Prepared by the USGS National Wildlife Health Center
in cooperation with the U.S. Fish and Wildlife Service

Tularemia

Circular 1297

U.S. Department of the Interior
U.S. Geological Survey

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By Milton Friend

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DIRK KEMPTHORNE, Secretary

U.S. Geological Survey
P. Patrick Leahy, Acting Director

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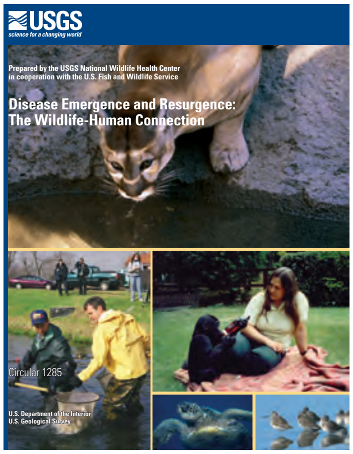

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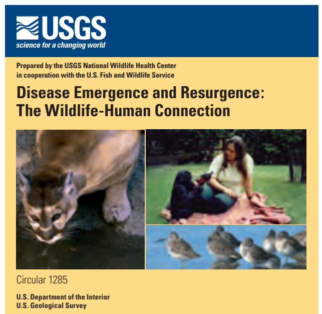

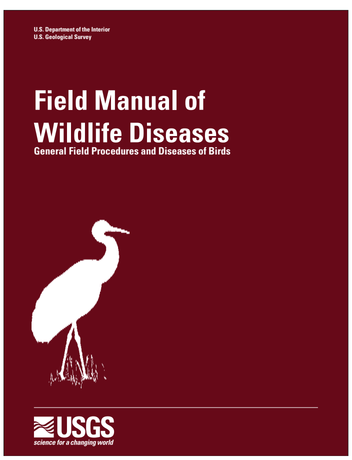

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Preface

"It was the best of times, it was the worst of times…"
Charles Dickens, 1859

The continually emerging story of the bacterial disease tularemia (*Francisella tularensis*) is akin to a major theme of the Charles Dickens classic, "A Tale of Two Cities."[1] That theme is "the possibility of resurrection and transformation, both on a personal level and on a social level."[2] Within the USA, tularemia is primarily a disease of times past; in 1994, it was removed from the notifiable list of diseases because of the low number of human cases.[3] However, tularemia has recently re-emerged as a threat for contemporary society in the USA and elsewhere. Global social unrest and political issues have elevated concerns over the use of *F. tularensis* as a biological weapon,[4] causing its reinstatement as a notifiable disease in the USA in 2000.[5]

Like the differences in life within the cities of London and Paris at the time of Dickens' novel, the consequences from infection by *F. tularensis* are associated with different characteristics of the organism. One form of this bacterium typically results in inconsequential negative impacts on human health while the other commonly results in serious illness, and even death. The latter outcome, the broad spectrum of species infected, and because *F. tularensis* is one of the most infectious organisms known for humans and animals[6, 7] have resulted in a history of development, and some use of this organism as a biological weapon.[5, 8]

F. tularensis has been classified as a Category A select agent because of its potential as a biological weapon.[4] This classification highly regulates scientific investigations and other possession and/or use of this agent as a way of protecting society from its nefarious use. Beyond concerns of intentional introduction of tularemia is the presence of this disease among the global plethora of emerging infectious diseases impacting humans and animals.[9] Tularemia clearly is an emerging and resurging disease[4] and one likely to gain increased prominence as a disease to be anticipated. Wildlife are an important component of the ecology of tularemia, including the maintenance of *F. tularensis* in nature and in disease transmission. This publication emphasizes the wildlife component of tularemia and is presented in a non-technical format to be useful for a broad audience with varying levels of biological knowledge. Technical terms are defined in a glossary. The citations serve as the foundation for the information presented and as a gateway to the scientific literature for those seeking greater detail. This publication is one of a series of publications on selected emerging diseases to supplement Disease Emergence and Resurgence: The Wildlife-Human Connection.[9]

Milton Friend

Acknowledgments

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Tularemia

By Milton Friend

> "I know of no other infection of animals communicable to man that can be acquired from sources so numerous and so diverse" (Parker[10]).
>
> "The causative agent of tularemia, *Francisella tularensis*, is one of the most infectious pathogenic bacteria known…" (Dennis et al.[4]).

Synonyms

Colloquial terms for tularemia have their origins in several countries. Those synonyms include clinical manifestations of the disease, sources of disease, recognition of early investigators associated with this malady and geographic areas of occurrence (Table 1).

Overview

Tularemia is a highly **infectious disease** caused by the **bacterium** *Francisella tularensis*. Infections in humans are not **contagious** and most often result from contact with infected wildlife, ingestion of or contact with contaminated water, or bites from **ticks** and other **arthropods** that have fed on infected wildlife. Aerosol transmission is another way humans can become infected. Disease is expressed in different clinical forms, and varies in severity depending on the **virulence** of the organism, dose, and site of inoculum.[4] Tularemia has a broad geographic distribution in the Northern Hemisphere and is more restricted elsewhere.[11] A wide variety of species have been naturally infected by *F. tularensis*;[11–13] the number of species reported to be susceptible to infection exceeds 300, according to a recent report, which does not include some of the cold-blooded species such as **fish** and **snakes** (Table 2) reported by others.[14]

Table 1. Tularemia, a disease of many names.

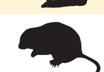
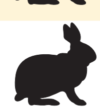
Country	Synonyms	Primary animal hosts
USA[13,15–18]	Plague-like disease of rodents, plague-like lymphadenitis, conjunctivitis *tularensis*, Francis' disease, deerfly fever, rabbit fever, rabbit disease, cattle-fly fever, Pahvant Valley fever or plague, glandular-type tick fever, *Bacterium tularense*	Beavers, water voles, rabbits 
Japan[19,20]	*Yato-byo* (hare disease), hare meat poisoning	Japanese hares 
Former Soviet Union[19,21]	*Sibirskaia iazva* (Siberian ulcer), epidemic polyadenitis, water-rat trappers' illness, epidemic lymphadenitis, *khvar* ("the ailment")	Water voles 
Norway[22,23]	*Leemands soet* (lemming fever), hare plague	Lemmings, hares 
Sweden	Hare plague	Hares 

Table 2. Diversity of host species for *Francisella tularensis*.

Representative species	Number of species[a]
Mammals	
	190
Invertebrates	
	88
Birds	
	23
Amphibians	
	3
Reptiles	
	Very few
Fish	
	Very few

[a]Data presented for mammals, invertebrates, birds, and amphibians are from a recent scientific review of tularemia.[14] These data represent relative numbers of species in each of the groups that have been found to be susceptible to infection by *F. tularensis*, but are less than the cumulative total of all reports. For example, approximately twice the species of birds shown are documented within this chapter as being susceptible to infection by *F. tularensis*. Also, only limited investigations have been undertaken with amphibians, reptiles, and fish.

Background

The history of tularemia is both that of a disease of two ages and a "tale of two diseases." Tularemia is thought to have evolved as a disease of wild animals in both the New World and the Old World about 11 million years ago during the end of the **Miocene** or early **Pliocene**.[24,25] The transition between those **epochs** was a time of rapid evolution for land **mammals** and the evolution of *Francisella* spp. is thought by some to be associated with that of **rabbits** and **hares**. The present forms of *F. tularensis* have different levels of virulence for humans in the Old World than those in the New World.[25]

Tularemia was first described as a disease of humans prior to the discovery of the causative agent (Table 3) and probably occurred in Japan as early as 1818 and in Norway since at least 1890[26] and perhaps as early as 1653.[27] The first verified human cases occurred early in the 20th century (Table 4). Within North America, the first case supported by laboratory diagnosis occurred in 1914 in an Ohio meat cutter.[28,29] However, retrospective evaluations indicate that the first two human cases occurred in 1904 in California and in 1907 in Arizona.[15] Six additional cases in Utah during 1908 and 1910 of what is now known to be tularemia were diagnosed as deerfly fever.[30] Dr. Edward Francis provided the linkages between disease syndromes in the United States, Japan, and the former Soviet Union (Table 1) as being caused by bacteria of the genus that now bears his name.[19,31]

Table 3. Examples of historic diseases of humans now believed to be occurrences of tularemia.

Disease	Year	Location
Lemming fever	1653	Norway[27]
Siberian ulcer	1741	Western Siberia[21]
Hare meat poisoning	1818, 1837	Japan[26]
Steinkrankheit	1825	Siberia[32]
Pestis minor	1877–79	Astrakhan, former Soviet Union[32]
Typhus associated with buboes	1877–78	Astrakhan, former Soviet Union[32]
Deerfly fever	1908–10	Utah, USA[30]
Plague-lilke disease of rodents	1908–11	California, USA[17]
Epidemic polyadenitis	1921	Irtysh River, former Soviet Union[21]
Epidemic lymphadenitis	1925	Voronezh Oblast, former Soviet Union[21]

The first North American case of tularemia in wild animals supported by a laboratory diagnosis occurred in 1912 during plague studies in California **ground squirrels**.[16] Francis proposed the name tularaemia to differentiate this disease from **rodent** plague because of the characteristic **septicemia** seen.[24] Other investigations established the presence of tularemia in meat market cottontail rabbits in Washington, D.C.[33]

Reported human cases of tularemia within the USA were greatest during the 1930s and 1940s, averaging over 1,000 cases per year. Since then, the yearly average has fallen below 200; however, the past importance of tularemia as a human disease, considerations of tularemia as a biological weapon,[4] and several recent major **epidemics** have caused renewed interest in this disease.[5]

Causative Agent

Tularemia is caused by infection with a small, **aerobic**, **pleomorphic**, nonspore-forming, **Gram-negative coccobacillus** now classified as *F. tularensis,*[34] following the original name of *Bacterium tularense*[16] and other designations.[11,35] Combinations of biochemical, epidemiological, virulence,and **pathogenesis** data have been used to subdivide *F. tularensis* into two major **biovars** (subspecies). Biochemical and molecular studies of isolates have identified different varieties of those subspecies (Box 1), raised a number of questions about the taxonomy of *Francisella* spp., and have also provided some enhanced insights regarding the ecology of tularemia.

Despite taxonomic questions and strain differences, a basic understanding of tularemia in humans and wildlife can be gained by viewing tularemia as being caused by type A and type B subspecies,[36] which distinguishes the highly virulent strains of the bacterium (type A) for humans from less virulent strains (type B). In North America, these different strains of *F. tularensis* have typically been associated with infections of different species of wildlife (Fig. 1). Only type A forms (*F. tularensis tularensis*) are moderately to highly virulent for humans and animals. Type A strains can cause illness in humans from an inoculum containing as few as 10 organisms.[37] Type B strains (e.g., *F. tularensis holarctica*) can also cause high mortality in wildlife but are generally of low virulence for humans. These strains usually require an inoculum of 10,000 organisms or more to cause illness in humans.[37] Type A, once thought to be present only in North America, has recently been found in arthropods in Europe.[38]

Table 4. First documentation of tularemia in selected countries.

Continent	Country[a]	Year[b]	Case
North America	USA	1911	Animal[17]
	Canada	1929	Animal[39]
	Mexico	1944	Human[40]
South America	Colombia	1948	Human[41]
	Venezuela	1948	Human[42]
	Argentina	1953	Human[42]
	Ecuador	1958	Human[43]
Europe	Austria	1917/1935[c]	Human[44,45]
	Former Soviet Union	1926	Human[25]
	Norway	1926/1929[d]	Human[46]
	Germany	1928	Human[45]
	Italy	1931	Animal[40]
	Sweden	1931	Human[50]
	Czechoslovakia	1936	Human[45]
	Greece	1938	Human[32]
	Finland	1938	Human[47]
	France	1938	Animal[41]
	Poland	1942	Animal[32]
	Yugoslavia	1944	Human[32]

Table 4. First documentation of tularemia in selected countries—Continued.

Continent	Country[a]	Year[b]	Case
Europe	Netherlands	1961	Animal[48]
	Romania	1997	Human[49]
	Belgium	1947[e]	Human[41]
	Switzerland	1948	Human[41]
	Denmark	1949	Animal[41]
	Bulgaria	1951	Animal[51]
	Spain	1952	Animal[13]
	Croatia	1952[h]	Human[52]
	Kosovo	1999	Human[53,54]
Middle East	Turkey	1913/1936[f]	Human[55]
	Iran	1970	Animal[48]
Africa	West Africa	1936	Human[56]
	Tunisia	1938	Animal[56]
	Ruanda-Urundi	1951	Human[41]
	French Cameroons	1952	Human[41]
Austro-Asia	Japan	1924	Human[57]
	Thailand	1954	Human[41]
	China[g]	1980	Human[58]
	Australia[i]	2003	Human[59]

[a]For several countries (i.e., Ecuador, Colombia, Thailand), reports could only be found of a single case of tularemia and in others (i.e., Argentina, French Cameroons), a small number of cases were reported for a single year. Those data do not establish tularemia as being enzootic in those countries as it cannot be determined if the human cases reported were acquired within country or elsewhere (see Fig. 2).

[b]The variability in reporting by different countries is such that earlier occurrences of laboratory-confirmed cases of tularemia likely exist for some countries. Also, retrospective analyses of disease reports from times prior to the isolation and identification of *F. tularensis* as the cause of tularemia clearly indicate the appearance of this disease in some countries in the 1800s; examples include Japan, the former Soviet Union, and Norway.[50]

[c]Designated as the first documented human case in Europe based on serology and clinical signs; first major human epidemic did not occur until 1936;[56] the first human cases associated with that epidemic occurred the previous year (1935).

[d]Report includes two human cases from 1926 diagnosed in 1929 based on serology taken in 1929 and clinical signs from 1926; the first human cases with isolation of *F. tularensis* are from 1929.[46]

[e]Most reports for the first appearance of tularemia in the Netherlands (Holland) are for 1953 rather than the 1947 date given by a few authors.

[f]An early case from 1913 diagnosed on basis of serology and clinical signs is reported; the first isolations of *F. tularensis* are from cases in 1936.[56]

[g]Report exists suggesting that tularemia may have affected soldiers in China and Burma during World War II.[56]

[h]First year for compulsory reporting of human cases.[52]

[i]First report of tularemia in the Southern Hemisphere.[59]

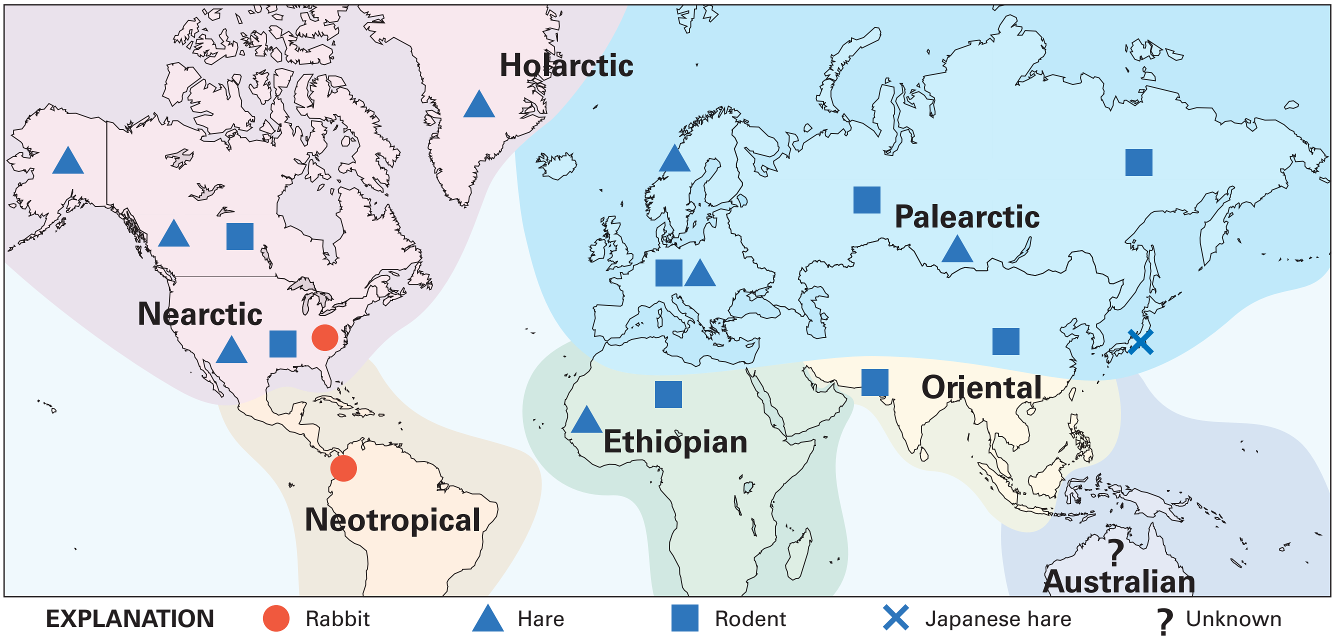


Figure 1. General distribution by biogeographic region of type A and type B strains of *Francisella tularensis* and their primary wildlife vectors.

Pathogen	Type of organisim[a]	Primary area of occurrence	Principal wildlife vectors
Francisella tularensis tularensis	A	North America	Rabbits[b]
F. tularensis holarctica[c]	B	Throughout **Nearctic** and **Palearctic** region (**Holarctic**)	Hares, rodents[d]
F. tularensis mediasiatica	B	Central Asia	Rodents[e], hares
F. tularensis novicida	B	North America, Australia	Unknown[f]

[a]Type A organisms typically cause moderate to severe disease in humans while type B organisms cause mild disease unless complications develop.

[b]Cottontail rabbit in Central and Eastern USA, Mexico, and Latin America; black-tailed jackrabbits in West; and snowshoe hare in Northern areas.

[c]Includes Japanese strains previously designated *F. tularensis* subsp. *holarctica*, biovar *japonica* Rodionova.[5,7,59]

[d]Beaver, muskrat, and voles in North America and Eurasia; varying hare, European brown hare, and Japanese hare in Eurasia along with voles (especially water vole) and muskrat.

[e]Voles, gerbils, and other small rodents.

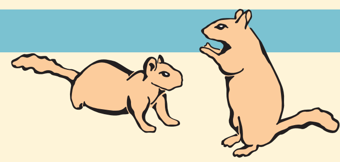
[f]Closely linked to waterborne transmission.

Box 1 The Journey of *Bacterium tularense* to *Francisella tularensis*

The nomenclature for the various subspecies of the bacterium causing tularemia has changed many times. As scientists developed a greater understanding of the genetic, biochemical, and molecular properties of the different strains of this organism, its geographic distribution, and the differences in the severity of disease in humans infected by these different forms of the bacterium, the nomenclature evolved. Highlights associated with these changes in nomenclature are provided here to document the transition that has occurred, the relations between nomenclature and enhanced knowledge of the epidemiology of tularemia, and to provide a basic understanding of the different nomenclature that is encountered within the literature.

Discovery

1912



Bacterium tularense

McCoy *and* Chapin name the bacteria they isolated from California ground squirrels with a "plague-like" disease; the species name is drawn from Tulare County, California, the location for their investigations.

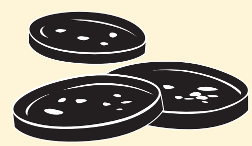
Transitions

1920s–1946

Bacterium tularensis

Dr. Edward Francis determines that the disease reported by McCoy and Chapin and several other disease syndromes from North America, Asia, and Europe are all the same disease and suggests the name tularaemia to reflect the bacteremia often found in association with this disease.[26,33] The species name is later changed from from *tularense* to *tularensis*.

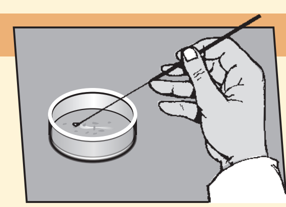
Bacterium tularensis
Bacillus tularensis
Brucella tularensis
Pasteurella tularensis



Over time, the causative bacterium is placed in different genera by different investigators based on the properties of this bacterium relative to other bacteria. No general acceptance exists for any of the classifications.[11]

A Home at Last

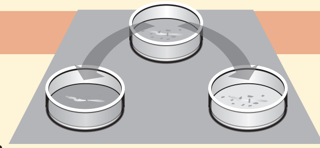
1947–1959



Francisella tularensis

Agreement is reached among leading microbial taxonomists that the bacterium causing tularemia should be placed in an independent genus. That genus is designated *Francisella* in honor of the investigations of Dr. Francis.[34,60]

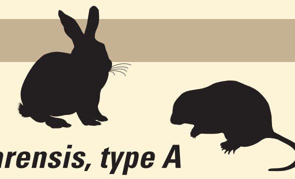
A Family Divided
1959–1961



Francisella tularensis tularensis
Francisella tularensis palearctica

Increasing notice is given to the marked differences in the severity of tularemia in humans in North America in comparison to other parts of the world. This difference is attributed to there being two major varieties of the bacterium: one occurring in the **Nearctic Region** (*tularensis tularensis*) and the other in the **Palearctic Region**. [60] (See figure 1.)

Kinship
1961–1970

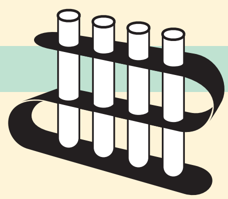


Francisella tularensis, type A
Francisella tularensis, type B

It is shown that the geographic separation for different variants of the causative bacterium is not valid; tularemia cases of low severity caused by similar bacteria occur in the Nearctic and Palearctic Regions. Also, severe human cases of tularemia in North America are associated with different wildlife vectors than milder human cases.

It is proposed that two distinct types of tularemia exist in North America and that they can be defined as tick-borne tularemia of rabbits (type A) and waterborne tularemia of rodents (type B). It is also noted that type B is comparable to tularemia in Europe and Asia.[61]

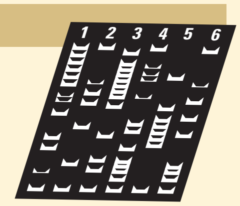
Family Ties
1970



Francisella tularensis nearctica
Francisella tularensis holarctica (syn. palaearctica)
Francisella tularensis mediaasiatica
Francisella tularensis holarctica a. japonica
Francisella novicida

Based on biochemical and pathogenic properties, the bacterium causing tularemia was divided into four geographic subspecies associated with North America (*F. t. nearctica*), throughout the **Holarctic Region** (*F. t. holarctica*), central Asia (*F. t. mediaasiatica*), and Japan (*F. t. japonica*). The placement of *F. novicida*, an organism found only in Utah, was a significant question as only rodents at that time were known to be affected.[62]

The Present



Francisella tularensis biovar (subspecies) tularensis (syn. nearctica; also known as type A)
Francisella tularensis biovar palaearctica (syn. holarctica, type B)
Francisella tularensis palaearctica mediaasiatica
Francisella tularensis palaearctica japonica

More recent evaluations classify *F. tularensis* into four distinct subspecies:[5,7]
Francisella tularensis tularensis
Franciselllla tularensis holarctica
Francisella tularensis mediasiatica
Francisella tularensis novicida

Unique isolations of organisms associated with human cases of tularemia[63-65], aided by molecular technology, are continuing to refine the nomenclature for organisms within the genus *Francisella*. That technology indicates that *F. novicida* and *F. tularensis* are indistinguishable and has resulted in support for *F. novicida* being considered a subspecies of *F. tularensis*.[7] Also, an additional species not involved with tularemia, *F. philomiragia,* has been added to the genus *Francisella*.[11,66,77] Further changes in the nomenclature for *Francisella* are likely.

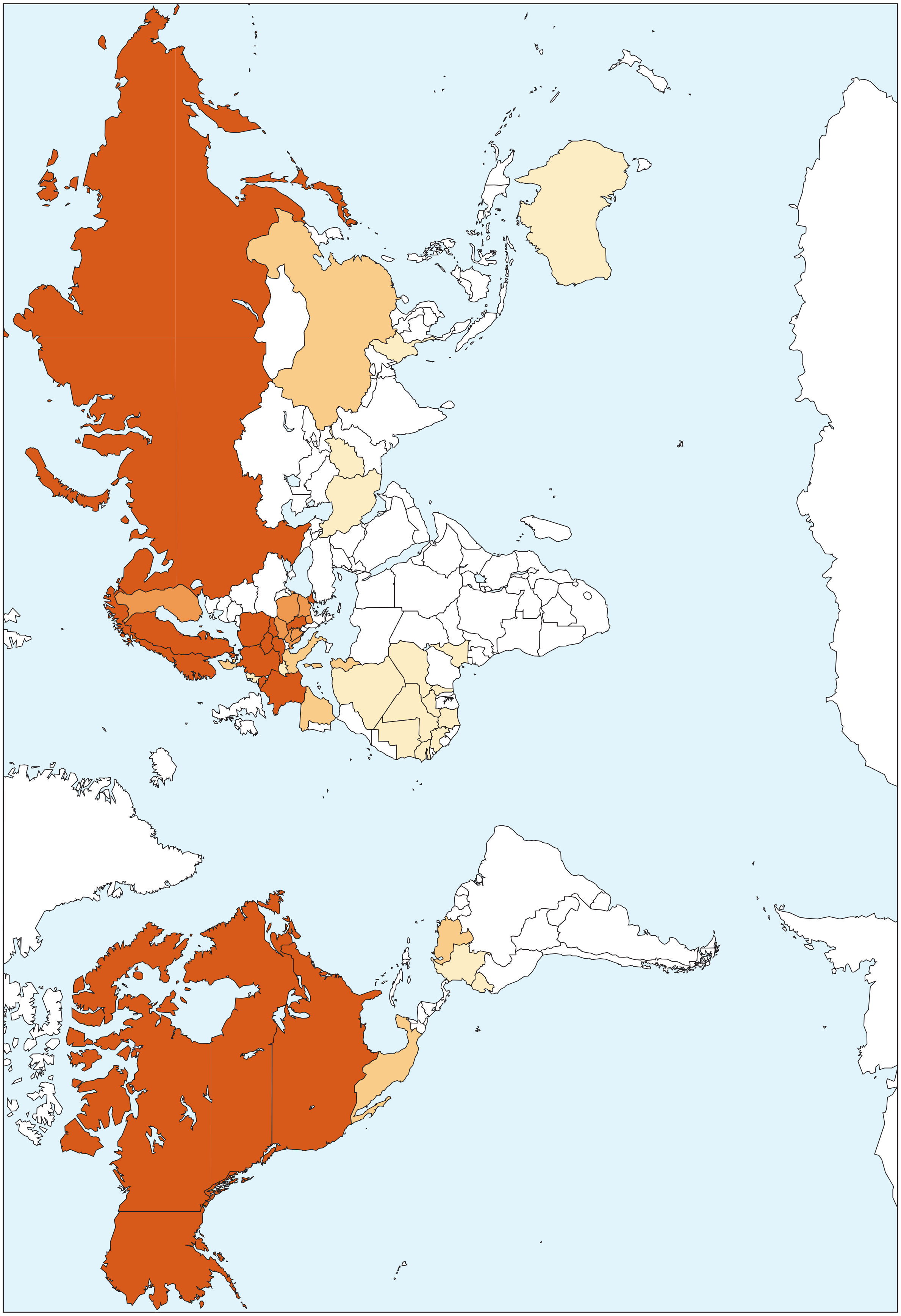


Figure 2. Reported occurrence of tularemia by country.

Geographic Distribution

Tularemia occurs throughout much of North America and **Eurasia** (Fig. 2) but has a patchy distribution in the Northern Hemisphere (Holartic Region). In the USA, tularemia has been reported from every state except Hawaii.[12] It has also been reported in every province of Canada.[68] Although documentation is poor for the remainder of North America, tularemia is known to occur as far south in North America as Guadalajara, Mexico.[11,36] The geographic distribution of tularemia in Scandinavia, the former Soviet Union, and in Japan is well documented (Fig. 3). Far less is known about the geographic distribution and the prevalence of tularemia in many other countries. Conflicting reports about the presence or absence of tularemia in some countries is partly due to questionable documentation for some areas and sporadic occurrences in new areas (Table 5). It is generally accepted that tularemia is absent from New Zealand and Central America. However, until 2003, tularemia had not been reported from Australia.[59]

Figure 3. Geographic distribution of tularemia in Norway,[22] Sweden,[69,70] Japan,[71] and the former Soviet Union.[25,66]

Table 5. Recent examples of tularemia in nontraditional geographic locations.

Location	Year	Human cases	Cause	Comments
Tuscany, Italy	1982	49	Contaminated village water system; infected hare suspected source	Only two cases previously reported in Italy; thought to be associated with importation of hares for hunting purposes.[72]
Western Bosnia	1985	?	Infected hares	Poswar outcome.[53]
Central Spain	1997	585	Infected hares	Only one case previously documented in Spain; outbreak associated with hare hunting.[49]
Central Spain	1998	19	Contaminated water and **crayfish**	Site far removed from 1997 epidemic; sewage plant suspected as contamination source; exposure of humans associated with crayfish fishing and cleaning.[49]
Kosovo	1999–2000	327	Rodent-contaminated food and water	First outbreak of tularemia in Kosovo; associated with postwar environmental conditions.[53, 54]
Southern Sweden	2000	270	Primarily mosquito bites	Widespread outbreak in a geographic area where tularemia was previously rare. One of the factors correlated with human cases was owning a cat.[70]
Northern Territory, Australia	2003	1	Waterborne infection	First report from Australia and from the Southern Hemisphere. Suggestion that infections by *F. tularensis* novicida may be more common and widespread than previously thought.[59]

Table 6. Examples of reported human cases of tularemia by country.

Country	Year of first report	Reporting period	Number of cases	Average per year
USA	1911	1924–1960	30,851	857.0
		1990–2000[a]	1,368	136.8
Japan	1924	1924–1994	1,372	19.6
Former Soviet Union	1926	1926–1942	73,300	4,581.3
Canada	1929	1930–1950	79	4.0
		1946–1958	73	6.1
Sweden	1931	1931–1996	5,963	91.7
France	1938	1946–1947	404	36.7

[a]Not a reportable disease from 1985 through 1999. Therefore, the number of cases may be somewhat less than occurred, even though cases generally still were reported.

Patterns and Trends

In general, reported human tularemia cases have substantially declined during the past half-century within **endemic** areas of the world;[11, 73, 74] however, human cases have been reported during the past few years in areas where tularemia had not previously been found (Table 5). Fewer outbreaks of this disease are also being reported for wildlife, but, because wildlife disease surveillance is passive in most of the world, disease activity is most likely underreported. In humans, tularemia, especially the milder forms, is also undoubtedly underrecognized and underreported.[4] Nevertheless, reported human cases provide sufficient information for evaluating patterns and trends for this disease. Although tularemia is widely endemic in Eurasia, it is typically a disease of Northern and Central Europe; Scandinavia and countries of the former Soviet Union report the most human cases. In Asia, tularemia is most prevalent in Japan (Table 6).

In the USA, 15 human cases of tularemia with 2 deaths were recorded prior to 1924[36] and a total of 30,851 human cases were reported between 1924 and the end of 1960. However, a steady decline in the number of cases began in the 1940s[75] after the high of 2,291 cases in 1939.[76] Less than 200 cases were reported during the 1990s (Fig. 4). In addition to reduced case numbers, geographic prevalence of tularemia within the USA has changed (Fig. 5). In contrast to the more eastern occurrence of tularemia cases during the first half of the 20th century, most human cases currently occur in the South, Central, and Western States, especially Missouri, Arkansas, Oklahoma, South Dakota, and Montana.[4] Educating the public about tularemia and sources of infection has helped to reduce the number of cases.[24] Changes in the pattern of disease may also reflect local and regional changes in wildlife and insect vector populations due to changes in the landscape and in human activities, such as trapping and hunting that have altered human interactions with wildlife **reservoir hosts**.

The general pattern of tularemia within the USA is sporadic, small clusters of human cases. Tularemia is more likely to occur in males than females, in children younger than 10, and adults aged 50 or older,[4] and may reflect activity patterns that enhance opportunities for exposure. Most cases now result from arthropod bites during the summer months (Fig. 6). Cases during winter are most common in hunters and trappers who handle infected animal carcasses.[77, 78] The largest reported epidemic in the USA involved 50 tick-associated cases among military personnel on maneuvers in Tennessee.[79] The largest reported wildlife associated **epizootic** resulted in a similar number of cases among muskrat trappers in Vermont.[78] Despite the low number of human cases associated with individual events, the persistence of *F. tularensis* in nature has resulted in substantial numbers of humans contracting tularemia over the years. Also, the potential for this disease to be "explosive" was vividly demonstrated in Europe during World War II when thousands of Soviet and German soldiers on the Eastern European front contracted tularemia.[4] Recent outbreaks, 585 confirmed human cases in Spain[49] and 327 confirmed cases in Kosovo,[53] attest to the continuous potential for tularemia to jeopardize human health.

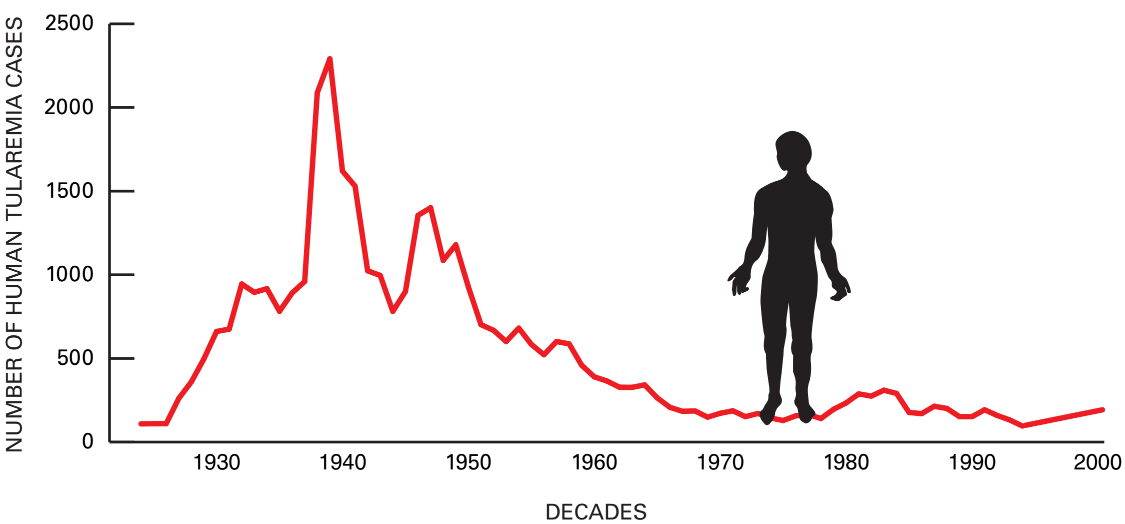


Figure 4. Reported human cases of tularemia in the USA, 1924–2000. Tularemia was not a reportable disease during the period of 1995 through 1999, but was reinstated to that status at the start of 2000.[80–83]

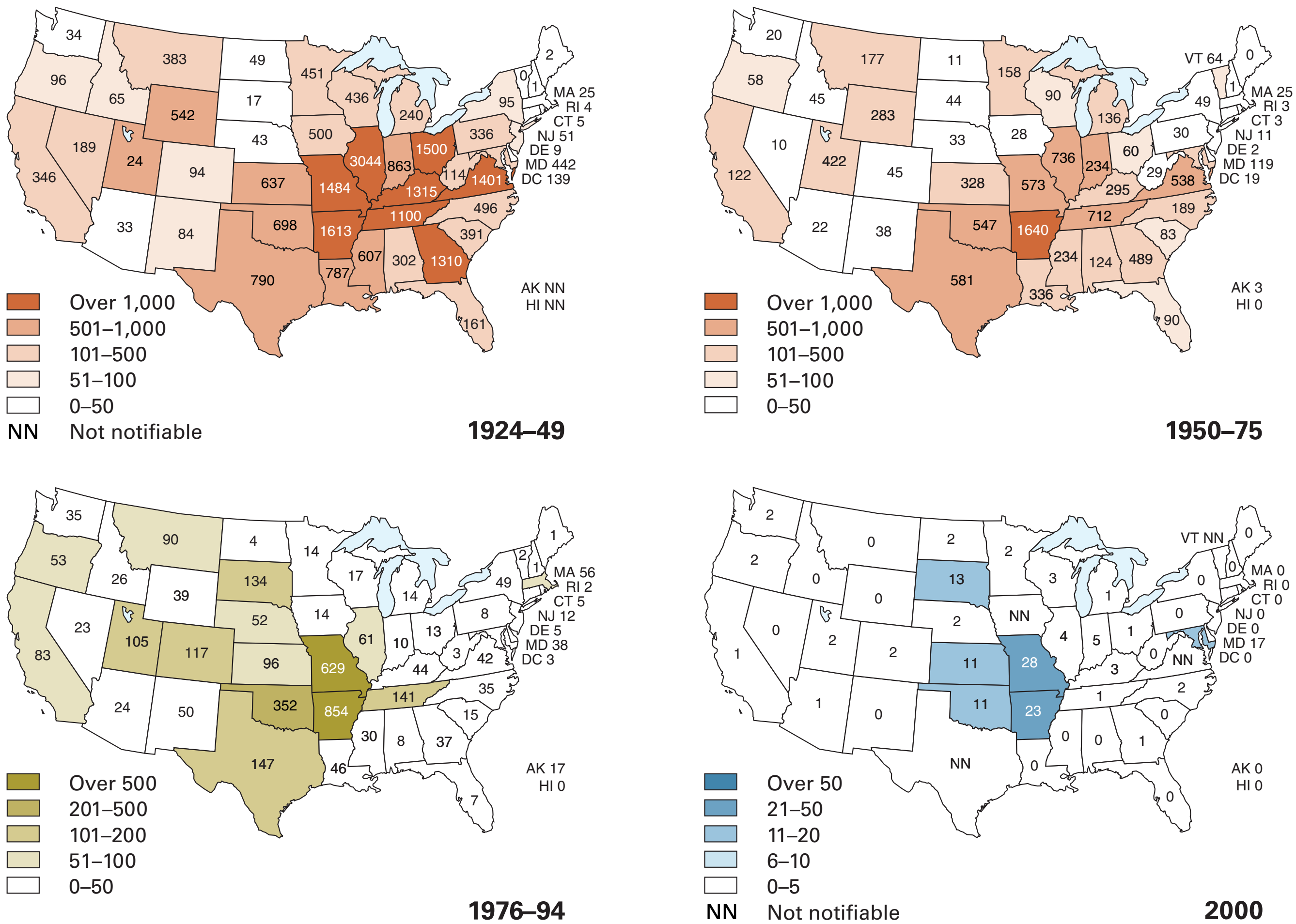
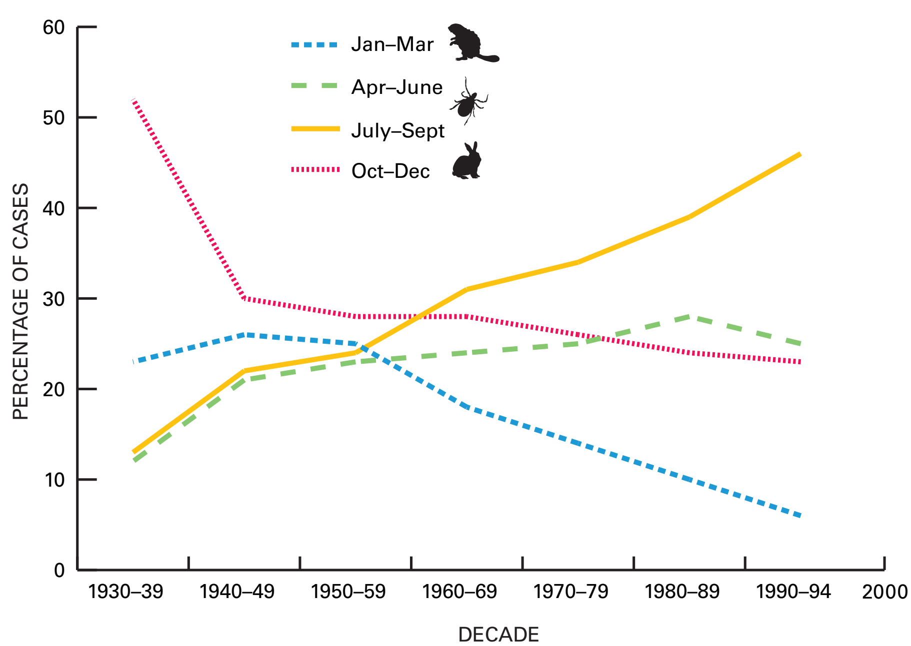


Figure 5. Geographic distribution of human cases of tularemia within the USA (not a reportable disease from 1995–1999).[80–82]

Figure 6. Seasonal occurrence by decade of human cases of tularemia within the USA. The major decline of the 1930s and 1940s in the percentage of cases during October to December is likely due to reduced hunting activities associated with males being involved with World War II. Similarly, the decline since the 1950s in the percentage of human cases during January to March is likely associated with reduced trapping of muskrat and beaver due to the declining fur market. Major increases over time in the percentage of cases during other periods of the year reflects both the decreases in cases previously associated with hunting and trapping and increased outdoor recreation by the general public that facilitates tick-borne cases of tularemia.[80–82]



Species Susceptibility

"Few, if any, **zoonotic** disease agents have a broader host distribution than *F. tularensis*." (Hopla and Hopla[11])

Wild mammals are the primary hosts of *F. tularensis*, especially species within the orders Lagomorpha, Rodentia, and Sciuromorpha (Table 7). Sheep are the domestic mammal most commonly associated with tularemia (Table 8), but within recent years domestic cats have become an increasing source for human cases of this disease.[84–89] **Birds** are fairly resistant,[11] but a variety of species have acquired natural infections (Box 2) and mortality has been reported in some instances. **Invertebrates**, primarily ticks, have substantial roles both in the maintenance of *F. tularensis* in nature and in disease **transmission** (Table 9). A variety of other species has also been infected naturally or experimentally (Table 10).

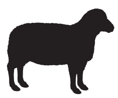
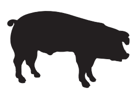
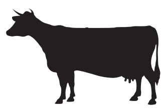
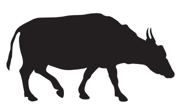
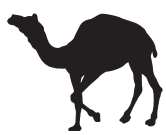
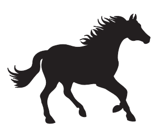
Table 7. A synopsis of North American mammals known to be susceptible to infection by *Francisella tularensis* and probability of human infection.[a]

Family	Species	Source for human infection[b]
Cervidae	**Mule deer, white-tailed deer**	Common
Antilocapridae	Pronghorn	Rare
Ursidae	Black bear	Rare
Canidae	Coyote, red fox, gray fox, kit fox	Occasional
Felidae	Bobcat	Rare
Mustelidae	Mink, badger, spotted **skunk**, striped skunk, weasel, black-footed ferret	Occasional
Procyonidae	Raccoon	Occasional
Erethizontidae	Porcupine	Rare
Soricidae	Wandering shrew	Occasional
Leporidae	Snowshoe or varying hare, black-tailed jackrabbit, white-tailed jackrabbit, cotton-tail rabbit (eastern, desert, brush, pygmy, mountain)	Very common
Dipelphidae	Opossum	Rare
Castoridae	Beaver	Very common
Muridae (formerly Cricetidae)	Mouse (deer, canyon, piñon, western harvest, and house); white-footed mouse (redwood, Sonoran, Osgood); rat; muskrat; woodrat (white-throated, dusky-footed, bushy-tail, desert); Norway rat; meadow vole (Sawatch, Drummond's, Tule); vole (California, montane)	Very common
Heteromyidae	Pocket mouse (Great Basin, long-tailed); kangaroo rat (Ord's, chisel-toothed, Great Basin)	Rare
Sciuridae	Chipmunk (eastern, least, cliff); woodchuck; yellow-bellied marmot; ground squirrel (antelope, Townsend's, Piute, Richardson's, Wyoming, Columbian, Uinta, California); white-tailed prairie dog, black-tailed prairie dog; squirrel (gray, red, fox, Wind River pine)	Very common
Zapodidae	Jumping **mice**	Rare

[a]Adapted and modified from Reilly[13] with some additions.

[b]Relative importance varies for species identified within family groups.

Table 8. Domestic animals naturally infected with *Francisella tularensis.*

Species	Probabillity for disease[a]	Comments
Sheep 	High	Humans in the USA, Canada, and Russia have become infected from shearing, skinning, and slaughtering infected sheep and from infected ticks previously attached to sheep.[90–92]
Goats 	Low	Rarely have clinical disease.
Swine 	Intermediate[b]	Infections are primarily in young animals, due to bites from infected ticks and from eating infected rodents.[27]
Cattle 	Moderate[c]	Bites of infected insects and contaminated pasture and water may result in fatal infections;[27] 57–91 percent of cattle tested in a tularemia enzootic area of the former Soviet Union had antibody to *F. tularensis*.[93]
Water buffalo 	Low	Chronically infected experimentally and shed *F. tularensis* in urine for as long as 37 days.[19]
Camel 	Moderate	Isolation of *F. tularensis* in Kazakhstan region of former Soviet Union;[25] camels are highly susceptible and are commonly infected in the desert areas of that country. Transmission to camels is thought to be by biting **midges** that have fed on infected **gerbils**.[94]
Horse 	Intermediate	More resistant than cattle, but **foals** heavily infested with infected ticks have died.[95]
Cat[d] 	Moderate	Reported to be highly resistant by early investigators in the former Soviet Union. However, tularemia has been diagnosed in domestic cats within that region and also in Europe, Asia,[27] and North America[96–99]; cats can directly (bites and scratches) and indirectly (transfer of infected ticks) transmit tularemia to humans.[84,100]
Dog 	Intermediate	More resistant than cats, but numerous cases have occurred in Europe, the former Soviet Union, and in the USA; most involve hunting dogs and dogs associated with sheep ranching.[27,101] Transmission to humans is mechanical, from contaminated mouth parts following the killing and sometimes consumption of infected rabbits, and from infected ticks.

[a]With the exception of sheep and cats, tularemia in domestic animals is uncommon in North America.

[b]Infection relatively common but clinical disease seldom reported.

[c]Clinical disease is relatively common in this species.

[d]Recent studies indicate that cats are mildly to highly susceptible to infection by *F. tularensis* and may die from tularemia. However, this disease is infrequently recognized in cats because clinical signs often mimic other infectious diseases.[84,85,96–100]

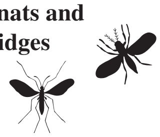
Table 9. General importance of invertebrates in the natural history of tularemia.

[**a** designates the role of the species in maintaining foci of *Francisella tularensis*; **b** designates role of the species in infecting humans]

		Transmission role	
Species type	**Comments**	**Nature[a]**	**Humans[b]**
TICKS	*"It is generally accepted that ticks are of major importance in maintaining the enzootic foci of tularemia."*[11]		
	• Ticks are biological vetors, some species of which serve as both hosts and reservoirs for *F. tularensis*. • Ticks may harbor *F. tularensis* in their saliva/gut for as long as 2 decades.[31] • Tularemia in North America is primarily a tick-borne disease.[45]		
Hard ticks 	Those of the genera *Ambylomma* and *Dermacentor* are usually resposnsible for human cases, while those of the genera *Ixodes* and *Haemophysallis*, because they seldom feed on humans, are of greater importance for maintaining enzootic foci among wildlife.[11,19] Primary vectors of type A strains of tularemia.	High	High
Soft ticks 	Although experimental infection can occur, not important in the ecology of tularemia.[11,19] Viability of *F. tularensis* following laboratory infection was at least 674 days in one species and 701 days in another.[19,36]	Localized—low	Not important
MITES			
	Natural infections demonstrated but, in general, do not support prolonged development with the mite; primarily mechanical vectors.[102] General belief that mites are unimportant may be based on inadequate evidence, as gamisid mites are reported to be principal vectors in some associations.[19] Persistence of *F. tularensis* for 47 days in infected mites and transmission via bite has been documented in the former Soviet Union. Mites of the genus *Hirstionyssus* are thought to transmit infection in water **voles** during winter and in other rodents during spring and summer.[41] Because these mites feed repeatedly, they may continuously maintain infections in the host population for long periods. Also, experimental studies in the USA with the rat mite resulted in transovarial and transphasic transmission of *F. tularensis* within the mite and infection of mice by eating the infected mites.[94]	Localized—low	Not important
BITING FLIES			
Deerflies, stable flies, and horseflies 	Efficient vectors in specific areas such as Utah[103] and the former Soviet Union;[19] most transmission occurs between June and September in the western USA.[41] Mechanical vectors that acquire *F. tularensis* by feeding on infected host or substrate and transmit agent when a blood meal is taken within a few days. Hares, water voles, and contaminated water are primary sources for horseflies to acquire *F. tularensis* in the former Soviet Union; they remain infective for 2–3 days;[94,102] deerflies in Utah acquire *F. tularensis* primarily by feeding on infected jackrabbits and transmit the organisim when they bite humans.[103]	Localized—high	Localized—high
Mosquitoes 	Not important in the transmission of *F. tularensis* in North America but are historic vectors in Russia and Sweden.[11] Serve as mechanical vectors. Species of the genus *Aedes* commonly feed on tularemic water voles in the former Soviet Union where they transmit *F. tularensis* between voles and from voles to humans. *F. tularensis* can maintain itself in **mosquitoes** for up to 43–50 days and can be transmitted by the bite of the mosquito for up to 22–35 days.[94]	Localized—high	Localized—high

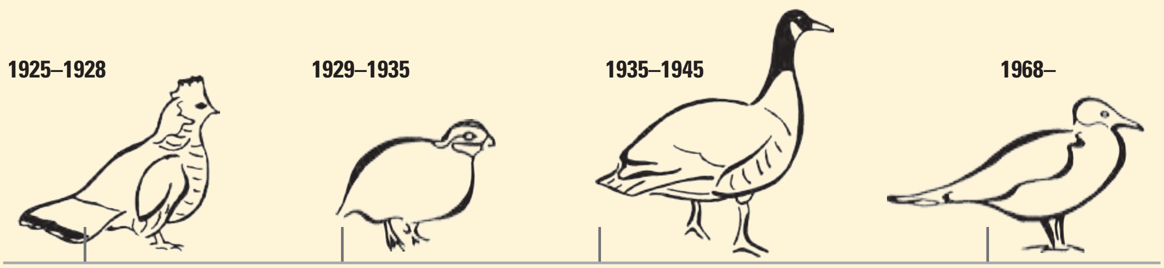
Table 9. General importance of invertebrates in the natural history of tularemia—Continued.

[**a** designates the role of the species in maintaining foci of *Francisella tularensis*; **b** designates role of the species in infecting humans]

Species type	Comments	Transmission role	
		Nature[a]	**Humans**[b]
BITING FLIES—Continued			
Gnats and midges 	*Culicoides* are occasional vectors of infection from hares to humans and between hares; gnats attack hairy parts of head and neck.[19] In desert regions of Western Siberia, these smallest of all biting flies may also vector tularemia between gerbils, gerbils and camels, and camels and humans.[94]	Localized—high	Localized—low
Blackflies 	Too little information to know the significance, if any, for these species.[102]	Unknown	Unknown
OTHERS			
Fleas 	Can be infected experimentally, are infected in nature, and can retain infection for long periods of time.[19] Although not considered important as a vector of *F. tularensis* to humans, they may have a greater role than is currently recognized in the transmission of *F. tularensis* between rodents.[11,102] The squirrel flea has the distinction of having been the first ectoparasite found infected with *F. tularensis*.[41] Experimentally infected fleas have maintained viable *F. tularensis* for 355 days and some species shed *F. tularensis* in their feces for up to 30 days.[94]	Localized—low	Not important
Lice 	Sucking **lice** may have a more important role than thought in the transmission of *F. tularensis* within a species.[19] Experimental studies have shown infection to persist for as long as 35 days and that lice are capable of transmitting *F. tularensis* among rodents.[41] However, the high degree of host specificity precludes transmission between species. There is no evidence that lice of humans are an important source of human infection.	Low	Not important
Bedbugs 	Capable vectors with infection being transmitted by ingestion of contaminated feces;[19] laboratory infections have resulted in feces remaining infective from 36–88 days in one evaluation[12] and for as long as 250 days in another.[41]	Not important	Not important
Caddis flies 	Become infected through water contaminated with *F. tularensis* and infect species that feed on them.[102]	Not important	Not important
Snails 	Same as **caddis flies.**	Not important	Not important

Birds and Tularemia *Box 2*

In general, the role of birds in the ecology of tularemia is poorly understood. Because early investigations showed most birds to be relatively resistant to clinical disease even though they could be infected[104,105] and because most human cases of tularemia are associated with **lagomorphs** and rodents, few investigations have focused on birds and tularemia. Nevertheless, within the USA, human cases of tularemia have been associated with preparing game birds, such as **pheasant**, **grouse**, and **quail**, for consumption.[106–109] Pheasants, partridges (ruffed grouse), and prairie chickens are reportedly the sources of 11 human cases of tularemia in an early summary of this disease in Wisconsin.[106] These cases, along with other human cases reported from **upland game birds**, contrast with expectations based on experimental studies.



1925–1928: Early experimental studies stimulated by the 1925–1926 precipitous decline of rabbit and grouse populations in Minnesota show that ruffed grouse and blue grouse are susceptible to infection.[89] Ring-necked pheasants[110] produced antibody against *Francisella tularensis* when inoculated with this organism but did not exhibit clinical disease.[111]

1929–1935: Tularemia is established as a natural disease of wild birds by the isolation of *Pasteurella (= Francisella) tularensis* from a quail dying in the wild[112] and from dead and dying sage grouse.[109] Infected ticks are collected from healthy sharp-tailed grouse and ruffed grouse.[110]

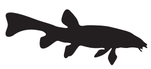
1935–1945: Evidence emerges that *F. tularensis* isolated from grouse is of lower virulence than organisms isolated from rabbits. In addition, isolates from bird ticks are also of lower virulence.[113] The organism involved may be a type B strain rather than the type A strain commonly seen in rabbits and hares in North America. Isolates of *F. tularensis* are also obtained from naturally infected gulls and the great horned owl. **Waterfowl** are infected experimentally.[102] Pheasants in experimental studies in Japan are resistant to clinical disease but researchers conclude that pheasants could become **carriers** of *F. tularensis*.[114]

1968–: An experimental study demonstrating high susceptibility of several species of oceanic birds to *F. tularensis* also discloses large numbers of viable bacteria in the **cloacal contents** of infected birds.[115] That finding poses questions relative to the potential for migrating water birds to contaminate surface waters via their body discharges.

The role of birds in the ecology of tularemia appears to be associated more with the persistence of this disease in nature than with direct transmission of *F. tularensis* to humans. In some areas, North American grouse share ticks with hares and cottontail rabbits, which helps maintain the natural foci of disease that is then transferred to humans from rabbits and hares (Fig. 13). Transmission occurs by contact with infected lagomorphs or arthropods, such as biting flies and other ticks that feed on humans and lagomorphs.[36] Also, infected birds may be a source for fecal contamination of surface waters with *F. tularensis*. This was postulated for the first outbreak of tularemia in Vermont when nearly 50 people involved with trapping and handling muskrats contracted tularemia within a 4-week period.[78] Migrating birds have also been considered a potential factor in the spread of tularemia throughout Central Europe,[56] primarily by transporting infected ticks into new areas where they then infect small rodents or hares. For example, in 1983 on the island of Stora Karlsö in Southern Sweden, tularemia was established as a tick-borne disease of mountain hare, probably from migrating birds carrying infected ticks. This is the only area of Sweden where ticks are primary vectors of tularemia, whereas mosquitoes are the primary vector elsewhere.[116,117]

Available information from most bird-associated human cases of tularemia suggests entry of the organism through punctures or abrasions in the skin while preparing birds for consumption (i.e., skinning and dressing). Wearing protective gloves can protect against this type of exposure. Regardless, the potential for contracting tularemia from contact with birds is low and should not be a major concern, even in areas where tularemia is enzootic. However, the potential for translocation of ticks infected with tularemia should be considered when moving birds for conservation and other purposes to new locations.

Table 10. Incidental species susceptible to *Francisella tularensis.*

Species type		Comments
Frogs and toads		Spontaneous infections of lake frogs and green toads in Russia. Conflicting information relative to susceptibility level. Studies in Turkey showed that experimentally infected frogs contaminated water that then infected other frogs placed in that water. Some of the newly infected frogs established latent infections and excreted virulent *F. tularensis* back into the water.
Turtles		The **snapping turtle** has been infected by *F. tularensis*.
Fish		Naturally acquired *F. tularensis* documented for a loach in Kazakhstan. Human infections in the USA have been associated with handling **catfish** but most likely involved mechanical transfer of bacteria from contaminated waters on the external surfaces of the fish being handled.[118,119] Experimental studies have failed to result in infection of six species of fish.[120]
Crustaceans		Two species of *Gammarus* and freshwater **crab** with naturally acquired *F. tularensis* in the former Soviet Union. **Fairy shrimp** were sources of *F. tularensis* in the Western USA.
Mollusks		*Francisella tularensis* isolated from six different species within the former Soviet Union. **Snails** were sources of *F. tularensis* in the Western USA.
Annelids		*Francisella tularensis* isolated from leeches in the Ukraine.
Snakes		Human infection associated with the skinning of a bull snake.[44]
Spiders		A human case of tularemia in Oklahoma is attributed to the bite of a spider, presumably the brown spider.[121]

Human Infections

Tularemia (type A infections) in humans is a moderately severe disease that follows a well-described course (Box 3) leading to the development of one of several clinical syndromes dependent on the route of exposure, dose, and virulence of the infecting organism.[4,12] Prior to the use of antibiotics for the treatment of tularemia, infection resulted in death in 5 to 15 percent of the cases within North America; this has fallen to 1 to 3 percent during recent years[12] and now averages less than 2 percent. However, untreated cases of tularemia that progress to **systemic infections** may result in severe disease with high rates of fatality. Outside of the USA, human deaths rarely exceed 1 percent because of the less virulent forms of *F. tularensis* present.[49] Immunity following clinical disease is usually lifelong.[11]

The ulceroglandular form of tularemia is the primary clinical syndrome seen in humans, accounting for 70 to 85 percent of North American cases.[11,31] The classical ulcerated skin **lesion** associated with this form of disease is generally found on the fingers or hands of those that acquire infection from wildlife (Box 3). Multiple **cutaneous** ulcerations have been reported in muskrat trappers[78] and others experiencing multiple exposures.[11] However, typically only a single ulcer is present at the site of entry for **parenteral inoculation** of *F. tularensis* by insect vectors, bone splinters, knife wounds, or pre-existing lesions when skinning or dressing infected wild animals.[19] Enlargement of **lymph nodes** is another common clinical sign of this form of tularemia in humans (Box 3).

Animal Infections

Clinical cases of tularemia are infrequently observed in free-ranging wildlife as infected animals are often severely **moribund** or dead when found. Also, the clinical appearance of tularemia in afflicted wildlife commonly is not diagnostic. Among the clinical signs reported for hares and cottontail rabbits afflicted with tularemia[12,14,24,19] are depression in behavior, easy capture, exhaustion, tameness, stupor, rubbing their nose and forefeet into the ground, not rearing their head or carrying their front feet well, recurrent spasms, and stagger.

Death from tularemia following infection of sensitive species such as rabbits and hares is usually about 2–10 days.[14] Some cottontail rabbits that became affected with tularemia following their placement within a large enclosure were dead within 7 days. In two instances, apparently healthy rabbits trapped within that enclosure were found dead of tularemia 3 days later.[122]

Nonspecific field signs for tularemia-infected domestic sheep include lagging behind the flock, labored breathing, rigid gait, diarrhea and frequent urination.[73] Often, large numbers of the ticks that transmit tularemia to sheep are found at the base of the sheep's ear and on the neck,[73] a condition that affords a high index for suspicion of tularemia.[19] Tularemia in domestic cats can range from mild to fatal disease and result in a broad spectrum of clinical signs, such as marked behavioral depression, enlarged lymph nodes, spleen, and liver, along with acute oral ulcerations and changes in blood chemistry.[100,123]

The extent and appearance of gross lesions of tularemia differ somewhat for different species of wild mammals, and, in some instances, may resemble those of **bubonic plague** and **tuberculosis**.[104] In rodents, the lesions resemble that of **paratuberculosis**.[13] Lesions are more pronounced in less sensitive species, such as **squirrels**, because of the prolonged course of disease.[14] Typical lesions visible on the surface of the liver, spleen, and lymph nodes are pale white to gray, often slightly raised necrotic foci, ranging in size from pinpoint to a few millimeters in diameter (Fig. 7). Similar lesions may also occur on the lungs and in the bone marrow; the spleen and liver may have a dark bluish-red coloration and be enlarged.[13,24]

Obtaining a Diagnosis

Wildlife

When one is determining causes of wildlife mortality, describing the field conditions associated with the dead animals is often as important as the carcasses. Fully record field observations and include observation notes along with any carcasses submitted for laboratory evaluations. Field examination of carcasses is not recommended when tularemia is suspected because of the potential for human exposure, the need for laboratory evaluations to confirm tularemia, and the potential for further contaminating the environment. Take appropriate precautions when collecting field specimens, keeping in mind the various routes for exposure to *F. tularensis*, such as skin contact, aerosol exposure, and ticks.

Double bag carcasses in a manner that protects the integrity of the outer bag and avoids contamination of the exterior surfaces of that bag. The diagnostic laboratory processing the specimens will provide guidance on preservation and shipping methods. In general, diagnosis is based on the combined results of necropsy findings and isolation of *F. tularensis* from the carcass. When only tissues, ticks, or environmental samples are available for testing, a combination of laboratory assays, including animal inoculations, are used to isolate and identify the presence of *F. tularensis* in those specimens. **Serology** can also be used to identify specific antibodies present in blood.

Humans

The diagnosis of tularemia in humans is supported by a variety of assays and clinical evaluations readily interpreted by physicians. However, in a small number of the cases, diagnosing tularemia during early stages of the disease may be difficult because of the multiple clinical syndromes presented (Box 3).[4,11] In addition, the current low number of tularemia cases in humans within the USA has resulted in a low index of diagnostic suspicion among clinicians and laboratory workers.[4] In many other parts of the world, the number of human cases of tularemia is also declining and may be creating similar situations. Nevertheless, early treatment is often needed, especially in North America because of the presence of the more virulent type A strains, to prevent the progression of infection to the more serious clinical syndromes. Those seeking medical assistance can aid their health professionals by providing information about their activities prior to becoming ill (i.e., outdoor recreation, contact with animals, and similar information) that might reflect the potential for exposure to tularemia and other **zoonoses**.

Figure 7. Gross lesions of tularemia. The "spots" within the liver of this beaver are focal necrosis and are typical lesions of tularemia seen in infected lagomorphs and rodents.

Box 3 Tularemia and You: Forms of Infection

Humans are highly susceptible to *Francisella tularensis* and infection can range from mild, unapparent cases to severe illness that may progress to death. Under some circumstances, untreated mild infections can progress to severe disease. Susceptibility to infection, multiple sources and routes for exposure, and the consequences from infection are among the reasons why *F. tularensis* is considered a potential biological weapon. Recent events involving **bioterrorism** have resulted in the Working Group on Civil Biodefense developing consensus-based recommendations for response by medical and public health professionals if tularemia is used domestically as a biological weapon.[4]

The virulence of the organism, dose, and route of exposure are important factors influencing the clinical form and severity of disease. In general, the course of clinical disease is abrupt and includes sudden onset of fever (38–40°C), shaking chills, generalized body aches that often are prominent in the low back, headache, sore throat, and thick nasal discharge (**coryza**). Nausea, vomiting, sweats, fever and chills, progressive weakness, general discomfort (**malaise**), loss of appetite (**anorexia**), and weight loss may also occur as the disease progresses.[4] Several primary clinical forms of tularemia have been described to categorize human infections. Those highlighted below are described in greater detail by Cunha,[31] Dennis et al.,[4] and others.

1 Ulceroglandular Tularemia

Most North American cases of tularemia (70 to 85 percent) are of this type and generally arise from handling contaminated carcasses or following a tick or other infective arthropod bite. Hunters and trappers are especially prone to exposure from contaminated carcasses during tularemia outbreaks within the species being pursued because gloves are seldom worn when handling animals. Hikers, campers, and others may be exposed to arthropods such as ticks and biting flies that have previously fed on infected animals. For example, deerfly bites were the source of two July 2001 cases of tularemia in Wyoming.[124] During that same time, one of two cases among rabbit hunters in Utah was attributed to a deerfly bite while camping and the other to handling a rabbit that may have been ill.[125] During the summer of 2000, there was a cluster of 10 cases, including one death, on Martha's Vineyard, Massachusetts; these 10 men were all involved in outdoor activities.[126] Ulceroglandular tularemia typically involves a painful, hard, discolored skin lesion that appears in 3–5 days at the site of exposure. Two days later, a firm, punched-out tender ulcer with raised edges is formed. Disease progression involves the spread of the organism from the skin lesion to the **lymphatics**, producing painful enlargement of the **lymphatic glands**. Further spread of the organism through the bloodstream may follow with associated impacts on major organs and other body systems.

2 Glandular Tularemia

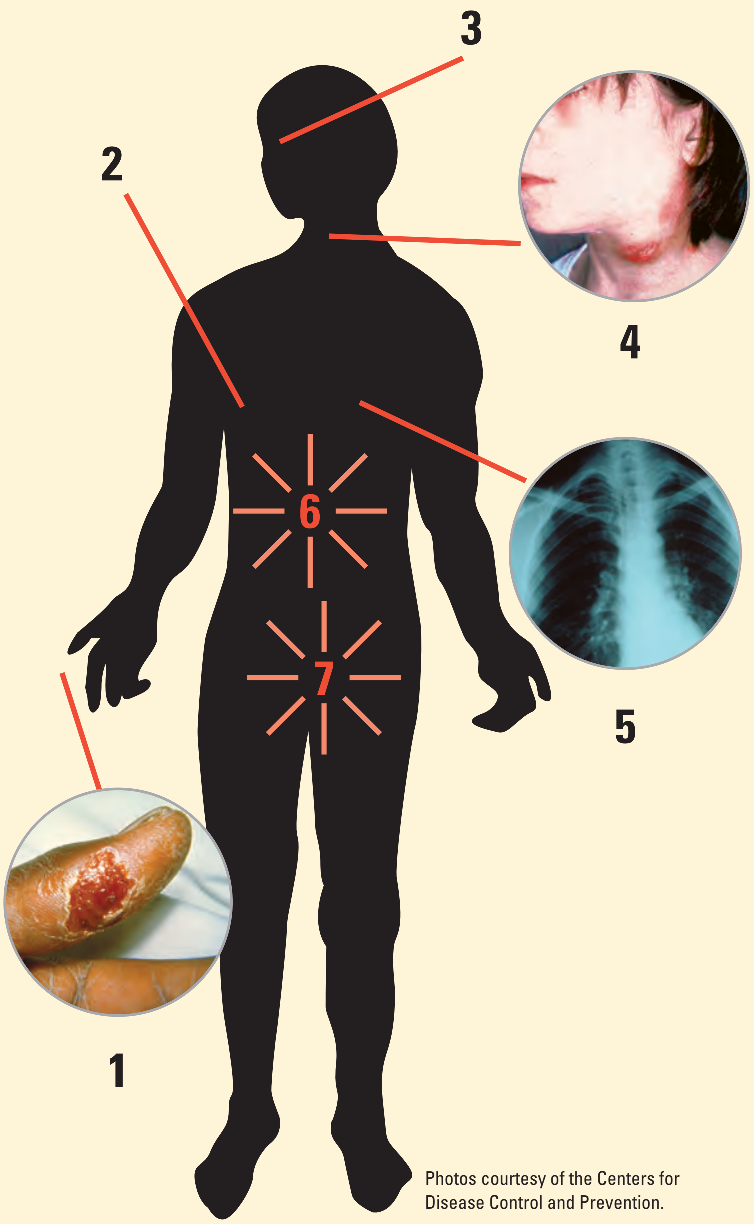
Similar to the ulceroglandular form, but no skin lesions are evident to indicate the site and cause of exposure. About 5 to 10 percent of human cases are of this type.

3 Oculoglandular Tularemia

In 1914, Dr. Derrick Vail presented a paper titled "A Case of 'Squirrel Plague' Conjunctivitis in Man" before the Ophthalmatic Section of the Michigan State Medical Society. He contended there was no precedent for this case in the written ophthalmic literature and believed it to be the first report of infection of the human eye by the agent causing a plague-like disease among rodents, notably the California ground squirrel.[28] The patient was a Cincinnati meat cutter in an inexpensive restaurant and was thought to have become infected by handling wild rabbits purchased by the restaurant. About 1 to 5 percent of tularemia cases within the United States are of this form. Exposure generally involves direct contamination of the eye by fingers, water spray, and aerosol transmission. For example, handling of a wild baby rabbit brought into the home likely contaminated the fingers of one individual who acquired oculoglandular tularemia.[127] This form of tularemia can be quite painful and in extreme cases may result in a loss of vision. Clinical signs may include ulceration of the **conjunctiva** and the development of abnormally large amounts of fluids (**edema**) within the eye. Tearing, pussy discharge from the area of infection, sensitivity to light, and ocular pain are also associated with the infection. Enlargement of regional lymph nodes also occurs.

4 Oropharyngeal Tularemia

This form of tularemia is acquired by drinking contaminated water, ingesting contaminated food, and, in some instances, by inhaling contaminated droplets or aerosols. Contaminated wells that serve as public water supply have been a source for numerous human cases of tularemia in Europe.[53,55,72] Contamination generally results from infected animals contaminating water that feeds the well, or by those animals entering the well itself. War, civil strife, and other conditions that may negatively impact the quality of public water supplies in tularemia endemic areas can contribute to the occurrence of this disease. The ingestion of inadequately cooked meat from infected game animals, including birds, is another source for infection.[36] This form of tularemia may result in a painful sore throat accompanied by inflammation of the mouth, tonsillitis, and swelling of the throat that is accompanied by fluid discharge. Lymph nodes can also become enlarged.



Photos courtesy of the Centers for Disease Control and Prevention.

5 Tularemia Pneumonia

This can result from inhaling contaminated aerosols or, as a secondary outcome, from spread of the organism from infection at other infected sites within the body. Cases of tularemia with primary lung involvement are most common in persons in high-risk occupations, such as laboratory workers. Outside of the laboratory, large outbreaks associated with handling *F. tularensis*-contaminated hay have occurred in rural communities of Scandinavia and in other countries.[128] *Francisella tularensis*-laden aerosols are developed by handling infected dead animals, examining pets with respiratory infections, and from handling agar plates on which the organism has been isolated.[129] Clinical symptoms are highly variable, as is the course and severity of disease. There is an absence of skin ulcers and enlarged lymph nodes with this form of disease. The significance of infection is reflected in this form of tularemia rapidly progressing to severe pneumonia, respiratory failure, and death in some instances. About 10 percent of cutaneous cases (ulceroglandular) and 50 percent of septicemias are complicated by pneumonia.[129] Prior to the use of modern antibiotics to treat these infections, pleuropneumonic cases had a fatality rate of 30 to 60 percent.[26]

6 Typhoidal Tularemia

The diagnosis for this systemic form of tularemia is complicated by the absence of signs that identify either a site of entry by the organism, location of infection within the body, and a variety of symptoms also associated with other diseases. About 5 to 15 percent of human cases of tularemia are of this type.[11] A personal history of sudden onset of acute illness associated with outdoor activity or contact with animals provides reason for consideration of this disease in tularemia endemic areas. The high case-fatality rate (30 to 60 percent) associated with this form of tularemia underlines the importance of providing physicians with a good personal history of recent activities associated with the outdoors and animal contacts, including companion animals that are allowed to roam outdoors.

7 Tularemia Sepsis

This form of tularemia, like typhoidal tularemia, lacks specific clinical signs for guiding a rapid diagnosis. The consequences of tularemia sepsis are often grave, unless treated promptly, as septic shock (circulatory failure due to the release of **endotoxins** by high levels of bacteria within the blood) and other complications lead to severe illness and often to death.

The number of human cases of tularemia in the USA has decreased significantly from more than 1,000 per year prior to 1950 to less than 200 per year in the 1990s.[130] Nevertheless, tularemia remains a global disease worthy of consideration as outdoor activities are pursued in areas where this disease is known to exist.

Box 4 Human Movement of Tularemia

Because tularemia is not normally spread from person to person, efforts to prevent this disease may sometimes be less than rigorous. There also appears to be a willingness to accept risks that may facilitate outbreaks of tularemia that ultimately result in human cases. For example, moving infected animals and/or arthropod vectors of tularemia to new locations has established new geographic foci for this disease.

1 The Massachusetts Experience

Prior to 1937, only three cases of tularemia had been documented in humans within the State of Massachusetts, all of which involved infections acquired outdoors. From 1937, the first year that releases of wild rabbits were reported, through 1940, nearly 26,300 Western rabbits were released into Massachusetts. During 1946, about 3,000 more wild rabbits were imported, primarily from Arkansas and Kansas. The Cape Cod area saw the first locally acquired human case of tularemia in 1937. Tularemia has persisted in this tick-infested area since then.[126] Other early human cases of tularemia following rabbit releases include a 1941 case near Lawrence (northeastern Massachusetts) and cases during 1946 from Martha's Vineyard and Boston.[131] These imported rabbits were certified at the shipping points by accredited health authorities who stated there had been no outbreaks of tularemia in the counties in which the rabbits were trapped and that these counties were free from **contagious** and **infectious** rabbit diseases. Nevertheless, 2 of 136 rabbits that were examined during 1940 following their death during transit or shortly after arrival at game clubs were found to have tularemia. Those rabbits were found in shipments from Missouri and Arkansas, states with a combined total of more than 900 human cases of tularemia during the period of 1937–1940.[131]

Between 2000 and the end of summer 2005, nearly 40 human tularemia cases were diagnosed on Martha's Vineyard. Most of the cases are associated with landscaping, grounds caretaking, and gardening. Landscapers in this area are at greatest risk of contracting tularemia.[132–134]

2 Italy

During 1971, several thousand black-tailed jackrabbits trapped in an enzootic area for tularemia in southern Idaho were shipped (along with their *Dermacentor parumpertus* ticks) to Italy for release on private hunting preserves. At that time, tularemia had not been isolated from wildlife or ticks from that country.[24] Up to one million hares (jackrabbits) were imported to Italy for hunting in 1982 from several countries, including some from countries in which tularemia is present. The first reported major outbreak of tularemia in Italy occurred in Tuscany during 1982 in an area where hares are regularly imported for sporting purposes and was thought to be caused by an infected hare falling into and contaminating a public water supply. A total of 49 human cases occurred during a 3-week period from consumption of the contaminated water.[72] A total of 223 cases were recorded by the end of August 1984.[135]

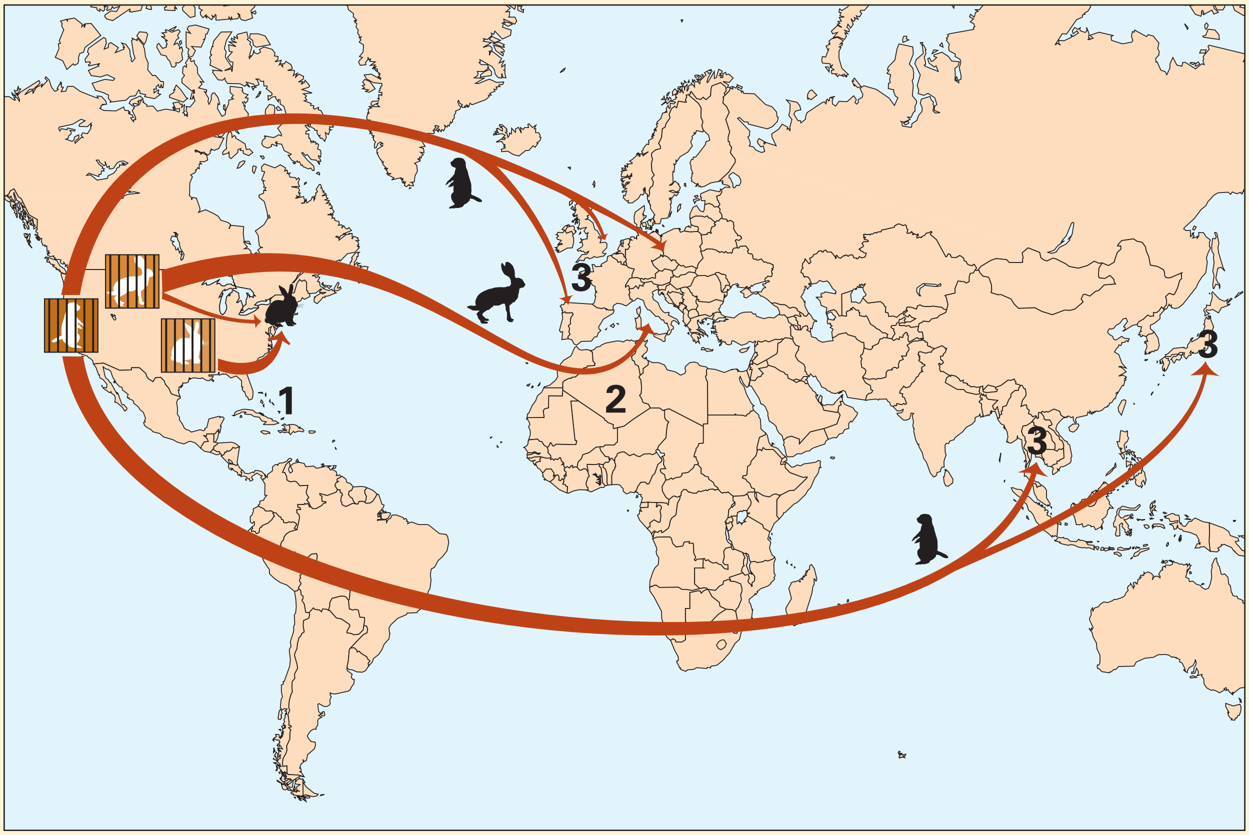
3 Prairie Dogs

Investigations of a 2002 outbreak of tularemia involving wild-caught, black-tailed prairie dogs at a commercial facility in the United States disclosed that in the 2 months prior to diagnosis of the problem, hundreds of potentially infected animals were shipped to several states and other nations.[136] The first reported prairie dog-to-human tularemia transmission was associated with this epizootic.[137] These animals are primarily sold as pets and, in addition to markets within the United States, were also shipped to Japan, the Czech Republic, the Netherlands, Belgium, Spain, Italy, and Thai-

Disease Ecology

Tularemia remains a persistent disease of humans because of the well-adapted relations that exist between *F. tularensis* and its small mammal and arthropod hosts. Those relations result in the ecology of this disease being as diversified as the morphology of *F. tularensis*.[19] What is representative for tularemia in one geographic area or set of environmental conditions may deviate greatly from that of another location and other environmental conditions. Thus, tularemia is a disease of many faces, a chameleon that adapts to various environmental conditions.

Occurrences of tularemia within geographic areas vary over time due to changing environmental conditions and because of human actions and behavior patterns. For example, the occurrence of tularemia in the former Soviet Union as a significant disease of humans is closely associated with the



land. As a result, international surveillance and investigations were mobilized in an attempt to minimize the potential for disease occurrence.[138,139]

Wild-captured prairie dogs from Texas for use as laboratory animals for study of an unrelated human disease introduced tularemia into a Missouri laboratory animal facility.[140] In unrelated events, research institutions in Boston, Massachusetts, and Houston, Texas, also received wild-caught prairie dogs infected with tularemia.[136]

Decades ago it was noted that:

"…we are in an era of emerging zoonoses, which will involve extension of old problems into new areas and the evolvement of entirely new problems in zoonoses" (Hess).[141]

Tularemia is a classic old problem that continues to be extended into new areas by human actions. Greater steps, including more rigid control of **wildlife translocations** and better wildlife disease surveillance, need to be taken so that human actions do not spread this disease any further.[24]

development of water vole trapping as a major activity. This activity was stimulated by the economic returns from water vole pelts and the great abundance of this species.[142]

Landscape changes affect plant, insect, and animal communities that are important components of the ecology of tularemia and many other diseases. Human activities within those landscapes influence the potential for exposure to *F. tularensis*. In addition, the great mobility of modern society has created a global community with expanded opportunities to encounter tularemia within different types of landscapes. Therefore, it is prudent to consider tularemia from a global ecology perspective rather than from just a local perspective. This broader perspective is also useful for evaluating disease risk that may be associated with wildlife **translocations** for conservation, zoological collections, sporting purposes, or other reasons (Box 4).

The concept of type A and type B tularemia as distinct diseases is useful for understanding the ecology of the disease in North America. Type A tularemia is a tick-borne disease of rabbits and is generally of moderate to high virulence for humans and other species. Arthropods, other than ticks, can vector this form of disease. Transmission can also occur by other means such as by direct contact with infected animals. In North America, 90 percent of tularemia cases in humans are caused by type A strains (Fig. 8), whereas tularemia involving rabbits elsewhere is comparable to type B tularemia, a disease of low virulence for humans.[61]

Type B tularemia is typically a waterborne disease generally vectored by true rodents (i.e., species with only two incisor teeth above and below for gnawing, such as beaver and mice). About 5 to 10 percent of human tularemia cases within North America are attributed to this form of disease.[61] Prairie dog-associated cases have been of this type.[136,139] The low virulence of type B results in many undiagnosed cases because infected individuals may not seek medical assistance. Also, when medical assistance is sought, the general nature of an uncomplicated course of disease may result in a misdiagnosis.

A wide variety of species can become infected by type A and type B forms of *F. tularensis* and both can cause severe disease resulting in mass mortalities of wildlife. Species contributing to the ecology of tularemia may be reservoir hosts important for the maintenance or perpetration of tularemia in nature (e.g., ticks) or simply be sources of infection for other species and are not directly involved in the maintenance of *F. tularensis* during periods of disease quiescence.[24] Reservoir hosts are the species of ecological importance and are also the species of primary importance for the occurrence of tularemia in humans (Fig. 9).

The ideal **vertebrate** reservoir host is highly susceptible to infection, is not killed by the infection, and remains as an infective source for other species for prolonged periods of time. Typically, only a minimal number of organisms are required for invasion of the host by the **pathogen**. Multiplication of the disease agent within the reservoir host results in infective levels of *F. tularensis* either circulating in the blood or being excreted through body discharges such as feces and urine over time. In some instances, *F. tularensis* may follow a recurring pattern of presence and absence throughout the life of the host.

Lagomorphs

The Lagomorphs (hares, rabbits, and **pikas**) and Rodentia (rodents) are the most important vertebrates in the ecology of tularemia. Hares and rabbits, but not pikas, are globally important natural foci of tularemia and as sources for infection of humans (Box 5).[11] The rabbit and hare tularemia cycle of North America is tick-borne and involves type A strains of *F. tularensis*. Human infections generally result from contact with infected rabbits, bites from ticks that have fed on infected rabbits, and to a lesser extent from other means, including the consumption of inadequately cooked contaminated meat (Fig. 10). The Old World rabbit, known to many as the domestic rabbit, is relatively resistant to the indigenous strains of *F. tularensis* within its native geographic area and is not an important source of infection for humans or other mammals.[11] However, fatal infection has resulted from experimental exposure to a virulent type A organism.[104,143]

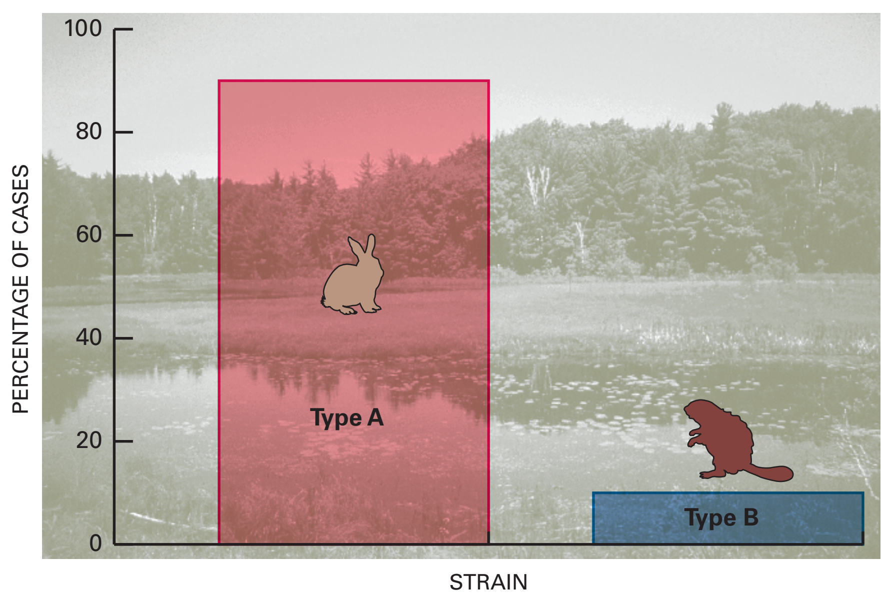


Figure 8. Relative frequency within North America of tularemia cases diagnosed in humans caused by different strains of *Francisella tularensis.*

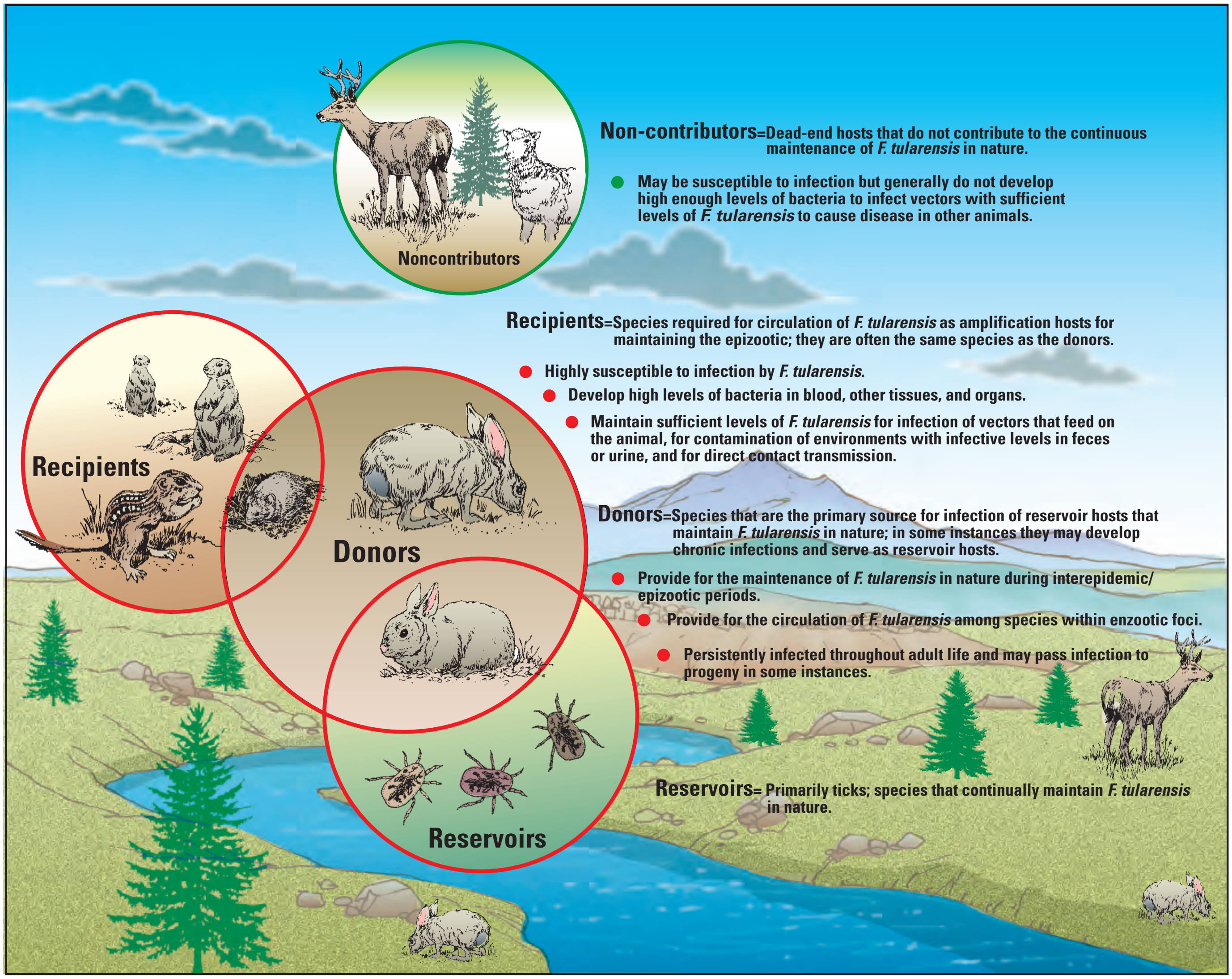


Illustration by John M. Evans

Figure 9. Non-contributor, reservoir, donor, and recipient species in the ecology of tularemia. The persistence of tularemia as an enzootic disease is to a large extent dependent upon the composition and interactions of animal and vector populations present within a specific habitat. The roles for these different species can be thought of as reservoir, donor, recipient, and non-contributing hosts.[142] The composition and numbers of these various species and their interactions are often greatly influenced by human actions and by environmental factors.

Box 5 "Keep the Bare Hands Out of a Wild Rabbit"

Rabbits and hares are globally important in the ecology of tularemia. Within the New World, the cottontail rabbit, black-tailed jackrabbit, and snowshoe hare are the lagomorphs associated with tularemia.[44] Several other species are involved in the Old World.[14,45,56] A significant difference between tularemia in New World and Old World lagomorphs is that the strains of *Francisella tularensis* isolated from New World lagomorphs are of much greater virulence for humans (Jellison type A strains). However, large-scale epizootics from tularemia occur both in New World and Old World lagomorphs.

The collective importance of rabbits and hares as a source for human cases of tularemia is great because of human contacts from hunting,[144] the large numbers of these animals utilized as food,[33,145] and the role of these species as hosts for ticks that can transmit tularemia.[36] Some perspective on the magnitude of human contacts with wild rabbits and hares in the USA is provided by an evaluation made decades ago. In 1932 it was reported that an estimated 25 million wild rabbits and hares are killed annually in the USA for food and fur.[36] During recent years, fur harvests of wildlife have declined greatly within the USA, but many millions of rabbits and hares are still harvested by sport hunting and for other purposes.

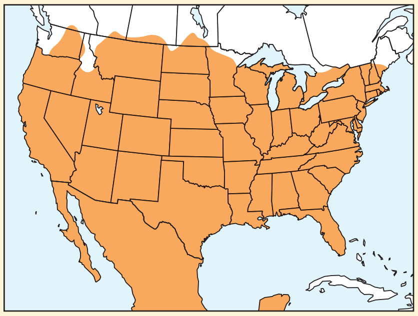
The large number of human cases of tularemia associated with direct contact with rabbits and hares in the USA caused a leading tularemia investigator to state, "Keep the bare hands out of a wild rabbit."[44] He concluded that about 1 percent of wild rabbits and hares in the USA are naturally infected with *F. tularensis*, thereby providing a continuous risk for humans, even when epizootics are not occurring.

Wild lagomorphs are also a significant indirect source of human cases of tularemia. A number of reports, mostly from Old World countries, suggest that public water supplies have become contaminated with *F. tularensis* by tularemic rabbits falling into those water sources. Substantial numbers of human cases have resulted from such events.[72]

NEW WORLD

Cottontail rabbit (*Sylvilagus spp.*)

There are 2 subgenera and 14 species of cottontail rabbits. These species occupy ranges that extend from Southwestern Canada (mountain cottontail) and southern Manitoba to as far south as Venezuela (eastern cottontail) and Argentina (forest rabbit).[146] The cottontail rabbit is the most important vertebrate in the ecology of tularemia within the USA.[36,44,147] The eastern cottontail and the desert cottontail are the most important of these species in the transmission of tularemia to humans[102] though hares are more important in some western and southern areas.[148]



Cottontail rabbit distribution in North America[149]

More than 10,000 human cases and over 500 deaths from tularemia within the USA were attributed to cottontail rabbits by the early 1970s. Many of those cases occurred in Illinois. From 1926 to 1948 there were more than 3,000 human cases of tularemia in Illinois, approximately twice the number for that time period of any other state. The great majority of these cases were due to contact with cottontails.[144] Ecological studies disclosed that weather in Illinois is an interactive factor with cottontail populations and tularemia. When cottontail populations are higher than average and warm weather precedes opening day of the hunting season, the risk of contracting tularemia is substantially higher. When cottontail populations are average, the risk of infection closely follows a curve of the mean

Photo by Milton Friend

Cottontail rabbit

date of the first 10 freezing autumn nights. That is, the earlier the mean date for frosts, the lower the risk. When cottontail populations are well below average, human tularemia cases are low even during warm autumns.[144] The opening of the rabbit season after several frosts have occurred results in most ticks having left their rabbit hosts and also decreases the likelihood of tularemic rabbits still being alive.[150] A number of state wildlife conservation agencies have considered these regulations when setting the hunting season for cottontail rabbits.[144,150,151]

Illinois is no longer one of the leading states in the number of human cases of tularemia. From 1976 to 1994, 61 human cases were reported from Illinois; however, 11 states reported many more cases than that.[152,153] The reasons for this change in status are in part related to reduced human contacts with cottontails in Illinois. The Illinois harvest for this species from 1956 to 1977 declined by 58 percent and the number of hunters declined by 33 percent in association with a 33 percent reduction in farms and changes in agriculture that reduced habitat and opportunities for rabbit hunting.[154]

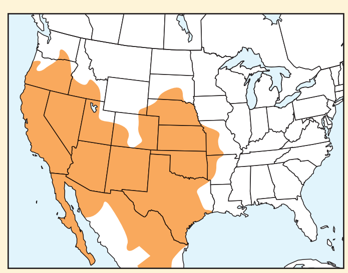
Cottontail rabbits have also been associated with pneumonic forms of tularemia in urban and other areas. This form of tularemia can be very severe with a mortality rate of 30 percent[155] and generally involves exposure through inhalation. For example, in the late 1970s in the Washington, D.C. area, three men training their dogs during the summer in an undeveloped wooded area adjacent to a housing complex handled a rabbit caught and killed by one of their dogs. The handling activities involved familiarizing their dogs with the rabbit’s scent. All three men contracted tularemia pneumonia and the dog that captured the rabbit died of unknown causes (no examination done) shortly after the owner became ill.[156]

In the early 1970s, five children were diagnosed with tularemia pneumonia. The source for infection was attributed to their poking a dead, partially opened rabbit with a stick.[155] The rabbit was caught and killed by their dog while the children were in a wooded area of a neighborhood park in urban Baltimore, Maryland. A dead cottontail that was mowed over in a lawn was probably the source of infection in one of the human cases during a pneumonia tularemia outbreak on Martha’s Vineyard, Massachusetts in 2000.[132] A cluster of seven tularemia cases, five of which were pneumonic, previously occurred on Martha’s Vineyard among a group of people sharing a cottage for a week. Their dogs killed several rabbits in the vicinity of the cabin and they most likely became exposed when the wet dogs shook rainwater from their fur when entering the cabin after their “rabbit hunting” forays.[157] These examples illustrate that neither tularemia nor cottontails are restricted to rural and natural environments. The cottontail is common in urban and suburban areas where it is often found in yards and in vegetated areas adjacent to walkways.

Because of the popularity of the cottontail rabbit as a game animal, like the jackrabbit, large numbers have been translocated to restock depleted habitat and establish new populations.[147,154] Kansas, Missouri, Texas, Maryland, New Jersey, and Pennsylvania are among the states that have received cottontails for stocking wildlife areas. Typically, disease has received little consideration in carrying out this activity.[154]

Black-tailed jackrabbit (*Lepus californicus*)

Globally, there are 22 species of hares and jackrabbits, several of which are important hosts in the ecology of tularemia. In North America, the black-tailed jackrabbit is the most important of these species and occupies a general range that extends across much of the Western and Central conterminous USA and south to Northern Mexico and Baja California.[146] Historic evaluations indicate that jackrabbits are the source of about 30 percent of human cases of tularemia caused by lagomorphs.[12] Human cases of tularemia acquired from jackrabbits are more typically contracted during spring and summer than autumn,[148] or historically, from market rabbits during winter.[33] In general, the taking of jackrabbits has been loosely regulated relative to bag limits and time of year for harvest. They are considered a pest species by many and in the past have commonly been harvested as feed for domestic animals raised for their fur. That practice has resulted in cases of tularemia in cats, dogs, and chickens[148] as well as in ranched mink and foxes.[158–160] Historically, jackrabbits were



Black-tailed jackrabbit distribution in North America[149]

rounded up and large numbers of them killed to reduce depredation on crops and to reduce competition with livestock for forage on open range. The largest rabbit drive on record took place in California in 1892, involved about 8,000 people, and resulted in the harvest of about 20,000 to 30,000 rabbits.[161]

Despite being considered a pest species by some segments of society, jackrabbits are a desired species for others. To establish populations for hunting, jackrabbits have been translocated, including large-scale releases in Florida, Virginia, New Jersey, Massachusetts, Maryland, and in Italy.[161]

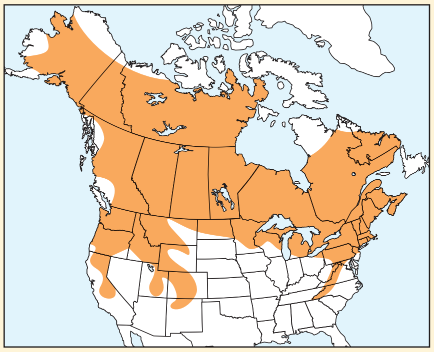
Photo by Milton Friend

Black-tailed jackrabbit

The primary role of jackrabbits in the ecology of tularemia may be the maintenance of this disease in nature through its principal ectoparasite, the tick *Dermacentor parumapertus*.[102] This tick rarely feeds on humans but can transmit tularemia among jackrabbits and perhaps other small rodents. The enzootic jackrabbit foci for tularemia is transferred to humans through direct contact with infected jackrabbits and by the bite of deerflies and other **tabanids** that have fed on an infected jackrabbit prior to biting a human.[24] Jackrabbits may also be a component of tularemia epizootics among range sheep in the western United States. Tularemia in sheep kept on rangelands is associated with infestations by the tick *D. andersoni*;[102] human cases follow as a result of processing wool, meat, and other products from the infected sheep.[162] In some situations tularemia may be a secondary outcome of tularemia cycling between ticks and jackrabbits.[61,91] Sheep and jackrabbits share sagebrush areas where *D. andersoni* is abundant.[102] The immature stages of this tick (larvae and nymphs) feed on a great variety of small mammals including jackrabbits and rodents while the adults feed on larger mammals including sheep, in addition to feeding on humans.[36]

Snowshoe hare (*Lepus americanus*)

The snowshoe hare is also called the snowshoe rabbit and the varying hare. Like other species of *Lepus* that live in a snowy winter climate, they molt into a white winter pelage. The snowshoe hare is generally found in coniferous forests—rather than in the open type of habitat occupied by jackrabbit—and in the great diversity of habitats including fields, farms, woodlands, deserts, swamps, prairies, and **hardwood**, **rain** and **boreal** forests occupied by various species of cottontail rabbits.[146] The snowshoe hare is the most important small game animal in Canada because in remote areas it is often a mainstay winter food for Indians, homesteaders, and trappers.[163] It is also the main food source for several **carnivores**.[147]



Snowshoe hare distribution in North America[149]

The first isolation of *F. tularensis* from wildlife in Canada was made from a snowshoe hare in British Columbia, but anecdotal information suggests a much earlier presence of tularemia in Canada and in snowshoe hares.[164,165] However, despite early reports that snowshoe hares are as important a source of tularemia for humans as cottontail rabbits and jackrabbits, that evaluation is no longer considered to be valid.[36,147,150] More recent information indicates that while snowshoe hares maintain tularemia in nature, and can transmit *F. tularensis* to humans, they account for less than 1 percent of the total source of human infection.[12]

Photo by Charles Krebs

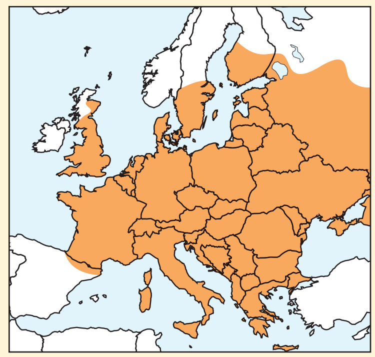
Snowshoe hare (winter pelage)

Unlike other species of North American lagomorphs, the snowshoe hare appears to be relatively resistant to clinical disease and mortality from tularemia despite the findings of antibody to *F. tularensis* that provide evidence of susceptibility to infection.[147] The low-grade infection that commonly occurs is likely a factor in the small number of human cases of tularemia associated with this species,[44,147] despite the large numbers of snowshoe hares that are harvested. For example, a historical report states that "about 2,000,000 varying hares are caught each winter in Maine."[166] More recent data indicates that hunters in Michigan harvest about 200,000 to 400,000 snowshoe hares annually.[167] However, in some situations the snowshoe hare may be an important source for human cases of tularemia. Over a 5-year period, Douglas County, Wisconsin, ranked fourth in number of snowshoe hares harvested in the State and second in the number of human cases of tularemia.[106]

OLD WORLD

European brown hare/Cape hare (*Lepus europaeus/capensis*)

Debate exists whether or not the Cape hare is a separate species or only a race (variant) of the brown hare.[168] The 4th Edition of *Walker's Mammals of the World* recognizes *Lepus capensis* as the brown hare and gives its distribution as the entire Palearctic region south of the coniferous forest zone except Northwestern China and Japan and all nonforested parts of Africa.[146] Others identify *Lepus europaeus* as the European brown hare and note the densest populations are found in open country, preferably that with lush brushy vegetation. *L. europaeus* prefers pastureland to hayfields,[168] while *L. capensis* is found occasionally in coniferous forests in addition to its usual habitat of open country.[169]



Brown hare distribution in Europe[168]

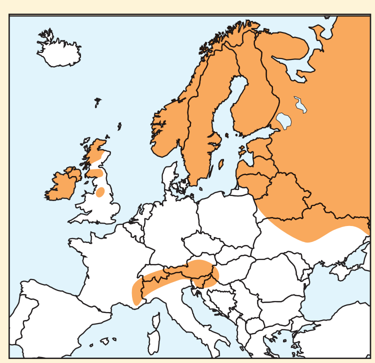
The European brown hare is reported to be the most common reservoir and vector for tularemia in Central Europe, along with rodents; tularemia causes 3 percent of the annual mortality in this species in France.[14] Although rodents are the primary hosts and vectors of tularemia in the former Soviet Union, brown hares are important in the Northern Caucasus, the Ukraine, and in the Central and Western Provinces (Oblasts) of the Russia Soviet Federative Socialist Republic (RSFSR). Cape hare are commonly found infected by *F. tularensis* throughout much of southern Kazakhstan, especially in the spring.[102] Tularemia is reported to cause mortality of up to 80–90 percent in cape hare populations in some areas.[168]

Photo by Laurie Campbell

Brown hare

Mountain hare (blue hare) (*Lepus timidus*)

The mountain hare inhabits the tundra and coniferous forest zones from Scandinavia to Eastern Siberia, the Alps of Europe, and is also found in Scotland, Sakhalin, and Hokkaido.[146] It is also referred to as the varying hare because of changes in coloration during the year due to pelage changes. The mountain hare serves as both a reservoir of tularemia in nature and as a source for infection of humans.[19] In the former Soviet Union, it is important in the European part of the RSFSR, in West Siberia, and Yakuts-



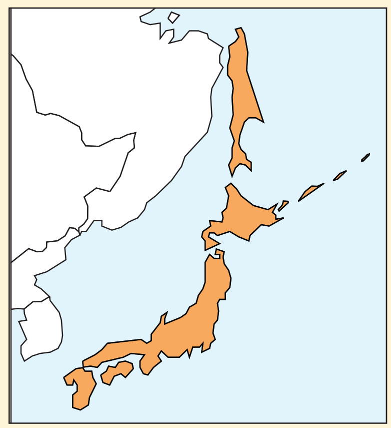
Distribution of mountain hare in Europe[168] kaya.[102] Mountain hare are also an important species in the ecology of tularemia in Scandinavia.[14,117] Tularemia in Sweden is correlated with population peaks of field vole and mountain hare.[69] In Norway, mountain hare also are closely associated with human tularemia cases and have caused tularemia when carcasses are fed to ranched foxes.[102]

Photo by Jonathan Jordan, Sheffield, UK

Mountain hare in its winter pelage

Japanese hare (*Lepus brachyurus*)

The Japanese hare and a subspecies, the Etigo hare, are the primary sources of tularemia in Japan. The geographic distribution of these hares coincides with that of human tularemia cases.[57, 102] More than 90 percent of those cases are contracted from hares[74, 170] and nearly all of those from the Japanese hare.[57,71,171]



Distribution of Japanese hare[71]

Japanese hare (winter pelage)

Clearly, rabbits and hares are important hosts and vectors for tularemia, yet the European wild rabbit, more commonly known in North America as the domestic rabbit, is relatively resistant to infection by the indigenous type B strains of its natural geographic range and is not a common source of human disease.[19]

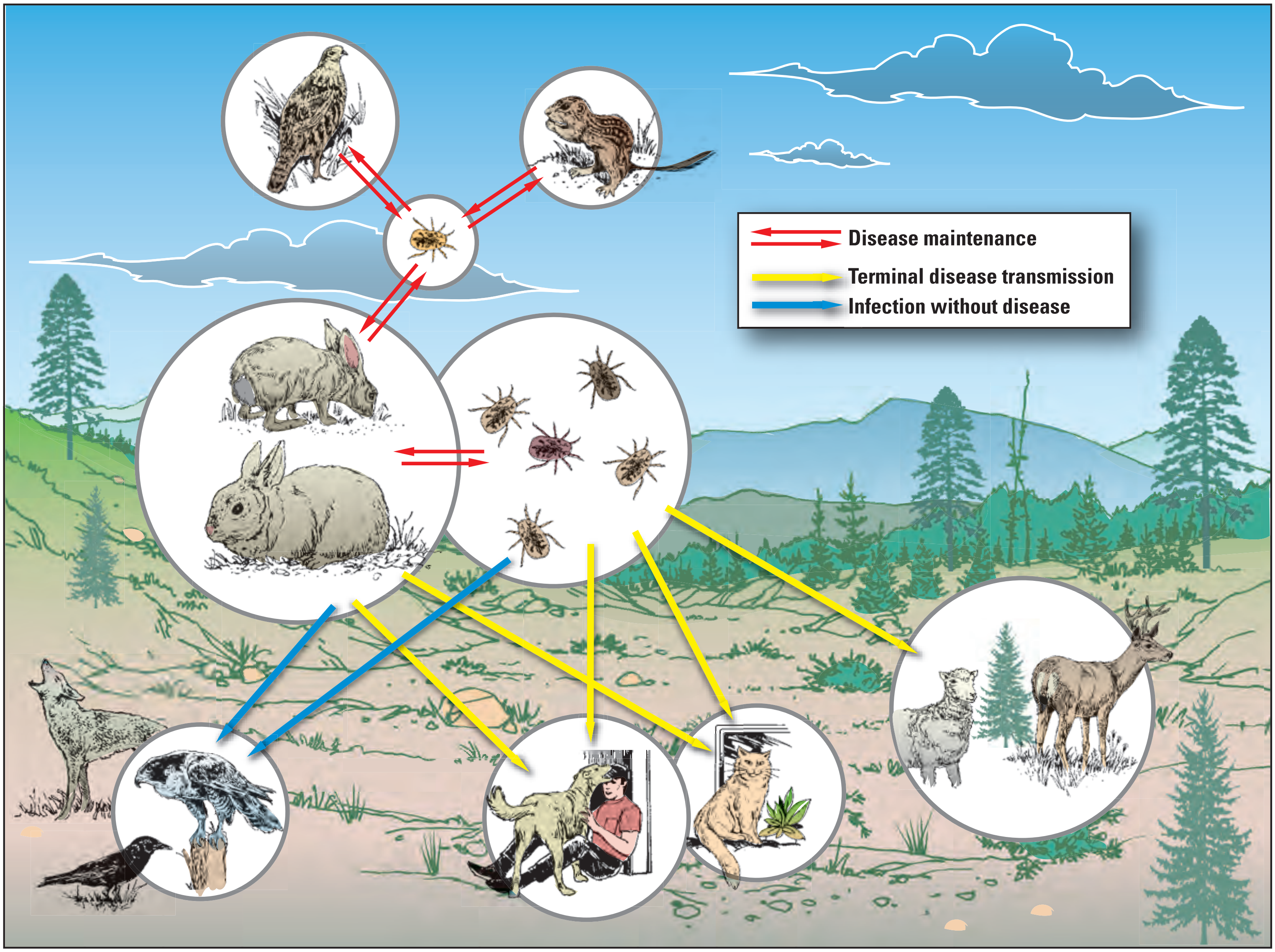


Illustration by John M. Evans

Figure 10. Pathways, hosts, and primary vector associations for lagomorphs and tularemia in North America.

Box 6 Rodents and Tularemia

"Rodents are the chief source of infection of tularemia and the reservoir of its virus [bacteria] in the external world." (Karpoff and Antonoff[172])

Mouse-like and other small rodents of varying sizes from **voles** and lemmings to muskrat and beaver are important hosts in the ecology of tularemia. Most, if not all, rodent species are highly susceptible to infection. They are hosts for the immature stages of a variety of ticks that can transmit tularemia, and they contribute to the ecology of tularemia in other ways, including contamination of freshwater used by humans and at times through the contamination of agriculture products such as hay and cereal grains. Worldwide, rodents are responsible for more human cases of tularemia than rabbits and hares, despite the prominence of lagomorphs as a source for human infection. Fortunately, the virulence for humans of *F. tularensis* from rodents is far less than that from North American rabbits and hares. Nearly all field isolates evaluated from rodents are of the Jellison type B variety. The following species, from among the many species of rodents known to be susceptible to tularemia, are worthy of note because of their prominence in epizootics and epidemics of this disease.

Ground squirrels (*Spermophilus spp.*)

The first North American recognition of tularemia as a disease in wild animals involved California ground squirrels.[17] At least nine North American species of ground squirrels have now been found to be infected with *F. tularensis* in nature.[12] Recognition that McCoy's "plague-like disease of rodents" was tularemia raised questions about how many other mortality events of ground squirrels, prairie dogs, and other small terrestrial rodents thought to be plague (*Yersinia pestis*) may also involve tularemia.

Ground squirrels are important hosts for several species of ticks that are vectors of tularemia[36] and contribute to the natural history of this disease. They also serve as a potential source for direct contact transmission to humans.[28] However, ground squirrels have not been a prominent species in outbreaks of tularemia since the initial investigations of McCoy and Chapin,[16,173] and there have been few human cases of tularemia directly attributed to ground squirrels.[75] Nevertheless, ground squirrels are commonly infected by *F. tularensis*. At high population levels, these usually herbivorous animals are known to feed on the flesh of carcasses and even prey upon other warm-blooded animals. This behavior facilitates disease transmission within those species.[174]

Historically, population levels for some species of ground squirrels reached such high levels that they were considered major pests. The level of depredation was such that farmers attempted to obtain sick squirrels during the "squirrel plagues" at the start of the 20th century and release them as a form of "biological warfare" against the ground squirrel hordes of that time.[28] The human risks associated with such actions are high as it is likely that *F. tularensis* type A strains were involved[36] rather than the lower virulence type B strains found in aquatic and semi-aquatic rodents.

Photo by Milton Friend

California ground squirrel

Tree squirrels
(*Sciurus spp.*)

Tree squirrels are widely distributed in the Americas and are found in deciduous, coniferous, and tropical forests, both humid and arid. Although they spend most of their time in the trees, they come to the ground to forage for food and to bury nuts and acorns.[146] The gray squirrel and fox squirrel, which are hunted, are the squirrel species most commonly involved in the direct transmission of tularemia to humans. Infected squirrels have caused human cases of tularemia as a result of contact transmission in the preparation of the animal for cooking[10,175] and by arthropod vectors that transfer from squirrels to humans. Improper cooking of diseased animals is another pathway for human infection. Bites from squirrels handled in the outdoors and from squirrels kept within the home as pets have also resulted in human cases of tularemia.[10,176] Natural infections of squirrels by *F. tularensis* have also been documented for the European red squirrel in Sweden and in North America for the red squirrel and Wind River pine squirrel.[12]

Photo by Phil Myers

Red squirrel

Photo by Milton Friend

Gray squirrel

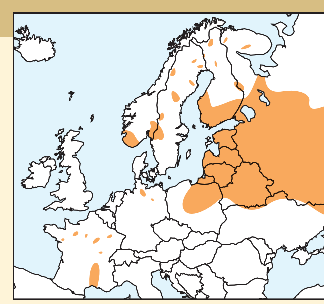
Beaver
(*Castor spp.*)

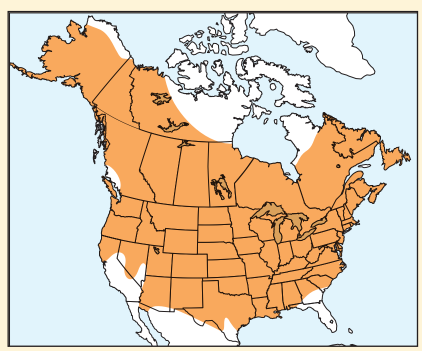
Beaver are the largest rodent native to North America and Europe. Both the European beaver and the North American beaver were among the most widely distributed mammalian species prior to their exploitation by humans. The North American beaver has been successfully introduced into Finland[146] and the European beaver (*Castor fiber*) has been restored to many areas from which it had been extirpated.[177] Beaver are highly susceptible to tularemia[10,178–180] and have been the source for numerous human cases of this disease.[180] The first documentation of tularemia epizootics in beaver is from 1939–40,[181–183] but retrospective evaluations of large-scale mortality events like those described by Seton[164] suggest that tularemia has caused mortalities in this species since at least the 1920s.

Heavy contamination by *F. tularensis* of surface waters has been a consistent finding associated with tularemia epizootics in beaver and is likely the source for infection of those animals.[180,181] Because of their high susceptibility to tularemia, beaver are not an important reservoir host but instead serve primarily as a source for infection of humans who may handle these animals or their pelts during trapping and fur-trade operations. Beaver that die from tularemia also can contaminate the waters they inhabit.

A closer association between humans and beaver was present in North America in earlier times than exists today. This species probably contributed to the development of the USA and Canada more than any other animal because of the value of its pelts. Settlers moved westward following the quest by trappers for the financial rewards from the fur trade.[146] Human exposure to tularemia from beaver in the USA today is more likely to be associated with removing beaver from an area because their impacts conflict with human use of the area and also from recreational uses of water inhabited by beaver.

Distribution of European beaver[168]





Distribution of beaver in North America[149]

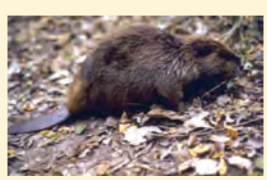


Photo by Julia Gregory, Texas Parks & Wildlife Dept.

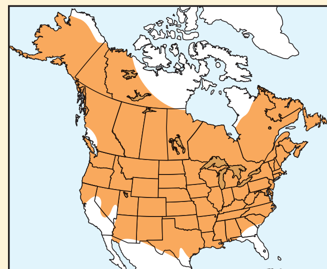
North American beaver

Muskrat
(*Ondatra zibethicus*)

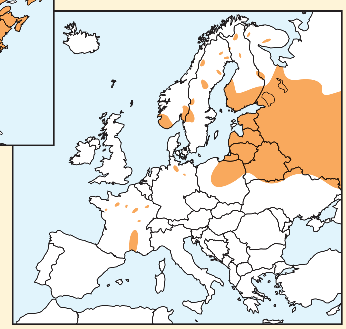
The muskrat is a New World species that has been introduced into the Old World. It was first introduced in the former Soviet Union in 1927 and cases of tularemia in this species within that geographic area were first documented in the Novisbirsk region in 1939. However, muskrat have not attained the abundance or geographic distribution of the water vole and are regarded to be of lesser importance in the ecology of tularemia than that species.[180]

Photo by R. Town, U.S. Fish and Wildlife Service

Muskrat



Distribution of muskrat in North America[149]



Distribution of muskrat in Europe[168]

Muskrat occur widely over a geographic area that extends from Alaska and Labrador in the North to parts of Texas and California in the South.[146] Like the beaver, this species is trapped for its fur. It has been reported that muskrat pelts are 40 percent more durable than other pelts and at one time were the greatest source of revenue from trapping in North America.[169] As recently as the trapping season of 1976–77, the value of the North American harvest of muskrat pelts was approximately $45 million.[146] In some areas, the meat is also eaten. Muskrat meat is commonly referred to as "marsh-rabbit," an appropriate term since muskrat, like rabbit, are an important source of human cases of tularemia.

Like beaver, muskrat-trapping activities are the primary source for human cases of tularemia. Muskrat are also highly susceptible to tularemia and suffer large-scale epizootics that may then contribute to the contamination by *F. tularensis* of the waters in which they die.[181] The first North American human cases of tularemia associated with muskrat were described in 1929[184] and for some time were thought to be anomalies.[36] However, it was later recognized that tularemia acquired from muskrat and beaver is more common than apparent. This is because of the nonspecific febrile illness that generally results from uncomplicated infections.[185] The largest number of documented human cases (47) in North America associated with a single outbreak of tularemia in muskrat occurred in Vermont. That event was also the first time tularemia was documented in that state.[78]

Voles ("Meadow mice")
(*Microtus spp.*)

The genus *Microtus* consists of 6 subgenera and more than 60 species distributed throughout much of the globe except for South America, southern areas of Eurasia continent, and further south in the Old World.[146] "Boom and bust" populations are a common dynamic both in the New World and the Old World for many of these species, several of which are considered to be important in the ecology of tularemia.[186] Tularemia has often been associated with major die-offs of voles during population highs. In North America, tularemia epizootics frequently result in the death of beaver, muskrat, and voles during the same event because of the intimate contacts that occur between these species (Figs. 9 and 11). Beaver and muskrat commonly share aquatic habitat and interface with voles at the bank areas of that habitat.[36]

Photo by Phil Myers

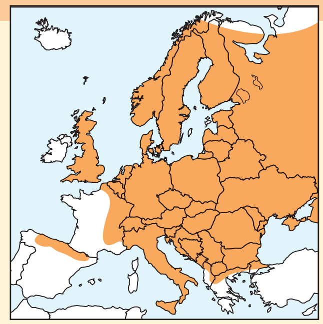
Meadow vole

Voles are thought to be involved in maintaining long-term contamination of waterbodies. For example, voles are suspected as being the source for continual contamination in Montana by *F. tularensis* of two small streams for 16 months beyond the end of a tularemia epizootic involving muskrat and beaver.[180] Like beaver and muskrat, voles are highly susceptible to tularemia; unlike beaver and muskrat, voles may also become chronically infected and serve as a source for contamination of surface waters by *F. tularensis* through their body discharges.[187] Contamination of waters by voles could then initiate epizootics in species such as muskrat and beaver whose carcasses would then further contaminate those waters.[180,181] Laboratory studies have resulted in some voles developing chronic infections of the kidneys and shedding *F. tularensis* in their urine.[174,188,189] If this occurs in nature it would be an important mechanism for maintaining *F. tularensis*-infected waters over long periods of time and for initiating tularemia outbreaks in wildlife[11] that then serve as a bridge for human cases.[11,19]

Small rodents are probably the species most often infected with *F. tularensis* and are also the most common source for human infection in Europe.[19] Species commonly involved include water voles, lemmings, red-backed voles, and *Microtus* spp.[11] The water vole is the most important of these species because of its broad geographic distribution, abundance, and contact with humans.[19,21,25] The shedding of *F. tularensis* into water by voles is thought to be the underlying cause for much of the tularemia reported in Eurasia.[11] For example, the water supply is considered to be the most important source of *F. tularensis* in Turkey, with infected rodents being the source of contamination.[55]

Water vole (*Arvicola terrestris*)

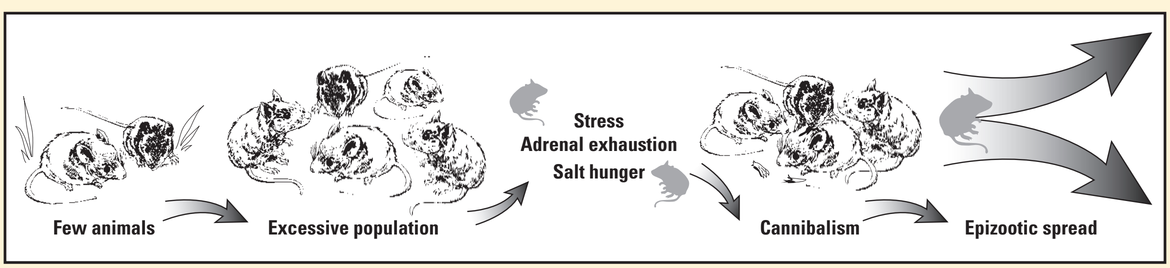
Distribution of water vole in Europe[168]



The water vole is one of three species in the genus *Arvicola* and is the largest microtine rodent in the Old World, having a body size about two-thirds the length of the muskrat. It is distributed throughout most of Europe and Siberia, and in parts of Southwestern Asia.[146] It is the most common animal source of human cases of tularemia in Eurasia, partly because of direct contacts, including harvest of its pelt.[19] Millions of these animals are trapped annually for their fur.[142] The magnitude of human cases of tularemia attributed to this species in the former Soviet Union alone far exceeds that reported for any other species anywhere else in the World. During 1928, four and a half million water vole pelts from the Ural area were sold in the fur market. At that time the first epidemic wave of tularemia was occurring in the former Soviet Union and water voles were essentially the sole source of human infection.[32] About 1,000 tularemia cases occurred in Russia in 1928 in persons skinning these animals for their pelts.[44] Previously described disease syndromes known as water-rat-trapper's illness and Siberian ulcer, now known to be tularemia, are historically associated with trapping these animals[19] and support the presence of tularemia in the former Soviet Union long before the 1926 initial diagnosis of tularemia in Russia.

Water vole

In addition to being highly susceptible to tularemia, water voles may become chronically infected, thereby serving as disease reservoirs during periods between epizootics.[24,180] High population levels "trigger" widespread epizootics of tularemia among rodents,[25] perhaps by stimulating shedding of *F. tularensis* organisms, thereby resulting in waterborne transmission as a means for initiating the epizootic. In addition, stress-related aggression and cannibalism could also serve as a means for initial disease transmission.[174] Regardless of the mechanisms involved, the water vole is an important species in the Old World ecology of tularemia.



A leading North American investigator has theorized that the evolution and spread of tularemia organisms has occurred with *Rodentia*, in contrast to the viewpoint of an equally prominent Russian investigator who theorizes that the evolution of *Francisella* was mainly within *Lagomorpha* and less within *Rodentia*.[102] In either case, the long association of *Francisella* with these two major groups of animals has afforded eons of time for adaptive host-parasite relations to be formed. Within this context, the population dynamics and associated behavioral characteristics of high population levels of voles and other small rodents results in a theory that cannibalism is a major factor for epizootic spread of type B infection in terrestrial rodents.[174]

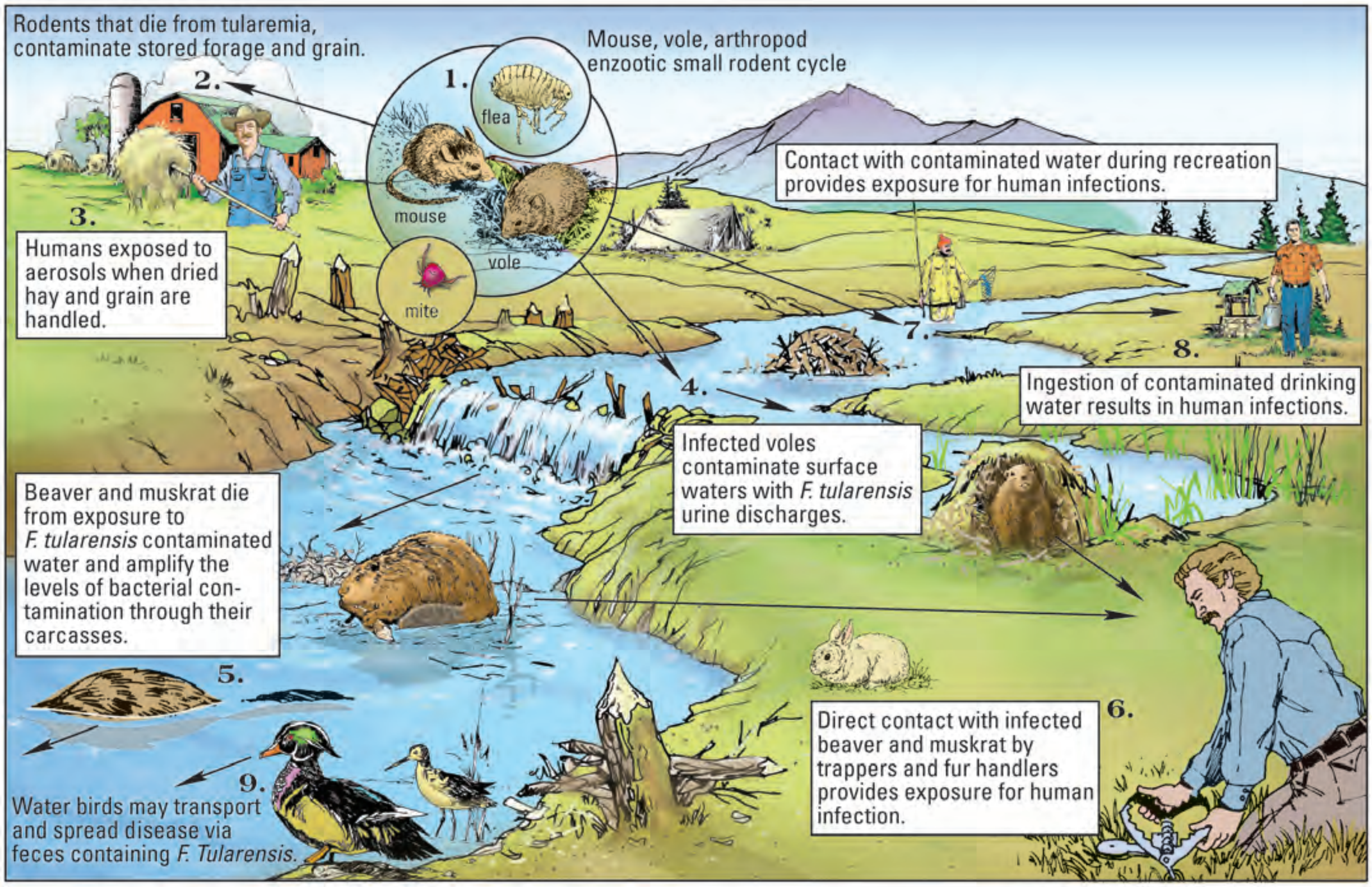


Illustration by John M. Evans

Figure 11. Rodents and tularemia in North America: general pathways for infection.

Rodents

Rodents are of greater importance than rabbits and hares for maintaining **enzootic** foci for tularemia in many areas of the Old World. They are also of major importance generally because they are highly susceptible to infection and are hosts for immature stages of several important tick vectors of the genera *Dermocentor, Ixodes* and *Amblyomma*.[11,190,239] The primary North American rodent hosts for *F. tularensis* type B are species of the genera *Microtus* (meadow mice and voles), along with muskrat and beaver. Rodents within the family Sciuridae (primarily tree and ground squirrels) can also be locally important hosts for tularemia (e.g., California ground squirrel) (Box 6). In contrast with earlier times, tularemia has become a more prominent disease of prairie dogs since the 1990s.[136–139] Direct contact with infected rodents, their ectoparasites, and ingestion and inhalation of water and other materials contaminated by them are the typical ways in which tularemia is transmitted to humans (Fig. 11).

In Eurasia, voles, especially those of the genus *Microtus*, also contribute to human infections of tularemia by their contamination of terrestrial and aquatic environments. Examples include occasional large epidemics of tularemia among agriculturists as a result of processing grain or stacked hay contaminated by voles and other rodents,[32,128,191] contamination of public-water supplies,[25] and infection of workers in a sugar beet processing plant from water spray contaminated with *F. tularensis*.[26,174]

Carnivores

Clinical cases of tularemia in wild carnivores are rare. **Canids** are not believed to have a major role in the maintenance of tularemia in nature, and they are not important as a source for human infections,[11,19] although human cases have been attributed to handling red **foxes**.[44,106] The first documented outbreak of tularemia in wild canids involved gray foxes in Minnesota.[192] Other documentation of tularemia in carnivores is limited to incidental cases.

High percentages of carnivore and **scavenger** species with antibody titers from serological surveys indicate past exposure to *F. tularensis*,[193,194] thereby illustrating the susceptibility of carnivores to natural infections and their ability to survive those infections. Coyotes infected experimentally have developed clinical disease in some studies but not others. In some instances carnivores may indirectly contribute to tularemia cycles by being a host for adult ticks that are part of the disease transmission cycle. However, because carnivores generally do not develop a **bacteremia** following exposure to *F. tularensis*[24] they are unable to infect the ticks but may serve to help maintain tick vector populations.

Birds

Numerous species of birds of several families have been naturally infected with *F. tularensis* (Tables 11–17). Also, there are close associations between the species of birds most commonly infected and the environment where tularemia occurs. Upland game birds (Tables 11 and 12) share habitats with hares and rabbits and in some instances share tick-vectors of tularemia. Various **waterbird**s (Table 13) frequent areas possibly contaminated with *F. tularensis* by rodents, and birds may become exposed through ingestion of contaminated water, sediment, and invertebrates; by aerosols created as they land, take-off, and splash around in those waters; or by infected insects feeding on the birds. Preying upon sick and dead rodents and lagomorphs afflicted by tularemia is the likely primary route for exposure of predatory and scavenger species of birds (Tables 14–16). Environmental associations also extend to poultry (Table 17) that have died from tularemia after being fed wild rabbit meat and viscera.[36] Nevertheless, few epizootics of tularemia in wild birds have been documented and, in general, birds are not considered to be an important component of the ecology of tularemia.[11,19] Perhaps the most significant roles of birds in the ecology of tularemia are their potential to transport infected arthropod vectors to

Table 11. Upland game birds reported to be naturally infected with *Francisella tularensis.*

Species	Geographic area	Bird mortality	Human cases	Comments
Dove (species not specified) 	Former Soviet Union	Insufficient information	No cases reported	*F. tularensis* isolated from tissues.[25,107]
Ring-necked pheasant 	USA	No cases reported	One or more cases of bird origin reported	Human cases of tularemia reported in association with preparing harvested birds for consumption.[107.108,175,195]
Cooper (copper[a]) pheasant	Japan	No cases reported	One or more cases of bird origin reported	Human cases associated with preparing pheasants for consumption.[57]
Pheasant (species not specified)	Japan	No cases reported	One or more cases of bird origin reported	Human cases associated with preparing pheasants for consumption.[57]
Bobwhite quail 	USA	Death attributed to tularemia	One or more cases of bird origin reported	Bacterium isolated from dead birds;[111] human cases associated with hunter-killed birds also reported.[15,109,196]
Japanese quail	Former Soviet Union	Insufficient information	No cases reported	*F. tularensis* isolated from tissues of bird from Western Siberia.[25]
Blue grouse (Columbian grouse)	USA	No cases reported	One or more cases of bird origin reported	[109]
Ruffed grouse 	USA	Death attributed to tularemia	One or more cases of bird origin reported	Tularemia was initially thought to be widespread and involved in population declines of this species,[110,197] but is no longer considered a cause of population declines; human cases have been associated with hunter-killed birds.[175]
Sage hen (Sage grouse)	USA	Death attributed to tularemia	One or more cases of bird origin reported	A grouse-rabbit-tick cycle suggested by early investigators.[109]
Sharp-tailed grouse	USA	Death attributed to tularemia	No cases reported	[110]
Willow grouse	USA	No cases reported	No cases reported	Moderate virulence strain of *F. tularensis* isolated from ticks removed from grouse, suggesting grouse were source of infection for ticks.[102]
Capercaillie 	Former Soviet Union	No cases reported	No cases reported	Bacterium isolated from tissues of bird from Byelorussia.[25]

[a]Spelling inconsistencies in the literature.

new areas,[19] the use of serology from predatory and scavenger species to monitor tularemia activity in their prey species,[194] and the potential for infected birds to contaminate surface waters through body discharges (Box 2).

Invertebrates

Ticks are the most important arthropods in the ecology of tularemia (Table 18). Persistently infected with *F. tularensis*, some Ixodidae ticks pass the infection through their eggs to the next generation. In addition to being a major reservoir host, they have a persistent role in the transmission of *F. tularensis* to humans (Fig. 12). Following infection, ticks amplify the number of bacteria for retransmission of *F. tularensis* (**biological vectors**). Therefore, ticks are true reservoir hosts that may perpetuate specific endemic/enzootic foci for tularemia during interepidemic/enzootic periods.[11,24,102,240] **Hard ticks** (Ixodidae) are major vectors of *F. tularensis* to humans and they maintain tularemia in the Northern Hemisphere (Fig. 13).

A variety of factors influence the role of particular species of ticks in the ecology of tularemia. Feeding patterns and host range are of primary importance.[11] For example, within the USA, *Dermacentor andersoni* is a direct source for human infection, but *D. parumapertus* is not because they rarely attach to humans.[24] *D. parumapertus* is a vector among wild mammals; larval and nymphoidal stages feed on rodents, and the adult feeds on jackrabbits. Its role in the ecology of tularemia is maintaining infections in mammals as sources for infection of other arthropods, such as deerflies. Infected mammals also serve as potential sources for environmental contamination and for contact disease transmission with, or by ingestion of those mammals. In contrast, subadult stages of *D. andersoni* feed on small rodents and lagomorphs and the adult ticks feed on large wild mammals, livestock and humans. The broad host range of *D. andersoni* results in this tick being a source for infection of humans as well as maintaining endemic foci of tularemia in nature.[24]

Transmission of *F. tularensis* by ticks is not limited to tick bites. **Coxal fluid** and feces of infected ticks contain viable *F. tularensis*, and may contaminate the bite wound and other broken surfaces of the skin. Although most of the consideration of tick-borne tularemia in North America is focused on type A strains involving a tick-lagomorph cycle, ticks also vector type B strains of *F. tularensis* in Eurasia, North America,[11] and Japan.[170] Much of that vectoring involves infection of rodents by immature stages of ticks. No arthropod-borne human cases of tularemia were reported in Japan prior to 1951; however, there has been a steady increase in the percentage of cases transmitted by this means since 1960, peaking at about 10 percent of tularemia cases during the period of 1980–1989. Most of these cases have been tick transmitted.[170]

Other blood-sucking arthropods also contribute to the transmission of tularemia (Table 18). Rather than being infected by *F. tularensis*, as are ticks, these other arthropods transmit tularemia mechanically. In essence, the insect's mouthparts and surface areas become contaminated while they feed on infected animals or in contaminated environments, then they feed on a susceptible host and infect them. The importance of different types of arthropods varies with

Table 12. Response of upland game birds to laboratory exposure to *Francisella tularensis.*

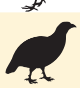
Species	Response			Comments
	Mortality	Antibody	Agent isolation	
Mourning dove 	Occurrence	Occurrence	Occurrence	Aerosol exposure at high dosage resulted in infection but low susceptibility to disease.[198]
Ring-necked pheasant 	Occurrence	Occurrence	Occurrence	Species not very susceptible and reported to be immune to infection under field conditions.[199]
Bobwhite quail 	Occurrence	Not determined	Occurrence	Fatal infections in quail fed infective material.[111,196]
Hungarian partridge 	Occurrence	Information not given	Information not given	Highly susceptible; fatal infection resulted from inoculation of a skin abrasion.[199]
Blue grouse	Occurrence	Not determined	Occurrence	Highly susceptible.[148,196]
Ruffed grouse 	Occurrence	Not determined	Occurrence	Mortality paralleled that for highly susceptible guinea pigs and rabbits;[199] tularemia also transmitted to grouse by infected ticks in the laboratory.[197]

Table 13. Reported susceptibility of waterbirds to *Francisella tularensis.*

Species	Geographic area	Type of exposure	Bird mortality	Human Cases	Comments
WATERFOWL					
Canada goose 	USA	Natural	No cases reported	One or more cases of bird origin reported	[200]
Green-winged teal	USA	Experimental, natural	Death attributed to tularemia	Not applicable	Single bird infected died and *F. tularensis* recovered from its tissues.[10]
Mallard duck	USA	Experimental, natural	Death attributed to tularemia	Not applicable	Birds infected orally and by injection; pure cultures of *F. tularensis* recovered from tissues of birds that died;[10] seropositive birds found in nature.[194]
GALLINULES AND RAILS					
Gray moorhen 	Former Soviet Union	Natural	Insufficient information	No cases reported	Bacterium isolated from tissues of birds in Byelorussia.[25]
Corncrake	Former Soviet Union	Natural	Insufficient information	No cases reported	Bacterium isolated from tissues of birds from Western Siberia.[25]
GULLS AND TERNS					
Black-headed gull 	Former Soviet Union	Natural	Insufficient information	No cases reported	Bacterium isolated from tissues of bird from Moscow region.[25]
California gull	USA	Natural	No cases reported	No cases reported	Multiple seropositive birds.[194]
Franklin gull	Canada, USA	Natural	Insufficient information	No cases reported	Tissues from a carcass collected during routine surveillance were positive for *F. tularensis* in Canada;[201] isolations were also made in the USA from gull tissues.[200]
Common tern	Former Soviet Union	Natural	Insufficient information	No cases reported	Bacterium isolated from tissues of birds from Western Siberia.[25]
Sooty tern 	USA	Experimental	Death attributed to tularemia	Not applicable	Bird died 5 days following respiratory exposure and had high levels of *F. tularensis* in cloacal contents.[115]
White tern	USA	Experimental	Death attributed to tularemia	Not applicable	Results inconclusive due to intolerance of birds to captivity; dose as few as 250 organisms may have been lethal.[115]
Common noddy 	USA	Experimental	Death attributed to tularemia	Not applicable	Lethal infections induced by respiratory route.[115]
White-cap noddy	USA	Experimental	Death attributed to tularemia	Not applicable	Highly susceptible; large numbers of organisms found in cloaca; high level of bacteremia.

Table 14. Birds of prey reported to be naturally infected with *Francisella tularensis.*

Species	Geographic area	Bird mortality	Human cases	Comments
HAWKS				
Red-tailed hawk 	USA	No cases reported	No cases reported	Isolation of bacterium from tissues of a bird collected by shooting.[202]
"Chicken hawk"	USA	No cases reported	One or more cases of bird origin reported	Species not identified.[108]
Kite	Russia	Insufficient information	No cases reported	Isolation of bacterium from tissues of a bird found in nature.[25]
Prairie falcon 	USA	No cases reported	No cases reported	Based on serology.[194]
OWLS				
Great horned owl 	USA	Death attributed to tularemia	One or more cases of bird origin reported	Reported as a source of a human case of tularemia;[108] bacterium isolated from tissues of a dead nestling.[203]
Great Basin screech owl	USA	No cases reported	No cases reported	Based on serology.[194]
Ural owl	Sweden	Death attributed to tularemia	No cases reported	Bird observed sick in nature prior to death; *F. tularensis* isolated from tissues at necropsy.[204]
BUZZARDS				
Rough legged buzzard 	Sweden	Death attributed to tularemia	No cases reported	Bird found dead in nature; *F. tularensis* identified in tissues at necropsy by fluorescent antibody technique.[204]

Table 15. Response of birds of prey to laboratory exposure to *Francisella tularensis.*

[IM, intramuscular; IP, **intraperitoneal**; SC, subcutaneous]

Species	Geographic area	Response			Comments
		Mortality	Antibody	Agent isolation	
HAWKS					
Red-shouldered hawk 	USA	Occurrence	Inconclusive finding	Occurrence	Six-week-old birds fed viscera of guinea pigs dying of tularemia.[205]
Eastern red-tailed hawk	USA	Occurrence	Occurrence	Occurrence	Adult bird fed viscera of guinea pigs dying of tularemia.[205]
Goshawk	Sweden	No occurrence	Occurrence	Occurrence	Fed mice that died of tularemia or were incoculated via IM, SP, or SC routes; antibody persisted for the 77 days of the experiment and reached 1:1,280 in one bird.[206]
Sparrow hawk 	Sweden	No occurrence	Not determined	No occurrence	No evidence of infection following IM inoculation.[206]
OWLS					
Tawny owl 	Sweden	No occurrence	Not determined	Not determined	Two birds exposed via IM route survived and failed to exhibit clinical signs of diseases.[206]
Great-horned owl	USA	No occurrence	No occurrence	No occurrence	Unable to infect adult birds and mature birds not considered to be susceptible.[203]
BUZZARDS					
Rough-legged buzzard 	Sweden	No occurrence	Not determined	No occurrence	[206]
Common buzzard	USA	No occurrence	Occurrence	No occurrence	[206,207]

Table 16. Reported susceptibility of *Corvidae, Laniidae,* and *Alaudidae* to infection by *Francisella tularensis.*

Species	Geographic area	Type of exposure	Bird mortality	Human cases	Comments
Raven 	Sweden, USA	Natural	No cases reported	No cases reported	Several apparently healthy birds were shot; some exhibited tissue lesions suggestive of tularemia and were **fluorescent antibody** positive.[208] Seropositive birds also found in western USA.[194]
Crow 	Insufficient information	Natural	Insufficient information	Insufficient information	[209]
Crow	Austria, former Soviet Union, Japan	Natural	Insufficient information	Insufficient information	Species not identified.[27,57,210]
Hooded crow	Sweden	Experimental	No cases reported	Not applicable	Birds were exposed by being fed mice that died of tularemia or by intramuscular injection; short term antibody response but not clinical disease.[206]
Azure-winged magpie 	Former Soviet Union	Natural	Insufficient information	Insufficient information	[209]
Common magpie	Former Soviet Union	Natural	Insufficient information	Insufficient information	[209]
Loggerhead shrike 	USA	Natural	No cases reported	No cases reported	Antibody detected in sera.[194,211]
Horned lark	USA	Natural	No cases reported	No cases reported	Antibody detected in sera.[194]

Table 17. Reported susceptibility of domestic bird species to infection by *Francisella tularensis.*

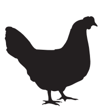
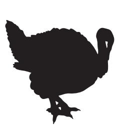
Species	Geographic area	Type of exposure	Bird mortality	Human cases	Comments
Pigeon 	Japan, USA	Experimental	No cases reported	Not applicable	Highly resistant[17] but may carry the bacterium for a period of time after exposure.[57,209] Intramuscular inoculation resulted in septicemia in some birds.[212]
	Europe	Natural	No cases reported	No cases reported	Highly resistant but may spread infection via excretions.[101]
Chicken 	USA	Experimental	Death attributed to tularemia	Not applicable	Highly resistant but may harbor *F. tularensis* for as long as 27 days.[209] Baby chicks are susceptible and *F. tularensis* grows readily in chick embryo tissue culture;[101] high titer antiserum produced by roosters inoculated intravenously with *F. tularensis*.[213] Intramuscular inoculation resulted in death of one bird.[212]
	USA, Japan	Natural	Death attributed to tularemia	One or more cases of bird origin reported	Mortality of "backyard chickens" from tularemia after being fed wild rabbit meat and viscera;[36] human case in Japan associated with preparing chicken for food.[57]
Domestic turkey 	USA	Experimental	No cases reported	Not applicable	Highly resistant to laboratory infection;[209] seropositive birds found during testing of flocks.[194]

Table 18. Arthropod species of primary importance in transmission of *Francisella tularensis.*

Species[a]	Area of importance	Comments
TICKS 		
Amblyomma americanum (Lone Star tick)	North America	One of three primary vectors of human cases within the USA;[31] accounts for about 60 percent of cases during recent decades.[11] A host and a vector.[27]
Dermacentor albipictus (Winter, elk, or moose tick)	North America	Reported as a vector.[102]
D. andersoni (Rocky Mountain wood tick)	North America	One of three primary vectors of human cases within the USA; [31] “Second only to direct contact with rabbits as a source of human infection.”[10]
D. occidentalis (Pacific Coast tick)	North America	Reported as a vector;[14] *F. tularensis* isolated from ticks removed from cattle.[215]
D. parumapertus (Rabbit dermacentor)	North America	Important vector in transmitting *F. tularensis* from jackrabbit to jackrabbit but seldom feeds on humans.[103]
D. pictus (Meadow tick)	Eurasia	Vector for human cases.[24] One of three principal tick vectors in the former Soviet Union.[26] Vectors tularemia in France.[27]
D. marginatus	Eurasia	One of three principal tick vectors in the former Soviet Union.[26] Vectors tularemia in France.[11]
D. reticulatus	Europe	Important for initiation and acceleration of epizootics involving natural foci in Slovakia.[216]
D. variabilis (American dog tick)	North America	One of three primary vectors of human cases within the USA.[31] A host and a vector.[27]
Haemaphysalis chordeilis (Bird tick)	North America	Reported as a vector.[102]
H. concinna	Europe	Supports maintenance of *F. tularensis* in nature in Slovakia.[216]
H. flava	Japan	One of three important tick vectors in Japan.[71]
H. leporis-palustris (Rabbit tick)	North America	Important for maintenance of tularemia in nature as infections of lagomorphs and birds.[19] Rarely vectors tularemia to humans.[14]
Ixodes angustus	North America	Infected ticks removed from tundra vole in Alaska.[102]
I. apronophorus	Eurasia	Principal vector in some areas of the former Soviet Union;[27] primarily a vector among rodents.[41]
Ixodes dentatus	North America	Same as *H. leporis-palustris*.[14]
I. trianguliceps	Eurasia	Involved in forest foci of tularemia in the former Soviet Union.[66]
I. japonensis	Japan	One of three important tick vectors in Japan.[71]
I. nipponensis	Japan	Same as *I. japonensis*.[102]

the geographic area but most, except for ticks, appear to have little biological significance in either maintaining tularemia in nature or in directly transmitting *F. tularensis* to humans. Tabanids in North America and in the former Soviet Union and mosquitoes in Scandinavia and the former Soviet Union are exceptions.

Deerflies have been responsible for the transmission of numerous cases of tularemia in Utah.[19,103] *Chrysops discalis* is a primary vector of deerfly fever (tularemia), but other species, including *C. fulvaster* and *C. aestavans,* have also been found infected and were the first spontaneously infected tabanids to be reported in North America.[11] Several species of tabanids have also been found infected in the former Soviet Union.[142,214]

In general, the source of infection for **biting flies** is thought to be sick mammals, especially hares. Tabanids have also been observed to feed on carcasses of animals dead as long as 48 hours, and under experimental conditions have transmitted *F. tularensis* from such feedings to normal animals.[19] However, infection can also occur by other means. Hares, water voles, and contaminated water are the primary routes for infection of tabanids in the former Soviet Union. The tabanids remain infective for 2–3 days.[142,214]

Table 18. Arthropod species of primary importance in transmission of *Francisella. tularensis*—Continued.

Species[a]	Area of importance	Comments
TICKS—CONTINUED		
I. pacificus (Western black-legged tick)	North America	Reported as a vector.[102]
I. persuleatus (Taiga tick)	Europe	Reported as a vector.[27]
I. Scapularis (Deer or black-legged tick)	North America	Reported as a vector.[102]
I. ricinus (European castor bean tick)	Eurasia	Vector for human cases.[24] Supports maintenance of *F. tularensis* in nature in Slovakia.[216] Frequently found infected throughout much of its Palearctic distribution.[102]
Rhipicephalus rossica	Eurasia	Vector for human cases.[24] One of three principal tick vectors in the former Soviet Union.[142]
R. pumilio	Eurasia	Involved in "Tungai" foci of tularemia.[66]
BITING FLIES		
Chrysops discalis (Deerfly) 	North America	First presumed important vector of *F. tularensis* in the USA;[102] the most significant vector of the 97 North American species of deerflies.[174]
C. fulvaster	North America	First naturally infected biting flies reported in North America.[102]
C. aestuans	North America	Same as *C. fulvaster.*
C. relictus	Eurasia	One of the two most important vectors in the former Soviet Union.[102] First infections found in Rostov region.[25]
Chrysozona pluvialus	Eurasia	Same as *C. relictus*; large-scale 1957 outbreak of tularemia involved transmission of infections by this species to humans and rodents.[209]
Tabanus autumnalis (Horsefly)	Eurasia	First infections found in Astrakhan region of the former Soviet Union.[25]
T. flavoguttatus	Eurasia	Same as *T. autumnalis.*
T. bromius	Eurasia	First infections found in Perm region of the former Soviet Union.[25]
MOSQUITOES		
Aedes cinereus 	Sweden, former Soviet Union	Particularly adapted to feeding on small mammals, especially water voles.[102,217]
A. excrucians	Sweden, former Soviet Union	Same as *A. cinereus* but also feeds on other animals.[102]

[a] The species identified in this table are those most frequently mentioned in the literature in a manner that suggests they have an important role in the ecology of tularemia. Many additional species are cited in various review papers as being vectors of *F. tularensis*.[11,12,15,16,30,33,35,36]

Mosquitoes of the genera *Aedes*, *Mansonia*, *Theobaldia*, and *Anopheles* have been shown to be capable of **mechanical transmission** of *F. tularensis*. Therefore, in theory, mosquitoes that feed on infected hosts should be able to retransmit the bacteria during their next blood meal.[19] Nevertheless, despite the abundance of mosquitoes in tularemia enzootic areas of North America, they have not been important in the transmission of *F. tularensis*[11] Only one sample of mosquitoes from North America has tested positive for *F. tularensis*. In contrast, mosquitoes are important vectors of tularemia in the former Soviet Union and in Sweden.[11,217,221]

Sucking lice, in addition to ticks, biting flies, and mosquitoes, can also transmit *F. tularensis*. However, their high degree of host specificity precludes a major role as interspecies vectors of tularemia.[11] Other types of arthropods have also been identified as being capable of mechanically transmitting *F. tularensis* (Table 9).

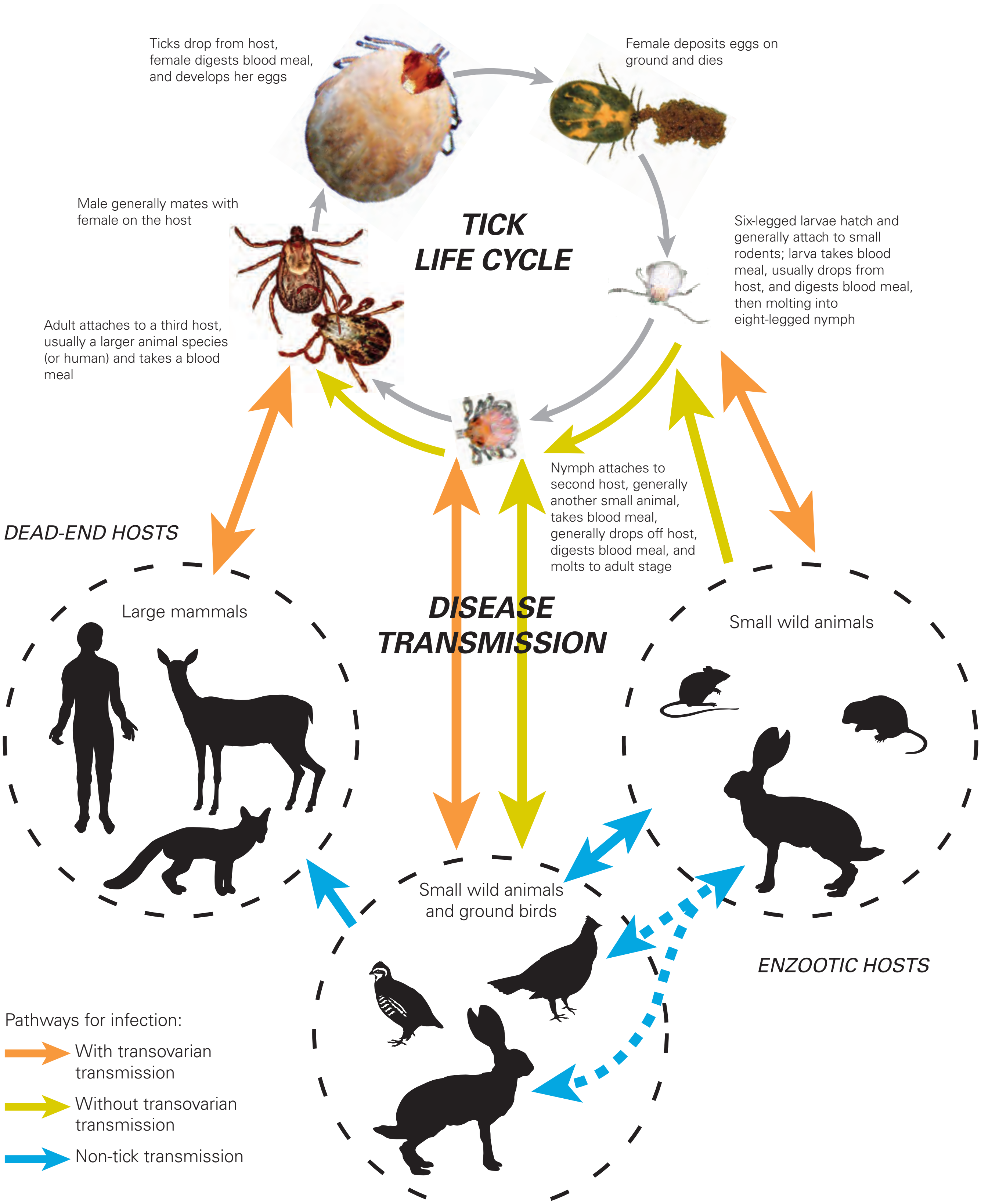


Figure 12. Generalized life cycle for three-host Ixodid ticks that commonly vector tularemia, and pathways for the transfer of *Francisella tularensis* between ticks, animals, and humans. *Dermacentor albipictus* is a notable exception by completing its entire life cycle on a single host. [Tick photographs by Jim Lalisch and Wayne Kramer, University of Nebraska-Lincoln, Department of Entomology.]

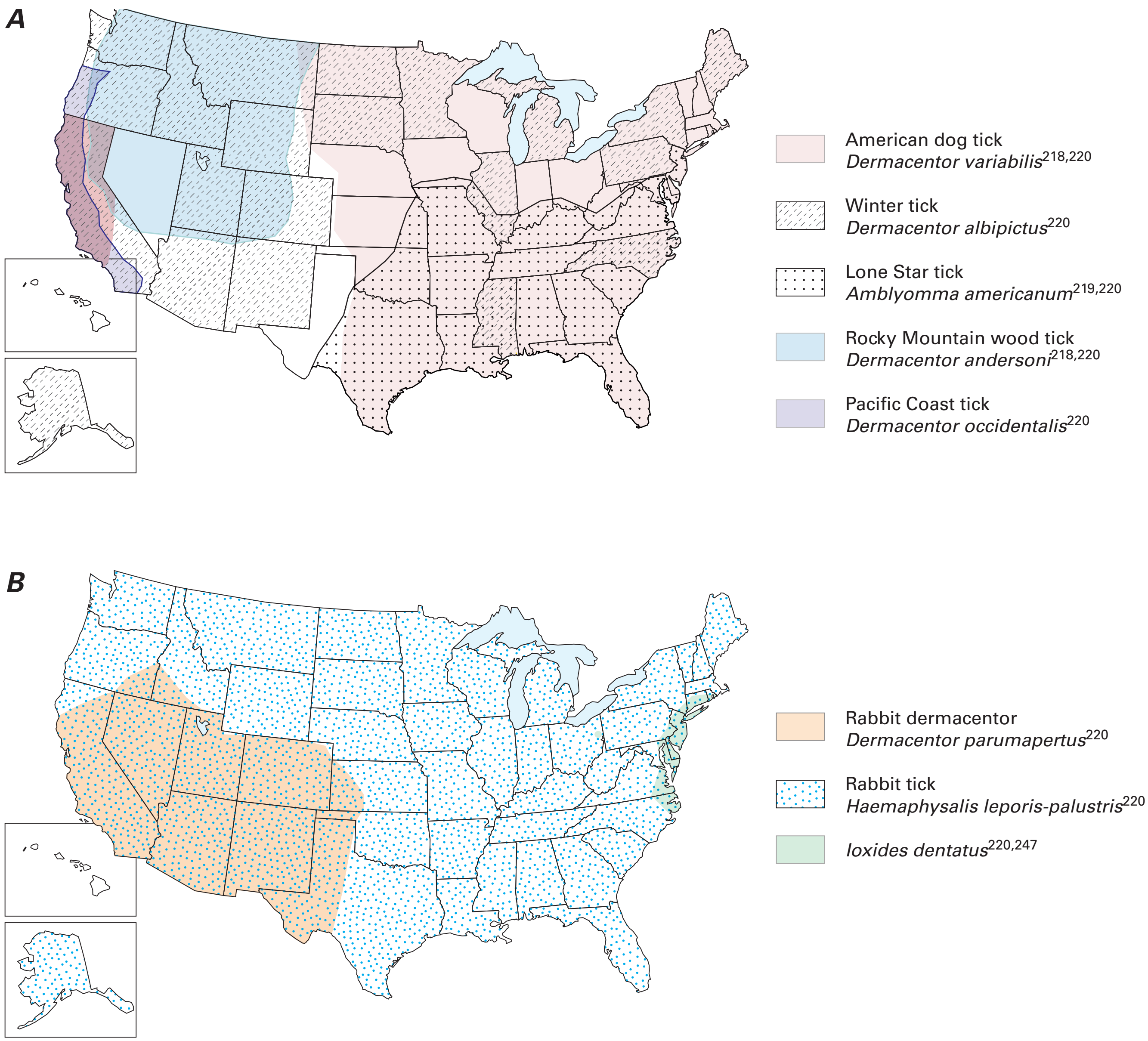


Figure 13. General geographic ranges for the primary tick vectors of tularemia in North America; *A*, species commonly feeding on humans, *B*, species that rarely feed on humans but do feed on birds and small mammals.

Domestic Animals

Sheep are associated with tularemia to a greater degree than any other species of domestic animal (Table 8). Individual epizootics of tularemia have killed more than 1,000 sheep,[90] and associated economic losses due to residual effects have also resulted from animals that survive infection.[11,19] However, in laboratory tests sheep are reasonably resistant to tularemia. It is thought that weather, body condition and perhaps heavy infestations of ticks, that in some instances result in tick paralysis, are confounding factors associated with tularemia on rangeland. Outbreaks generally occur in the spring, especially during the lambing season when sheep are in a somewhat weakened condition due to physiological stress. The tick, *Dermacentor andersoni*, is the primary source for infection of sheep in North America. Contaminated water has not been associated with tularemia outbreaks in sheep.[102] In some instances, tularemia epizootics in sheep have been preceded by epizootics in jackrabbits or other species.[158]

Human cases of tularemia have been associated with the sheep industries of North America[162] and the former Soviet Union.[91] Cases in the latter situation have been associated with workers in the meat packing industry rather than with rangeland conditions. Serologic evidence from North America indicates that contact with infected sheep has resulted in cases of tularemia occurring in sheep shearers.[174] Other livestock species have far less involvement with tularemia (Table 8) and are not considered to have an important role in the ecology or transmission of this disease.

Companion Animals

The role of companion animals (primarily cats and dogs) is unclear but appears to be increasing in importance (Box 7) and is predicted to be of greater importance in the future.[11] Companion animals such as dogs and cats are exposed to a variety of habitats where they become infected as they travel with people or as they roam outside. In Massachusetts, a 10-year-old girl became infected by saliva from her dog that presumably acquired *F. tularensis* from feeding on cottontail rabbits.[36]

Raising wildlife in captivity is another way that humans may contract tularemia. In one incident, a 16-month-old child contracted tularemia after being bitten by a pet gray squirrel allowed to be outside the home during much of the day.[176] In another situation, after bringing a wild baby rabbit home, an 18-year-old contracted oculoglandular tularemia.[127] Additional human cases of tularemia have been acquired from other species and circumstances involving wild species brought into the home.

Environmental Persistence

An important early discovery in the ecology of tularemia was that surface waters and mud in stream bottoms and ponds can become contaminated with *F. tularensis* and that the organism can survive at infective levels in those substrates for more than a month.[181] Survival of *F. tularensis* in nature is dependent upon a variety of factors such as temperature, direct exposure to sunlight, and other physical factors that generally affect the survival of microbes (Table 19). The source for contamination of surface waters is primarily urine and feces from infected animals (primarily voles) and the carcasses of animals dying from tularemia. Experimental studies have shown that one infected water vole, lemming, or mouse can contaminate up to 500,000 liters of water with *F. tularensis*.[142] Once contaminated, water may become an important vehicle for contamination or infection of biting insects, vertebrate animals, and humans. About 50 percent of mice became infected when the concentration of *F. tularensis* in water reached 100 to 1,000 organisms per liter and about 90 percent when the concentration reached 10,000 organisms per liter.[142] These high infection rates from low concentrations of organisms are due to the high susceptibility of some species of rodents (lethal dose for a mouse can be as low as one organism[222]) and results in water being an important medium for disease transmission. Direct contact, ingestion, and aerosols containing *F. tularensis* are all routes for exposure, depending on the species involved.

Well water and tap water from urban water systems have also been contaminated by *F. tularensis*.[24] During 1998, a waterborne outbreak of tularemia occurred among individuals fishing for crayfish in Spain.[49] Infective dusts from contaminated hay, litter, and other substrates associated with agriculture are occasional sources for infection of humans, and perhaps other species, but are less important than infective surface waters.

Cats, Dogs, and Tularemia

Box 7

"Cats…make it possible for the stay-at-home to acquire tularemia." (Evans et al.[224])

Companion animals have been an important component of human culture throughout recorded history. Dogs and cats are, by far, the primary species kept as companion animals and tularemia is a disease that can take advantage of the close and frequent contacts that occur between humans and these species. Cats and dogs may become indirectly involved in the transmission of tularemia by harboring ticks infected with *Francisella tularensis* that detach themselves within the household and then reattach themselves to humans. In addition, humans can become infected by crushing ticks between their fingers when removing them from companion animals. A highly unusual form of indirect transmission occurred as an aerosol exposure when dogs shook off rainwater within a cabin after killing tularemia infected rabbits.[225] Direct transmission by bite and scratch wounds inflicted by cats has occurred on numerous occasions.[84,226] In addition, there has been at least one case of tularemia resulting from a dog licking the face of a child.[225]

The results of natural and experimental infections of dogs and cats by *F. tularensis* can range from an absence of clinical disease to death. As for other species, the severity of disease is mediated by a number of factors including age of the animal and route of exposure. In general, very young animals are more susceptible than young adults. Dogs are moderately resistant to tularemia but serious disease leading to mortality can result following subcutaneous or intramuscular inoculation of *F. tularensis*. Cats are more susceptible to tularemia than dogs (see Table 8).[225]

The transmission of *F. tularensis* from cats and dogs to humans has involved healthy animals as well as animals with clinical cases of tularemia. However, it is unlikely that dogs and cats with clinical cases of tularemia are a source for direct infection of humans. Instead, mechanical transfer of bacteria occurs from the contaminated mouths and claws of pets that have recently fed on diseased small rodents and rabbits. The relatively prolonged survival of *F. tularensis* within the environment (see section on Environmental Persistence) and low infective dose for humans of as few as 10 organisms[5,227] facilitates mechanical transmission. Veterinarians and others who might contact infected tissues and body fluids during postmortem examinations of animals that die of tularemia or, less likely, during procedures involving the evaluation and treatment of clinical cases are at greater risk than the general population.[228]

Nearly all of the documented cases of tularemia in domestic cats and those involving transmission of this disease from cats to humans have two common denominators. First, these cats are allowed to roam outside of the home in rural or near rural areas. Second, these cats hunt, kill, and consume infected small rodents and rabbits.[84,229] City dwellers are not immune to this means for exposure to tularemia, because domestic cats often accompany their owners to such areas during excursions to the "family cabin" and on vacations.

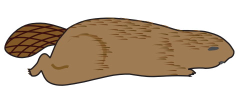
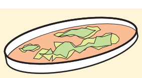
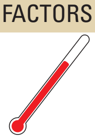
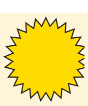
Photos by Milton Friend

Points to Ponder

Tularemia has implications for wildlife managers and those who are involved with wildlife in other ways. Mink and fox ranchers have used jackrabbit carcasses as feed that caused tularemia outbreaks among their animals.[158,159] Tularemia has also erupted in beaver farms from contaminated water,[178] illustrating the need for considering the relative "purity" and sources of food and water when rearing susceptible wildlife in captivity. Propagation of wildlife for sporting purposes, reintroduction, and enhancement of existing populations is currently more popular than fur farming. Regardless of the purpose for raising animals, the same principals for disease prevention exist. Tularemia can negate wildlife propagation efforts by killing animals after they are released (Fig. 14). Further, translocating hares, rabbits, and prairie dogs has introduced tularemia into new areas (Box 4).[24,31,72,223] The wildlife pet trade is another form of translocations contributing to tularemia outbreaks.[136,137]

Wildlife population impacts by tularemia are of a temporary nature. Widespread, major epizootics have reduced wild beaver and muskrat populations, temporarily reducing fur harvests.[13] Epizootics assumed to be caused by tularemia on the Upper Red River and Hudson Bay were reported to have persistent negative impacts on beaver populations and on those who depend on them for cultural and economic purposes for years.[164] Other impacts have been associated with the cottontail rabbit, the most frequently hunted game animal in the United States.[174] Fear of tularemia has reduced hunting cottontails in some areas, resulting in lost revenues for local

Table 19. Examples of environmental persistence of *Francisella tularensis*.

Environmental substrate	Survival time	Comments
Water 	14 weeks 90 days 4 months 3 months 3 weeks	Field samples stored at 7ºC[180] ?[27] At 4–6ºC[25] Tap water[19] At 20–21ºC in presence of carcass of a water vole dead from tularemia.[142]
Soil 	14 weeks 30 days 62 days	Mud samples stored at 7ºC[25] Humid soil[27,181] Mud[232]
Fodder 	4 months 6 months 133 days	Grain, straw at 4–6ºC[25] Dry straw litter[19] Wheat grain[27]
Live ticks 	764 days 701 days 700 days	Virulence maintained within body of *Ornithodoros turicata*[27] *Ornithodoros parkeri*[19] *Dermacentor marginatus*[25]
Animal carcass 	3 to less than 4 weeks At least 20 days 4 + 31 days	General survival in carcass tissues[180] Hides of water rats that died of tularemia (15–20ºC)[181] Urine in bladder of beaver dead of tularemia and storage of that urine at 15–28ºC[181]
Laboratory culture 	22 years	At 10ºC[27] (Culture media not reported.)
DESTRUCTIVE FACTORS		
Heat 	10 minutes	At 56–58ºC[27]
Direct sunlight 	3 hours	At 29ºC[19,27]

communities.[144] For example, half of 160 farmers interviewed in a Wisconsin survey curtailed cottontail rabbit hunting because of “rabbit fever.”[106] Conversely, the role of tularemia as a population regulation factor for small rodents is often considered a benefit.[12,230] However, epidemic-like spread of tularemia among humans has been associated with a periodic cycling of mouse populations and tularemia in the former Soviet Union[27] and in Central Europe.[45,56]

Disease Prevention and Control

The heavy use of the outdoors is part of the American lifestyle and is a factor relative to the potential for humans to contract tularemia. During 1996, 77 million people, or about 40 percent of the population 16 years of age or older, enjoyed some recreational activity in the USA relating to fish and wildlife.[231] Also, for people who have a subsistence-based lifestyle, contacts with wildlife and the environment provide more opportunities for exposure to *F. tularensis* than for those who are outdoors for recreational purposes.

However, tularemia has become the “forgotten disease” in many areas of North America despite its prominence during the first half of the 20th century. This perspective is reflected in current statements that refer to tularemia as a rare infectious disease.[26] Nevertheless, tularemia remains persistent in nature and can cause serious illness in humans.

The multiple routes for exposure (Fig. 15), and the high degree of invasiveness and infectiousness of *F. tularensis* complicate prevention of human cases of tularemia in enzootic areas. Nevertheless, people can minimize their potential exposure to *F. tularensis*. The general population is best protected from tularemia by avoiding contact with arthropod vectors, animal hosts, and contaminated environments. To a great extent, actions should be guided by public education, the availability of timely information of tularemia activity, and the selective use of immunizations for high-risk segments of society if a suitable vaccine is developed (Box 8).

Figure 14. An endangered Delmarva fox squirrel that was a postrelease casualty of tularemia.

Monitoring and surveillance of wildlife for tularemia activity in enzootic areas provides assessments useful for public health advisories and guidance for managers of public use areas such as National Parks and other outdoor recreation areas. The recent resurgence of tularemia in an enzootic geographic area extending over parts of Austria, the Czech Republic, and West Slovakia was clearly evident in hares prior to becoming an epidemic involving more than 200 human cases in West Slovakia alone.[233,234]

Monitoring activities need to be appropriately focused for the geographic area being evaluated, as “one size does not fit all.” In some instances monitoring relatively resistant species, such as coyote, which prey upon highly susceptible species involved in the transmission of tularemia, such as jackrabbits, may be the best approach. For other situations, monitoring might be focused on arthropod vectors, such as ticks, or focused on surface waters. Monitoring approaches should be guided by the fact that specific foci for tularemia generally involve only a small number of primary species despite the broad host range of species susceptible to *F. tularensis*.[11] Species other than those of primary importance tend to have incidental exposures and are not reliable indices for tularemia activity.

Surveillance for tularemia should be integrated with broader wildlife disease diagnostic activities and with that for domestic animals and human health. The diagnosis of tularemia as the cause of mortality in a beaver at a National Wildlife Refuge in Wisconsin during routine wildlife disease diagnostic activities provided early detection of tularemia activity. Wildlife managers temporarily closed portions of the refuge to minimize the potential for human exposure to tularemia. In another instance, the diagnosis of tularemia in an endangered Delmarva fox squirrel found by a hiker provided evidence of disease activity in a terrestrial environment (Fig. 14); actions followed to modify human use of the area and reintroduction plans for the fox squirrel.[235]

A reasonable precaution is to avoid drinking untreated water from lakes, rivers, and streams. This precaution also provides protection against a variety of other diseases such as **giardiasis**. In addition, avoid contact uses of water where dead rodents, hares, or rabbits are observed in those or adjacent environments.

As for other arthropod transmitted diseases, the use of insect repellant and protective clothing can provide effective barriers against exposure when in areas where insect vectors are the primary means for transmission of *F. tularensis*. Frequent body searches and prompt removal of ticks can also greatly reduce the risk for human infections from tularemia and other tick-borne diseases. Companion animals such as dogs and cats can bring infected ticks into the home, potentially infecting their owners. The use of tick collars, routine inspection of pets, and the careful removal of ticks are other actions that can be taken for disease prevention.[170]

Box 8 Tularemia—Who Is At Risk?

The overall global risk for contracting tularemia has decreased greatly during recent years. Within the USA, the reduced number of annually reported cases was a major factor in the 1994 removal of tularemia from the list of nationally notifiable diseases. Because of increased threats of bioterrorism, tularemia was reinstated to the list in 2000.[4] Nevertheless, tularemia remains a well-entrenched zoonosis. Areas historically known for this disease continue to have periodic outbreaks and tularemia sporadically appears in new places. The adage that, "one size fits all," does not apply to either the risk for exposure to tularemia or guide preventive actions that should be considered. In general, risk for infection is related to personal lifestyle and occupation.

Highest Risk Situations

Photo by Milton Friend

Laboratory-acquired infections are a significant risk for those involved in diagnostic and other laboratory investigations with *Francisella tularensis*.[238] Factors that elevate risk within this work environment include the potential for aerosol exposure associated with laboratory work, the low number of organisms required for aerosol infections, and the high concentration of organisms often present in the investigative materials. Because of these factors, laboratory investigators are often vaccinated, although, within the USA, the vaccines in use have been experimental. The Working Group on Civilian Biodefense recommends that the live vaccine strain [an attenuated (low virulence) form of *F. tularensis*] be used only in laboratory personnel routinely working with *F. tularensis*. Protection afforded by the live vaccine has been considerably better than that provided by the killed vaccine.[4]

Moderate Risk Situations

Photos by Milton Friend

Lower, but moderate risks for exposure to *F. tularensis* are commonly associated with a variety of nonlaboratory activities. Historically, activities such as hunting,[241] trapping,[78] and butchering wild game[33] have been closely associated with human cases of tularemia, especially when those activities have involved the taking of rabbits, hares, beaver, muskrat, and water voles.[44,144,147,185,242] Within the USA and many other countries, market hunting of wild game has been banned. As a result, "rabbit fever," which was often contracted by those who sold and butchered cottontail rabbits, is no longer a problem for commercial butchers.[36] In addition, trapping of species typically associated with tularemia has declined greatly. However, many native peoples and others continue to pursue these activities as part of their culture, livelihood (i.e. hunting guides), and for subsistence. The subsistence use of wildlife often involves salient species in the ecology of tularemia. Because these activities often take place in areas where tularemia in wildlife is common, it is likely that this segment of society has an elevated exposure rate to *F. tularensis*. For example, as many as 62 percent of native men in Alaska have tested positive for tularemia, most likely type B infections. Serologic evidence also indicates that large numbers of cases have occurred within North America in muskrat trappers.

Under some circumstances, farmers are also placed in moderate risk situations for exposure to *F. tularensis*. Hay and water supplies in rural areas have been the source for numerous human cases of tularemia following their contamination by small rodents. Aerosol exposure from handling contaminated hay infected more than 676 people during one event.[128] High population densities of small rodents such as mice, voles, and lemmings in tularemia enzootic areas are a warning sign for potential outbreaks of this disease and should trigger surveillance for tularemia activity in those populations. Findings from that surveillance are important for risk assessment and for guiding actions to protect human health within farming communities. A persistent foci of tularemia, with a high percentage of pneumonic cases, on Martha's Vineyard, Massachu-

Photo by Milton Friend

setts, since 2000 has placed landscapers at risk. The wearing of protective face masks has been recommended for those engaged in such activities at that location.[5,133]

Military personnel also have experienced major exposures to *F. tularensis*. The largest tick-borne cluster of tularemia cases within the USA occurred among troops on maneuvers in Tennessee.[79] Tens of thousands of Russian and German troops on the eastern front contracted tularemia in a series of outbreaks that occurred during World War II. However, it has been suggested that the outbreaks may have resulted from biological warfare rather than naturally acquired infections.[4]

The emergence of tularemia in prairie dogs, in combination with the popularity of these animals as wildlife pets and the inadequacy of health evaluation requirements for these animals, results in elevated risks for humans to contract tularemia from prairie dogs.[136,137]

Wildlife disease investigators, biologists, and law enforcement agents along with veterinary clinicians are others with potential elevated risks for exposure to *F. tularensis*, depending on the circumstances of their field activities and clinical practice.

Field biologists and wildlife law enforcement agents are often the initial personnel to encounter wildlife mortality events, often of unknown causes, and gather specimens for evaluation by disease specialists. Exposures to such mortality events have inherent risks that differ somewhat with the wildlife species involved.

Veterinarians with on-farm activities encounter a variety of diseases in the animals they treat, as do clinicians who provide services for zoological collections and wild animal parks.[243] Tularemia has been the cause of illness and death of numerous animals in these types of environments,[244,245] including recent outbreaks in zoos in Arizona that killed several **primates**.[246] Zoo outbreaks of tularemia often involve an interface with wild rodents, which also could be a potential source for human exposure. In addition, the increasing number of cases of tularemia in companion animals, especially the domestic cat, provides another potential source for veterinarians to become exposed to *F. tularensis*.

In most instances, wildlife disease specialists are the least likely of those within this risk group to encounter "surprise" exposures to tularemia. Field observations made by those reporting wildlife mortality events, past history of disease events on the area involved, and, in many instances, preliminary diagnostic evaluations from specimens already submitted often provide wildlife disease specialists with an initial foundation for their investigations.

Normal Risk Situations

Because tularemia is strongly linked to rabbit, hare, and rodent populations, human contact with these animals is risky when tularemia is active. Hiking, camping, fishing, hunting, and other forms of outdoor recreation are activities where humans could have contact with infected animals, be bitten by infected arthropods such as ticks, or have contact with contaminated surface waters. Numerous cases of tularemia have been associated with humans capturing sick wildlife by hand. Healthy wildlife are seldom approachable by humans so it's best to avoid contact with animals easily captured and possibly diseased.

Also, the potential for human exposure to *F. tularensis* by means other than contact with diseased animals should not be underestimated. Contact entry of *F. tularensis* via contaminated water has occurred though small abrasions in the skin, aerosol exposures by sprays and splashes resulting from human activities in those waters, and by ingestion.[49,51,118,119,172,181,200] For example, a major, but unusual, outbreak of tularemia occurred in Spain among people fishing for crayfish in a contaminated stream.[49]

Photo by Milton Friend

The best prevention against tularemia is sound information about the presence of active disease in areas where outdoor activities are to be carried out and general knowledge of the ecology of this disease. The sound application of this information provides a basic foundation for enjoying and working in the outdoors in a manner that minimizes risks for exposure to *F. tularensis*, even when disease is present.

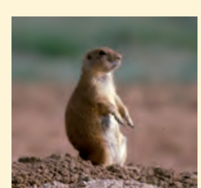


Photo by Milton Friend

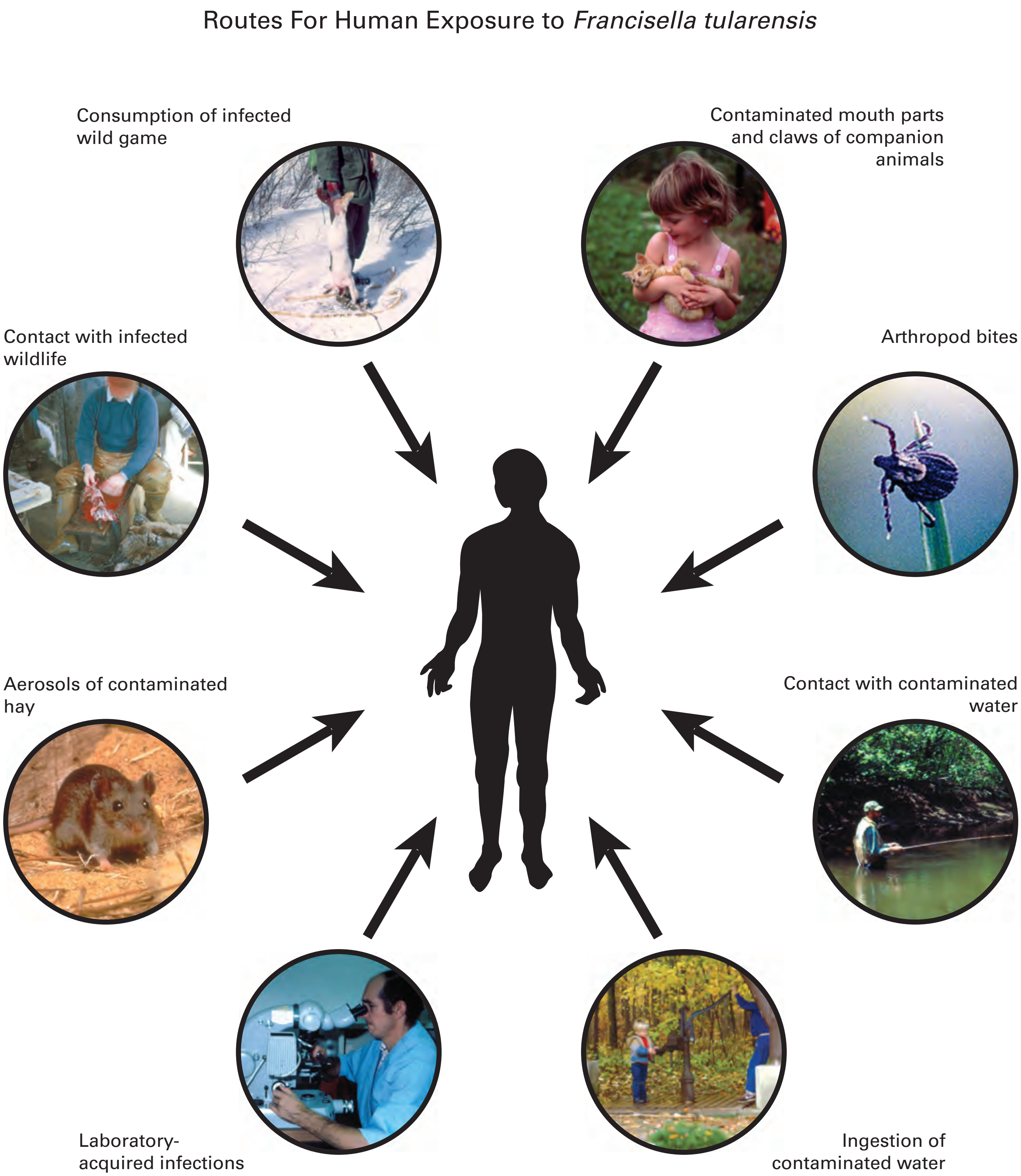


Figure 15. Humans can acquire tularemia by many routes and from numerous sources. (Mouse and tick photographs courtesy of the Center for Disease Control, microsope photograph by James Runningen, other photographs by Milton Friend.)

The use of rubber or latex gloves should be standard for hunters, trappers, and others who process wildlife for food or hides, especially those species commonly associated with tularemia (i.e., rabbits, hares, muskrats, etc.). Game should be thoroughly cooked when used for food.

Current numbers of tularemia cases in humans do not warrant reducing targeted vertebrate and invertebrate populations that are sources for disease maintenance and transmission. Within the USA, and in many other countries, such actions would invoke strong public outcry in opposition to the concept and its application. Also, tularemia may serve as a natural control of rodent populations that would otherwise cause significant negative impacts.[230] The rapid rodent population crashes often associated with tularemia may prevent enzootics of sylvatic plague in species susceptible to both diseases.[12]

Vaccination of high-risk individuals, such as hunters, trappers, and laboratory workers, has often been proposed and explored to some extent.[236] Immunization of humans was initiated in the former Soviet Union in the 1930s because of the high incidence of tularemia in that country. Many millions living in tularemia-endemic areas were given a live attenuated vaccine.[237] However, vaccination has generally not been widely applied elsewhere. Vaccination of individuals may become feasible within the United States in the near future, especially those with high risk for tularemia (Box 8). A live attenuated vaccine is being tested as an investigational new drug, but protection afforded has been uneven. Some of the volunteers were not protected against aerosol challenges with virulent *F. tularensis*. Data from the investigations undertaken are under review by the U.S. Food and Drug Administration (FDA) to determine the future availability of the vaccine.[4]

Treatment

Infection of humans by *F. tularensis* is treatable by antimicrobial therapy. Treatment recommendations have been developed for circumstances when a high degree of focus on the infected individual is possible as well as for large-scale events where this type of focus is not possible.[4]

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Glossary

Terms are defined relative to meaning within this publication.

Aerobic bacteria Requires the presence of oxygen for survival, in contrast to anaerobic bacteria that only exist in the absence of free oxygen.

Amphibians Cold-blooded vertebrates that live both on land and in water, have limbs instead of fins, have no claws on their toes, and have moist skin unprotected by external covering (e.g., scales, feathers, or hair); salamanders, newts, frogs, and toads.

Annelids Elongated, segmented metazoan invertebrates, above the lower worms; have a coelom (epithelium-lined space between the body wall and the digestive tract), like earthworms and leeches.

Anorexia Lack of appetite; severe and prolonged inability or refusal to eat.

Antigen Foreign proteins and other substance that, upon entering the body, stimulates the hosts immune system to produce specific substances, such as an antibody, to react with the antigen as a means for protecting the host from harmful invasion.

Antilocapridae A family of antelope containing the single living genus and species, the pronghorn *Antilocarpa americana,* that occurs in open grasslands and desert areas of western North America from southern Manitoba, Canada, to northern Mexico.

Arthropods Invertebrates belonging to the Phylum Arthropoda, here referring to members of the Classes Arachnida (spiders, ticks, mites, and scorpions) and Insecta (e.g., mosquitoes, flies, lice, fleas) that are disease vectors (e.g., mosquitoes and West Nile fever; ticks and tularemia).

Bacteremia The presence of bacteria in the blood.

Bacterium Singular of bacteria.

Bedbugs Small, wingless, flattened, oval, reddish, blood-sucking insects of the genus *Cimex* that feed on humans (e.g., *Cimex lectularius*), usually at night, and are found in houses, furniture, and unclean beds.

Biological vectors Arthropods in which the infecting organism develops or multiplies to become infective for other species.

Bioterrorism The use of biological agents, such as pathogenic organisms or agricultural pests, for terrorist purposes.

Biovar In the classification of bacteria, strains with sufficiently distinct characteristics (e.g., chemical, molecular) to be considered a subspecies of a taxonomic species.

Biowarfare Biological warfare; the use of biological weapons by one nation against another.

Bioweapons Any weapon usable in biological warfare and bioterrorism.

Birds Warm-blooded vertebrates with wings and feathers (although the wings are poorly developed for some species and they are flightless); belonging to the Class Aves.

Birds of prey Birds that primarily feed on the flesh of animals (e.g., amphibians, reptiles, mammals and other birds). Typically hawk-like birds, owls, eagles, condors, and vultures.

Biting flies Insects of the Order Diptera with mouthparts adapted to biting and piercing vertebrate animals; examples include deer flies and horse flies.

Biological transmission Disease transfer requiring an amplification host (often an arthropod) for development and/or multiplication of the disease agent necessary for infection of another host.

Blackflies Small, dark-colored, biting flies in the Family Simuliidae, whose larvae attach to rocks in flowing water; important vectors of *Leucocytozoan* spp., blood parasites of birds.

Boreal forests Predominantly coniferous (evergreen) native forests of northern latitudes.

Bubonic plague A severe bacterial disease of humans due to infection by *Yersinia pestis*; acute regional enlargement and inflammation of lymph nodes (*buboes*) is typical of this most common form of plague in humans. The “black death” of earlier times.

Buzzards Large hawk-like birds of prey, including New World vultures.

Caddis flies Insects of the Order Trichoptera with four membranous wings, slender antennae, and aquatic larvae; important food source for fish and birds.

Camels Primarily domesticated species of one-humped (*Camelus dromedarius*) and most two-humped camels; the only two-humped camel in a wild state (*C. bactrianus*) inhabits the Gobi Desert in Mongolia.

Canids Mammals within the Family Canidae (e.g., wolves, coyote, jackals, foxes, and other dog-like animals).

Carnivores Mammals with teeth and other body adaptations for feeding on flesh; primarily species belonging to the Order Carnivora (e.g., wolves, bears, raccoons, weasels, civets, hyenas, and tigers).

Catfish Bottom-feeding finfish with a scaleless skin, a broad, flat head and a strong single spine associated with both the dorsal and pectoral fins; barbels (fleshy appendages) are present on the face area. North American species include catfish, bullhead, stonecat, and madtoms.

Chicken hawk An informal name often used for a variety of hawk species.

Cloacal contents Fecal, urinary, and other discharges found in a common chamber at the end of the intestinal tract for most birds, reptiles, amphibians, and many fishes.

Companion animals Animals maintained by humans as pets (e.g., dogs, cats, captive wildlife, horses).

Conjunctiva The mucous membrane that lines the inner surface of the eyelid and the exposed surface of the eyeball.

Contagious disease Disease capable of being transmitted from one individual to another; communicable. All contagious diseases are infectious, but not all infectious diseases are contagious, as some must be vectored by infected insects or other means.

Coryza Acute, profuse, free discharge from the nostrils associated with inflammation of the nasal mucus membrane and air passages of the head and throat.

Coxal fluid Body fluid of ticks that may be discharged if limbs become detached when attempting to remove attached and engorged ticks.

Crayfish A freshwater crustacean that resembles a lobster in appearance except for its small size.

Crustaceans Fauna with a chitinous exoskeleton, such as crabs, lobsters, and shrimps, including barnacles, sow bugs, water fleas, and beach hoppers.

Cutaneous Pertaining to the skin.

Disease carriers Animals infected with infectious agents and showing no clinical signs of disease, but are capable of transmitting the infection.

Doves Pigeon-like birds belonging to the Family Columbidae. Domestic pigeons are often referred to as rock doves. Within North America, mourning doves, and white-winged doves are the most abundant wild species.

Edema Accumulation of abnormal amounts of fluid in the intercellular spaces within tissues of the body; generally in subcutaneous tissues but can be systemic, as well as localized.

Emerging infectious diseases Infectious diseases that have newly appeared and/or increased in frequency of occurrence within the past three decades, or threaten to increase in the near future relative to populations affected, geographic distribution, or magnitude of effects.

Endemic A disease that commonly is present within a human population or a geographical area.

Endotoxins Heat-stable toxins released from disrupted cells of some species of gram-negative bacteria, such as vibrios and brucellae; large doses can produce hemorrhagic shock and severe diarrhea, smaller doses cause fever and other manifestations.

Enzootic An animal disease that commonly is present within a population or a geographical area.

Epidemic An outbreak of disease affecting a disproportionately large number of humans within a population, community, or region during a period of time.

Epizootic A disease affecting a greater number of animals than normal; typically involving many animals in the same region at the same time.

Epoch An extended period of time characterized by distinctive development and/or events; a division of geologic time.

Eurasia The geographic area encompassing Europe and Asia.

Fairy shrimp Transparent freshwater branchiopod crustaceans of the Order Anostraca.

Fish Refers to finfish (e.g., cold-blooded strictly aquatic vertebrates with a well differentiated skull and a bony skeleton), in contrast to shellfish (invertebrates) and jawless fishes.

Fleas Small, wingless, bloodsucking insects within the Order Siphonaptera with laterally compressed bodies and legs adapted for jumping; some are important vectors of zoonotic diseases, such as plague.

Fluorescent antibody A laboratory assay system utilizing fluorescent dyes as stains for the detection of antibody against specific pathogens.

Foals Young (of the year) horses.

Foxes In North America, term pertains to arctic, red, kit (swift), and gray fox.

Frogs Amphibians that, along with toads, are within the Order Anura. Adult specimens of both have short, squat bodies, powerful hind legs, and lack a tail (see Toads).

Gerbils Old World burrowing desert rodents belonging to the genus *Gerbillus* (and related genera) with long hind legs adapted for leaping.

Giardiasis A common parasitic zoonoses resulting from infection of the small intestine by protozoans within the Genus *Giardia*. Humans typically become infected via contaminated food and water.

Gnats Small, biting flies within the Order Diptera.

Gram-negative coccobacillus Oval- shaped bacterial cells intermediate between spherical (coccus) and rod-shaped (bacillus) forms; gram-negative bacteria do not retain the purple dye when treated by Gram's stain for differentiating bacteria into two major groups (gram-negative and gram positive).

Ground squirrels Typically, burrowing small rodents of the Family Sciuridae (e.g., in the USA, thirteen-lined ground squirrel, rock squirrel, and antelope ground squirrel), but this term often includes species in other genera, such as chipmunks and prairie dogs.

Grouse Ground-dwelling, chicken-like birds of the Family Tetronidae with short to medium length tails (in contrast to pheasants); referring here to the ruffed grouse (*Bonasa umbellus*), unless specified otherwise.

Hard ticks Arthropods of the Family Ixodidae that are important for disease transmission; includes ticks of the genera *Dermacentor*, *Amblyomma*, *Ixodes*, and *Haemaphysalis*.

Hardwood forest Forests primarily composed of deciduous trees of hardwood (e.g., beech, birch, and maple are types of forests).

Hares *Lagomorphs* of the Family *Leporidae* whose young are furred at birth, have open eyes, and are able to run a few minutes after birth, in contrast to rabbits, which are born naked, blind, and helpless.

Holarctic The biogeographic region encompassing the Nearctic and Palearctic subregions (the northern parts of the Old World and New World).

Infectious disease A disease caused by the invasion of a host by pathogenic microorganisms. The pathogen may be a bacterium, virus, fungus, parasite or a prion (infectious protein).

Intraperitoneal Within the peritoneal cavity (in mammals, the double-layered sac that lines the area around the viscera below the diaphragm).

Invertebrates Animals lacking a spinal column (e.g., insects, crustaceans).

Kite Falcon-like hawks of the Family Accipitridae.

Lagomorphs Mammals within the Order Lagomorpha (rabbits, hares, and pikas).

Lesion Pathological change in the appearance of tissues or loses of normal function due to pathogens, injury, or other causes.

Lice Small, wingless, usually flattened insects that are parasitic on animals and/or plants and derive their nutrition by feeding on their hosts blood or other body components; true lice infest animals, including humans, and transmit several important diseases.

Lymphatics The system of lymph and lymph vessels that drain the tissue fluids of the body and return lymph to the blood.

Lymphatic glands The aggregation of cells within the lymphatic system into functional areas for the secretion or excretion of lymph within the body (e.g. lymph nodes).

Lymphatic system That part of the body's circulating system that recovers fluids and proteins which have exited cells and tissues and returns those materials to the blood; cellular debris and foreign materials are cleaned in this system by phogocytosis (e.g., white blood cell engulfment and consumption of foreign materials) and filtration.

Lymph nodes Rounded, encapsulated aggregations of lymphoid tissue distributed throughout the body along the lymphatic system. These nodes filter the flow of lymph circulating within the body.

Malaise A vague, general, and unfocused feeling of illness and fatigue.

Mammals Warm-blooded vertebrate animals that possess hair during some part of their life and suckle their young.

Mechanical transmission Disease transfer involving contact with surfaces contaminated by pathogens; this may occur from bites, scratches, contact with inanimate objects, and by other means allowing disease causing levels of the pathogen to enter the host.

Microbe Minute, microscopic living organisms that perform various biological functions essential for life processes (i.e., digestion); some microbes are referred to as germs because of their capacity to cause disease and include various forms of bacteria, fungi, protozoa (single-cell parasites), and viruses.

Migratory birds Species of birds that undertake seasonal geographic movements to meet their living and life-cycle requirements (e.g., waterfowl, shorebirds, many passerines).

Midges Very small, two-winged flies, many of which render painful bites and some of which vector infectious diseases.

Mice Small rodents with a pointed snout, relatively small ears, elongated body, and slender, nearly hairless tail; species primarily are within the genus *Mus*.

Miocene Period from 11 million to 25 million years ago during which the formation of high mountains occurred (e.g., Alps, Rockies, Himalayas).

Mites Minute arthropods related to spiders and usually having transparent or semitransparent bodies; parasitic forms for humans and animals feed primarily on the skin, causing various types of irritation of the tissue and also vector some infectious diseases.

Mollusks In general, shell-bearing invertebrates that have soft, unsegmented bodies (e.g., snails, clams, conchs, shells, scallops, oysters); also highly specialized carnivores often lacking an external shell and having long flexible tentacles, eyes, and a powerful beak (e.g., squid and octopi).

Moribund Being in a state of dying.

Mosquitoes Blood-sucking, small dipteran insects of the Family Culicidae that are important vectors for disease transmission (e.g., West Nile fever, malaria).

Nearctic The biogeographic subregion that includes Greenland, arctic America, and the parts of North America north of tropical Mexico (see Fig. 1).

Palearcarctic The biogeographic subregion that includes Europe, Asia north of the Himalayas, Arabia, and Africa north of the Sahara (See Fig. 1).

Paratuberculosis Johne's disease (*Mycobacterium paratuberculosis*), an infectious bacterial disease of wild and domestic ruminants that clinically resembles tuberculosis (*Mycobacteruim tuberculosis*) but is different.

Parenteral inoculation Entry by injection other than through the alimentary canal (e.g., subcutaneous, intramuscular, etc.).

Pathogens Typically microorganisms capable of inducing disease, but broadly includes all disease-inducing agents.

Pathogenesis The progression of agent-caused events within the body following exposure to a pathogen (disease agent) that results in disease, morbidity, and/or death.

Pheasant Long-tailed and often brightly colored Old World gallinaceous birds of the Family Phasianidae.

Pikas Short-eared, small rabbit-like mammals within the Order Lagomorpha; also referred to as coney and rock rabbit.

Pleomorphic An organism that has multiple distinct forms (e.g., a specific bacterium that can appear as spherical and rod-like forms).

Pliocene Period from 1 million to 11 million years ago during which the Antarctic Ice Age set in; on land, rapid evolution of mammals occurred.

Quail Any of various small, short-tailed gallinaceous birds of the Family Phasianidae.

Rabbit Small, long-eared mammals within the Family Leporidae (hares and rabbits) of the Order Lagomorpha (pikas, rabbits, and hares). Rabbits are born naked, blind, and helpless in a fur-lined nest; hares are born fully haired, with open eyes, and are able to run within minutes after birth. Some species commonly referred to as rabbits are actually hares (e.g., jack rabbit and snowshoe rabbit) while the Belgian hare is actually a rabbit.

Rain forest Tropical woodlands having an average annual rainfall of at least 100 inches and also characterized by lofty broad-leaved evergreen trees forming a continuous canopy.

Reptiles Vertebrates of the Class *Reptilia* that breathe by means of lungs and have external coverings of scales or bony plates; includes snakes, lizards, crocodiles, turtles, and dinosaurs.

Reservoir host The host that maintains the disease agent in nature and that provides a source of infection to susceptible hosts (see Fig. 9).

Rodent A diverse group of mammals characterized by incisor teeth that grow throughout life and must be worn away by cutting and gnawing hard materials. Species within the Order Rodentia include squirrels, mice, rats, voles, chipmunks, gophers, lemmings, beaver, porcupines, and many others.

Scavengers Animals that feed on dead carcasses, other carrion, and refuse (e.g., vultures, crows, hyenas, and jackals).

Septicemia Blood poisoning; persistence of pathogenic microorganisms and/or their toxins in the blood.

Serology Laboratory evaluations of the serum portion of blood for the purpose of detecting and measuring host antibody response to infectious agents and other antigens.

Serotype A group of closely related microorganisms distinguished by a characteristic set of antigens.

Snails Mollusks of the Class Gastropoda; most have a single enclosing shell or valve (usually spiral). Snails are a mobile, predatory species (often carnivores) that are important developmental hosts for pathogens causing several major parasitic diseases.

Snakes Scaled, limbless, sometimes venomous reptiles of the Suborder Serpentes having long, cylindrical tapering bodies.

Snapping turtles Any of numerous large freshwater turtles within the Family Chelydridae that have rough shells and powerful hooked jaws capable of closing suddenly.

Soft ticks Eight-legged arthropods of the Family Argasidae characterized by their soft, membranous external shells.

Spiders Invertebrates within the arachnids (spiders, mites, scorpions, and ticks) having an unsegmented abdomen that is constricted at the base and two or more pairs of abdominal spinnerets for producing silk threads for cocoons for their eggs or webs to capture prey.

Squirrel Tree squirrels of the Family Sciuridae; small to medium-sized arboreal rodents having long bushy tails and strong hind legs.

Systemic infections Those affecting the body as a whole.

Tabanids Bloodsucking biting flies, such as horseflies and gadflies, that can inflict painful bites and may mechanically vector infectious disease.

Ticks Blood-sucking, parasitic arthropods that have a hard body (ixodid ticks) or a soft body (argasid ticks); ticks are important disease vectors.

Toads In general, anurans with less smooth skin than that of most frogs; toads are also more terrestrial than frogs and hop rather than jump.

Translocation Human capture of wildlife at one geographic area and their transportation and release at a different geographic area.

Transovarian Transovarial; transmission of pathogens from the maternal organism (parent) by invasion of the ovary and infection of eggs, to individuals of the next generation (common in mites and ticks).

Tuberculosis A serious disease resulting from infection by bacteria within the genus *Mycobacterium*; *M. tuberculosis* is the primary cause of tuberculosis in humans, M. bovis for other mammals, and *M. avium intracellular* for birds. However, humans have been infected by all three species, and *M. tuberculosis* also affects nonhuman primates.

Turtles Reptiles with shells that cover the body; some species are found in freshwater habitats, others in marine environments (sea turtles), and still others are terrestrial (tortoises).

Upland game birds Chicken-like terrestrial birds commonly hunted for sport and food (i.e., chachalacas, grouse, partridges, pheasants, prairie-chicken, ptarmigan, quail, and turkeys).

Virulence The degree or ability of a pathogenic organism to cause disease.

Vertebrates All animals having spinal columns; mammals, birds, reptiles, amphibians, and boney and cartilaginous fishes.

Voles Small rodents of the genus Microtus (and related genera) that typically have a stout body, rather blunt nose (in contrast to mice), and small ears.

Waterbirds Bird species that utilize water environments as primary habitat (e.g., waterfowl, wading birds, gulls, terns, cormorants, and many others).

Waterfowl Birds within the Family Anatidae, collectively; all species of ducks, geese, and swans.

Zoonoses Infectious diseases transmissible between animals and humans, and vice versa.

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