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Tularemia
Rabbit Fever
Deer Fly Fever
Ohara's Disease
Francis Disease

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Overview

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



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In today's presentation we will cover information regarding the organism that causes tularemia 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 signs observed. Finally, we will address prevention and control measures for tularemia, as well as actions to take if tularemia is suspected.

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The Organism

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The Organism

- *Francisella tularensis*
 - Gram negative
 - Intracellular pathogen
 - Macrophages
 - Survival-persistence
 - 3-4 months in mud, water, dead animals
 - More than 3 years in frozen meat
 - Easily killed by disinfectants
 - Inactivated by heat



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Tularemia is caused by *Francisella tularensis*, a Gram negative, non-spore forming intracellular pathogen. The bacterium multiplies within macrophages and the major target organs are the lymph nodes, lungs, spleen, liver, and kidney. There are several subspecies of *Francisella tularensis* which vary in virulence and distribution. Two of the four subspecies account for the majority of human illness; these are *F. tularensis* biovar tularensis (or Jellison type A) and *F. tularensis* biovar palaeartica (or Jellison type B). The other subspecies of *F. tularensis* are *mediasiatica* and *novicida*.

The organism is relatively resistant in the environment, surviving 3-4 months in mud, water or dead animals. Rabbit meat frozen at 5°F has remained infective >3 years. Chlorination of water during water treatment will kill the organism. The organism is easily killed by various disinfectants, including 1% hypochlorite (bleach), 70% ethanol, glutaraldehyde, and formaldehyde. It can also be

inactivated by moist heat (121°C for at least 15 minutes) and dry heat (160-170°C for at least 1 hour).

(Image: CDC Photo Image Library)

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Subspecies	
<ul style="list-style-type: none"> • <i>F. tularensis</i> biovar tularensis (Type A) - More virulent - North America - Reservoirs <ul style="list-style-type: none"> • Rabbits, hares • Ground squirrels • Ticks 	<ul style="list-style-type: none"> • <i>F. tularensis</i> biovar holarctica (Type B) - Less virulent - Eurasia and North America - Reservoirs <ul style="list-style-type: none"> • Muskrats • Voles, mice, rats • Other rodents

F. tularensis tularensis (or Jellison type A) is the major cause of tularemia in the U.S. It is highly virulent and the subspecies that may be used for biowarfare. It occurs naturally in North America and possibly in parts of Europe. The primary reservoirs include a variety of rabbit and hare species (cottontails, jackrabbits, and snowshoe hares), as well as ground squirrels and various tick species. Subspecies *F. tularensis holarctica* (Jellison type B) is less virulent and often results in a milder, often sub-clinical disease. It occurs in beavers, muskrats, and voles in North America, and in hares and small rodents in Eurasia.

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History
<p>History</p>

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History	
<ul style="list-style-type: none"> • 1907: First described in humans • 1911: California ground squirrels • 1930 to 1940s <ul style="list-style-type: none"> - Large waterborne outbreaks - Europe and the Soviet Union • 1950 to 1960s <ul style="list-style-type: none"> - U.S. biological warfare program 	

Tularemia was first described in humans in 1907. The disease was then discovered in the U.S. in 1911 in California ground squirrels suffering a plague-like illness. The organism was originally named *Bacterium tularense* named after Tulare County, CA, where the mammal cases occurred. During the 1930s-40s, the Soviet Union and Europe experienced large waterborne outbreaks. *Bacterium tularense* was later renamed *Pasteurella tularensis*, and in 1947, the organism was again renamed to *Francisella tularensis* in honor of Edward Francis, a U.S. Public Health Service surgeon who had dedicated his career to the study of all aspects of tularemia. In the 1950s and 1960s, the U.S. military developed weapons that aerosolized the organism.

(Photo: California ground squirrel)

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History


- 1966 to 1967: Sweden
 - Largest recorded airborne outbreak
 - Exposed during farm work
 - Most had typical acute symptoms
 - Other signs
 - 32% various exanthemas
 - 31% pharyngitis, 26% conjunctivitis
 - 10% pneumonia, 9% oral ulcers
 - All recovered with treatment

The largest recorded airborne tularemia outbreak occurred in Sweden in 1966-1967. Over 600 patients were infected with the Type B (*F. tularensis* biovar holarctica) strain. Most of those infected were exposed while doing farm work that created contaminated aerosols, particularly when rodent-infested hay was being sorted and moved from field storage sites to barns. Most had typical acute symptoms of fever, fatigue, chills, headache, and malaise. Although airborne exposure would be expected to principally manifest as pleuropneumonic infection, only 10% had symptoms of pneumonia, such as dyspnea and chest pains. Other “forms” of tularemia were noted in a variable proportion of patients: 32% had various skin exanthemas, 31% had pharyngitis, 26% had conjunctivitis, and 9% had oral ulcers. Patients responded well to treatment and no deaths were reported.

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History: Martha’s Vineyard

- 1930
 - Cottontail rabbits introduced
 - First human case
- 1978
 - First cluster of pneumonic cases (7)
- 2000
 - Second cluster of cases (15)
 - Risk factors: landscapers with lawn mowing and bush cutting activities



Tularemia is endemic on Martha’s Vineyard, an island off the coast of Cape Cod, Massachusetts. It first occurred in the 1930s, after game clubs introduced cottontail rabbits from Arkansas and Missouri (endemic States). Shortly after the first cases of tularemia were reported. The only reported outbreaks of pneumonic tularemia in the U.S. occurred on Martha’s Vineyard in 1978 and 2000. In 1978, the cluster of cases involved seven persons who all lived together in a cottage. Epidemiological investigation attributed exposure to a wet dog which aerosolized *F. tularensis* when it shook itself inside of the cottage. In 2000, 15 cases were identified; 11 had pneumonic tularemia, two had the ulceroglandular form, and 2 experienced fever and malaise without localized signs. Epidemiologic investigation determined that landscaping (i.e., lawn mowing, brush cutting) was associated with infection. Investigation also suggested that *F. tularensis* was shed in animal (rodent) excrement and infected people after it was mechanically aerosolized and inhaled.

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Transmission

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Transmission

- Reservoirs
 - Mammals, ticks, and some birds
 - Ticks and rabbits most important
 - Rodent-mosquito cycle in Russia, Sweden
- Infectious dose
 - Small for inoculation or inhalation (10-50 organisms)
 - Large for oral (10^8 organisms)




There are many known reservoirs -- at least 14 species of ticks, 6 species of flies, several mosquito species, over 100 wild mammal species, and 25 species of birds. Ticks and rabbits are the source for most human cases in the United States. A rodent-mosquito cycle has been described in Russia and Sweden. People can become infected by as few as 10 organisms via inoculation or inhalational route but require a larger dose (10^8) via ingestion.

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Transmission

- Vector-borne
 - Ticks
 - Transovarial transmission
 - 14 species
 - *Derma-centor andersonii*
 - *Derma-centor variabilis*
 - *Amblyomma americanum*
 - Mosquitoes, flies
 - Infrequent
 - *Chrysops discalis* (Deer fly)

Tularemia can be transmitted through arthropod bites, including *Derma-centor andersonii*, *Derma-centor variabilis*, *Amblyomma americanum*, and less commonly the deer fly, *Chrysops discalis*. Tick bites are the most common method of transmission to people. Transovarial transmission occurs in ticks, and they can be infective for life. Flies are a less common source of transmission and are only infective for 14 days.


[Top photo: *Derma-centor variabilis* (American dog tick); Middle photo: *Amblyomma americanum* (Lone Star Tick); Bottom photo: *Chrysops discalis* (deer fly).]

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Transmission

- Direct
 - Contact with tissues of rabbits or other infected mammals
 - Skinning, necropsy
 - Handling contaminated skins, paws
 - Bite wounds
- Ingestion
 - Undercooked meat
 - Contaminated water



Direct contact, which can occur via hunting or skinning animals, or contact with meat when preparing food, are important routes of exposure. Tularemia has been rarely transmitted via bites and scratches from coyotes, squirrels, skunks, hogs, cats, and a dog whose mouth was contaminated by eating an infected animal. Transmission is possible through contaminated blood, tissue, or water coming in contact with eyes, mouth, or breaks in the skin. Transmission has also been documented through handling or ingesting undercooked meat (especially rabbits). Water-borne outbreaks can result from contaminated drinking water in rural areas.

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Transmission

- Aerosol
 - Contaminated dust (hay, grain, soil)
 - Farmers
 - Landscapers
 - Laboratory testing
 - Accidental exposures
- Not person-to-person

Respiratory infections sometimes occur in farmers who are exposed through activities such as piling hay. Cases have been reported after mowing lawns, possibly from running over an animal carcass. Laboratory-associated infections have also occurred. Person-to-person transmission has not been documented.


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Epidemiology

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Epidemiology

- Northern hemisphere only
 - North America
 - Europe
 - Russia
 - China
 - Japan



Tularemia occurs in the temperate regions of the Northern Hemisphere (North America (including Mexico), Europe, Soviet Union, China, and Japan).

(Map from Clin Micro Review 2002;15(4):631-46.)

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Epidemiology

- Nationally notifiable in the U.S.
 - About 100 cases per year
 - Year round disease
 - Summer - tick/deerfly abundance
 - Early winter - rabbit hunting season

In the United States, tularemia occurs year-round and is a nationally notifiable disease. Typically there are about 100 cases per year in the United States. Most cases occur from June-September (corresponding to peak arthropod season) but a slight increase in the number of cases in winter has been associated with rabbit hunting.

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Tularemia in the U.S.



This map shows the reported cases of tularemia in the U.S. from 2000-2008. Tularemia has been reported in every state, except Hawaii. Tularemia is considered endemic in Arkansas, Missouri, South Dakota, and Oklahoma. Tularemia became a nationally notifiable disease in 2000.

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<p style="text-align: center;">Tularemia in the U.S.</p> <ul style="list-style-type: none">• Sources of infection<ul style="list-style-type: none">- Endemic areas<ul style="list-style-type: none">• Ticks, rabbits- Western U.S.<ul style="list-style-type: none">• Biting flies, ticks• Texas, 2011<ul style="list-style-type: none">- Serological evidence of infection identified in feral swine
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In endemic areas (Arkansas, Missouri, South Dakota, and Oklahoma) ticks and rabbits are usually the sources of infection. In Utah, Nevada, and California, biting flies are common vectors, while ticks are the primary vectors in the Rocky Mountains. In 2011, researchers at Texas Tech tested feral swine for evidence of tularemia infection; antibody levels in these swine indicated that past and present infections with *Francisella tularensis* had occurred. However, the subspecies was not identified as of April 2011.

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<p style="text-align: center;">Disease in Humans</p>

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<p style="text-align: center;">Human Disease</p> <ul style="list-style-type: none">• Incubation<ul style="list-style-type: none">- 3 to 15 days- Affected by strain virulence, dose• Six disease forms in humans• All forms start with:<ul style="list-style-type: none">- Sudden fever- Chills- Headache- Myalgia

Severity of infection and incubation period in humans varies depending on the subspecies, route of infection, and dose. There are 6 clinical syndromes/manifestations of tularemia based on the route of exposure to the agent. All forms initially present with flu-like symptoms, including fever, chills, headache, and myalgia.

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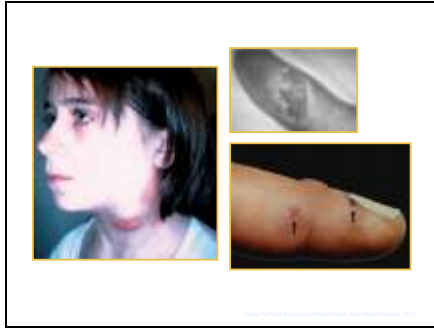
<p style="text-align: center;">Human Disease</p> <ul style="list-style-type: none">• Ulceroglandular<ul style="list-style-type: none">- Most common- Ulcer and regional lymphadenopathy<ul style="list-style-type: none">• Ulcer 1 week-months• Glandular<ul style="list-style-type: none">- Regional lymphadenopathy, no ulcer- Second most common• 75-85% of all cases

The ulceroglandular form is the most common presentation of tularemia. This usually occurs as a consequence of a bite from an arthropod vector which has previously fed on an infected animal. Some cases occur following the handling of infected meat, with infection occurring via cuts or abrasions. An ulcer develops at the site of infection and the local lymph nodes are enlarged. The lymph nodes are painful, swollen, and may rupture and ulcerate. The ulcer may last from 1 week to several months. With the glandular presentation, there is no apparent primary ulcer, but there are one or more enlarged lymph nodes. Ulceroglandular and glandular presentations account for 75-85% of naturally occurring tularemia cases.

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Ulcers and ulceroglandular lesion of tularemia.

(Images from CDC Photo Image Library.)

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Human Disease

- Oculoglandular
 - Conjunctiva infected
 - By contaminated fingers
 - Contaminated material splashed into eye
 - Conjunctivitis
 - Regional lymphadenopathy
 - Severe form
 - Ulceration of conjunctiva
 - Ocular discharge

The oculoglandular form of tularemia is rare and occurs when the conjunctiva becomes infected. This may occur either by rubbing the eyes with contaminated fingers or by splashing contaminated materials in the eyes. Cleaning carcasses or rubbing the area of a tick bite and then the eye can result in this form of tularemia. Clinical presentation involves initial flu-like signs with conjunctivitis and painful swelling of the regional lymph nodes. In severe forms, the conjunctiva may be ulcerated and ocular discharge may be present.

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Human Disease

- Oropharyngeal
 - Ingestion
 - Hand-to-mouth
 - Consumption of undercooked meat or water
 - Pharyngitis, diarrhea, abdominal pain, vomiting, GI bleeding, nausea
 - Pseudomembrane may develop over tonsils


The oropharyngeal presentation of tularemia occurs following ingestion of the organisms in either undercooked meat (especially rabbit) or contaminated water. Hand-to-mouth transfer can also occur. Infection may produce painful pharyngitis (with or without ulceration), abdominal pain, diarrhea, and vomiting. A pseudomembrane may cover the tonsils and can be mistaken for diphtheria.

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Human Disease

- Typhoidal
 - Acute
 - Septicemia
 - Without lymphadenopathy or ulcer
- Pulmonary
 - Inhalation of aerosol
 - Spread through bloodstream
 - Complications from other forms
- Case-fatality (untreated): 30-60%



The most severe and fatal forms of tularemia are typhoidal and pulmonary. The typhoidal form involves systemic infection and can develop from the oropharyngeal form of tularemia. Pulmonary tularemia is due to inhalation of infectious organisms or dissemination of organisms through the bloodstream. Ten to 15% of the ulceroglandular and ~50% of the typhoidal cases result in the pulmonary form of disease. Organisms can become airborne as animals are skinned or eviscerated. Inhalation of infectious material may be followed by pneumonic disease or a primary septicemic (typhoidal type) syndrome with a 30-60% case-fatality rate if untreated. Radiographic signs are not sufficient for diagnosis. Additionally, respiratory signs and symptoms may be minimal or absent and, when present, are often nonspecific.

[Photo: Chest radiograph of patient with pulmonary tularemia – infiltrates in left lower lung, tenting of diaphragm

(probably caused by pleural effusion), and enlargement of left hilus. Source: Armed Forces Institute of Pathology.]

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Diagnosis

- Culture and isolation
 - Definitive diagnosis
 - Biological safety level III
- Serology
 - ELISA, microagglutination
 - Cross-reactions possible
- PCR
- Immunofluorescent staining
 - Tissue samples
 - Blood

In humans, tularemia is often diagnosed by serology. Commonly used serological tests include tube agglutination, microagglutination and enzyme-linked immunosorbent assays (ELISA). Cross-reactions can occur with *Brucella* spp., *Legionella* sp., *Proteus* OX19, and *Yersinia* spp., usually at low titers. Definitive diagnosis of tularemia is made from the isolation of *F. tularensis* from clinical specimens such as blood, exudates, or biopsy material from a lesion or lymph node. Because of the highly infectious nature of this organism, laboratories should practice biological safety level III (BSL-3) safety procedures. Tularemia can also be diagnosed by PCR or immunofluorescent staining of *F. tularensis* antigens in tissue samples or blood, and by serology.

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Treatment and Prognosis



- Antibiotic treatment
 - Streptomycin (drug of choice)
- Prognosis
 - Untreated
 - <8% mortality overall (all cases)
 - Case-fatality for typhoidal and pneumonic (30-60%)
 - Treated
 - <1% mortality overall (all cases)
- Type A has higher case-fatality rate
- Long-term immunity

F. tularensis is susceptible to a variety of antibiotics. Streptomycin is the antibiotic of choice but gentamicin, doxycycline, and ciprofloxacin have also been used. The prognosis for tularemia varies. Untreated tularemia has an overall mortality rate of less than 8%, and less than 1% with treatment. Type A (*F. tularensis tularensis*) organisms are more virulent with an overall case-fatality rate of 5-15%. Typhoidal and pulmonary forms of disease account for most of these cases. Type B (*F. tularensis holarctica*) is less virulent and even without treatment produces few deaths. If untreated, general symptoms usually last 1-4 weeks but may continue for months. Treatment, however, is usually delayed due to misdiagnosis. Following recovery from infection, antibody titers can persist for years, but subsequent infections may occur.

S I d e 2 9	<h3>Animals and Tularemia</h3>	<p>A variety of animal species are affected by <i>F. tularensis</i>. Disease in animal species typically mimics clinical signs seen in humans.</p>
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S I d e 3 0	<h3>Wildlife Disease</h3> <ul style="list-style-type: none"> • Usually found dead • Rabbits and hares <ul style="list-style-type: none"> - Weakness, fever, ulcers, abscesses, lymphadenopathy - Behave strangely <ul style="list-style-type: none"> • Easily captured because they run slowly • Rub their noses and feet on the ground • Muscle twitches • Other: anorexia, diarrhea, dyspnea 	<p>As mentioned before, rodents and lagomorphs (rabbits and hares) are reservoirs for <i>F. tularensis</i>. These animals are susceptible to tularemia. Often signs of disease are not seen in wildlife species, and animals are usually found dead or dying. Death, typically from fatal septicemia, occurs in 8-14 days. Rabbits and hares may exhibit strange behavioral patterns such as rubbing their noses and feet on the ground or displaying muscle twitches. Additionally, they may be easily captured because they run/hop slowly (due to weakness that develops from the disease). If clinical signs are noted they may include weakness, fever, ulcers, abscesses at the inoculation site, and lymphadenopathy. Infected rodents are also an important source of infection for arthropods, other animals, humans, and the environment. Clinical presentation in experimentally infected red foxes included anorexia, diarrhea, and dyspnea.</p>
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S I d e 3 1	<h3>Large Animal Disease</h3> <ul style="list-style-type: none"> • Sheep <ul style="list-style-type: none"> - Outbreaks in enzootic areas <ul style="list-style-type: none"> • Following severe winter • Heavy tick infestations - Fever, weight loss, lymphadenopathy, dyspnea, diarrhea, isolate from flock, rigid gait - Death in young 	<p>Tularemia has resulted in high-mortality outbreaks in sheep in enzootic areas in Canada, the U.S. (Montana and Idaho), and the former Soviet Union. Outbreaks generally occur in association with reduced body condition after a severe winter, a decreased plane of nutrition, and heavy tick infestations. Clinical signs reported include fever, weight loss, regional lymphadenopathy, and diarrhea. Ill animals will also separate themselves from the flock, have a rigid gait, and may have respiratory difficulty. Death most commonly occurs among younger animals, but pregnant ewes may abort. Necropsy may reveal infarcts of the regional lymph nodes as well as pneumonic foci.</p>
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S I d e 3 2	<h3>Large Animal Disease</h3> <ul style="list-style-type: none"> • Equine <ul style="list-style-type: none"> - Fever, depression, dyspnea, ataxia, stiffness, limb edema • Swine <ul style="list-style-type: none"> - Latent infection in adults - Clinical signs in young <ul style="list-style-type: none"> • Fever, dyspnea, depression • Bovine <ul style="list-style-type: none"> - Appear to be resistant  	<p>Horses have been occasionally reported to be infected with tularemia. Symptoms reported have included fever, depression, dyspnea, ataxia, stiffness, lack of coordination, and limb edema. In these cases horses were parasitized by a large number of ticks. Infected young swine suffer from fever, dyspnea, and depression, while disease in adults becomes latent. Cattle seem to be resistant to developing clinical disease.</p>
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Companion Animal Disease

- Cats
 - Fever, depression, anorexia
 - Listlessness, apathy
 - Ulcerated tongue and palate
- Dogs
 - Fever, anorexia, myalgia
 - Ocular and nasal discharge
 - Abscess at site of infection




Cats can rarely become infected when hunting rodents in endemic areas or consuming dead lagomorphs. Cats may transmit the infection to humans. Tularemia in cats can range from nonclinical infection to mild illness with lymphadenopathy to severe infection and death. Signs seen in reported cases include fever, depression, anorexia, listlessness, and apathy, and some cases had an ulcerated tongue and palate. Natural infection of tularemia in dogs is considered rare and dogs are considered relatively resistant to tularemia. When acquired, it is typically through ingestion of an infected rodent, but disease can come from inoculation by an infected tick. Illness is usually transient and self-limiting, but may be more severe in young pups. Signs reported (both from natural and experimental cases) include: fever, ocular and nasal discharge, abscess (possibly draining) at the site of infection, uveitis, and conjunctivitis.

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Post Mortem Examination

- Variable by species
 - Gray necrotic foci
 - Pin-point to several millimeters in diameter
 - Lymph nodes, spleen, liver
 - Thrombosis and infarcts of small blood vessels
 - Enlarged and discolored spleen and liver



Pathologic findings vary greatly between species. There will often be gray necrotic foci on the lymph nodes, spleen, and liver. These lesions may contain a central area of caseous necrosis. Thrombosis of small blood vessels may also be a common finding. Enlargement and discoloration of the spleen and liver have also been reported. Pneumonia-like lesions have been reported in dogs.

(This photo shows the pinpoint gray necrotic lesions on a liver from a rabbit infected with tularemia. Image from Michigan Department of Natural Resources.)

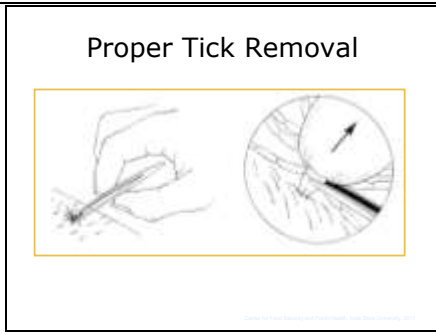
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Treatment of Animals

- Remove ticks as soon as possible
 - Proper removal technique
 - Wash hands after removal
 - Apply antiseptic to bite wound
- Streptomycin
 - Antibiotic of choice

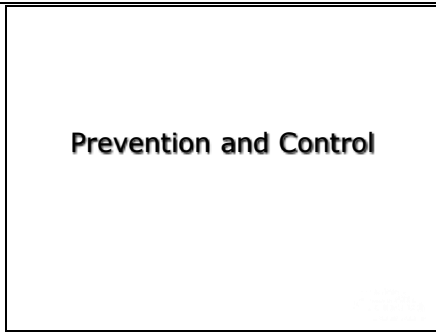
Treatment for animal species is typically supportive when clinical disease develops. Streptomycin is the antibiotic of choice, but tetracycline and chloramphenicol may be used alternatively, as some strains may be streptomycin resistant. Removal of ticks from infested animals may also help prevent further transmission of the organism. Proper removal techniques should be used and antiseptic applied to the site following removal.

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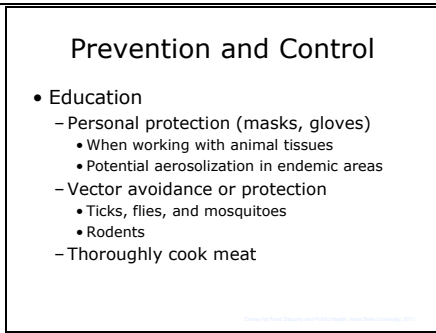


The best way to remove a tick is with fine-pointed tweezers. Grab as closely to the skin as possible and pull straight back, using steady but gentle force. Do not squeeze the body of the tick as this will inject tick gut contents into the wound and may lead to infection. Burning, using oil or Vaseline, or other non-traditional methods to remove ticks are ineffective and not recommended. Proper disposal of the tick is equally important. Place the tick in a jar of alcohol in the event the tick will need to be identified or tested for disease.

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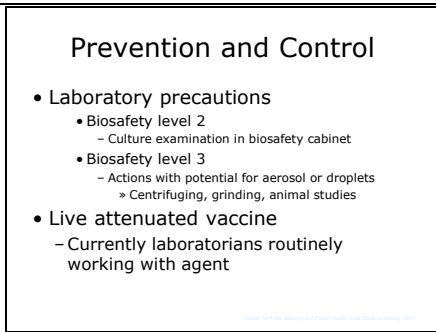


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One of the best preventative steps in the avoidance of tularemia outbreaks is education. This is especially important in areas where tularemia is endemic. Personal protection equipment (i.e., gloves, masks) should be worn when working with potentially infected animal tissues (i.e. skinning rabbits, necropsy on reservoir species). Additionally, as seen in the Martha's vineyard outbreaks, masks should be worn during activities that may potentially aerosolize the agent (i.e., grass mowing or bush cutting). It is also important to educate about prevention activities and avoidance of ticks, flies, and mosquitoes (potential arthropod carriers of tularemia). Since *F. tularensis* can also persist in food and water, unchlorinated water should be avoided for drinking, bathing, or swimming. Additionally, meat from potential reservoir species (i.e. rabbits, rodents) should be thoroughly cooked.

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Microbiology laboratory personnel should be alerted when tularemia is clinically suspected. Routine diagnostic procedures can be performed in biological safety level 2 (BSL-2) conditions. Examination of cultures in which *F. tularensis* is suspected should be carried out in a biological safety cabinet. Manipulations of materials with a potential for aerosol or droplet production (i.e., centrifuging, grinding, etc.) will require BSL-3 conditions. A live attenuated vaccine was developed in the Soviet Union in the 1930s and used to

vaccinate millions of persons living in tularemia-endemic areas. In the U.S., a live attenuated vaccine derived from the avirulent live vaccine strain has been used to protect laboratory personnel routinely working with *F. tularensis*. Until recently, this vaccine was available only as an investigational new drug, however, it is currently under review by the FDA to determine its future availability.

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<p style="text-align: center;">Tularemia as a Biological Weapon</p> <ul style="list-style-type: none">• History• WHO estimate<ul style="list-style-type: none">- 50 kg virulent <i>F. tularensis</i> particles aerosolized- City of 5 million people<ul style="list-style-type: none">• 250,000 people ill- 19,000 deaths• CDC estimate<ul style="list-style-type: none">• \$5.4 billion/100,000 people exposed <p style="text-align: right;"><small>Center for Food Security and Public Health, Iowa State University, 2011</small></p>

Francisella tularensis has long been considered a potential biological weapon. It was one of a number of agents studied at Japanese germ warfare research units in Manchuria between 1932-1945. It may have been intentionally used on Soviet and German soldiers during World War II. The U.S. military developed weapons to disseminate *F. tularensis* aerosols in the 1950-60s. It is also suspected that the Soviet Union produced strains of engineered *F. tularensis* resistant to antibiotics and vaccines in the 1990s. In 1969, the World Health Organization (WHO) estimated that if 50 kg of virulent *F. tularensis* particles were aerosolized over a city with 5 million people, the result would be 250,000 illnesses and 19,000 deaths. Illness would be expected to persist for several weeks, and disease relapses would occur during the following weeks or months. Recently, the Centers for Disease Control and Prevention (CDC) estimated the economic impact associated with an outbreak of tularemia to be \$5.4 billion for every 100,000 people exposed (total base cost to society).

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<p style="text-align: center;">Additional Resources</p> <ul style="list-style-type: none">• World Organization for Animal Health (OIE)<ul style="list-style-type: none">- www.oie.int• U.S. Department of Agriculture (USDA)<ul style="list-style-type: none">- www.aphis.usda.gov• Center for Food Security and Public Health<ul style="list-style-type: none">- www.cfsph.iastate.edu• USAHA Foreign Animal Diseases ("The Gray Book")<ul style="list-style-type: none">- www.usaha.org/pubs/fad.pdf <p style="text-align: right;"><small>Center for Food Security and Public Health, Iowa State University, 2011</small></p>

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Center for Food Security and Public Health, Iowa State University, 2011