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BUNNY RABBITS AND BIOTERRORISM—TULAREMIA

TULAREMIA, also known as rabbit or deer-fly fever, is an infrequent disease of hunters, lawn mowers (the people doing the mowing and not the machines), and young children playing in the grass. It has recently gained notoriety as a “category A” (really scary!) potential agent of bioterrorism.¹ This *CD Summary*, the latest in our occasional briefings about bioterrorism and priority agents, outlines the epidemiology of naturally occurring tularemia, presents the clinical syndromes, diagnosis, and treatment of this disease, and discusses some implications for our fight against bioterrorism.

OVERVIEW

Tularemia is primarily a disease of the Northern Hemisphere. It was first described by Edward Francis in 1911 as a disease of rodents. In the 1930s and 1940s tularemia was recognized as the cause of several large waterborne outbreaks in Europe. The incidence of tularemia in the US has declined from several thousand per year prior to 1950, to less than 200 per year today.

Tularemia is caused by *Francisella tularensis*, a non-motile, aerobic, non-spore-forming Gram-negative coccobacillus. This organism is found in a variety of mammals, including rodents, rabbits, voles, and squirrels, as well as in insects, such as ticks, flies, and mosquitoes. It is a hardy bacterium that can survive for extended periods of time in the environment, and it can be recovered from contaminated soil, water, and plants. Although it is resistant to freezing, it is sensitive to heat and disinfectants. *F. tularensis* comes in two basic flavors, or biovars: type A, which is highly virulent in humans and animals and is the most common type in North America; and type B, which is less virulent and thought to cause most of the human cases in Europe and Asia.

EPIDEMIOLOGY

Tularemia occurs throughout Eurasia and North America. Every state in the US except Hawaii has reported cases. Most cases in the US are reported from rural areas of the South Central states, South Dakota, and Montana (see map).² People become infected primarily through handling contaminated animals; the bite of infective deer flies, mosquitoes, or ticks; direct contact or ingestion of contaminated food, water, or soil; or through inhalation of infective aerosols. No person-to-person transmission has been documented. Most cases occur in the summer, through insect bites; cases in the winter occur primarily in hunters who have handled infected carcasses. The highest numbers of cases occur in children and in men ≥ 50 years of age. From 1993–2002, 23 cases of tularemia were reported in Oregon (range 1–5 per year). Nineteen (83%) of these cases occurred in men. Cases occurred in residents of 12 counties (see map), and were evenly spread across all age groups.

Several outbreaks of inhalational tularemia have been documented. In 1966–7 in Sweden, more than 600 persons in a farming area became ill with tularemia. The outbreak had its peak during the winter, and was likely due to farmers moving rodent-infested hay. In the US, small clusters of inhalational tularemia have been seen in laboratory workers, and (in case you needed an

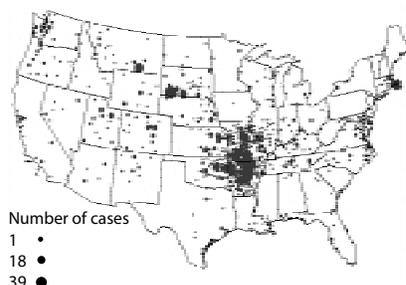
excuse to avoid yard work) in persons mowing lawns, thereby disturbing bacteria in the soil. In 2000, an outbreak of 15 cases occurred on Martha’s Vineyard, likely due to mowing lawns and cutting brush.³

CLINICAL FEATURES

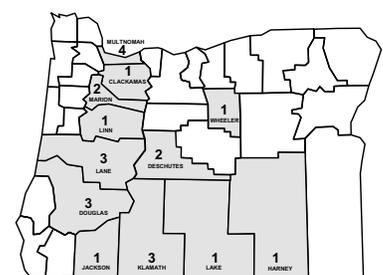
The infectious dose of *Francisella tularensis* is extremely low: 10–50 organisms can cause disease. The incubation period is 3–5 days (range 1–21 days) after an inoculation or inhalational exposure. The organism can enter the body through a variety of portals: skin, mucus membranes, GI tract, and lungs. General symptoms include fever, malaise, myalgias, headache, chills, rigors, and sore throat.

Tularemia has six clinical forms, depending on the site of infection. Ulceroglandular tularemia is the most common form of the disease, accounting for 75–85% of naturally occurring cases. Concurrent with the constitutional symptoms, a cutaneous papule occurs at the site of inoculation. This papule progresses to a pustule, and develops into a tender, indolent ulcer, sometimes with eschar. Patients also have regional lymphadenopathy. Pneumonic tularemia includes prominent respiratory symptoms of coryza, non-productive cough, and substernal pain or tightness. Radiographic signs include peribronchial infiltrates, bronchopneumonia, pleural effusions, and hilar lymphadenopathy.

Reported cases of tularemia, United States, 1990–2000



Reported cases of tularemia, Oregon, by county of residence, 1993–2002





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Mortality is 30–60% if untreated, but <10% if treated. Other clinical forms of the disease include: typhoidal (GI symptoms and sepsis); glandular (regional adenopathy without skin lesion), oculoglandular (painful purulent conjunctivitis with adenopathy), and oropharyngeal (pharyngitis with adenopathy).

LABORATORY DIAGNOSIS

If you suspect tularemia in a patient, alert laboratory personnel to your suspicion. They will need to be attentive to the organism's specific growth requirements (media supplemented with cysteine are recommended) and slow growth, and need to take special precautions because of the low infectious dose and risk of contracting disease in the laboratory. Laboratory diagnosis of *F. tularensis* includes Gram staining; isolating *F. tularensis* from body fluids, including exudates, secretions, and blood; direct fluorescent antibody stain; slide agglutination test; and serology with demonstration of a four-fold or greater rise in titer from acute to convalescent sera. PCR can also be done but is not widely available.

FRANCISELLA TULARENSIS AS A BIOLOGIC WEAPON

So why is an infection of bunny rabbits a potential for bioterrorism? The answer lies in its low infectious dose, its ability to survive in the environment, the fact that it can be disseminated via aerosol, and that, untreated, inhalational tularemia causes severe illness and death.[†]

[†] The World Health Organization (in 1969) determined that a 50-kg aerosol of *Francisella tularensis*, released over a city of 500,000 people, would cause 60,000 casualties and 4,500 deaths.⁴

In 1932–45, the Japanese developed and tested tularemia as a biologic weapon among the Chinese in Manchuria. During World War II, tularemia was thought to have caused the deaths of thousands of Soviet and German soldiers on the Eastern Front. During the 1950s and 1960s, the US military tested and stockpiled *F. tularensis*. It was never used (of course), and in 1969, President Nixon halted the production of biologic weapons in the US.

POST-EXPOSURE PROPHYLAXIS

So how should a clinician respond if bioterrorists unleash *Francisella tularensis*? It depends on whether the event is overt or covert. If the fact of an exposure is announced before clinical cases occur (an overt event), exposed persons should receive 14 days of oral antibiotics (doxycycline or ciprofloxacin). If the release is covert and the event is discovered only after persons start to become ill, potentially exposed persons should be watched to see if they develop fever. Persons with fever should be evaluated for tularemia and placed on appropriate antibiotic therapy.¹ A live-attenuated vaccine has been developed and used in members of the military. However, it is not currently available for general use, and its role in post-exposure prophylaxis is unknown.

TREATMENT

Fortunately, several readily available antibiotics are effective in the treatment of tularemia. Streptomycin or gentamicin for 10 days is considered first-line therapy. Ciprofloxacin and other fluoroquinolones have also been used. Doxycycline and chloramphenicol can be used, but because these drugs are bacteriostatic, relapses may occur.¹

SUMMARY

Tularemia occurs naturally in all states in the continental US, primarily in rural settings, among hunters exposed to infected animal carcasses, or young children bitten by infected insects (and rarely among people mowing lawns or cutting bushes). Tularemia in an urban setting without other obvious risk factors may be a tipoff to an intentional release. BT tularemia is most likely to be the pneumonic or typhoidal form, whereas naturally occurring disease is more commonly cutaneous. Tularemia can be treated with antibiotics.

If you suspect tularemia in a patient, please call your local public health department, within one working day (or immediately, if a suspected BT incident). We depend on astute clinicians to inform us of unusual cases or clusters of disease so that we can evaluate whether or not they are of public-health significance—including whether they signal a bioterrorist attack.

For more information about tularemia as a BT agent, check out the following web sites.

- <http://www.bt.cdc.gov/agent/tularemia/index.asp>
- <http://healthlinks.washington.edu/nwcp/bttrain/clinicians.html>
- <http://www1.umn.edu/cidrap/content/bt/tularemia/>
- <http://www.idsociety.org/bt/>

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