## TULAREMIA

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<th>Animal Group(s) Affected</th>
<th>Transmission</th>
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<td>All warm-blooded animals</td>
<td>Arthropod vectors such as ticks, biting flies, and, in some areas, mosquitoes. Inhalation of aerosolized infectious material Ingestion of contaminated food or water</td>
<td>Depends on route of infection; general: lethargy, anorexia, pyrexia Transdermal exposure is marked by ulcer at site of inoculation; lymphadenopathy. Oral exposure: lymphadenopathy Inhalation: pneumonia, coughing Skinning dead infected animals; contaminated water</td>
<td>Clinical signs can be severe and death result if untreated. Pneumonic form: severe. Septicemia often death occurs without prior signs</td>
<td>Antibiotics: streptomycin, gentamicin, tetracyclines, doxycycline</td>
<td>Pest control; sanitation</td>
<td>High zoonotic potential</td>
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**Sheet Revised on:** 29 October 2010; 30 July 2013  
**Fact Sheet Reviewed by:** Wayne Conlan; Bruno Chomel; Paola Pilo; Francesco C. Origgi

### Susceptible animal groups: Natural infection in mammals and birds.

### Causative organism: *Francisella tularensis* - four subspecies: most commonly associated with disease outbreaks are *F. tularensis subsp tularensis* (type A) and *F. tularensis subsp holarctica* (type B), while *F. tularensis subsp mediasiatica* and *novicida* are rarely associated with severe infections. Type A and B can be distinguished by the ability of type A to ferment glycerol and polymerase chain reaction test (PCR).

### Zoonotic potential: This issue is very high with only 10-50 organisms need to be inhaled to cause severe infection.

### Distribution: Throughout the Northern hemisphere, this disease represents one of the largest host distributions of any zoonotic disease. Type A only occurs in North America, whereas type B found throughout Northern hemisphere. In North America, geographic overlap of both subspecies is present, although type A associated with highest disease incidence and mortality rate. Changes involving climate and animal, as well as vector distribution, seem to cause emergence or re-
emergence in areas considered non-critical for appearance of Francisella tularensis. Arthropods, such as ticks, mosquitoes and biting flies, are common vectors associated with transmission of F. tularensis. While ticks are believed to be the primary biological vectors, transmission by mosquitoes and biting flies is believed to be mostly mechanical through their mouthparts. Infection of a patient through a ringtail possum in Tasmania, Australia, indicated the emergence of F. tularensis type B in the Southern hemisphere.

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<th>Incubation period</th>
<th>generally 3-5 days, but 1-14 days possible</th>
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**Clinical signs:** Clinical presentation of tularemia varies with the route of infection. First development: non-specific signs such as depression, lethargy, anorexia, vomiting, diarrhea, marked pyrexia, or peracute death without prior clinical signs; Clinical disease in humans includes forms of ulceroglandular, glandular, ocuologlandular, oropharyngeal, pneumatic, and typhoidal disease. First three forms occur via local infection through arthropod bites, injuries, or mechanical transfer involving skin and lymphoid tissue, and result in local or even generalized lymphadenopathy. Skin ulcers may form at the site of dermal infection. Oropharyngeal form - ingestion of contaminated food or water involving the tonsils and retropharyngeal lymph nodes. Pneumonic form as most severe clinical form of tularemia, leading to mortality if untreated that results from direct inhalation of organisms from infected tissue. Typhoidal form - systemic disease: high fever, but without lymphadenitis or cutaneous lesions. All forms can develop into secondary septicemia, pleuropneumonia, and meningitis. F. tularensis is usually invading and replicating in vector-derived cells and hemolymph, and in macrophages within the host. Cytokines, such as intereferon-gamma and tumor necrosis factor, produced by T-cells are critical for activation of macrophages and cell-mediated and protective immunity. Yet, F. tularensis is able to proliferate in macrophages without destroying the host cell. It also has developed good survival and adaptation strategies using surface proteins to suppress innate immune response, which makes it harder to diagnose and control it within the host. New research has discovered that F. tularensis is also able to invade erythrocytes. The high hemoglobin and iron content in erythrocytes could influence the virulence gene expression in F. tularensis. Yet, erythrocytes do not support replication of the pathogen and, therefore, do not seem to be a major contributor to the pathogenesis of tularemia.

**Post mortem, gross, or histologic findings:** Gross: congested organs - mostly lungs, lymph nodes, spleen, liver - with multiple light tan miliary foci on the surface, as well as in the parenchyma. Histopathology: pyogranulomatous lymphadenitis, tonsillitis, splenitis, hepatitis and pneumonia with necrotic foci.

**Diagnosis:** Although culture is considered the “gold standard” diagnostic tool to confirm tularemia, recovery of live organisms of F. tularensis from carcasses can pose a challenge. The bacterium is very slow growing and has special biochemical needs so poor competitive characteristics in the presence of other bacterial pathogens. Selective antibiotic media (CHAB-A) are needed for isolating the bacteria from contaminating environmental flora in carcasses; Western blot and microagglutination assay demonstrate the highest level of sensitivity and specificity for F. tularensis, higher than enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence (IFA). A combination of at least two serological tests, such as ELISA and Western blot, was demonstrated to be a suitable diagnostic tool for laboratory confirmation of both individual cases, and larger epidemiological studies. Immunohistochemistry (IHC) has been successfully used for post mortem diagnosis in formalin-fixed tissue.

To detect serologic titers in live animals or humans, besides microagglutination, latex or tube agglutination, a novel competitive ELISA test, can be recommended. Real-time PCR, Multiplex qPCR, 16S rDNA sequencing, and molecular subtyping using differential insertion sequence amplification and regions of differences (RD), can be especially useful for samples where organisms are non-culturable or nonviable. Serology is often difficult as short term diagnosis due to low antigenicity of the organism. Repeated serology necessary for evaluation of titer development. Although some commercially available serologic
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Tests are available showing good results, these should be interpreted cautiously because of the quick onset of clinical signs as compared to the development of humoral response; clinically silent cases have been reported; and antibodies in humans can persist for years. A recombinase PCR amplification assay has been developed for rapid detection of *F. tularensis*. Investigation into molecular level of host macrophage survival and innate immune response to infection with *F. tularensis* enabled the identification of newer tools for diagnosis of and immunologic prevention of tularemia in laboratory animals and humans.

| Material required for laboratory analysis: | The best result is achieved by immediate culturing of fresh tissue, or by immediate freezing of tissue specimens from carcasses for subsequent culture. Blood samples are often used to confirm serologic titers in live animals or humans. |
| Relevant diagnostic laboratories: | The contagious nature of *F. tularensis* poses an additional challenge to laboratory personnel, high biohazardous risk of infection via inhalation of aerosolized bacteria. Testing for tularemia demands a laboratory setting with a minimum biological safety level 2 (BSL-2), and testing procedures performed according to BSL-3 regulations. |

Confirmation of results are suggested in Centers for Disease Control and Prevention, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Division of Vector-Borne Infectious Diseases, Bacterial Diseases Branch, Foothills Campus, Fort Collins, Colorado, 80522, USA

| Treatment: | Streptomycin is considered the treatment of choice in humans with tularemia. Other chemotherapeutics, such as gentamicin, tetracyclines, chloramphenicol, and fluoroquinolones, have been used successfully. Tetracyclines and chloramphenicol are bacteriostatic, and require a longer treatment period of at least 14-21 days. |
| Prevention and control: | A live attenuated vaccine strain of *F. tularensis* type B was developed in the Soviet Union for immunization of humans. Although this live vaccine serum (LVS) strain was also shown to be effective against the type A strain and oral infection, this vaccine was not fully effective against infection acquired by inhalation. Currently, newer LVS vaccine affords no better efficient protection against an aerosolization challenge by *F. tularensis*. Subunit or recombinant vaccines have been more recently researched, but any results did not show better prevention efficacy than the LVS. Ongoing trials were completed to develop vaccine using mutant strains or nonpathogenic *F. novicida* strain, but they have not shown improved protection efficacy over the LVS, either. Some research is concentrating on virus-vectored vaccine for better stimulation of immunity in presence of *F. tularensis*. Good pest control is the best defense against development of *F. tularensis* carrying population on zoo grounds. |

| Suggested disinfectant for housing facilities: | Diluted hypochlorite, quaternary ammonium disinfectants are useful. |

| Notification: | Reportable disease at a variety of levels – city, county, state, and federal as *F. tularensis* is considered a Category A, Bioterrorism agent. |

| Measures required under the Animal Disease Surveillance Plan: |  |
| Measures required for introducing animals to infected animal: | Regular quarantine in a clean environment; reduce access to potential vectors, and host animals. |

| Conditions for restoring disease-free status after an outbreak: | Pest and vector control are necessary to minimize exposure. |

| Experts who may be consulted: | Jeannine M. Petersen, PhD, Nordin S. Zeidner, DVM, PhD Centers for Disease Control and Prevention National Center for Zoonotic, Vector-Borne, and Enteric Diseases Division of Vector-Borne Infectious Diseases, Bacterial Diseases Branch |
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