Tularemia

Signs and Symptoms	• Fever, chills, malaise, headache, additional symptoms depending on type and route of exposure: ulceroglandular (cutaneous ulcer with regional lymphadenopathy), glandular (regional lymphadenopathy with no ulcer), oculoglandular, (conjunctivitis with preauricular lymphadenopathy), oropharyngeal (stomatitis; pharyngitis; or tonsillitis with cervical lymphadenopathy), intestinal (intestinal pain, vomiting, and diarrhea), pneumonic (primary pleuropulmonary disease), typhoidal (febrile illness without early localizing signs and symptoms)	
Incubation	Usually 3-5 days (range 1-14 days)	
Case classification	**Clinical criteria**: clinically compatible with one of the above described categories	
	Confirmed: clinically compatible with detection of *F. tularensis* by isolation or ≥ fourfold change in serum antibody titer	**Probable**: clinically compatible with detection of *F. tularensis* by elevated titers (without fourfold or greater change) in patient with no history of tularemia vaccination OR fluorescent assay OR through nucleic acid testing, such as PCR
Differential diagnosis	Extensive depending on presentation, including: anaplasmosis, brucellosis, cat scratch fever, ehrlichiosis, bacterial or viral endocarditis, influenza or parainfluenza, legionellosis, Lyme disease, leishmaniasis, mycobacterial infection (TB and other), mycoplasma, pericarditis, plague, bacterial or viral pharyngitis, bacterial or viral pneumonia, psittacosis, Q fever, rickettsial infection, salmonellosis, syphilis	
Treatment	Appropriate antibiotics. See: https://www.cdc.gov/tularemia/clinicians/index.html	
Duration	Days to weeks; overall 6% mortality	
Exposure	Reservoirs are wild mammals (especially rabbits, hares, voles, squirrels, muskrats, and beavers), and ticks or deerflies that bite wild animals. Can be direct contact with animal or contaminated material, arthropod bite, ingestion of contaminated water or food, or inhalation during landscaping or farm work. Laboratory exposure from handling culture.	
Laboratory testing	Local Health Jurisdiction (LHJ) and Communicable Disease Epidemiology (CDE) can arrange testing if an outbreak is suspected • Washington State Public Health Laboratories perform PCR, culture and biotyping. • **Best specimens**: 1–2 mL of both acute and convalescent (4+ w) sera (done at CDC); isolate needs Category A handling – call PHL (206-418-5400) for shipping instructions • Keep isolate at **room temperature**, serum or tissue **cold,** ship with Reference form: http://www.doh.wa.gov/Portals/1/Documents/5230/302-018-BioterrorismSpecimen.pdf or Serology form: http://www.doh.wa.gov/Portals/1/Documents/5230/302-017-SerVirHIV.pdf • Specimen Collection and Submission Instructions http://www.doh.wa.gov/Portals/1/Documents/5240/SCSI-Francisella-tularensis-V1.pdf	
Public health actions	LHJ can consult with CDE 877-539-4344 for testing in outbreak investigations • **Immediately** suspect report bioterrorism event or potential outbreak (206-418-5500) • Identify potential sources of exposure, particularly occupational exposures including landscaping or farm work, laboratory work • Identify others sharing an exposure and evaluate for symptoms • Evaluate potential laboratory exposure to a specimen (aerosol) or culture (on bench). If exposures, recommend post-exposure prophylaxis (high) or fever watch (low risk). • Recommend safe handling of animals and measures to avoid tick bites *Infection Control:* standard precaution (no person-to-person transmission)	

Tularemia

1. DISEASE REPORTING

A. Purpose of Reporting and Surveillance

1. To assist in diagnosis.
2. When the source is a risk for only a few individuals (e.g., animal exposure), to inform those individuals how they can reduce their risk of exposure.
3. To educate potentially exposed persons, including laboratory personnel, about signs and symptoms of disease, thereby facilitating early diagnosis and treatment.
4. To determine the endemicity and epidemiology of the disease in Washington State.
5. To raise the index of suspicion of a possible bioterrorism event if no natural exposure source is identified.

B. Legal Reporting Requirements

1. Health care providers: **immediately notifiable to local health jurisdiction**
2. Health care facilities: **immediately notifiable to local health jurisdiction**
3. Laboratories: *Francisella tularensis* **immediately notifiable to local health jurisdiction**; specimen submission required – culture or other appropriate clinical material (2 business days).
4. Veterinarians: **suspected human cases notifiable immediately to the local health jurisdiction**; animal cases notifiable to Washington State Department of Agriculture (see: http://app.leg.wa.gov/WAC/default.aspx?cite=16-70).

5. Local health jurisdictions: **suspected and confirmed cases are immediately notifiable** to the Washington State Department of Health (DOH) Office of Communicable Disease Epidemiology (CDE) (1-877-539-4344 or 206-418-5500).

C. Local Health Jurisdiction Investigation Responsibilities

1. **If bioterrorism is suspected, notify CDE immediately (24/7): 1-877-539-4344 or 206-418-5500.**
2. Facilitate the transport of specimens to the Washington State Public Health Laboratories (PHL) for confirmatory testing.
3. Educate potentially exposed persons, including laboratory personnel, about signs and symptoms of disease and recommend antibiotic prophylaxis if indicated.
4. Report all *confirmed* and *probable* cases to CDE (see definitions below). Complete the tularemia report form (http://www.doh.wa.gov/Portals/1/Documents/5100/210-049-ReportForm-Tularemia.pdf) and enter the data in the Public Health Issues Management System (PHIMS).

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic Agent

Francisella tularensis are small, aerobic, non-motile, gram-negative coccobacilli. Most human cases are due to *F. tularensis* subspecies *tularensis* (Jellison type A) and *F. tularensis* subsp. *holarctica* (Jellison type B); type A tends to cause more severe disease.

B. Description of Illness

The nature of the illness usually reflects the route of transmission, as well as the virulence of the infecting strain. Almost all cases have a rapid onset of fever, chills, malaise, and headache along with symptoms falling into one or more of the following forms:

1. **Ulceroglandular**

   Patients present with a papule that develops into a non-healing skin ulcer at the inoculation site (i.e., arthropod or animal bite) and large, tender regional lymph nodes. This is the most common form of tularemia.

2. **Glandular**

   Patients present with large, tender lymph nodes without skin lesions. This form is generally acquired through the bite of an infected tick or deer fly or from handling sick or dead animals.

3. **Oculoglandular**

   Patients present with severe, painful conjunctivitis (usually unilateral) with regional lymphadenopathy in front of the ear (preauricular nodes). This form occurs if bacteria enter through the eye, such as touching the eyes while handling an infected animal.

4. **Oropharyngeal**

   Patients may have severe throat pain, mouth ulcers, exudates on the throat and tonsils, tonsillitis, and cervical lymphadenopathy after ingesting contaminated food or water.

5. **Intestinal**

   Patients may have intestinal pain, vomiting and diarrhea after ingesting contaminated food or water.

6. **Pneumonic (pulmonary)**

   Pneumonic tularemia can be a primary infection following inhalation of organisms, or secondary to other forms when the organism spreads through the blood and localizes in the lung or pleural spaces. The pneumonic form is the most probable presentation of illness in a bioterrorist attack. Symptoms include fever, non-productive cough, difficulty breathing, and pleuritic chest pain. Patchy bilateral infiltrates, pleural effusion and hilar lymphadenopathy may be seen on chest X-ray.

7. **Septicemic or Typhoidal**

   Septicemic tularemia can develop after any mode of acquisition. Patients may present with a variety of symptoms including fever, chills, headache, muscle aches, sore throat, abdominal pain, diarrhea, and vomiting. This form of blood-borne infection can also lead to shock, DIC, or other complications.

C. Tularemia in Washington State

Tularemia is an endemic zoonosis in Washington. Most years, 1 to 5 cases are reported, though up to 10 annually have occurred. Potential sources of infection reported by residents include arthropod and animal bites, contaminated water, skinning or handling animal carcasses, and aerosol exposure while farming or using power landscape tools such as lawn mowers and weed eaters. Two ticks capable of transmitting tularemia, *D. variabilis* (American dog tick), and *D. andersoni* (Rocky Mountain wood tick) can be found in Washington; all *Dermacentor* ticks collected for surveillance in Washington are tested for *F. tularensis*. The first and only detection of *F. tularensis* in a *D. variabilis* tick occurred in 2016, in a tick collected from Spokane County. Most endemic exposures are in western Washington. The majority of *F. tularensis* isolates in Washington are type B. Generally, infection is more common in men than in women.

During 2004-2005 a statewide serosurvey of more than 360 outdoor pet cats and dogs indicated that 0.6% had been exposed to tularemia. The incidence was highest in dogs and cats tested in southwest Washington (4.5%).

D. Vectors and Reservoirs

The primary reservoirs of *F. tularensis* are wild mammals (especially rabbits, hares, voles, squirrels, muskrats, and beavers). Arthropods that bite these animals (e.g., ticks, deerflies) act as vectors that maintain the life cycle of the organism and can themselves remain infective for prolonged periods. Humans and domestic animals are usually dead-end hosts (i.e., they do not transmit the infection to others).

E. Modes of Transmission

Infection can occur by direct contact with an infected animal, through an arthropod bite, by ingestion of contaminated meat or water, or through inhalation of the organism. The infection progresses from the portal of entry, thereby determining the form of illness.

In Washington approximately 50% of cases may be transmitted by aerosolization of contaminated dust while using farm and landscaping equipment. This exposure causes the pneumonic form of tularemia. Common sources of ulceroglandular tularemia include arthropod bites (ticks, deer flies); animal bites; and inoculation of skin with contaminated water, blood or tissue (e.g., while handling animal carcasses). Inoculation of eyes with contaminated stream water resulting in oculoglandular disease has occurred in Washington. Oropharyngeal infection may occur after eating undercooked meat of infected animals or drinking contaminated water; this form is uncommon in humans regionally, but is effective in transmission among animals.

This organism is **extremely dangerous** to handle in a laboratory. It easily aerosolizes to cause lab-acquired infections; the infectious dose is estimated between 10-25 bacteria. Cultures for a patient (or animal) with suspected tularemia should **not** be attempted without special containment facilities. Clinicians suspecting tularemia should alert the laboratory receiving specimens (See Section 4).

F. Incubation Period

Usually 3–5 days (range 1–14 days).

G. Period of Communicability

Not directly transmitted from person to person. Unless treated, the infectious agent may be found in the blood during the first two weeks of disease and in lesions for a month, sometimes longer.

F. tularensis is quite hardy, surviving in water, mud, and animal carcasses for prolonged periods. Rabbit meat frozen at -15°C (5°F) has remained infective longer than 3 years. Ticks can be infected for life. Flies are not thought to be maintenance vectors; they can be infective for 14 days.

H. Treatment

Tularemia is treated with appropriate antibiotic therapy. For further details regarding treatment see: https://www.cdc.gov/tularemia/clinicians/index.html. In recent decades, reported mortality is 6%, with some variation by subspecies and subtype.

3. CASE DEFINITIONS

A. Clinical Criteria for Diagnosis

An illness characterized by several multiple forms, including the following:

- Ulceroglandular (cutaneous ulcer with regional lymphadenopathy)
- Glandular (regional lymphadenopathy with no ulcer)
- Oculoglandular (conjunctivitis with preauricular lymphadenopathy)
- Oropharyngeal (stomatitis; pharyngitis; or tonsillitis with cervical lymphadenopathy)
- Intestinal (intestinal pain, vomiting, and diarrhea)
- Pneumonic (primary pleuropulmonary disease)
- Typhoidal (febrile illness without early localizing signs and symptoms).

Clinical diagnosis is supported by evidence of or history of a tick or deerfly bite, exposure to tissues of a mammalian host of *F. tularensis*, exposure to potentially contaminated dust or water, or laboratory exposure.

B. Laboratory Criteria for Diagnosis

1. Presumptive:
   - Elevated serum antibody titer(s) to *F. tularensis* antigen (without documented fourfold or greater change) in a patient with no history of tularemia vaccination; OR
   - Detection of *F. tularensis* in a clinical specimen by fluorescent assay; OR
   - *Francisella tularensis* detection through nucleic acid testing, such as PCR
2. Confirmatory:
   - Isolation of *F. tularensis* in a clinical specimen: OR
   - Fourfold or greater change in serum antibody titer to *F. tularensis* antigen.

C. Case Definition (2017)

1. *Probable*: a clinically compatible case with presumptive laboratory results.
2. *Confirmed*: a clinically compatible case with confirmatory laboratory results.

4. DIAGNOSIS AND LABORATORY SERVICES

A. Diagnosis

Francisella tularensis can be isolated from a variety of bodily fluids and tissues including wound exudate, lymph node, pleural fluid, and blood, but isolation requires processing on special culture media. It is a highly infectious organism and has caused infection in laboratory workers. Health care providers should alert laboratory personnel regarding specimens when tularemia is suspected. Suspect cultures should be immediately sent to a reference laboratory with BSL3 capabilities. Extreme caution should be used to avoid exposure within the laboratory by aerosol. Follow-up of workers is needed if laboratory exposures occur (see Section 5E). **Confirmatory laboratory testing must be performed by a Laboratory Response Network (LRN) laboratory such as the Washington State Public Health Laboratories (PHL).**

The diagnosis of tularemia can also be made by rapid laboratory tests, such as direct fluorescent antibody (DFA) and real-time polymerase chain reaction (PCR), or by serology demonstrating a 4-fold change in antibody titers between acute and convalescent sera. Convalescent sera are best drawn at least 4 weeks after illness onset; hence, this method is not useful for clinical management. A single serum specimen can be tested, but results may be inconclusive.

B. Tests Available at the Washington State Public Health Laboratories (PHL)

PHL can culture clinical specimens for *F. tularensis* and can provide identification of *F. tularensis* from pure isolates. PHL can determine the biotype (subspecies) of the isolate using biochemical tests. PHL also performs PCR and DFA. Serologic tests are not performed at PHL but will be forwarded to the CDC for testing (biotyping is not possible from serology). Contact the Office of Communicable Disease Epidemiology for approval prior to collection and shipment of specimens (206-418-5500 or 1-877-539-4344).

Note that PHL requires all clinical specimens have two patient identifiers, a name **and** a second identifier (e.g., date of birth) both on the specimen label and on the submission form. Due to laboratory accreditation standards, specimens will be rejected for testing if not properly identified. Also include specimen source and collection date.

C. Specimen collection

1. Serologic tests

   For antibody testing, 1–2 mL of both acute and convalescent sera are preferred. Submit serum in tightly sealed screw-cap tube with Parafilm M™ or pressure-sensitive labeling tape. Place labeled tubes in individual self-sealing plastic bags. Use sufficient absorbent material to secure contents and contain any leakage during shipment. Ship cold, not frozen, with a completed PHL serology form: http://www.doh.wa.gov/Portals/1/Documents/5230/302-017-SerVirHIV.pdf.

2. PCR

   For PCR testing, submit 1-2mL of whole blood stored in EDTA. Specimen should be collected <5 days after symptom onset and preferably prior to initiation of antibiotic treatment. Ship cold, not frozen with a completed PHL bioterrorism form: http://www.doh.wa.gov/Portals/1/Documents/5230/302-018-BioterrorismSpecimen.pdf

3. *F. tularensis* isolates (culture)

   Tularemia isolates required Category A handling. Prior to sending isolates, clinical laboratories need to call PHL (206-418-5400) to get instructions for accepted packing and shipping. Isolates should be submitted with a completed PHL Reference Bacteriology form: http://www.doh.wa.gov/Portals/1/Documents/5230/302-013-Micro.pdf. Appropriate specimens include swab or scrapping of skin lesions, lymph node aspirate or biopsy, pharyngeal washing, sputum specimen, or gastric aspirate, depending on the form of illness. For details, see: http://www.doh.wa.gov/Portals/1/Documents/5240/SCSI-Francisella-tularensis-V1.pdf

5. ROUTINE CASE INVESTIGATION

Interview the case and others who may be able to provide pertinent information. (For evaluation of a possible bioterrorist event, see Section 6 – Managing Special Situations)

A. Evaluate the Diagnosis

Collect copies of laboratory results. **Confirmatory laboratory testing should be performed by a reference laboratory such as Public Health Laboratories (PHL).** Facilitate submission of laboratory specimens to PHL for confirmation. Proceed with investigation after presumptive or confirmatory laboratory results are available for sporadic cases. During an outbreak event or a potential bioterrorism situation, start any needed investigations before laboratory results are available.

B. Manage the Case

No follow-up is needed. Care for hospitalized patients using standard precautions.

C. Identify Potential Sources of Infection

Review clinical presentation and history to determine appropriate potential exposures (i.e., pneumonia would indicate likely inhalation exposure [use of landscaping or farming tools, dust, bioterrorism]; ulceroglandular tularemia would indicate possible inoculation via insect or animal bite/handling). Investigate possible exposures during the 1–14 days before onset, including a history of:

1. Skinning or eviscerating wild game (especially rabbits or wild rodents);
2. Bites or scratches by wild or domestic animals;
3. Increased biting fly activity in the area and/or fly bites (deer and horse flies are usually active between late spring and early fall);
4. Recent tick bite;
5. Drinking untreated water or exposure to untreated water;
6. Eating inadequately cooked wild game (especially rabbit);
7. Contact or possible contact with dust or other aerosols associated with soil, grain or hay;
8. Work in a laboratory.

D. Identify Contacts/Others Exposed

1. Identify persons who participated with the case in any of the activities listed above and contact them, as well as any acquaintance or household member with similar illness. If any are ill, inform them (or their physician) of possible exposure to tularemia, in order to facilitate proper diagnosis and therapy. (Note: Anyone meeting the probable case definition for tularemia should be reported and investigated in the same manner as a confirmed case.)
2. Identify laboratory workers or health care providers exposed to cultures/isolates and educate them of symptoms of illness to facilitate diagnosis. See Management of Others Exposed (below) for prophylactic antibiotic recommendations.

E. Management of Contacts/Others Exposed

1. Since the infection is not spread person-to-person, no follow-up is necessary for contacts of the case.
2. Laboratory-acquired infections are a significant concern, thus prompt follow-up is required to evaluate laboratory staff for exposure to a culture.
    a. *F. tularensis* is highly infectious when grown in culture and has resulted in laboratory-acquired infections. Assess the nature of exposure for each laboratory worker who handled the specimen at any point it was in the lab, i.e., worked with the culture on an open bench, sniffed a plate, conducted procedures that generate aerosols (such as spills, vortexing, catalase tests, etc.). Exposures can be classified as high risk or low risk (see below). Identify the date the culture was handled and incubation period (range 1-14 days) to evaluate whether the maximum incubation period has already passed or not.
    b. For persons with *high-risk* exposures such as laboratory personnel who worked with a specimen on an open bench or had direct skin contact, recommend doxycycline or ciprofloxacin orally for 14 days. There are special recommendations for certain groups including pregnant women.

    See: Dennis DT, Inglesby TV, Henderson DA, et al. Tularemia as a biological weapon: Medical and public health management. JAMA 2001;285:2763–73.

    c. For persons with *low-risk* exposures or persons previously vaccinated, recommend observation for fever and other signs of illness for the duration of the potential incubation period. Treat with antibiotics if symptoms develop.

F. Environmental Measures

1. If the source of infection appears to be associated with rabbit or rodent hunting, this fact should be publicized in order to encourage proper handling of wild game carcasses. Please give the Office of Communicable Disease Epidemiology (CDE) prior notice of any planned media releases on game-associated tularemia (877-539-4344 or 206-418-5500), so that CDE can notify and coordinate with the Washington Department of Fish and Wildlife.
2. If the suspected source is farm animals, contact CDE which will contact the Washington State Department of Agriculture.

3. If waterborne transmission is suspected from a drinking water source, the water supply will need to be decontaminated. Contact CDE which will contact the DOH Office of Drinking Water. Standard levels of chlorine in municipal water are protective.

6. MANAGING SPECIAL SITUATIONS

A. Bioterrorist Event

F. tularensis has been classified as a "category A" agent (of greatest concern) for bioterrorism because of its very low infectious dose (10–50 organisms), its ability to survive in the environment, the fact that it can be easily disseminated by aerosol, and potential severe illness and death with untreated inhalational tularemia. One should suspect bioterrorist spread of tularemia if there is a cluster of unusual pneumonia cases (atypical patient profile, e.g., young; otherwise healthy individuals affected, severe illness; low response to standard antibiotic treatment) particularly in persons in a building with a common ventilation system. ***If there is any suspicion of potential bioterrorism, call the Office of Communicable Disease Epidemiology immediately (24/7) at 1-877-539-4344 or 206-418-5500.***

In the setting of a biological attack, antibiotic prophylaxis for 14 days post-exposure with ciprofloxacin or doxycycline may be recommended for those with a suspected or known exposure to *F. tularensis*, as determined by public health officials.

7. ROUTINE PREVENTION

A. Immunization recommendations

There is currently no licensed commercial vaccine available against tularemia.

B. Prevention recommendations

1. Hunters, trappers, and food preparers should be instructed to wear gloves when skinning wild game, to keep their hands/gloves away from their eyes, and to thoroughly wash their hands after handling wild game carcasses. Wild game meat should be cooked “well done” (to at least 74°C/165°F). Freezing does not inactivate the organism.
2. Persons should be instructed to drink only treated water when in wilderness areas to avoid bacterial and protozoan diseases that can be transmitted via surface water.
3. Persons should avoid tick and insect bites when in high-risk areas.
   - Wear long pants and a long-sleeved shirt. Tuck your pant legs into socks or boots and shirt into pants. This can help keep ticks on the outside of your clothing where they can be more easily spotted and removed.
   - Wear light colored, tightly woven clothing which will allow the dark tick to be seen more easily. The tight weave makes it harder for the tick to attach itself.
   - Use tick repellent when necessary, and carefully follow instructions on the label. Products containing 20% to 30% DEET, picardin, or IR3535 are very effective in repelling ticks. Take special care when using repellents on children.
   - Check yourself, your children, and pets thoroughly for ticks after risk activities outdoors. Carefully inspect areas around the head, neck and ears. If you find a tick attached to the skin, promptly remove it. Use tweezers to grasp the tick as close to the

skin as possible. With a steady motion, pull the tick straight out. Wash your hands and the bite area, and apply antiseptic to the bite. Do not crush ticks; this could result in direct inoculation of bacteria. For more information, see: http://www.cdc.gov/lyme/removal/index.html.

- Monitor a tick bite for local infection and be alert for early symptoms of tick-borne disease over the next month or so, particularly "flu-like" symptoms or rash. If you develop symptoms, contact your health care provider.

ACKNOWLEDGEMENTS

This document is a revision of the Washington State Guidelines for Notifiable Condition Reporting and Surveillance published in 2002 which were originally based on the Control of Communicable Diseases Manual (CCDM), 17th Edition; James Chin, Ed. APHA 2000. We would like to acknowledge the Oregon Department of Human Services for developing the format and select content of this document.

UPDATES

January 2011: The Legal Reporting Requirements section has been revised to reflect the 2011 Notifiable Conditions Rule revision. Section 4 was updated to reflect current lab submission requirements.

November 2012: The guideline was revised to reflect the new outline format, which combined previous sections 5 (Routine Case Investigation) and 6 (Controlling Further Spread) into a single section 5 (Routine Case Investigation). The laboratory exposure assessment (section 5-E) was expanded.

February 2015: Routine review.

January 2017: PCR added as presumptive laboratory for classification; front page added. Section 2C updated to include current WA findings, Section 4C updated to include submission instructions for whole blood. Front page added.