

TULAREMIA SURVEILLANCE PROTOCOL

Draft

Tularemia may occur from an unintentional exposure resulting from contact with infected animals or from the bite of arthropods that have fed on infected animals. It may occur from intentional exposures such as in a bioterrorist (BT) event. When necessary this protocol addresses unintentional and intentional exposures separately; otherwise the protocol applies to both situations. This protocol applies when a case of tularemia is highly suspected and does not apply to cases with non-specific flu-like, gastrointestinal, neurologic, or rash-like symptoms.

Public Health Action

The state and LHDs should do the following:

1. Prior to the occurrence of a tularemia case
 - a. Protect employee health
 - i. Identify high risk employees: Identify employees that will be involved in the response to a BT event and may be at high risk for tularemia. High risk individuals may include 1) laboratory workers who test specimens and environmental samples, 2) state and local epidemiologic response teams who go on site to conduct exposure assessments during an outbreak investigation, 3) hazmat teams, industrial hygienists, health department sanitarians, and other personnel that may collect environmental samples, and 4) first responders such as law enforcement and security personnel that respond to a BT event.
 - ii. Educate high risk employees: Employee risk is minimal except in cold, wet environments where tularemia may be stable in the environment. Educate high risk employees about tularemia from a BT event. Provide them fact sheets about tularemia.
 - iii. Personal Protective Equipment (PPE): Educate employees on the use of proper PPE, provide appropriate PPE to employees for use during an outbreak, and ensure fit testing for employees for respirator use (see Preventive Interventions section.)
 - b. Assemble and train a BT epidemiologic response team:
 - i. Assemble a BT epidemiologic response team: Identify staff for a BT epidemiologic response team that can adequately respond to a large outbreak by conducting surveillance and epidemiologic investigations after a BT event.
 - ii. Surge capacity for BT epidemiologic response team: Identify pools of individuals for surge capacity for the investigation team during large outbreaks. A detailed plan for surge capacity is described in the WV Public Health Preparedness Plan for Surveillance and Epidemiologic Response.
 - iii. Train BT epidemiologic investigation team: Periodically train and pre-drill individuals on the team in their respective responsibilities during an outbreak.

- c. Educate health care providers and the public in the recognition and diagnosis of tularemia.
 - d. Educate providers and laboratories to report tularemia infections to the local health department in the patient's county of residence **immediately**.
 - e. Educate veterinarians to report veterinary tularemia to the WV Department of Agriculture.
2. When a tularemia case is reported
- If a suspected case of tularemia is reported, the LHD should contact the Infectious Disease Epidemiology Program (IDEP) immediately (do not wait for lab confirmation to contact IDEP),** and should anticipate that a BT epidemiologic response team of state, local, and hospital personnel will be formed to respond to the outbreak.
- a. Confirm cases:
 - i. For each suspected case, immediately obtain a complete clinical and laboratory history. Using the *Tularemia Case Investigation Form*, obtain information and determine whether a case is clinically or laboratory confirmed (See Case Definition).
 - ii. Assure that appropriate laboratory specimens are obtained on each suspected case (see Laboratory Notes). Specimens of blood or bone marrow, serum, biopsy tissue, scraping, or swab of ulcer, aspirate of involved tissue are to be sent to the local hospital laboratory (sentinel lab or previous called Level A lab) for preliminary confirmation of *F. tularensis*. If results are suspicious, the specimens will be sent to the WV Office of Laboratory Services (OLS) (reference or previously called a Level B lab) for confirmation. Specimens will be packaged and shipped to OLS according to the OLS laboratory protocol.
 - b. Confirmation of an intentional or unintentional exposure and notification procedure:

Immediately determine whether the case was due to an unintentional, non-BT exposure (see Hypothesis Testing Section 2.g below).

 - i. Check for natural exposure to *F. tularensis* within 14 days prior to onset of symptoms including (1) contact with infected voles, hares, rabbits, (2) insect bites (deer fly, ticks, mosquito), (3) ingestion of improperly cooked rabbit, squirrel, etc., and (4) hunting associated with exposure.
 - ii. If no clear source is identified on initial interview begin active surveillance to identify other cases.

Notify IDEP immediately if more than 1 case is identified or if a BT event is suspected. IDEP will notify the State Epidemiologist who will notify the State Health Commissioner. The WVBPH shall coordinate the response with other federal, state and local agencies according to the notification procedure in the WV Public Health Threat Preparedness Surveillance and Epidemiologic Response Plan.
 - c. Activate the BT epidemiologic response team: Activate staff on BT epidemiologic response team and review responsibilities in the investigation.
 - d. Protect employee health:

- i. Identify all high risk employees (See Section 1.a).
- ii. Assure protection of employee health following procedures in Preventive Interventions section.
- e. Case Finding:
 - i. Develop a working case definition: Develop a working case definition for the outbreak investigation. After the outbreak has been identified, a working case definition may be considered as follows: a 1) suspected case which is a clinically compatible case of tularemia while laboratory confirmation is pending which has a confirmed exposure to *F. tularensis*, 2) a probable case, or 3) a confirmed case of tularemia (See Case Definition Section).
 - ii. Begin enhanced passive surveillance: Immediately begin enhanced passive surveillance as needed with health care providers and laboratories in the county.
 - (1) Educate health care providers and the public in the recognition and diagnosis of tularemia.
 - (2) Educate providers and laboratories to immediately report possible tularemia infections that meet the 'Working Case Definition' to the local health department in the patient's county of residence.
 - (3) Educate veterinarians to report confirmed or suspected cases of tularemia to the West Virginia Department of Agriculture.
 - iii. Prepare for active surveillance: If necessary, alert the regional epidemiologist and be prepared to expand active surveillance throughout the region, e.g., be prepared to interview providers and patients, and review/abstract patient records.
 - iv. Confirm new cases: Receive and screen reports of suspected cases, and confirm new cases.
 - v. Develop line list of cases: Develop a line listing of all clinically and laboratory confirmed cases using a *Case Line Listing Form*. Record information on case ID number, name, age, date of birth, location (hospital, clinic, home), time of onset of symptoms, classification of case (pending, ruled out, suspected, clinically confirmed, and laboratory confirmed), lab confirmation status (confirmed, negative, pending), status of clinical information (complete or incomplete), and status of exposure information (complete or incomplete).
- f. Maintain the line listing of cases and develop a risk factor/exposure data base:
 - i. Track cases on case line list and ensure that clinical and laboratory information are collected from health providers and laboratories, if not done.
 - ii. Develop and maintain a data base of pertinent clinical and exposure data for hypothesis testing.
 - (1) Compile clinical, laboratory, and exposure assessment data as they are collected or submitted by health providers and labs.
 - (2) Review data for completeness and complete pending case investigations and incomplete exposure assessments.
 - (3) Develop and maintain electronic database for hypothesis testing.
- g. Hypothesis testing:
 - i. Exposure assessment: Conduct an assessment of the source and characteristics of exposure immediately after a case is suspected as follows:

- (1) Interview a representative sample of cases and obtain a complete risk factor and exposure history, including travel and activities during the case's exposure period (1-14 days before symptom onset).
 - (2) If a possible BT event or intentional exposure location/source is suspected, continue the interview with the same sample of cases. Obtain more detailed information, including the type, location, and specific areas, duration, relative amount, and method of dissemination of exposure for the possible BT event.
- ii. Analyze the clinical, laboratory, risk factor, and exposure assessment data to test plausible hypotheses for the source and location of exposure.
- h. Identify exposed population:
- i. After *F. tularensis* is confirmed from OLS in an environmental sample or clinical specimen (See Laboratory Notes), and exposure characteristics are determined, define the exposed population.
Definition of an exposed individual: An exposed individual will be a person who shared or possibly shared airspace that was contaminated by *F. tularensis*; or had direct contact with or ingestion of contaminated material such as powder or other environmental exposures as part of a BT event, infected animal tissue or fluid, or contaminated food, water, or soil; or had inhaled infected aerosols.
 - ii. Develop a line listing of all persons possibly exposed using the *Exposed Individual Line Listing Form*. Record each person's exposure risk based upon proximity to exposure.
- i. Surveillance of exposed population:
- i. Contact and referral of exposed: **Assure that all exposed individuals are contacted within 24 hours, if possible**, and educate them about signs and symptoms of tularemia and to seek medical attention immediately if symptoms develop. For large populations, alert the public through media announcements. Post exposure prophylaxis for tularemia is only effective if began within 24 hours after exposure.
 - ii. Surveillance of exposed individuals: Conduct surveillance of all exposed individuals for 14 days.
- j. Prevention and Control:
- i. After the source has been identified, remove people from the environment (e.g., contaminated by a BT event) until decontamination is achieved.
 - ii. Post exposure prophylaxis: Post exposure prophylaxis is only effective if initiated within 24 hours after exposure. PEP should be given for 14 days. In the event that a person was discovered to have been exposed after the first few case(s) were reported then the PEP would not be beneficial and the person should be under surveillance for fever.
 - iii. Treatment of Cases: Recommend to the State Health Commissioner that cases should receive treatment according to current guidelines (See Treatment Section.) Recommend to the State Health Commissioner the amount of vaccine or antibiotics that are needed for PEP or treatment.

Disease Prevention Objectives

To prevent disease in high risk populations through:

1. Education of health care workers in standard precautions when working with tularemia patients.
2. Education of personnel who may enter exposed areas in the proper use of protective clothing and respirators.

Disease Control Objectives

Prevent unnecessary illness and death through rapid identification of populations exposed to tularemia so appropriate treatment or post exposure prophylaxis can quickly be administered.

Surveillance Objectives

To rapidly detect and confirm a case of tularemia if it occurs in WV.

Public Health Significance

In the United States tularemia is endemic in rural areas with moderate climates, particularly in the Midwestern states. Over the last decade, annual incidence has been less than 200 cases nationwide. Between 1985 and 1992, 1409 cases and 20 deaths were reported in the United States. Persons in all age groups were affected but most were children younger than 10 years and adults aged 50 or older. Most cases occur in June through September, when arthropod-borne transmission is most common. Cases in winter usually occur among hunters and trappers who handle infected animal carcasses. Tularemia is almost entirely a rural disease, although urban and suburban exposures occasionally do occur.

There have been only two cases of tularemia in West Virginia from 1990 to 2002; however, under-diagnosis and under-reporting are likely to occur.

In the fall of 2001, however, 11 cases of inhalational anthrax and 11 cases of cutaneous anthrax were linked to weapons grade *B. anthrax* sent through the mail. This attack on citizens of the U.S. demonstrate the intentional release of anthrax spores through the mail and highlights the need for public health preparedness to meet the challenge of bioterrorism. A World Health Organization expert committee reported that an aerosol dispersal of 50kg of virulent *F. tularensis* over a metropolitan area with 5 million people would result in 250,000 incapacitating casualties, including 19,000 deaths.

Clinical Description

Francisella tularensis can infect humans through the skin, mucous membranes, gastrointestinal tract, and lungs. The major target organs are the lymph nodes, lungs, and pleura, spleen, liver, and kidney. The primary clinical forms of tularemia vary in severity and presentation according to virulence of the infecting organism, dose, and route of exposure. Tularemia presents in six forms: pneumonic, typhoidal, ulceroglandular, glandular, oculoglandular and oropharyngeal

Pneumonic: The pneumonic form can be due to hematogenous spread of systemic infection from a distant site, but this term is generally used to describe infection in the lung as a result of direct inhalation of aerosolized bacteria (primary pneumonic), which is not associated with skin ulcers or lymphadenopathy. An aerosol exposure would likely result initially in a non-specific, flu-like illness consisting of sudden onset of fever, and malaise and usually lower back pain/myalgia, headache and temperature/pulse dissociation (has been noted in as many as 42% of patients). A dry or slightly productive cough and substernal pain would be the first signs of disease. Chest x-ray abnormalities may not be present in the early stages.

Typhoidal: Presents as severe systemic disease without skin ulcers, regional lymphadenopathy or pneumonia. Any route of infection possible.

Ulceroglandular: The ulceroglandular form typically arise from handling a contaminated carcass or following an infective arthropod bite. A local cutaneous papule appears at the inoculation site at about the same time of onset of generalized symptoms, becomes pustular, and ulcerates within a few days of its first appearance. The ulcer is tender, generally has an indolent character, and may be covered by eschar. Typically, one or more regional afferent lymph nodes may become enlarged and tender within several days of the appearance of the papule. Even with antibiotic treatment, the affected nodes may become fluctuant and rupture.

Glandular: Glandular tularemia is characterized by regional lymphadenopathy without an ulcer.

Oculoglandular: This form occurs as the result of contamination of the eye either from direct contact with infected material or theoretically from an aerosol exposure.

Oropharyngeal: This form is acquired by drinking contaminated water, ingesting contaminated food, and, sometimes, by inhaling contaminated droplets or aerosols. Affected persons may develop stomatitis but more commonly develop exudative pharyngitis or tonsillitis, sometimes with ulceration. Pronounced cervical or retropharyngeal lymphadenopathy may occur.

Etiologic Agent

Francisella tularensis is a highly infectious, slow-growing, nonmotile, aerobic, gram-negative coccobacillus. It has a thin lipopolysaccharide-containing envelope and is a hardy non-spore forming organism that survives for weeks at low temperatures in water, moist soil, hay, straw, and decaying animal carcasses.

Reservoir

Tularemia is a zoonotic bacterial disease that is carried by numerous wild animals, especially rabbits, hares, voles, muskrats, beavers and some domestic animals being the usual animal hosts. Also various hard ticks that have fed on infected animals harbor the virus.

Mode of Transmission

Humans become infected with *F. tularensis* by various modes, including bites by infective arthropods, handling infectious animal tissues or fluids, direct contact with or ingestion of contaminated water, food, or soil, and inhalation of infective aerosols. Although airborne *F. tularensis* from an intentional release would be expected to principally cause primary pleuropneumonic infection, some exposures might contaminate the eye, resulting in ocular tularemia; penetrate broken skin, resulting in ulceroglandular disease; or cause oropharyngeal disease with cervical lymphadenitis. Although *F. tularensis* is highly infectious and pathogenic, its transmission from person to person has not been documented.

Incubation Period

Related to the virulence of the infecting strain and the site of inoculum; the range for development of symptoms is from 1-14 days. An airborne exposure (e.g., from a BT event) would likely cause symptoms in 3-5 days.

Infectious Period

Not directly transmitted from person to person. Unless treated, the infectious agent may be found in the blood during the first 2 weeks of disease and in lesions for a month, sometimes longer.

Outbreak Recognition

Outbreaks of any form of tularemia should be rapidly investigated to rule out a bioterrorism event. Intentional aerosol release should be suspected if cases occur in nonendemic areas or when no discernible risk factors for exposure are identified. One case of tularemia due to intentional exposure is an outbreak.

Case Definition

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

Clinical Case Description:

- 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.

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.

Laboratory criteria for diagnosis:

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.

Confirmatory:

- Isolation of *F. tularensis* in a clinical specimen or
- Fourfold or greater change in serum antibody titer to *F. tularensis* antigen.

Case classification:

Probable case:

- a clinically compatible case with laboratory results indicative of presumptive infection.

Confirmed case:

- a clinically compatible case with confirmatory laboratory results.

Laboratory Notes

Environmental samples

Environmental samples may be taken if possible and appropriate for exposure assessment.

Specimens

The following clinical specimens may be collected for testing for *F. tularensis*: blood, serum, or bone marrow; biopsy, scraping, or swab of ulcer; or spleen, liver, or abscess biopsy.

Laboratory tests

Environmental samples should be sent to OLS for testing (Reference lab or previously called a Level B lab). Clinical specimens should be sent to hospitals or Sentinel lab (previously called a Level A lab) for rule-out or presumptive testing for *F. tularensis*. If sentinel lab tests indicate suspicious findings consistent with *F. tularensis* isolates should be sent to OLS for confirmation.

The following tests may be run on environmental and clinical specimens by Laboratory Response Network (LRN) sentinel(S) and reference (R) labs:

| Test Procedure | LRN Level | |
|---|-----------------------|-----------------------|
| | S | R |
| Gram stain | x | x |
| Routine Culture: 1. Colonial morphology 2. No growth on MacConkey or EMB agars 3. Broth growth characteristics 4. Biochemical reactions (catalase oxidase, betalactamase, XV (or satellite test), and urease) 5. Cysteine supplement growth requirement on SBA | x x x x x | x x x x x |
| Confirmatory tests: 1. Slide agglutination 2. Serum agglutination 3. Direct fluorescence-antibody (DFA) assay | | x x x |
| Additional confirmatory tests: 1. Polymerase Chain Reaction (PCR) | | x |

Preventive Interventions

Isolation of tularemia patients is not recommended given the lack of human-to-human transmission. Standard precautions are recommended for treatment of patients. Bodies of deceased should be handled with standard precautions. Autopsy procedures that likely cause aerosols should be avoided. Clothing and linens contaminated with body fluids of patients should be disinfected per standard precautions protocols.

1. Personal protective equipment(PPE): Proper PPE including clothing and respirator use must be employed by all personnel who are exposed to *F. tularensis* by entering an environmentally contaminated exposure zone. In a BT event (See CDC, "Interim Recommendations for the Selection and Use of Protective Clothing and Respirators Against Biological Agents," October 24, 2001.)
2. Infection control procedures: Standard precautions are recommended for patient care and persons who have face-to-face contact with patients.
3. Environmental exposures: Known aerosol releases in smaller areas with visible standing water or wet surfaces should be decontaminated with a two-step process involving spraying with 10% bleach, followed by 70% alcohol ten minutes later. Exposed skin and clothing can be washed with soap and water. *F. tularensis* can survive for weeks at low temperatures in water, moist soil, hay, straw, and decaying animal carcasses. After the source of an exposure has been identified (e.g., contaminated by a BT event), remove people from the environment until decontamination is achieved.
4. Immunoprophylaxis: Prophylaxis of all exposed individuals within 24 hours of exposure and treatment of cases is recommended (see Treatment Section).
5. In the event of a naturally occurring case, the following preventive interventions may be considered depending on the circumstances of the exposure:
 - a. Educate the public to avoid bites of ticks, flies and mosquitoes and to avoid drinking, bathing, swimming or working in untreated water where infection prevails among wild animals.
 - b. Use impervious gloves when skinning or handling animals, especially rabbits. Cook the meat of wild rabbits and rodents thoroughly.
 - c. Prohibit interstate or interarea shipment of infected animals or their carcasses.
 - d. Remove people from the source of infected cats, rodents, or their fleas.

Treatment

Treatment and post exposure prophylaxis recommendations are based on JAMA, 283(17), May 3,2000. In a contained casualty setting, where a modest number of people require treatment, parenteral antibiotic therapy is recommended. Preferred parenteral forms of the antimicrobials streptomycin or gentamicin are recommended. In a mass casualty setting, intravenous or intramuscular therapy may not be possible, so oral therapy, preferably with doxycycline (or tetracycline) or ciprofloxacin, should be administered. **Post-exposure prophylaxis is only effective if initiated within 24 hours after exposure.**

A safe, live attenuated vaccine offering moderate protection versus pneumonic tularemia has been used in the U.S. since 1959 with very limited availability for laboratory workers at high risk. As tularemia has a relatively short incubation period, and the vaccine has a delayed effect, it is not recommended for post-exposure prophylaxis. The IND vaccine is not licensed and is under review by FDA.

The following guidelines are for treatment of patients with tularemia in the contained and mass casualty settings and for post-exposure prophylaxis:

1. Treatment of Patients with tularemia in a contained casualty setting*

| Patient Category | Preferred Choices | Alternative Choices |
|-----------------------|---|---|
| Adults | Streptomycin, 1g IM twice daily Gentamicin, 5 mg/kg IM or IV once daily† | Doxycycline, 100 mg IV twice daily Ciprofloxacin, 400 mg IV twice daily† Chloramphenicol, 15 mg/kg IV 4 times daily† |
| Children | Streptomycin, 15 mg/kg IM twice daily (maximum daily dose 2 g/d) Gentamicin, 2.5 mg/kg IM or IV 3 times daily† | Doxycycline, If >= 45 kg, give adult dosage If < 45 kg, give 2.2 mg/kg IV twice daily Ciprofloxacin, 15 mg/kg IV twice daily‡ Chloramphenicol, 15 mg/kg IV 4 times daily† |
| Pregnant Women | Gentamicin, 5 mg/kg IM or IV once daily† Streptomycin, 1 g IM twice daily | Doxycycline, 100 mg IV twice daily Ciprofloxacin, 400 mg IV twice daily† |
| Breastfeeding women** | Preferred choice: Gentamicin, 5 mg/kg IM or IV QD Alternative choice: Ciprofloxacin, 400 mg IV BID Doxycycline, 100 mg IV BID | |

* 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 U.S. food and Drug Administration-approved use.

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

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2. Treatment of patients with tularemia in a mass casualty setting or for postexposure prophylaxis*

| Patient Category | Preferred Choices |
|-----------------------|---|
| Adults | Doxycycline, 100 mg orally twice daily Ciprofloxacin, 500 mg orally twice daily† |
| Children | Doxycycline,** If >=45kg give adult dosage If <45 kg then give 2.2 mg/kg orally twice daily Ciprofloxacin, 15 mg/kg orally twice daily†‡ |
| Pregnant Women | Doxycycline, 100 mg orally twice daily Ciprofloxacin, 500 mg orally twice daily† |
| Breastfeeding women** | Doxycycline, 100 mg po BID OR Ciprofloxacin, 500 mg po BID |

* One antibiotic, appropriate for patient age, should be chosen from among alternatives. The duration of all recommended therapies is 14 days. PEP should be given only early in the incubation period (within 24 hours after exposure).

† Not a U.S. food and Drug Administration-approved use.

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

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3. Management of special groups

Pregnant women:

In a contained casualty situation, short courses of gentamicin are likely to pose a low risk to fetuses when used to treat pregnant women. Rare cases of fetal nerve deafness and renal damage have been reported with other aminoglycosides but have not been reported with gentamicin. The benefits of gentamicin in treating pregnant women with tularemia are expected to outweigh any potential risk to fetuses. In a mass casualty situation, oral ciprofloxacin is considered the best alternative to gentamicin for pregnant women.

Immunosuppressed persons:

There is scant experience in treating tularemia in immunosuppressed patients. However, considering the greater occurrence in immunocompetent patients of tularemia relapses and treatment failures following use of bacteriostatic antimicrobial agents compared with aminoglycosides, streptomycin or gentamicin should be used when possible to treat patients with known immune dysfunction in either contained casualty or mass casualty situations.

Surveillance Indicators

1. Time between suspicion of tularemia and first report to public health.
2. Completeness of investigation including risk factor and exposure data collection.
3. Time between suspicion of tularemia and completion of clinical history.
4. Time between suspicion of tularemia and completion of risk factor and exposure data collection for BT event.
5. Time from suspicion of tularemia and identification of source of exposure in BT event.