

Tularemia

*rabbit fever, deerfly fever,
Ohara's disease, Francis disease*

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Etiology

Tularemia results from infection by *Francisella tularensis* (formerly known as *Pasteurella tularensis*), a Gram negative, non-motile coccobacillus. Two subspecies exist: *F. tularensis tularensis* (also known as Jellison type A) and *F. tularensis holarctica* (Jellison type B). *F. tularensis tularensis* is found in lagomorphs in North America and is highly virulent for humans and domestic rabbits; *F. tularensis holarctica* is less virulent and occurs in beaver, muskrats and voles in North America and in hares and small rodents in Eurasia.

Geographic Distribution

Tularemia occurs in North America, continental Europe, Russia, China, and Japan. The subspecies *F. tularensis tularensis* is found in North America; *F. tularensis holarctica* is seen in North America and Eurasia.

Transmission

F. tularensis can be transmitted by ingestion, inhalation, arthropod-borne transfer or direct contact through the skin and mucous membranes. Organisms are found in the blood and tissues of infected animals and can survive for long periods on fomites including food and water. Aquatic animals may develop tularemia after being immersed in contaminated water. Carnivores sometimes become infected after ingesting a contaminated carcass. Vectors for *F. tularensis tularensis* include ticks (including *Dermacentor andersoni*, *D. variabilis* and *Amblyomma americanum*) and biting flies (particularly deerflies). *F. tularensis holarctica* is also transmitted by mosquitoes in Russia. Rarely, the organism is spread by animal bites.

F. tularensis can survive for long periods of time in arthropod vectors and in the environment. Individual flies may carry the organism for 2 weeks and ticks throughout their lifetimes. Viable bacteria can also be found for weeks to months in the carcasses and hides of infected animals and in fomites including grain dust, straw, water, soil and bedbugs. This organism is highly resistant to freezing; live organisms have been found after 3 years in rabbit meat stored at -15°C . *F. tularensis* has been weaponized.

Disinfection

F. tularensis is easily killed by disinfectants including 1% hypochlorite, 70% ethanol, glutaraldehyde, and formaldehyde. It can also be inactivated by moist heat (121°C for at least 15 min) and dry heat ($160-170^{\circ}\text{C}$ for at least 1 hour). This bacterium remains viable at freezing temperatures for months to years.

Infections in Humans

Incubation Period

The incubation period in humans is 3 to 15 days; clinical signs usually appear after 3 to 5 days.

Clinical Signs

Six forms of tularemia are seen in humans: typhoidal, ulceroglandular, glandular, oculoglandular, oropharyngeal and pneumonic. The form of the disease depends on the inoculation site.

Typhoidal tularemia usually occurs after inhalation but can also develop after skin inoculation or ingestion. The clinical signs may include fever, prostration, headache, nausea and weight loss. Some patients become extremely weak and develop recurring chills and drenching sweats. A nonspecific rash may be seen but lymphadenopathy is usually absent. Pneumonia is particularly common in the typhoidal form and can be severe.

Ulceroglandular tularemia usually occurs after infection through the skin or mucous membranes. The clinical signs may include fever, chills, headache and malaise. The regional lymph nodes are typically enlarged and painful; they may suppurate and drain

profusely. An inflamed papule usually develops where the initial transmission occurred; it quickly turns into a pustule then ulcerates. On the extremities, single ulcers with thin, colorless, scanty exudates are usual. Glandular tularemia is characterized by fever and tender lymphadenopathy without a skin ulcer. Infection of the conjunctiva results in oculoglandular tularemia; this form is characterized by painful, unilateral, purulent conjunctivitis with preauricular or cervical lymphadenopathy. In some cases, there may be chemosis, periorbital edema and multiple small nodules or ulcerations on the conjunctiva. When the ulceroglandular disease occurs only in the throat, it is called oropharyngeal tularemia. In this form, there is an acute exudative or membranous pharyngotonsillitis with cervical lymphadenopathy.

Pneumonic tularemia can occur after inhalation or by secondary hematogenous spread. Victims develop severe, sometimes fulminant, atypical pneumonia. There may be signs of lung consolidation and, in some cases, delirium. Sometimes, the only symptoms may be a dry, unproductive cough, with decreased breath sounds and substernal discomfort. The pneumonic form can occur with any other form and has a high mortality rate. It develops in 10 to 15% of all cases of ulceroglandular tularemia and about 50% of cases of typhoidal tularemia.

Communicability

Person to person transmission has not been seen; however, infectious organisms can be found in the blood and other tissues.

Diagnostic Tests

Tularemia is often diagnosed by immunofluorescent staining of *F. tularensis* antigens in tissue samples or blood, and by serology. Commonly used serologic tests include tube agglutination, microagglutination and enzyme-linked immunosorbent assays (ELISA). A rising titer is diagnostic. Significant titers begin to appear during the second week of infection, although some specific antibodies are seen within the first 7 days. Cross-reactions occur with *Brucella* species, *Proteus* OX19, and *Yersinia*.

Tularemia can also be diagnosed by isolating *F. tularensis* from blood, sputum, pharyngeal or conjunctival exudates, ulcers, lymph nodes and gastric washings. *F. tularensis* does not grow well on standard media but may be isolated on media containing cysteine or sulfhydryl compounds. On McCoy medium, colonies are small, prominent, round and transparent. Confluent, milky, mucoid colonies develop on Francis medium and modified Thayer/Martin agar. Growth is slow and may take up to 3 weeks. Identification is by the absence of growth on ordinary media, morphology, immunofluorescence and slide agglutination. Organisms are non-motile, Gram negative small coccobacilli, with bipolar staining in young cultures. Bacteria from older cultures may be pleomorphic. *F. tularensis tularensis* can be distinguished

from *F. tularensis holarctica* by glycerol fermentation, ribosomal RNA probes and polymerase chain reaction (PCR) tests. Organisms in culture are highly infectious to humans and special precautions must be taken during isolation.

Treatment and Vaccination

F. tularensis is susceptible to a variety of antibiotics. Relapses are not common but can occur if treatment is stopped before all bacteria are eliminated. Live attenuated vaccines may be recommended for people at a high risk of infection, such as laboratory workers.

Morbidity and Mortality

Tularemia can affect all ages. Infections occur most often in hunters, butchers, farmers, fur handlers and laboratory workers. In natural infections, ulceroglandular tularemia is the most common form; it occurs in 75 to 85% of cases. The typhoidal form is seen in 5 to 15%, the glandular form in 5–10% and the oculoglandular form in 1 to 2%. Typhoidal tularemia would be expected to be the predominant form after an attack by aerosolized *F. tularensis* in a biological weapon.

The mortality rate is approximately 30 to 35% for untreated *F. tularensis tularensis* infections and 5 to 15% for *F. tularensis holarctica* infections. Typhoidal tularemia is the most dangerous form; if untreated, the case fatality rate is approximately 35%. In contrast, the case fatality rate for the untreated ulceroglandular form is 5%. Naturally acquired cases are rarely fatal if treated; case fatality rates up to 1–3% are cited by some authorities. Higher fatality rates would be expected after a biological attack. Permanent immunity usually develops after a single episode of tularemia.

Infections in Animals

Species Affected

More than a hundred species of animals can be infected with *F. tularensis*. The natural hosts include cottontail and jack rabbits, hares, voles, vole rats, squirrels, muskrat, beaver and lemmings. Among domestic animals, sheep seem to be particularly susceptible to clinical disease. Tularemia has also been seen in dogs, cats, pigs and horses; cattle seem to be resistant. Infections in birds, reptiles and fish have been reported.

Incubation Period

The incubation period is 1 to 10 days.

Clinical Signs

The full spectrum of clinical signs is not known in animals. Many cases may be asymptomatic. Signs of septicemia can be seen in sheep and other mammals; symptoms may include fever, lethargy, anorexia, stiffness, increased pulse

and respiration, coughing, diarrhea and pollakiuria. Rabbits and rodents may be depressed, anorectic and ataxic, with a roughened coat and tendency to huddle. Anorexia, weight loss and vomiting have been reported in cats. Skin lesions are rarely seen in animals. Symptoms usually last 2 to 10 days in susceptible animals and may end in prostration and death. Susceptible species may be found dead without other symptoms.

Communicability

Yes. Infectious organisms can be found in the blood, tissues and feces. Humans and other animals can be infected through the skin or mucous membranes; routes of transmission include aerosols and ingestion. Infected cats may be able to transmit the organism in bites.

Diagnostic Tests

Impression smears of liver, spleen, bone marrow, kidney, lung or blood may be helpful for a presumptive diagnosis; small Gram negative coccobacilli can sometimes be found inside cells and scattered among tissue debris. *F. tularensis* is very small (0.2–0.7 μm) and easy to miss. Definitive diagnosis is by immunofluorescent detection of organisms in impression smears from these tissues, agglutination with specific antiserum, culture and occasionally serology. Animal inoculation can be used but it is dangerous and not recommended for routine identification.

F. tularensis can be isolated from enlarged lymph nodes, blood and tissues including liver, spleen and bone marrow; overgrowth of other bacteria may prevent recovery from animals found dead. This organism does not grow well on standard media but can be isolated on media containing cysteine or sulfhydryl compounds. On McCoy medium, colonies are small, prominent, round and transparent. Confluent, milky, mucoid colonies develop on Francis medium and modified Thayer/Martin agar. Growth is slow and may take up to 3 weeks. Identification is by the absence of growth on ordinary media, morphology, immunofluorescence and slide agglutination. The organisms are non-motile, Gram negative, small coccobacilli, with bipolar staining in young cultures. Bacteria from older cultures may be pleomorphic. *F. tularensis tularensis* can be distinguished from *F. tularensis holarctica* by glycerol fermentation, ribosomal RNA probes and polymerase chain reaction (PCR) tests. Organisms in culture are highly infectious to humans and special precautions must be taken during isolation.

Serology is occasionally useful. Species sensitive to tularemia typically die before specific antibodies develop; however, significant titers can be found in more resistant species such as sheep, cattle, pigs, moose, dogs and birds. Available tests include tube agglutination and enzyme-linked immunosorbent assay (ELISA).

Treatment and Vaccination

Tularemia can be treated with various antibiotics but long-term treatment may be necessary; early treatment is expected to reduce mortality. Vaccines are not marketed specifically for animals.

Morbidity and Mortality

Tularemia is relatively common and often fatal in wild animals; disease is particularly common among rabbits, rodents, pheasants and quail. This disease is rare among domestic rabbits and rodents, but may be seen in animals kept outside. Outbreaks of *F. tularensis tularensis* infections, characterized by high mortality, have been seen in sheep. Mortality rates up to 15% are seen in untreated lambs.

Post-Mortem Lesions [Click to view images](#)

Most animals with acute tularemia are in good body condition. The most consistent lesions are miliary, grayish-white necrotic foci in the liver (**tul1**) and sometimes the spleen, bone marrow and lymph nodes. Some of these necrotic foci may be barely visible. Enlargement of the liver, spleen and lymph nodes is also common. In rabbits, the white necrotic foci on a dark, congested liver and spleen have been compared to the Milky Way. Congestion and edema is frequent in the lungs; consolidation and fibrinous pneumonia or pleuritis may also be found. The abdominal cavity sometimes contains fibrin. In some species, the lesions can resemble tuberculosis and granulomas may be found in the liver, spleen, kidneys and lungs.

Internet Resources

Centers for Disease Control and Prevention (CDC) Tularemia Pages
<http://www.bt.cdc.gov/agent/tularemia/index.asp>

Material Safety Data Sheets—
Canadian Laboratory Center for Disease Control
<http://www.hc-sc.gc.ca/pphb-dgspsp/msds-ftss/index.html#menu>

Medical Microbiology
<http://www.gsbs.utmb.edu/microbook>

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

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

USAMRIID's Medical Management of Biological Casualties Handbook
<http://www.vnh.org/BIOCASU/toc.html>

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