by infection with *M bovis* rather than infection with *M avium* subsp *avium* or *M avium* subsp *paratuberculosis*.[76] These results are then used to classify animals as negative for infection (the response to the test is negative), suspected to have infection (the response to the test is unclear), or reactor (the response to the test is positive). Although skin tests are useful tools in tuberculosis-testing programs, they have the drawback of requiring the individual performing the test to visit a production facility or premises on which the animals are kept on 2 occasions: 1 to administer the tuberculin, and another to assess the results of the test. Other diagnostic methods that rely on cellular immune response and are performed in vitro (such as lymphocyte blastogenic assays or γ-interferon tests) have been developed and used, with results that are comparable to those obtained with intradermal tests.[77-79] A commercially available γ-interferon test for cattle[c] has been recommended for use as a supplemental diagnostic test for *M bovis* infection in cattle herds.[80] Recently, a protein (referred to as ESAT-6) has been identified in the early phase of *M bovis* infection in cattle.[81,82] This may be important in the early detection of tuberculous animals, before results of other tests are found to be positive. However, immunologic tests have been found to be unreliable in some species (eg, elephants); isolation of the causative agent is then necessary for diagnosis.[21,83]

Mycobacterial culture is still considered to be the gold standard by which to confirm a diagnosis of tuberculosis. Because of the slow growth of *M tuberculosis* complex bacilli, culture results are usually obtained after 3 to 6 weeks. Recently, polymerase chain reaction techniques have been reported to be useful in the diagnosis of *M tuberculosis* and *M bovis*.[21,22,68] A DNA probe has been developed for identifying *M bovis* in formalin-fixed, paraffin-embedded tissues, and results of this analysis are available in a few days[84]; recently, a modification of this polymerase chain reaction assay was used to detect *M avium*.[85]

The development of molecular techniques for differentiating strains of *M bovis*, such as DNA fingerprinting (restriction fragment length polymorphism), has been useful in outbreak investigations in animals and humans to identify potential sources of infection or relatedness of strains.[10,18,68,86,87] By use of this technique, the restriction fragment length polymorphism pattern of an isolate of *M bovis* from an elderly Michigan resident matched the unique pattern of the deer and cattle strain that was circulating in the northeastern portion of the Lower Peninsula of Michigan; this isolate had not previously been detected in a human in Michigan since routine speciation of isolates began in 1994. Although multiple exposure possibilities were explored, the conclusion of the epidemiologic investigation conducted by the Michigan Department of Community Health was that exposure to deer from the endemically infected area of Michigan was the most probable source of infection for this patient.[37] Although DNA fingerprinting is a useful tool, the tests must be conducted under carefully controlled conditions to avoid contamination and false-positive findings. More importantly, results of these tests do not indicate the source and direction of the infection (ie, results of the test cannot indicate which of 2 infected populations was the source of infection for the other).

Control

Control programs for tuberculosis in animals are primarily focused on control of infection with *M bovis*. These programs can be considered as having 4 components: prevention, treatment, eradication, and surveillance. Disease prevention primarily focuses on reducing opportunities for animals to be exposed to the pathogen of concern and reducing the likelihood that an exposed animal will become infected after exposure. On cattle farms, the major source of *M bovis* is infected cattle that either reside on the farm or are introduced to the herd from another facility. Basic herd hygiene and biosecurity practices (eg, routine testing for tuberculosis and quarantine of imported animals, manure management, and maintenance of feed and

water hygiene) have been found to reduce the risks of spread of *M bovis* on cattle farms.[69,88-90]

It has been necessary to establish population control measures for wild reservoir animals (ie, possums, badgers, and white-tailed deer) that may shed tubercle bacilli and contaminate feed and water. Although the main reservoir of *M bovis* is cattle, there are several instances in which wildlife reservoirs (including European badgers,[91,92] brushtail possums,[93] deer,[42,94,95] African Cape buffalo,[25,44,96] and wild boar[97]) have been important sources of infection for cattle. Reservoir animals infected with tubercle bacilli that interact with cattle may be the source of herd infections and significant production losses.[25,69]

The **BCG (Bacillus of Calmette and Guerin)** vaccine has been used in humans in some countries in which tuberculosis is prevalent in the population. Unfortunately, the BCG vaccine does not completely prevent infection in cattle or other animals[28,98]; moreover, vaccinated animals yield positive results on the tuberculin skin test, which precludes the use of the vaccine in the United States or other countries with eradication programs. In several countries where *M bovis* infection has been reported in wild animals, a BCG vaccine has been evaluated as an immunizing agent.[61,99-101] It should be noted that there is considerable interest in the development of new DNA vaccines; however, they have not been accepted for use in food-producing animals.

Until the discovery of the antituberculosis drug isonicotinic acid hydrazide, there was no practical treatment for tuberculosis. Elephants receiving isonicotinic acid hydrazide along with rifampicin or ethambutol have successfully recovered from tuberculosis after 6 months of treatment. In Brazil and South Africa, investigators have suggested that it is feasible to treat cattle with isoniazid, and guidelines have been developed for treatment of infective animals with antituberculosis drugs, but the treatment of tuberculosis in cattle is not allowed in the United States nor in many other countries.[42] When treatment is attempted, appropriate regimens must be followed; for elephants with *M tuberculosis*-complex infections, this involves administration of 360 doses of 3 drugs within a 15-month period, with concurrent testing for serum drug concentrations.[102]

In domestic livestock herds, depopulation is an effective way of removing *M bovis* from a livestock operation. After a waiting period (12 months in the United States) in which livestock is not allowed on the depopulated site, the facility can be restocked. Although depopulation is an effective tool for controlling tuberculosis for the livestock industry as a whole, the effects can be devastating both financially and emotionally to individual farmers. As an alternative to depopulation of herds in the United States, the USDA allows regulatory agencies to develop herd-specific test-and-slaughter programs for individual livestock operations.[101]

Depending on the reservoir species involved, eradication of *M bovis* infection in wildlife can be highly problematic. The size and distribution of wildlife populations are often unknown, the extent of disease in the population can be difficult (if not impossible) to estimate accurately, and aspects of animal behavior associated with the distribution of the disease in the wild may be unclear. The control of tuberculosis in cervids and other wild animals is limited to population control because intradermal testing of those animals is not practical. Population control is usually exercised through trapping and removal programs,[59] directed hunts to reduce animal numbers,[25] or provision of incentives to hunters (ie, unlimited hunting permits and increased duration of the hunting season) to increase the number of animals removed during the hunting season.[26,43] In addition to population control, wildlife behavior modification has been used as a tool to reduce the spread of the disease in the wildlife population. In the outbreak of *M bovis* in free-ranging white-tailed deer in Michigan, large-scale winter feeding in 1 area of the state that had continued for decades had dramatically increased the numbers of deer in the area and created conditions in which large numbers of normally timid animals would congregate around feed piles.[42,50] After the discovery of tuberculosis in wildlife, bans were placed on feeding and baiting of animals in areas where they may gather during cold weather or other conditions associated with limited food supply.[50] After these measures had been applied over a 6-year period, the apparent prevalence of tuberculosis in deer in a 12-county area in Michigan decreased by 50%.[26]

A final component of any tuberculosis control and eradication program is routine surveillance to detect any changes in development of the disease. This includes antemortem testing and slaughter surveillance of livestock and captive animal species.

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