

Tularemia (*Francisella tularensis*)



Public Health Branch

1. Case Definition

1.1 Confirmed Case:

Clinical illness* with laboratory confirmation of infection:

- Isolation of *Francisella tularensis* from an appropriate clinical specimen (e.g., sputum, blood, swab from ulcer);
- OR
- A significant (e.g., fourfold or greater) change in serum antibody titre to *F. tularensis* antigen;
- OR
- Detection of *F. tularensis* nucleic acid (1).

1.2 Probable Case:

Clinical illness* with non-confirmatory laboratory evidence:

- Detection of *F. tularensis* in a clinical specimen by fluorescent assay;
- OR
- $\geq 1:128$ microagglutination titre or $\geq 1:160$ tube agglutination in a single serum specimen (1).

*Clinical illness is characterized by the following major distinct forms. Clinical diagnosis is supported by evidence or history of a tick or fly bite, exposure to the tissues of a mammalian host of *Francisella tularensis* or exposure to potentially contaminated water (1).

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.

Pneumonic: primary pleuropulmonary disease.

Typhoidal: febrile illness without early localizing signs and symptoms (1).

2. Reporting and Other Requirements

Laboratory:

- All positive laboratory results for *Francisella tularensis* are reportable to the Public Health Surveillance Unit by secure fax (204-948-3044).
- Clinical laboratories are required to submit isolates from individuals who tested positive for *F. tularensis* to Cadham Provincial Laboratory within seven days of isolation.

Health Care Professional:

- Probable (clinical) cases of tularemia are reportable to the Public Health Surveillance Unit using the *Clinical Notification of Reportable Diseases and Conditions* form <http://www.gov.mb.ca/health/publichealth/cdc/protocol/form13.pdf> ONLY if a confirmatory positive lab result is not anticipated.
- Cooperation in Public Health investigation is requested when required.

Regional Public Health or First Nations Inuit Health Branch (FNIHB):

- Once the case has been referred to Regional Public Health or FNIHB, the *Communicable Disease Control Investigation Form* <http://www.gov.mb.ca/health/publichealth/cdc/protocol/form2.pdf> should be completed and returned to the Public Health Surveillance Unit by secure fax (204-948-3044).

3. Clinical Presentation/Natural History

Clinical presentation and severity of tularemia depends on the strain, inoculation route, the infectious dose, and the immune status of the host (2, 3). There are six major patterns of illness, ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic and typhoidal (3). Sudden high fever, chills, fatigue, general body aches, headache and nausea accompany all forms of tularemia (4). The most common form of the disease is ulceroglandular tularemia, which usually occurs as the result of a bite from an arthropod vector which has previously fed on an infected animal (3). An ulcer forms at the site of infection (3). Bacteria are disseminated from this site via the lymphatic system to regional lymph nodes (3, 5). The enlargement of the lymph nodes often resembles the classic bubo associated with bubonic plague (3). Glandular tularemia occurs when patients present with regional lymphadenopathy but without an ulcer (3, 6). Oculoglandular tularemia presents as severe conjunctivitis and preauricular lymphadenopathy (6). The ingestion of contaminated food or water can result in oropharyngeal tularemia (5). Oropharyngeal tularemia is characterized by severe exudative stomatitis, pharyngitis or tonsillitis and cervical lymphadenopathy (6). Pneumonic disease usually results from inhalation of bacteria but it can also occur as a complication of ulceroglandular, glandular, oculoglandular or oropharyngeal tularemia (5). Naturally occurring cases of inhalation tularemia can arise from farming activities which involve the handling and subsequent generation of dust from hay which has previously been the site of residence of infected rodents (5). Pneumonic tularemia is characterized by fever, dry cough, chest pain and hilar adenopathy (3). Typhoidal tularemia is a febrile illness that is not associated with prominent lymphadenopathy and does not fit into any of the

other major forms (3). The portal of entry is unclear (3). Symptoms of typhoidal tularemia may include any combination of fever with chills, headache, myalgias, sore throat, anorexia, nausea, vomiting, diarrhea, abdominal pain and cough (3), without the localizing symptoms of other syndromes (7). Refer to Table 1 below for clinical forms of tularemia and transmission.

Secondary skin rashes, usually within the first two weeks of symptoms may occur (3). Secondary skin manifestations of tularemia are erythema multiforme, erythema nodosum, and papular lesions (8). Rarely, *F. tularensis* otomastoiditis has been reported and was related to aquatic inoculation (9). The most common complications of tularemia are lymph node suppuration and persistent debility (3). Despite the organism's high infectivity, asymptomatic infection with *F. tularensis* is known to occur (10). Infection induces long-lasting immunity in humans, but reinfection with a milder clinical course has been reported (11).

4. Etiology

Tularemia is caused by the intracellular bacterium *Francisella tularensis*, a small pleomorphic coccobacillus (6). Two subspecies cause tularemia in North America, *F. tularensis* subspecies *tularensis* (type A) and *F. tularensis* subspecies *holarctica* (type B) (6). The high infectiousness and virulence of the organism and ease of aerosol spread make it a potential bioterrorism agent (12). Type A is found almost exclusively in North America and is highly virulent in humans (13). Type B exists throughout North America, Asia and Europe and is less virulent in humans (13), usually causing mild infections with low mortality rates (8).

Table 1: Clinical Forms of Tularemia and Transmission

Form	Signs and Symptoms	Possible Modes of Transmission
Ulceroglandular	Regional lymphadenopathy with ulcer.	Bite from an infected tick or insect or from handling infected animals.
Glandular	Regional lymphadenopathy with no ulcer.	Bite from an infected tick or insect or from handling infected animals.
Oculoglandular	Conjunctivitis and preauricular lymphadenopathy.	Touching eyes after handling an infected animal or exposure to dust or aerosols containing the organism.
Oropharyngeal	Stomatitis or pharyngitis or tonsillitis and cervical lymphadenopathy.	Eating or drinking contaminated food or water.
Pneumonic	Fever, dry cough, chest pain, hilar adenopathy.	Breathing dust or aerosols containing the organism or hematogenous spread of other untreated forms of tularemia (e.g., ulceroglandular).
Typhoidal	Any combination of general symptoms (e.g., fever, chills, headache) without the localizing syndromes of other syndromes.	Unknown, could be any mode (3, 4, 6, 7).

5. Epidemiology

5.1 Reservoir and Vectors

Francisella tularensis can infect many animal species, most importantly rabbits, hares, and rodents, especially muskrats, voles and beavers (6). Rodents and lagomorphs are considered to be part of the enzootic cycle of *F. tularensis*, whereas domestic cats and primates are considered to be incidental hosts (14). Tularemia has also been diagnosed in hamsters in breeding facilities. Ticks are considered major reservoir hosts (15). Ticks and flies (e.g., deer fly) are the most important vectors for tularemia in the United States (3). *F. tularensis* has been detected in at least 13 different species of ticks (16). Mosquitoes are believed to be the most frequent insect vector in Sweden, Finland and the former Soviet Union (3). Wild animals sold as pets (e.g., prairie dogs) are also potential vectors (3). *F. tularensis* may survive for long periods in water, mud and animal carcasses, even if frozen (3).

5.2 Transmission

F. tularensis is transmitted to humans by arthropod bites (ticks, flies); by direct contact with infected animals, infectious animal tissues or fluids; by ingestion of contaminated water or food; or by inhalation of infective aerosols (16). Transmission of *F. tularensis* to humans occurs most often through the bite of an insect or contact with contaminated animal products (9). There is no human-to-human transmission (16). There are no data to suggest that tularemia might be spread among humans by mosquitoes or other arthropods (16). Outbreaks of tularemia have been linked to transmission by deer flies (17). Vector-borne transmission generally leads to the ulceroglandular form of tularemia (11). Airborne transmission has occurred from processing hare meat (3). Skinning, dressing and eating infected animals, including rabbits, muskrats, beavers, squirrels and birds have transmitted tularemia,

occasionally resulting in large outbreaks in hunters (3). Oropharyngeal tularemia outbreaks have been associated with consumption of contaminated drinking water (18). Refer to Table 1 above for transmission routes and clinical forms of tularemia.

5.3 Occurrence

Tularemia has been reported in many countries of the northern hemisphere (16). In the United States of America, most human tularemia cases are reported from the south-central region (15). Sweden, Finland and Turkey have reported the highest incidence of tularemia worldwide (19). The Scandinavian countries regularly experience outbreaks of *F. tularensis* subsp. *holarctica*, at least some of which have been linked to contamination of water wells by infected dead rodents (20).

The disease is known to occur at all ages and males have a higher incidence in all age categories, possibly related to more frequent outdoor professional and leisure activities (16). The number of cases in a particular area often shows wide variation from year to year which may be related to climatic factors such as temperature and precipitation (16). In most countries where tularemia is endemic (e.g., Sweden, Turkey, United States), the disease is seasonal with most cases occurring in late spring, summer and early autumn (10, 16, 19, 21). However, seasonality depends on the predominant mode of transmission and can be bimodal, with arthropod associated infections occurring in the warmer months, and rabbit associated infections occurring in the winter (4). Outbreaks of the disease in humans often follow outbreaks of tularemia in rodents (16). Epidemics among humans can be triggered by war and social disruption (4).

Canada:

Nine cases of tularemia were reported to the Public Health Agency of Canada in 2013 and 10 cases in 2014 (22).

Manitoba:

Four cases were reported to Manitoba Health, Seniors and Active Living in 2013 and two cases were reported for each of 2014 and 2015. No human outbreaks were reported.

5.4 Incubation Period

The mean incubation period is 3 -5 days, but may range from 1 -21 days (16).

5.5 Risk Factors

The elderly, people with respiratory illness or whose immune systems are already compromised are most at risk of developing severe illness from *F. tularensis* (23). Type A tularemia is usually more severe than Type B tularemia (23). Lawn mowing and brush cutting have been identified as risk factors for acquiring infection as dead infected animals may be disturbed and create aerosols (15). Handling wild animals (e.g., skinning infected lagomorphs and rodents) puts individuals at greater risk of infection with *F. tularensis*. Living under circumstances of substandard housing, hygiene and sanitation due to social and economic disruption is also a risk factor for tularemia (7).

5.6 Period of Communicability

There is no human-to-human spread (3).

6. Laboratory Diagnosis

F. tularensis may be recovered from blood, sputum, aspirated material from lymph nodes and swabs from ulcers. The diagnosis of tularemia can be established serologically by a fourfold or greater change in serum antibody titre to *F. tularensis* antigen between acute and convalescent

specimens. Serology and nucleic acid detection are referred out. Culture is only performed by special arrangement with the laboratory due to the high infectious risk. The requisition should indicate “suspect tularemia” so that appropriate precautions may be taken. Laboratories are reminded that *F. tularensis* is a BSL-3 organism, and should be appropriately handled.

7. Key Investigations for Public Health Response

- History of outdoor activities with ticks, or fly bites, or other animal exposures (3).
- Recent acquisition of pet rodents, hares or rabbits, especially if the pet became ill or died within 21 days of acquisition (23).
- In cases of suspected waterborne tularemia, inspection of wells (where drinking water came from a well) for dead rodents (24).

8. Control

8.1 Management of Cases

- Consultation with Infectious Diseases is recommended for all cases of tularemia.
- Streptomycin or gentamicin, usually for 10 days, is recommended for the treatment of tularemia unless contraindicated (3, 6). A longer course may be required for more severe illness (6). Ciprofloxacin is an alternative for mild disease in individuals 18 years of age and older (6).
- The optimal antibiotic regimens for the treatment of pregnant or immunocompromised patients are unknown (3).
- **Infection Prevention and Control:** Routine Practices are required for hospitalized patients. Refer to the Manitoba Health, Seniors and Active Living document *Routine Practices and Additional Precautions: Preventing the*

Transmission of Infection in Health Care available at:

<http://www.gov.mb.ca/health/publichealth/cdc/docs/ipc/rpap.pdf> .

8.2 Management of Contacts of Cases and Exposed* Individuals

*Refers to individuals who have been exposed to the same suspected source of *Francisella tularensis* as the case.

- No prophylaxis is required for contacts of cases with tularemia because human-to-human transmission does not occur (3).
- Adults with suspected or proven high risk exposure to *F. tularensis* (e.g., laboratory exposure to the organism) should receive prophylaxis with either ciprofloxacin 500 mg or doxycycline 100 mg given orally twice daily for 14 days (3).
- Observation without prophylactic antibiotics is appropriate for exposed children (except during a bioterrorist event) and for adults with lower risk exposures (3).
- A 14-day course of prophylactic doxycycline or ciprofloxacin (which is only approved for specific indications in patients younger than 18 years of age) is recommended for children and adults after exposure to an intentional release of *F. tularensis* (i.e., bioterrorism) (6).
- Antibiotic prophylaxis after potential exposures of unknown risk such as tick bites, is not recommended (3).

8.3 Management of Outbreaks

An outbreak is defined as the occurrence of case(s) in a particular area and period of time in excess of the expected number of cases.

- Outbreaks should be investigated to identify a common source of infection and prevent further exposure to that source.

The extent of outbreak investigations will depend upon the number of cases, the likely source of contamination and other factors.

- Public Health Inspectors may be asked to assist the Medical Officer of Health in outbreak investigations, particularly in regards to food recalls, product testing, drinking water or environmental inspections.
- Public notification should occur. The level of notification will usually be at the discretion of regional Public Health and/or the provincial Public Health Branch for local outbreaks, but may be at the discretion of the Federal Government for nationally linked outbreaks.
- Public education on prevention. Refer to section 8.5 below.

8.4 Management of Bioterrorist Threats or Suspected Bioterrorist Activity

- *Francisella tularensis* is considered to be a potential agent for deliberate use, particularly as an aerosol (4). It is classified as a Category A biological agent due to its low infectious dose, ability to cause severe disease, ease of dissemination and environmental stability (25-28).
- For bioterrorist threats or suspected bioterrorist activity, the police should be contacted at 911 (24 hours) as well as the Office of Disaster Management Duty Officer at: 204-793-1632 (24 hours).

8.5 Preventive Measures:

- Protective clothing (gloves, mask and eye protection) should be used for skinning, dressing or other handling of dead animals (3). The effectiveness of using a mask is unknown, and no recommendations for a specific type of mask can be made.

- Wild game should be cooked thoroughly before consumption (3).
- Avoid exposure to blood-sucking arthropods by wearing long-sleeved clothing, and using repellents or mosquito nets (16).
- Protect food stores and water sources from contact with animals or their feces (16).
- Chlorination of drinking water (18).
- Well owners should ensure that all openings to the well are plugged or covered to prevent rodent entry (24).
- Wash hands thoroughly with soap and water or alcohol based hand rub (ABHR) after being licked or bitten by household pets or after handling them or their belongings (e.g., toys, cages, bedding) (23).
- Education of veterinarians to promote recognition of tularemia in domestic cats (14).
- Education of landscapers (this includes all persons who mow lawns) who perform aerosol-generating activities (10).
 - Landscapers should be advised to survey their work areas for carcasses or excreta and if found, to avoid them or dispose of them properly (10).
 - Equipment should be maintained in good working order. The protective skirting and collection bags found on mowers should be kept intact (10).
 - Landscapers not already using respiratory protection might consider doing so when generating aerosols (10). The effectiveness of masks in preventing occupational exposure to *F. tularensis* has not been evaluated (10).

References

1. Public Health Agency of Canada. Case Definitions for Communicable Diseases under National Surveillance. *Canada Communicable Disease Report CCDR* 2009; 35S2: 1-123.
2. Pedati C, House J, Hancock-Allen J et al. Increase in Human Cases of Tularemia – Colorado, Nebraska, South Dakota, and Wyoming, January-September 2014. *Morbidity and Mortality Weekly Report MMWR* 2015; 64(47):1317-1318.
3. Penn RL. *Francisella tularensis* (Tularemia). In: Mandell GL, Bennett JE, Dolin R eds. *Principles and Practice of Infectious Diseases 8th ed.* Elsevier, Philadelphia, 2015.
4. Heymann David L. Tularemia. In: *Control of Communicable Diseases Manual 20th ed.* American Public Health Association, Washington, 2014; 650-654.
5. Ellis J, Oyston PCF, Green M and Titball RW. Tularemia. *Clinical Microbiology Reviews* 2002; 15(4): 631-646.
6. American Academy of Pediatrics. Tularemia. In: Pickering LK ed. *Redbook 2012 Report of the Committee on Infectious Diseases 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics, 2012; 768-769.
7. Reintjes R, Dedushaj I, Gjini A et al. Tularemia Outbreak Investigation in Kosovo: Case Control and Environmental Studies. *Emerging Infectious Diseases* 2002; 8(1):69-73.
8. Tezer H, Ozkaya-Parlakay A, Aykan H et al. Tularemia in Children, Turkey, September 2009 – November 2012. *Emerging Infectious Diseases* 2015; 20(1): 1-7.
9. Guerpillon B, Boibieux A, Guenne C et al. Keep an Ear Out for *Francisella tularensis*: Otitis Media Cases after Canyoneering. *Frontiers in Medicine* 2016; 3. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4776157/> .
10. Feldman KA, Stiles-Enos D, Julian K et al. Tularemia on Martha’s Vineyard: Seroprevalence and Occupational Risk. *Emerging Infectious Diseases* 2003; 9(3):350-354.
11. Eliasson H, Broman T, Forsman M and Bäck E. Tularemia: Current Epidemiology and Disease Management. *Infect Dis Clin N Am* 2006; 20:289-311.
12. Johansson A, Lärkeryd A, Widerström M et al. An Outbreak of Respiratory Tularemia Caused by Diverse Clones of *Francisella tularensis*. *Clinical Infectious Diseases* 2014; 59(11):1546-53.
13. Avashia SB, Petersen JM, Lindley CM et al. First Reported Prairie Dog-to-Human Tularemia Transmission, Texas, 2002. *Emerging Infectious Diseases* 2004; 10(3):483-486.
14. Kugeler KJ, Mead PS, Janusz AM et al. Molecular Epidemiology of *Francisella tularensis* in the United States. *Clinical Infectious Diseases* 2009; 48:863-70.
15. Keim P, Johansson A and Wagner DM. Molecular Epidemiology, Evolution, and Ecology of *Francisella*. *Ann. N. Y. Acad. Sci* 2007; 30-66.
16. World Health Organization. WHO Guidelines on Tularaemia, 2007 http://apps.who.int/iris/bitstream/10665/43793/1/789241547376_eng.pdf .
17. Calanan RM, Rolfs RT, Summers J et al. Tularemia Outbreak Associated with Outdoor Exposure Along the Western Side of Utah Lake, Utah, 2007. *Public Health Reports* 2010; 125:870-876.
18. Chitadze N, Kucholoria T, Clark DV et al. Water-Borne Outbreak of Oropharyngeal and Glandular Tularemia in Georgia : Investigation and Follow-up. *Infection* 2009; 37:514-521.

19. Desvars A, Furberg M, Hjertqvist M et al. Epidemiology and Ecology of Tularemia in Sweden, 1984 – 2012. *Emerging Infectious Diseases* 2015; 21(1):32-39. Related Conditions. *N ENGL J MED* 2015; 372:954-62.
20. Afset JE, Larssen KW, Bergh K et al. Phylogeographical pattern of *Francisella tularensis* in a nationwide outbreak of tularemia in Norway, 2011. *Euro Surveill* 2015; 20(19):pii=21125.
21. Centers for Disease Control and Prevention. Tularemia---United States, 1990—2000. *MMWR* 2002; 51(09):182-184.
22. Public Health Agency of Canada. Notifiable Diseases On-line: Tularemia <http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/charts?c=y1> .
23. Public Health Agency of Canada. Tularemia –Frequently Asked Questions, 2004. Available at: <http://www.phac-aspc.gc.ca/tularemia/tul-qa-eng.php> .
24. Larssen KW, Afset JE, Heier BT et al. Outbreak of tularemia in central Norway, January to March 2011. *Euro Surveill* 2011; 16(13):pii=19828. Available at: <http://www.eurosurveillance.org/images/dynamic/EE/V16N13/art19828.pdf> .
25. Centers for Disease Control and Prevention. Biological and Chemical Terrorism: Strategic Plan for Preparedness and Response. Recommendations of the CDC Strategic Planning Workgroup. *Morbidity and Mortality Weekly Report MMWR* 2000; 49(No.RR-4):1-14.
26. Centers for Disease Control and Prevention. Public Health Assessment of Potential Biological Terrorism Agents. *Emerging Infectious Diseases* 2002; 8(2):225-230.
27. Public Health Agency of Canada. *Francisella tularensis* – Material Safety Data Sheets (MSDS) 2011.
28. Adalja AA, Toner E and Inglesby TV. Clinical Management of Potential Bioterrorism-