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Bovine Tuberculosis

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Overview

- Organism
- History
- Epidemiology
- Transmission
- Disease in Humans
- Disease in Animals
- Prevention and Control
- Actions to Take

In today's presentation we will cover information regarding the organism that causes bovine tuberculosis and its epidemiology. We will also talk about the history of the disease, how it is transmitted, species that it affects (including humans), and clinical and necropsy signs observed. Finally, we will address prevention and control measures, as well as actions to take if bovine tuberculosis is suspected.

[Photo: Jersey cows. Source: Brandi Huddle/Iowa State University/CFSPH]

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THE ORGANISM

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The Organism

- *Mycobacterium bovis*
  - Gram positive bacterium
  - Acid fast
  - *M. tuberculosis* complex
- Persists in the environment
  - Cold, dark, moist conditions

***M. tuberculosis* complex**

- *M. tuberculosis*
- *M. africanum*
- *M. canettii*
- *M. caprae*
- *M. bovis*
- *M. pinnipedii*
- *M. microti*

Bovine tuberculosis results from infection by *Mycobacterium bovis*, a Gram positive, acid-fast bacterium in the *Mycobacterium tuberculosis* complex of the family Mycobacteriaceae. The *M. tuberculosis* complex is composed of seven closely related species: *M. tuberculosis, M. africanum and M. canettii* (found in humans) and the animal adapted species *M. bovis* (bovine), *M. caprae* (goats), *M. pinnipedii* (seals), and *M. microti* (rodents). *M. bovis* can survive for several months in the environment, particularly in cold, dark and moist conditions.

Source: Homolka S, Niemann S, Russell DG, Rohde KH (2010) Functional Genetic Diversity among *Mycobacterium tuberculosis* Complex Clinical Isolates: Delineation of Conserved Core and Lineage-Specific Transcriptomes during Intracellular Survival. PLoS Pathog 6(7): e1000988.

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HISTORY

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History

- 1898
  - *M. bovis, M. tuberculosis* differentiated
- Early 1900s
  - TB was leading cause of death in U.S.
  - 10% of cases likely caused by *M. bovis*
- 1917
  - State-Federal Cooperative Bovine TB Program established

In 1898, the bovine and human forms (*M. bovis* and *M. tuberc*ulosis) of tuberculosis were differentiated. In the early 20th century, tuberculosis (TB) was the leading cause of death in the United States, taking roughly 148,000 human lives in 1900. It is estimated that 10 percent or more of TB cases were actually due to the bovine form, contracted by contact with cattle, cattle products, or swine. The State-Federal Cooperative Bovine Tuberculosis Program was initiated in 1917; this is discussed later in the presentation.

Source: Olmstead AL and Rhode PW. An Impossible Undertaking: The Eradication of Bovine Tuberculosis in the United States. 2004. Available at: www.unc.edu/~prhode/Impossible_Undertaking.pdf.

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EPIDEMIOLOGY

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Geographic Distribution

- Once worldwide
  - Control programs established
  - Many regions now free of bovine TB
- U.S.
  - Eradicated in most states
  - Few infected herds
  - Wildlife foci exist

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.

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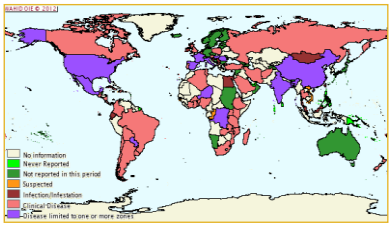
Geographic Distribution



This map, from the World Organization for Animal Health (OIE) shows the distribution of bovine TB from January to June 2011. Red indicates a current disease event, purple indicates disease limited to one or more zones, dark green indicates disease not reported in this period, and light green indicates disease never reported.

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TRANSMISSION

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Transmission in Humans

- Ingestion
  - Unpasteurized dairy products
  - Raw or undercooked meat
- Aerosol
- Breaks in the skin
- Person-to-person
  - Rarely
  - Immunosuppressed

M. bovis 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.

[Photo: Bottles of raw milk. Source: Kyle McDaniel/Wisconsin State Journal]

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Transmission in Animals

- Most animals = spillover hosts
  - Do not maintain *M. bovis*
  - May transmit to other animals
- Cattle = reservoir hosts
  - Aerosol
  - Ingestion (calves)
  - Cutaneous, genital, congenital (rare)
  - Asymptomatic carriers occur

Most animal species are considered to be spillover hosts. Populations of spillover hosts do not maintain *M. bovis* indefinitely in the absence of maintenance 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. Bovine tuberculosis is usually maintained in cattle populations, but a few other species can become reservoir hosts. 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.

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Transmission in Animals

- Ingestion
  - Pigs, ferrets, cats, deer
- Respiratory
  - Cats
- Bites and scratches
  - Cats, badgers
- Inhalation
  - Non-human primates, badgers

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. 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.

[Photo: Badger. Source: U.S. Fish and Wildlife Service National Digital Library]

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DISEASE IN HUMANS

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Disease in Humans

- Higher incidence
  - Countries with uncontrolled bovine disease
  - Occupational risk groups
- Clinical manifestations
  - Asymptomatic
  - Localized lymphadenopathy
  - Skin disease
  - Pulmonary disease

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. 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.

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DISEASE IN ANIMALS

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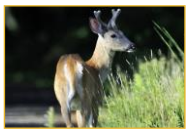
Species Affected

- Maintenance hosts
  - Cattle
  - Opossums, ferrets
  - Badgers
  - Bison, elk
  - Kudu, African buffalo
  - White-tailed deer
- Spillover hosts
  - Sheep, goats, horses, pigs, dogs, others



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.

[Photo: White-tailed deer. U.S. Fish and Wildlife Service National Digital Library]

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Disease in Cattle

- Clinical signs
  - Develop over months
  - May become dormant, reactivate
- Early stage may be asymptomatic
- Late stage
  - Progressive emaciation
  - Fever, weakness, inappetence
  - Moist cough
  - Enlarged, draining lymph nodes

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. Early infections are often asymptomatic. 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.

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Disease in Other Animals

- Cats
  - Weight loss, fever, dehydration, vomiting, diarrhea, dough
  - Enlarged lymph nodes, skin infections
  - Deformity of forehead/bridge of nose
  - Blindness, retinal detachment
- Brush-tailed opossums, badgers
  - Pulmonary disease

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. 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. 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 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.

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Post Mortem Lesions

- Granulomas (tubercles)
  - Appearance
    - Yellow
    - Caseous
    - Calcified
    - May resemble abscesses
  - Found in lymph nodes and organs

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. 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. Lesions are sometimes found on the female genitalia, but are rare on the male genitalia. In cervids, tubercles are most common in the lymph nodes of the head and thorax, particularly the medial retropharyngeal lymph nodes. *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. In contrast, brush-tailed opossums tend to have extensive lung caseation and necrosis.

[Photo: (Top): Elk, lung & lymph node. The lung contains multiple coalescing foci of caseous necrosis surrounded by thin pale fibrous tissue capsules (tubercles). Source: Dr. G. Wobeser, Canadian Cooperative Wildlife Health Centre/CFSPH; (Bottom): Bovine, lung. Lung parenchyma is almost entirely replaced by variably-sized, coalescing, raised pale nodules. Source: Armed Forces Institute of Pathology/CFSPH]

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Morbidity and Mortality

- Cattle in developed countries
  - Disease and death are rare
  - Routine testing identifies reactors
- Maintenance hosts: prevalence
  - Badgers: 40%
  - Brush-tailed opossums: 50%
  - Michigan white-tailed deer: 2 to 4%
  - Elk: 1 to 5%
  - Cats: up to 50% on affected farms

In countries with control programs, bovine tuberculosis is often confined to one or two animals in a herd; most reactors are detected during routine testing and mortality from tuberculosis is rare. In two studies of transmission from naturally infected reactor cattle, 0-40% of susceptible contacts became infected and 0-10% developed gross lesions. 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.

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Differential Diagnosis

- Bovine pleuropneumonia
- *Pasteurella*
- *Corynebacterium pyogenes*
- Aspiration pneumonia
- Traumatic pericarditis
- Caseous lymphadenitis
- Melioidosis
- Chronic aberrant liver flukes

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. 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.

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Diagnosis: Live Cattle

- Tuberculin skin test
  - Caudal fold
    - Preliminary screening of cattle
  - Comparative cervical
    - Re-testing of reactors
  - Single cervical
    - Preliminary screening of cervids

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.

[Photo: tuberculin caudal fold skin test on a cow.]

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Laboratory Diagnosis

- Histopathology/microscopic exam
- Culture, biochemical tests
- PCR
- Ancillary to the tuberculin test
  - Lymphocyte proliferation test
  - Gamma-interferon test
  - ELISA

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. 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*. 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.

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PREVENTION AND CONTROL

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Recommended Actions

- Notification of authorities
  - Federal Area Veterinarian in Charge (AVIC)
    http://www.aphis.usda.gov/animal_health/area_offices/
  - State veterinarian
    http://www.aphis.usda.gov/emergency_response/downloads/nahems/fad.pdf

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

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Bovine TB Eradication Program

- Initiated in 1917
- State-based classification system
  - Accredited Free**
  - Modified Accredited Advanced
  - Modified Accredited
  - Accredited Preparatory
  - Non-accredited
- Program changes coming in future

The State-Federal Cooperative Bovine Tuberculosis Program was initiated in 1917. Under the current program, states status is determined by the prevalence of infected cattle and bison herds as follows:

- Accredited Free states—have no infected herds.
- Modified Accredited Advanced states—prevalence of infected cattle and bison herds is <0.01%.
- Modified Accredited states–prevalence of infected cattle and bison herds is < 0.1%.
- Accredited Preparatory states—prevalence of infected cattle and bison herds is <0.5%.
- Non-accredited states—do not meet the provisions of the tuberculosis UMR or have a herd prevalence rate of 0.5% or greater.

Most states have achieved Accredited Free status, with a few remaining states in Modified Accredited Advanced or split Modified Accredited Advanced/ Modified Accredited status. In the U.S., bovine TB has nearly been eradicated. The prevalence rate in cattle herds is now less than 0.001%; however, sporadic cases continue to occur. The bovine TB eradication program is undergoing changes related to surveillance and movement restrictions in coming years.

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Prevention and Control

- Test-and-slaughter
  - Eradication in domesticated animals
- Test-and-segregate
  - May be used in early stages of eradication by some countries
- Slaughter surveillance
- Cleaning and disinfection

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.

[Photo: Disinfectant jugs. Source: Danelle Bickett-Weddle. CFSPH]

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Prevention and Control

- Wildlife reservoir hosts
  - Complicate eradication efforts
  - Culling
  - Prohibit supplemental feeding
  - Barriers to feed access
  - Prevent contact with livestock
- Vaccines not currently available
- Treatment not advised

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

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Additional Resources

- Center for Food Security and Public Health
  - www.cfsph.iastate.edu
- USDA APHIS: Bovine Tuberculosis
  - http://www.aphis.usda.gov/animal_health/animal_diseases/tuberculosis/

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Acknowledgments

Development of this presentation was made possible through grants provided to the Center for Food Security and Public Health at Iowa State University, College of Veterinary Medicine from the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, the Iowa Homeland Security and Emergency Management Division, and the Multi-State Partnership for Security in Agriculture.

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Last Updated: March 2012