Tularemia Backgrounder

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Causative agent

Tularemia (also known as rabbit fever and deerfly fever) is caused by the bacterium *Francisella tularensis*. The bacterium is a gram-negative coccobacillus. It is classified as a facultative (it can survive under a variety of conditions), intracellular (lives within the cells of the host) bacterium, but there is scientific evidence that it may be an obligate intracellular bacterium (that can only grow within host cells) in mammalian hosts.

The bacterium was first identified in 1911 by McCoy from infected ground squirrels in Tulare County, California. The first described human case of tularemia occurred in a restaurant worker in Cincinnati in 1914.

Five subspecies of *F. tularensis* have been identified, but only two subspecies, *F. tularensis* subsp. *tularensis* (also called Jellison type A or Biovar A) and *F. tularensis* subsp. *holarctica* (also called Jellison type B, Biovar B, or *F. tularensis* subsp *palaearctica*), are considered clinically significant in humans. *F. tularensis* subsp. *tularensis* is highly infective for rabbits, humans, and cats. Based on phylogenetic analysis, *F. tularensis* subsp. *tularensis* has recently been subdivided into 2 subpopulations, A.I. (also called type A-east) and A.II. (also called type A-west). *F. tularensis* subsp. *holarctica* is more frequently associated with rodents and aquatic mammals (muskrats, mice, beaver, voles, water voles), and is less infective for rabbits and humans.

F. tularensis subsp *mediaasiatica* is found in Central Asia, and has not been associated with human infections. *F. tularensis* subsp *novicida* is found in the United States, Australia, and Canada; it is capable of causing tularemia-like illness, but is less infectious.

Natural distribution

Tularemia most often affects lagomorphs (rabbits and hares) and rodents; however, it has been reported as affecting more than 200 species of wild and domestic mammals. In North America, infections are most common in snowshoe hares, black-tailed jackrabbits, and eastern and desert cottontails. Infections in birds, fish, amphibians, and reptiles are relatively rare. Natural infection of prairie dogs with *F. tularensis* subsp *holarctica* has been reported. Tularemia has been observed in pet monkeys and nonhuman primates housed in zoos and laboratories. Carnivores are susceptible, but require high doses of the bacterium to become infected. Although they rarely exhibit obvious signs of disease, wild carnivores may play a role as reservoirs of the bacteria. Antibodies to *F. tularensis* were detected in 32% of coyotes and 38% of raccoons in Nebraska in 2005.

Domestic animals and humans are usually considered accidental hosts; however, outbreaks occurring in sheep in Canada, the United States, and Russia have resulted in high mortality. Outbreaks have also been identified in commercially bred mink, beaver, and fox. Although not common, disease has been identified in domestic cats. A 2006 serological survey of 91 privately owned, healthy cats in New York and Connecticut determined that 12% of the cats had antibodies to *F. tularensis*, indicating prior exposure to the bacteria. Dogs appear to be more resistant to infection, but may serve as reservoirs for the bacterium or as maintenance hosts for the tick vector. The worldwide incidence of tularemia in humans is not well documented, and the number of reported cases has declined in recent years.

Geographically, tularemia occurs in temperate regions of the Northern Hemisphere, and has been reported in Canada, Mexico, and the United States (all states except Hawaii). *F. tularensis* subsp *tularensis* is found almost exclusively in North America, whereas *F. tularensis* subsp *holarctica* exists in North America, Asia, and Europe. Within the United States, more than half of the human tularemia cases reported from 1990-2000 originated from Arkansas, Missouri, South Dakota, and Oklahoma. Peaks are associated with high insect vector activity and rabbit hunting. Approximately 100-200 human cases are reported annually in the United States. The bacteria are endemic on Martha's Vineyard in Massachusetts, and outbreaks have occurred in 1978 and 2000.

The A.I. (type A-east) subpopulation of *F. tularensis* subsp *tularensis* is found primarily in the central and eastern United States, whereas the A.II. (type A-west) subpopulation occurs primarily in the western region of the country. The distribution of the A.I. subpopulation of *F. tularensis* subsp *tularensis* is associated with the distribution

of the American dog tick (*Dermacentor variabilis*) and the Lone Star tick (*Amblyomma americanum*), whereas the A.II. subpopulation is associated with the Rocky Mountain wood tick (*Dermacentor andersoni*) and the deerfly (*Chrysops discalis*). *F. tularensis* subsp *holarctica* infections tend to occur along major waterways or in areas of high rainfall. Disease associated with type A.II (A-west) infections may be less severe than type A.I. (A-east) or *holarctica* subspecies infections.

With the exception of the Iberian Peninsula, tularemia is distributed throughout Europe and Mediterranean Africa, and has been identified in Bulgaria, China, Iran, Israel, Japan, Korea, Norway, the former Soviet Union, Sweden, and Turkey.

The bacteria can survive in mud, soil, decaying animal carcasses, or water for long periods of time. It has been successfully cultured from water and mud samples for up to 14 weeks, in tap water for up to 3 months, and in dry straw bedding for at least 6 months.

Transmission

F. tularensis infection can be transmitted by arthropod (e.g. tick and deerfly) bites, inhalation of aerosolized bacteria, eating contaminated food or tissues, drinking contaminated water, and handling infected animals or tissues. Ticks are the most important vectors of *F. tularensis*, transferring the bacterium between rabbits, hares, and rodents and serving as a reservoir of the bacteria. Ticks may maintain the infection throughout their life cycle, increasing the risk of transmission to numerous hosts.

Deerflies, horseflies, mosquitoes, sucking lice, and biting flies may also transmit the bacteria from one animal to another animal or human. In endemic areas (areas where the bacteria are established), transmission to humans and other domestic animals usually occurs via bites from infected arthropods, or the bacterium may enter scratches or knife cuts exposed to infected animal tissues.

Sheep and domestic cats can be sources of infection for humans. Human tularemia cases have occurred following direct contact with infected cats and through cat bites or scratches from infected cats. Shearing infected sheep can also result in human infection.

The first evidence that prairie dogs can transmit *F. tularensis* subsp *holarctica* to humans was documented in 2002. Wild-caught prairie dogs, destined for sale as exotic pets in the United States, the Netherlands, the Czech Republic, and Belgium, died in large numbers at a commercial holding facility in Texas. Fourteen of 20 exposed personnel reported symptoms consistent with tularemia. The cannibalization of carcasses by other prairie dogs in the same pen was believed to play a major role in propagating the infection.

Human-to-human transmission is considered to be rare. Tularemia has been reported in a human patient following kidney transplantation from an infected organ donor.

Doses as low as 10 colony-forming units can cause infection, making the bacteria one of the most infectious pathogens known. Because of the potential for human infection and the rapidity of spread of the organism, the World Organisation for Animal Health (OIE) has classified tularemia as a listed animal disease that requires notification of OIE. In recognition of the potential for use in bioterrorism, *Francisella tularensis* is classified as Category A agent due to its ease of spread, potential for high mortality rates, major public health impact, and potential for inducing public panic and social disruption.

Occupations that involve increased contact with infected animals, animal tissues, insect vectors, soil, or cultures of *F. tularensis* bacteria are at higher risk of exposure and disease. These occupations include veterinarians, wildlife handlers, farmers, sheep handlers and shearers, hunters, trappers, meat handlers, cooks, landscapers, and laboratory workers.

Clinical signs of tularemia in animals and humans

Rabbits, hares, and rodents—Clinical signs in rabbits, hares, and rodents have not been well described, because affected animals have most often been found dead. Experimentally infected animals exhibit weakness, fever, ulcers, swollen lymph nodes, and abscesses. Death usually occurs in 8 to 14 days.

Sheep—Tularemia in sheep is typically a seasonal disease, coinciding with tick infestations. Clinical signs include fever, a stiff gait, diarrhea, frequent urination, weight loss, and difficulty breathing. Affected sheep may isolate themselves from the remainder of the flock. High death rates may be observed. Death is most common in young animals, and pregnant ewes may abort.

Cattle—Natural infection does occur in cattle, based on detectable immune responses. However, the clinical signs of disease in this species are not well known.

Horses—Reports of clinical disease in horses are limited; however, fever, breathing difficulty, incoordination, and depression have been described. Affected horses have had extensive tick infestation.

Domestic cats—Cats infected with *F. tularensis* experience disease ranging from inapparent infection to sepsis (toxic shock due to bacterial infection of the blood and organs) and death. Clinical signs may include fever, depression, swollen lymph nodes, abscesses, ulceration of the mouth or tongue, gastroenteritis, enlarged liver or spleen, icterus (jaundice), loss of appetite, weight loss, pneumonia, and shock.

Dogs—Reports describing clinical signs of tularemia in dogs are limited, although there is evidence of antibody production indicating exposure to the bacteria. Natural infection apparently occurs with some regularity, but clinical illness is inapparent or mild. Clinical signs observed are related to mode of transmission and include fever, depression, mucopurulent (mucus with pus) discharge from the nose and/or eyes, pustules at the sites of contact, swollen lymph nodes, and loss of appetite. In most cases, disease has been self-limiting with supportive treatment. Puppies may be more likely than adult dogs to develop disease. Dogs that were experimentally infected after they were fed infected tissues developed clinical signs similar to those of natural infection. The injection of *F. tularensis* into the skin of dogs resulted in fever, pustules at the site of injection, and swollen lymph nodes.

Nonhuman primates—Tularemia has been observed in squirrel monkeys, black and red tamarins, talapoins, and a lowland gorilla. Clinical signs include depression, lethargy, loss of appetite, dehydration, vomiting, diarrhea, swollen lymph nodes, pinpoint hemorrhages in the skin, and sudden death.

Humans—The incubation period is typically 3 to 5 days, but may range from 1 to 21 days. Fever, chills, headache, muscle soreness, and vomiting are followed by more specific signs of disease that depend on route of entry, the amount of bacteria introduced, and the potency (virulence) of the bacteria. All forms of tularemia can progress to pleuropneumonia (infection of the lungs and the membranes lining the lungs and chest), meningitis (inflammation of the membranes covering the brain and spinal cord), shock, and death. Underlying diseases or immunocompromise (transplant or AIDS patients) increase the risk of severe, prolonged infection and death. *F. tularensis* subsp *holarctica* infection tends to produce less severe disease than the *tularensis* subspecies, and has been reported to occur in typhoidal and ulceroglandular forms.

Ulceroglandular tularemia is the most common form (75 to 85% of reported cases). An ulcer is evident at the site of entry, usually the fingers or hands in cases associated with exposure to rabbits, hares, or rodents. Swollen lymph nodes are observed; the lymph nodes may open, drain pus, and scar. Signs of glandular tularemia are similar, but no skin ulcer is evident.

Oropharyngeal tularemia often results from eating contaminated food or water. This form produces swelling of the throat and tonsils as well as the nearby lymph nodes.

Pulmonary tularemia represents about 30% of contracted infections and is caused by inhalation of aerosolized bacteria. Pneumonia in one or both lungs is the typical clinical sign. This syndrome has the highest mortality rate; without treatment, approximately 60% die.

Typhoidal tularemia results from eating contaminated food or water, and is uncommon. Clinical signs include fever, severe weakness, weight loss, and abdominal pain. Because the signs observed are nonspecific and resemble many other diseases, diagnosis of the typhoidal form can be challenging. Mortality rates can range from 40 to 60% if prompt treatment is not provided.

Oculoglandular tularemia results from contamination of the conjunctiva (the membranes around the eyes). Ulcerated bumps, which are usually located on the lower eyelid, are accompanied by swollen lymph nodes.

Overall, the case fatality rates (the number of clinically ill cases that die from the disease) for tularemia caused by *F. tularensis* subsp *tularensis* is 5-15% without treatment. In the United States, the overall case fatality rate is less than 2%.

Diagnosis

ELISA, hemagglutination, microagglutination, and tube agglutination are used to identify agglutinating antibodies in serum. Fluorescent antibody assays and polymerase chain reaction (PCR) may also be of value in detecting the bacteria in samples. Isolation of *F. tularensis* from clinical specimens (e.g., blood, exudates, and biopsy samples) confirms infection; however, many laboratories are reluctant to attempt this because of the high risk of infection associated with handling the bacteria. A minimum of biological safety level II (BSL-2) protocol is recommended when handling suspected or confirmed *F. tularensis* samples. Results of routine laboratory tests (e.g., complete blood counts and serum biochemical analyses) are usually nonspecific.

Tularemia is generally a postmortem diagnosis in wild animals. For sheep, clinical confirmation is through serology or isolation of the etiologic agent. For humans, a presumptive diagnosis is based on clinical signs and a history of exposure. In nonendemic areas (areas where the bacteria are not considered to be established), a single serum titer of 1:160 or greater is considered diagnostic. In endemic areas (areas where the bacteria are established), a 4-fold increase in antibody levels between samples obtained 2 to 4 weeks apart is considered to be diagnostic.

Prevention

For humans and other animals, tick control is an important part of prevention. The use of insect repellants containing DEET is recommended. Contact with untreated water should be avoided when contamination with *F. tularensis* is suspected, and wild game should be thoroughly cooked before consumption. In endemic areas, handling of dead and dying animals should be avoided. Gloves should be worn when handling wild game, their skins, and carcasses. Equipment used in the diagnosis, care, or collection of animals suspected or known to be infected should be properly disposed of (contaminated medical waste) or disinfected. Because many landscaping activities can produce aerosolization of the bacteria from the soil, landscapers in endemic areas may be at higher risk of respiratory exposure and pulmonary tularemia; the use of respiratory protection is recommended in endemic areas.

A vaccine is currently being evaluated by the Food and Drug Administration, but it is not currently available and its effectiveness is unknown at this time. The United States Department of Defense has developed an experimental tularemia vaccine for laboratory and other high-risk workers, but it is not available to the public.

Treatment

Tularemia is a reportable disease in the United States. State or Federal animal health officials should be notified immediately if tularemia is suspected. Streptomycin and tetracyclines (especially doxycycline) are the antibiotics of choice for treating wild and domestic animals. For humans, streptomycin has been preferred, with doxycycline, gentamicin, and chloramphenicol as alternatives. Fluoroquinolones, such as gatifloxacin and moxifloxacin, have also shown promise in the treatment of tularemia. Chloramphenicol has been used to treat associated meningitis.

Infection control

Healthcare professionals assisting animal and human patients should wear personal protective clothing (e.g., gowns, gloves, and face masks). Because *F. tularensis* is a highly infectious organism, diagnostic laboratories should be notified that tularemia is on the list of differential diagnoses when specimens are submitted. Biological safety level II is recommended for diagnostic work on suspect material; biological safety level III is required for culture. The simple act of opening a culture plate of *F. tularensis* can produce infection by aerosolized bacteria.

Use of tularemia as a biological weapon

F. tularensis is classified as a Category A agent of bioterrorism because of its high infectivity, ease of spread, and its potential to cause severe disease. Possible mechanisms for spreading the bacteria include contamination of food or water and aerosolization.