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Review article

Francisella tularensis: an arthropod-borne pathogen

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Abstract – Arthropod transmission of tularemia occurs throughout the northern hemisphere. Few pathogens show the adaptability of *Francisella tularensis* to such a wide array of arthropod vectors. Nonetheless, arthropod transmission of *F. tularensis* was last actively investigated in the first half of the 20th century. This review will focus on arthropod transmission to humans with respect to vector species, modes of transmission, geographic differences and *F. tularensis* subspecies and clades.

***Francisella tularensis* / tularemia / arthropod / transmission**

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1. INTRODUCTION

Tularemia is a bacterial zoonotic disease of the northern hemisphere. The etiologic agent is *Francisella tularensis*, a gram-negative coccobacillus that is highly infectious and may be transmitted to humans by a number of different routes, including handling infected animals, ingestion of contaminated food or water, inhalation of infective aerosols and arthropod bites (ticks and insects) [18, 40]. Two subspecies of *F. tularensis* cause most human illness, subspecies *tularensis*, also known as type A, and subspecies *holarctica*, referred to as type B [36]. Whereas type B infections occur throughout the northern hemisphere, type A infections are limited to North America. Type A strains have been further divided into two genetically distinct subpopulations, A1 and A2, which differ with respect to clinical severity [48]. In the USA, A1 strains occur primarily in the eastern half of the country while A2 strains occur only in the west [13, 48].

Arthropod-borne transmission of tularemia was first established by Francis in 1919 when he isolated the etiologic agent from a Utah patient with "deer fly fever", an ulceroglandular condition described by Pearse in 1911 [15, 28]. In subsequent laboratory studies, Francis and Mayne confirmed transmission from infected to healthy animals by deer fly bite [16]. Tick borne tularemia was recognized in 1923 by physicians in Idaho who noted enlargement of lymph nodes in response to a tick bite [28]. *F. tularensis* was first isolated from ticks by Parker studying *Dermacentor andersoni* in Montana in 1924 [37].

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Vector-borne transmission of tularemia is now known to occur throughout the northern hemisphere, with varying degrees of frequency in differing geographic regions. Two primary disease manifestations, ulceroglandular and glandular, can arise from the bite of an infected vector [11, 18]. Ulceroglandular tularemia, the most common form associated with arthropod bite, is characterized by an ulcer at the site of the tick bite and enlargement of regional lymph nodes. Glandular tularemia is characterized by regional adenopathy without an identifiable skin ulcer. If either form is not treated with appropriate antibiotics, secondary complications can arise, including suppuration and skin eruptions, and less commonly pneumonia and meningitis [12, 17, 19, 26, 50].

In nature, *F. tularensis* is associated with a wider range of hosts than most other zoonotic pathogens; natural infections have been found in >100 species [23]. Maintenance in nature is primarily associated with rodents and lagomorphs. The two *F. tularensis* subspecies, type A and type B, are associated with differing animal hosts; type A is more commonly associated with lagomorphs (rabbits and hares), whereas type B is more frequently associated with rodents [2]. Ectoparasites likely play an important role in maintenance by disseminating *F. tularensis* infection within the host population. Some arthropods are also capable of transmitting *F. tularensis* to other susceptible hosts, including humans.

Few pathogens show the adaptability of *F. tularensis* to varying vector, host and environmental conditions. Since *F. tularensis* is endemic on different continents in differing ecologies, many variations occur in local transmission cycles. Little, however, is known about the mechanisms important for adaptation of this organism to such a wide diversity of arthropod vectors. Arthropod transmission of *F. tularensis* was last actively investigated in the time period from 1920 to 1955, prior to identification of the two *F. tularensis* subspecies, type A and type B by Olsufiev in 1958 [28, 36]. As a result, much of the older arthropod studies cannot be accurately interpreted with respect to the infecting strains. Moreover, identification of the two type A clades, A1 and A2, both of which have been linked to vector-borne transmission, only occurred within the last five years [13, 29, 48].

This review will focus on arthropod transmission to humans, giving a historical perspective of what is known with respect to the primary human vectors, hard ticks, flies and mosquitoes, focusing on species for which data exists to support their role as vectors in nature. Although sporadic cases of vector-borne transmission have been documented throughout the northern hemisphere, for the purposes of this review, geographic regions where arthropod transmission occurs most frequently will be emphasized. Geographic differences in vectors as well as *F. tularensis* subspecies and clades will also be discussed as well as questions to be addressed by future studies.

2. ARTHROPOD VECTORS OF *F. TULARENSIS* AND MODES OF TRANSMISSION

Infections with *F. tularensis* in nature have been documented in a number of different arthropods, including fleas, lice, midge, bedbugs, ticks, mosquitoes and flies [2, 23, 35]. Despite the diversity of naturally infected arthropods, only a subset of these have been identified as important for transmitting *F. tularensis* to humans [3]. These include hard ticks, deer flies, horse flies and mosquitoes (Tab. I).

Outbreaks of tularemia due to tabanid, deer fly or horse-fly, transmission have occurred multiple times since this route of transmission was first described in the early 1900's, with the most recent outbreak occurring in Utah (USA) in 2007 [15, 30, 41].

Transmission of *F. tularensis* to humans by tabanid bite is mechanical. Deer flies and horse flies inflict a painful bite, resulting in interrupted feedings because of host-defense behavior [14]. If after beginning to feed, the deer fly or horse fly is dislodged from the host, it will often actively and persistently seek the nearest available host to continue feeding [27, 31]. This propensity of deer flies and horse flies to feed on multiple hosts,

Table I. Arthropod vectors considered significant with respect to transmitting *F. tularensis* to humans.

Arthropod	Species	Mode of transmission	Geographic regions
Deer-fly	*C. discalis* *C. relictus*	Mechanical	USA Russia
Horse-fly	*H. pluvialis*	Mechanical	Russia
Mosquito	*A. cinereus* *O. excrutians*	Mechanical	Sweden Russia
Tick (Hard)	*D. andersoni* *D. variabilis* *A. americanum*	Biological	USA

during a short period of time, is important for triggering acute outbreaks of tularemia. Although the term "deer fly fever" has often been used specifically to link tabanids to the transmission of *F. tularensis*, it is important to note that other bacterial as well as viral pathogens can be mechanically transmitted by tabanids [14].

Long-term survival of *F. tularensis* does not occur in tabanids, consistent with their role as mechanical vectors. The deer fly, *Chrysops discalis,* was shown by Francis in 1921 to transmit *F. tularensis* to animals only up to 4 days after initial infection and to survive within *C. discalis* for 14 days under laboratory conditions [16]. Flies were shown to be consistently infected up to 5 days in the laboratory, with a decline in infection after that time period, suggesting that *F. tularensis* does not multiply in *C. discalis*. Localization experiments within the deer fly have never been performed; it is presumed that mechanical transmission is due to the presence of *F. tularensis* on fly mouthparts.

Naturally infected tabanids include the deer fly species *C. discalis, C. fulvaster*, *C. eastuans* and *C. relictus* and horse fly species *Haematopota pluvialis* and *Tabanus autumnalis*, *T. flavoguttatus* and *T. bromius* [2, 8, 30, 31, 35]. Of these, *C. discalis, C. relictus* and *H. pluvialis* have most often been identified in association with tularemia epidemics and outbreaks [30, 35] (Tab. I).

Mosquito-borne infection has been linked to some of the largest epidemics of tularemia ever reported (> 400 cases) [7, 10]. Like deer flies, mosquitoes are considered to be mechanical vectors of tularemia, capable only of transmitting the disease transiently in nature. Parker showed experimentally in 1932 that multiple mosquito species, including *Aedes* spp., could transmit disease to laboratory mice by mechanical transfer [43]. Modes of mechanical transfer included interrupted feeding between infected and healthy hosts, mediated presumably on contaminated mouthparts. Also excrement deposited during feeding or by crushing the infected mosquito on the skin allowed for transfer, particularly if followed by rubbing or scratching.

Mosquitoes (*Aedes vexans*) were shown by Olsufiev in 1941 under laboratory conditions to transmit infection to guinea pigs, white mice, water rats, field mice, hares, woodchucks, and sheep up to 27 days after feeding on sick water rats [35]. However, mosquitoes, liking biting flies, are not believed to be important for long-term maintenance of *F. tularensis* in nature, as multiplication of *F. tularensis* has not been observed in mosquitoes nor has *F. tularensis* been identified in the eggs of experimentally infected mosquitoes [11, 35, 43]. It has been suggested that mosquito larvae could become infected with *F. tularensis* during development in contaminated water, though direct evidence is lacking [11]. Localization experiments within the mosquito have not been performed, thus is not clear if the organism might be present in salivary glands or on contaminated mouthparts. Naturally infected mosquitoes found during tularemia epidemics and repeatedly in nature include *Aedes cinereus* and *Ochlerotatus excrucians* [23, 34, 35].

Tick-borne transmission usually results in sporadic cases, but occasional outbreaks have been reported [32, 45, 46, 50]. In contrast to deer flies, horse flies and mosquitoes, ticks are considered significant biological vectors, not only capable of transmitting *F. tularensis* between animals and to humans by bite, but also sustaining the organism for long periods of time in nature [23]. The life cycle of most hard ticks requires two years for completion and includes the four stages, egg, larva, nymph and adult. Transtadial transmission of *F. tularensis* from larva to adult has been demonstrated under laboratory conditions for a number of tick species including *Dermacentor andersoni*, *Dermacentor variabilis* and *Amblyomma americanum* [20, 22, 37, 42, 44]. At each stage of the life cycle (larvae, nymph and adult), a blood meal is required either for morphogenesis or for egg-laying. As a result, hard ticks feed up to three times during their two year life cycle, allowing the possibility for a single tick to transmit disease with each bite. The human biting ticks found naturally infected and considered significant with respect to human cases include *D. andersoni, D. variabilis* and *A. americanum* [3].

Localization of *F. tularensis* in hard ticks has identified the organism in the gut as well as hemolymph. Petrov reported that *F. tularensis* penetrated through the gut into the hemolymph and salivary glands of the species, *D. marginatus* [23]. However, *F. tularensis* infection has never been documented in the salivary glands of the primary human biting ticks. Multiplication of *F. tularensis* is believed to take place in immature stages up through the adult. Hopla showed in *A. americanum* a gradual increase in the number of organisms per tick from larval infection to emergence of adults [21]. In comparison, Petrov noted in *D. marginatus* an increase in organisms (*F. tularensis* type B) after feeding and a decrease after molting [42].

Conflicting results have been recorded with respect to the effect of *F. tularensis* on tick viability and whether *F. tularensis* is transmitted transovarially. In some experiments, significant mortality has been noted in ticks after infection with *F. tularensis* whereas in other cases, no effect on mortality was noted [4, 21, 23, 44]. Petrov observed that vulnerability of ticks increased with the degree of infection (*F. tularensis* type B) and was greatest in the nymphal stage [42]. Similarly, transovarial transmission was demonstrated in early experiments for several species of hard ticks (*D. variabilis, D. andersoni*), while later experiments failed to confirm passage of *F. tularensis* to progeny of infected female ticks (*D. variabilis, D. marginatus*) [1, 4, 21, 38, 44]. Infected unfed larvae of *A. americanum* have been found in nature, suggesting that transovarial transmission may occur to some extent in nature [5]. It is generally considered that transovarial transmission is the exception rather than the rule in nature [23].

In several species of ticks, including human biting ticks, *Francisella* like endosymbionts (FLEs) have been identified [47]. Localization experiments in *D. andersoni* have shown the FLE is present in female reproductive tissues, but not salivary glands [33]. Guinea pigs fed on by FLE infected *D. andersoni* did not become ill or develop an immune response to the FLE, suggesting the FLE is not transmitted by ticks [33]. The effect of FLEs, if any, on vector competency and transmission of *F. tularensis* by ticks is not known.

3. GEOGRAPHIC DIFFERENCES FOR ARTHROPOD VECTORS TRANSMITTING *F. TULARENSIS*

Epidemiological characteristics of vector-borne tularemia vary throughout the northern hemisphere. In the USA, Sweden, Finland and Russia, arthropod bite is a common mode of transmission to humans, whereas, in Central Europe, arthropod-borne disease accounts for only a small percentage of human cases [2, 25, 49]. Contact with infected animals and ingestion of contaminated food or water are more common modes of transmission in central Europe [25]. Additionally, the arthropod transmitting disease to humans can vary within a given geographic area. For example, in the western USA, both deer flies and ticks are considered important vectors, whereas in the eastern USA, only ticks are

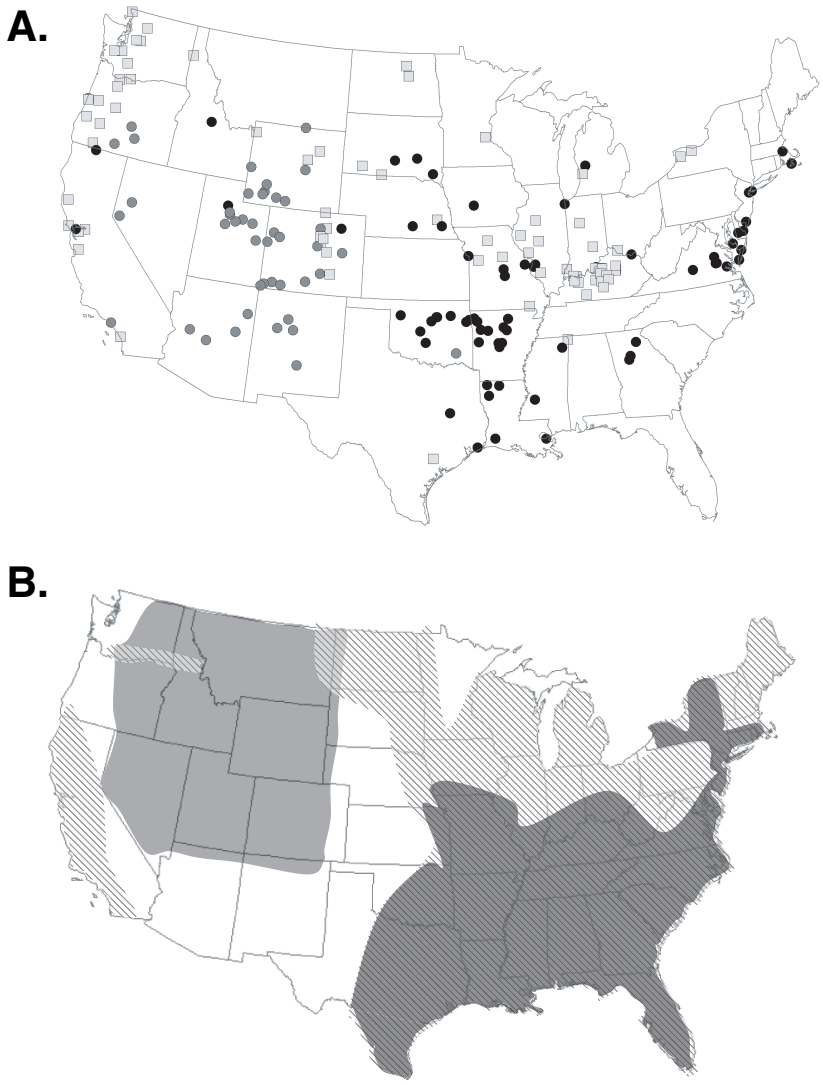

Figure 1. (**A**) The distribution of human infections caused by *F. tularensis* subsp. *holarctica* (type B) (light gray squares) and subsp. *tularensis* clades A1 (black circles) and A2 (gray circles) in the USA. Human infection data is from Staples et al. [48]. Cases are plotted randomly with the county of infection. Infections represent all routes of exposure (arthropod, animal contact, inhalation, etc.). (**B**) Approximate geographic distributions of tick species associated with human tularemia in the USA, *D. variabilis* (light gray diagonal striped shading), *A. americanum* (black shading) and *D. andersoni* (gray shading). Tick distributions are from Brown et al. [3].

considered of significance [24]. These geographic differences are presumably linked to the absence or presence as well as abundance of differing vector and host species.

In the northern countries of Sweden, Finland and Russia, mosquitoes have been identified as the primary vector transmitting disease to humans. Naturally infected *A. cinereus* were first identified during an epidemic of tularemia in Sweden in 1938 [34]. In Russia, *A. cinereus* as well as *O. excrucians*, have repeatedly been found infected

in nature [23, 35]. Both mosquito species are found primarily in sub-arctic climates[1]. Thus, the geographic distribution of these mosquitoes may play a role in the association between mosquito transmission and sub-arctic regions.

In the USA, tick bite is one of the predominant modes of transmission [6]. The three tick species most important for human transmission include *D. andersoni*, *D. variabilis* and *A. americanum*. Within the USA, the distribution of these ticks varies [3] (Fig. 1B). *D. andersoni* is found throughout the Rocky Mountains at elevations about 1000 m to over 3000 m, whereas *A. americanum* is distributed in the southeastern states and along the Atlantic seaboard. *D. variabilis* has the widest distribution, being found in the eastern and midwestern USA, as well as California and Oregon [3].

D. variabilis and *A. americanum* are the two tick species found in regions of the USA reporting the highest incidence of tick-borne tularemia (Arkansas, Missouri, Oklahoma) [6]. These two tick species have a high affinity for humans, which likely contributes to their success as vectors of tularemia [39]. In addition, all stages of *A. americanum*, from larval to adult, will bite humans, which could contribute to vector efficiency of this species, if transovarial transmission occurs [22]. Distribution of these three ticks lies primarily in the USA, with some overlap into Mexico or Canada. The limited geographic range of these tick species likely contributes to the epidemiology of tick-borne disease. *A. americanum, D. variabilis* and *D. andersoni* are not found outside North America. It has been suggested previously that the penchant for *Dermacentor* spp. in the USA to feed on humans is responsible for the high incidence of tick-borne tularemia in the USA, in contrast to the tendency of the *Dermacentor* spp. present in Europe and Asia to feed on animals [25].

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Transmission by deer flies and horse flies has been associated with western regions of the USA and Russia, respectively. Jellison showed in 1950 that the distribution of tularemia in the western USA corresponded with the geographic distribution of the deer fly, *C. discalis* [27]. The interaction between *C. discalis* and jackrabbits appears critical for transmission to humans, as jackrabbit epizootics often precede outbreaks of tularemia among humans [15]. *C. discalis* has been proposed to show a preference for feeding on jackrabbits and only in the western USA does the distribution of jackrabbits and *C. discalis* overlap [27]. The horse fly, *H. pluvialis* and deer fly, *C. relictus*, have been linked to cases of human illness in Russia [35]. Both are believed to bite infected water voles (*Arvicola terrestris)* and transmit the disease to humans. As water vole epizootics have been shown to precede human epidemics, co-occurrence of *H. pluvialis* or *C. relictus* and *A. terrestris* may be important for this transmission cycle [9,35].

4. LINKAGE OF *F. TULARENSIS* SUBSPECIES/CLADES TO TRANSMITTING ARTHROPOD

Classification of the two *F. tularensis* subspecies (type A and type B) as well as the two type A clades (A1 and A2) occurred subsequent to the period of active investigation of vector-borne tularemia in the northern hemisphere [13, 29, 36, 48]. Moreover, distinctions in the epidemiology of vector-borne infections attributed to type B, A1 and A2 have only recently emerged [48]. For example, type A infections have been strongly linked to tick transmission. In a retrospective analysis of >300 cases of human tularemia in the USA, 74% of tick transmitted cases were attributed to type A [48]. Moreover, in regions of the USA reporting the highest incidence of tick-borne illness (Arkansas, Missouri, Oklahoma), type A infections predominate (Fig. 1A) [48]. Both *A. americanum* and *D. variabilis* are present in this disease focus (Fig. 1B).

The factors contributing to the linkage between type A and tick transmission are not

clear. Although both type A and type B have been isolated from *D. variabilis* [32], natural infection rates for type A versus type B in *D. variabilis* are not known. Similarly, no data exists with respect to identification of type A or type B in naturally infected *A. americanum*, however, laboratory experiments have provided evidence that *A. americanum* can transmit type A strains [22]. Of note, type B has only been identified in *D. variabilis* in the northern states of Montana and South Dakota, outside the geographic range of *A. americanum* (Fig. 1B) [32, 45, 46]; thus, the possibility exists that *A. americanum* may only transmit type A. Consistent with this notion, the distribution of infections due to type A and type B in the USA appear to differ; with type B infections predominating in the northern USA and type A infections predominating in the southern USA (Fig. 1A).

Among type A strains, both A1 and A2 infections have been linked to tick transmission. The differing geographic distributions for infections caused by A1 and A2 have been associated with differences in elevation and habitat type between the eastern and western USA, with A1 infections generally occurring at lower elevations than A2 infections [13, 41] (Fig. 1A). The geographic differences in infections caused by A1 versus A2 may also reflect co-evolution with different vector species. Distribution of the A1 subpopulation is spatially correlated with that of *A. americanum* and *D. variabilis*, whereas distribution of the A2 subpopulation correlates with that of *D. andersoni* (Fig. 1).

Type B strains have been tightly associated with transmission by mosquito; this mode of transmission has been documented in regions of the northern hemisphere where only type B occurs. It is not clear whether mosquitoes selectively transmit type B strains, as transmission studies with type A strains have not been performed. The mosquito species known to transmit tularemia, *A. cincereus* and *O. excrutians*, are largely restricted to the subarctic climates where type B predominates. Thus, the overlapping distribution of type B and these mosquito species appears important for this association. Additionally, if mosquito larvae become infected with *F. tularensis* during development in contaminated water, this could play a role in the linkage between type B strains and mosquitoes, as type B persists for prolonged periods in watercourses [11].

5. CONCLUSION

Arthropod transmitted tularemia remains a concern worldwide. Tick-borne tularemia plays a prominent role in the primary USA disease focus of Arkansas, Missouri and Oklahoma and deer fly epidemics continue to occur sporadically in the western USA. Mosquito-borne transmission continues to occur in Sweden, occasionally resulting in large epidemics. However, arthropod-borne transmission of tularemia was last actively investigated in the mid 1900's and many important questions remain to be addressed. What mechanisms contribute to both biological and mechanical transmission? Has *F. tularensis* adapted a mechanism for survival on tabanid mouthparts? Does *F. tularensis* reside in the salivary glands of arthropods and if so does it replicate there? Is regurgitation a mechanism of transmission? Do mosquito larvae become infected in *F. tularensis* contaminated water, and if so, can they then transfer the disease to humans and animals? What is the relationship between *F. tularensis* subspecies and clades with regard to the differing arthropod vectors, ticks, mosquitoes and deer fly? What are natural infection rates for type A and type B in human biting ticks? What is the vector transmission efficiency and competency for type B, A1 and A2 strains in the human biting ticks *D. andersoni*, *D. variabilis* and *A. americanum*? Do FLEs interfere with vector transmission of *F. tularensis* by ticks? What pathogen specific genes are important for transmission? Are there other human biting vectors that act as vectors of *F. tularensis* and with what frequency? As suggested by Hopla, perhaps we are a priori so convinced that tularemia organisms are tick transmitted in the southern USA, that tabanid flies have been overlooked in certain areas[1]. The same can be stated with regards to the role of mosquitoes

in transmission outside the sub-arctic region, or the role of vectors other than hard ticks, mosquitoes and tabanid flies throughout the northern hemisphere. The study of mechanical vectors in nature is notoriously difficult, as infection is only transient. Nonetheless, given that arthropod-borne transmission of *F. tularensis* to humans continues to occur worldwide, there is a need to address these questions. Increasing our understanding of vector-borne tularemia is critical for public health prevention.

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