

Tularemia

Investigative Guidelines

May 2022

REPORT WITHIN 1 WORKING DAY

1. DISEASE REPORTING

1.1 Purpose of Surveillance and Reporting

1. To identify the source of infection of individual case-patients, to determine the risk of transmission from the source, and to stop transmission.
2. To identify others exposed and promote timely prophylaxis or treatment.
3. To identify swiftly and to mitigate any cluster of illness that might result from intentional release of this potential agent of bioterrorism.
4. To identify microbiology laboratorians who may have been exposed through handling of specimens or cultures to ensure prompt recognition and treatment of any resulting illness.
5. To identify potential recurrent sources of transmission of enzootic tularemia to people in Oregon.

1.2 Laboratory and Physician Reporting Requirements

Laboratories and healthcare providers are required to report cases immediately upon diagnosis or identification.

Laboratories must submit isolates to the Oregon State Public Health Laboratory (OSPHL).

1.3 Local Public Health Authority (LPHA) Reporting and Follow-Up Responsibilities

1. Report all confirmed and presumptive cases to the Oregon Public Health Division (OPHD) immediately (971-673-1111).
2. OPHD would also like to hear about suspect cases, and can provide guidance to LPHAs, providers, or laboratories as needed.
3. Begin follow-up investigation immediately. Complete the fields shown in Orpheus. Investigate and conduct follow up for potential exposures at laboratories within your health department's jurisdiction. (See § 6.1.) (If laboratories outside the case jurisdiction are involved, OPHD will notify the relevant LPHAs to advise follow up.)
4. Coordinate with the OSPHL to ship samples and ensure confirmatory Laboratory Response Network (LRN) reference testing (see § 3.4).

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5. The CDC Tularemia Case Investigation form, available at <http://public.health.oregon.gov/DiseasesConditions/DiseasesAZ/Pages/disease.aspx?did=14>, will ordinarily be completed by OPHD. Counties with the time and inclination to complete it and send it to us may certainly do so, and we will be most appreciative.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

Francisella tularensis is a small, non-motile, aerobic, non-spore-forming gram-negative intracellular coccobacillus. It is highly infectious (infectious dose: 10–50 organisms) and can survive for weeks to months on fomites. The organism can survive for years in frozen meat. It can be killed with a solution of 10 parts water to one part fresh household bleach, by 70% ethanol, glutaraldehyde, or formaldehyde, as well as by moist heat (121°C for 15 minutes) or dry heat (160°–170°C for at least 1 hour). Two major subspecies, with different biochemical and epidemiological characteristics, are found in the U.S.: *F. tularensis* subspecies *tularensis* (type A) and *F. tularensis holarctica* (type B). Type A is generally considered to be more virulent than type B (infective dose for type A: 10 bacteria when injected subcutaneously; 25 when inhaled as an aerosol). Both subspecies are found in Oregon, though most cases here have been due to subspecies *holarctica*.

2.2 Description of Illness

To a great extent, the nature of the illness reflects the route of transmission (see below, §2.4), as well as the virulence of the infecting strain. Symptoms could include rapid onset of fever, chills, headache, malaise, dry cough and fatigue. Bacteremia, should it develop, may last for two weeks if untreated; mouth and throat lesions may harbor the organism for up to a month. Illness usually falls into one of the following categories:

1. Ulceroglandular (majority of naturally occurring cases)

Patients present with enlarged, tender, localized lymphadenopathy and a painful papule in the region draining into these nodes. This develops into a slowly progressive, non-healing ulcer (21%–87% of cases in the U.S. [CSTE 2009]).

2. Glandular

Similar to the ulceroglandular form, but without evidence of a cutaneous lesion. The skin lesion may have healed, or is minimal and therefore overlooked (3%–20% of cases in the U.S.).

3. Oculoglandular

Early manifestations include photophobia and excessive lacrimation, progressing to painful, purulent conjunctivitis (usually unilateral) with pre-auricular, sub-mandibular, or cervical lymphadenopathy (0%–5% of cases in the U.S.).

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4. Oropharyngeal

Presents with fever and severe sore throat. Exudative pharyngitis or tonsillitis is seen on physical examination. Cervical, pre-parotid and retro-pharyngeal lymphadenopathy may be present. (0%–12% of cases in the U.S.).

5. Typhoidal

This form of tularemia is difficult to diagnose, as it is not associated with prominent lymphadenopathy. Symptoms are nonspecific and could include high fever, nausea, vomiting, diarrhea, abdominal pain, cough, and pneumonia. (5%–30% of cases in the U.S.).

6. Pneumonic (pulmonary)

Occurs as a primary infection following inhalation of organisms; or secondary to hematogenous spread, primarily from ulceroglandular or typhoidal forms. Certain occupations are at increased risk for primary pneumonic tularemia, including sheep shearers, farmers, landscapers and laboratory workers. The pneumonic form is the most likely presentation from an intentional release of the organism. Pneumonic tularemia resembles pneumonic plague, with symptoms including nonproductive cough, dyspnea, and pleuritic chest pain. Chest X-ray may show patchy infiltrates and hilar adenopathy or may be initially normal. Untreated, pneumonic tularemia has a 30%–60% mortality rate. (7%–20% of cases in the U.S.).

7. Intestinal

A rare form of tularemia. Cases present with intestinal pain, vomiting, and diarrhea. Intestinal tularemia occurs after consumption of contaminated, undercooked meat, or of contaminated water.

2.3 Reservoirs

Tularemia is found in more than 250 species of mammals, birds, reptiles and fish. In the U.S., cottontail rabbits (*Sylvilagus* spp.), are important reservoir hosts for type A strains. A wide variety of mammals, especially rodents (e.g., beavers, voles, muskrats) are associated with type B strains. Biting insects, such as the wood tick *Dermaocentor andersoni* found in the Pacific Northwest, and the deer fly *Chrysops discalis*, can serve as vectors. Domestic cats are at risk of infection due to their predation on small animals and can be a source of human infection. Humans are dead-end hosts

2.4 Sources and Routes of Transmission

Probably no bacterial agent has more diversified modes of transmission than *F. tularensis*. Infection can occur (i) by direct contact with infected animals, infectious animal tissues or fluids; (ii), by arthropod bite; (iii) by ingestion of contaminated water or food; or, (iv) by inhalation of infective aerosols. There is no human-to-human transmission. As noted above, the portal of entry determines the form of illness.

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1. Direct contact

The most common route of natural transmission is contact while skinning or dressing wild game, especially rabbits and rodents. Infected blood or lymph may enter through cuts, abrasions, or possibly even intact skin (leading to ulceroglandular disease); or, by being splashed into the eyes (leading to oculoglandular disease).

Less commonly, transmission may result from the bites or scratches of dogs, cats, carnivorous mammals, or birds of prey that have killed or fed on infected animals.

2. Arthropod Bite

Blood-feeding arthropods such as biting flies and ticks transmit the organism between animals and man. Ticks are important in transmitting *F. tularensis* among rodent or rabbit species, but most of these ticks feed rarely if at all on man. In the Pacific Northwest, the only tick vector of any relevance to human transmission is *Dermacentor andersoni*, the Rocky Mountain wood tick.

3. Waterborne/Foodborne

F. tularensis can be introduced into a stream or pond if an infected animal dies in or near water. Ingestion or contamination of mucosal surfaces with this water can lead to oropharyngeal or typhoidal disease. Eating undercooked, contaminated rabbit or hare meat can result in typhoidal disease.

4. Airborne Transmission

Inhalation of *F. tularensis* can cause either pulmonary or typhoidal disease. If a large number of organisms is inhaled, the infection may be fulminant and rapidly fatal. Infectious aerosols can be generated while handling animal hides, cleaning areas contaminated with dried rodent carcasses (e.g., barns, feed bunks, etc.), moving or winnowing contaminated grain, or by mowing or weed-whacking over infected animal carcasses. Airborne transmission is also the most likely form of transmission in a bioterrorist attack.

Laboratory personnel are at risk of contracting tularemia via the airborne route, as *F. tularensis* is highly infectious when grown in culture. Therefore, laboratory personnel should be alerted when tularemia is suspected. All work with suspect cultures of *F. tularensis* should be done in a certified biological safety cabinet. Contact OSPHL 503-693-4100, for additional information.

2.5 Incubation Period

Ranges from 1–14 days; but usually 3–5 days.

2.6 Period of Communicability

Not directly transmitted from person to person.

2.7 Treatment

Streptomycin or gentamicin for 10–14 days can be used in adults and children. Ciprofloxacin and other fluoroquinolones have also been used. Tetracycline is a useful substitute, but relapses are common after using it.

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See model protocols on our website for recommended treatment in a mass-casualty setting, as well as options for post-exposure prophylaxis:

www.oregon.gov/oha/PH/PREVENTIONWELLNESS/VACCINES/IMMUNIZATION/IMMUNIZATIONPROVIDERRESOURCES/Documents/SOTularemia.pdf

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.1 Confirmed Case Definition

Illness characterized by a clinical presentation of one or more distinct forms:

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

AND

- Culture and identification of *F. tularensis* from clinical or autopsy specimens or isolates by an LRN laboratory,* OR
- Fourfold or greater change in serum antibody titer between acute and convalescent sera to *F. tularensis* antigen. Antibodies usually appear in week 2 of the disease.

*Standard blood cultures are usually negative, and Gram stains of skin lesions, sputum, or lymph node aspirates are rarely informative.

3.2 Presumptive Case Definition

A clinically compatible case

AND

- Elevated serum antibody titer(s) to *F. tularensis* antigen (without documented fourfold or greater change) in a case with no history of tularemia vaccination, OR
- Detection of *F. tularensis* in a clinical or autopsy specimen by direct fluorescent assay, OR
- Detection of *F. tularensis* in a clinical or autopsy specimen by polymerase chain reaction (PCR).

3.3 Services Available at Oregon State Public Health Laboratory (OSPHL)

OSPHL performs confirmatory testing of suspected *F. tularensis* isolates using standard LRN reference procedures, including biochemical identification, DFA, and PCR. In rare circumstances, the OSPHL accepts primary clinical specimens for testing. Consult with the OSPHL if this is needed.

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- Isolates must be accompanied by a completed General Microbiology Test Request Form, available at www.bitly.com/phl-forms.
- Follow all required specimen collection and submission requirements posted on the OSPHL Lab Test Menu:
www.oregon.gov/OHA/PH/LABORATORYSERVICES/Pages/zFrancisellatularensisC.aspx

F. tularensis serology is performed by the CDC using microagglutination. It is unlikely that LPHAs will be directly involved in packing or shipment of tularemia specimens. Consult with ACDP and OSPHL if this testing is needed.

All samples should be classified and shipped as Category A, infectious substances (UN2814).

If you get inquiries about this, feel free to refer questions to the OSPHL (503-693-4100) for consultation.

4. CASE INVESTIGATION

4.1 Identify the Source of the Infection

Investigate possible exposures 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 dogs, cats, birds of prey, or other animals;
3. Increased deer fly activity in the area or fly bites (in eastern Oregon, deer and horse flies are usually active between late spring and early fall);
4. Recent tick bite;
5. Drinking untreated water or eating wild game (especially rabbit);
6. Contact or possible contact with dust or other aerosols associated with livestock or grain farming activity;
7. Contact with postpartum or other body fluids from an infected animal; or
8. Work in a clinical laboratory.

4.2 Identify Other Potentially Exposed Persons (Contacts)

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 (*n.b.* – anyone meeting the presumptive case definition should be reported and investigated in the same manner as a confirmed case). If anyone with an exposure similar to that of the case-patient becomes ill, refer the ill person for medical evaluation. For evaluation and management of laboratory workers' exposures or evaluation of a possible bioterrorist event, see §6.

4.3 Environmental Evaluation

1. If the infection appears to be associated with rabbit or rodent hunting, this fact should be publicized to encourage proper handling of wild game

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carcasses. The Oregon Department of Fish and Wildlife should be given prior notice of any media releases on game-associated tularemia.

2. If the suspected source is a farm animal, contact the OPHD Epi on-call, and we will inform the Oregon Department of Agriculture. If exposure is from a wild animal, we'll check in with the Department of Fisheries and Wildlife.
3. If waterborne transmission is suspected, determine whether it involves a nominally potable water source. Consult with your local environmental health experts or the Oregon Public Health Division Drinking Water Section.

5. CONTROLLING FURTHER SPREAD

5.1 Education

1. Hunters should be instructed to wear gloves when skinning wild game and to keep their hands and gloves away from their eyes. They should wash their hands thoroughly after handling wild game carcasses.
Wild game meat should be cooked "well done" – i.e., to at least 65°C (150°F).
2. People should be instructed to drink only treated water when in the wilderness to avoid bacterial and protozoan diseases that can be transmitted via surface water
3. DEET-based insect repellents can be used to reduce the possibility of bites by deer flies or ticks. Overuse of this repellent on children should be avoided, as excess application can lead to seizures.

5.2 Isolation and School or Day Care Restrictions

Cases with draining lesions should be cared for in accordance with standard precautions. No restrictions are indicated for outpatient management.

5.3 Follow-up of Exposed Persons

Fever watch for 14 days after the exposure or post-exposure prophylaxis is recommended for laboratory personnel with unprotected exposure to *F. tularensis* (e.g., working with specimens outside of containment) and others with possible exposure to *F. tularensis* aerosols; e.g., from an intentional release.

1. During a fever watch, exposed people should monitor their temperature and observe for signs and symptoms consistent with tularemia (e.g., chills, headache or body aches) for 14 days after their last exposure. (See the *Health Assessment Form for Tularemia Exposure* <http://bit.ly/tularemiahealthform> as a medical monitoring tool.) Instruct exposed persons to seek medical attention immediately should they develop a fever (a single oral temperature above 101°F or 38.3°C) during this time.
2. Post-exposure prophylaxis model protocols can be found at www.oregon.gov/oha/PH/PREVENTIONWELLNESS/VACCINES/IMMUNIZATION/IMMUNIZATIONPROVIDERRESOURCES/Documents/SOTularemia.pdf

Also, see §6 for managing exposures to laboratory workers and bioterrorism events.

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5.4 Protection of Contacts

Not necessary.

5.5 Environmental Measures

Generally, none necessary. In some cases, improvements to drinking water supplies may be warranted, or, perhaps, vector control in the case of a bunny invasion.

6. MANAGING SPECIAL SITUATIONS

6.1 Laboratory Worker Exposure

Immediately contact all laboratories that processed the specimen, as they may not be aware of the final isolate identification. Ask laboratory managers to determine which laboratory personnel had contact with the specimen, and encourage them to contact the OSPHL (503-693-4100) to coordinate follow-up. If a laboratory worker has been exposed to *Francisella tularensis*, occupational health personnel should be notified immediately. In consultation with OPHD, follow up with the laboratory and exposed workers to discuss post-exposure management options; depending on the type and extent of the exposure, these include a fever watch and possibly post-exposure prophylaxis. See §5.3 for instructions for how to conduct a fever watch. There are no established criteria for determining whether a given worker should be managed by a fever watch or with prophylaxis, but factors to consider include: (1) the extent of the exposure (workers who sniff the cultured plate are at greater risk than those who worked with the organism on the bench); (2) the incubation period, which may have passed by the time the specimen is identified as *Francisella*, making the question moot; and (3) the level of concern of the laboratory worker. OPHD epidemiologists should be consulted to help in this determination.

6.2 Bioterrorism Event

F. tularensis has been classified as a "category A" agent (of greatest concern) for bioterrorism because of its very low infectious dose, its ability to survive in the environment, the fact that it can be easily disseminated by aerosol, and that untreated inhalational tularemia has the capacity to cause severe illness and death. One should suspect intentional spread of tularemia if there is a cluster of unusual pneumonia in persons who share a common exposure (e.g., a building with a common ventilation system). If a cluster of presumptive or confirmed pulmonary tularemia is recognized, people who have experienced the same exposure should be identified, given post-exposure prophylaxis, and instructed about how to do a fever watch as outlined in §5.3.

Call OPHD at 970-673-1111 *immediately, day or night* if you suspect an intentional exposure.

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UPDATE LOG

- May 2022. Updated laboratory information. Minor edits for clarity. (Cavanaugh, Humphrey-King, Leman, Nickla)
- March 2019: Updated case definition and laboratory information. Checked and updated links. Minor edits for clarity (Leman, Humphrey-King, Nickla)
- July 2014. Edited and clarified “Local Health Department Responsibilities” (Section 1.3). Added information about relative frequency of various clinical presentations in Section 2.2. Updated “Laboratory Services” section (3.4). Minor edits for clarity throughout. Attached health assessment form. (Watts, Leman)
- September 2013. Updated language, reference to case report form, and standing orders. Revised Sections 5C, 6A, and 6B to clarify response actions. (T. Watts)
- September 2010. Updated language, added reference to CDC form, and added medical monitoring form and guidance for exposed laboratory workers. (B. Progulske)
2002. Original version (K. Hedberg)