Slide 1

Tularemia

Rabbit Fever
Deer Fly Fever

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Overview

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

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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 tularemia.

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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
    - >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. 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 also easily killed by various disinfectants, including 1% hypochlorite (bleach), 70% ethanol, glutaraldehyde and formaldehyde. It can also be inactivate by moist heat (121^{o}C for at least 15 minutes) and dry heat (160-170^{o}C for at least 1 hour). 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. *F. tularensis* biovar tularensis (or Jellison type A) and *F. tularensis* biovar palaearctica (or Jellison type B). The other subspecies of *F. tularensis* are *mediasiatica* and *novicida*. Image from: CDC Photo Image Library.

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Subspecies

- *F. tularensis* biovar tularensis (Type A)
  - More virulent
  - Found in North America
  - Reservoirs
    - Rabbits and hares
    - Ground squirrels
    - Ticks

- *F. tularensis* biovar palaearctica (Type B)
  - Less virulent
  - Found in Eurasia and North America
  - Reservoir
    - Muskrats, water rats
    - Voles, mice, rats
    - Other rodents

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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 includes 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 beaver, muskrats and voles in North America and in hares and small rodents in Eurasia.

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History

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History

- 1907: First described in humans
- 1911: California ground squirrels

- 1930-1940's
  - Large waterborne outbreaks
  - Europe and the Soviet Union
- 1950-1960's
  - US biological warfare program

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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 1930-40's, the Soviet Union and Europe experienced large waterborne outbreaks. In 1947, the organism was renamed *Francisella tularensis* in honor of Edward Francis, a U.S. Public Health Service surgeon who had dedicated his career (since 1914) to the study of all aspects of tualaremia. In 1950's and 1960's the U.S. military developed weapons that aerosolized the organism. Photo: California ground squirrel.

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History

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

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The largest recorded airborne tularemia outbreak occurred in Sweden in 1966-1967. Over 600 patients were infected with the Type B (*F. tularensis* biovar palaearctica) strain. Most of those infected were exposed while doing farm work that created contaminated aerosols, particularly with 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% has various skin exanthemas, 31% had phayngitis, 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
  - Introduction of cottontail rabbits
  - First human case soon reported

- 1978
  - First cluster of pneumonic cases (7)
  - Wet dog inside cottage
- 2000
  - Second cluster cases (15)
    - 11 pneumonic, 2 ulceroglandular, 2 fever and malaise
  - Risk factors: landscapers with lawn mowing and bush cutting activities

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Tularemia is endemic on Martha's Vineyard, an island off the coast of Cape Cod, Massachusetts. In the 1930's, game clubs introduced cottontail rabbits from Arkansas and Missouri (endemic States) to Cape cod and Martha's Vineyard. Shortly after this introduction, the first cases of tularemia were reported in Martha's Vineyard. The only two reported outbreaks of pneumonic tularemia in the United States 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. During the outbreak in 2000, 15 cases were identified; 11 of which had pneumonic tularemia, two had ulceroglandular form and 2 only experienced fever and malaise without localized signs. Epidemiologic investigation determined that the cases were primarily in persons occupationally associated with landscaping.

Risk factors were increased for those that had lawn mowing and bush cutting activities, which was though to generate aerosols of the organism for dispersal. Investigation also proposed that *F. tularensis* was shed in animal (rodent) excrement and infected people after it was mechanically aerosolized and inhaled. One patient did remember cutting brush around a dead rabbit.

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Transmission

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Transmission

- Reservoirs
  - Many mammals, ticks, and some birds
    - Rabbits, hares, beavers, muskrats, domestic animals, hard ticks
  - Ticks and rabbits most important
  - Rodent-mosquito cycle in Russia, Sweden
- Infectious dose
  - Small for inoculation or inhalation (10-50)
  - Large for oral (10^8)

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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
      - *Dermacentor andersonii*
      - *Dermacentor variabilis*
      - *Amblyomma americanum*
  - Mosquitoes, flies
    - Infrequent
      - *Chrysops discalis* (Deer fly)

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Tularemia can be transmitted through arthropod bites, including *Dermacentor andersonii*, *Dermacentor 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: *Dermacentor 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
- Ingestion
  - Undercooked meat
  - Contaminated water
    - Waterborne outbreaks

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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 from hay, grain or soil
  - Laboratory testing procedures
- Bites or scratches (rare)
- Not person-to-person

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Person-to-person transmission has not been documented. Airborne outbreaks can occur from moving rodent-contaminated hay, threshing corn, or lab accidents.

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Epidemiology

Tularemia occurs in the temperate regions of the Northern Hemisphere (North America, Europe, Soviet Union, China, Japan, and Mexico). Map from Clin Micro Review 2002;15(4):631-46.

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Epidemiology

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

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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 winter has been associated with rabbit hunting.

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Epidemiology

- Nationally notifiable in the United States
  - About 100 cases per year
  - Summer – tick/deerfly abundance
  - Early winter – rabbit hunting season

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This map shows the total cases (90) of tularemia in the United States during 2002; Martha's Vineyard (off the coast of Cape Cod, Mass.), Missouri and the surrounding states have had high rates of infection in recent years. [N=Reporting of disease not required in this jurisdiction]. Map from the Summary of Notifiable Diseases 2002, CDC website. Between 1990-2000, 124 human cases of tularemia were reported annually. Tularemia has been reported in every state, except Hawaii. Over half of these cases occurred in four states: Arkansas (23%), Missouri (19.4%), South Dakota (7%) and Oklahoma (6.6%). Tularemia is considered endemic in these states and 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. Tularemia became a nationally notifiable disease in 2000.

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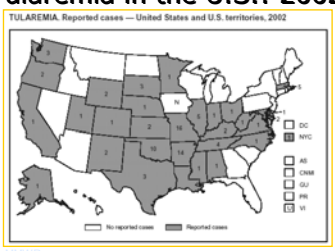
Tularemia in the U.S.: 2002



MMWR

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Disease in Humans

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Human Disease

- Incubation
  - 3-15 days
  - Varies with virulence of strain and dose
- Initially all forms start with
  - Sudden fever
  - Chills
  - Headache
  - Myalgia
- 6 clinical syndromes
  - Ulceroglandular
  - Glandular
  - Oculoglandular
  - Oropharyngeal
  - Typhoidal
  - Pulmonary

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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 bases on the route of exposure to the agent. All forms initially present as flu-like symptoms, including fever, chills, headache, and myalgia.

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Human Disease

- Ulceroglandular
  - Most common
  - Ulcer and regional lymphadenopathy
    - Ulcer 1 week-months
- Glandular
  - Regional lymphadenopathy, no ulcer
  - Second most common
- 75-85% of all cases

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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 ulcer. The ulcer may last from 1 week to several months. With 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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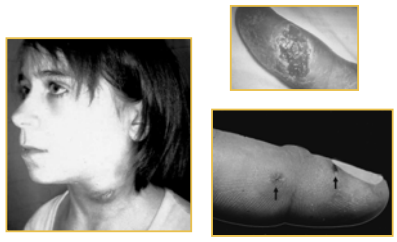

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Ulcers and ulceroglandular lesion of tularemia. Images from CDC Photo Image Library.

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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

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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

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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 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%

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The most severe forms (and most fatalities) of tularemia are the typhoidal and pulmonary forms. 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 in ~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. Although there have been descriptions of a triad of findings for tularemic pneumonia – ovoid opacities, pleural effusions, and hilar adenopathy – these radiologic manifestations are neither sensitive nor specific enough to render them diagnostically useful. 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 hilum. Source: Armed Forces Institute of Pathology.

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Diagnosis

- Immunofluorescent staining
  - Tissue samples
  - Blood
- Serology
  - ELISA, Microagglutination
  - Titer: four-fold increase
- PCR
- Culture and isolation
  - Caution needed for laboratory workers
  - Biological safety level III

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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). There is a rise in antibodies in the second week of disease. A titer of <1:20 is not diagnostic, but a four-fold increase in titer may be suggestive. Cross-reactions can occur with *Brucella* species. 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 nor lymph node. Because of the highly infectious nature of this organism, laboratories should practice biological safety level III (BSL-3) safety procedures.

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Treatment and Prognosis

- Antibiotic treatment
  - Streptomycin (drug of choice)
- Prognosis
  - Untreated
    - Symptoms last 1-4 weeks to months
    - <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

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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 with the form of disease that manifests and the subspecies of the organism infected with. Overall, 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. The mortality rate for all types of untreated tularemia is less than 8% and drops to less than 1% when treatment. Treatment, however, is usually delayed due to misdiagnosis. Following recovery from infection, antibody titers can persist for years, but subsequent infections may occur.

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Animals and Tularemia

A variety of animal species are affected by *F. tularensis.* Disease in animal species typically mimics clinical signs seen in humans.

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Wildlife Disease

- Usually found dead
- Rabbits and hares
  - Weakness, fever, ulcers, abscesses, lymphadenopathy
  - Behave strangely
    - Easily captured because they run slowly
    - Rub their noses and feet on the ground
    - Muscle twitches
    - Other: anorexia, diarrhea, dyspnea

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As mentioned before, rodents and lagomorphs (rabbits and hares) are one of the reservoirs for *F. tularensis*. 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. Lesions in rodents resemble those of bubonic plague or paratuberculosis, with caseous lymph nodes and grayish white foci in the spleen.

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Large Animal Disease

- Sheep
  - Outbreaks in enzootic areas
    - Following severe winter
    - Heavy tick infestations
  - Fever, weight loss, lymphadenopathy, dyspnea, diarrhea, isolate from flock, rigid gait
  - Death in young

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Tularemia has resulted in high-mortality outbreaks in sheep in enzootic areas in Canada, the US (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 and pregnant ewes may abort. Necropsy may reveal infarcts of the regional lymph nodes as well as pneumonic foci.

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Large Animal Disease

- Equine
  - Fever, depression, dyspnea, ataxia, stiffness, limb edema
- Swine
  - Adults: Latent
  - Young
    - Fever, dyspnea, depression
- Bovine
  - Appear to be resistant

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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.

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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

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Cats can become infected (although rare) and fall ill when hunting rodents in endemic areas or by consuming dead lagomorphs. Cats can then in turn 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 can come from inoculation from and 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, conjunctivitis

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Post-Mortem Examination

- Varies greatly between 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

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Pathologic findings will 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
- Streptomycin
  - Antibiotic of choice

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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 in further transmission of the organism. Proper removal techniques should be used and antiseptic applied to the site following removal.

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Proper Tick 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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Prevention and Control

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Prevention and Control

- Education
  - Personal protection (masks, gloves)
    - When working with animal tissues
    - Potential aerosolization in endemic areas
  - Vector avoidance or protection
    - Ticks, flies and mosquitoes
    - Rodents
  - Thoroughly cook meat

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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 in 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 aerosolized 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. There is a live attenuated vaccine, which is given intradermally by scarification. Live attenuated strains of *holarctica* biotype have been used extensively as vaccines since 1940s and are effective.

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Prevention and Control

- Laboratory precautions
  - Biosafety level 2
    - Culture examination in biosafety cabinet
  - Biosafety level 3
    - Actions with potential for aerosol or droplets
      - Centrifuging, grinding, animal studies
- Live attenuated vaccine
  - Currently laboratorians routinely working with agent

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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 1930's and used to vaccinated millions of persons living in tularemia-endemic areas. Here in the U.S., a live attenuated vaccine derived from the avirulent live vaccine strain has been used to protect laboratorians 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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Tularemia as a Biological Weapon

- History
- WHO estimate
  - 50 kg virulent *F. tularensis* particles aerosolized
  - City of 5 million people
    - 250,000 people ill
      - 19,000 deaths
- CDC estimate
  - $5.4 billion/100,000 people exposed

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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 has also been suggested that it may have been intentionally used on Soviet and German soldiers during World War II. The U.S. military developed weapons to disseminated *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 persists 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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Acknowledgments

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