Tuberculosis

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[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 prolif-

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

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*M avium u

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 antituber-
M bovis

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