Zoonosis Update

Tularemia

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I know of no other infection of animals communicable to man that can be acquired from sources so numerous and so diverse. In short, one can but feel that the status of tularaemia, both as a disease in nature and of man, is one of potentiality.

—R. R. Parker, 1934[1]

Background

Tularemia, also known as rabbit fever and deerfly fever, is a bacterial zoonosis caused by the small, pleomorphic, gram-negative coccobacillus *Francisella tularensis*. The organism can infect numerous species of animals; in the United States, rodents and lagomorphs are the important epizootic hosts, and various species of ticks are important maintenance hosts and biologic vectors. Of 4 biogroups of the organism, 2 account for most clinical disease; these biogroups can be distinguished biochemically, epidemiologically, and by virulence testing. Jellison type A (*F tularensis* subsp *tularensis*) ferments glycerol, is highly virulent for laboratory rabbits, and is found predominately in North America; Jellison type B (*F tularensis* subsp *holarctica,* formerly susbsp *palaearctica*), which is less virulent than type A, is found throughout Europe and Asia but also in North America. *Francisella tularensis* subsp *mediaasiatica* is not known to cause infections in humans and is found in Central Asia. *Francisella novicida* was previously considered a separate species but is now classified as another biogroup of *F tularensis. Francisella tularensis* subsp *novicida* is of low virulence[2] and has been isolated from human patients with a tularemia-like illness in the United States and Canada.[3]

Tularemia was first described by McCoy in 1911 as a plague-like illness of California ground squirrels. In 1912, McCoy and Chapin[4] published a paper on the syndrome and the causative agent, which was originally called *Bacterium tularense* after Tulare County, where the work was done. The first described clinical case in which *F tularensis* was implicated as the etiologic agent occurred in 1914, when the oculoglandular form was reported in a restaurant worker in Cincinnati.[5] Edward Francis, a US Public Health Service surgeon, dedicated much of his scientific career to research on the organism, including classifying the various clinical manifestations of the disease, cultivating the organism, developing serologic tests, and elucidating its various mechanisms of transmission. In 1947, the agent was renamed *Francisella tularensis* in his honor.

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Epidemiology

Tularemia occurs throughout temperate regions of the Northern Hemisphere, including North America, continental Europe, the former Soviet Union, China, Korea, and Japan. The disease in humans is nationally notifiable in the United States and has been reported from all states but Hawaii. In the first half of the 20th century, tularemia infection in the United States was relatively common; the peak number of reported cases was 2,291 in 1939.[6] Since the 1950s, the number of reported cases has declined dramatically; a mean of 124 cases was reported annually between 1990 and 2000 (**Fig 1**). During this same period, over half of the human cases reported to the national Centers for Disease Control and Prevention were reported from Arkansas (23%), Missouri (19.4%), South Dakota (7%), and Oklahoma (6.6%; **Fig 2**). Cases have been reported in all months of the year, but most case onset is reported from May through August, corresponding to transmission via arthropod bites. Historically, a winter peak in incidence, associated with rabbit hunting, was also noticed. In humans, the incidence is highest in persons aged 5 to 9 years and in persons aged ≥ 75 years; males have a higher incidence in all age categories. Native Americans are disproportionately represented.[7]

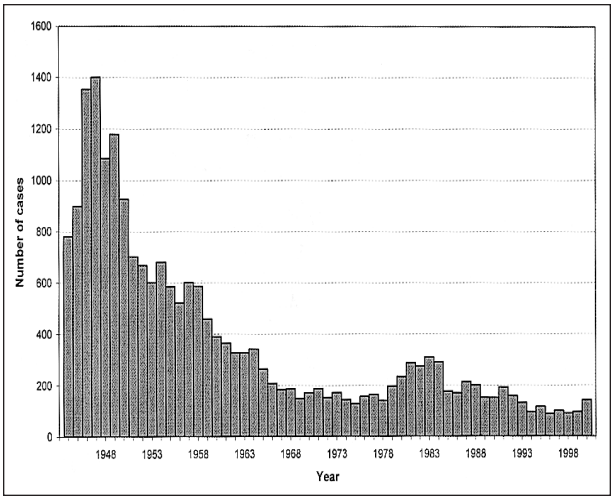

Figure 1—Number of reported human cases of tularemia by year—United States, 1944–2000.

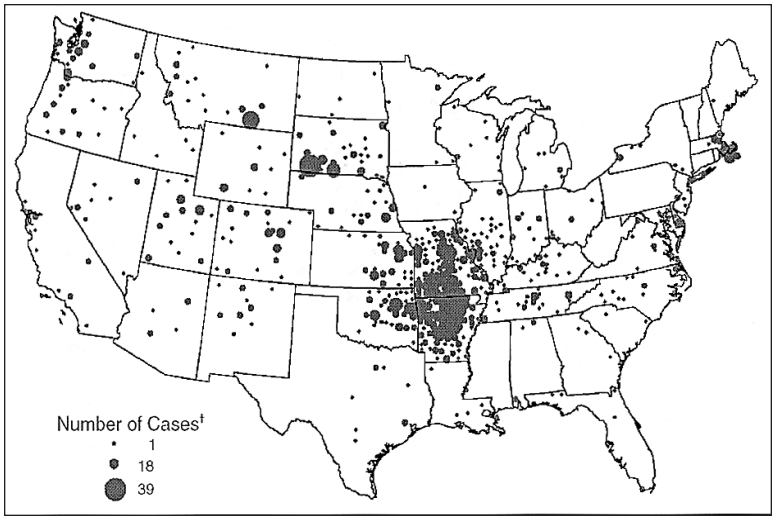

Figure 2—Reported cases* of tularemia—United States, 1990–2000. *Based on 1,347 human patients reporting county of residence in the lower continental United States. Alaska reported 10 cases in 4 counties during 1990–2000. †Circle size is proportional to the number of cases (range, 1 to 39).

Ecology

Francisella tularensis can infect a diverse population of animals, including more than 100 species of wild and domestic mammals as well as humans, 25 species of birds, and several species of amphibians and reptiles.[8] In the United States, lagomorphs (particularly *Sylvilagus* spp) are most commonly infected and important in the transmission of *F tularensis* to humans. Because ticks can maintain infection throughout their life cycle, they are not only important vectors but also important reservoirs of the disease. In the United States, tularemia outbreaks in humans have been associated with contact with muskrats[9] and beavers.[10] In addition to contact with lagomorphs, sporadic cases have been acquired through contact with squirrels,[11,12] sheep,[13] pheasants,[14] and nonhuman primates.[15] Epizootics have been reported in vole (*Microtus* spp),[16,17] beaver (*Castor canadensis*), and muskrat (*Ondatra zibethica*) populations.[10] Natural infection with *F tularensis* has also been recognized in wild-caught prairie dogs (*Cynomys ludovicianus*),[18] marmosets (*Callithrix jacchus*),[19] raptors,[20] quail,[21] mink and fox,[22] and numerous other species.[8]

Of domestic species, cats and dogs can acquire infection, although clinical illness is more common in cats. Dogs may serve as reservoirs for the organism or maintenance hosts for the tick vector.[23,24] Of livestock, sheep are most commonly affected; other livestock species may have serologic evidence of exposure to *F tularensis*, although clinical disease is rare. Infection in nonhuman primates has been reported[25-28] in a pet monkey and animals housed in zoos and laboratory facilities.

Francisella tularensis does not form spores but can survive in water, soil, and decaying animal carcasses. The organism has been isolated from water and mud samples stored at 7°C for as long as 14 weeks, in tap water for as long as 3 months, and in dry straw litter for at least 6 months.[8]

Mode of Transmission

Francisella tularensis is highly infectious, and as few as 10 to 50 organisms inhaled or injected intradermally can reliably cause disease in humans.[29,30] Natural transmission of *F tularensis* to humans can occur through various modes—the most common in the United States are via an arthropod bite, such as that of a tick or deerfly,[31] and through direct contact with infected tissues. There are numerous reports[32-39] of acquisition of tularemia through direct contact with infected cats, through breaks of the skin (cat bite or scratch), and in at least 1 instance where no abrasion or wound was recalled.[35] Clinical illness in cats is not necessary for transmission to occur.[39] It has been speculated that dogs can mechanically transmit the bacterium after mouthing an infected animal or becoming wet with contaminated water[40]; in 1 instance, inhalation of the organism occurred while shearing a dog.[41] Human cases have resulted from contact with *F tularensis*-infected sheep,[6,13] including contact during shearing. *Francisella tularensis* can also be transmitted to humans by ingestion of the organism in contaminated food or drink, after exposure to contaminated water, and through inhalation. People who mow lawns or cut brush in tularemia-endemic areas may be at increased risk of pneumonic tularemia.[42] Laboratory transmission of *F tularensis* occurs readily because the organism is easily aerosolized, sometimes simply by opening a culture plate; at 1 time tularemia was second only to viral hepatitis as an occupationally acquired infection of laboratory workers.[43] Person-to-person transmission of *F tularensis*, even in cases of pneumonic tularemia, has not been convincingly documented, although specimens obtained from ulcers or buboes should be considered infectious.

In the United States, the most common tick vectors of tularemia are the American dog tick (*Dermacentor variabilis*), the Lone Star tick (*Amblyomma americanum*), and the Rocky Mountain wood tick (*D andersoni*), although other ticks are known to be naturally infected.[44] Deerflies, and possibly other biting arthropods such as mosquitoes, can mechanically transmit the organism. Dogs and cats acquire infection through the bite of an infected arthropod or by ingestion of, or direct contact with, infected tissues.

Because of the high infectivity of *F tularensis*, its relative ease of dissemination, and its potential to cause severe disease, the organism is classified as a Category A agent of bioterrorism.[45] *Francisella tularensis* could be used as a biologic weapon if aerosolized or used to contaminate food or water. The Johns Hopkins University Working Group on Civilian Biodefense believes that the greatest adverse medical and public health consequences would be realized following the intentional release of aerosolized *F tularensis*.[46]

Clinical Signs

In humans, tularemia is characterized by acute