

Tularemia occurs in North America, Europe, the former Soviet Union, China, and Japan. In the United States, it occurs year round; incidence may be higher in adults in early winter due to contact with rabbits during hunting seasons^{1,7}. In children, it is more common during the summer when ticks and flies are abundant. Accidental transmission in laboratory settings has occurred^{1,3,4,5}.

In Arizona, tularemia circulates naturally among rabbits and rodents and is usually found in areas above 3,000 feet. Past Arizona cases have been related to exposure to a rabbit or rabbit carcass, a dog that had rabbit carcass exposure, skinning an elk, and possibly insect bites.¹¹

A. Agent:

Francisella tularensis is a gram negative bacterium^{1,4,5,6,7}.

B. Clinical Description:

Clinical diagnosis is supported by evidence or history of a tick or deerfly bite, exposure to tissues of a mammalian host of *Francisella tularensis*, or exposure to potentially contaminated water^{1,4,5,6,7}. Symptoms could include sudden fever, chills, headaches, diarrhea, muscle aches, joint pain, dry cough, and progressive weakness^{1,4,5,6,7}. Pneumonia, chest pain, bloody sputum and trouble breathing may develop^{1,4,5,6,7}. Without treatment, infection could progress to respiratory failure, shock, and death. The symptoms are dependent upon the site of infection and/or route of transmission^{1,4,5,6,7}.

An illness characterized by several distinct forms, including^{1,4,5,6,7}:

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

Differential Diagnosis:

Plague

C. Reservoirs:

Type A infections may be acquired from rabbits or ticks^{1,7,8}. Type B infections are often associated with other hosts including hares and rodents^{1,7,8}. Domestic mammals may also be a reservoir. Ticks, mosquitoes, and flies may also play a role in the transmission of disease^{1,4,5,6,7}.

D. Mode of Transmission:

Through the bite of certain arthropods; by inoculation of skin, conjunctival sac, or oropharyngeal mucosa with contaminated water, blood, or tissue while handling carcasses of infected animals; by handling or ingesting insufficiently cooked meat of infected animal hosts; by drinking contaminated water; by inhalation of dust from contaminated soil, grain, or hay; rarely, from the bite of a coyote, squirrel, skunk, hog, cat, or dog whose mouth presumably was

contaminated from eating an infected animal; and from contaminated pelts and paws of animals^{1,4,5,6,7}. Laboratory infections occur and frequently present as primary pneumonia or typhoidal tularemia^{1,4,5,6,7}.

E. Incubation Period:

Ranges from 1–14 days; average 3–5 days^{1,4,5,6,7}.

F. Period of Communicability:

Tularemia is not directly transmitted from person-to-person. However, the drainage from tularemia lesions is potentially infectious. Flies can remain infective for 14 days and ticks can remain infectious throughout their lifetime^{1,4,5,6,7}.

G. Susceptibility and Resistance:

All ages are susceptible and long-term immunity follows infection; however, reinfection has been reported^{1,4,5,6,7}.

H. Treatment:

Antibiotics used to treat tularemia include streptomycin, gentamicin, doxycycline, and ciprofloxacin^{1,4,5,6,7}. Treatment usually lasts 10–21 days depending on the stage of illness and the medication used. Although symptoms may last for several weeks, most patients completely recover^{1,4,5,6,7}.

Disease Management

I. Clinical Case Definition¹⁰:

An illness characterized by several distinct forms, including the following^{1,4,5,6,7}:

Ulceroglandular - This is the most common form of tularemia and usually occurs following a tick or deer fly bite or after handling an infected animal. A cutaneous ulcer appears at the site where the organism entered the body, accompanied by regional lymphadenopathy.

Glandular - Similar to ulceroglandular tularemia; regional lymphadenopathy without an ulcer. Also generally acquired through the bite of an infected tick or deer fly or from handling sick or dead animals.

Oculoglandular - This form occurs when the bacteria enter through the eye when a person is butchering an infected animal and touches his/her eyes. Symptoms include conjunctivitis with preauricular lymphadenopathy.

Oropharyngeal - This form results from eating or drinking contaminated food or water. Patients may have sore throat, mouth ulcers, stomatitis or pharyngitis or tonsillitis and cervical lymphadenopathy.

Pneumonic - This is the most serious form of tularemia. Symptoms primarily involve those associated with pleuropulmonary disease, such as cough, chest pain, and difficulty breathing. This form results from breathing dusts or aerosols containing the organism. It can also occur when other forms of tularemia (ulceroglandular) are left untreated and the bacteria spread through the bloodstream to the lungs.

Typhoidal – This form is most often associated with febrile illness without early localizing signs of symptoms indicative of an exposure route.

J. Laboratory Criteria for Diagnosis¹⁰:

Confirmatory Testing

- Isolation of *F. tularensis* in a clinical specimen, **OR**
- Fourfold or greater change in antibody titer to *F. tularensis* antigen between acute and convalescent serum specimens obtained ≥ 2 weeks apart

Supportive Testing

- Detection of *F. tularensis* in a clinical or autopsy specimen by a polymerase chain reaction (PCR), **OR**
- 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

Case Classification¹⁰

Confirmed	A clinically compatible case with confirmatory laboratory results.
Probable	A clinically compatible case with supportive laboratory results.

Criteria to Distinguish a New Case from an Existing Case¹⁰

Serial or subsequent cases of tularemia experienced by one individual should only be counted if there is an additional epidemiologically compatible exposure and new onset of symptoms. Because the duration of antibodies to *F. tularensis* is not known, mere presence of antibodies without a clinically-compatible illness AND an epidemiologically compatible exposure within 12 months of onset may not indicate a new infection, especially among persons who live in endemic areas¹⁰.

K. Classification of Import Status:

N/A

L. Laboratory Testing:

Submission of isolates to the Arizona State Public Health Laboratory (ASPHL) is required to confirm or rule out *F. tularensis*. Serological testing is available at Centers for Disease Control and Prevention (CDC) for difficult or unusual cases. Specimens sent to CDC must have prior authorization from the ADHS Office of Infectious Disease Services (OIDS)¹⁰.

IMPORTANT: Call ADHS-OIDS at (602)-364-3676 or email ybzd@azdhs.gov before sending specimens.

The [Arizona State Lab Submission Form](#) must be completed and submitted with the specimen for all testing at the ASPHL. Consider collecting an additional specimen to send concurrently to Translational Genomics Research Institute (TGen) for genetic analysis. (Sending specimens from ASPHL after identification of a select agent is very difficult.)

Collection^{1,4,5,6,7}:

- Specimens suspected of containing *Francisella tularensis* should be collected and submitted with extreme caution. Tularemia is currently listed as the third most common reported laboratory-associated bacterial infection^{1,2,3,4,5,6,7,9}.
- Clinical samples that may be submitted to the laboratory for isolation of *F. tularensis* include ulcer scrapings/swab, lymph node biopsies, tissue biopsy, bronchial/tracheal washings, sputum, pharyngeal washes, pleural fluid, and aspirates.

- Organisms are invariably present in significant numbers in fluid from obvious local lesions. Skin around the lesion should be cleansed with alcohol and allowed to dry before opening the papule and exposing the fluid.

TEST	SPECIMEN TYPE	TRANSPORT	AVAILABILITY
PCR	Clinical: Whole blood (200 µl minimum), isolate (liquid or plated)		ASPHL
	Environmental: Powder, environmental swab		
Culture	Clinical: Blood, tissue biopsy, aspirates, ulcer scrap/swab	Any media containing cysteine supplementation is acceptable, cysteine glucose blood agar is preferred	ASPHL
	Environmental: Water, soil (mud), air, plants (green/wood), food/drink, paper, powder, environmental swabs, containers, animal tissues, blood, bone, hair, abscess, vectors (mosquito, fleas, ticks)		
DFA	Isolate (liquid or plated), ulcer swab, aspirate, tissues, bronchial/tracheal wash, pleural fluid, sputum, abscess material, bone marrow scrapings		CDC

M. Assessing Laboratory Results:

F. tularensis requires an enriched medium for growth. The historic medium of choice is cysteine glucose blood agar; however any media containing cystine supplementation is acceptable. Cultures are observed for 5–7 days before reporting as negative. Cultures are observed for typical colonial morphology. Suspect colonies are checked microscopically by Gram staining, where they appear as faintly staining gram-negative coccobacilli. Confirmation of the isolate is determined by Direct Fluorescent Antibody, Real-Time PCR and/or serological agglutination testing. All positive cultures are reported to the submitting agency and ADHS. *F. tularensis* isolates are forwarded to CDC in Atlanta, GA by special request.

N. Outbreak Definition:

There are no formal outbreak definitions; however, the investigator may consider the possibility of an outbreak when there is an unusual clustering of cases in time and/or space.

Investigation Guidelines

O. Time Frame:

Report all confirmed, probable, and suspect cases to ADHS OIDS Epidemiology by telephone or through MEDSIS within 24 hours. Investigational activities should begin immediately. Suspected outbreaks should be entered into the Outbreak Module in MEDSIS within 24 of receipt of report.

P. Forms:

- [CDC Tularemia Case Report Form](#)

Q. Investigation Steps:

▪ Confirm Diagnosis

- i. Identify any symptoms of tularemia, record date of onset.
- ii. Collect demographic data:
 - Birth date, county, sex, race/ethnicity, travel history, occupation.
- iii. Collect medical information:
 - Date/location first seen by healthcare provider, radiographic and laboratory findings, initial diagnosis, treatment given (if any), outcomes or complications.

Interview the case or proxy to determine source and risk factors; focus on a 2 week incubation period prior to illness onset. Travel data should be submitted in MEDSIS by filling out the Travel Table.

- Patient's occupation; note specific job duties, industry type, and location. At-risk occupations could include outdoor occupations, lawn mowing or landscaping, hunting, contact with sick or dead animals, or laboratory workers.
- Exposure to ticks, deerflies, or other biting flies.
- Contact or ingestion of undercooked meat.
- Contact or ingestion of soil or untreated water.
- Pets in home, noting illness in pets or the bringing home of dead animals.
- Note any travel outside of the county during the incubation period.
- If no other risk factors are identified, start to consider intentional contamination or bioterrorism situations.

▪ Contact Investigation

- i. Any person in contact with the source of infection is defined as a contact. This may include physical contact with an infected animal or a contaminated product, ingestion of contaminated food, or inhalation.
- ii. Examine all potential exposures based on the possible source and potential modes of transmission to define who may be at-risk.
- iii. Identify those who participated in at-risk activities and contact them to identify if they are experiencing any symptoms.
- iv. Investigate the clinical laboratory that handled the *F. tularensis* isolates to ensure standard procedures were in place to minimize the risk of transmission.

▪ Isolation, Work and Daycare Restrictions

- i. Isolation: Not recommended. Contact precautions should be taken for open lesions and universal precautions during patient care.
- ii. Concurrent disinfection of discharges from ulcers, lymph nodes, or conjunctival sacs.

▪ Case Management

Report on any changes in patient status (i.e., discharge, death).

▪ Contact Management

- i. Symptomatic contacts (as determined by risk of exposure to source) should be strongly urged to contact their physician for a medical evaluation and are followed-up as suspect cases. Ensure that the physician is aware of possible exposure, in order to facilitate proper diagnosis and therapy.
- ii. Contact Monitoring:

- Asymptomatic persons who were potentially exposed should continue to monitor themselves for any fever illness throughout a 14- day period following exposure.
 - Contacts developing fever or flu-like illness within 14 days of presumed exposure should be referred to their medical provider for evaluation.
- iii. Antimicrobial prophylaxis is usually not recommended, except in certain situations in the laboratory or where there is aerosolized exposure to significant quantities of agent.

▪ **Environmental Measures**

- i. An environmental investigation around the area where exposure likely occurred can be conducted by the local jurisdiction.
- ii. Laboratory personnel should be alerted when tularemia is suspected or confirmed^{2,3,9}.
 - Routine diagnostic procedures can be performed in biosafety level 2 conditions, with examination of cultures done in a biological safety cabinet.
 - Manipulation of cultures and other procedures that might produce aerosols or should be conducted under biosafety level 3 conditions.
 - The local public health jurisdiction should be notified if laboratory exposures to *F. tularensis* occur.
- iii. Bodies of patients who die of tularemia should be handled using standard precautions.
 - Autopsy procedures likely to produce aerosols or droplets should be avoided.
- iv. Clothing or linens contaminated with body fluids of patients with tularemia should be disinfected per standard hospital procedure.
- v. *Francisella tularensis* can remain viable for weeks in a cold, moist environment including water and soil.

▪ **Education**

As opportunities allow, the following general messages should be distributed:

- Inspect your yard before mowing to avoid mowing over sick or dead animals.
- Consider using dust masks when mowing to reduce your risk of inhaling the bacteria.
- Use insect repellent containing 20% to 30% DEET.
- Wear long pants, long sleeves, and long socks to keep tick and deer flies off your skin.
- Remove attached ticks promptly with fine-tipped tweezers.
- Wash your hands often, using soap and warm water, especially after handling animal carcasses.
- Hunters should be instructed to wear gloves when skinning wild game and to keep their hands/gloves away from their eyes. They should thoroughly wash their hands after handling wild game carcasses.
- Wild game meat should be cooked to at least 150°F (65°C).
- Drink only treated water when camping and/or hiking.
- Note any change in the behavior of your pets (especially rodents, rabbits, and hares) or livestock, and consult a veterinarian if they develop unusual symptoms.

R. Outbreak Guidelines:

Notify ADHS Vector-borne and Zoonotic Disease Program immediately!

S. Special Situations:

Intentional Contamination^{2,4,5,7,9}:

F. tularensis is a potential bioterrorism weapon^{2,4,5,7,9}. If the case has no remarkable travel history and is not employed in an occupation that is prone to exposure, then a bioterrorist

Special Situations

event should be considered^{2,4,5,7,9}. A weapon using airborne *F. tularensis* would likely result 3–5 days later in an outbreak of acute, undifferentiated febrile illness with incipient pneumonia, pleuritis, and hilar lymphadenopathy^{2,4,5,7,9}. Due to the possible delay of laboratory confirmation of agent, specific epidemiological, clinical, and microbiological findings that suggest the possibility of an intentional release of *F. tularensis* should result in the immediate issue of a health alert^{2,4,5,7,9}.

- If suspected:
 - Notify the Program Manager/Supervisor, Office Chief, Bureau Chief, Preparedness manager (and ADHS epidemiologists if local jurisdiction) immediately.
 - Implement Chain of Custody procedures for all samples collected, as they will be considered evidence in a criminal investigation.
 - Work to define population at risk which is essential to guide response activities. Public health authorities will play the lead role in this effort, but must consult with law enforcement, emergency response and other professionals in the process. The definition may have to be re-evaluated and redefined at various steps in the investigation and response.
 - Once the mechanism and scope of delivery has been defined, identify symptomatic and asymptomatic individuals among the exposed and recommend treatment and/or chemoprophylaxis.
 - Establish and maintain a detailed line listing of all cases and contacts with accurate identifying and locating information.
- Diagnosis: Physicians who suspect inhalational tularemia should promptly collect specimens of respiratory secretions and blood and alert the laboratory to the need for special diagnostic and safety procedures.
- Vaccination: Not generally available in the United States, with the exception of laboratory workers. Not useful in management of ill patients.
- Treatment:
 - In a mass casualty setting, doxycycline and ciprofloxacin, administered orally, are the preferred choices for treatment of both adults and children.
 - Drug-resistant organisms might be used as a weapon, conduct antimicrobial susceptibility testing quickly, and alter treatments as needed.
 - Antibiotics for treating patients infected with tularemia in a bioterrorist event are included in the national pharmaceutical stockpile maintained by CDC, as are ventilators and other emergency equipment.
- Post-exposure prophylaxis (PEP):
 - If an attack is discovered before individuals become ill, exposed persons should receive PEP of oral doxycycline or ciprofloxacin for 14 days.
 - If an attack is discovered only after individuals become ill, persons not ill but who were potentially exposed should begin a fever watch. Those who develop an otherwise unexplained fever or flu-like illness within 14 days of presumed exposure should begin treatment as outlined above.
 - PEP of close contacts of tularemia patients is not recommended because person-to-person transmission is not known to occur.
- Environmental decontamination:
 - Information is not available about survivability of an intentionally released aerosol form of *F. tularensis*, but a short half-life is predicted due to desiccation, solar radiation, oxidation, and other environmental factors.
 - It is considered a very limited risk from secondary dispersal.

- Following an urban release, the risk to humans of acquiring tularemia from infected animals or arthropods is likely small and can be reduced by educating the public to avoid sick or dead animals and to take precautions to protect against biting arthropods.

Laboratory Exposure:

F. tularensis is highly infectious when grown in culture, and laboratory-acquired infections have been documented. The isolation of *F. tularensis* from clinical specimens, especially if unanticipated, can generate concern among laboratory workers about possible exposure^{2,3,9}.

- **Fever watch:** Workers monitor their temperature with instructions to seek immediate treatment for tularemia if they develop a fever (usually defined as a single oral temperature above 101°F or 38.5°C)^{2,3,9}.
- **Antimicrobial prophylaxis:** Doxycycline (100 mg orally BID X 14 days) is generally recommended for prophylaxis in adults. Ciprofloxacin (500 mg orally BID) is not FDA-approved for prophylaxis of tularemia but has demonstrated efficacy in various studies, and may be an alternative for patients unable to take doxycycline^{2,3,9}.
- There are no set criteria for determining who should be managed by fever watch and who would benefit from immediate prophylaxis, but factors to consider when making this decision include^{2,3,9}:
 - Nature of exposure - workers who report sniffing a culture plate or conducting procedures that generate aerosols are probably at greater risk than those who simply worked with the organism on the bench.
 - Incubation period - incubation period for tularemia is 3–5 days (range 1–14 days). Much of this period may have passed by the time of identification, in which case, the remaining risk of infection is low.
 - Level of concern - some laboratory workers may be very anxious regarding their risk of infection, while others may be more concerned about taking medications unnecessarily.

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