Virginia Department of Health
Tularemia: Guidance for Healthcare Providers
Key Medical and Public Health Interventions after Identification of a Suspected Case

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1. Epidemiology

Tularemia is a zoonotic bacterial disease caused by the bacterium *Francisella tularensis*. *F. tularensis* is designated as a Category A bioterrorism agent (i.e., one can be easily disseminated or transmitted with a higher rate of mortality than a Category B agent). *F. tularensis* is also designated as a select agent, which means that it could be developed as a bioterrorism agent and possession, use or transfer of the organism requires registration with the Centers for Disease Control and Prevention (CDC) through the Federal Select Agent Program.

There are three subspecies of *F. tularensis* with differing virulence that cause disease among humans: *F. tularensis* ssp. *tularensis* (type A), ssp. *holartica* (type B) and ssp. *novicida*. The most virulent form, *Francisella tularensis* ssp. *tularensis,* is found only in North America. The case-fatality rate of type A infection before the introduction of appropriate antimicrobials was up to 30%. If appropriate antibiotic therapy is provided, the case-fatality rate is relatively low. Two distinct groups of Type A have been identified: Group A. 1 (found in the central United States and California) and Group A. II (found in the western United States at higher elevations). *F. tularensis* ssp. *holartica* is referred to as Type B. This form of *F. tularensis* is more prevalent and is less virulent than Type A. Patients with Type B infection recover, even without treatment, with few fatalities. *F. tularensis* ssp. *novicida* is the rarest form and is associated with the mildest presentation. It is typically associated with waterborne-acquired infections.

F. tularensis is widespread throughout the Northern hemisphere. In the United States, naturally-occurring infections have been reported from all states except Hawaii. However, it is most common in the south central United States, the Pacific Northwest, and parts of Massachusetts.

Transmission of *F. tularensis* occurs primarily via tick or deer fly bites or handling infected animals. In the United States., several different types of ticks (e.g., dog tick, wood tick and lone star tick) can transmit *F. tularensis* to humans. Deer flies have been shown to transmit tularemia in the western

part of the country. Infections from tick and deer fly bites usually take the form of ulceroglandular or glandular tularemia. *F. tularensis* can be transmitted to humans via inoculation of the skin, conjunctival sac, or oropharyngeal mucosa with contaminated water, blood or tissue when handling infected animal carcasses. In particular, this can occur when hunting or skinning infected rabbits, muskrats, prairie dogs and other rodents, or performing necropsies. Other animals are susceptible to tularemia, including domestic cats and pet hamsters. Infection from handling animals can result in glandular, ulceroglandular and oculoglandular tularemia. Oropharyngeal tularemia can result from eating under-cooked meat of infected animals.

Other means by which humans might be exposed to *F. tularensis* include inhaling dust or aerosols contaminated with the bacteria. This type of exposure would most likely occur during farming or landscaping activities, especially when machinery, such as mowers or tractors, runs over infected animals or carcasses. This type of exposure is rare, but can lead to pneumonic tularemia. Water can also become contaminated with *F. tularensis* via exposure to infected animals. Humans who drink contaminated water that has not been treated might contract oropharyngeal tularemia. *F. tularensis* is highly infectious when grown in culture and laboratory-acquired infections have been documented.

Approximately 230 cases in the United States and 2 cases in Virginia are reported annually. Tularemia is more common during May–September. Males are affected more frequently than females, and the disease is more common among children than adults.

2. Clinical Manifestations

The incubation period for tularemia is usually from 3–5 days. The range is 1–14 days. Symptom onset is abrupt and resembles influenza, with high fever (as high as 104°F), chills, fatigue, generalized body aches, headache and nausea.

Tularemia is characterized by several distinct forms:

- Ulceroglandular: occurs following a tick or deer fly bite or after handling of an infected animal; cutaneous ulcer at site where the organism entered the body with regional lymphadenopathy; most common syndrome
- Glandular: generally acquired through the bite of an infected tick or deer fly or from handling sick or dead animals; regional lymphadenopathy with no ulcer; common syndrome
- Oculoglandular: occurs when the bacteria enter through the eye and might occur during butchering of an infected animal and touching of eye occurs; conjunctivitis with preauricular lymphadenopathy; less common syndrome
- Oropharyngeal: occurs from eating or drinking contaminated food or water; stomatitis or pharyngitis or tonsillitis and cervical lymphadenopathy; less common syndrome
- Intestinal: intestinal pain, vomiting and diarrhea; uncommon syndrome
- Typhoidal: febrile illness without early localizing signs and symptoms; less common syndrome
- Pneumonic: most serious form, occurring after breathing in dusts or aerosols containing the organism, including inhalation after intentional release of the organism or when other forms of the disease are left untreated and the bacteria spread through the bloodstream to the lungs

3. Laboratory Testing and Diagnosis

Notification when Tularemia is Suspected
If tularemia is suspected, the healthcare provider should immediately report the case to the local health department per Virginia's disease reporting regulations. The local health department will discuss options for public health testing. If VDH approves public health testing, specimens may be sent to the Division of Consolidated Laboratory Services (DCLS). The health department will facilitate notification and shipment to DCLS. Specimens potentially containing *F. tularensis* should never be shipped to DCLS without prior approval.

Laboratory Biosafety
Laboratory personnel **must** be alerted if tularemia is suspected so that they can take appropriate precautions. Diagnostic procedures with clinical materials should be performed using biosafety level (BSL)-2 precautions. All work with suspect cultures of *F. tularensis* should be done in a biological safety cabinet. Manipulation of isolates and other procedures that might produce aerosols or droplets (e.g., grinding, centrifuging, vigorous shaking, animal studies) should be conducted using BSL-3 precautions. Identification using commercial identification systems is not recommended because of the potential for generating aerosols and the high likelihood of misidentification. Because of the highly infectious nature of *F. tularensis*, consultation with DCLS is strongly recommended. The DCLS Emergency Officer can be reached 24/7 at 804-335-4617.

Diagnostic Testing
Tularemia is diagnosed by identifying *F. tularensis* by culture. Commercial identification systems are not recommended because of biosafety reasons (see above) and because the bacteria might be misidentified as other bacteria (e.g., *Haemophilus influenzae* (satellite or XV positive) and *Aggregatibacter* spp. (includes previous *Actinobacillus* spp.). Specimens to culture depend on the clinical form of tularemia, but could include blood, swabs of skin lesions or wounds, lymph node aspirates, pharyngeal swabs, sputum specimens, or gastric washings. Note that blood cultures are often negative.

A presumptive diagnosis of tularemia can be made using direct fluorescent antibody testing, immunohistochemical staining, or PCR. In addition, serologic testing to detect a 4-fold change in antibody titers between acute and convalescent specimens (collected >14 days after the acute specimen) can be used for diagnosis. Because serologic testing is available at multiple commercial laboratories, this type of testing is not routinely conducted by public health laboratories.

Sample Collection
Instructions for testing at DCLS or CDC are shown in Table 1. Because of the highly infectious nature of this organism, consultation with DCLS about specimen collection and handling is strongly recommended. The DCLS Emergency Officer can be reached 24 /7 at 804-335-4617.

Table 1. Sample Collection Instructions for Testing Suspected Tularemia at DCLS/CDC*

Test and Turnaround Time	Acceptable Samples	Amount	Instructions
Florescent Antibody (FA) test (performed at CDC) Estimated turnaround time: 15 business days upon specimen receipt OR Polymerase Chain Reaction (PCR) test (performed at DCLS) Estimated turnaround time: < 1 business days upon specimen receipt	Tissue: Biopsy of ulcer or wound; autopsy tissue	1 gram	Place in sterile container; moisten with sterile broth or saline. Ship to lab immediately at room temperature; if more than 2 hours, freeze and ship on dry ice.
	Lymph node aspirate	1-2 cc	Ship to lab immediately; if more than 2 hours, refrigerate.
Serology (only performed at CDC) Estimated turnaround time: 10 business days upon specimen receipt	Serum	Acute and convalescent sera (collected >14 days apart)	Collect in red top or tiger top tube. Remove serum and place in sterile tube, then store frozen.
Bacterial isolate from culture Estimated turnaround time: < 1 business day upon specimen receipt for presumptive identification via PCR and 2-3 business days upon specimen receipt for confirmation.	Blood, skin, ulcers, lymph node drainage, gastric washings or respiratory tract secretions		Ship suspicious isolates (tiny Gram-negative coccobacilli) on slant (preferred) or agar plate at room temperature

*Adapted from American Society for Microbiology's Sentinel Level Clinical Laboratory Guidelines for Suspected Agents of Bioterrorism and Emerging Infectious Diseases: *Francisella tularensis* (2016). If tularemia is suspected, notify the local health department immediately to discuss the case and laboratory testing. If VDH approves testing, specimens may be sent to the Division of Consolidated Laboratory Services (DCLS) with the DCLS Clinical Microbiology/ Virology Request Form; include the name of the test on the form. For questions about specimen collection, the DCLS Emergency Officer can be reached 24/7 at 804-335-4617.

Case Definitions used by Public Health

The current CDC case definition for tularemia is available at https://wwwn.cdc.gov/nndss/conditions/tularemia/. Note that a case definition is set of uniform criteria used to define a disease for public health surveillance. Case definitions enable public health to classify and count cases consistently across reporting jurisdictions, and should not be used by healthcare providers to determine how to meet an individual patient's health needs.

4. Treatment

Recommendations for tularemia treatment are summarized in Table 2. Those who develop an unexplained fever or flu-like illness within 14 days of presumed exposure should begin standard treatment. Antibiotics used to treat tularemia include streptomycin, gentamicin, doxycycline and ciprofloxacin. Treatment usually lasts 10 to 21 days, depending on the stage of illness and the medication used. Although symptoms might last for several weeks, most patients completely recover.

Table 2. Tularemia treatment recommendations*

Adults (excluding pregnant women) Preferred Choices: • Streptomycin, 1 g IM twice daily or • Gentamicin, 5mg/kg IM or IV once daily† Alternative Choices: • Doxycycline, 100mg IV twice daily or • Chloramphenicol, 15 mg/kg IV 4 times daily† or • Ciprofloxacin, 400 mg IV twice daily†
Pregnant Women Preferred Choices: • Gentamicin, 5 mg/kg IM or IV once daily† or • Streptomycin, 1 g IM twice daily Alternative Choices: • Doxycycline, 100 mg IV twice daily or • Ciprofloxacin, 400 mg IV twice daily†
Children Preferred Choices: • Streptomycin, 15 mg/kg IM twice daily (should not exceed 2 g/d) or • Gentamicin, 2.5 mg/kg IM or IV 3 times daily† Alternative Choices: • Doxycycline, o If weight ≥ 45 kg, 100 mg IV twice daily o If weight < 45 kg, give 2.2 mg/kg IV twice daily or • Chloramphenicol, 15 mg/kg IV 4 times daily† or • Ciprofloxacin, 15 mg/kg IV twice daily†±

Adapted from: Dennis DT, Inglesby TV, Henderson DA, et al. Consensus Statement: Tularemia as a Biological Weapon: Medical and Public Health Management. JAMA. 2001;285(21): 2763-2773. Treatment recommendations in a mass casualty event are not shown. For additional information on dosing, please consult with the package inserts.

*Treatment with streptomycin, gentamicin or ciprofloxacin should be continued for 10 days; treatment with doxycycline or chloramphenicol should be continued for 14–21 days. Persons beginning treatment with intramuscular (IM) or intravenous (IV) doxycycline, ciprofloxacin, or chloramphenicol can switch to oral antibiotic administration when clinically indicated.

†Not a US Food and Drug Administration-approved use.

±Ciprofloxacin dosage should not exceed 1 g/d in children.

5. Postexposure Prophylaxis

Recommendations for tularemia postexposure prophylaxis (PEP) are summarized in Table 3. If a known biological attack using *F. tularensis* has occurred and exposed persons are identified during the incubation period (i.e., before they become ill), then individuals should receive prophylactic treatment with 14 days of oral doxycycline or ciprofloxacin as outlined in Table 3. If an attack is discovered only after some individuals become ill, persons potentially exposed should begin surveillance for a fever. Postexposure prophylactic treatment of close contacts of tularemia patients is not recommended because person-to-person transmission is not known to occur naturally. Laboratory personnel potentially exposed to the agent should be assessed on a case-by-case basis. For high-risk exposures in the laboratory, including needle stick, spill, centrifuge accident, sniffing a culture plate, or conducting procedures that generate aerosols, prophylaxis should be given. For these and other exposures, the local health department should be consulted to help assess the risk and conduct surveillance (in conjunction with DCLS).

Table 3. Postexposure prophylaxis (PEP) and monitoring recommendations for tularemia exposures* (*Regimens may also be used for treatment in severe circumstances, such as mass casualty setting, when standard IM or IV treatment is impractical or unavailable*)

Adults (excluding pregnant women) Preferred Choices: Doxycycline, 100 mg orally twice daily Ciprofloxacin, 500 mg orally twice daily†
Pregnant Women Preferred Choices: Ciprofloxacin, 500 mg orally twice daily Doxycycline, 100 mg orally twice daily
Children Preferred Choices: Doxycycline, • If weight ≥ 45 kg, give 100 mg orally twice daily • If weight < 45 kg, give 2.2 mg/kg orally twice daily Ciprofloxacin, 15 mg/kg orally twice daily†±

Adapted from: Dennis DT, Inglesby TV, Henderson DA, et al. Consensus Statement: Tularemia as a Biological Weapon: Medical and Public Health Management. JAMA. 2001;285(21): 2763-2773. For additional information on dosing, please consult with the package inserts.

*One antibiotic, appropriate for patient age, should be chosen from among alternatives. The duration of all recommended therapies for prophylaxis and treatment in severe circumstances (e.g., mass casualty event when IM or IV treatment is not available) is 14 days.

†Not a US Food and Drug Administration-approved use.

±Ciprofloxacin dosage should not exceed 1 g/d in children.

6. Vaccination

A vaccine is not generally available in the United States.

7. Infection Control

Standard Precautions should be used for managing patients and handling clinical materials. People who have tularemia do not need to be isolated. Confirmed spread of the bacteria from person to person has been documented only twice (once through organ transplant and once through accidental cutaneous inoculation during autopsy).

8. Decontamination

Persons with direct exposure to powder or liquid aerosols containing *F. tularensis* should wash body surfaces with soapy water. Standard levels of chlorine in water should protect against waterborne infection. Clothing or linens contaminated with body fluids of patients with tularemia should be disinfected per standard hospital procedure.

Following an intentional release of *F. tularensis*, the risk to humans of acquiring tularemia from infected animals or arthropod is considered minimal and could be reduced by avoidance of sick or dead animals and by using protective measures against biting arthropods.

9. Postmortem Practices

If tularemia is suspected as a cause of death, the district Office of the Chief Medical Examiner should be notified immediately (see http://www.vdh.virginia.gov/medExam/ContactUs.htm). Bodies of patients who die of tularemia should be handled using standard precautions. Autopsy procedures likely to produce aerosols or droplets should be avoided.

10. Public Health Measures

- Suspected or confirmed tularemia cases should be reported immediately to the local health department. See http://www.vdh.virginia.gov/local-health-districts/.
- Tularemia is considered to be a potential agent for deliberate use, particularly if used as an aerosol threat. Cases presenting as primary pneumonia require prompt identification and specific treatment to prevent a fatal outcome.
- Laboratory specimens should be sent to the state public health laboratory (DCLS) for confirmation of agent and other studies after VDH has approved testing. For questions about specimen collection, the DCLS Emergency Officer can be reached 24/7 at 804-335-4617.
- Designated public health authority should begin an epidemiologic investigation immediately, including fever surveillance of individuals potentially exposed to *F. tularensis*.
    - Collect detailed information from the patient to identify the source of the exposure.
    - Investigate contacts of the case-patient for compatible illness to identify a potential common exposure.
    - Suspected food items (e.g. ingested contaminated wild game meat) should be collected for possible testing.
    - VDH will work with the CDC, Federal Bureau of Investigation (FBI), and other state or federal agencies as necessary.
- Implement control measures to prevent disease and additional exposures.
    - For laboratorians or others potentially exposed who might have worked with the agent before identification as *F. tularensis*, PEP and postexposure monitoring might be recommended based on a risk assessment.

- Healthcare providers should use standard precautions when caring for patients with tularemia.
- To prevent insect bites, people should use insect repellent containing 20%–30%DEET (N,N-diethyl-m-toluamide), picaridin, or IR3535; wear long pants, long sleeves, and long socks; promptly remove ticks attached to the skin with fine-tipped tweezers.
- People should avoid handling sick or dead animals. If contact with such animals cannot be avoided, people should use care and wear gloves during handling of these animals, particularly rabbits, muskrats, prairie dogs and other rodents.
- To prevent potential aerosolization of *F. tularensis* during lawn mowing, people should check the area for carcasses before mowing and should not mow over carcasses. Wearing masks while mowing or conducting landscaping activities might also reduce the risk of inhaling the bacteria, but this has not been studied.
- People should thoroughly cook game meat before eating.

11. References and Resources

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