

Chapter 24

TULAREMIA

MARTIN E. EVANS, M.D.^{*} ; AND ARTHUR M. FRIEDLANDER, M.D.[†]

INTRODUCTION

THE INFECTIOUS AGENT

THE DISEASE

Epidemiology

Pathogenesis

Clinical Manifestations

Diagnosis

Treatment

PROPHYLAXIS

SUMMARY

^{*}Lieutenant Colonel (Ret), Medical Corps, U.S. Air Force; Assistant Professor of Internal Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799; currently, Associate Professor, Division of Infectious Diseases, Department of Internal Medicine, University of Kentucky School of Medicine, Lexington, Kentucky 40536-0084

[†]Colonel, Medical Corps, U.S. Army; Chief, Bacteriology Division, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland 21702-5011; and Clinical Associate Professor of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20814-4799

INTRODUCTION

Tularemia is a zoonosis caused by the Gram-negative, facultative intracellular bacterium, *Francisella tularensis*. The disease is characterized by fever, localized skin or mucous membrane ulceration, regional lymphadenopathy, and, occasionally, pneumonia.

In 1911, G. W. McCoy discovered the disease in Tulare County, California, as a cause of a plague-like illness in ground squirrels.¹ An organism was isolated and named *Bacterium tularense*.^{2,3} The first bacteriologically confirmed case of human dis-

ease was reported in 1914.⁴ Edward Francis subsequently described transmission by deer flies via infected blood and coined the term *tularemia* in 1921.⁵ Transovarian transmission in ticks was reported in 1926.⁶ In 1959, the Soviets proposed changing the genus name to *Francisella* in recognition of the contributions of Edward Francis to the understanding of this disease.⁷ *F tularensis* has been considered an important biological warfare threat because of its very high infectivity after aerosolization.

THE INFECTIOUS AGENT

F tularensis is a nonmotile, obligately aerobic, Gram-negative coccobacillus. There are two biovars⁸:

- *F tularensis* biovar *tularensis* is the most common isolate in the United States. It is recovered from rodents and ticks, and is highly virulent for rabbits and humans. It produces acid from glycerol and has citrulline ureidase activity.
- *F tularensis* biovar *paleartctica* is more common outside the United States. It is recovered from water, mosquitoes, and aquatic

mammals, and is relatively avirulent for rabbits and humans. It does not produce acid from glycerol, and does not have citrulline ureidase activity.

The subspecies are indistinguishable serologically, although they may be distinguished by 16S ribosomal ribonucleic acid (rRNA) analysis.⁹ A capsule has been reported that may contribute to virulence.^{10,11} *F tularensis* may have a lipopolysaccharide (LPS),¹² but the biological activity of the LPS has not been well characterized and its role in pathogenicity is unclear. No known toxins are produced.

THE DISEASE

Epidemiology

Tularemia occurs in North America, Europe, the Middle East, Russia, and Japan, but is rare in the United Kingdom, Africa, and Central and South America. In the United States, the disease is most prevalent in Arkansas, Illinois, Missouri, Texas, Virginia, and Tennessee, although cases have been reported from all states except Hawaii.^{13,14}

The principal reservoir of tularemia in North America is the tick; more than 10 species have been implicated.^{13,14} *F tularensis* is maintained in tick populations by transovarial passage, and is probably transmitted to humans via feces since the bacterium has not been found in the tick salivary glands. The bacterium has been isolated from 55 other arthropods and more than 100 nonarthropods.¹³ In North America, the rabbit is the most common vertebrate associated with transmission of tularemia. In other areas of the world, such as the former Soviet Union, tularemia is maintained in

water rats and other aquatic mammals. Pharyngitis, abdominal pain, and fever may result from the ingestion of contaminated water in these areas.¹⁵ With the disruption of normal sanitation during World War II, hundreds of thousands of civilians and large numbers of Russian troops contracted tularemia.¹⁶

The reported incidence in the United States since 1967 has been fewer than 200 cases per year. This compares with 2,291 cases reported in 1939 and more than 1,100 cases per year during the 1940s.^{17,18} The decline in incidence may be due to a declining interest in rabbit hunting, less recognition of the disease by physicians, or inadvertent cure of the disease by physicians who treat febrile patients with aminoglycoside antibiotics.¹³

Pathogenesis

F tularensis is usually introduced into the host through breaks in the skin, or through the mucous membranes of the eye, respiratory tract, or gas-

trointestinal tract.^{19–23} Ten virulent organisms injected subcutaneously, and 10 to 50 organisms given by aerosol can cause infection in humans.^{23–25}

After inoculation, *F tularensis* is ingested by and multiplies within macrophages.²⁶ The host defense against *F tularensis* is mediated primarily by (a) T-cell-independent mechanisms, which appear early (< 3 days after infection), and (b) T-cell-dependent mechanisms, which appear later (> 3 days after infection). In the T-cell-independent mechanisms, macrophages, which have ingested bacteria, secrete tumor necrosis factor- α (TNF- α). TNF- α stimulates natural killer (NK) cells to produce interferon- γ (IFN- γ), which, in turn, feeds back on macrophages and stimulates the cells to kill intracellular bacteria through the production of nitric oxide.^{26–28} In the T-cell-dependent mechanism, macrophages present bacterial antigen in the context of the major histocompatibility complex (MHC-II) to cluster of differentiation 4+ (CD4+) T lymphocytes. These cells respond by proliferating and secreting TNF- α , IL-2, and IFN- γ , which stimulate the macrophages to kill intracellular bacteria.^{27–32} Cell-mediated immunity constitutes the major protective mechanism.³³

The role of humoral immunity and neutrophils in the host defense against *F tularensis* is unclear. Specific immunoglobulins (IgG, IgA, and IgM) appear within 1 week of infection, and passive transfer of immune serum protects naive mice against challenge with attenuated vaccine strains.^{34–37} This protection, however, is not evident when mice are challenged with virulent wild-type strains.³⁸ Although some of the antibodies produced are opsonic and facilitate phagocytosis by neutrophils, neutrophils are not efficient in killing ingested bacteria.^{39,40} Recent studies using animals depleted of neutrophils suggest that neutrophils are important in resistance to infection with attenuated strains, but the relevance of these findings to virulent wild-type tularemia is unknown.⁴¹ Overall, these data suggest that the humoral immune response plays a limited role in the host defense against naturally acquired infection.³³

Clinical Manifestations

Tularemia can be divided into the ulceroglandular (75% of patients) and the typhoidal (25% of patients) forms, based on the clinical signs. Patients with ulceroglandular tularemia have lesions on the skin or mucous membranes (including the conjunctiva), lymph nodes larger than 1 cm in diameter, or both. Patients with typhoidal tularemia, on the

other hand, present with lymph nodes smaller than 1 cm in diameter and without skin or mucous membrane lesions. This simplified scheme is suggested instead of the more-complicated, previous classification (ie, ulceroglandular, glandular, oculoglandular, typhoidal), because it is more in keeping with the clinical, pathophysiological, and prognostic aspects of the disease.¹³

After an incubation period of 3 to 6 days,^{42–45} patients with the ulceroglandular form of the disease develop a constellation of symptoms consisting of fever (85%), chills (52%), headache (45%), cough (38%), and myalgias (31%). The fever is often accompanied by a pulse-temperature disassociation (ie, the pulse increases less than 10 beats per min per 1°F increase in temperature above normal⁴⁶). Patients may also complain of chest pain, vomiting, arthralgia, sore throat, abdominal pain, diarrhea, dysuria, back pain, or stiff neck.¹³

A cutaneous ulcer occurs in approximately 60% of patients and is the most common sign of tularemia. Ulcers are generally single lesions of 0.4 to 3.0 cm in diameter, with heaped-up edges (Figure 24-1). Lesions associated with infection acquired from mammalian vectors are usually located on the upper extremities, whereas lesions associated with infection acquired from arthropod vectors are usually located on the lower extremities. Ulcerative lesions are almost always accompanied by regional lymphadenopathy.¹³

Enlarged lymph nodes are seen in approximately 85% of patients, and may be the initial, or the only, sign of infection. Nodes are usually tender and 0.5 to 10 cm in diameter (mean 2.0 cm). Although enlarged nodes usually occur as single lesions, they may appear in groups or in a sporotrichoid distribution. The appearance of enlarged nodes in upper or lower extremities and the correlation

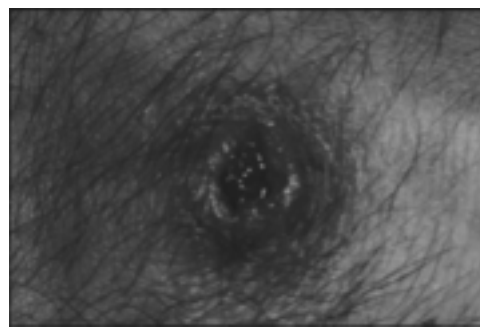


Fig. 24-1. Cutaneous ulcer of tularemia. Photograph: Courtesy of William Beisel, M.D., Colonel, Medical Corps, US Army (Ret).

with the vector is the same as for ulcerative lesions.¹⁹ Enlarged lymph nodes may become fluctuant, drain spontaneously, or persist for as long as 3 years.²²

Pharyngitis may occur in up to 25% of patients with tularemia.^{13,22,47,48} The posterior pharynx may not be inflamed; however, there may be erythema, exudate, petechiae, hemorrhage, or ulcers. On occasion, patients with pharyngitis may also develop a retropharyngeal abscess or suppuration of regional lymph nodes.^{47,49–51} Pneumonia commonly accompanies pharyngitis, perhaps reflecting acquisition of the disease by the aerosol route.

The lower respiratory tract is involved in 47% to 94% of patients.^{13,52,53} The variability in these figures is probably due to the variable use of chest radiographs during patient evaluations. Patients present with nonproductive or productive cough, and less commonly with pleuritic chest pain, shortness of breath, or hemoptysis. Examination of the sputum is not helpful for making the diagnosis of tularemia pneumonia. Chest radiographs show that approximately 50% of patients have pneumonia, and 1% or fewer have hilar adenopathy without parenchymal involvement. Pleural effusions are seen in 15% of patients with pneumonia. Interstitial patterns, cavitary lesions, bronchopleural fistulae, and calcifications have been reported in patients with tularemia pneumonia (Figure 24-2).^{53–62} Approximately 30% of patients with ulceroglandular tularemia and 80% of patients with typhoidal tularemia have pneumonia. The higher incidence of pneumonia in patients with typhoidal tularemia probably accounts for the higher mortality associated with this form of the disease.¹³

Other, infrequent clinical syndromes associated with tularemia include pericarditis, enteritis, appendicitis, peritonitis, erythema nodosum, and meningitis.^{13,22,63–66}

Patients usually do not have abnormalities in the hematocrit, hemoglobin, or platelet levels. The peripheral white blood cell count may range between 5,000 and 22,000 cells per microliter, but it is usually only mildly elevated. Differential blood cell counts are usually normal, although patients may have a lymphocytosis late in the disease.^{13,67} Patients may have microscopic pyuria, which may lead to the erroneous diagnosis of a urinary tract infection.^{13,68} Mild elevations in lactic dehydrogenase, serum transaminases, and alkaline phosphatase are commonly seen. Some patients may experience rhabdomyolysis associated with elevations in the serum creatine kinase and urinary myoglobin lev-

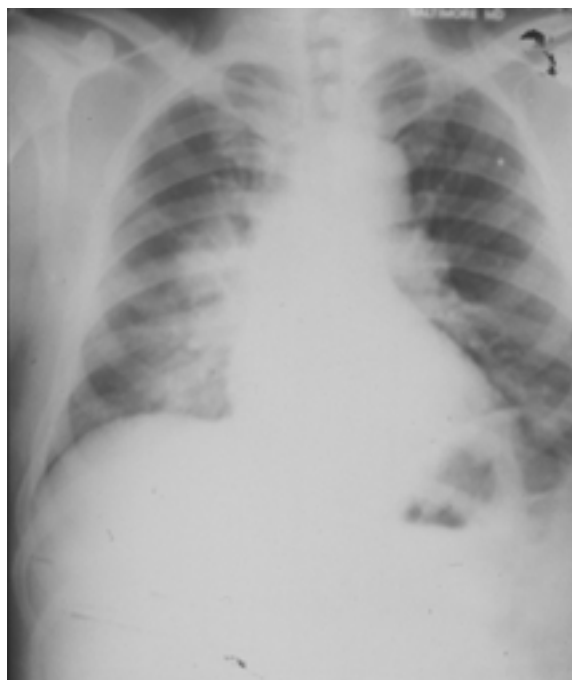


Fig. 24-2. Chest roentgenogram of tularemia pneumonia showing bilateral infiltrates. Photograph: Courtesy of William Beisel, M.D., Colonel, Medical Corps, US Army (Ret).

els.⁶⁹ The cerebrospinal fluid is usually normal, although mild abnormalities in protein, glucose, and blood cell count have been reported.¹³

Diagnosis

Tularemia can be diagnosed by recovery of *F tularensis* in culture, or from serologic evidence of infection in a patient with a compatible clinical syndrome. Although the organism is difficult to culture,^{24,25,53,70} it can be recovered from blood, ulcers, conjunctival exudates, sputum, gastric washings, and pharyngeal exudates.^{23,70} Recovery may be possible even after the institution of appropriate antibiotic therapy.²³ The organism grows poorly on standard media. On media containing cysteine or other sulfhydryl compounds (eg, glucose cysteine blood agar, thioglycollate broth), *F tularensis* appears as small, smooth, opaque colonies after 24 to 48 hours of incubation at 37°C. The bacterium has occasionally been recovered on charcoal yeast extract (CYE),⁷¹ or Thayer-Martin agar,⁷² or from radiometric detection systems if the media are subcultured onto chocolate agar.^{73,74} The organism can readily be recovered from animals inoculated with infectious materials, but

this is rarely done because of the likelihood of epizootics within the animal colony and the risk of infection to laboratory workers.^{75,76} Identification of the organism is made on the basis of its growth characteristics and bacterial agglutination or fluorescent staining using antisera specific for *F tularensis*.

Most diagnoses of tularemia are made serologically using bacterial agglutination or enzyme-linked immunosorbent assay (ELISA). Measurable levels of antibodies that agglutinate *F tularensis* appear within 1 week of infection,^{35,77} but levels high enough to allow confidence in the specificity of the serologic diagnosis (an agglutination titer > 1:160, for example) do not appear until more than 2 weeks after infection.^{13,34-36} The serologic response may be blunted by prior administration of antibiotics.⁷⁸ Because antibodies to *F tularensis* may cross-react with *Brucella*,⁷⁹⁻⁸¹ *Proteus* OX19,^{30,82} and *Yersinia* organisms,^{30,36,82,83} and because detectable antibody levels may persist for many years after a bout of tularemia,^{13,36} the serologic diagnosis of an acute infection should, ideally, be made only if a 4-fold or greater increase in serologic response is seen during the course of the patient's illness.

PROPHYLAXIS

Antibiotic prophylaxis after exposure to tularemia is difficult. The optimal bactericidal antibiotics such as streptomycin are impractical because they must be given parenterally. Limited studies⁹³ carried out in small numbers of human volunteers showed that treatment with tetracycline begun 24 hours after exposure to an aerosol of tularemia protected subjects from disease. An oral dose of 2 g/d for 14 days was necessary.

Vaccines to prevent tularemia have included those made from killed, whole cells and live, attenuated strains. A whole-cell, killed vaccine was developed by L. Foshay and associates⁹⁴ in the 1930s, but proved to be of limited efficacy. Experimental studies²⁴ done with human volunteers showed that this vaccine reduced the frequency of systemic symptoms but did not prevent the local lesion after intracutaneous challenge. Additional studies²⁵ with aerosol challenge in humans showed that the killed vaccine neither prevented nor modified the disease.

SUMMARY

Tularemia is a zoonotic disease caused by infection with the Gram-negative, facultative intracellular bacterium, *Francisella tularensis*. The organism

Treatment

Patients with tularemia who do not receive appropriate antibiotic treatment may have a prolonged illness characterized by malaise, weakness, weight loss, and other symptoms that last for months.^{22,82,84,85} Before the availability of effective antibiotics, ulceroglandular and typhoidal tularemia had mortalities of approximately 4% and 35%, respectively.^{44,57} With appropriate treatment, tularemia has an overall mortality of approximately 1% to 2.5%.^{13,86,87}

Streptomycin is the drug of choice for the treatment of tularemia. The drug is bactericidal, and patients treated with streptomycin usually respond within 48 hours of its administration.^{19,42,58,88} Relapses are uncommon, and resistance has not been reported.^{70,89} Other aminoglycosides such as gentamicin have been used with some success and are probably reasonable alternatives.¹³ Bacteriostatic drugs such as chloramphenicol and tetracycline are often efficacious, but relapses occur if the drug is given too early in the course of the disease or if is not continued long enough.^{13,23,70} To date, there is only limited clinical experience with erythromycin and the fluoroquinolones.^{31,71,90-92}

A live, attenuated vaccine had been developed and used in humans in the Soviet Union in the 1940s and 1950s.⁹⁵ The vaccine proved to be a mixture of variants of varying virulence. At the U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, in 1961, H. T. Eigelsbach and C. M. Downs⁹⁶ further purified and characterized a strain from this vaccine. This derivative was called live vaccine strain (LVS). Extensive evaluations^{16,25,97,98} have demonstrated that the LVS vaccine protected human volunteers against an aerosol challenge with virulent *F tularensis*.

Evidence based on an analysis of laboratory-acquired infections⁹⁹ indicates that immunization with the live, attenuated LVS vaccine prevents the typhoidal and ameliorates the ulceroglandular forms of tularemia. The LVS vaccine is currently available as an Investigational New Drug from the U.S. Army Medical Research and Materiel Command, Fort Detrick, Frederick, Maryland 21702-5011.

is highly infectious by both the cutaneous and aerosol routes. Naturally occurring tularemia occurs most commonly in its ulceroglandular form; pa-

tients present with a cutaneous ulcer or mucous-membrane lesion and regional tender lymphadenopathy. The typhoidal form occurs in 25% of naturally occurring cases; patients present with systemic symptoms without local lesions or marked lymphadenopathy. Pneumonia occurs in up to 80% of patients with typhoidal tularemia.

A biological warfare attack with aerosolized *F tularensis* would probably produce pneumonia with

or without accompanying mucous membrane lesions. Diagnosis is usually established by serology, as the organism is difficult to culture. The treatment of choice is streptomycin, with other aminoglycoside drugs being reasonable alternatives. Immediate postexposure antibiotic prophylaxis with tetracycline prevents disease. A live, attenuated vaccine, available as an Investigational New Drug, is effective against aerosol infection.

REFERENCES

1. McCoy GW. Plague-like disease in rodents. *Public Health Bull.* 1911;43:53–71.
2. McCoy GW, Chapin CW. Further observations on a plague-like disease of rodents with a preliminary note on the causative agent, *Bacterium tularensis*. *J Infect Dis.* 1912;10:61–72.
3. McCoy GW, Chapin CW. Studies of plague, a plague-like disease, and tuberculosis among rodents in California. *Public Health Bull.* 1912;53:3–23.
4. Wherry WB, Lamb BH. Infection of man with *Bacterium tularensis*. *J Infect Dis.* 1914;15:331–340.
5. Francis E. Tularemia (Francis 1921), I: The occurrence of tularemia in nature as a disease of man. *Public Health Reports.* 1921;36:1731–1751.
6. Parker RR, Spencer RR. Hereditary transmission of tularemia infection by the wood tick *Dermacentor andersoni* Stiles. *Public Health Reports.* 1926;41:1403–1407.
7. Rockwood SW. Tularemia: What's in a name? *ASM News.* 1983;49:63–65.
8. Eigelsbach HT, McGann VG. Gram-negative aerobic rods and cocci. Genus *Francisella* Dorofe'ev 1947, 176^{AL}. In: Krieg NR, Hold JG, eds. Vol 1. *Bergey's Manual of Systematic Bacteriology*. Baltimore, Md: Williams & Wilkins; 1986: 394–399.
9. Forsman M, Sandström G, Jaurin B. Identification of *Francisella* species and discrimination of type A and type B strains of *F tularensis* by 16S rRNA analysis. *Appl Environmental Microbiol.* 1990;56:949–955.
10. Pavlova IB, Meshcheryakova IS, Emelyanova OS. Study of the microstructure of the two races of the tularemia bacterium in strains with different degrees of virulence. *J Hyg Epidemiol Microbiol Immunol.* 1967;11:320–327.
11. Cherwonogrodzky JW, Knodel MH, Spence MR. Increased encapsulation and virulence of *Francisella tularensis* live vaccine strain (LVS) by subculturing on synthetic medium. *Vaccine.* 1994;12:773–775.
12. Fulop MJ, Webber T, Manchee RJ, Kelly DC. Production and characterization of monoclonal antibodies directed against the lipopolysaccharide of *Francisella tularensis*. *J Clin Microbiol.* 1991;29:1407–1412.
13. Evans ME, Gregory DW, Schaffner W, McGee ZA. Tularemia: A 30-year experience with 88 cases. *Medicine.* 1985;64:251–269.
14. Jellison WL. *Tularemia in North America, 1930–1974*. Missoula, Mont: University of Montana; 1974: 276.
15. Karpoff SP, Antonoff NI. The spread of tularemia through water, as a new factor in its epidemiology. *J Bacteriol.* 1936;32:243–258.
16. McCrumb FR Jr. Aerosol infection of man with *Pasteurella tularensis*. *Bacteriol Rev.* 1961;25:262–267.

17. Brooks GF, Buchanan TM. Tularemia in the United States: Epidemiologic aspects in the 1960's and follow-up of the outbreak of tularemia in Vermont. *J Infect Dis*. 1970;121:357–359.
18. Olsen PF. Tularemia. In: Hubbert WT, McCulloch WF, Schnurrenberger PR, eds. *Diseases Transmitted From Animals to Man*. Springfield, Ill: Charles C Thomas; 1975: 191–222.
19. Evans ME, McGee ZA. Tularemia. In: Kass EH, Platt R, eds. *Current therapy in infectious diseases*. Philadelphia, Pa: BC Decker; 1983: 18–19.
20. Francis E. Tularemia. *Atlantic Med J*. 1927;30:337–344.
21. Quan SF, McManus AG, von Fintel H. Infectivity of tularemia applied to intact skin and ingestion in drinking water. *Science*. 1956;123:942–943.
22. Foshay L. Tularemia: A summary of certain aspects of the disease including methods for early diagnosis and the results of serum treatment in 600 patients. *Medicine*. 1940;19:1–83.
23. McCrumb FRJ, Snyder MJ, Woodward TE. Studies on human infection with *Pasteurella tularensis*: Comparison of streptomycin and chloramphenicol in the prophylaxis of clinical disease. *Trans Assoc Am Phys*. 1957;70:74–80.
24. Saslaw S, Eigelsbach HT, Wilson HE, Prior JA, Carhart S. Tularemia vaccine study, I: Intracutaneous challenge. *Arch Intern Med*. 1961;107:121–133.
25. Saslaw S, Eigelsbach HT, Prior JA, Wilson HE, Carhart S. Tularemia vaccine study, II: Respiratory challenge. *Arch Intern Med*. 1961;107:134–146.
26. Fortier AH, Polsinelli T, Green SJ, Nacy CA. Activation of macrophages for destruction of *Francisella tularensis*: Identification of cytokines, effector cells, and effector molecules. *Infect Immun*. 1992;60:817–825.
27. Anthony LSD, Ghadirian E, Nestel FP, Kongshavn PAL. The requirement for gamma interferon in resistance of mice to experimental tularemia. *Microb Pathog*. 1989;7:421–428.
28. Leiby DA, Fortier AH, Crawford RM, Schreiber RD, Nacy CA. In vivo modulation of murine immune response to *Francisella tularensis* LVS by administration of anticytokine antibodies. *Infect Immun*. 1992;60:84–89.
29. Anthony LSD, Kongshavn PAL. H-2 restriction in acquired cell-mediated immunity to infection with *Francisella tularensis* LVS. *Infect Immun*. 1988;56:452–456.
30. Surcel H, Ilonen J, Poikonen K, Herva E. *Francisella tularensis*-specific T-cell clones are human leukocyte antigen class II restricted, secrete interleukin-2 and gamma interferon, and induce immunoglobulin production. *Infect Immun*. 1989;57:2906–2908.
31. Surcel H, Syrjälä H, Karttunen R, Tapaninaho S, Herva E. Development of *Francisella tularensis* antigen responses measured as T-lymphocyte proliferation and cytokine production (tumor necrosis factor alpha, gamma interferon, and interleukin-2 and -4) during human tularemia. *Infect Immun*. 1991;59:1948–1953.
32. Karttunen R, Surcel H-M, Andersson G, Ekre H-PT, Herva E. *Francisella tularensis*-induced in vitro gamma interferon, tumor necrosis factor alpha, and interleukin 2 responses appear within 2 weeks of tularemia vaccination in human beings. *J Clin Microbiol*. 1991;29:753–756.
33. Tärnvik A. Nature of protective immunity to *Francisella tularensis*. *Rev Infect Dis*. 1989;11:440–451.
34. Syrjälä H, Koskela P, Ripatti T, Salminen A, Herva E. Agglutination and ELISA methods in the diagnosis of tularemia in different clinical forms and severities of the disease. *J Infect Dis*. 1986;153:142–145.
35. Sato T, Fujita H, Ohara Y, Homma M. Microagglutination test for early and specific serodiagnosis of tularemia. *J Clin Microbiol*. 1990;28:2372–2374.

36. Koskela P, Salminen A. Humoral immunity against *Francisella tularensis* after natural infection. *J Clin Microbiol.* 1985;22:973–979.
37. Fortier AH, Slayter MV, Ziemba R, Meltzer MS, Nacy CA. Live vaccine strain of *Francisella tularensis*: Infection and immunity in mice. *Infect Immun.* 1991;59:2922–2928.
38. Thorpe BD, Marcus S. Phagocytosis and intracellular fate of *Pasteurella tularensis*, III: In vivo studies with passively transferred cells and sera. *J Immunol.* 1965;94:578–585.
39. Hood AM. Virulence factors of *Francisella tularensis*. *J Hyg (Camb).* 1977;79:49–60.
40. Proctor RA, White JD, Ayala E, Canonico PG. Phagocytosis of *Francisella tularensis* by rhesus monkey peripheral leukocytes. *Infect Immun.* 1975;11:146–151.
41. Sjostedt A, Conlan JW, North RJ. Neutrophils are critical for host defense against primary infection with the facultative intracellular bacterium *Francisella tularensis* in mice and participate in defense against reinfection. *Infect Immun.* 1994;62:2779–2783.
42. Francis E. Tularemia. In: Christian HA, ed. *Industrial Diseases and Infectious Diseases*. Vol 1. Oxford, England: Oxford University Press; 1948: 955–989.
43. Giddens WR, Wilson JWJ, Dienst FT, Hargrove MD. Tularemia, an analysis of one-hundred forty-seven cases. *J La State Med Soc.* 1957;109:93–98.
44. Pullen RL, Stuart BM. Tularemia: Analysis of 225 cases. *JAMA.* 1945;129:495–500.
45. Young LS, Bicknell DS, Archer BG. Tularemia epidemic: Vermont, 1968: Forty-seven cases linked to contact with muskrats. *N Engl J Med.* 1969;280:1253–1260.
46. Bazett HC. Studies on the effects of baths on man, I: Relationship between effects produced and the temperature of the bath. *Am J Physiol.* 1924;70:412–429.
47. Hughes WT, Etteldorf JN. Oropharyngeal tularemia. *J Pediatr.* 1957;51:363–372.
48. Butler T. Plague and tularemia. *Pediatr Clin North Am.* 1979;26:355–366.
49. Levy HB, Webb CH, Wilkinson JD. Tularemia as a pediatric problem. *Pediatrics.* 1950;6:113–122.
50. Everett DE, Templer JW. Oropharyngeal tularemia. *Arch Otolaryngol.* 1980;106:237–238.
51. Anschultz RR. Tularemia with extensive pharyngitis. *Am J Dis Child.* 1941;62:150–153.
52. Blackford SD, Casey CJ. Pleuropulmonary tularemia. *Arch Intern Med.* 1941;67:43–71.
53. Overholt EL, Tigertt WD. Roentgenographic manifestations of pulmonary tularemia. *Radiology.* 1960;74:758–764.
54. Archer VW, Blackford SD, Wissler JE. Pleuropulmonary manifestations in tularemia: A roentgenographic study based on thirty-four unselected cases. *JAMA.* 1935;104:897–898.
55. Avery FW, Barnett TB. Pulmonary tularemia: A report of five cases and consideration of pathogenesis and terminology. *Am Rev Respir Dis.* 1967;95:584–591.
56. Dennis JM, Bourdreau RP. Pleuropulmonary tularemia: Its roentgen manifestations. *Radiology.* 1957;68:25–30.
57. Dienst FTJ. Tularemia, a perusal of three-hundred thirty-nine cases. *J La State Med Soc.* 1963;115:114–127.

58. Hunt JS. Pleuropulmonary tularemia: Observations on 12 cases treated with streptomycin. *Ann Intern Med.* 1947;26:263–276.
59. Ivie JM. Roentgenological observations on pleuropulmonary tularemia. *Am J Roentgenol.* 1955;74:466–471.
60. Kennedy JA. Pulmonary tularemia: A discussion of the disease as a clinical entity, with a report of three cases. *JAMA.* 1942;118:781–787.
61. Miller RP, Bates JH. Pleuropulmonary tularemia: A review of 29 patients. *Am Rev Respir Dis.* 1969;99:31–41.
62. Rubin SA. Radiographic spectrum of pleuropulmonary tularemia. *Am J Roentgenol.* 1978;131:277–281.
63. Lovell VM, Cho CT, Lindsey NJ, Nelson PL. *Francisella tularensis* meningitis: A rare clinical entity. *J Infect Dis.* 1986;154:916–918.
64. Adams CW. Tularemic pericarditis. *Dis Chest.* 1958;34:1–8.
65. Jager BV, Ransmeier JC. Constrictive pericarditis due to *Bacterium tularense*: Report of a case and review of reported cases of pericarditis occurring with tularemia. *Bull Johns Hopkins Hosp.* 1943;72:166–178.
66. Kleibl K. Les tularémides Érythèmes polymorphes et érythèmes nouveaux tularémiques [in French]. *Med Mal Infect.* 1971;11:447–451.
67. Gelfand MS, Mehra N, Simmons BP. Tularemia and atypical lymphocytosis. *J Tenn Med Assoc.* 1989;8:417–418.
68. Penn RL, Kinasewitz GT. Factors associated with a poor outcome in tularemia. *Arch Intern Med.* 1987;147:265–268.
69. Kaiser AB, Reives D, Price AH, et al. Tularemia and rhabdomyolysis. *JAMA.* 1985;253:241–243.
70. Overholt EL, Tigertt WD, Kadull PJ, et al. An analysis of forty-two cases of laboratory-acquired tularemia: Treatment with broad-spectrum antibiotics. *Am J Med.* 1961;30:785–806.
71. Westerman EL, McDonald J. Tularemia pneumonia mimicking Legionnaire's disease: Isolation of organisms on CYE agar and successful treatment with erythromycin. *South Med J.* 1983;76:1169–1171.
72. Berdal BP, Soderlund E. Cultivation and isolation of *Francisella tularensis* on selective chocolate agar as used routinely for the isolation of gonococci. *Acta Pathol Microbiol Immunol Scand [B].* 1977;85:108–109.
73. Fowler J, Taylor R, Gelfand M. Tularemia pneumonia—Tennessee. *MMWR.* 1983;32:262–263.
74. Provenza MJ, Klotz SA, Penn RL. Isolation of *Francisella tularensis* from blood. *J Clin Microbiol.* 1986;24:453–455.
75. Pike RM. Laboratory associated infections: Summary and analysis of 3,921 cases. *Health Lab Sci.* 1976;13:105–108.
76. Francis E. Immunity in tularemia. *Trans Assoc Am Physicians.* 1936;51:394–398.
77. Syrjälä H, Herva E, Honen J, Saukkonen K, Salminen A. A whole-blood lymphocyte stimulation test for the diagnosis of human tularemia. *J Infect Dis.* 1984;150:912–915.
78. Saslaw S, Carhart S. Studies with tularemia vaccines in volunteers, III: Serological aspects following intracutaneous or respiratory challenge in both vaccinated and nonvaccinated volunteers. *Am J Med Sci.* 1961;241:689–699.
79. Francis E, Evans AC. Agglutination, cross-agglutination and agglutination absorption in tularemia. *Public Health Rep.* 1926;41:1273–1295.
80. Ransmeier JC, Ewing CL. The agglutination reaction in tularemia. *J Infect Dis.* 1941;69:193–205.

81. Saslaw S, Carlisle HN. Studies with tularemia vaccines in volunteers challenged with *Pasteurella tularensis*. *Am J Med Sci*. 1961;242:166–172.
82. Warring WB, Ruffin JS. A tick-borne epidemic of tularemia. *N Engl J Med*. 1946;234:137–140.
83. Koskela P, Herva E. Cell-mediated immunity against *Francisella tularensis* after natural infection. *Scand J Infect Dis*. 1980;12:281–287.
84. Taylor RR. Report on tularemia with its diagnosis and treatment. *JAMA*. 1950;47:47–50.
85. Van Metre TEJ, Kadull PJ. Laboratory acquired tularemia in vaccinated individuals: A report of 62 cases. *Ann Intern Med*. 1959;50:621–632.
86. Rohrbach BW, Westerman E, Istre GR. Epidemiology and clinical characteristics of tularemia in Oklahoma, 1979 to 1985. *South Med J*. 1991;84:1091–1096.
87. Taylor JP, Istre GR, McChesney TC, Satalowich FT, Parker RL, McFarland LM. Epidemiologic characteristics of human tularemia in the southwest-central states, 1981–1987. *Am J Epidemiol*. 1991;133:1032–1038.
88. Woodward TE. Chemosuppression of specific infections with antibiotics. *J Chronic Dis*. 1962;15:611–622.
89. Woodward TE. Tularemia. In: Beeson PB, McDermott W, Wyngaarden JB, eds. *Textbook of Medicine*. Philadelphia, Pa: WB Saunders; 1979: 465–468.
90. Halstead CC, Kulasinghe HP. Tularemia pneumonia in urban children. *Pediatrics*. 1978;61:660–662.
91. Kudelina RI, Olsufiev NG. Sensitivity to macrolide antibiotics and lincomycin in *Francisella tularensis holarctica*. *J Hyg Epidemiol Microbiol Immunol*. 1980;24:84–88.
92. Syrjälä H, Schildt R, Raisainen S. In vitro susceptibility of *Francisella tularensis* to fluoroquinolones and treatment of tularemia with norfloxacin and ciprofloxacin. *Eur J Clin Microbiol Infect Dis*. 1991;10:68–70.
93. Sawyer WD, Dangerfield HG, Hogge AL, Crozier D. Antibiotic prophylaxis and therapy of airborne tularemia. *Bacteriol Rev*. 1966;30:542–548.
94. Foshay L, Hesselbrock WH, Wittenberg MJ, Rodenberg AH. Vaccine prophylaxis against tularemia in man. *Am J Pub Health*. 1942;32:1131–1145.
95. Tigertt WD. Soviet viable *Pasteurella tularensis* vaccines: A review of selected articles. *Bacteriol Rev*. 1962;26: 354–373.
96. Eigelsbach HT, Downs CM. Prophylactic effectiveness of live and killed tularemia vaccines, I: Production of vaccine and evaluation in the white mouse and guinea pig. *J Immunol*. 1961;87:415–425.
97. McCrumb FR Jr. Commission on Epidemiological Survey. Review of tularemia: Studies on tularemia vaccine 1960–62. In: *Annual Report*. Washington, DC: Armed Forces Epidemiological Board; 1962: 81–86.
98. Hornick RB, Eigelsbach HT. Aerogenic immunization of man with live tularemia vaccine. *Bacteriol Rev*. 1966;30:532–538.
99. Burke DS. Immunization against tularemia: Analysis of the effectiveness of live *Francisella tularensis* vaccine in the prevention of laboratory-acquired tularemia. *J Infect Dis*. 1977;135:55–60.